Time-dependent risk of depression, anxiety, and stress-related disorders in patients with invasive and in situ breast cancer.

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Novelty and Impact

Patients with invasive breast cancer are at long-term increased risk of developing depression, anxiety and stress-related disorders. Risk of mental disorders was highest shortly after diagnosis, especially among young patients presenting with aggressive tumor characteristics and undergoing chemotherapy.

Patients with in-situ breast cancer only experienced a short-term increased risk of stress-related disorders. The observed time-dependent risk patterns shed light on the need of timely interventions for specific subgroups of invasive breast cancer patients.

List of abbreviations

ICD: International Classification of Diseases

ER: estrogen receptor

CCI: Charlson Comorbidity Index

SIR: standardized incidence ratio

CI: confidence interval

HR: hazard ratio

Abstract

Despite concerns about the mental health of breast cancer patients, little is known regarding the temporal risk pattern and risk factors of common mental disorders among these patients. We estimated standardized incidence ratios (SIRs) of depression, anxiety and stress-related disorders in a Swedish nationwide cohort of 40,849 women with invasive and 4,402 women with in-situ breast cancer (2001-2010, median follow-up = 4.5 years). The impact of patient, tumor and treatment characteristics was analyzed using flexible parametric survival models in a regional cohort of 7,940 invasive breast cancer patients (2001-2013, median follow-up = 7.5 years). Women with invasive breast cancer showed increased rates of depression, anxiety and stress-related disorders [overall SIR (95% CI) = 1.57 (1.46-1.69), 1.55 (1.43-1.68) and 1.77 (1.60-1.95), respectively]. SIRs were highest shortly after diagnosis, but remained increased up to 5 years. Younger age at diagnosis, comorbidity, higher-grade disease, lymph node involvement and chemotherapy were independently associated with the risk of depression and anxiety in invasive cancer patients, with chemotherapy and higher-grade disease conferring short-term risk only, while comorbidities were mainly associated with late-onset events. No clinical risk factors were identified for stress-related disorders except for a greater risk associated with younger age. Patients with in-situ cancer only showed an increased incidence of stress-related disorders during the first six months after diagnosis [SIR (95% CI) = 2.76 (1.31-5.79)]. The time-dependent risk profile of invasive cancer patients may guide health care professionals for timely and targeted psycho-oncologic interventions.

Key words:

Breast cancer; Depression; Anxiety; Stress-related disorders

Introduction

Breast cancer is increasingly prevalent nowadays, and mental disorders caused by the existential threat of the disease and its therapeutic side effects are common in breast cancer [1, 2]. Consequently, more breast cancer patients than before are suffering from mental disorders [3], including mainly depression, anxiety, and stress-related disorders [4]. The burden of these disorders is substantial, as patients with a comorbid mental disorder are not only affected in their psychological well-being, but also experience problems in work performance [5], treatment adherence [6, 7], and overall quality of life [8] .

Despite the considerable impact on long-term health, little is known about the time-dependent risk pattern of depression, anxiety and stress-related disorders in breast cancer patients. Previous studies have mainly focused on depression or anxiety, and were limited by cross-sectional design or short-term follow-up [3, 9-14]. As a result, risks by time since diagnosis have rarely been described. Moreover, few studies have addressed the mental health situation of carcinoma in-situ patients [15-17]. A lower incidence of depression has been reported among patients with in-situ compared to invasive breast cancer [18]. However, whether or not these patients experience similar risks of depression and other mental disorders compared to the general female population is unknown.

Available evidence regarding the impact of patient, tumor and treatment characteristics is also not entirely consistent. Most large-scale studies have reported a strong influence of non-tumor-related factors (e.g. younger age at diagnosis and comorbidity) on the risk of depression and anxiety [3, 9, 10, 19], but the impact of chemotherapy and tumor-related characteristics is less conclusive [19-21]. Part of this inconsistency might be due to the presence of time-dependent effects, which are particularly relevant for tumor and treatment-related factors as their effect may diminish once the diagnosis is set or therapy is completed. Since the efficacy of preventive measures is dependent on early and timely interventions, time-dependent analyses may help to identify subgroups of patients at greatest risk by time since diagnosis.

In the present study, we aimed to assess the risks of depression, anxiety and stress-related disorders in a large nationwide cohort including patients with invasive and in-situ breast cancers. We further aimed to identify high-risk patient groups by doing additional analysis in a regional cohort of invasive breast cancer patients with detailed information on patient, tumor and treatment characteristics, and considering potential time-dependent effects.

