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SEVERE PSYCHOLOGICAL STRESS ASSOCIATED WITH A CANCER DIAGNOSIS

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Severe psychological stress associated with a cancer diagnosis
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To my beloved family

ABSTRACT

Receiving a cancer diagnosis leads to severe psychological distress. Previous studies have shown increased risk for various health consequences following a cancer diagnosis, including mental disorders, life-threatening cardiovascular events, and suicide. However, whether the severe stress response after a cancer diagnosis impacts cancer progression and healthcare use pattern for cancer patients is not clear yet. Furthermore, whether potential interventions, including beta-blocking agent treatment and shortened waiting-time during cancer diagnostic workup, could reduce such stress response and its related adverse health outcomes needs to be investigated.

In study I, to investigate whether stress-related mental disorders, as indicators of a severe stress response to cancer diagnosis, were associated with an increased mortality among cancer patients, we performed a prospective cohort study including 244,261 adult cancer patients diagnosed during 2004-2009 in Sweden. Stress-related mental disorders diagnosed after cancer diagnosis were used as the primary exposure, and cancer-specific mortality was used as the main outcome of interest. In this study, an increased cancer-specific mortality was found in relation to stress-related mental disorders, especially the first-onset mental disorders.

In study II, we assessed the impact of stress-related mental disorders on rate of hospital admissions after cancer diagnosis, by a prospective cohort study including 218,508 adult cancer patients diagnosed between 2004 and 2009 in Sweden. Stress-related mental disorders diagnosed from 90 days before to 90 days after cancer diagnosis were associated with an increased risk of any hospital admissions as well as hospital admissions for external injuries, infections, and cardiovascular diseases from 90 days after cancer diagnosis onward.

In study III, we explored the role of beta-blocking agent treatment on the risk of severe cardiovascular events after cancer diagnosis, in a cohort study of all adult cancer patients diagnosed during 2006-2013 in Sweden. Beta-blocking agent treatment during 90 days before cancer diagnosis was not found to be associated with a decreased risk of cardiovascular death or hospital admission due cardiovascular diseases, either during the 90 days after cancer diagnosis or thereafter.

In study IV, we performed a randomized clinical trial including men clinically evaluated for suspected prostate cancer, to quantify the stress experience during the diagnostic workup of prostate cancer and assess its association with waiting-time. Patients in the intervention group had a fast-track workup with the shortest possible waiting-time, whereas the control group received the usual care. We presented baseline data at randomization and follow-up data at the first urologist visit, and found that depression symptoms and self-rated sleep quality score were reduced among men in the fast-track workup group, compared to the control group.

In conclusion, stress-related mental disorders diagnosed around cancer diagnosis, as indicators of the severe stress response to cancer diagnosis, were associated with an increased cancer-specific mortality and increased rate of hospital admission. Beta-blocking agent

treatment was not associated with a decreased risk of severe cardiovascular events immediately following a cancer diagnosis. For men with suspected prostate cancer, a shortened waiting-time during the diagnostic workup might lead to reduced risks of depression and sleeping problem.

LIST OF SCIENTIFIC PAPERS

I. Zhu J, Fang F, Sjölander A, Fall K, Adami HO, Valdimarsdóttir U. **First-onset mental disorders after cancer diagnosis and cancer-specific mortality: a nationwide cohort study.** Ann Oncol. 2017 Aug 1;28(8):1964-1969.

II. Zhu J, Sjölander A, Fall K, Valdimarsdottir U, Fang F. **Mental disorders around cancer diagnosis and increased hospital admission rate – a nationwide cohort study of Swedish cancer patients.** BMC Cancer. 2018 Mar 27;18(1):322.

III. Zhu J, Smedby KE, Valdimarsdóttir U, Sjölander A, Eloranta S, Udumyan R, Fall K, Fang F. **Beta-blocking agents and risk of severe cardiovascular events following a cancer diagnosis.** Manuscript.

IV. Zhu J, Fang F, Chen R, Davidsson S, Carlsson J, Messing-Eriksson A, Andrén O, Andersson SO, Valdimarsdottir U, Fall K. **Fast-track clinical workup for men with suspected prostate cancer: first report from a Randomized Clinical Trial.** Manuscript.

CONTENTS

LIST OF ABBREVIATIONS

CNS	Central Nervous System
HPA	Hypothalamic–Pituitary–Adrenal
NRN	National Registration Number
ICD	International Classification of Diseases
ATC	Anatomical Therapeutic Chemical
DDD	Defined Daily Dose
HR	Hazard Ratio
CI	Confidence Interval
hd-PS	high-dimensional Propensity Score
PSA	Prostate Specific Antigen
IPSS	International Prostate Symptom Score
QOL	Quality Of Life
HADS	Hospital Anxiety and Depression Scale
NCCN	National Comprehensive Cancer Network
ECG	Electrocardiogram
AUC	Area Under the Curve
HRV	Heart Rate Variation
SDRR	Standard Deviation of all Normal to Normal intervals

1 BACKGROUND

1.1 Psychological stress and stress response

American physiologist Walter Cannon first mentioned the modern word ‘homeostasis’ in the beginning of the 20th century [1], and a few decades later the synonym ‘stress’ was first used with its current meaning and popularized by Hans Selye [2]. The homeostasis is the living status all organisms strive to, which is a dynamic balance constantly challenged by intrinsic or extrinsic disturbing forces. The disturbing forces are usually called stressors, and the stress is defined as a state of threatened homeostasis [3]. All the physiological and behavioral responses acting by organisms with the aim to maintain homeostasis during stress are referred as ‘stress response’ [4]. When the homeostasis is threatened and the stressor exceeds certain severity or threshold, the adaptive systems will be activated and respond to the specific stressor functionally [4].

The stress response is an innate reaction that is evolved to maintain homeostasis and protects organism from stressor. The processes take place in both the central nervous system (CNS) and various peripheral organs and tissues by the pathways of endocrine and autonomic limbs [3]. Through the endocrine limb, arginine vasopressin and corticotropin-releasing hormone secreted from hypothalamus stimulates corticotropin secretion from the anterior pituitary, which, as consequence, activates the adrenal cortex to release large quantities of glucocorticoid hormones [5]. The autonomic nervous system reacts rapidly during stress and regulates a range of essential functions through the sympathetic and parasympathetic nervous system, including cardiovascular, respiratory, endocrine, and other systems [5]. After being activated during stress, these stress pathways stimulate their target systems, leading to increased oxygenation and nutrition in brain, heart, and skeletal muscles [6-8].

However, inappropriate activity or responsiveness of the stress system, in the form of overloading or long duration, might impair growth, development, and increase the risk of dysfunction in many systems, including mood, endocrine, metabolic, cardiovascular, and immune systems [3]. For example, chronic stress is associated with reduced rewarding value in mesolimbic dopaminergic system in terms of inhibiting dopamine release in many terminal areas, including hypothalamus [9]. The inability to cope with life events, which can increase secretion of corticosteroids, has been associated with increased risk for depression, abdominal obesity, osteoporosis, and cardiovascular diseases [10].

Potential biomarkers of stress response

Stress response can be measured through interview and self-report measurements. Psychological symptoms and disorders that are potentially induced by exposure to stressful events are frequently assessed when measuring stress response [11]. Commonly used measures for acute and chronic stresses include the Profile of Mood States [12] and the Impact of Events Scale [13]. Other instruments have been designed to additionally assess the frequency and extent of such symptoms within a specific time period. For example, different

instruments are nowadays available in the assessment of acute or chronic stressful events [14], including Survey of Recent Life Experiences for major life events, Stockholm Marital Stress Scale for stress of marriage, Job Content Questionnaire for work related stress, and Bergen Social Relationships Scale for social stress. There are also questionnaires to assess coping abilities, personality traits (Type-D personality trait), and psychological and physical changes of stress experiences (Perceived Stress Scale).

Stress response might also be indicated by experiencing severe negative health outcomes. For example, suicide attempt or completed suicide [15], diagnosis of a psychiatric disorder [16], prescription of psychotropic drugs, or experience of severe cardiovascular events [17] have all been associated with severely stressful life events, including natural disasters [18], war [19], and economy collapse [20].

Various biomarkers have been introduced to assess stress response. The physiological changes of stress system can be evaluated through measurement of bio-samples, including blood, saliva, urine, hair, and proxy autonomic markers [11]. Cortisol is commonly used as indicator for hypothalamic-pituitary-adrenal (HPA) axis activation. The elevated level of cortisol is a reflection of activated corticotropin-releasing hormone pathway, which can inhibit the HPA system via negative feedback to the hippocampus [21]. During 'stress reactivity', cortisol increases from baseline level following the onset of a stressor, and then returns to baseline level again at 'stress recovery' [21]. Similar with HPA-axis activation, the extent of change in the sympathetic-adrenal-medullary activation can also be assessed by biomarkers. For example, the levels of catecholamines, e.g. adrenaline and noradrenaline, secreted from adrenal glands are usually evaluated in blood and urine samples. Additionally, indirect effects of sympathetic-adrenal-medullary activation, e.g. vital signs, can be identified by the use of proxy autonomic measures [22], including blood pressure [23], heart rate variation [24], and respiratory rate [25].

Severe stress response to a cancer diagnosis

Receiving a cancer diagnosis, independent of the cancer disease itself or cancer treatment, may serve as a severe psychological stress to cancer patients and lead to serious health consequences [26, 27]. Severe stress response after a cancer diagnosis may reflect low stress resilience, lack of social support, preexisting psychological problems, chronic stress exposure, etc., and may potentially alter cancer progression. Previous studies have shown increased risks for various health consequences following a cancer diagnosis, including posttraumatic stress disorder [16], depression [27, 28], other psychiatric disorders [29, 30], suicide [31, 32], and life-threatening cardiovascular events [15, 17, 33-35]. In a meta-analysis including 24 hospital-based studies of cancer patients, around one third of cancer patients were found to have a prevalent mental disorder [28].

For cancer patients, the severe stress response may arise even before receiving the final diagnosis. We have shown in a recent study a rapid rise of mental disorders not only immediately after cancer diagnosis but also during the year before diagnosis [36]. The stress

response to a cancer diagnosis is therefore likely present at all stages of cancer course, during the diagnostic workup [37], while making treatment decision [38], as well as when experiencing treatment side effects [39], the increasing physical distress [40], disease recurrence and metastasis [41], and eventually the end of life issues [41].

1.2 Severe stress response, healthcare use, and cancer mortality

The role of psychological factors on cancer progression has been an interesting research topic over the last decades. Data from animal studies, e.g. of ovarian and prostate cancers, suggest that behavioral stress may change the microenvironment of cancer cells, and subsequently promote tumor progression and shorten survival [42, 43]. In a murine breast cancer model, adverse social environment has been associated with the pathways that are known to increase breast cancer growth, including up-regulated lipid synthesis and gene expression of glycolytic pathway [44].

Findings from human studies on the role of stress response on cancer survival are however inconclusive. In a meta-analysis of 165 prospective studies, stressful life experience or negative emotional response was shown to be associated with poorer cancer survival or greater cancer-specific mortality, especially among patients with lung, breast, and hematopoietic cancers [45]. Stress response to a breast cancer diagnosis, in terms of hopelessness and helplessness, was suggested to significantly reduce the disease-free survival in two studies [46, 47]. Similar factors were however not found to be associated with the length of breast cancer survival in other studies [48, 49].

Findings from human studies on the role of mental disorders on cancer survival are in general less conflicting. Mental disorders are major contributors to the health burden of the general population, and the magnitude of such contribution is increasing [50]. Mental disorders have been associated with increased risk for many chronic illnesses, including coronary artery disease [51] and stroke [52], as well as disability-adjusted life-years [50]. Among cancer patients, mental disorders were shown to be associated with a higher risk of mortality as well as longer hospital stay [53]. Mental morbidities have also been associated with a shorter event-free cancer survival and shorter time to relapse [47]. In a population-based cohort study, prostate cancer patients with a recently diagnosed depression were shown to have worse overall survival, potentially due to compromised compliance to treatment [54]. Among non-small cell lung cancer patients, depression at baseline and shortly after cancer diagnosis was also shown to predict worse survival [55]. Similarly, increased risk for all-cause mortality was observed among colorectal and blood cancer patients with depressive symptoms [56]. Most of the literature so far has focused on depression, whereas the role of other stress-related mental disorders (e.g., stress reaction and adjustment disorder and anxiety) on cancer progression and healthcare use has rarely been assessed.

