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Post-traumatic stress and cancer: Findings from a cross-sectional nationally representative sample

Tyler S. Kaster[a], Jordana L. Sommer[b,e], Natalie Mota[c,d], Jitender Sareen[b,d], Renée El-Gabalawy[b,c,d,e,*,1]

[a] Department of Psychiatry, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[b] Department of Psychology, Faculty of Arts, University of Manitoba, Winnipeg, Canada
[c] Department of Clinical Health Psychology, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada
[d] Department of Psychiatry, Max Rady College of Medicine, University of Manitoba, Winnipeg, Canada
[e] Department of Anesthesiology, Perioperative and Pain Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada

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ABSTRACT

Objective: Trauma and post-traumatic stress disorder (PTSD) have been associated with a variety of physical conditions; however, their relationship with cancer is unclear.
Methods: Using the cross-sectional 2012–2013 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC-III; $N = 36{,}309$), we examined the association between trauma, PTSD and cancer (breast, gastrointestinal, 'other', and 'any'). Respondents were categorized into three groups: no-trauma, trauma-exposed, and PTSD using DSM-5 criteria. We conducted cancer- and sex-stratified regression analyses to examine the relationship between PTSD and cancer using the non-trauma exposed group as the reference.
Results: Cancer prevalence was significantly greater in PTSD than trauma-exposed and no-trauma exposed respondents, and greater in trauma-exposed than no-trauma exposed respondents. After adjusting for covariates, odds of cancer were significantly greater in PTSD compared to non trauma-exposed respondents for 'any' cancer (adjusted odds ratio [AOR]: 2.99; 95% CI = [2.31, 3.88], gastrointestinal (GI) cancer (AOR: 17.48; 95% CI = [8.09, 37.77]), and 'other' cancer (AOR: 3.21; 95% CI = [2.41, 4.27]). Breast cancer was non-significant. Although both males and females with PTSD had significantly increased odds of 'any', GI, and 'other' cancer, differential findings emerged across sexes for those who were trauma exposed, compared to non-trauma exposed.
Conclusion: Traumatic exposure and PTSD appear to be associated with cancer. The comorbid relationship between traumatic exposure, PTSD and cancer differs by cancer type and sex.

1. Introduction

Post-traumatic stress disorder (PTSD) is a mental disorder arising from exposure to a traumatic experience that results in distressing re-experiencing, avoidance, and hyperarousal symptoms, as well as negative alterations in cognition and mood (American Psychiatric Association, 2013). It is a highly prevalent disorder with an estimated lifetime prevalence of 7.8% (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995), and has been associated with a number of physical conditions including cardiovascular disease, diabetes, gastrointestinal disease, musculoskeletal disorders, and other diseases (Boscarino, 2004). Preliminary evidence also suggests a relationship between trauma exposure, PTSD, and cancer; however, research has been mixed regarding the nature of this relationship. This is an important issue for further study because there is a high prevalence of anxiety following cancer diagnosis – in one study 19% and 22.6% of patients had clinical and subclinical levels of anxiety (Linden, Vodermaier, MacKenzie, & Greig, 2012). Conversely, there is evidence that stress-related

Abbreviations: AOR, adjusted odds ratio; AUDADIS-5, Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-5 Version; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; GI, gastrointestinal; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; OR, odds ratio; PTSD, post-traumatic stress disorder

* Corresponding author at: Departments of Clinical Health Psychology and Anesthesiology, Perioperative and Pain Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, 2nd Floor Harry Medovy House, 671 William Avenue, Winnipeg, Manitoba, R3E 0Z2, Canada.
E-mail address: renee.el-gabalawy@umanitoba.ca (R. El-Gabalawy).
[1] Adjunct Appointments: Departments of Psychiatry and Psychology.

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psychosocial factors, such as anxiety broadly, may adversely affect cancer incidence and survival (Chida, Hamer, Wardle, & Steptoe, 2008).

Cross-sectional studies suggest an association between trauma and/or PTSD with greater odds of cancer in primary care patients, veterans, and the general population (Odds ratio [OR] range = 2.38–5.21) (El-Gabalawy, Blaney, Tsai, Sumner, & Pietrzak, 2018; Norman et al., 2006; Sareen et al., 2007) but these studies are unable to articulate the direction of association. Specifically, it is unclear whether cancer as a traumatic experience increases risk of PTSD or whether a history of trauma exposure/PTSD increases risk of cancer. Empirical support for the former association comes from a recent meta-analysis that found a 1.66 greater odds (95%CI = [1.09, 2.53]) of PTSD in cancer survivors compared to controls (Swartzman, Booth, Munro, & Sani, 2017). Indeed, a recent review of the PTSD and cancer literature concluded "being diagnosed with and treated for cancer is highly stressful and might lead to persistent [PTSD] psychopathology in a minority of patients" (Page 6; Cordova, Riba, & Spiegel, 2017). While cancer may be experienced as a trauma and lead to PTSD in some individuals, the vast majority of individuals who receive a cancer diagnosis do not develop PTSD (Brewin, Andrews, & Valentine, 2000). For trauma/PTSD increasing risk of cancer, which theoretically could be mediated through mechanisms such as behaviour (i.e. smoking) (Mills, Teesson, Ross, & Peters, 2006) or physiological changes such as inflammation (Michopoulos, Powers, Gillespie, Ressler, & Jovanovic, 2017), direct empirical support for this hypothesis is lacking. To date there has been one longitudinal population-level study assessing the incidence of cancer following PTSD diagnosis, which failed to find any increased incidence of cancer for individuals with PTSD (standardized incidence ratio = 1.0; 95%CI = [0.88, 1.20]). Therefore, while cross-sectional and longitudinal studies suggest an association between traumatic experiences, PTSD and cancer, there remain important characteristics of this relationship that are unknown.