Methods

Study populations

We performed a Swedish register-based study including: 1) a nationwide cohort of invasive and in-situ breast cancer patients; and 2) a regional cohort including invasive breast cancer patients in the Stockholm-Gotland area. (Figure 1)

The nationwide cohort was defined based on the Swedish Cancer Register and included all women diagnosed with primary invasive or in-situ breast cancer (N=50,652) at the age of 20-80 years between 2001 and 2009. In Sweden, diagnoses of invasive and in-situ breast cancers are reported by a pathologist according to international rules and the register is considered to have almost 100% completeness [22, 23]. To estimate the relative risks of depression, anxiety and stress-related disorders, the nationwide cohort was compared to the general female population identified from the Swedish national census conducted in 1990 (including 3,545,230 women).

The regional cohort included 9,038 women diagnosed with primary invasive breast cancer (at the age of 20-80 years) between 2001 and 2008 as identified through the Stockholm-Gotland Breast Cancer Register. This quality register on breast cancer has about 99% completeness and provides detailed information on tumor and treatment characteristics and routine follow-up on locoregional recurrences and distant metastases [24].

Follow-up of the nationwide cohort started from the date of breast cancer diagnosis, and ended on the date of the first mental health outcome, death, emigration, a new cancer diagnosis or end of follow-up (December 31st, 2010),whichever came first. Information on death and emigration was obtained through cross-linking the cohort to the Swedish Causes of Death Register and the Swedish Migration Register, using the unique personal identification numbers. Follow-up of the regional cohort was conducted in the same manner as the nationwide cohort, except for an extension of follow-up until December 31st, 2013. Median follow-ups of the nationwide and regional cohorts were 4.5 years (max 10 years) and 7.5 years (max 13 years), respectively (Table 1).

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

Mental health outcomes

All mental health outcomes were identified through the Swedish Patient Register, which has nationwide coverage for inpatient hospitalizations in Sweden since 1987. Since 2001, Swedish counties are also obliged to report hospital-based outpatient physician visits. In Sweden, individuals visiting hospital-based psychiatric clinics following a primary care's doctor referral are interviewed by psychiatrists, who make diagnostic decisions according to the World Health Organization guidelines on mental disorders [25]. All diagnoses were coded according to the Swedish version of the 10th revision of the International Classification of Diseases (ICD-10): depression (F32-F33), anxiety (F40-F41) and stress-related disorders (F43) (eTable 1). For the present analysis, only primary diagnoses based on either an inpatient or outpatient hospital visit were considered. Since we aimed to study new-onset events, patients who had been diagnosed with a mental disorder [ICD-10 (1997-) : F0-F4; ICD-9 (1987-1996) : 290-300, 303-306, and 308-311; and ICD-8 (1969-1986) : 290-300, 303-305, 307, and 309] prior to the breast cancer diagnosis were excluded from the cohort, leaving 40,849 patients with invasive and 4,402 patients with in-situ cancer in the nationwide cohort, and 7,940 patients with invasive cancer in the regional cohort. (Figure 1)

To complement the definition of mental health outcomes based on hospital diagnoses, we also assessed the incidence of psychiatric medication use, extracted from the Swedish Prescribed Drug Register. Psychiatric medications were defined according to the Anatomical Therapeutic Chemical (ATC) Classification System: antidepressant (N06A), anxiolytics (N05B), hypnotics and sedatives (N05C). Since prescription data are only available from July 2005 onward, we only included breast cancer patients diagnosed between July 1st 2006 and December 31st 2009, and excluded patients who had a prescription of antidepressants, anxiolytics, hypnotics and/or sedatives in the year prior to the breast cancer diagnosis, leaving 19167 patients for this analysis. The same exclusion criteria were applied to the general population cohort. Follow-up time started from July 1st 2006 and ended at the date of prescription, death, emigration, a new primary cancer diagnosis, or December 31st 2010, whichever came first.

Patient, tumor and treatment characteristics

We extracted the following patient, tumor and treatment characteristics from the Stockholm-Gotland Breast Cancer Register for the regional cohort of invasive breast cancer patients: age at diagnosis, tumor size, histological grade, estrogen receptor (ER) status, axillary lymph node involvement, distant metastasis, chemotherapy, endocrine therapy, radiotherapy, and surgery. Information on comorbidities

prior to diagnosis was obtained from the Swedish Inpatient Register and summarized according to the Charlson Comorbidity Index (CCI) score [26].

