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Pre-existing stress-related diagnoses and mortality: a Danish cancer cohort study

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Abstract

Background: We evaluated the association between pre-existing stress-related diagnoses and mortality in a Danish population-based cancer cohort.

Methods: We included Danish cancer patients diagnosed 1995–2011 who had a stress-related diagnosis prior to cancer diagnosis. Cancer patients without a prior stress-related diagnosis were matched 5:1 to the stress disorder cohort by cancer site, age group, calendar period, and sex. We computed 5-year cumulative incidence of cancer-specific and all-cause mortality by category of stress-related diagnosis. We computed hazard ratios (HR) and 95% confidence intervals (CI) associating stress-related diagnoses with mortality, by follow-up time, category of stress-related diagnosis, stage, comorbidity status, and cancer type.

Results: We identified 4,437 cancer patients with a pre-existing stress-related diagnosis and 22,060 matched cancer cohort members. The 5-year cumulative risk of cancer-specific mortality among those with a pre-existing stress-related diagnosis was 33% (95% CI: 32%, 35%) compared with 29% (95% CI: 28%, 29%) among those without a prior stress-related diagnosis. Cancer patients with a pre-existing stress-related diagnosis had 1.3-times the cancer-specific mortality rate compared with comparison cohort members (95% CI: 1.2, 1.5). This increase persisted across categories of stress-related diagnosis. The association varied by stage and cancer type, with more

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Author contributions: LJC, TPA, JLG, and HTS conceptualized the research question and developed the methodologic approach; HTS, JLG, and TPA facilitated the data acquisition; KV conducted the formal analyses; LJC, TPA, JLG, TLL, and HTS provided feedback on results and methodologic considerations; HTS and TLL provided supervision; LJC drafted the initial manuscript; all authors provided feedback and approved the final manuscript.

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pronounced associations among those diagnosed with late stage at diagnosis, and haematological malignancies.

Conclusions: We observed that cancer patients with pre-existing stress-related diagnoses had an increased rate of cancer-specific and all-cause mortality. Our results suggest that psychiatric comorbidities may be an important consideration for cancer prognosis, and cancer treatment informed by patient history may improve outcomes.

Precis:

Cancer patients with pre-existing stress-related diagnoses had an increased rate of cancer-specific and all-cause mortality. Our results suggest that psychiatric comorbidities may be an important consideration for cancer prognosis, and cancer treatment informed by patient history may improve outcomes.

Keywords

Stress-related disorders; trauma; neoplasms; prognosis; cancer survivorship

Introduction

Advancements in screening, diagnostic workup, and treatment of cancer have radically improved prognosis across most cancer types;[1] however, adverse outcomes among cancer survivors are an important public health problem. Many cancer patients present with comorbid conditions at diagnosis.[2] Comorbidities can inform clinical decisions of cancer therapies to improve health outcomes through coordinated care that accounts for patient history.[2] Psychiatric comorbidities may play a role in the progression of different cancer types by impacting prognosis through treatment compliance, or through direct influence on underlying biologic pathways.[3–5]

Stress-related diagnoses are psychiatric disorders characterized by severe emotional or behavioural symptoms in response to stressors or traumatic events.[6,7] The focus on stress-related diagnoses and their sequelae as major influences on the public's health has increased in recent years due to a growing recognition of the impact these events can have across all domains of health and functioning.[8,9] The link between psychological stress and cancer is not well understood. Although biologic plausibility highlights chronic stressors as a mechanism of increased inflammation and perturbations to the DNA,[4,10] our previous work examining the associations between posttraumatic stress disorder (PTSD), adjustment disorders and cancer incidence suggested a null association.[11,12] Similar results were reported in a study from the Nurses' Health Study.[13] However, a study from the Finnish Twin Cohort observed an increase in breast cancer risk among women who reported stressful life events.[14]

The risk of exacerbation of posttraumatic psychopathology following a new major stressor—such as a cancer diagnosis—among persons who have previously experienced posttraumatic psychopathology is high.[15] Retraumatization and increased mental health symptomatology may lead to hesitancy to engage in recommended care, adversely impacting cancer outcomes.

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The association between psychiatric symptomology in response to stress or stressors (as measured by stress-related diagnoses) and cancer prognosis remains largely unexplored.[16] A study in Sweden reported that women diagnosed with cervical cancer and who had an adjustment disorder diagnosis within one year of their cancer diagnosis had 1.3 times the cancer-specific mortality rate compared with women without an adjustment order diagnosis (hazard ratio [HR]=1.3, 95% confidence interval [CI] 1.1, 1.5).[17] However, no study has evaluated the association between pre-existing stress-related diagnoses and cancer outcomes in a nationwide cohort of cancer patients. In this study we evaluated the role of pre-existing stress-related diagnoses on cancer-specific and all-cause mortality in a Danish population-based cohort.

Materials and Methods

Source population and data collection

Study data were derived from Danish population-based registries. Denmark provides universal tax-funded health care with residency-based entitlement and availability of government-maintained nationwide registries, providing longitudinal sources of routinely collected administrative, health, and clinical quality data.[18] Each Danish citizen and legal resident is assigned a Civil Personal Registry (CPR) number, which allows for unambiguous linkage across registries.[19] We used the Danish Cancer Registry (DCR) to identify eligible cancer patients.[20] The DCR has recorded nearly all cancer diagnoses since 1943. This study builds on a previously funded parent study formed to examine multiple outcomes of stress-related diagnoses.[11,15] We included all invasive cancer diagnoses between 1 January 1995 and 31 December 2011 (n=950,013). Cancer patients were excluded if they had an invalid CPR number, cancer diagnosis occurred after death or emigration, or they immigrated to Denmark after cancer diagnosis. There were 530,301 patients diagnosed with cancer during the study period and therefore eligible to be included.