1.3 Beta-blocking agents and severe stress response to cancer diagnosis

Randomized trials have found that beta-blocking agents can reduce occurrence of comorbidity, improve symptoms, and as a result lead to decreased mortality among patients with severe cardiovascular diseases, including heart failure [57, 58], cardiac arrest [59], and acute myocardial infarction [60]. The decreased mortality tended to be persistent across disease severity, and was noticed among patients with both mild to moderate [57, 61-63] and severe [58] heart failure. Cardiovascular events were commonly reported as a severe stress response among cancer patients [15, 17, 33, 36]. Pre-clinical studies have suggested that beta-blocking agents inhibit the autonomic nerves system [64, 65], which is usually stimulated by psychological distress. Findings from observational studies have also associated beta-blocking agents with reduced risk for overall mortality and cancer-specific mortality among cancer patients [66-68]. However, whether or not beta-blocking agents would reduce the risk of severe cardiovascular events directly after receiving a cancer diagnosis is not known.

1.4 Psychological stress and stress response during the diagnostic workup of prostate cancer

Prostate cancer diagnostic workup may be an important source of emotional stress [69]. High (50–64%) prevalence of anxiety has been reported in men investigated for and diagnosed with prostate cancer [70, 71]. Among patients evaluated for a suspected prostate cancer, prostate biopsy was found to be most stressful; around 20% of the men underwent prostate biopsy reported high psychological distress and tense or anxious mood [72]. One study used quantitative measurements of stress hormones throughout the prostate cancer diagnostic workup and found that the time period when waiting for a final cancer diagnosis was more stressful than the post-diagnosis period [37]. In a study investigating the level and prevalence of anxiety and depression among men undergoing diagnosis for prostate cancer, waiting for biopsy result was found to lead to the highest median Visual Analogue Scale score and the most stress [27]. In a study on the short-term effect of prostate cancer screening, anxiety level was found to be highest in men who had a biopsy, but not received a result yet [73]. Similarly, serum cortisol, as a bio-marker for psychological stress, was found to peak in the stage of waiting for biopsy result, among men that underwent prostate cancer screening [74].

2 AIMS

In this thesis, the overall aim was to investigate the severe stress response among cancer patients, especially around and after receiving cancer diagnosis. Using mental disorders as indicator of severe stress response to receiving a cancer diagnosis, we wanted to understand the role of stress response on the healthcare use pattern and cancer-specific mortality. We further aimed to explore the dynamic change of psychological stress experience during cancer diagnostic workup and assess the potential use of different interventions in preventing a severe stress response among cancer patients.

The specific aims were:

- To examine the role of mental disorders newly diagnosed after the cancer diagnosis, as an indicator of a severe stress response to the cancer diagnosis, on cancer-specific mortality.
- To estimate the effect of mental disorders diagnosed immediately before or after a cancer diagnosis on the subsequent rate of hospital admissions for common comorbidities among cancer patients, including infections, injuries, and cardiovascular diseases.
- To explore the association of beta-blocking agents used shortly before cancer diagnosis with the risk of severe cardiovascular events after cancer diagnosis.
- To characterize and quantify the psychological stress experience and assess its association with waiting-time during diagnostic workup for prostatic cancer, from a randomized clinical trial.

3 STUDY MATERIALS

3.1 Swedish population and health registers

In Sweden, every resident is assigned a unique national registration number (NRN) at the time of birth or immigration, which is used in all national population and health registers [75]. Major events in an individual's life are all recorded in these registers, such as birth, education, work, marriage, family relationships, medical records, immigration, and death. The unique NRN allows cross-linkages between these registers and subsequently individual follow-up of the entire nation. And prior to academic research, all the individual records were anonymized and de-identified.

Cancer Register

The Swedish Cancer Register was founded in 1958 and covers the entire population of Sweden. Healthcare providers, including clinicians and pathologists, are required by law to report all newly diagnosed cancer cases to the register [76]. This register includes mainly three types of information as following:

1) Data on the patient, including the Swedish NRN, age at diagnosis, gender, and place of residence;

2) Medical data, including cancer site, date of diagnosis, and histological type. From year 2004, information on cancer stage has also been collected;

3) Follow-up data, including date of death, causes of death, and date of migration.

Patient Register

The Swedish Patient Register was founded in 1964/1965, and since 1987 it has national coverage for all discharge records from inpatient care visit in Sweden [77]. Each year, about 1.5 million hospital discharge records are reported to this register. From 1997 and onward, surgical daycare procedures are also reported to the Patient Register, and since 2001, all counties in Sweden are obliged to report hospital-based outpatient specialist visits to the Patient Register. The register covers currently >80% of the entire country regarding outpatient visits.

Diagnoses in this register are coded according to the Swedish revisions of the International Classification of Diseases (ICD) codes, and from 1997 onward the 10th ICD codes have been used. The Patient Register is essential for population-based epidemiological research because it allows us to for example study the incidence and prevalence of different diseases, examine the effect and consequences of different interventions, and establish cohorts of patients with a certain disease or condition.

Prescribed Drug Register

The Swedish Prescribed Drug Register contains information on all dispensed drugs and covers the entire Swedish population, since July 2005. The register holds data on all dispensed drugs classified according to the Anatomical Therapeutic Chemical (ATC) System, including dispensing date, quantity, daily dose, and defined daily dose (DDD) of the prescribed drug [78].

Causes of Death Register

The Swedish Causes of Death Register contains data from 1961 and is updated every year, including information on date as well as underlying and contributory causes of death [79]. The Causes of Death Register covers all deaths in Sweden, and the causes of death are coded according to ICD codes.

Other registers

Longitudinal Integration Database for Health Insurance and Labor Market Studies, as a part of Statistics Sweden's Business Register, has since 1990 annually updated information regarding labor market, and educational and social sectors for all individuals at age 16 onward in Sweden.

Finally, the Total Population Register includes information about birth, marriage status, migration, and death for all residents of the country from 1968 [80]. For example, Migration Register is part of the Total Population Register and holds information on dates of migration that was used to determine the end of follow-up for different cohort studies included in the thesis.

3.2 Randomized clinical trial

A randomized clinical trial based in the Urology Department at Örebro University Hospital was performed to include all men referred to the hospital for suspected prostate cancer. Eligible participants were men 85 years or younger, who were able to speak and write Swedish and did not show signs of advanced prostate cancer, or severe psychiatric or somatic diseases.

Since October 2016, all eligible men have been invited to participate and those who accept are randomized to either a fast-track intervention or to a usual care control group. Until May 2018, 204 men had participated in the study and were randomized. The fast-track diagnostic workup entails the possible shortest waiting-time: 1 week from randomization to the urologist visit (biopsy if needed), 1 week from biopsy to diagnosis, and 1 week from diagnosis to treatment decision. In the control group, the usual care involves waiting-times of approximately 1 week-3 months, about 2 weeks, and 2 weeks, respectively, during these steps. Men in both arms are first assessed at the urology clinic for baseline characteristics directly after randomization, and then again before the urologist visit. The men will be further followed and assessed at time of diagnosis, 1 month after diagnosis, and two additional times during follow-up (6 and 12 months after urologist visit/biopsy). Written informed consent is obtained from all participants. The study was also registered in the trial database at Research and Development of Sweden (FoU Sweden, ID 207411).

4 STUDY DESIGN AND METHODS

4.1 First-onset mental disorders and cancer-specific mortality

Taking advantage of the Swedish national health registers, we performed a retrospectively defined cohort study including all cancer patients diagnosed during 2004-2009 in Sweden. Based on the Cancer Register, 244,261 adult cancer patients (≥ 30) were included after exclusion of diagnosis at autopsy and emigration before cancer diagnosis. We followed these patients from date of cancer diagnosis until death, emigration, or December 31, 2010 through cross-linkages to the Causes of Death Register and the Migration Register.

Stress-related mental disorders, including mood-, anxiety- and substance abuse disorders, were used as the primary exposure, reflecting the severe stress response to cancer diagnosis. Cancer-specific mortality identified from Causes of Death Register was used as the primary outcome. Cancer patients were defined as having a cancer-specific death, if their cancer diagnosis and the underlying cause of death indicated the same site or group of cancer.

4.1.1 Cancer site and stage

Cancers were classified and grouped according to the 7th Swedish revision of the ICD codes, including facial cancer (140-148), digestive cancer (150-159), lung and thorax cancer (160-165), bone cancer (196), skin cancer (190-191), soft tissue cancer (197), breast cancer (170), other female genital cancer (171-176), male genital cancer (177-179), urinary cancer (180-181), CNS and eye cancer (180-181), endocrine cancer (194-195), and hematologic cancer (200-207).

In the Cancer Register, the completeness of information on cancer stage at diagnosis has been high since 2004, and we used FIGO stage for gynecologic cancers (ICD-7: 171-176) and TNM for other cancers (except for hematological and CNS malignancies). Cancer stage was accordingly classified as localized cancer (T localized/N0/M0 or FIGO 0, I), local spread cancer (T advanced/N0/M0 or FIGO II), regional spread cancer (any T/N+/M0 or FIGO III), and advanced cancer (any T/any N/M+ or FIGO IV) [81]. The conventional values of T record

were assessed and assigned to the corresponding T-localized and T-advanced categories, for each specific cancer type separately (Table 1).

Table 1. Conventional T values corresponding to T localized or T advanced.

Cancer site	T localized	T advanced
Lip/oral cavity, Pharynx, Larynx, Paranasal sinuses, Salivary glands, Oesophagus, Stomach, Small intestine, Colon/rectum, Anal canal, Liver, Gallbladder, Extrahepatic bile ducts/ampulla, Pancreas, Lung, Pleura, Vulva, Vagina, Cervix, Corpus, Penis, Prostate, Testis, Kidney, Pelvis/ureter, Bladder, Urethra, Sarcoma of orbit	T1 – T2	T3 – T4
Thyroid, Skin, Melanoma, Breast, Eye	T1 – T3	T4
Bone, Soft tissue, Ovary, Fallopian tube, Trophoblastic	T1	T2 – T3

4.1.2 Stress-related mental disorders

Mental disorders were ascertained through the Patient Register. For all cancer patients, we identified the first mental disorder diagnosis (ICD10: F00-F99) after cancer diagnosis. The following mental disorders were included as stress-related mental disorders: mental and behavioral disorders due to psychoactive substance use (ICD10: F10-F16, F18-F19), depression (ICD10: F32-F33), stress reaction/adjustment disorder (ICD10: F43), anxiety (ICD10: F40-F41), and somatoform/conversion disorder (ICD10: F44-F45). These mental disorders (e.g. mood-, anxiety- adjustment- and substance abuse disorders) are commonly diagnosed among cancer patients [36, 82], with highly increased risks noticed immediately before and after cancer diagnosis [36], and are also potentially related to severe psychological stress [83, 84]. Other mental disorders (ICD10: F00-F99 excluding stress-related mental disorders mentioned above) were used as the secondary exposure. Exposure was used as time-dependent variable, so cancer patients were classified as exposed from the date of their mental disorder diagnosis. We further divided the main exposure according to time since cancer diagnosis, e.g. a diagnosis of mental disorders within 90 days after cancer diagnosis or beyond 90 days after cancer diagnosis.

4.1.3 Cancer-specific mortality

Underlying cause of death was identified by cross-linking the cohort to the Causes of Death Register. If the underlying cause of death for a cancer patient was the same cancer site or group as the cancer diagnosis, the patient was defined as having a cancer-specific death.

4.1.4 Statistical analysis

We used Cox proportional hazards regression to assess the association of mental disorders after cancer diagnosis with cancer-specific mortality, yielding hazard ratios (HRs) with 95% confidence intervals (CIs).

We calculated HRs of cancer-specific mortality for patients with mental disorders (stress-related and others) after cancer diagnosis compared to patients without any mental disorders after cancer diagnosis. We further calculated HRs for patients with stress-related mental disorders diagnosed within 90 days after cancer diagnosis or beyond.

To specifically explore the role of first-onset mental disorders (i.e. patients with a mental disorder diagnosed after cancer diagnosis but without a history of mental disorders before cancer diagnosis), separate analyses for patients with and without a history of mental disorders before cancer diagnosis were performed. History of mental disorders was obtained from January 1st 1987 until date of cancer diagnosis. We conducted the analysis first for all cancer types together, and then separately for the most common cancer sites or groups, including breast cancer, prostate cancer, colorectal cancer, lung cancer, renal or bladder cancer, melanoma, hematological malignancies, and severe cancers. We combined cancers of esophagus, liver, and pancreas into one group of severe cancers.