Statistical analyses

We first compared the risk of depression, anxiety and stress-related disorders in invasive and in-situ breast cancer patients with that observed in the general population using standardized incidence ratios (SIRs; the ratio of observed number of events to expected number of events), overall and stratified by age and time since diagnosis. The expected number of events was calculated by multiplying the number of person-years observed in age (5-year categories), calendar period (1-year categories), and region of residence (North, Stockholm-Gotland, South, Southeast, Uppsala-Örebro, West) specific strata of the breast cancer cohorts by the incidence rates of each outcome in the corresponding strata of the general female population. Calculation of the confidence intervals (CIs) was based on Poisson distribution and potential linear trends of SIRs by age group were examined using Chi-Square tests. We used Kaplan-Meier curves to assess the cumulative incidences of all three mental health outcomes and compared these to the cumulative incidences observed in age-matched individuals from the general population.

In the regional cohort, we further analyzed the risk of depression, anxiety and stress-related disorders by patient, tumor and treatment characteristics. Flexible parametric survival models [27] were used to estimate hazard ratios (HRs) with 95% CIs and the proportional hazards assumption was tested using likelihood ratio tests of time by covariate interactions. The flexible parametric model is similar to the Cox proportional hazards model in that it provides a HR and additionally allows the effect of exposure variables to vary over time. In all models, time since diagnosis was the underlying time scale and a restricted cubic spline, with four internal and two boundary knots (five degrees of freedom) placed at quintiles of the event times, was used for the baseline hazard. In case of non-proportionality, time-dependent effects were modelled by adding interaction terms with time using a second spline with three degrees of freedom and HRs were reported at different time points after diagnosis.

We constructed three models to analyze the impact of patient, tumor and treatment related factors: 1) models adjusting for age and calendar period of diagnosis. 2) grouped models including respectively all patient, all tumor or all treatment characteristics with additional adjustment for age and calendar period; 3) multivariable models including all variables. Missing indicators were included for the analysis of tumor and treatment characteristics in all models. We also conducted two extra analyses to evaluate the impact of disease recurrence and newly developed comorbidities on the association with patient, tumor and

treatment characteristics. For this analysis, person-time was additionally censored at recurrent events (defined as distant metastasis or locoregional recurrence) or diagnosis of new comorbid disease during follow-up.

Statistical analyses were performed using Stata software (version 13.0; Stata Corporation, College Station, TX).

Results

Risk of depression, anxiety and stress-related disorders in breast cancer patients compared to the general female population

Patients with invasive breast cancer were at increased risk of developing mental disorders compared to the general female population (Table 2), with the overall SIRs being of similar magnitude for depression, anxiety and stress-related disorders [SIR (95% CI) = 1.57 (1.46-1.69), 1.55 (1.43-1.68) and 1.77 (1.60-1.95), respectively]. Risk of mental disorders was highest during the first year after diagnosis, with the SIR for stress-related disorders being most pronounced ($SIR_{0\text{-}6month}$= 4.22, 95% CI = 3.44-5.19).The SIRs for all three mental disorders remained elevated up to five years. No overall increased risk of mental disorders was found among patients with in-situ breast cancer, except for an increased risk of stress-related disorders shortly after diagnosis ($SIR_{0\text{-}6\ months}$ = 2.76, 95% CI = 1.31-5.79).

In invasive cancer patients, the risk of depression and anxiety was highest among those diagnosed at younger age (*P* for trend = 0.03 and 0.02 respectively), while no interaction with age was found for stress-related disorders. SIRs for mental disorders did not vary by age in patients with in-situ breast cancer.

Patients with invasive cancer were more likely to receive psychiatric medication prescriptions, with SIRs for all medications being long-term increased (up to 4.5 years), but of highest magnitude during the first months after diagnosis. In-situ breast cancer patients were also more likely to use psychiatric medications, especially shortly after diagnosis with only the SIR for antidepressants being increased up to 2 years (eTable 2). In invasive cancer patients, a similar age trend for psychiatric medication use was observed as for the anxiety and depression diagnoses, with SIRs for all types of medication being highest in those diagnosed at younger age. As for the clinical diagnoses, no age interaction was found for psychiatric medication use in patients with in-situ cancers.