Beyond temporality, it also remains unclear if the relationship between trauma/PTSD and cancer varies by type of cancer, which has been suggested by prior work examining adverse childhood events and adult cancers (Holman et al., 2016). Furthermore, given the substantial sex differences in both PTSD and cancer (Kessler et al., 1995; Siegel, Miller, & Jemal, 2017), it is unknown how the PTSD and cancer relationship may vary based on sex. As well, the PTSD and cancer relationship may vary based on the nature of the traumatic experience leading to PTSD diagnosis. Finally, no study has used PTSD diagnostic criteria from the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013), which introduced changes in diagnostic criteria whose impact on the relationship between trauma exposure, PTSD and cancer is unknown (Cordova et al., 2017).

To address these knowledge gaps, the objectives of this study were to, first, use data from a large nationally representative sample containing detailed PTSD symptom information to determine associations between trauma exposure and PTSD with several reported cancer diagnoses, as well as the role of sex in this association. Second, we aimed to compare sociodemographic, trauma, and temporal characteristics of adults with PTSD, with and without reported concurrent cancer diagnoses. Our primary hypothesis is that both traumatic experiences and PTSD will be independently significantly associated with cancer after accounting for covariates. Our secondary hypothesis is that the association will differ based on type of cancer, sex, and type of traumatic experience. With respect to the latter, given the previous research establishing a stronger association between cancer predicting PTSD, we hypothesize that the prevalence of illness-related traumatic experiences as the index trauma will be significantly higher among those with PTSD and comorbid cancer, compared to those with PTSD alone.

2. Methods

2.1. Sample

The National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III) is a cross-sectional, nationally representative survey of civilian, non-institutionalized adults aged ≥ 18 years old, residing in the United States (including the District of Columbia, Alaska, and Hawaii) (Grant et al., 2014). Of the initial 59,725 households contacted, there was an overall survey response rate of 60.1%, which resulted in a final sample size of 36,309 with interviews conducted between April 2012 and June 2013. Further details on the methodology, and sampling and procedures has been detailed elsewhere (Grant et al., 2014). Respondents provided informed consent and all research protocols were approved by the National Institutes of Health and Westat Institutional Review Boards. The NESARC-III data access committee approved this study, and institutional ethics approval was obtained from the University of Manitoba for analysis of these data.

2.2. Assessment

Survey interviews were conducted face-to-face by trained lay interviewers employed by Westat. Psychiatric diagnoses were based on the DSM-5 (American Psychiatric Association, 2013), and were obtained using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-5 Version (AUDADIS-5) (Grant et al., 2015), a semi-structured interview. In addition to PTSD, the AUDADIS-5 assessed 4 mood disorders (major depressive disorder, bipolar I disorder, bipolar II disorder, and persistent depressive disorder); 5 anxiety disorders (generalized anxiety disorder, specific phobia, social anxiety disorder, panic disorder, agoraphobia); alcohol, nicotine and 9 other substance use disorders (heroin, non-heroin opioids, sedatives/tranquilizers, cannabis, stimulants, cocaine, club drugs, hallucinogens, and solvents/inhalants). In previous studies concordance between the AUDADIS-5 and clinician-administered, semi-structured interviews was fair to moderate for depressive disorders, anxiety disorders, and PTSD (kappa = 0.24-0.59) (Hasin, Shmulewitz et al., 2015), and fair to good for substance use disorders (kappa = 0.40-0.72) (Hasin, Greenstein et al., 2015).

2.3. Traumatic exposure and PTSD

Respondents were divided into three trauma-defined groups based on self-reported trauma exposure and PTSD symptoms: (1) no lifetime trauma exposure formed the "no trauma" group, (2) lifetime trauma exposure (with or without subthreshold PTSD symptoms) formed the "trauma-exposed" group, and (3) lifetime trauma exposure with symptom severity meeting DSM-5 PTSD criteria formed the "PTSD" group.

PTSD diagnosis requires exposure to actual or threatened death, serious injury, or sexual violence through directly experiencing the event, witnessing the event, learning the event occurred to a close family/friend, or experiencing repeated exposure to aversive details of the event (Criterion A), and resulting symptoms of: intrusion (Criterion B), avoidance of stimuli associated with the traumatic exposure (Criterion C), negative alterations in mood and/or cognition (Criterion D), and marked alterations in arousal and reactivity associated with the traumatic event (Criterion E). Diagnostic criteria for the PTSD group were: endorsing exposure to a traumatic event (Criterion A), a minimum number of symptoms from all four symptom domains ($\geq$1 symptom for Criteria B & C and $\geq$2 symptoms for Criteria D & E), duration of symptoms longer than 1 month, and experiencing significant distress. While other models of the dimensional structure of PTSD exist (Armour, Műllerová, & Elhai, 2016), DSM-5 is the structure most commonly used by healthcare providers (American Psychiatric Association, 2013).

In the PTSD group, we assessed the following trauma and PTSD symptom characteristics: (1) number of traumatic exposures (single vs. multiple), (2) trauma category of the worst traumatic exposure (8 categories: injurious, sexual, psychological, combat, witness, terrorism/natural disaster, illness, and other [Specific events described in Appendix A]), and (3) number of years since PTSD onset (≤5 Years vs > 5 Years).

Respondents who endorsed exposure to a traumatic event but endorsed no PTSD symptoms or symptoms insufficient for PTSD diagnosis were included in the trauma-exposed group.

2.4. Cancer diagnosis

In the NESARC-III respondents were asked whether they had any of the following cancers during the past 12 months: breast, liver, mouth/tongue/throat/esophagus, and 'other'. Participants were then asked if a doctor or health professional told them that they had the specified cancer. We used the latter, more stringent criteria to identify cancer diagnosis. Liver and mouth/tongue/throat/esophagus cancer were combined into gastrointestinal (GI) cancer because of similar behavioural risk factors, enhanced statistical power, and to ensure adequate cell sizes (Chuang, Lee, Wu, Straif, & Hashibe, 2015; El-Zayadi, 2006; Maasland, van den Brandt, Kremer, Goldbohm, & Schouten, 2014). 'Other' cancer was any other cancer not listed, and 'any' cancer included all cancer diagnoses assessed.