Stress-related diagnoses

The *International Classification of Diseases, Tenth Revision* (ICD-10) includes five diagnoses that could be given following a stressful or traumatic event,[6] which include: acute stress reaction (*i.e.,* a diagnosis given in the immediate aftermath of the event),[21] posttraumatic stress disorder (*i.e.,* a diagnosis given following a traumatic vent and a timed period of nonrecovery) (PTSD),[22] adjustment disorders (*i.e.,* a diagnosis given after a stressful event and a timed period of nonrecovery),[23] and other reactions to severe stress and reactions to severe stress, unspecified (*i.e.,* diagnoses given following the event without full diagnostic criteria for another stress-related diagnosis). Stress-related diagnoses were ascertained from the Danish Psychiatric Central Research Register (DPCRR) and the Danish National Patient Registry (DNPR) covering all Danish hospitals, and defined as having an incident ICD code relating to a stress-related diagnosis between 1 January 1995 through 31 December 2011 and before the cancer diagnosis.[24,25] We included inpatient and outpatient clinic diagnoses that corresponded to a primary or secondary stress-related diagnosis. A primary diagnosis refers to the condition which led to admission, whereas a secondary diagnosis is a condition that coexists at the time of admission. Stress-related diagnoses were identified for acute stress reaction, PTSD, adjustment disorders,

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other reaction to severe stress, and reaction to severe stress, unspecified (ICD-10 codes in Appendix 1). The DPCRR has collected inpatient data since 1969 and outpatient clinic data since 1995, recording treatment dates and up to 20 diagnoses for each registered treatment session. The DNPR has recorded diagnoses made during inpatient stays at non-psychiatric hospitals since 1977. Validation studies of the registry have shown high validity compared with computer-generated diagnoses or independent re-interview.[24,26,27] Previous validation of the stress-related diagnoses showed good validity for more mild and transient diagnoses, (such as acute stress reactions, other reactions to severe stress, and reactions to severe stress, unspecified), and high validity for more severe, stringently diagnosed or chronic disorders, such as PTSD and adjustment disorder.[27]

Matched Cancer Cohort

Cancer cohort members were stratified based on a stress-related diagnosis before cancer (n=4,437) and those without a stress-related diagnosis before cancer (n=525,864). We created matched comparison cohorts of cancer patients without a formal diagnosis of acute stress reaction, PTSD, adjustment disorder, other reaction to severe stress, or reaction to severe stress, unspecified prior to their cancer diagnosis. Members of the comparison cohort were individually matched to stress-related disorder cohort members by specific cancer site (Appendix 1), age group (≤15, 16–19, 20–29, 30–39, 40–49, 50–59, 60–69, and ≥70 years), calendar period (1995–1999, 2000–2004, 2005–2009, 2010–2011), and sex, at a ratio of 5 to 1. Sampling was performed using an internal SAS macro, which used simple random sampling to select with replacement from the comparison population. We constructed cohorts with consideration of any stress-related diagnosis, and by categories of stress-related diagnoses—acute stress reaction, PTSD, adjustment disorder, other reaction to severe stress, and reaction to severe stress, unspecified.

Mortality

The outcomes of interest included cancer-specific mortality and all-cause mortality, identified from the Danish Cause of Death Registry.[28] Cancer-specific mortality was based on the underlying cause of death, in accordance with World Health Organization reporting guidelines.[28]

Covariates

From the DCR, we collected information surrounding the cancer diagnosis, including age at diagnosis, sex, cancer site and type of cancer (*i.e.*, hematologic malignancies, hormone-related cancers, immune-related cancers, smoking and alcohol-related cancers, and other cancer types) [Appendix 1], and stage (localized, regional, or distant). Psychiatric comorbidities were obtained from the DPCRR and the DNPR, which included depression, alcohol abuse, substance abuse, and schizophrenia diagnosed before cancer diagnosis. Information on somatic comorbidities at cancer diagnosis were ascertained from the DNRP (Appendix 1). We report information on individual comorbidities and summarized the comorbidities for each subject by calculating a Charlson Comorbidity Index (CCI) score (CCI=0 vs CCI=1+).[29]

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Statistical Analysis

We present the frequency and proportion of patient demographics, matching factors, history of depression, history of substance abuse, CCI, and the distribution of the categories of stress-related or trauma diagnoses in the total study population and separately among cancer patients with a history of stress-related diagnoses and among the comparison cohort. We also present the distribution of specific comorbidities and site of cancer diagnosis in eTables 1 and 2.

Cohort members were followed from their date of cancer diagnosis until the first of emigration, death, or 31 December 2018. We calculated the 5-year cumulative incidence for cancer-specific mortality, treating other mortality events as a competing risk, and all-cause mortality by category of stress-related diagnosis. For both mortality 5-year cumulative incidence measures, we computed risk differences comparing those with and without stress-related diagnoses with corresponding 95% CI.