Figure 2 shows the cumulative incidences of mental disorders by time since diagnosis. The 5-year cumulative incidences of depression, anxiety and stress-related disorders in invasive cancer patients were 2.1%, 1.5% and 1.1% respectively. The corresponding cumulative incidences were respectively 1.4%, 1.1% and 0.7% for in-situ cancer patients and 1.2%, 0.9% and 0.6% for the general population.

Risk of depression, anxiety and stress-related disorders by patient, tumor and treatment characteristics in invasive breast cancer patients

Risk profiles of invasive cancer patients were similar for depression and anxiety in multivariable models (Table 3), with younger patients and patients with comorbidities being at higher risk. We also observed an increased risk of anxiety in patients with distant metastases, higher-grade tumors and chemotherapy treatment, as well as an increased risk of depression in patients with a positive lymph node status. In contrast, no clinical risk factors were found for stress-related disorders, except for an increased risk with younger age at diagnosis. Overall, associations with histological grade, lymph node status and chemotherapy were stronger in grouped models (including only tumor or treatment factors), highlighting the close correlation between these variables (eTable 3).

Tests for proportional hazards showed that the effects of comorbidities, histological grade and chemotherapy were not constant over time (Figure 3 and eTable 4). Comorbidities were only associated with increased risks of depression and anxiety ~3 years after diagnosis, while the impact of histological grade and chemotherapy was mainly limited to the first two years after diagnosis.

Analyses with additional censoring at recurrent events or newly developed comorbidities returned similar effect estimates (eTable 5), indicating that these events had no strong impact on the observed associations with patient, tumor and treatment characteristics.

Discussion

Key results

In this large-scale register-based study, we found that patients with invasive breast cancer had a 60% increased risk of developing depression, anxiety and stress-related disorders within 10 years of diagnosis, compared to the general female population. Although mental disorder risk was highest shortly after diagnosis, the incidence of all three mental disorders remained increased up to five years. Younger age at diagnosis, comorbidities, higher histological grade, positive lymph node status and chemotherapy

were all independently associated with the risk of depression and anxiety in invasive cancer patients, with histological grade and chemotherapy contributing to short-term risk only, while comorbidities were mainly associated with late-onset events. Younger age at diagnosis was the only identifiable risk factor for stress-related disorders in invasive breast cancer patients. No overall increased risk of mental disorders was found among patients with in-situ breast cancer, except for an increased risk of stress-related disorders in the first six months after diagnosis.

Interpretation

Few studies have evaluated the risk of depression, anxiety and stress-related disorders in breast cancer patients as compared to the general population. The risk estimates observed for depression and anxiety in invasive breast cancer patients are in agreement with findings from two Danish register-based studies [19, 28], supporting the generalizability of risk estimates within Nordic countries. Of note, the cumulative incidences in register-based analyses are lower than the incidences observed in studies using clinical interviews [4, 29, 30], which may indicate that our absolute risk estimates represent an underestimation, but capture the most severe and clinically relevant cases. The higher incidence of psychiatric medication prescriptions than hospital visits also support this argument.

The excess risk of mental disorders shortly after diagnosis can be explained by direct psychological reactions to the actual diagnosis [31]. In addition, we found a long-term increased risk of depression, anxiety and stress-related disorders, potentially due to side effects from extensive medical treatment, or medical sequelae of breast cancer (such as lymphedema, numbness in hands and chest) which may trigger the re-experience of a traumatic event [32, 33].

Patients diagnosed with in-situ breast cancer did not show an increased risk of mental disorders, except for a nearly three-fold increased risk of stress-related disorders in the first six months after diagnosis, as well as a short-term increased risk of psychiatric medication use. One explanation is that in-situ breast cancer is generally conceived less of a life threatening disease. Moreover, patients with in-situ breast cancer do not experience strong side effects of chemo/endocrine therapy, as they usually undergo surgery and/or radiotherapy only.

A large number of studies have assessed the risk of mental disorders by patient, tumor and treatment characteristics [3, 9, 10, 19-21], and younger age at diagnosis has consistently been associated with an increased risk of depression and anxiety [9, 19, 28, 34, 35]. The lower mean age at diagnosis of depression and

anxiety than the mean age of breast cancer diagnosis (Table 1) also supports this notion. The impact of age is usually attributed to more aggressive tumor characteristics and treatment in younger patients [36], but our study demonstrates that the effect of age is independent of cancer subtype and treatment. Younger age at diagnosis was also the only risk factor related to stress-related disorders, which is in agreement with previous studies [37, 38], stressing the importance of this factor as indicator of overall mental disease risk [34, 37, 39]. In general, younger patients might experience greater psychological distress from a cancer diagnosis, as a diagnosis early in life may have a larger impact on future well-being from a personal, socioeconomic and physical perspective. In case of breast cancer, a younger age at diagnosis is more likely to influence work ability [5], sexual life [40], motherhood [41] and fertility [42] compared to a diagnosis later in life.