We also calculated the HRs of cancer-specific mortality for specific stress-related mental disorders. Finally, we stratified the analysis by age at diagnosis, sex, calendar period of diagnosis, educational level, and cancer stage at diagnosis, to assess potential effect modifiers of the studied association.

In all statistical analyses, age at follow-up was used as the underlying timescale and we adjusted for age at cancer diagnosis (as a continuous variable), sex, calendar period of diagnosis (2004-2006 and 2007-2009), educational level (≥9 years, <9 years), and disease stage at diagnosis. In the analysis for any cancer we further adjusted for cancer site or group, and in the analysis of hematological malignancies we further adjusted for cancer subtype (Hodgkin lymphoma, non-Hodgkin lymphoma, myeloma, and leukemia).

To test whether cancer patients exposed to mental disorders would receive different treatment compared to other cancer patients, leading to potentially different survival, we performed an additional analysis among patients with a cancer for which surgical treatment is commonly used as the primary treatment, including prostate, lung, and colorectal cancers. In this analysis, we ascertained records of surgical treatments, and compared the percentage of as well as the waiting-time for surgical treatments, among cancer patients exposed and unexposed to mental disorders after diagnosis.

All the statistical analyses were carried out in SAS 9.4 (SAS Institute, North Carolina, United States) and Stata13.1 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). The study was approved by the Regional Ethical Review Board at the Karolinska Institutet, Stockholm, Sweden.

4.2 Stress-related mental disorders around cancer diagnosis and hospital admission

Based on the Swedish Cancer Register, we conducted a cohort study, including all adult patients (30 years and above) with a first primary cancer diagnosed between 2004 and 2009 in Sweden (N=251,214). Patients with cancer diagnosed at autopsy or emigrated before cancer diagnosis were not included. Because the occurrence of mental disorders might be physiologically related to the lesion of CNS [85, 86], patients with CNS tumors (N=6,061) were excluded.

As indicator of a severe stress response toward the diagnostic process and the eventual diagnosis of cancer, stress-related mental disorders diagnosed from 90 days before to 90 days after cancer diagnosis were used as the primary exposure of interest, and other mental disorders diagnosed at the same time window were used as the secondary exposure. After further excluding cancer patients that died within 90 days after cancer diagnosis, we included 218,508 patients in the analysis and followed them from 91st day after diagnosis until date of death, date of emigration, or December 31st 2010, whichever occurred first. During follow-up, we studied all kinds of hospital admissions as well as the three most common reasons for hospital admission including external injuries, infections, and cardiovascular diseases.

4.2.1 Hospital admission after cancer diagnosis

We assessed hospital admissions by cross-linking the cancer patients to the Patient Register. The dates of admission and discharge were identified for each admission, and used to calculate the length of hospital stay. Consecutive hospital admissions between hospitals or departments were treated as one admission event. The main discharge diagnosis was retrieved and used as the reason of each hospitalization. The analysis was first performed for any hospital admission together after cancer diagnosis, as a proxy for overall impatient healthcare utilization. We then performed the analysis separately for the three types of common hospital admissions, including external injuries (ICD10: S00-S99, T00-T36, T51-T79, T89-T95, T97-T98.2, T98.4-T99) - both unintentional injuries (ICD10: V01-X59, Y85-Y86) and self-harm (ICD-10: X60-X84, Y870) [87], infections (ICD10: A00-A99, B00-B99), and cardiovascular diseases (ICD10: I00-I99). The length of hospital stay could reflect the demand of healthcare, so we also performed the analysis for hospital admissions of different durations (<4 days, 4-10 days, and >10 days).

4.2.2 Statistical analysis

Cox proportional hazards regression was used to assess the association between mental disorders diagnosed from 90 days before to 90 days after a cancer diagnosis with the subsequent rate of hospital admissions. In the analysis, we also used a clustered sandwich estimator to account for intra-individual correlation, since cancer patients might be repeatedly admitted to hospital. The analysis was first performed for all cancer patients together, and then separately for patients with the most common cancer type, including breast cancer, prostate cancer, colorectal cancer, lung cancer, melanoma, kidney or bladder cancer, severe cancers, and hematological malignancies.

In all statistical analyses, age at follow-up was used as the underlying timescale and we additionally adjusted for age at cancer diagnosis (as a continuous variable), sex, calendar year of cancer diagnosis (2004-2009), cancer type, cancer stage at diagnosis (except for hematological cancers), educational level (≥9 years or <9 years), and history of mental disorders (yes or no). History of mental disorders was ascertained from the Patient Register, assessing anytime from 2001 to 90 days before cancer diagnosis. In the analysis for

hematological cancers, we further adjusted for cancer subtype (Hodgkin lymphoma, non-Hodgkin lymphoma, myeloma, and leukemia).

To assess potential effect modifiers of the studied associations, we further stratified the analyses by age group (≤65, 66-75, and >75 years), sex, calendar period of diagnosis (2004-2006, 2007-2009), educational level, history of mental disorders, and cancer stage at diagnosis.

Cancer patients receiving a diagnosis of mental disorder around their cancer diagnosis could have different types of cancer treatment compared to other patients, which might lead to different hospital admission rates. For cancers that are commonly treated by surgery, including prostate, lung, or colorectal cancers, we performed a sensitivity analysis by further adjusting for surgery (yes or no).

All the statistical analyses were performed using SAS 9.4 (SAS Institute, North Carolina, United States) and Stata15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). The study was approved by the Regional Ethical Review Board at the Karolinska Institutet, Stockholm, Sweden.

4.3 Beta-blocking agents and severe cardiovascular events after cancer diagnosis

We conducted a cohort study including all adult cancer patients (age at diagnosis ≥30) diagnosed from 2006 to 2013 in Sweden. After exclusion of diagnoses confirmed at autopsy (N=599), individuals that had ever emigrated out of Sweden before cancer diagnosis (N=12,808), and patients with hematological cancers and central nervous system tumors (N=33,029), our analytic cohort comprised 305,422 cancer patients.

Cancer patients that used beta-blockers during the 90 days before cancer diagnosis, including the day of diagnosis, were classified as exposed. We followed cancer patients from date of diagnosis until emigration, death, or end of 2014, whichever occurred first. Severe cardiovascular events occurred during follow-up were our main outcome of interest, which was defined as a death with a cardiovascular disease as the underlying cause of death, or a hospital admission with a cardiovascular disease as the main discharge diagnosis.

4.3.1 Treatment of beta-blockers shortly before cancer diagnosis

All dispenses of beta-blockers (ATC: C07AA, C07AB, C07AG, and C07FB) before cancer diagnosis were identified from the Swedish Prescribed Drug Register. Treatment period of beta-blockers was calculated from the most recent dispense and started from the dispensing date. According to information of the prescription, we estimated the duration of treatment from the division of total amount of dispensed drug by recommended daily dose. Multiple records for an identical beta-blocker at the same collection date were identified and summed up. Any record of unused beta-blockers that were returned to the pharmacies was also retrieved and the returned amount was detracted from total amount of the drug. In the study cohort, only cancer patients with a treatment period of beta-blockers that overlapped with the 90 days' time-period before cancer diagnosis were classified as "exposed". Patients with missing information on recommended daily dose from the Drug Register were excluded.

Exposed to beta-blocker treatment was further classified according to recommended daily dose (high: recommended daily dose >0.5 defined daily dose, and low: recommended daily dose ≤0.5 defined daily dose), receptor activity (non-selective [ATC: C07AA], selective [ATC: C07AB], alpha and beta blocking agents [ATC: C07AG], and combined tablets of beta-blockers and calcium channel blockers [ATC: C07FB]), and time to cancer diagnosis (current use: treatment period covering the date of cancer diagnosis, and recent use: treatment period not covering the date of cancer diagnosis).

4.3.2 Severe cardiovascular events after cancer diagnosis

A hospital admission with a cardiovascular disease as the main discharge diagnosis (identified from the Patient Register; ICD-10: I00-I99), or death with a cardiovascular disease as the underlying cause of death (identified from the Causes of Death Register) were identified and defined as a "severe cardiovascular event". The main outcome was then classified as fatal or non-fatal cardiovascular event. A hospital discharge for which cardiovascular disease was indicated as the main discharge record that was followed by a death due to a cardiovascular disease within 30 days after the discharge, and a death due to a cardiovascular disease that was not preceded by a related hospital admission were classified as fatal event. A hospital discharge for which cardiovascular disease was indicated as the main discharge record that did not lead to

a death within 30 days were classified as non-fatal event. The severe cardiovascular events were also classified by specific diagnoses, including myocardial infarction (ICD-10: I20-I25), hypertension or aortic rupture (ICD-10: I10-I13, I71, I72), stroke (ICD-10: I60-I64), embolism (ICD-10: I26, I74, I80-I82), and arrhythmia or heart failure (ICD-10: I44-I50).

4.3.3 Ascertainment of comorbidity

A high-dimensional propensity score (hd-PS) algorithm [88] was performed to select covariates. We identified all records of specialist-based healthcare use from the 365 days to 90 days before cancer diagnosis for all cancer patients. We used 5 data dimensions, including 1) clinical diagnoses (ICD-10) and 2) medical procedures (Swedish Classification of care measures) from an outpatient specialist visit, 3) discharge diagnoses (ICD-10) and 4) medical procedures from an inpatient specialist visit, as well as 5) prescribed drugs (ATC), from either the Patient Register or the Prescribed Drug Register. We set the granularity to three digits for clinical diagnoses, medical procedures, and drugs. The first 100 most prevalent codes from each dimension were selected to candidate empirical covariates. Each code was assessed by how frequently it was recorded for each patient, and divided into three levels (once, sporadic, and frequent). We prioritized covariates across data dimensions by their potential for controlling for confounding that was not conditional on exposure and other covariates, leading to the top 500 covariates of all covariates (5*100*3) being included in the final hd-PS algorithm [88].

We also introduced Chronic Disease Score [89, 90] to calculate the prescribed medication-based comorbidity for each cancer patient. All prescribed drugs from 365 days to 90 days before cancer diagnosis were identified from the Prescribed Drug Register and the number of distinct prescribed drugs was used as the comorbidity measure; the potential range of values is 0-35. Drugs that had the same first three digits of ATC codes were considered as the same class.

4.3.4 Statistical analysis

We used Cox proportional hazards regression to assess the association of beta-blocker treatment with the risk of severe cardiovascular events after cancer diagnosis. We mainly

focused on the first 90 days after cancer diagnosis. To estimate the temporal pattern of the association, we also performed the analysis during more than 90 days after cancer diagnosis. The analysis was first performed for any severe cardiovascular events, and then separately for fatal, non-fatal, and diagnosis-specific event. We also performed the analysis separately according to receptor selectivity, recommended daily dose, and recentness of use of beta-blockers. We analyzed all cancer patients together first, and then separately patients with the most common cancer types, including breast cancer, prostate cancer, colorectal cancer, lung cancer, malignant melanoma, kidney or bladder cancer, and severe (esophageal, liver, and pancreatic) cancers.

To assess potential effect modifiers of the associations, we further stratified the analyses by age at diagnosis (≤65, 66-75, and >75 years), sex, calendar period (2006-2007, 2008-2009, 2010-2011, and 2012-2013), educational level (post-secondary school, secondary school, ≤9 years), cancer stage at diagnosis, Chronic Disease Score (0, 1-2, 3-5, and ≥6), beta-blocker history (yes or no), cardiovascular disease history (yes or no), and mental disorder history (yes or no). Patients that had at least one diagnosis of cardiovascular disease (ICD-10: I00-I99) or mental disorder (ICD-10: F00-F99) through inpatient or outpatient care, or that had dispensed beta-blockers more than 90 days before cancer diagnosis were classified as having a history of cardiovascular disease, mental disorder, or beta-blocker use, respectively. The latest diagnosis for cardiovascular disease history was further classified according to ICD-10 codes as mentioned above.

To assess whether the observed associations were specific to beta-blockers, we performed similar analysis for diuretics (ATC: C03), calcium channel blockers (ATC: C08), and agents acting on the renin-angiotensin system (ATC: C09), using the same 90 days before cancer diagnosis to classify exposure status.

In all statistical models, we used calendar period of follow-up as the underlying timescale and additionally adjusted for age at diagnosis (as a continuous variable), sex, cancer type, cancer stage at diagnosis, educational level, beta-blocker history, cardiovascular disease history, mental disorder history, hd-PS, and other antihypertensive medicines (diuretics, calcium channel blockers, and agents acting on the renin-angiotensin system).