We fit Cox proportional hazards regression models to compute the HRs and 95% CIs associating stress-related diagnoses with cancer-specific and all-cause mortality, both in the full cohort and by category of stress-related diagnosis. We verified the proportional hazards assumption by examining the ln-ln survival curves for each exposure and covariates. No gross violations were identified. We present unadjusted HRs, which control for matching factors only, and multivariable-adjusted HRs that additionally control for stage, depression, substance abuse, and CCI. [11,15,17] The covariates included in the multivariable adjusted models were chosen based on literature review and subject matter knowledge. Separate analyses were carried out for exposure categories by follow-up time to explore the potential acute and long-term impact of stress-related diagnoses on mortality (within 1 year after cancer diagnosis, >1 to 24 years after cancer diagnosis, and anytime in the 24 years after cancer diagnosis). To evaluate if the associations between prior stress-related diagnoses and cancer mortality were modified by stage, CCI score, or cancer type, we computed strata-specific HRs and 95% CIs for the associations between stress-related diagnoses and mortality within strata of cancer stage, CCI score, and cancer type. The most commonly diagnosed cancers include breast, prostate, lung and colorectal cancers. Therefore, we additionally computed the 5-year cumulative incidence and HRs of cancer-specific and all-cause mortality separately for each of these four cancer types (eTable 3 and 4). All analyses were carried out in SAS v9.4 (Carey, NC).

Results

Cohort Description

The study cohort included 26,497 cancer patients, of whom the majority were over 50 years of age (76%) and female (66%) [Table 1]. Among those with a stress-related diagnosis before cancer, 7.3% were diagnosed with an acute stress reaction, 5.9% were diagnosed with PTSD, 67% were diagnosed with adjustment disorder, 2.2% were diagnosed with other reaction to severe stress, and 18% were diagnosed with reaction to severe stress, unspecified. The median time between any stress diagnosis and cancer diagnosis was 5.0

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years (interquartile range 2.2–8.9). Additionally, among those with a prior stress diagnosis, 1,610 (36%) had a subsequent stress or trauma diagnosis.

The cohort included 5.5% of patients diagnosed with haematological cancers, 22% hormone-related cancers, 31% immune-related cancers, 30% smoking and alcohol-related cancers, and 11% of other cancer sites. Cancer patients with a pre-existing stress-related diagnosis were more likely to have a history of depression (22% vs 1.3%), a history of alcohol abuse (14% vs 1.0%), and have one or more somatic comorbidities (42% vs 25%) than patients in the comparison cohort. A cancer-specific death and all-cause mortality event were also more common among cancer patients with a previous stress-related diagnosis compared with patients without a previous stress-related diagnosis (38% vs. 35% and 54% vs. 46%, respectively).

Previous stress-related diagnoses and mortality

Table 2 presents the five-year cumulative incidence of cancer-specific and all-cause mortality among exposed and comparison cohort members, as well as the five-year cumulative incidence differences associating pre-existing stress-related diagnoses with cancer-specific and all-cause mortality. Among cancer patients with any previous stress-related diagnosis, the 5-year cumulative incidence for cancer-specific mortality was 33% (95% CI: 32%, 35%) compared with 29% (95% CI: 28%, 29%) among those without a prior stress-related diagnosis. We observed an excess cancer-specific mortality risk of 4.6% (95% CI: 3.1%, 6.2%) among those with a stress-related diagnosis compared with those without. The 5-year cumulative incidence of all-cause mortality was 41% (95% CI: 39%, 42%) among cancer patients with any previous stress-related diagnosis, and 33% (95% CI: 32%, 34%) among those without a prior stress-related diagnosis. The excess all-cause mortality risk was 7.8% (95% CI: 6.2%, 9.4%) among those with a prior stress-related diagnosis compared with those without a prior stress-related diagnosis. Across categories of stress-related diagnoses, the excess five-year mortality risks were similar among cancer patients with a diagnosis of adjustment disorder, other reaction to severe stress, and reaction to severe stress unspecified; however, they were near null for cancer patients diagnosed with acute stress-related reaction or PTSD before their cancer diagnosis.

Table 3 presents the HRs associating previous stress-related diagnoses with cancer-specific mortality by follow-up time. Among cancer patients with a previous stress-related diagnosis, we observed 1.3-times the estimated cancer-specific mortality rate compared with those without a prior stress-related diagnosis (95% CI: 1.2, 1.5). The associations for cancer-specific mortality persisted across category of stress-related diagnosis. Estimated cancer-specific HRs ranged from 1.2 to 1.5. HRs ranged 0.9 to 1.6 excluding deaths that occurred within the first year after diagnosis and 1.1 to 1.7 for deaths within the first year following a cancer diagnosis. The associations between stress-related diagnoses and all-cause mortality were generally more pronounced than the cancer-specific associations.