We also found an increased risk of depression and anxiety in patients with higher histological grade, lymph node positive disease and in patients treated with chemotherapy, as suggested by previous observations [19, 20, 34, 37, 43]. Patients might interpret higher histological grades and lymph node spread as a more severe diagnosis, and the effect of such mental reaction to diagnosis is expected to diminish with time, as corroborated by the short-term effect of grade in the present study. An impact of chemotherapy on mental health is biologically plausible. Release of pro-inflammatory cytokines during chemotherapy-induced cell damage may influence mood disorder pathophysiology [44-46]. Side effects of chemotherapy such as alopecia, nausea and vomiting may further increase the risk of depression and anxiety [47, 48]. Still, several population-based studies have reported conflicting results regarding the impact of chemotherapy on depression and anxiety [3, 19, 21]. One explanation for this inconsistency is the time-dependent effect of chemotherapy, as the impact of chemotherapy was only detectable in first two years after diagnosis, i.e. during and shortly after active treatment.

We further identified an independent association of comorbidities with the risk of depression and anxiety. Comorbidity is an established risk factor for mental disorders [9, 19]. Besides baseline comorbidity, cancer treatment may trigger new comorbid events, which could potentially increase the long-term risk of mental disorders. However, the consistent results in the extra analysis with additional censoring at these events do not support this hypothesis. Our study further shows that the impact of baseline comorbidities becomes more evident with increasing time since diagnosis. Together with the findings of tumor/treatment characteristic analyses, these results indicate that the short-term risk of depression and anxiety in breast cancer patients is more strongly influenced by cancer-specific factors, while comorbid conditions only have an impact in the long run. Thus, the individual risk profile of mental disorders is not

constant in breast cancer patients, but changes over time with respect to comorbidities, chemotherapy and histological grade.

Previous studies have shown that early short-term psycho-oncologic interventions (including education, coping skills training, psychotherapy and relaxation) are effective in controlling emotional distress, anxiety and depression, and that the largest effects are seen in studies which preselect cancer patients according to their personal distress levels [49, 50] . Our findings suggest that apart from emotional distress, knowledge of baseline clinical parameters may aid in the identification of patients in highest need for intervention. For example, young breast cancer patients presenting with aggressive tumor characteristics scheduled for chemotherapy may potentially benefit from targeted screening and counseling shortly after diagnosis. Simultaneously, the long-term increased risks of mental illness may indicate a need for long-term vigilance of specific subgroups based on age and comorbidity, though effectiveness data on continuous interventions in long-term survivors are scarce and require further study.

Strengths and Limitations

A major strength of our study is the large-scale population-based design and use of Swedish health registers, which minimizes selection and information biases. Other strengths include the abundant information on tumor and treatment characteristics in the regional breast cancer cohort and the use of flexible parametric models for capturing time dependent effects.

The present study also had limitations. First, we cannot rule out misclassification of the outcomes studied. Although recent validation studies have reported good agreement (more than 80%) between the Patient Register and medical records review/clinical diagnoses of depression and stress-related disorders [51, 52], no validation data are available for anxiety. Since the diagnostic work-up for anxiety is not different from depression and stress-related disorders (with primary care doctor's referral and interview by a psychiatrist), the validity of this outcome is considered to be of similar quality. We further tried to minimize potential misclassification by using main diagnoses only. Second, breast cancer patients are subject to increased medical surveillance than healthy individuals in the general population, especially shortly after diagnosis. Hence, the SIRs for mental disorders might be slightly over-estimated, although the long-term increased risk of depression and anxiety argues against a pure explanation of surveillance bias for the increased risks shortly after cancer diagnosis. Third, associations with tumor and treatment characteristics were addressed in the regional cohort only, as pathology and in-hospital treatment data are

not included in the nationwide cohort. Since oncological clinical practice does not vary across different regions of Sweden [53, 54] , we believe that these results are generalizable to the country as a whole. Also, we did not have information on psychosocial variables (such as previous traumatic life events, family history of mental disorders, socioeconomic and cohabitation status) in the regional cohort. Likewise, more detailed information on molecular subtyping may further facilitate the discrimination of aggressive cancers and the associated risk of mental disorders in future studies. Finally, the limited number of events among in-situ breast cancer patients may have resulted in reduced statistical power to identify associations, mainly in stratified analyses by age and time since diagnosis. Nevertheless, confidence intervals were reasonably narrow and results from the more powerful medication analysis were confirmatory, all arguing against a long-term increased risk of mental disorders and age-specific effects in this group of patients.