All the statistical analyses were performed using SAS9.4 (SAS Institute, North Carolina, United States) and Stata15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). The study was approved by the Regional Ethical Review Board at the Karolinska Institutet, Stockholm, Sweden.

4.4 Fast-track clinical workup for men with suspected prostate cancer

Based on the above-mentioned clinical trial, we randomized eligible participants referred to the Urology Department at Örebro University Hospital for suspected prostate cancer into intervention and control groups. In this study, we only presented baseline data at randomization and follow-up data at first urologist visit. Patients in the intervention group experienced a fast-track workup where the shortest possible waiting-time was targeted, whereas the control group followed the usual care. From randomization to first urologist visit, we measured and compared the indications and symptoms of psychological stress, including self-reported symptoms of distress (anxiety, depression, distress, sleep disruption) and stress biomarkers (heart rate variability and diurnal cortisol level), between these two groups.

4.4.1 Data collection

Before randomization, the research nurses collected information on patients' characteristics, including age, civil status (cohabitating or not), educational level (university or lower), living area (urban or rural), prostate specific antigen (PSA) level, comorbidity score (Charlson comorbidity index), and prostate symptom score. The prostate symptom score was assessed using the International Prostate Symptom Score (IPSS) and further evaluated in two aspects, including symptom score (score 0 to 35) and quality of life score (QOL, score 0 to 6) [91]. Different instruments, including questionnaire-based self-reported stress symptoms and measurements of stress biomarkers, were used to measure the stress experience at randomization and at first urologist visit.

4.4.2 Questionnaires

Before randomization, men were asked to complete the first questionnaire just after signing the informed consent when meeting with the research nurse. The second questionnaire was handed to the participants, so that they could complete it one day before their first urologist visit and

bring it back to the research nurse on the day of urologist visit. The combined 43-item questionnaire covers questions including indications and symptoms of psychological stress, anxiety, and depression. Specifically, we assessed levels of depression and anxiety with the Hospital Anxiety and Depression Scale (HADS) [92], self-evaluated distress with National Comprehensive Cancer Network (NCCN) distress thermometer [93], and sleep quality and disturbances through Åkerstedts Karolinska Sleep Questionnaire [94]. The HADS included 14 items including seven items related to anxiety and another seven related to depression. Total scores for anxiety and depression were computed by summarizing scores of the contributing seven items respectively. In case of a missing item, we replaced it with the mean of the answered items in the subscale, if at least half of that subscale had been answered [95]. NCCN distress thermometer is a one-item visual-graphic measurement (range: 0 to 10), usually used to measure psychological distress in individuals with cancer. The sleep questionnaire includes seven items assessing the following three indexes during the week before measurement: the sleep quality index was the mean of four sleep items (difficulty in falling asleep, repeated awakening, premature awakening, and disturbed sleep), the sleep apnea index was the mean of two sleep items (cessation of breathing during sleep and snoring), and the self-rated sleep quality score (range: 1 to 5) was one-item measurement. For all measures, a higher value indicated a poor outcome. The men also reported in the same questionnaire smoking (never, former, and current, respectively for cigarette and snuff), previous treatment for psychiatric disorder (anxiolytics or antidepressants, yes or no), and social support by partner and others (high, moderate, and low).

4.4.3 Saliva cortisol

Saliva samples were collected the day before randomization and the day before the first urologist visit. Three samples were collected at each day, including at awakening in morning, 2 pm, and 9 pm. The samples were stored according to the manufacturer's instructions (Salimetrics). Saliva cortisol was measured using the High Sensitivity Salivary Cortisol Enzyme Immunoassay Kit according to the manufacturer´s instructions (Salimetrics, USA; Item No. 1-3002). The minimum detectable level of cortisol in the kit was 0.007 µg/dL, and the detection range was 0.012 - 3.000 µg/dL.

4.4.4 Heart rate variability

Heart rate was measured using a handheld electrocardiogram (ECG) device (Zenicor-ECG® Medical systems, Zenicor Medical system AB, Stockholm, Sweden). Each patient was measured 3 x 30 second segments of ECG, when waiting for randomization and for first urologist visit. Heart rate was then analyzed to detect heart rate variation (HRV) for characterization of the individual's stress profile.

4.4.5 Statistical analysis

Linear regression was performed on the three measures of cortisol levels within a day for each individual. The slope ('β') of the regression line predicting cortisol level from time of day was used to represent each participant's cortisol diurnal rhythm [96]. The area under the curve (AUC) represented the total amount of secreted cortisol in the day. We also calculated two types of AUCs to provide different information about cortisol secretion: AUC with respect to ground (AUC_G) and AUC with respect to increase (AUC_I) [97].

The HRV was calculated as the degree of variation in the inter-beat intervals series ($HRV = \frac{\text{Standard devison of QRS to QRS intervals series}}{\text{Mean of QRS to QRS intervals series}} \times 100\%$) [98]. In addition, we also calculated the standard deviation of all normal to normal intervals (SDRR) for each ECG records, which is the most commonly used time domain measure of heart rate variability [99].

We compared the baseline characteristics between groups with t-test and Wilcoxon rank sum tests for continuous variables, and Chi-square test and Fisher's exact test for categorical variables. Due to the small number of men with symptoms for anxiety and depression above the defined cut-off values, these variables were analyzed as an ordinary score. To normalize data, measures of distress, anxiety, depression, sleep quality, and sleep apnea were square root transformed, whereas HRV and SDRR were natural log transformed prior to statistical analysis. To evaluate the effect of the intervention, group differences in change over time between randomization and the urologist visit were compared as differences in percent changes. Generalized linear model was then used to compare the changes over time between the intervention and the control groups. The analysis was first conducted without adjustment and

then adjusted for age, PSA level (log- transformed), Charlson comorbidity score, educational level, cohabitating status, living area, cigarette smoking, and snuff use.

All tests are two-sided and an alpha level of 0.05 was applied to assess statistical significance. All the statistical analyses were performed using SAS9.4 (SAS Institute, North Carolina, United States). This study was approved by the ethics committee at Örebro University Hospital.

5 RESULTS

5.1 First-onset mental disorders and cancer-specific mortality

After cancer diagnosis, 11,457 patients experienced a stress-related mental disorder, of which 7,236 were first-onset, and 10,688 patients were diagnosed with other mental disorders, of which 6,661 were first-onset (Table 2).

Compared to unexposed patients, patients diagnosed with stress-related mental disorders after cancer diagnosis had a 53% increased rate of cancer-specific mortality (Table 2). Stronger association was noted among patients with first-onset mental disorders after cancer diagnosis. Patients that experienced a recurrent mental disorder had only slightly elevated cancer-specific mortality. The increased cancer-specific mortality was observed for stress-related mental disorders both within and beyond 90 days after cancer diagnosis (Table 2). Cancer patients diagnosed with other mental disorders after cancer diagnosis also had increased cancer-specific mortality (62%, Table 2). The association was also stronger for first-onset, compared to recurrent, mental disorders (Table 2).

Table 2. Association of mental disorders with cancer-specific mortality, shown by time since cancer diagnosis

	Entire follow-up		90 days after cancer diagnosis		>90 days after cancer diagnosis	
	N	HR (95% CI)[1]	N	HR (95% CI)	N	HR (95% CI)
	Stress-related mental disorders					
Overall	11,457	1.53 (1.46 - 1.60)	3,232	1.30 (1.21 - 1.40)	9,314	1.68 (1.58 - 1.78)
History of mental disorders						
No	7,236	1.82 (1.71 - 1.92)	1,313	1.52 (1.37 - 1.69)	5,923	1.97 (1.84 - 2.11)
Yes	4,221	1.14 (1.05 - 1.24)	1,672	1.10 (0.98 - 1.22)	2,549	1.22 (1.08 - 1.38)
	Other mental disorders					
Overall	10,688	1.62 (1.55 - 1.70)	2,936	1.44 (1.35 - 1.54)	7,752	1.73 (1.63 - 1.84)
History of mental disorders						
No	6,661	1.85 (1.74 - 1.97)	1,060	1.65 (1.49 - 1.84)	5,601	1.96 (1.82 - 2.12)
Yes	4,027	1.36 (1.26 - 1.47)	1,876	1.30 (1.18 - 1.43)	2,151	1.45 (1.29 - 1.64)

[1] HR: Hazard ratio; CI: Confident interval.

In the analysis of specific cancers, an increased cancer-specific mortality by first-onset stress-related mental disorders was observed among all the common cancer types. In contrast, no association was noted for recurrent mental disorders in any cancer type (Table 3).

Table 3. Association of stress-related mental disorders after cancer diagnosis with cancer-specific mortality (HR, 95% CI)[1] among patients with different cancer types			
Cancer site/group	**Overall**	**No history of mental disorders**	**History of mental disorders**
Prostate cancer	1.84 (1.59 - 2.14)	2.42 (2.04 - 2.88)	1.23 (0.92 - 1.66)
Breast cancer	1.32 (1.10 - 1.57)	1.54 (1.26 - 1.89)	1.05 (0.73 - 1.50)
Lung cancer	1.42 (1.28 - 1.57)	1.68 (1.48 - 1.90)	1.14 (0.96 - 1.35)
Colorectal cancer	1.35 (1.20 - 1.53)	1.54 (1.33 - 1.79)	1.14 (0.91 - 1.42)
Melanoma	1.71 (1.23 - 2.37)	2.38 (1.66 - 3.42)	0.62 (0.25 - 1.56)
Hematological malignance	1.63 (1.40 - 1.91)	1.84 (1.54 - 2.20)	1.22 (0.89 - 1.67)
Renal/Bladder cancer	1.86 (1.55 - 2.24)	2.43 (1.95 - 3.02)	1.38 (0.98 - 1.93)
Severe cancers	1.19 (1.02 - 1.39)	1.30 (1.07 - 1.58)	1.34 (0.99 - 1.81)

[1] HR: Hazard ratio; CI: Confident interval.

In the stratified analysis, the excess cancer-specific mortality by first-onset stress-related mental disorders after cancer diagnosis did not appear to differ largely between men and women; neither did it differ by age, calendar period of diagnosis, or educational level (Table 4). However, the increased mortality was stronger among patients with a diagnosis of lower stage cancer compared to patients with more advanced stage disease.

Table 4. Association of first-onset and recurrent stress-related mental disorders after cancer diagnosis with cancer-specific mortality, stratified analyses				
	First-onset mental disorders		**Recurrent mental disorders**	
	N (%)	**HR (95% CI)[1]**	**N (%)**	**HR (95% CI)**
Sex				
Male	3,082 (42.59)	1.93 (1.77 - 2.10)	2,103 (49.82)	1.20 (1.07 - 1.34)
Female	4,154 (57.41)	1.71 (1.58 - 1.85)	2,118 (50.18)	1.10 (0.97 - 1.24)
Age at follow-up, years				
≤65	3,906 (53.98)	1.73 (1.59 - 1.89)	2,575 (61.00)	1.23 (1.10 - 1.38)
66-75	1,785 (24.67)	1.99 (1.78 - 2.21)	969 (22.96)	1.12 (0.95 - 1.31)
>75	1,545 (21.35)	1.77 (1.59 - 1.98)	677 (16.04)	0.98 (0.81 - 1.18)
Calendar period at diagnosis				
2004-2006	4,310 (59.56)	1.78 (1.65 - 1.91)	2,049 (48.54)	1.11 (0.98 - 1.25)
2007-2009	2,926 (40.44)	1.89 (1.72 - 2.07)	2,172 (51.46)	1.19 (1.05 - 1.34)
Educational level				
>9 years	4,705 (65.02)	1.75 (1.62 - 1.88)	2,603 (61.67)	1.12 (0.99 - 1.25)
≤9 years	2,515 (34.76)	1.88 (1.72 - 2.06)	1,611 (38.17)	1.13 (1.00 - 1.29)
Cancer stage[2]				
Localized	3,020 (41.74)	2.00 (1.73 - 2.31)	1,778 (42.12)	1.16 (0.91 - 1.46)
Local spread	826 (11.42)	2.04 (1.75 - 2.37)	512 (12.13)	1.35 (1.06 - 1.70)
Regional spread	1,041 (14.39)	1.85 (1.65 - 2.07)	562 (13.31)	1.29 (1.08 - 1.55)
Advanced	471 (6.51)	1.49 (1.32 - 1.69)	262 (6.21)	1.11 (0.92 - 1.35)
Unknown	1,139 (15.74)	1.65 (1.43 - 1.90)	710 (16.82)	1.11 (0.90 - 1.37)

[1] HR: Hazard ratio; CI: Confident interval.
[2] Patients with missing or unclear information of TNM/FIGO were classified as 'Unknown'.