2.5. Sociodemographic variables

The sociodemographic variables assessed were age (continuous variable), sex (male or female), race/ethnicity (White, Black, Hispanic, or other), marital status (married/common-law, widowed/separated/divorced, or never married), education (less than high school, high school completed, or some college or higher), and past year household income (US$ 0-19,999, 20,000-34,999, 35,000-59,999, 60,000+). These categorizations were in accordance with previous research (Pietrzak, Goldstein, Southwick, & Grant, 2011).

2.6. Analytic strategy

We calculated the prevalence of sociodemographic characteristics and cancer diagnoses among our three trauma-defined groups (no trauma, trauma-exposed, PTSD) using weighted cross-tabulations, and assessed group differences in these factors using chi-square analyses (for categorical data) and analyses of variance (ANOVAs; for continuous data). Post-hoc comparisons were completed to assess differences in cancer prevalence between trauma-defined groups (no trauma vs trauma-exposed; no trauma vs PTSD, trauma-exposed vs PTSD).

We used multiple logistic regression analyses to examine the association between the three trauma groups (independent variable) and cancer diagnoses (dependent variable), with the no trauma group as the reference category. We calculated three odds ratio models: (1) unadjusted (OR), (2) adjusted for sociodemographics (AOR; including age, sex race/ethnicity, marital status, education, and past year household income); and (3) adjusted for sociodemographics and other psychiatric disorders (AOR1; mood, anxiety, and substance use disorders). We stratified all analyses by sex and cancer type for descriptive purposes, which we then assessed using statistical interaction tests. We also performed a sensitivity analysis in which individuals with subthreshold PTSD – defined as individuals endorsing exposure to a traumatic event (Criterion A), and a minimum number of symptoms from ≥2 symptom domains (≥1 symptom for Criteria B and C or ≥2 symptoms for Criteria D and E) (McLaughlin et al., 2015) – were separated into a fourth group to determine the independent association with any cancer for each of no trauma (reference group), trauma exposed, subthreshold PTSD, and threshold PTSD groups.

In PTSD respondents, we used logistic regression analyses to examine the association between trauma characteristics (independent variable) with 'any' cancer diagnosis (binary dependent variable). We assessed the association with number of traumatic exposures, type of traumatic exposure endorsed, and number of years since PTSD onset in separated analyses. When examining the association with number of traumatic exposures (single vs. multiple), we used respondents endorsing a single traumatic exposure as reference. When assessing the association with type of worst traumatic exposure (injurious, sexual, psychological, combat, witness, terrorism/natural disaster, illness, and other), for a given traumatic exposure we combined respondents endorsing the seven other traumatic categories into a single reference group. When assessing the association with number of years since PTSD onset, we used respondents endorsing PTSD onset ≤5 years as reference. Alpha was set to 0.05 for all analyses and no corrections were made for multiple comparisons as this was an exploratory, rather than confirmatory, study as has been previously recommended (Bender & Lange, 2001). When observed cell size was < 5 we did not complete a logistic regression due to risk of overspecification. Taylor Series Linearization method was used for variance estimation in STATA 14 (Statacorp, College Station Texas, USA) to account for the survey's sampling design (Levy & Lemeshow, 2013). This study was reported according to STROBE guidelines for cross-sectional observational studies (von Elm et al., 2007).

3. Results

3.1. Sociodemographic & cancer characteristics

Sociodemographic characteristics of NESARC-III respondents for the three trauma-defined groups (no trauma, trauma-exposed and PTSD) demonstrated significant differences for all sociodemographic variables assessed (Table 1). Compared to respondents with no trauma exposure, trauma-exposed respondents tended to be older White individuals of either sex with a college or higher education and higher income, while those with PTSD tended to be younger white females with a lower income. There were significant differences in the prevalence of GI, 'other', and 'any' cancer between groups. Post-hoc comparisons revealed significant differences in which GI, 'other', and 'any' cancers were significantly more prevalent in the PTSD group followed by trauma-exposed, and then no trauma group (X^2 = 5.73–74.84, p < 0.05). The only exception to this trend was 'other' cancer in which cancer prevalence in the PTSD group did not significantly differ from the trauma-exposed group, though was significantly different from the no trauma group.

3.2. Trauma, PTSD and cancer

We found significant associations between the three trauma groups and cancer (Table 2). There were significantly greater odds of 'any' cancer for both the trauma exposed (AOR1: 1.52; 95%CI = [1.28, 1.81]) and PTSD (2.99; [2.31, 3.88]) groups compared to the no trauma group. In cancer-stratified analyses, the trauma exposed group was associated with significantly greater odds of GI (3.34; [1.80, 6.19]) and 'other' (1.66; [1.34, 2.05]) cancer and the PTSD group was associated with significantly greater odds of GI (17.48; [8.09, 37.77]) and 'other' (3.21; [2.41, 4.27]) cancer compared to the no trauma group. In our sensitivity analysis with four groups (no trauma, trauma exposed, subthreshold PTSD, and threshold PTSD), we found a similar pattern of findings as our primary analysis; however, effect sizes for subthreshold PTSD group were intermediate between trauma exposed and threshold PTSD group (Appendix B). In sex-stratified analyses, among males in the trauma exposed group there were significantly greater odds of GI (3.71; [1.65, 8.31]), 'other' (1.92; [1.42, 2.60]), and 'any' (1.94; [1.45, 2.59]) cancer relative to the no trauma group, while among females in the trauma exposed group, there were significantly greater odds for 'other' cancer (1.38; [1.04, 1.82]). Among males in the PTSD group

Table 1
Primary characteristics of respondents (N = 36,309).