Previous stress-related diagnoses and mortality by stage, CCI, and cancer type

In Table 4 we present the associations between any prior stress-related diagnosis and cancer-specific and all-cause mortality by cancer stage, CCI, and cancer type. Among those with

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localized cancer stage at diagnosis, the association between any stress-related diagnosis prior to cancer diagnosis with cancer-specific mortality was near null (HR=1.1, 95% CI: 0.9, 1.3). Among those with regional or distant stage at diagnosis, we observed 1.2 and 1.5-times the estimated cancer-specific mortality rate associating a prior stress-related diagnosis with cancer-specific mortality (95% CI: 1.0, 1.4 and 1.3, 1.8, respectively). Among those without existing comorbidities, we observed 1.3-times the estimated rate for cancer-specific mortality (95% CI: 1.2, 1.5). Among those with existing comorbidities, the estimate was similar (HR=1.2, 95% CI 1.0, 1.5). The association between stress-related diagnoses and cancer-specific mortality was most pronounced among those with a haematological cancer diagnosis (HR=1.9, 95% CI: 1.1, 3.4), and near-null among those with a hormone-related cancer diagnosis (HR=1.0, 95% CI: 0.9, 1.3). Associations for immune-related, smoking and alcohol-related, and other sites ranged 1.2–1.4. Associations with all-cause mortality stratified by stage, CCI, and cancer type were similar, although more pronounced.

Discussion

In this study we observed that cancer patients with pre-existing stress-related diagnoses had increased cancer-specific and all-cause mortality rates compared with cancer patients without pre-existing stress-related diagnoses. This increase in the estimated mortality rate persisted across nearly all categories of stress-related diagnoses and follow-up time, but were least pronounced among patients with a pre-existing diagnosis of acute stress reaction or PTSD. The association varied by stage and cancer type, with more pronounced associations among those diagnosed with regional or distant stage at diagnosis, and haematological malignancies.

To date, few studies that have examined the role of psychiatric diseases on cancer outcomes have primarily focused on anxiety and depression in relation to cancer mortality.[3,30] Although these psychiatric disorders are commonly comorbid with stress-related disorders, their manifestation is distinct.[31] Stress-related diagnoses involve a reaction to a stressful or traumatic event. The experience of a traumatic event, such as sexual assault, can contribute to reluctance to engage in primary care or cancer screening, which involve physical interactions that may feel threatening to a person who has experienced an existing traumatic event.[32,33] Furthermore, persons who have been previously diagnosed with a stress-related disorder are at an increased risk of retraumatization.[15] The experience of a new cancer diagnosis is a stressful life event that could lead to an exacerbation in posttraumatic psychopathology. This exacerbation may lead to hesitancy to engage in recommended cancer care and poor adherence to guideline treatment and follow-up care, which can adversely impact cancer outcomes. Previous studies have shown that stress-related diagnoses are associated with an increased risk of mortality in the general population, but in this study we relate these experiences to cancer-specific and all-cause mortality among those subsequently diagnosed with cancer.[15,34,35]

The majority of cancer patients with a previous stress-related diagnosis were diagnosed with adjustment disorder (67%). We have previously noted that adjustment disorder is the most common diagnosis following a stressful life event, likely because it is used as an overarching diagnosis for vague symptomatology, or for those who experience mild to moderate

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symptomatology.[36] Still, our results were comparable across stress-related diagnoses with stringent diagnostic criteria (*e.g.*, PTSD) and stress-related diagnoses that are meant to be catch-all diagnoses for persons who experience some posttraumatic symptomatology, but do not meet diagnostic criteria for the stringently defined disorders (*e.g.*, reaction to severe stress or adjustment disorder). This is consistent with other research that has shown that subsyndromal stress-related psychopathology can have a substantial impact on health and mortality.[15,37,38] However, in this sample we did not have information on the level of psychiatric severity for persons receiving adjustment disorder diagnosis, which may be important in future studies. These findings indicate that clinicians treating patients with cancer should be aware that subthreshold levels of psychopathology may be associated with an increased risk of mortality. Additional research to investigate the role of stress-related psychopathology on adherence to guideline treatment, treatment-related complications, and cancer recurrence could provide insight into interventions and clinical care that could improve outcomes for these patients.

Lu et al. evaluated the role of stressful life events, diagnosis of stress reaction, or adjustment disorder on cancer-specific mortality among women diagnosed with cervical cancer in a Swedish population-based cohort study.[17] The authors considered stress-related diagnoses that were recorded within one year of the patient's cancer diagnosis as they were interested in severe psychologic distress experienced in relation to the diagnosis and treatment of cervical cancer, which is in contrast to the current study.[17] They reported that patients exposed to psychologic distress had an increased risk of cancer-specific mortality (HR=1.3, 95%CI 1.1, 1.5) compared with those without a diagnosis related to psychologic distress.[17] Our results were similar, although the average time between a stress-related or trauma diagnosis and cancer diagnosis was 5 years and we did not examine to role of stress-related diagnoses that occurred following the cancer diagnosis.