Almost all subtypes (depression, anxiety, stress reaction and adjustment disorder, and mental and behavioral disorders due to psychoactive substance use) of first-onset stress-related mental

disorders were associated with an increased cancer-specific mortality, except somatoform/conversion disorder (Table 5).

Table 5. Association of specific diagnosis of stress-related mental disorders after cancer diagnosis with cancer-specific mortality.

	First-onset mental disorders[1]		Recurrent mental disorders	
	N (%)[3]	HR (95% CI)[2]	N (%)	HR (95% CI)
Stress reaction	832 (11.50)	1.78 (1.51 - 2.11)	283 (6.70)	1.02 (0.73 - 1.42)
Depression	3109 (42.97)	1.76 (1.62 - 1.92)	1720 (40.75)	1.02 (0.89 - 1.16)
Anxiety	2061 (28.48)	2.11 (1.92 - 2.33)	959 (22.72)	1.27 (1.08 - 1.49)
Substance abuse	926 (12.80)	1.50 (1.25 - 1.79)	1212 (28.71)	1.29 (1.12 - 1.49)
Somatoform/conversion disorder	308 (4.26)	1.20 (0.82 - 1.76)	47 (1.11)	1.36 (0.64 - 2.92)

[1] Patients without any mental disorders (ICD10: F00-F99) before cancer diagnosis.
[2] HR: Hazard ratio; CI: Confident interval.

Prostate cancer patients with a first-onset stress-related mental disorder post diagnosis had similar percentage of surgery ($p>0.05$) compared to the unexposed patients; lung and colorectal cancer patients with first-onset mental disorders were on the other hand slightly more likely to have surgery ($p<0.05$) compared to the unexposed patients. Among patients with surgery, all prostate, lung, and colorectal patients with exposure to first-onset mental disorder had similar waiting-time from diagnosis to surgery compared to the unexposed patients ($p>0.05$) (Table 6). Adding surgery into the survival analysis did not alter our results greatly: HR=2.44 (95%CI: 2.05-2.90) for prostate cancer; HR=1.67 (95%CI: 1.47-1.90) for lung cancer; and HR=1.55 (95%CI: 1.34-1.79) for colorectal cancer.

Table 6. Proportion of and waiting-time for surgical treatment by first-onset stress-related mental disorders after cancer diagnosis, analyses of patients with prostate, lung, or colorectal cancers

	No mental disorders	First-onset stress-related mental disorders	
Prostate cancer			
Surgery[1], (*N*, %)			*p*=0.19
No	32,580 (73.05)	883 (74.77)	
Yes	12,019 (26.95)	298 (25.23)	
Waiting-time, days (mean, SD)[2]	171.10 (189.87)	155.20 (163.22)	*p=0.15*
Lung cancer			
Surgery[3], (*N*, %)			*p<0.01*
No	12,145 (89.06)	343 (80.52)	
Yes	1,492 (10.94)	83 (19.48)	
Waiting-time, days (mean, SD)	99.79 (103.73)	112.59 (155.42)	*p=0.29*
Colorectal cancer			
Surgery[4], (*N*, %)			*p<0.05*
No	17,507 (73.71)	542 (68.78)	
Yes	6,245 (26.29)	246 (31.22)	
Waiting-time, days (mean, SD)	55.90 (138.43)	62.79 (168.37)	*p=0.45*

[1] According to Swedish Classification of care measures (KVA), prostatectomy was included as the surgical treatment for prostate cancer (KVA: KEC00, KEC01, KEC10, KEC20).
[2] SD: Standard division.
[3] According to Swedish Classification of care measures (KVA), following surgical treatments for lung cancer were included: lung resection (KVA: GDB10, GDB11, GDB20, GDB21), lobectomy of lung (KVA: GDC00-GDC97), and pulmonectomy (KVA: GDD00-GDD97).
[4] According to Swedish Classification of care measures (KVA), following surgical treatments for colorectal cancer were included: resection of right-sided semicolon (KVA: JFB30, JFB31), transverse colon (KVA: JFB40, JFB41), left semicolon (KVA: JFB43, JFB44), sigmoid colon (KVA: JFB46, JFB47), other part of colon (KVA: JFB50, JFB51), and colon with rectum (KVA: JFB53, JFB54, JFB60, JFB61, JFB63, JFB64).

5.2 Stress-related mental disorders around cancer diagnosis and hospital admission after cancer diagnosis

A total of 4,105 patients (1.88%) had a diagnosis of stress-related mental disorders and 3,594 (1.64%) had a diagnosis of other mental disorders, during 90 days before to 90 days after cancer diagnosis.

Compared to the cancer patients without any mental disorder during 90 days before to 90 days after cancer diagnosis, patients exposed to stress-related mental disorders experienced 35% increased rate of any hospital admission; whereas patients with other mental disorders had 7% increased rate (Table 7). Both associations were more pronounced for hospitalizations of long duration (>10 days). Among the three common hospital admissions, the strongest association by stress-related mental disorders was noticed for hospitalizations due to external injuries (unintentional injuries HR=1.85, 95%CI: 1.62 - 2.12; intentional injuries HR=6.64, 95%CI: 1.09 - 40.31), followed by infections, and cardiovascular diseases. For other mental disorders, an increased rate was only noted for external injury- and infection-related hospitalizations.

Table 7. Associations of mental disorders with rate of hospital admission

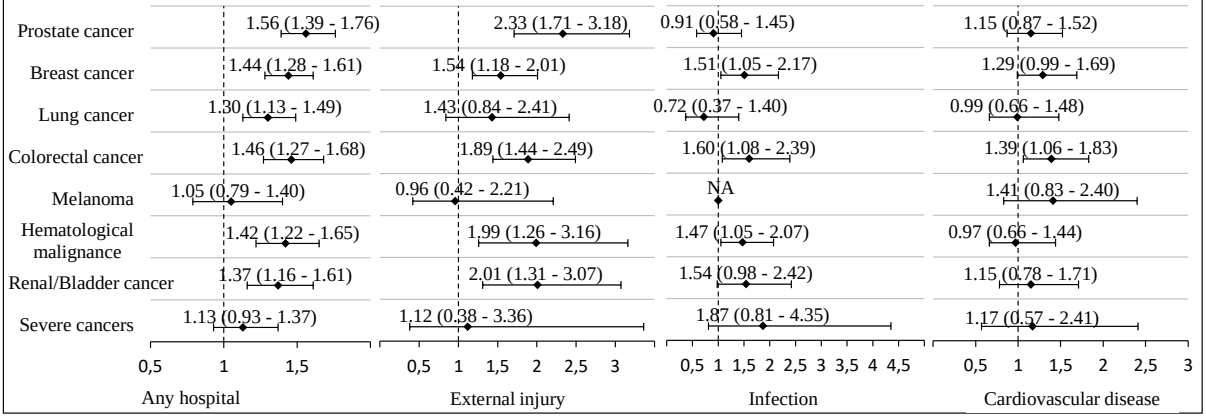
	Stress-related mental disorders; HR (95% CI)[1]	Other mental disorders; HR (95% CI)
Any hospital admission	1.35 (1.28 - 1.41)	1.07 (1.01 - 1.13)
Main discharge diagnosis		
Injury	1.89 (1.67 - 2.14)	1.36 (1.20 - 1.55)
Infection	1.28 (1.08 - 1.52)	1.19 (1.00 - 1.42)
Cardiovascular disease	1.16 (1.03 - 1.30)	0.91 (0.80 - 1.03)
Duration of admission		
<4 days	1.25 (1.18 - 1.33)	1.01 (0.93 - 1.10)
4-10 days	1.32 (1.25 - 1.40)	1.04 (0.98 - 1.10)
>10 days	1.63 (1.53 - 1.73)	1.24 (1.15 - 1.33)

[1] HR: Hazard ratio; CI: Confident interval.

A diagnosis of stress-related mental disorders around cancer diagnosis was associated with an increased rate of hospital admission among almost all cancer patients except for patients with

melanoma and severe cancers (Figure 1). Increased rate of hospital admission due to external injuries was found among almost all cancer patients except for patients with lung, melanoma and severe cancers. Among patients of breast, colorectal, and hematological cancers, an increased rate of hospital admission for infections was observed, whereas only patients with colorectal cancer was noted to have an increased rate of hospital admission for cardiovascular diseases.

Figure 1. Associations of stress-related mental disorders with hospital admission, by cancer types



Cancer patients with a diagnosis of stress-related mental disorders around cancer diagnosis had on average a greater number of hospital admissions during follow-up (mean: 2.83; standard deviation: 3.91) compared to patients with other mental disorders (mean: 2.01; SD: 2.85). In the stratified analysis, we found similar results for all patients, regardless of sex, age, calendar period, educational level, previous mental disorders, or cancer stage (Table 8).

Table 8. Median times of hospital admission, and associations of stress-related mental disorders with rate of hospital admission, stratified analyses.			
	No mental disorders	**Stress-related mental disorders**	
	Median times of hospital admission (interquartile range)	**Median times of hospital admission (interquartile range)**	**HR (95% CI)[1]**
Sex			
Male	1 (0-3)	2 (1-4)	1.42 (1.32 - 1.52)
Female	1 (0-3)	1 (0-4)	1.28 (1.20 - 1.37)
Age at diagnosis, years			
≤65	1 (0-2)	2 (0-4)	1.36 (1.27 - 1.45)
66-75	1 (0-3)	2 (1-4)	1.36 (1.25 - 1.49)
>75	1 (0-3)	2 (0-3)	1.21 (1.11 - 1.31)
Calendar period at diagnosis			
2004-2006	2 (0-3)	2 (1-4)	1.34 (1.25 - 1.44)
2007-2009	1 (0-2)	1 (0-3)	1.36 (1.28 - 1.45)
Educational level			
>9 years	1 (0-3)	2 (0-4)	1.34 (1.26 - 1.43)
≤9 years	1 (0-3)	2 (0-4)	1.36 (1.27 - 1.46)
Previous mental disorders			
No	1 (0-3)	1 (0-3)	1.32 (1.24 - 1.41)
Yes	1 (0-3)	2 (1-4)	1.34 (1.25 - 1.43)
Previous cardiovascular diseases			
No	1 (0-3)	2 (0-4)	1.35 (1.28 - 1.43)
Yes	1 (0-3)	2 (1-4)	1.38 (1.27 - 1.50)
Cancer stage[2]			
Localized	1 (0-2)	1 (0-3)	1.48 (1.37 - 1.60)
Local spread	1 (0-3)	2 (0-4)	1.27 (1.12 - 1.43)
Regional spread	2 (1-3)	2 (1-4)	1.23 (1.12 - 1.37)
Advanced	2 (1-3)	2 (1-4)	1.08 (0.95 - 1.22)
Unknown	1 (0-3)	2 (0-4)	1.42 (1.27 - 1.60)

[1] HR: Hazard ratio; CI: Confident interval.
[2] Patients with missing or unclear information of TNM/FIGO were classified as 'Unknown'.

In the additional analysis further adjusting for surgery, we found similar increased rate of hospital admission by stress-related mental disorders among patients with prostate cancer (HR=1.56, 95%CI: 1.39-1.75), lung cancer (HR=1.32, 95%CI: 1.15-1.51), and colorectal cancer (HR=1.46, 95%CI: 1.27-1.69).

5.3 Beta-blocking agents and severe cardiovascular events after cancer diagnosis

During the 90 days before cancer diagnosis, 64,072 patients used beta-blockers. Cancer patients treated with beta-blockers tended to be older, have lower educational level, and have more comorbidities, compared to patients without beta-blockers (Table 9).