Conclusion

Patients with invasive breast cancer are at long-term increased risk of developing depression, anxiety and stress-related disorders, with risks being highest shortly after diagnosis. Younger age at diagnosis, comorbidity, higher-grade disease, lymph node involvement and chemotherapy are independent predictors of mental disorder risk, with tumor and treatment variables mainly influencing short-term risk, while comorbidities are more strongly associated with late-onset events. Patients with in-situ breast cancer only experience a short-term increased risk of stress-related disorders. The observed time-dependent risk profiles shed light on the needs of early interventions for specific subgroups of invasive breast cancer patients.

Conflict of Interest Disclosures:

The authors declare no conflicts of interest.

Author Contributions:

HY had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: KC, HY, JSB

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: HY, JSB

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: HY, FC, ALVJ

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References

1. Forouzanfar MH, Foreman KJ, Delossantos AM, Lozano R, Lopez AD, Murray CJ, Naghavi M. Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. *Lancet* 2011;**378**: 1461-84.

2. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin D, Forman D, Bray F. GLOBOCAN 2012 v1. 0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer. c2013 [cited 2013 Oct 17]. *globocan iarc fr/Default aspx Accessed* 2014.

3. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. *Bmj* 2005;**330**: 702.

4. Mehnert A, Brahler E, Faller H, Harter M, Keller M, Schulz H, Wegscheider K, Weis J, Boehncke A, Hund B, Reuter K, Richard M, et al. Four-week prevalence of mental disorders in patients with cancer across major tumor entities. *J Clin Oncol* 2014;**32**: 3540-6.

5. Carlsen K, Jensen AJ, Rugulies R, Christensen J, Bidstrup PE, Johansen C, Huitfeldt Madsen IE, Dalton SO. Self-reported work ability in long-term breast cancer survivors. A population-based questionnaire study in Denmark. *Acta Oncol* 2013;**52**: 423-9.

6. Demissie S, Silliman RA, Lash TL. Adjuvant tamoxifen: Predictors of use, side effects, and discontinuation in older women. *Journal of Clinical Oncology* 2001;**19**: 322-8.

7. He W, Fang F, Varnum C, Eriksson M, Hall P, Czene K. Predictors of Discontinuation of Adjuvant Hormone Therapy in Patients With Breast Cancer. *J Clin Oncol* 2015;33:2262-69.

8. Montazeri A. Quality of Life in Breast Cancer Patients: An Overview of the Literature. In: Preedy V, Watson R. *Handbook of Disease Burdens and Quality of Life Measures*ed.: Springer New York, 2010: 2829-55.

9. Wangel AM, Molin J, Moghaddassi M, Stman M. Prior psychiatric inpatient care and risk of cesarean sections: a registry study. *Journal of psychosomatic obstetrics and gynaecology* 2011;**32**: 189-97.

10. Bardwell WA, Natarajan L, Dimsdale JE, Rock CL, Mortimer JE, Hollenbach K, Pierce JP. Objective cancer-related variables are not associated with depressive symptoms in women treated for early-stage breast cancer. *J Clin Oncol* 2006;**24**: 2420-7.

11. Osborne RH, Elsworth GR, Hopper JL. Age-specific norms and determinants of anxiety and depression in 731 women with breast cancer recruited through a population-based cancer registry. *Eur J Cancer* 2003;**39**: 755-62.

12. Kissane DW, Clarke DM, Ikin J, Bloch S, Smith GC, Vitetta L, McKenzie DP. Psychological morbidity and quality of life in Australian women with early-stage breast cancer: a cross-sectional survey. *The Medical journal of Australia* 1998;**169**: 192-6.

13. Saboonchi F, Petersson LM, Wennman-Larsen A, Alexanderson K, Brannstrom R, Vaez M. Changes in caseness of anxiety and depression in breast cancer patients during the first year following surgery: Patterns of transiency and severity of the distress response. *European journal of oncology nursing : the official journal of European Oncology Nursing Society* 2014 ;18:598-604.