This study has limitations. We used mortality as the primary endpoints, but cancer recurrence may provide additional insight into the pathogenesis of the co-occurring disease burden. Moreover, pre-existing trauma or stress-related diagnoses likely impact patient's engagement in care, such as adherence and appropriate follow-up. Pre-existing stress-related diagnoses are also associated with health behaviours, which may adversely impact cancer outcomes.[39] We were unable to examine these potential mechanisms in the current study. There may be misclassification of the stress-related diagnoses. Previous validation efforts have shown that classification of stress-related diagnoses is highly specific;[27] however, the comparison cohort may not have been free of stress-related disorders at diagnosis, as many stress-related diagnoses are likely subsyndromal (*i.e.,* persons with some symptoms of post trauma psychopathology, but fail to meet diagnostic criteria for the actual disorder). This expected nondifferential misclassification of the exposure would likely bias our results toward the null. Inclusion of medication use may provide additional insight into the classification of reaction to severe stress-related diagnoses in the reference cohorts, but we were unable to incorporate medication use in the current study. There is a potential for residual confounding by comorbidities, substance use, and unmeasured confounding by smoking, which may explain the observed results. However, we attempted to limit this potential bias by matching the reference cohort to the exposed cohort based on specific cancer type. Additionally, we did not explore stress-related diagnoses that occurred after

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cancer diagnosis. These may be important mediating effects for cancer outcomes, but their role in disease progression is largely unexplored. Finally, Denmark provides universal tax-supported health care, which guards against barriers in access to care that may be observed in other population-based studies, such as the US. This would likely contribute to more accurate classification of diagnoses following a stressful or traumatic event and receipt of appropriate treatments, but may lead to difficulty in the generalizability of these results. Replication of the study results in a US-based sample would enhance our findings.

In summary, we observed that cancer patients with pre-existing stress-related diagnoses had an increased rate of both cancer-specific and all-cause mortality, which persisted across categories of stress-related diagnoses. Our results suggest that psychiatric comorbidities may be an important consideration for cancer prognosis, and an approach to cancer treatment that incorporates patient history with coordinated care may improve patient outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424. [PubMed: 30207593]
2. Sarfati D, Koczwara B, Jackson C. The impact of comorbidity on cancer and its treatment. CA Cancer J Clin. 2016;66(4):337–50. [PubMed: 26891458]
3. Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. Lancet Oncol. 2011 Feb 1;12(2):160–74. [PubMed: 21251875]
4. Yang EV, Glaser R. Stress-induced immunomodulation: Implications for tumorigenesis. Brain Behav Immun. 2003 Feb;17 Suppl 1:S37–40. [PubMed: 12615184]
5. McDonough EM, Boyd JH, Varvares MA, Maves MD. Relationship between psychological status and compliance in a sample of patients treated for cancer of the head and neck. Head Neck. 1996;18(3):269–76. [PubMed: 8860769]
6. Janca A, Ustün TB, Early TS, Sartorius N. The ICD-10 symptom checklist: a companion to the ICD-10 classification of mental and behavioural disorders. Soc Psychiatry Psychiatr Epidemiol. 1993 Oct;28(5):239–42. [PubMed: 8284737]
7. Casey P, Bailey S. Adjustment disorders: the state of the art. World Psychiatry Off J World Psychiatr Assoc WPA. 2011 Feb;10(1):11–8.
8. Gradus JL. Prevalence and prognosis of stress disorders: a review of the epidemiologic literature. Clin Epidemiol. 2017 May 3;9:251–60. [PubMed: 28496365]
9. Krause N, Shaw BA, Cairney J. A Descriptive Epidemiology of Lifetime Trauma and the Physical Health Status of Older Adults. Psychol Aging. 2004;19(4):637–48. [PubMed: 15584789]
10. Wessa M, Rohleder N, Kirschbaum C, Flor H. Altered cortisol awakening response in posttraumatic stress disorder. Psychoneuroendocrinology. 2006 Feb 1;31(2):209–15. [PubMed: 16154709]