Table 9. Association of beta-blocker use during the 90 days before cancer diagnosis with the risk of severe cardiovascular events during the 90 days after cancer diagnosis			
	Unexposed (N=341,350), %	**Exposed[1] (N=64,072), %**	**HR (95%CI)[2]**
Sex			
Male	51.70	56.47	1.15 (1.05-1.26)
Female	48.30	43.53	1.25 (1.12-1.40)
Age at diagnosis, years			
≤65	45.64	23.74	1.40 (1.17-1.68)
66-75	29.27	35.69	1.24 (1.09-1.41)
>75	25.10	40.57	1.12 (1.02-1.23)
Calendar period at diagnosis			
2006-2007	23.82	23.20	1.21 (1.04-1.40)
2008-2009	24.66	24.77	1.13 (0.98-1.30)
2010-2011	25.66	25.28	1.13 (0.98-1.30)
2012-2013	25.87	26.75	1.01 (0.84-1.21)
Educational level			
Post-secondary school	24.75	17.04	1.01 (0.84-1.21)
Secondary school	39.92	37.48	1.28 (1.13-1.44)
≤9 years	34.16	44.48	1.22 (1.10-1.35)
Missing	1.17	1.00	NA
Cancer stage[3]			
Localized	51.23	48.32	1.12 (0.99-1.26)
Local spread	12.27	14.30	1.24 (1.03-1.49)
Regional spread	11.86	11.08	1.24 (1.03-1.50)
Advanced	11.26	12.42	1.20 (1.00-1.43)
Unknown	13.39	13.88	1.23 (1.04-1.46)
Chronic Disease Score			
0	34.20	2.05	2.26 (1.74-2.93)
1-2	36.12	26.44	1.39 (1.17-1.63)
3-5	24.44	54.60	1.10 (1.00-1.21)
≥6	5.24	16.91	1.11 (0.96-1.28)
History of beta-blocking agents			
No	86.48	5.52	2.49 (2.18-2.84)
Yes	13.52	94.48	0.98 (0.91-1.06)
History of cardiovascular diseases			
No	71.63	31.71	1.44 (1.24-1.67)
Yes	28.37	68.29	1.13 (1.04-1.22)
History of mental disorders			
No	78.86	80.60	1.19 (1.11-1.29)
Yes	21.14	19.40	1.16 (0.93-1.45)

[1] Cancer patients with a treatment period of beta-blockers that overlapped with the 90 days' time-period before cancer diagnosis.
[2] HR: Hazard ratio; CI: Confident interval.
[3] Patients with missing or unclear information of TNM/FIGO were classified as 'Unknown'.

A stronger association was found between beta-blocker use during the 90 days before cancer diagnosis and severe cardiovascular events during the 90 days after cancer diagnosis, among patients with low chronic disease score, and patients without a history of beta-blocker use or cardiovascular disease (Table 9). Sex, age, calendar period, educational level, cancer stage, and history of mental disorders were not found to greatly modify the association.

Overall, cancer patients exposed to beta-blocker treatment during the 90 days before cancer diagnosis experienced 19% increased rate of severe cardiovascular events, compared to patients without such exposure (Table 10). The association was mainly attributable to non-fatal event, and was null for fatal event. In the analysis for specific diagnosis of severe cardiovascular events, patients with beta-blockers only had an increased rate for myocardial infarction, but not for other events. From 90 days after cancer diagnosis onward, a null result was noticed for the association between beta-blocker treatment and severe cardiovascular event, either overall or for fatal, non-fatal, or specific event separately (Table 10).

Table 10. Association of beta-blockers used during the 90 days before cancer diagnosis with the risk of severe cardiovascular events after cancer diagnosis, a population-based cohort study in Sweden 2006-2013

	Overall	**0-90 days after cancer diagnosis**	**>90 days after cancer diagnosis**
Severe cardiovascular events	1.03 (1.00-1.06)	1.19 (1.11-1.28)	1.00 (0.97-1.03)
Fatal or non-fatal events			
Fatal	0.97 (0.91-1.02)	1.08 (0.92-1.29)	0.95 (0.90-1.01)
Non-fatal	1.04 (1.01-1.07)	1.21 (1.12-1.31)	1.01 (0.98-1.05)
Specific diagnosis			
Myocardial infarction	1.00 (0.95-1.05)	1.22 (1.07-1.40)	0.97 (0.92-1.03)
Hypertension / aortic rupture	1.00 (0.90-1.11)	1.21 (0.88-1.67)	0.98 (0.88-1.09)
Stroke	0.98 (0.92-1.05)	1.02 (0.84-1.23)	0.98 (0.91-1.05)
Embolism	0.92 (0.85-1.00)	1.01 (0.84-1.22)	0.91 (0.83-1.00)
Heart failure / Arrhythmia	0.97 (0.91-1.03)	1.15 (0.96-1.37)	0.95 (0.89-1.01)

During the 90 days after cancer diagnosis, no increased rate of fatal events was noticed in relation to beta-blocker use during the 90 days before cancer diagnosis for any specific cancer. A positive association was noted between beta-blocker use and non-fatal cardiovascular events during the 90 days after cancer diagnosis among patients with lung cancer, colorectal cancer, and melanoma. Beyond 90 days after cancer diagnosis, no association was found for fatal or non-fatal event (Table 11).

Table 11. Association of beta-blockers used during the 90 days before cancer diagnosis with the risk of severe cardiovascular events after cancer diagnosis, by cancer type

	Within 90 days after cancer diagnosis		Beyond 90 days after cancer diagnosis	
	Fatal events	**Non-fatal events**	**Fatal events**	**Non-fatal events**
Cancer type				
Prostate cancer	1.46 (0.86-2.47)	1.07 (0.87-1.30)	0.97 (0.86-1.09)	1.00 (0.93-1.07)
Breast cancer	1.69 (0.78-3.63)	1.29 (0.94-1.76)	0.89 (0.74-1.07)	1.05 (0.95-1.17)
Lung cancer	1.47 (0.93-2.31)	1.37 (1.10-1.71)	1.01 (0.76-1.34)	1.12 (0.97-1.31)
Colorectal caner	0.80 (0.52-1.23)	1.35 (1.11-1.64)	0.89 (0.76-1.04)	0.92 (0.84-1.01)
Melanoma	2.60 (0.78-8.72)	1.72 (1.01-2.95)	0.95 (0.72-1.26)	1.04 (0.88-1.24)
Urinary/Bladder cancer	1.20 (0.71-2.03)	1.07 (0.84-1.36)	0.95 (0.80-1.13)	1.00 (0.89-1.11)
Severe cancers	0.71 (0.33-1.50)	0.74 (0.48-1.13)	0.71 (0.41-1.23)	1.24 (0.89-1.74)

No statistically significant association was found between beta-blockers and fatal cardiovascular events during the 90 days after cancer diagnosis, regardless of receptor activity, recommended daily dose, and recentness of use to cancer diagnosis (Table 12). Beyond 90 days after cancer diagnosis, a lower rate of fatal events was noted for the use of both non-selective and selective beta-blockers. Beta-blockers with low daily dose were also associated with a slightly decreased rate of fatal events more than 90 days after cancer diagnosis.

Table 12. Association of beta-blockers used during the 90 days before cancer diagnosis with the risk of severe cardiovascular events after cancer diagnosis, by subgroup of beta-blockers.

	Within 90 days after cancer diagnosis		Beyond 90 days after cancer diagnosis	
	Fatal events	**Non-fatal events**	**Fatal events**	**Non-fatal events**
Receptor activity				
Non-selective	0.74 (0.47-1.17)	1.06 (0.88-1.27)	0.86 (0.76-0.98)	1.12 (1.04-1.20)
Selective	1.07 (0.90-1.28)	1.21 (1.11-1.31)	0.91 (0.86-0.97)	1.00 (0.96-1.03)
Alpha and Beta	1.56 (0.92-2.64)	1.59 (1.23-2.06)	1.86 (1.55-2.22)	1.18 (1.04-1.33)
Combination with calcium channel blockers	1.20 (0.53-2.73)	0.97 (0.61-1.53)	1.12 (0.83-1.51)	1.00 (0.84-1.18)
Recommended daily dose				
High	1.16 (0.96-1.40)	1.25 (1.15-1.37)	1.03 (0.96-1.09)	1.05 (1.01-1.09)
Low	1.00 (0.82-1.22)	1.16 (1.06-1.28)	0.87 (0.82-0.93)	0.98 (0.94-1.02)
Recentness of use to cancer diagnosis				
Current	1.07 (0.90-1.27)	1.20 (1.11-1.30)	0.95 (0.90-1.01)	1.01 (0.98-1.05)
Recent	1.60 (0.89-2.86)	1.68 (1.27-2.22)	1.15 (0.91-1.46)	1.09 (0.94-1.27)

Increased rate for severe cardiovascular events both within the 90 days after cancer diagnosis and thereafter was noticed by use of diuretics and agents acting on the renin-angiotensin system, but not calcium channel blockers, during the 90 days before cancer diagnosis (Table 13). A slightly decreased rate of fatal events was found for calcium channel blockers during the entire follow-up (HR: 0.92, 95%CI: 0.88-0.97).

Table 13. Association of other antihypertensive drugs used during the 90 days before cancer diagnosis with the risk of severe cardiovascular events after cancer diagnosis, by time since cancer diagnosis

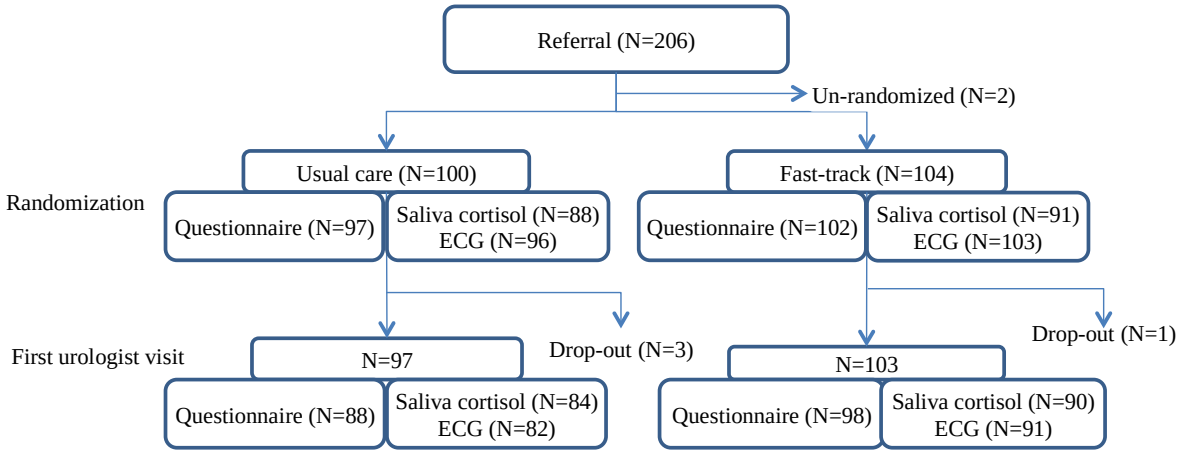
	All events[1]	Fatal or non-fatal events	
		Fatal	Non-fatal
Diuretics[2]			
Overall	1.21 (1.19-1.24)	1.39 (1.33-1.44)	1.20 (1.18-1.23)
0-90 days	1.33 (1.27-1.41)	1.30 (1.14-1.47)	1.35 (1.27-1.43)
>90 days	1.19 (1.16-1.22)	1.39 (1.34-1.45)	1.18 (1.15-1.22)
Calcium channel blockers[3]			
Overall	1.03 (1.00-1.05)	0.92 (0.88-0.97)	1.06 (1.03-1.08)
0-90 days	1.00 (0.94-1.06)	0.88 (0.76-1.03)	1.03 (0.96-1.10)
>90 days	1.03 (1.00-1.06)	0.93 (0.89-0.98)	1.06 (1.03-1.09)
Agents acting on the renin-angiotensin system[4]			
Overall	1.13 (1.11-1.16)	1.08 (1.04-1.12)	1.17 (1.14-1.20)
0-90 days	1.14 (1.08-1.20)	1.10 (0.97-1.24)	1.18 (1.11-1.25)
>90 days	1.12 (1.10-1.15)	1.08 (1.04-1.12)	1.16 (1.13-1.19)

[1] Severe cardiovascular events, including death due to cardiovascular diseases and hospital admissions with cardiovascular diseases as the primary discharge diagnosis.
[2] Diuretics (ATC: C03).
[3] Calcium channel blockers (ATC: C08).
[4] Agents acting on the renin-angiotensin system (ATC: C09).

5.4 Fast-track clinical workup for men with suspected prostate cancer

Among 206 men who came to the Urology Department at Örebro University Hospital with suspected prostate cancer, 204 were eligible and randomized. One man in the intervention group and three men in the control group dropped out between the two visits. A total of 102 of the 104 patients in the intervention group and 97 of the 100 patients in the control group answered questionnaires at randomization. A total of 98 of the 103 and 88 of the 97 patients in the two groups returned questionnaires at the urologist visit. Saliva samples were collected for 87.5% and 88.0% of the patients at randomization, and 87.4% and 86.6% at urologist visit, from the intervention and control groups, respectively. Almost all men were measured for ECG at randomization (99.0% in the intervention group and 96.0% in the control group), and 88.3% and 84.5% at urologist visit (Figure 2). The present study focused on patients who returned questionnaires at both randomization and first urologist visit, including 97 patients from the intervention group and 88 patients from the control group (Figure 2).