	No Trauma (N = 12,115)	Trauma Exposed (N = 21,597)	PTSD (N = 2,339)
Age (years; mean)***	45.21 (0.27)	47.46 (0.22)	43.33 (0.37)
Sex***			
Male	5,282 (48.1%)	9,781 (49.7%)	678 (32.0%)
Female	6,833 (51.9%)	11,816 (50.3%)	1,661 (68.0%)
Race/Ethnicity***			
White	5,222 (56.7%)	12,536 (70.7%)	1,313 (68.5%)
Black	2,918 (13.6%)	4,298 (10.9%)	480 (12.0%)
Hispanic	3,116 (21.3%)	3,453 (11.7%)	426 (13.4%)
Other	859 (8.4%)	1,310 (6.8%)	120 (6.2%)
Marital Status***			
Married/Common Law	5,487 (56.2%)	10,308 (59.7%)	898 (48.4%)
Widowed/Separated/ Divorced	2,801 (17.4%)	5,753 (20.0%)	779 (27.1%)
Never Married	3,827 (26.4%)	5,536 (20.4%)	662 (24.5%)
Education***			
< High School	2,471 (18.1%)	2,546 (10.0%)	406 (16.4%)
High School	3,657 (28.5%)	5,443 (24.4%)	631 (26.2%)
Some College or Higher	5,987 (53.4%)	13,608 (65.6%)	1,302 (57.4%)
Income***			
0-$19,999	3,647 (23.0%)	5,291 (18.3%)	884 (30.2%)
$20,000-$34,999	2,781 (20.4%)	4,438 (17.6%)	504 (20.6%)
$35,000-$59,999	2,540 (21.7%)	4,642 (21.0%)	489 (22.7%)
$60,000 +	3,147 (34.8%)	7,226 (43.1%)	462 (26.5%)
Cancer Diagnosis			
Breast Cancer	78 (0.7%)	113 (0.5%)	16 (0.6%)
GI Cancer (Liver & Head/ Neck)***	13 (0.1%)	58 (0.3%)[a]	14 (1.1%)[a b]
'Other' Cancer***	213 (2.1%)	729 (3.9%)[a]	97 (5.1%)[a]
'Any' Cancer***	292 (2.7%)	875 (4.6%)[a]	119 (6.3%)[a b]

Note: Statistical significance between groups: $p < 0.001$***. Post-hoc statistical significance: [a] significantly differs from no trauma group, $p < 0.01$. [b] significantly differs from trauma exposed group, $p < 0.05$.
Abbreviations: PTSD = post-traumatic stress disorder, N = number of respondents in each category and percentages are weighted.

there were significantly greater odds for GI (33.30; [11.43, 97.01]), 'other' (2.24; [1.42, 3.55]), and 'any' (3.38; [2.06, 5.57]) cancer, and similarly among females in the PTSD group there were greater odds of GI (6.53; [1.29, 32.98]), 'other' (3.17; [2.20, 4.57]) and 'any' (2.52; [1.81, 3.50]) cancer. Interaction analyses examining sex by trauma group yielded significant effects for other, and 'any' cancer ($p < 0.05$). These significant interaction effects provide justification for stratified analyses.

3.3. Trauma characteristics and cancer

Within the PTSD group, there were significant differences in the types of traumatic experiences endorsed by respondents with cancer compared to without cancer (Table 3). Specifically, respondents with PTSD endorsing an illness as their worst traumatic exposure had significantly greater odds of 'any' cancer (2.70; [1.24, 5.89]). In a post-hoc analysis we found that the prevalence of cancer was significantly higher in the respondents with PTSD who endorsed illness as their worst traumatic experience (13.0%) vs other traumatic experiences (5.8%) ($X^2 = 10.34$ $p < 0.01$). With respect to both number of traumatic exposures and timing of PTSD onset ($\leq$ 5 years versus > 5 years ago), there were no significant differences for respondents with cancer compared to without cancer.

4. Discussion

In the first comprehensive population-based study of trauma, DSM-5 PTSD and cancer, we found that the prevalence of cancer was significantly higher in respondents with trauma exposure compared to no trauma exposure, and highest in respondents with PTSD. Logistic regressions in which we adjusted for sociodemographics and comorbid psychiatric disorders confirmed this association between trauma/PTSD and cancer. We found that the prevalence of cancer was lowest in the no trauma group, higher in the trauma-exposed group, and highest in

Table 2
Association between trauma exposure, lifetime PTSD and cancer diagnosis stratified by sex and cancer type.

	No Trauma		Trauma Exposed				PTSD			
	N (%)	Reference	*N* (%)	OR (95% CI)	AOR (95% CI)	AOR1 (95% CI)	*N* (%)	OR (95% CI)	AOR (95% CI)	AOR1 (95% CI)
'Any' Cancer	292 (2.7%)	1.00	875 (4.6%)	1.70 (1.42-2.04)***	1.58 (1.32-1.88)***	1.52 (1.28-1.81)***	119 (6.3%)	2.37 (1.89-2.98)***	3.26 (2.58-4.13)***	2.99 (2.31-3.88)***
Male	108 (2.0%)	1.00	402 (4.8%)	2.41 (1.82-3.19)***	2.04 (1.51-2.76)***	1.94 (1.45-2.59)***	31 (5.9%)	2.99 (1.97-4.55)***	3.94 (2.48-6.25)***	3.38 (2.06-5.57)***
Female	184 (3.4%)	1.00	473 (4.4%)	1.31 (1.04-1.64)*	1.26 (1.01-1.59)*	1.24 (0.99-1.55)	88 (6.5%)	1.97 (1.47-2.65)***	2.62 (1.96-3.50)***	2.52 (1.81-3.50)***
Breast Cancer	78 (0.7%)	1.00	113 (0.5%)	0.72 (0.50-1.04)	0.75 (0.53-1.08)	0.78 (0.53-1.13)	16 (0.6%)	0.89 (0.48-1.68)	0.94 (0.50-1.76)	1.06 (0.54-2.06)
Male	–	1.00	–	–	–	–	–	–	–	–
Female	75 (1.2%)	1.00	110 (0.9%)	0.75 (0.52-1.10)	0.78 (0.54-1.12)	0.80 (0.55-1.17)	15 (0.8%)	0.65 (0.33-1.26)	0.89 (0.46-1.74)	1.00 (0.49-2.04)
GI Cancer	13 (0.1%)	1.00	58 (0.3%)	3.88 (2.05-7.32)***	3.47 (1.93-6.24)***	3.34 (1.80-6.19)***	14 (1.1%)	14.58 (6.65-31.95)***	16.25 (7.57-34.87)***	17.48 (8.09-37.77)***
Male	6 (0.1%)	1.00	30 (0.3%)	4.65 (2.10-10.27)***	3.85 (1.78-8.33)**	3.71 (1.65-8.31)**	9 (2.6%)	36.95 (13.26-102.97)***	32.30 (11.35-91.87)***	33.30 (11.43-97.01)***
Female	7 (0.1%)	1.00	28 (0.2%)	3.18 (0.97-10.35)	3.31 (1.10-9.92)*	3.15 (0.97-10.24)	5 (0.4%)	4.69 (1.13-19.44)*	5.97 (1.52-23.45)*	6.53 (1.29-32.98)*
'Other' Cancer	213 (2.1%)	1.00	729 (3.9%)	1.91 (1.55-2.35)***	1.74 (1.41-2.15)***	1.66 (1.34-2.05)***	97 (5.1%)	2.55 (1.95-3.33)***	3.66 (2.76-4.86)***	3.21 (2.41-4.27)***
Male	101 (1.9%)	1.00	377 (4.5%)	2.38 (1.78-3.19)***	2.03 (1.49-2.77)***	1.92 (1.42-2.60)***	24 (3.9%)	2.05 (1.32-3.18)**	2.68 (1.67-4.29)***	2.24 (1.42-3.55)**
Female	112 (2.2%)	1.00	352 (3.3%)	1.51 (1.15-1.98)**	1.43 (1.08-1.89)*	1.38 (1.04-1.82)*	73 (5.7%)	2.68 (1.95-3.70)***	3.46 (2.49-4.80)***	3.17 (2.20-4.57)***