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11. Ahern TP, Veres K, Jiang T, Farkas DK, Lash TL, Sørensen HT, et al. Adjustment disorder and type-specific cancer incidence: a Danish cohort study. Acta Oncol. 2018 Oct 3;57(10):1367–72. [PubMed: 29688114]
12. Gradus JL, Farkas DK, Svensson E, Ehrenstein V, Lash TL, Milstein A, et al. Posttraumatic stress disorder and cancer risk: a nationwide cohort study. Eur J Epidemiol. 2015 Jul 1;30(7):563–8. [PubMed: 25957083]
13. Schernhammer ES, Hankinson SE, Rosner B, Kroenke CH, Willett WC, Colditz GA, et al. Job Stress and Breast Cancer Risk: The Nurses' Health Study. Am J Epidemiol. 2004 Dec 1;160(11):1079–86. [PubMed: 15561987]
14. Lillberg K, Verkasalo PK, Kaprio J, Teppo L, Helenius H, Koskenvuo M. Stressful Life Events and Risk of Breast Cancer in 10,808 Women: A Cohort Study. Am J Epidemiol. 2003 Mar 1;157(5):415–23. [PubMed: 12615606]
15. Gradus JL, Antonsen S, Svensson E, Lash TL, Resick PA, Hansen JG. Trauma, Comorbidity, and Mortality Following Diagnoses of Severe Stress and Adjustment Disorders: A Nationwide Cohort Study. Am J Epidemiol. 2015 Sep 1;182(5):451–8. [PubMed: 26243737]
16. Batty GD, Russ TC, Stamatakis E, Kivimäki M. Psychological distress in relation to site specific cancer mortality: pooling of unpublished data from 16 prospective cohort studies. BMJ [Internet]. 2017 Jan 25 [cited 2020 Aug 19];356. Available from: http://www.bmj.com/content/356/bmj.j108
17. Lu D, Andrae B, Valdimarsdóttir U, Sundström K, Fall K, Sparén P, et al. Psychologic Distress Is Associated with Cancer-Specific Mortality among Patients with Cervical Cancer. Cancer Res. 2019 Aug 1;79(15):3965–72. [PubMed: 31253667]
18. Schmidt M, Schmidt SAJ, Adelborg K, Sundbøll J, Laugesen K, Ehrenstein V, et al. The Danish health care system and epidemiological research: from health care contacts to database records. Clin Epidemiol. 2019;11:563–91. [PubMed: 31372058]
19. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014 Aug;29(8):541–9. [PubMed: 24965263]
20. Gjerstorff ML. The Danish Cancer Registry. Scand J Public Health. 2011 Jul 1;39(7_suppl):42–5. [PubMed: 21775350]
21. Shalev AY. Acute stress reactions in adults. Biol Psychiatry. 2002 Apr 1;51(7):532–43. [PubMed: 11950455]
22. Kessler RC. Posttraumatic stress disorder: The burden to the individual and to society. J Clin Psychiatry. 2000;61(Suppl 5):4–14.
23. Carta MG, Balestrieri M, Murru A, Hardoy MC. Adjustment Disorder: epidemiology, diagnosis and treatment. Clin Pract Epidemiol Ment Health. 2009 Jun 26;5(1):15. [PubMed: 19558652]
24. Munk-Jørgensen P, Mortensen P. The Danish Psychiatric Central Register. Dan Med Bull. 1997 Feb 1;44(1):82–4. [PubMed: 9062767]
25. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015 Nov 17;7:449–90. [PubMed: 26604824]
26. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. Scand J Public Health. 2011 Jul 1;39(7_suppl):54–7. [PubMed: 21775352]
27. Svensson E, Lash TL, Resick PA, Hansen JG, Gradus JL. Validity of reaction to severe stress and adjustment disorder diagnoses in the Danish Psychiatric Central Research Registry. Clin Epidemiol. 2015 Mar 27;7:235–42. [PubMed: 25870515]
28. Helweg-Larsen K The Danish Register of Causes of Death. Scand J Public Health. 2011 Jul;39(7 Suppl):26–9.
29. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83. [PubMed: 3558716]
30. Wang Y-H, Li J-Q, Shi J-F, Que J-Y, Liu J-J, Lappin JM, et al. Depression and anxiety in relation to cancer incidence and mortality: a systematic review and meta-analysis of cohort studies. Mol Psychiatry. 2020 Jul;25(7):1487–99. [PubMed: 31745237]
31. Brady KT, Killeen TK, Brewerton T, Lucerini S. Comorbidity of psychiatric disorders and posttraumatic stress disorder. J Clin Psychiatry. 2000;61(Suppl7):22–32.

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32. Farley M, Golding JM, Minkoff JR. Is a history of trauma associated with a reduced likelihood of cervical cancer screening? J Fam Pract. 2002 Oct;51(10):827–31. [PubMed: 12401150]

33. Farley M, Minkoff JR, Barkan H. Breast Cancer Screening and Trauma History. Women Health. 2001 Oct 23;34(2):15–27. [PubMed: 11785855]

34. Boscarino JA, Figley CR. The Impact of Repression, Hostility, and Post-Traumatic Stress Disorder on All-Cause Mortality. J Nerv Ment Dis. 2009 Jun;197(6):461–6. [PubMed: 19525749]

35. Boscarino JA. Posttraumatic Stress Disorder and Mortality Among U.S. Army Veterans 30 Years After Military Service. Ann Epidemiol. 2006 Apr 1;16(4):248–56. [PubMed: 16099672]

36. Gradus JL, Bozi I, Antonsen S, Svensson E, Lash TL, Resick PA, et al. Severe Stress and Adjustment Disorder Diagnoses in the Population of Denmark. J Trauma Stress. 2014 Jun;27(3):370–4. [PubMed: 24948539]

37. El-Gabalawy R, Blaney C, Tsai J, Sumner JA, Pietrzak RH. Physical health conditions associated with full and subthreshold PTSD in U.S. military veterans: Results from the National Health and Resilience in Veterans Study. J Affect Disord. 2018 Feb 1;227:849–53. [PubMed: 29689700]

38. Fink DS, Gradus JL, Keyes KM, Calabrese JR, Liberzon I, Tamburrino MB, et al. Subthreshold PTSD and PTSD in a prospective-longitudinal cohort of military personnel: Potential targets for preventive interventions. Depress Anxiety. 2018;35(11):1048–55. [PubMed: 30099820]

39. Zen AL, Zhao S, Whooley MA, Cohen BE. Post-Traumatic Stress Disorder is Associated With Poor Health Behaviors: Findings From the Heart and Soul Study. Health Psychol. 2012 Mar;31(2):194–201. [PubMed: 22023435]

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Table 1:

Characteristics of cancer cohort members with a stress-related or trauma diagnosis before cancer diagnosis (n=4,437) and matched comparison cohort members (n=22,060), Denmark 1995–2011.