Figure 2. Enrollment of randomized clinical trial for men with suspected prostate cancer, from randomization to first urologist visit.



Men in the fast-track group experienced a shorter waiting-time to the urologist visit (mean=11 days) than men in the usual care group (mean=51 days, p for difference <0.01, Table 14). Patients of the intervention and control groups had similar characteristics, including age, pension rate, PSA level, IPSS score, Charlson comorbidity index, educational level, living area, civil status, smoking status, social support level, and previous anxiolytics/antidepressants use (all p>0.05, Table 14). The proportions of missing data were similar between the two groups (p>0.05, Table 14).

Table 14. Baseline characteristics and waiting-time for men with suspected prostate cancer (N=185) that were randomized to the usual workup and fast-track workup groups

	Usual Workup (N=88)		**Fast-track Workup (N=97)**		
Variables	**N(Missing)**	**Mean(SD)**	**N(Missing)**	**Mean(SD)**	***P***
Age, years	87(1)	67.6(9.59)	97(0)	66.74(7.56)	*0.51*[1]
Charlson comorbidity score	88(0)	2.86(1.38)	97(0)	2.78(1.39)	*0.69*[1]
PSA level, ng/mL	86(2)	8.58(9.31)	97(0)	6.45(4.33)	*0.24*[2]
IPSS_symptom	87(1)	13.84(7.81)	94(3)	12.9(7.93)	*0.43*[1]
IPSS_QOL	87(1)	2.45(1.52)	94(3)	2.47(1.56)	*0.93*[1]
Waiting-time, days	88(0)	51.35(46.64)	97(0)	11.24(6.53)	*<0.01*[2]
	Total N (Missing)	**N(%)**	**Total N (Missing)**	**N(%)**	***P***
University education	87(1)	28(32.18)	95(2)	31(32.63)	*0.98*[3]
Co-habitation	88(0)	77(87.5)	97(0)	87(89.69)	*0.64*[3]
Living in urban areas	88(0)	53(60.23)	97(0)	44(45.36)	*0.06*[3]
Pensioners	87(1)	59(67.82)	97(0)	63(64.95)	*0.60*[3]
Cigarette smoking	86(2)		91(6)		
Never		39(45.35)		49(53.85)	*0.31*
Former		39(45.35)		38(41.76)	
Current		8(9.3)		4(4.4)	
Snuff use	86(2)		90(7)		
Never		54(62.79)		60(66.67)	*0.65*

Former		18(20.93)		14(15.56)	
Current		14(16.28)		16(17.78)	
Use of antidepressants in the past month	81(7)	3(3.7)	95(2)	6(6.32)	*0.51*[3]
Use of anxiolytics in the past month	81(7)	1(1.23)	95(2)	7(7.37)	*0.07*[3]
Social support from partner	81(7)		86(11)		
High		53(65.43)		61(70.93)	*0.25*[3]
Moderate		10(12.35)		14(16.28)	
Low		18(22.22)		11(12.79)	
Social support from others	84(4)		87(10)		
High		14(16.67)		21(24.14)	*0.45*[3]
Moderate		12(14.29)		13(14.94)	
Low		58(69.05)		53(60.92)	

Abbreviation: N, number; SD, standard deviation; PSA, prostate specific antigen; IPSS, international prostate symptom score; QOL, quality of life.
[1] P-values based on T-test.
[2] P-values based on Wilcoxon rank sum test.
[3] P-values based on Chi-square test or Fisher's exact test when expected cell counts less than 5.

At both randomization and first urologist visit, no clear difference was noticed for self-reported distress, HADS depression score, anxiety score, sleep quality, and sleep apnea between the intervention and control groups (all $p>0.05$). However, the fast-track group reported a lower self-rated sleep quality score at first urologist visit (2.13 VS 2.49, $p<0.05$) than usual care group. From randomization to first urologist visit, a smaller increase in the self-rated sleep quality score was found for the fast-track group than the usual care group (p for difference <0.05). A difference was also noticed for the change of HADS depression score from randomization to first urologist visit (p for difference <0.05), i.e., the HADS depression score showed a small increase in the control group (1.41%) whereas a small decrease in the intervention group (-4.71%, Table 15).

Compared with the usual care group, patients in the fast-track group did no show different heart rate, HRV, or SDRR at either randomization or first urologist visit ($p>0.05$). No difference was found for the change of either HRV and SDRR from randomization to first urologist visit between these two groups ($p>0.05$). The saliva cortisol level in both the intervention and control groups showed a diurnal rhythm with peaking levels in the morning and the lowest levels in the evening (Table 15). However, no clear difference was noted for changes in slope, AUC_G, or AUC_I between the two groups ($p>0.05$).

Table 15. Changes in self-reported indicators of stress, heart rate variation, and saliva cortisol from randomization to first urologist visit among 185 men (88 in the usual care and 97 in the fast-track workup groups)

	Randomization (Mean (SD))		P^2	First urologist visit (Mean (SD))		P^2	Percent change		P^3	$P^{3,4}$
	Usual Care	Fast Track		Usual Care	Fast Track		Usual Care	Fast Track		
Distress (NCCN)[1]	1.83(0.64)	1.91(0.63)	0.38	1.94(0.63)	1.96(0.59)	0.85	10.37	7.21	0.47	0.53
HADS[1]										
Anxiety	2.24(0.77)	2.13(0.77)	0.37	2.18(0.77)	2.09(0.77)	0.41	-2.98	-2.05	0.76	0.36
Depression	1.99(0.65)	1.97(0.67)	0.83	2.00(0.65)	1.85(0.71)	0.14	1.41	-4.71	0.06	0.03
Sleep										
Sleep quality index[1]	1.43(0.22)	1.37(0.24)	0.08	1.43(0.20)	1.38(0.22)	0.14	-0.36	0.90	0.50	0.69
Sleep apnea index[1]	1.33(0.30)	1.29(0.25)	0.28	1.25(0.26)	1.22(0.21)	0.38	-3.37	-4.05	0.75	0.70
Self-rated quality score	2.20(0.84)	2.12(0.99)	0.56	2.49(1.07)	2.13(0.97)	0.02	19.23	4.31	0.01	0.008
ECG										
Heart rate	74(11)	74(12)	0.84	75(13)	77(14)	0.34	1.71	4.70	0.10	0.04
HRV[5]	1.30(0.45)	1.45(0.61)	0.06	1.33(0.53)	1.50(0.66)	0.06	6.17	10.14	0.51	0.77
SDRR[5]	3.07(0.59)	3.25(0.75)	0.07	3.08(0.75)	3.28(0.84)	0.10	2.28	2.91	0.86	0.71
Saliva cortisol										
Slope[6]	-0.013(-0.097-0.072)	-0.024(-0.119-0.070)	0.75	-0.014(-0.107 - 0.078)	-0.028(-0.126 - 0.069)	0.66	-8.34	-22.53	0.60	0.94
AUC_G[7]	1.30(0.75)	1.33(0.76)	0.76	1.26(0.77)	1.34(0.77)	0.51	-2.26	0.93	0.72	0.75
AUC_I[8]	-3.01(0.17)	-3.01(0.17)	0.88	-2.99(0.17)	-3.00(0.16)	0.61	0.68	0.40	0.78	0.55

Abbreviations: SD, standard deviation; NCCN, National Comprehensive Cancer Network; HADS: Hospital Anxiety and Depression Scale; ECG, electrocardiogram; HRV, heart rate variation; SDRR, standard deviation of R-R intervals; AUC_G, Area under the curve with respect to ground; AUC_I, Area under the curve with respect to increase.

[1] Square root [$\sqrt{(x+1)}$] transformed.

[2] P values based on T-test.

[3] P values based comparison between fast-track group and usual care group using generalized linear model.

[4] Model adjusted for age, PSA levels (log- transformed), Charlson comorbidity score, educational level, cohabitation status, living area, cigarette smoking, and snuff use.

[5] Natural log (x+1) transformed.

[6] Linear regression was performed on the three measures of cortisol levels within the day for each individual. The slope presented is the mean of parameter coefficient (and 95%CI) of the variable indicating time point (i.e., morning, noon, and night).

[7] ln (x) transformed, presented in mean (SD).

[8] -ln (-x+20) transformed, presented in mean (SD).

6 DISCUSSION

6.1 General discussion

6.1.1 Severe stress response to cancer diagnosis and its related health consequences

In study I, we used the diagnosis of stress-related mental disorders as the indicator of severe stress response to a cancer diagnosis, and investigated its impact on the cancer-specific mortality. We found that a first-onset stress-related mental disorder after cancer diagnosis was associated with increased cancer-specific mortality. The increased cancer-specific mortality was noted for all tested cancer sites. Our findings support the hypothesis that mental morbidities affect the survival prospects of patients with cancer. Our findings were supported by previous studies where mental disorders were shown to be associated with overall or cancer-specific mortality [100-103]. In this study, we found that the association of stress-related mental disorders with cancer-specific mortality was specifically pronounced among cancer patients that had no history of previous mental disorders. The first-onset stress-related mental disorders diagnosed after cancer diagnosis might therefore capture the severe stress reaction following the diagnosis and while living with cancer.

From study II, we found that a diagnosis of stress-related mental disorders shortly before and after cancer diagnosis increased the rate of hospital admission after cancer diagnosis. An increased rate was noted for both any hospitalization and hospitalizations due to specific reasons including external injury, infection, and cardiovascular disease. An increased rate was noted for all major cancer types, except for melanoma and esophageal, liver and pancreatic cancers. Slightly increased rate of hospitalization was also noticed due to other mental disorders, which might suggest an increased inpatient care use among individuals with impaired mental health in general. However, the magnitude of rate increase was greater among cancer patients with stress-related mental disorders, compared to other mental disorders.

Psychological stress can foster many health consequences in general, through the effects of stress hormones and neurotransmitters on disease processes and immune responses. The persistent activation of the HPA axis in the chronic stress response probably impairs the immune responses and contributes to tumor progression and survival [104]. From

experimental studies, the influence of adrenergic and glucocorticoid pathways on tumor progression has been noticed from both animal model [105] and human study [106]. In an animal model with implanted osteosarcomas and pancreatic adenocarcinomas, tumor was found to grow significantly faster in mice with disruption of circadian cortisol rhythms than others [107]. Loss of normal cortisol circadian, a similar change as observed in depression patients, was also noticed to increase mortality in lung [108] and metastatic breast cancer patients [109].

In line with previous findings that cancer patients had increased risks for self-harm and accidental death, especially shortly after diagnosis [110, 111], we found that stress-related mental disorders were associated with an increased rate hospitalization for external injuries among patients of all cancer types, except for melanoma. The underlying mechanisms for the increased risk of external injury after severe stress are not clear yet. However, mental distress [112] and worsening social and physical function secondary to cancer diagnosis might be an explanation. The occurrence of stress-related mental disorders could lead to cognitive impact and psychiatric symptoms which might contribute to the occurrence of intentional and unintentional injuries [113].

The increased rate of hospitalization due to infections after a clinical diagnosis of stress-related mental disorders was biologically plausible. Psychological stress in relation to caring for a demented relative for example was previously noticed to be associated with delayed wound healing [114]. Increased risk for wound infection was also found in animals suffering from restraint stress [115]. The potential mechanistic links between stress and infection have been better investigated. In previous studies, psychological stress was associated with impeded immune responses to infectious challenges, and might as a consequence lead to increased risk for contagion and prolonged infection episodes [116-118]. Further, depression and anxiety was noticed to directly affect the immune system and subsequently regulate the response to infections, by for example regulating the secretion of pro-inflammatory cytokines [119].

The finding that stress-related mental disorders were associated with increased rate of hospitalization due to cardiovascular diseases was also in line with previous studies. Various stress-related mental disorders, including depression [52, 120] and anxiety [121, 122], have

been related to increased risk of coronary artery disease and stroke. Interestingly, increased cardiovascular disease-related hospitalization was only found in relation to stress-related mental disorders, but not other mental disorders, in this study. This finding can further highlight the fact that it might be the severe stress response to the cancer diagnosis, instead of the impaired mental health in general, which led to increased risk of cardiovascular diseases among cancer patients.