Note: Statistical significance: $p < 0.05$*, $p < 0.01$**, $p < 0.001$***.
Abbreviations: OR = unadjusted odds ratio; AOR = model adjusted for age, sex (omitted for stratified analyses), marital status, ethnicity, education, household income; AOR1 = model adjusted for sociodemographics, any substance use disorder (drug/alcohol/nicotine), mood disorder, and anxiety disorder; N = number of respondents in each category; GI = gastrointestinal; CI = confidence interval; PTSD = post-traumatic stress disorder.
– = cell sizes too small to report.

Table 3
Trauma related characteristics and association with 'any' cancer diagnosis in PTSD respondents.

	PTSD & Cancer Diagnosis	PTSD & No Cancer Diagnosis	OR (95% CI)	AOR (95% CI)
Trauma Category[a]	***N* (%)**			
Injurious	27 (17.3%)	504 (21.4%)	0.76 (0.49-1.18)	0.81 (0.54-1.24)
Sexual	29 (23.7%)	608 (26.7%)	0.85 (0.53-1.38)	1.01 (0.61-1.69)
Psychological	15 (10.4%)	279 (12.3%)	0.83 (0.42-1.64)	0.93 (0.46-1.86)
Combat[b]	–	57 (3.1%)	–	–
Witness	25 (25.0%)	501 (24.3%)	1.04 (0.56-1.95)	0.87 (0.47-1.62)
Terrorism/Natural Disaster[b]	–	41 (2.0%)	–	–
Illness	15 (13.0%)	102 (5.1%)	2.78 (1.28-6.06)*	2.70 (1.24-5.89)*
Other[b]	–	113 (5.1%)	–	–
Number of Traumatic Exposures	***N* (%)**			
Single Trauma	15 (12.0%)	280 (11.8%)	1.00	1.00
Multiple Trauma	104 (88.0%)	1,933 (88.2%)	0.99 (0.53-1.84)	0.98 (0.48-2.01)
Number of Years Since PTSD Onset[c]	***N* (%)**			
≤5 Years	21 (17.5%)	470 (22.3%)	1.00	1.00
> 5 Years	96 (82.5%)	1,700 (77.7%)	1.36 (0.78-2.36)	1.08 (0.61-1.92)

Note: [a]Refers to respondent self-report of worst experienced trauma; trauma category variables were entered individually and number of traumas and number of years since PTSD onset were included as categorical variables; [b]No odds ratio was calculated due to n < 5 in one of the groups [c]Age was excluded as a covariate due to overlap with the independent variable. Statistical significance: $p < 0.05$*, $p < 0.01$**, $p < 0.001$***. – = cell sizes too small to report. Abbreviations: PTSD = post-traumatic stress disorder; OR = unadjusted odds ratio; AOR = adjusted for age, sex, marital status, ethnicity, education, household income; *N* = number of respondents; CI = confidence interval.

respondents with DSM-5 PTSD, which suggests an independent association of cancer with both traumatic experiences and PTSD symptoms. Furthermore, in sensitivity analyses, both subthreshold and threshold PTSD groups had increased odds of 'any' cancer, though the magnitude of association for subthreshold PTSD was significantly smaller than for threshold PTSD (as indicated by non-overlapping confidence intervals). This raises the possibility of a relationship between greater number of PTSD symptoms (i.e., greater severity) and the association with cancer, which has been found in the association between PTSD and cardiovascular disease (Sumner et al., 2015). Our findings are also consistent with prior epidemiologic studies which found greater odds of cancer in veterans with trauma exposure compared to without exposure (El-Gabalawy et al., 2018); greater odds of cancer in community respondents with PTSD compared to no PTSD (Sareen et al., 2007); and greater odds of cancer in female primary care patients with a history of sexual trauma (Norman et al., 2006). Furthermore, we also found differences in the relationship between trauma/PTSD and cancer that varied by sex, cancer type, and nature of index trauma. Our results suggest that the relationship between trauma/PTSD and cancer is influenced by several characteristics including the traumatic experience itself, the individual's sex, and type of cancer.