Characteristic	Total N (%)	Stress-related N (%)	Comparison N (%)
Total	26497 (100)	4437 (100)	22060 (100)
Stress or Trauma diagnosis			
Acute stress reaction		325 (7.3)	
PTSD		262 (5.9)	
Adjustment disorder		2965 (67)	
Other reaction to severe stress		97 (2.2)	
Reaction to severe stress, unspecified		788 (18)	
Age groups, years			
0 – 15 years	74 (0.3)	13 (0.3)	61 (0.3)
16 – 19 years	58 (0.2)	12 (0.3)	46 (0.2)
20 – 29 years	610 (2.3)	106 (2.4)	504 (2.3)
30 – 39 years	1563 (5.9)	265 (6.0)	1298 (5.9)
40 – 49 years	4293 (16)	720 (16)	3573 (16)
50 – 59 years	7563 (29)	1261 (28)	6302 (29)
60 – 69 years	6775 (26)	1131 (25)	5644 (26)
70+ years	5561 (21)	929 (21)	4632 (21)
Gender			
Female	17441 (66)	2921 (66)	14520 (66)
Male	9056 (34)	1516 (34)	7540 (34)
History of Depression			
Yes	1271 (4.8)	976 (22)	295 (1.3)
No	25226 (95)	3461 (78)	21765 (99)
History of Schizophrenia			
Yes	166 (0.6)	88 (2.0)	78 (0.3)
No	26331 (99)	4349 (98)	21982 (100)
History of Substance Abuse			
Yes	117 (0.5)	86 (1.9)	31 (0.2)
No	26380 (96)	4351 (98)	22029 (100)
History of Alcohol Abuse			
Yes	822 (3.1)	600 (14)	222 (1.0)
No	25675 (97)	3837 (86)	21838 (99)
Charlson comorbidity index			
Medium or high (CCI = 1+)	7456 (28)	1862 (42)	5594 (25)
Low (CCI = 0)	19041 (72)	2575 (58)	16466 (75)
Calendar period at cancer			
1995 – 1999	1780 (6.7)	299 (6.7)	1481 (6.7)
2000 – 2004	5551 (21)	931 (21)	4620 (21)

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Characteristic	Total N (%)	Stress-related N (%)	Comparison N (%)
2005 – 2009	12057 (46)	2017 (45)	10040 (45)
2010 – 2011	7109 (27)	1190 (27)	5919 (27)
Type of cancer			
Haematological	1467 (5.5)	246 (5.5)	1221 (5.5)
Hormone related	5935 (22)	988 (22)	4947 (22)
Immune related	8084 (31)	1349 (30)	6735 (31)
Smoking and Alcohol related	8014 (30)	1343 (30)	6671 (30)
Other Sites	2997 (11)	511 (12)	2486 (11)
Stage			
Localized	14233 (54)	2321 (52)	11912 (54)
Regional spread	4797 (18)	777 (18)	4020 (18)
Distant Metastases	3765 (14)	685 (15)	3080 (14)
Missing/unknown	3702 (14)	654 (15)	3048 (14)
Cancer-specific mortality			
Yes	9404 (35)	1670 (38)	7734 (35)
No	17093 (65)	2767 (62)	14326 (65)
All-cause mortality			
Yes	12667 (48)	2415 (54)	10252 (46)
No	13830 (52)	2022 (46)	11808 (54)

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Table 2:

Five-year cumulative incidence for cancer-specific and all-cause mortality by stress-related diagnoses and matched comparison cohort members in Denmark, 1995–2011.

	Cancer-Specific Mortality[a]			All-Cause Mortality[a]		
Category of Stress-related Diagnosis	**Cumulative Incidence Exposed (95% CI)**	**Cumulative Incidence Comparison (95% CI)**	**Cumulative Incidence Difference (95% CI)**	**Cumulative Incidence Exposed (95% CI)**	**Cumulative Incidence Comparison (95% CI)**	**Cumulative Incidence Difference (95% CI)**
Any	33 (32, 35)	28 (28, 29)	4.6 (3.1, 6.2)	41 (39, 42)	33 (32, 34)	7.8 (6.2, 9.4)
Acute stress reaction	28 (23, 33)	27 (25, 29)	0.5 (−5.1, 6.0)	36 (31, 41)	33 (31, 35)	2.8 (−2.9, 8.5)
PTSD	26 (21, 32)	24 (22, 26)	2.4 (−3.6, 8.3)	31 (25, 37)	28 (26, 31)	2.7 (−3.5, 8.8)
Adjustment Disorder	34 (33, 36)	29 (29, 30)	4.9 (3.0, 6.8)	42 (40, 44)	34 (33, 35)	8.1 (6.2, 10)
Other reaction to severe stress	32 (23, 41)	24 (20, 28)	7.8 (−2.5, 18)	37 (28, 47)	27 (23, 31)	10 (−0.1, 21)
Reaction to severe stress	34 (30, 37)	28 (27, 29)	5.6 (1.9, 9.3)	43 (40, 46)	33 (31, 34)	10 (6.5, 14)

[a]Adjusted for matching factors by design: type of cancer, age group, calendar period, and sex

Abbreviations: PTSD: posttraumatic stress disorder; CI= confidence interval

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Table 3:

Hazard ratios (HR) and 95% confidence intervals (CI) associating stress-related diagnoses with cancer-specific and all-cause mortality, Denmark 1995–2011.