14. Mehnert A, Koch U. Psychological comorbidity and health-related quality of life and its association with awareness, utilization, and need for psychosocial support in a cancer register-based sample of long-term breast cancer survivors. *Journal of psychosomatic research* 2008;**64**: 383-91.

15. van Gestel YR, Voogd AC, Vingerhoets AJ, Mols F, Nieuwenhuijzen GA, van Driel OJ, van Berlo CL, van de Poll-Franse LV. A comparison of quality of life, disease impact and risk perception in women with invasive breast cancer and ductal carcinoma in situ. *Eur J Cancer* 2007;**43**: 549-56.

16. Rakovitch E, Franssen E, Kim J, Ackerman I, Pignol JP, Paszat L, Pritchard KI, Ho C, Redelmeier DA. A comparison of risk perception and psychological morbidity in women with ductal carcinoma in situ and early invasive breast cancer. *Breast Cancer Res Treat* 2003;**77**: 285-93.

17. Lauzier S, Maunsell E, Levesque P, Mondor M, Robert J, Robidoux A, Provencher L. Psychological distress and physical health in the year after diagnosis of DCIS or invasive breast cancer. *Breast Cancer Res Treat* 2010;**120**: 685-91.

18. Danese MD, O'Malley C, Lindquist K, Gleeson M, Griffiths RI. An observational study of the prevalence and incidence of comorbid conditions in older women with breast cancer. *Ann Oncol* 2012;**23**: 1756-65.

19. Suppli NP, Johansen C, Christensen J, Kessing LV, Kroman N, Dalton SO. Increased risk for depression after breast cancer: a nationwide population-based cohort study of associated factors in denmark, 1998-2011. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2014;**32**: 3831-9.

20. Purushotham AD, Upponi S, Klevesath MB, Bobrow L, Millar K, Myles JP, Duffy SW. Morbidity after sentinel lymph node biopsy in primary breast cancer: results from a randomized controlled trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2005;**23**: 4312-21.

21. Hughson AV, Cooper AF, McArdle CS, Smith DC. Psychological impact of adjuvant chemotherapy in the first two years after mastectomy. *British medical journal* 1986;**293**: 1268-71.

22. Helgesson O, Bengtsson C, Lapidus L, Merck C, Sparen P. Malignant disease observed in a cohort of women. A validation of Swedish Cancer Registry data. *Scand J Soc Med* 1994;**22**: 46-9.

23. Garne JP, Aspegren K, Moller T. Validity of Breast-Cancer Registration from One Hospital into the Swedish National Cancer Registry 1971-1991. *Acta Oncol* 1995;**34**: 153-6.

24. Colzani E, Liljegren A, Johansson AL, Adolfsson J, Hellborg H, Hall PF, Czene K. Prognosis of patients with breast cancer: causes of death and effects of time since diagnosis, age, and tumor characteristics. *J Clin Oncol* 2011;**29**: 4014-21.

25. WHO. *The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*ed.: Geneva: World Health Organization, 1992.

26. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of chronic diseases* 1987;**40**: 373-83.

27. Royston P, Parmar MKB. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med* 2002;**21**: 2175-97.

28. Hjerl K, Andersen EW, Keiding N, Mortensen PB, Jorgensen T. Increased incidence of affective disorders, anxiety disorders, and non-natural mortality in women after breast cancer diagnosis: a nation-wide cohort study in Denmark. *Acta psychiatrica Scandinavica* 2002;**105**: 258-64.

29. Zainal NZ, Nik-Jaafar NR, Baharudin A, Sabki ZA, Ng CG. Prevalence of depression in breast cancer survivors: a systematic review of observational studies. *Asian Pacific journal of cancer prevention : APJCP* 2013;**14**: 2649-56.

30. Kang JI, Sung NY, Park SJ, Lee CG, Lee BO. The epidemiology of psychiatric disorders among women with breast cancer in South Korea: analysis of national registry data. *Psycho-oncology* 2014;**23**: 35-9.

31. Spiegel D. Mind matters in cancer survival. *JAMA : the journal of the American Medical Association* 2011;**305**: 502-3.

32. Amir M, Ramati A. Post-traumatic symptoms, emotional distress and quality of life in long-term survivors of breast cancer: a preliminary research. *Journal of anxiety disorders* 2002;**16**: 195-206.

33. Kornblith AB, Herndon JE, 2nd, Weiss RB, Zhang C, Zuckerman EL, Rosenberg S, Mertz M, Payne D, Jane Massie M, Holland JF, Wingate P, Norton L, et al. Long-term adjustment of survivors of early-stage breast carcinoma, 20 years after adjuvant chemotherapy. *Cancer* 2003;**98**: 679-89.