In sex-stratified analyses, we found that males in the trauma exposed group had greater odds of all cancer types (compared to the no trauma group), while females had greater odds for only 'other' cancer. We found that there was a significant interaction effect between sex and trauma group for other, and 'any' cancer while we were underpowered to detect a sex interaction for breast cancer given only three males endorsed this cancer type. In cancer-stratified analyses, there was a significant relationship between PTSD and cancer, with particularly strong effect sizes for GI cancer for both men and women. Of note, cell sizes were limited in these regressions and confidence intervals were large for GI cancer and PTSD in the most stringent model; therefore results should be interpreted with caution. However, the trauma exposed group, compared to the no trauma group, was significantly associated with GI cancer in men only in the most stringent model. This is an important finding because GI cancer is 2.4–3.5 times more prevalent in men than women (Bosch, Ribes, Díaz, & Cléries, 2004; Curado & Hashibe, 2009). The relationship between GI cancer and trauma/PTSD will need to be examined in future longitudinal studies, and whether males have particular characteristics that uniquely contribute to the association between trauma exposure/PTSD and GI cancer (Nicholas, 2000).

Last, we found that respondents with PTSD who endorsed illness as their worst trauma (index trauma) compared to other traumatic exposures were significantly more likely to report a cancer diagnosis. Unfortunately, the NESARC-III data does not include information on the specific type of illness that is a traumatic event, and therefore we cannot determine if the illness reported is cancer. However, our results suggest that for respondents with comorbid PTSD and cancer, a large proportion of them have had traumatic experiences due to illness, cancer or otherwise. Additionally, a post-hoc analysis revealed that a significantly larger proportion of individuals indicated they had cancer among those with PTSD reporting illness as their worst trauma (13%) compared to those with PTSD endorsing another type of trauma as their worst trauma (5.8%). Because of this study's cross-sectional design we are only able to speculate about the nature of this association, though prior work has demonstrated that illness, and in particular cancer, may be the traumatic event that leads to or re-invokes PTSD symptoms in some people (Swartzman et al., 2017). This is relevant clinical information because PTSD related to illness may influence an individual's use of healthcare resources, which may ultimately affect their clinical outcome (Tedstone & Tarrier, 2003).

4.1. Limitations and future work

While our results are important contributions to the understanding of the relationship between traumatic exposure, PTSD and cancer, some limitations need to be considered. First, while we were able to describe the relationship between trauma/PTSD and cancer we are unable to draw conclusions regarding causality due to the cross-sectional design and lack of timing of trauma relative to cancer diagnosis. Second, we did not have information on details of the traumatic experience, which is particularly relevant for the 'illness' traumatic experience type and whether this illness was cancer. However, given that respondents endorsing illness as the worst traumatic experience had a significantly higher prevalence of cancer suggests that many of these illness experiences may be cancer. Similarly, we did not have information available on subtypes of cancer to examine the association between benign cancers (such as non-melanoma dermatologic cancer) and cancers with poor prognosis (such as pancreatic or lung cancer). Third, we were unable to assess PTSD symptom severity comparing those with and without cancer. Last, due to the lack of data on the timing of traumatic experiences we were unable to account for adverse childhood experiences, which have also been associated with physical illnesses

including cancer (Holman et al., 2016). While the results of this study are exploratory, they provide important hypotheses that can be tested in future confirmatory studies using prospective cohorts to address causality and include information on a broader range of cancers. These future studies should also assess the association with anxiety symptoms more broadly (i.e. using a dimensional approach), to further understand the complex relationship between psychological distress and cancer (Kessler, 2002). This may enable further understanding of the complex relationship between trauma, PTSD, and cancer

5. Conclusion

Our results suggest that trauma, PTSD, and cancer are associated with one another. The prevalence of cancer increased along the spectrum from no trauma to trauma-exposed through to respondents meeting DSM-5 PTSD criteria. The nature of the trauma/PTSD and cancer relationship varied by both sex and cancer type. We found that the association between trauma, PTSD, and cancer varied by the type of traumatic exposure as we found greater odds of cancer only when respondents endorsed illness as the worst traumatic exposure. Our work provides evidence for the association between trauma, PTSD, and cancer and the influence of sex, cancer-type and traumatic experience while also highlighting areas for future study using longitudinal designs.

Data access

Data for this study is available through the National Institute on Alcohol Abuse and Alcoholism.

Declaration of interests

All authors have approved the final article. The authors declare that they have no conflict of interest. TSK has received research support from the University of Toronto and the Clinician Scientist Program through the Department of Psychiatry at the University of Toronto. JLS has no disclosures. JS is supported by a CIHR Foundation grant # 333252 (2015-2022) to examine the impact of Posttraumatic Stress Disorder in community and military populations. RE and NM have received support from the University of Manitoba (Start-Up Funding) and the Canadian Institutes of Health Research SPOR Chronic Pain Network (RE only).

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Appendix A

DSM-5 Criterion A Traumatic Event Assessment

- Interviewers were instructed as follows:
  - First to show a first list of 34 stressful life experiences and ask:
  - "In your ENTIRE life, have any of these stressful or traumatic events EVER happened to YOU PERSONALLY?"
  - "In your entire life, have you EVER PERSONALLY WITNESSED any of these traumatic or stressful events happening to a friend, relative or ANY OTHER person?"
  - "In your entire life, have you EVER been REPEATEDLY EXPOSED to the details of any of the traumatic or stressful events [listed]? Please do not include events that you saw in pictures, on television or at the movies or in video games unless at work."
- Next, to ask:
  - "Did you EVER personally experience, witness, or become exposed to the details of any other kind of traumatic or stressful event that could have caused or threatened death, serious injury, or sexual violation?"
- Next, to show a second list of potentially observed stressful life events and ask:
  - In your entire life, did you EVER LEARN OR HEAR that any of the events [listed] happened to a relative or close friend? Include ONLY those events that you LEARNED or HEARD about that happened to a relative or close friend that were especially violent or accidental.
  - Did you EVER LEARN or HEAR that any other kind of traumatic or stressful life events like this happened to a relative or close friend?
- To ask respondents who responded "yes" to one of the above were asked the followup question:
  - "[Referring to list of 34 traumatic events] Which of these experiences would you single out as the MOST stressful and upsetting to you? Please just tell me the number to the left of the event on the card."
- The interviewers then proceeded to ask about PTSD symptoms for the most stressful event experienced.