6.1.2 Role of beta-blocking agents on modulating stress response

From study III, we found that treatment with cardio-protective beta-blocking agents within 90 days before and at the time of cancer diagnosis was not associated with reduced risk of severe cardiovascular events overall, during the first 90 days after cancer diagnosis. Previous studies have shown that cancer patients are at increased risk for cardiovascular events and mortality immediately after their cancer diagnosis, which might be attributable to the severe psychological stress in relation to the cancer diagnosis [15, 17, 33, 34]. However, cancer patients treated with beta-blockers within 90 days before or at the time of cancer diagnosis were not found to have decreased risk of severe cardiovascular events compared to other cancer patients. In fact, we observed an increased risk of non-fatal cardiovascular events, particularly among new users of beta-blockers (i.e., individuals without a previous history of beta-blocker use before cancer diagnosis). Patients with beta-blockers had however similar risk of fatal cardiovascular events after cancer diagnosis, compared to patients without beta-blocker use.

Previous clinical studies have shown that beta-blockers, as a class, are effective in reducing mortality among patients with severe cardiovascular diseases, including congenital long QT interval syndrome [123], cardiac arrest [124], and ventricular tachycardia [59, 125]. In randomized, placebo-controlled trials, consistent and significant reduction of mortality was also noticed in relation to beta-blocker use, especially among survivors of acute myocardial infarction [60, 126-128]. The fact that cancer patients that used beta-blockers shortly before cancer diagnosis had increased risk of non-fatal cardiovascular events, but similar risk of fatal cardiovascular events as patients not using beta-blockers might suggest that beta-blockers are specifically useful in preventing cardiovascular mortality immediately after cancer diagnosis.

The potentially protective role of beta-blockers in preventing fatal cardiovascular events in relation to the experience of severe psychological stress is biologically plausible. Such biological plausibility might include both the generic cardio-protective and the anti-stress properties of the drug. Beta-blocking agents, as a group, have been associated with attenuated cardiac stimulation induced by the sympathetic nervous system and ventricular arrhythmia [129]. By blocking the beta-adrenergic receptors [130], beta-blockers can reduce the effect of catecholamines that increase myocardial oxygen consumption, and decrease oxygen requirements of the myocardium by reducing heart rate, systemic arterial pressure, and myocardial contractility both at rest and during exercise [131, 132]. Beta-blockers favorably affect the biological properties of the dilated cardiomyopathy, by improving intrinsic systolic function and increasing diastolic perfusion time [133] to augment or maintain overall coronary blood flow. By raising the threshold of ventricular-fibrillation in the ischemic myocardium [129], beta-blockers have been found to reduce the occurrence of ventricular fibrillation and risk of cardiac arrest during the acute phase of myocardial infarction [134, 135].

6.1.3 Fast-track diagnostic workup and psychological stress among men with suspected prostate cancer

Study IV was the first report for a randomized clinical trial, and showed the results between the first hospital contact (i.e., randomization) to the first urologist visit among patients undergoing a diagnostic workup for prostate cancer. Our findings from this study did not indicate a coherent pattern with regard to differences in self-reported indicators and physiological measurement of stress, including anxiety, depression, distress, sleep quality, sleep apnea, heart rate variability, and the diurnal cortisol slope. However, statistically significant changes from randomization to first urologist visit were noticed in depression symptoms and the self-rated sleep quality score, indicating a benefit of the fast-track workup intervention.

In earlier observational studies, psychological stress has been noticed to peak before receiving the final cancer diagnosis, which may be equal to or even greater than the stress experienced after cancer diagnosis [27, 37, 136]. However, few studies had compared the

physiological effect of different waiting-times during a prostate diagnostic workup. Our findings clearly show the feasibility of a clinical intervention with fast-track diagnostic workup for prostate cancer. In this study, almost all men that agreed to participate were randomized and only a few dropped out between randomization and the first urologist visit. The study further shows how diagnostic workup for prostate cancer can be effectively managed to reduce the ordinary waiting-time for urologist visit by an average of 40 days.

We did not find significant differences of the changes in heart rate variability and diurnal cortisol from randomization to the first urologist visit, comparing men in the fast-track workup group with men in the usual care group. It is possible that these physiological measurements are better in detecting severe or chronic emotional stress [137, 138]. Previous neurobiological evidence suggests that heart rate variability is influenced by stress, and is a potential assessment of psychological health and stress [138]. However, the sensitivity of heart rate variability is influenced by variation of the measurements, including varying duration of assessment and the use of time- and frequency-domain analysis [138]. Similarly, for cortisol, the correlation between short-term salivary cortisol excretion and self-reported psychological stress varies in earlier studies. Flattening of the diurnal cortisol slope, indicating a slower rate of decline in cortisol across the day, has been related to both chronic and acute psychosocial stress [139]. However, weak correlations between short-term salivary cortisol and self-reported stress has been shown both in adults [140] and children [141]. In individuals with low levels of stress, saliva cortisol has further been found to have a low intra-individual stability [142]. A longer follow-up of the present trial with more participants is there needed to explore the differences further.

6.2 Strength and limitations

6.2.1 Strength

The major strength of studies I, II, and III is the large-scale population-based cohort design, the prospectively and independently collected data on exposure and outcome, and the complete follow-up. In studies I, II, and III, we included all eligible cancer patients diagnosed during specific periods in Sweden, using a nationwide cohort study design. Information on exposure and outcome was obtained from Swedish national health registers that have been

evaluated as both complete and accurate in general. In studies I and II, we obtained the information on stress-related mental disorders, cancer mortality, and hospital admission from the Patient [77] and Cancer Registers [76]. The information of beta-blocking agent treatment and severe cardiovascular events was extracted from the Prescribed Drug [78] and Patient Registers in study III. Minimal selection and information biases in the ascertainment of exposure and outcome were therefore assured for studies I, II, and III. The major strength of study IV is the randomized study design and the systemic assessments of the dynamic changes in different aspects of the stress response. Using a feasible fast-tack diagnostic workup intervention allowed the comparisons between different waiting-times from first hospital contact to first urologist visit.

6.2.2 Limitations

Bias

In studies I and II, we used stress-related mental disorders as the indicator of severe stress response in relation to a cancer diagnosis. The mental disorders are a group of diseases with an etiology likely including both genetic and non-genetic risk factors. The exposures, first-onset stress-related mental disorders after cancer diagnosis in study I and stress-related mental disorders around cancer diagnosis in study II might therefore potentially reflect the severe psychological reaction to receiving a cancer diagnosis, to living a life with cancer and its treatment, however, it could also be related to other factors independent of the cancer diagnosis-related stress response.

The severe stress response might include various health consequences and symptoms. Studies I and II mainly focused on the clinical diagnosis of stress-related mental disorders, as exposure, which likely captured the most severe cases of mental distress and stress symptom. In that case, patients who had less severe mental distress that did not lead to a clinical diagnosis of stress-related mental disorders would be classified as unexposed.

In the Prescribed Drug Register, only dispensed beta-blocking agents from pharmacies were recorded and used as the exposure of interest, the drugs administrated during hospital admissions were not recorded and therefore missing in the analysis of study III. However, in

study III, we calculated the treatment period for each beta-blocker dispense and defined the cancer patients with a treatment of beta-blockers any time during the 90 days before cancer diagnosis as exposed. Considering that the average length of hospital admission was less than 10 days in Sweden for cancer patients [143], we are confident that we correctly classified the exposure status of the participating cancer patients to a large extent.

In study IV, we only included participants who had completed questionnaires at both randomization and first urologist visit in the analysis. As a result the participants with missing questionnaire at either visit were excluded. The exclusion could be a source of selection bias that may have influenced the estimated associations between the target intervention (i.e., fast-track workup) and the self-reported stress response.

Confounding

Because of the register-based nature of studies I, II, and III, we had little information on potential confounders such as lifestyle factors that might both be related to the exposure and the outcome. In studies I and II, lifestyle factors (e.g. smoking and alcohol use) and social support, for example, could be a residual confounding for the associations studied. However, it is important to note that similar associations were noted for different cancer types, regardless of whether or not they had clear links with these factors (e.g. lung cancer and prostate cancer).

In study III, we also did not have detailed information on lifestyle factors (e.g. dietary factors) and disease severity (e.g. laboratory results, functional status) that might be related to both beta-blocker use and the risk of severe cardiovascular events. As a result, we performed a proxy adjustment with a high-dimensional propensity score, including all known factors potentially related to both exposure and outcome, which is commonly used in observational studies to reduce confounding when benchmarked against randomized trials [88].

Confounding by indication is another concern in study III, which might have led to a potentially underestimated protective effect of beta-blockers on severe cardiovascular events. Cancer patients with beta-blocker treatment have on average a higher risk of cardiovascular disease than other cancer patients, and patients using beta-blockers might further have a

higher risk of severe cardiovascular diseases compared to patients using other antihypertensive drugs (e.g., calcium channel blockers). For instance, beta-blocker treatment has since 2006 been recommended for patients with complicated and severer cardiovascular diseases, including heart failure [144], angina [145], and acute myocardial infarction [146], instead as the first-line agents for hypertension [147].

7 CONCLUSIONS

Cancer patients who were diagnosed with a stress-related mental disorder after cancer diagnosis had an increased cancer-specific mortality compared to cancer patients without a diagnosis of stress-related mental disorder. The increased cancer-specific mortality was mainly attributable to the first-onset stress-related mental disorders after cancer diagnosis. The findings support the hypothesis that mental distress may be strongly associated with the survival prospects of cancer, and motivate further studies on the underlying mechanisms, as well as closer monitoring and treatment of severe stress-related comorbidities in patients newly diagnosed with cancer.

Cancer patients receiving a diagnosis of stress-related mental disorders shortly before or after their cancer diagnosis experienced an increased rate of hospital admission afterwards, compared to cancer patients without such mental disorder. The increased need for hospital admissions among these patients was noticed for all common reasons for inpatient care, including external injury, infection, and cardiovascular disease. In the effort to prevent adverse health outcomes and improve healthcare among cancer patients, the findings suggest the benefit of better psychological management (e.g. surveillance and treatment) during cancer diagnostic workup and immediately after the diagnosis of cancer.

Treatment of beta-blocking agents shortly before and at the time of cancer diagnosis was not associated with a decreased hospital admission due to cardiovascular events or cardiovascular death, neither shortly after cancer diagnosis nor thereafter. The null association between beta-blocker use and fatal cardiovascular events, in clear contrast to the positive association noted for non-fatal events, after cancer diagnosis might suggest a specific protective role of beta-blockers on cardiovascular mortality.

The fast-track diagnostic workup, a clinically feasible intervention, for men with suspected prostate cancer was not associated with most of the measured biomarkers for stress response, including anxiety, distress, heart rate variability, and diurnal cortisol from hospital contact to first urologist visit. However, reduced depression symptom and less sleep problem were found among men of the intervention group compared to men of the usual care group.

8 FUTURE PERSPECTIVES

Cancer patients suffer commonly a severe stress response, related to cancer diagnosis, treatment, and the burden of living with cancer. In the thesis, we discussed the impact of severe stress response to a cancer diagnosis on the aspects of cancer survival and comorbidities. However, the role of stress response to cancer treatment such as surgery, and the impact of changed quality of life after cancer treatment on cancer survival, remains largely unraveled. Further studies should be performed focusing on the time period before and after primary cancer treatment for example.

Although all cancer patients are exposed to the difficulty of expecting or receiving a cancer diagnosis and experience severe psychological stress, only a minority suffers a severe adverse health outcome, suggesting that individual vulnerability and resilience factors are important [148]. Previous genetic studies have found genetic risk for stress-induced disorders such as post-traumatic stress disorders [149]. Genetic studies can therefore be performed to investigate the genetic factors related to the severe adverse health outcomes after a cancer diagnosis specifically.

In this thesis work, we did not find protective effect of beta-blocking agent use on acute cardiovascular events, after receiving a cancer diagnosis. The null result is most likely due to the shortcomings of observational studies, including for example bias by indication. Future clinical interventional studies should be performed where the experiment and the reference groups are identical apart from the use of beta-blockers. Furthermore, more studies are warranted in identifying potential interventions that can help to reduce stress response, decrease stress-related comorbidities, and improve cancer survival should be performed.

In the clinical trial of study IV, we only presented the first report based on the data from first hospital contact to first urologist visit. We will enroll more participants and extend the follow-up until cancer diagnosis, as well as 6 and 12 months after first urologist visit or biopsy. The relation between the fast-track intervention with the stress response during cancer diagnostic workup, cancer characteristics, and cancer survival will therefore be further investigated.

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