		Cancer-Specific Mortality		All-Cause Mortality	
Category of Stress-related Diagnosis	**Years since cancer diagnosis**	**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**	**Unadjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**
Any	≤1	1.9 (1.7–2.0)	1.6 (1.4–1.8)	1.9 (1.8–2.1)	1.6 (1.5–1.8)
	>1 – 24	1.2 (1.1–1.3)	1.1 (1.0–1.3)	1.4 (1.3–1.5)	1.2 (1.1–1.3)
	≤24	1.5 (1.4–1.6)	1.3 (1.2–1.5)	1.6 (1.6–1.7)	1.4 (1.3–1.5)
Acute stress reaction	≤1	1.5 (1.1–2.1)	1.7 (1.1–2.6)	1.6 (1.2–2.1)	1.7 (1.1–2.6)
	>1 – 24	1.0 (0.7–1.5)	0.9 (0.6–1.3)	1.2 (1.0–1.6)	1.0 (0.8–1.4)
	≤24	1.2 (1.0–1.5)	1.2 (0.9–1.6)	1.4 (1.1–1.6)	1.2 (1.0–1.6)
PTSD	≤1	1.7 (1.2–2.4)	1.4 (0.9–2.3)	1.7 (1.2–2.4)	1.4 (0.9–2.3)
	>1 – 24	1.2 (0.8–1.7)	1.2 (0.7–1.9)	1.2 (0.9–1.6)	1.1 (0.7–1.6)
	≤24	1.4 (1.1–1.8)	1.3 (1.0–1.9)	1.6 (1.6–1.7)	1.2 (0.9–1.7)
Adjustment disorder	≤1	1.9 (1.8–2.1)	1.6 (1.4–1.9)	2.0 (1.8–2.2)	1.6 (1.4–1.9)
	>1 – 24	1.2 (1.1–1.3)	1.0 (0.9–1.2)	1.4 (1.3–1.6)	1.2 (1.1–1.3)
	≤24	1.5 (1.4–1.6)	1.3 (1.1–1.4)	1.6 (1.6–1.7)	1.4 (1.2–1.5)
Other reaction to severe	≤1	1.1 (0.6–2.1)	1.2 (0.5–3.0)	1.0 (0.6–1.9)	1.2 (0.5–2.9)
	>1 – 24	1.5 (0.9–2.6)	1.6 (0.8–3.2)	1.7 (1.0–2.6)	1.5 (0.8–2.6)
	≤24	1.3 (0.9–2.0)	1.3 (0.8–2.2)	1.4 (1.0–1.9)	1.3 (0.8–2.0)
Reaction to severe stress	≤1	2.0 (1.6–2.4)	1.5 (1.1–2.0)	2.1 (1.8–2.6)	1.7 (1.3–2.2)
	>1 – 24	1.4 (1.2–1.7)	1.4 (1.1–1.8)	1.7 (1.4–1.9)	1.5 (1.2–1.8)
	≤24	1.7 (1.5–1.9)	1.5 (1.2–1.8)	1.9 (1.6–2.1)	1.6 (1.3–1.8)

[a] Adjusted for matching factors by design: type of cancer, age group, calendar period, and sex

[b] Adjusted for matching factors, depression, substance abuse, stage, and Charlson comorbidity index

Abbreviations: PTSD=posttraumatic stress disorder; HR= hazard ratio; CI= confidence interval

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Table 4:

Associations between stress-related and trauma diagnoses and cancer-specific and all-cause mortality by stage and comorbidity index, Denmark 1995–2011.

	Cancer-Specific Mortality		All-Cause Mortality	
	Unadjusted HR (95% CI)[a]	Adjusted HR (95% CI)[b]	Unadjusted HR (95% CI)[a]	Adjusted HR (95% CI)[b]
Stage				
Localized	1.2 (1.1–1.4)	1.1 (0.9–1.3)	1.6 (1.5–1.8)	1.3 (1.1–1.4)
Regional	1.4 (1.2–1.6)	1.2 (1.0–1.4)	1.5 (1.3–1.8)	1.2 (1.0–1.5)
Distant	1.7 (1.5–2.0)	1.5 (1.3–1.8)	1.7 (1.5–1.9)	1.5 (1.3–1.8)
Charlson Comorbidity Index				
Low (CCI=0)	1.4 (1.3–1.6)	1.3 (1.2–1.5)	1.5 (1.4–1.7)	1.4 (1.2–1.5)
High (CCI=1+)	1.6 (1.4–1.8)	1.2 (1.0–1.5)	1.6 (1.5–1.8)	1.3 (1.1–1.5)
Cancer Type				
Haematological Cancers	1.9 (1.5–2.4)	1.9 (1.1–3.4)	2.0 (1.6–2.5)	2.0 (1.2–3.3)
Hormone-related Cancers	1.2 (1.0–1.4)	1.0 (0.9–1.3)	1.5 (1.3–1.7)	1.2 (1.0–1.4)
Immune-related Cancers	1.3 (1.0–1.5)	1.2 (0.9–1.5)	1.6 (1.4–1.8)	1.4 (1.2–1.7)
Smoking and Alcohol-related Cancers	1.7 (1.5–1.8)	1.4 (1.3–1.6)	1.7 (1.6–1.8)	1.4 (1.3–1.6)
Other sites	1.4 (1.2–1.6)	1.3 (1.0–1.6)	1.6 (1.4–1.8)	1.4 (1.1–1.8)

[a] Adjusted for matching factors by design: type of cancer, age group, calendar period, and sex

[b] Adjusted for matching factors, depression, substance abuse, and Charlson comorbidity index or stage

Abbreviations: CCI=Charlson comorbidity index; HR= hazard ratio; CI= confidence interval

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