List of Stressful Life Events

1) Injurious
   - Serious/life-threatening injury
   - Injured in a terrorist attack
   - Physically abused before age 18
   - Beaten up by spouse/romantic partner
   - Beaten up by someone else
   - Kidnapped/held hostage
2) Sexual
   - Sexually abused before age 18
   - Sexually assaulted as an adult

3) Psychological
   - Saw a dead body or body parts
   - Stalked
   - Mugged, held up, threatened with a weapon or assaulted in any other way
4) Combat
   - Active military combat
   - Peacekeeper/relief worker
   - Refugee
   - Prisoner of war
5) Witness
   - All traumatic experiences to others that you personally witnessed/learned about/were repeatedly exposed to (refer to Card 45B)
6) Terrorism/Natural Disaster
   - Natural disaster, like flood, fire, earthquake, hurricane
   - Civilian in war zone/place of terror
7) Other
   - Juvenile detention or jail
   - Any other traumatic or stressful event that happened to you
8) Illness
   - Serious or life-threatening illness

Appendix B

Table B1

Table B1
Sensitivity analysis examining association between trauma exposure, lifetime subthreshold and threshold PTSD with 'any' cancer.

	No Trauma	Trauma Exposed	Subthreshold PTSD	PTSD
OR (95% CI)	1.00	1.60 (1.33-1.93)***	1.81 (1.46-2.24)***	2.37 (1.89-2.98)***
AOR (95% CI)	1.00	1.42 (1.18-1.70)***	1.85 (1.49-2.31)***	3.29 (2.60-4.17)***
AOR1 (95% CI)	1.00	1.39 (1.16-1.67)**	1.79 (1.44-2.22)***	3.16 (2.42-4.13)***

Note: Statistical significance: $p < 0.01$**, $p < 0.001$***.
Abbreviations: OR = unadjusted odds ratio; AOR = model adjusted for age, sex, marital status, ethnicity, education, household income; AOR1 = model adjusted for sociodemographics, any substance use disorder (drug/alcohol/nicotine), mood disorder, and anxiety disorder.

References

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders: DSM-v* (5th ed.). Arlington, VA: American Psychiatric Association Publishing.

Armour, C., Műllerová, J., & Elhai, J. D. (2016). A systematic literature review of PTSD's latent structure in the diagnostic and statistical manual of mental disorders: DSM-IV to DSM-5. *Clinical Psychology Review, 44*, 60–74. https://doi.org/10.1016/j.cpr.2015.12.003.

Bender, R., & Lange, S. (2001). Adjusting for multiple testing–when and how? *Journal of Clinical Epidemiology, 54*(4), 343–349. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11297884.

Boscarino, J. A. (2004). Posttraumatic stress disorder and physical illness: Results from clinical and epidemiologic studies. *Annals of the New York Academy of Sciences, 1032*, 141–153. https://doi.org/10.1196/annals.1314.011.

Bosch, F. X., Ribes, J., Díaz, M., & Cléries, R. (2004). Primary liver cancer: Worldwide incidence and trends. *Gastroenterology, 127*(5 Suppl. 1), S5–S16. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15508102.

Brewin, C. R., Andrews, B., & Valentine, J. D. (2000). Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. *Journal of Consulting and Clinical Psychology, 68*(5), 748–766. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11068961.

Chida, Y., Hamer, M., Wardle, J., & Steptoe, A. (2008). Do stress-related psychosocial factors contribute to cancer incidence and survival? *Nature Clinical Practice Oncology, 5*(8), 466–475. https://doi.org/10.1038/ncponc1134.

Chuang, S.-C., Lee, Y.-C. A., Wu, G.-J., Straif, K., & Hashibe, M. (2015). Alcohol consumption and liver cancer risk: A meta-analysis. *Cancer Causes & Control, 26*(9), 1205–1231. https://doi.org/10.1007/s10552-015-0615-3.

Cordova, M. J., Riba, M. B., & Spiegel, D. (2017). Post-traumatic stress disorder and cancer. *The Lancet Psychiatry*. https://doi.org/10.1016/S2215-0366(17)30014-7.

Curado, M. P., & Hashibe, M. (2009). Recent changes in the epidemiology of head and neck cancer. *Current Opinion in Oncology, 21*(3), 194–200. https://doi.org/10.1097/CCO.0b013e32832a68ca.

El-Gabalawy, R., Blaney, C., Tsai, J., Sumner, J. A., & Pietrzak, R. H. (2018). Physical health conditions associated with full and subthreshold PTSD in U.S. Military veterans: Results from the national health and resilience in veterans study. *Journal of Affective Disorders, 227*, 849–853. https://doi.org/10.1016/J.JAD.2017.11.058.

El-Zayadi, A.-R. (2006). Heavy smoking and liver. *World Journal of Gastroenterology, 12*(38), 6098–6101. https://doi.org/10.3748/WJG.V12.I38.6098.

Grant, B., Amsbary, M., Chu, A., Sigman, R., Kali, J., Sugawana, Y., ... Chou, P. (2014). *Source and accuracy statement: National epidemiologic survey on alcohol and related conditions-III (NESARC-III)*. Rockville, MD.

Grant, B. F., Goldstein, R. B., Smith, S. M., Jung, J., Zhang, H., Chou, S. P., ... Hasin, D. S. (2015). The alcohol use disorder and associated disabilities interview schedule-5 (AUDADIS-5): reliability of substance use and psychiatric disorder modules in a general population sample. *Drug and Alcohol Dependence, 148*, 27–33. https://doi.org/10.1016/j.drugalcdep.2014.11.026.

Hasin, D. S., Greenstein, E., Aivadyan, C., Stohl, M., Aharonovich, E., Saha, T., ... Grant, B. F. (2015). The alcohol use disorder and associated disabilities interview schedule-5 (AUDADIS-5): Procedural validity of substance use disorders modules through clinical re-appraisal in a general population sample. *Drug and Alcohol Dependence, 148*, 40–46. https://doi.org/10.1016/j.drugalcdep.2014.12.011.

Hasin, D. S., Shmulewitz, D., Stohl, M., Greenstein, E., Aivadyan, C., Morita, K., ... Grant, B. F. (2015). Procedural validity of the AUDADIS-5 depression, anxiety and post-traumatic stress disorder modules: Substance abusers and others in the general population. *Drug and Alcohol Dependence, 152*, 246–256. https://doi.org/10.1016/j.drugalcdep.2015.03.027.

Holman, D. M., Ports, K. A., Buchanan, N. D., Hawkins, N. A., Merrick, M. T., Metzler, M., ... Trivers, K. F. (2016). The association between adverse childhood experiences and risk of cancer in adulthood: A systematic review of the literature. *Pediatrics, 138*(Supplement), S81–S91. https://doi.org/10.1542/peds.2015-4268L.

Kessler, R. C. (2002). The categorical versus dimensional assessment controversy in the sociology of mental illness. *Journal of Health and Social Behavior, 43*(2), 171–188. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12096698.

Kessler, R. C., Sonnega, A., Bromet, E., Hughes, M., & Nelson, C. B. (1995). Posttraumatic stress disorder in the National Comorbidity Survey. *Archives of General Psychiatry, 52*(12), 1048–1060. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7492257.

Levy, P., & Lemeshow, S. (2013). *Taylor series linearization method for variance estimationSampling of populations: Methods and applications* (4th ed.). New York: John

Wiley & Sons.
Linden, W., Vodermaier, A., MacKenzie, R., & Greig, D. (2012). Anxiety and depression after cancer diagnosis: Prevalence rates by cancer type, gender, and age. *Journal of Affective Disorders, 141*(2–3), 343–351. https://doi.org/10.1016/J.JAD.2012.03.025.
Maasland, D. H., van den Brandt, P. A., Kremer, B., Goldbohm, R. A., & Schouten, L. J. (2014). Alcohol consumption, cigarette smoking and the risk of subtypes of head-neck cancer: Results from the Netherlands Cohort Study. *BMC Cancer, 14*(1), 187. https://doi.org/10.1186/1471-2407-14-187.
McLaughlin, K. A., Koenen, K. C., Friedman, M. J., Ruscio, A. M., Karam, E. G., Shahly, V., ... Kessler, R. C. (2015). Subthreshold posttraumatic stress disorder in the world health organization world mental health surveys. *Biological Psychiatry, 77*(4), 375–384. https://doi.org/10.1016/j.biopsych.2014.03.028.
Michopoulos, V., Powers, A., Gillespie, C. F., Ressler, K. J., & Jovanovic, T. (2017). Inflammation in fear- and anxiety-based disorders: PTSD, GAD, and beyond. *Neuropsychopharmacology, 42*(1), 254–270. https://doi.org/10.1038/npp.2016.146.
Mills, K. L., Teesson, M., Ross, J., & Peters, L. (2006). Trauma, PTSD, and substance use disorders: Findings from the Australian national survey of mental health and Well-being. *American Journal of Psychiatry, 163*(4), 652–658. https://doi.org/10.1176/ajp.2006.163.4.652.
Nicholas, D. R. (2000). Men, masculinity, and cancer: Risk-factor behaviors, early detection, and psychosocial adaptation. *Journal of American College Health: J of ACH, 49*(1), 27–33. https://doi.org/10.1080/07448480009596279.
Norman, S. B., Means-Christensen, A. J., Craske, M. G., Sherbourne, C. D., Roy-Byrne, P. P., & Stein, M. B. (2006). Associations between psychological trauma and physical illness in primary care. *Journal of Traumatic Stress, 19*(4), 461–470. https://doi.org/10.1002/jts.20129.
Pietrzak, R. H., Goldstein, R. B., Southwick, S. M., & Grant, B. F. (2011). Prevalence and axis I comorbidity of full and partial posttraumatic stress disorder in the United States: Results from wave 2 of the national epidemiologic survey on alcohol and related conditions. *Journal of Anxiety Disorders, 25*(3), 456–465. https://doi.org/10.1016/j.janxdis.2010.11.010.
Sareen, J., Cox, B. J., Stein, M. B., Afifi, T. O., Fleet, C., & Asmundson, G. J. G. (2007). Physical and mental comorbidity, disability, and suicidal behavior associated with posttraumatic stress disorder in a large community sample. *Psychosomatic Medicine, 69*(3), 242–248.
Siegel, R. L., Miller, K. D., & Jemal, A. (2017). Cancer statistics, 2017. *CA: A Cancer Journal for Clinicians, 67*(1), 7–30. https://doi.org/10.3322/caac.21387.
Sumner, J. A., Kubzansky, L. D., Elkind, M. S. V., Roberts, A. L., Agnew-Blais, J., Chen, Q., ... Koenen, K. C. (2015). Trauma exposure and posttraumatic stress disorder symptoms predict onset of cardiovascular events in women. *Circulation, 132*(4), 251–259. https://doi.org/10.1161/CIRCULATIONAHA.114.014492.
Swartzman, S., Booth, J. N., Munro, A., & Sani, F. (2017). Posttraumatic stress disorder after cancer diagnosis in adults: A meta-analysis. *Depression and Anxiety, 34*(4), 327–339. https://doi.org/10.1002/da.22542.
Tedstone, J. E., & Tarrier, N. (2003). Posttraumatic stress disorder following medical illness and treatment. *Clinical Psychology Review, 23*(3), 409–448. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12729679.
von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., Vandenbroucke, J. P., ... STROBE Initiative (2007). The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *The Lancet, 370*(9596), 1453–1457. https://doi.org/10.1016/S0140-6736(07)61602-X.