34. O'Connor M, Christensen S, Jensen AB, Moller S, Zachariae R. How traumatic is breast cancer? Post-traumatic stress symptoms (PTSS) and risk factors for severe PTSS at 3 and 15 months after surgery in a nationwide cohort of Danish women treated for primary breast cancer. *Br J Cancer* 2011;**104**: 419-26.

35. Cordova MJ, Andrykowski MA, Kenady DE, McGrath PC, Sloan DA, Redd WH. Frequency and correlates of posttraumatic-stress-disorder-like symptoms after treatment for breast cancer. *Journal of consulting and clinical psychology* 1995;**63**: 981-6.

36. Anders CK, Hsu DS, Broadwater G, Acharya CR, Foekens JA, Zhang Y, Wang YX, Marcom PK, Marks JR, Febbo PG, Nevins JR, Potti A, et al. Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. *Journal of Clinical Oncology* 2008;**26**: 3324-30.

37. Vin-Raviv N, Hillyer GC, Hershman DL, Galea S, Leoce N, Bovbjerg DH, Kushi LH, Kroenke C, Lamerato L, Ambrosone CB, Valdimorsdottir H, Jandorf L, et al. Racial disparities in posttraumatic stress after diagnosis of localized breast cancer: the BQUAL study. *J Natl Cancer Inst* 2013;**105**: 563-72.

38. Levine EG, Eckhardt J, Targ E. Change in post-traumatic stress symptoms following psychosocial treatment for breast cancer. *Psycho-oncology* 2005;**14**: 618-35.

39. Perez S, Galdon MJ, Andreu Y, Ibanez E, Dura E, Conchado A, Cardena E. Posttraumatic stress symptoms in breast cancer patients: temporal evolution, predictors, and mediation. *Journal of traumatic stress* 2014;**27**: 224-31.

40. Kedde H, van de Wiel HB, Weijmar Schultz WC, Wijsen C. Sexual dysfunction in young women with breast cancer. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2013;**21**: 271-80.

41. Ebenhan K, Leuteritz K, Barthel Y, Beutel ME, Papsdorf K, Weissflog G, Brahler E. Children and Employment - Resource or Stressors after Breast Cancer? *Geburtshilfe und Frauenheilkunde* 2013;**73**: 792-9.

42. Ruddy KJ, Gelber SI, Tamimi RM, Ginsburg ES, Schapira L, Come SE, Borges VF, Meyer ME, Partridge AH. Prospective study of fertility concerns and preservation strategies in young women with breast cancer. *J Clin Oncol* 2014;**32**: 1151-6.

43. Gallagher J, Parle M, Cairns D. Appraisal and psychological distress six months after diagnosis of breast cancer. *British journal of health psychology* 2002;**7**: 365-76.

44. Raison CL, Miller AH. Depression in cancer: new developments regarding diagnosis and treatment. *Biological psychiatry* 2003;**54**: 283-94.

45. Janelsins MC, Mustian KM, Palesh OG, Mohile SG, Peppone LJ, Sprod LK, Heckler CE, Roscoe JA, Katz AW, Williams JP, Morrow GR. Differential expression of cytokines in breast cancer patients receiving different chemotherapies: implications for cognitive impairment research. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2012;**20**: 831-9.

46. Kesler S, Janelsins M, Koovakkattu D, Palesh O, Mustian K, Morrow G, Dhabhar FS. Reduced hippocampal volume and verbal memory performance associated with interleukin-6 and tumor necrosis factor-alpha levels in chemotherapy-treated breast cancer survivors. *Brain, behavior, and immunity* 2013;**30 Suppl**: S109-16.

47. Choi EK, Kim IR, Chang O, Kang D, Nam SJ, Lee JE, Lee SK, Im YH, Park YH, Yang JH, Cho J. Impact of chemotherapy-induced alopecia distress on body image, psychosocial well-being, and depression in breast cancer patients. *Psycho-oncology* 2014;**23**: 1103-10.

48. Farrell C, Brearley SG, Pilling M, Molassiotis A. The impact of chemotherapy-related nausea on patients' nutritional status, psychological distress and quality of life. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2013;**21**: 59-66.

49. Faller H, Schuler M, Richard M, Heckl U, Weis J, Kuffner R. Effects of psycho-oncologic interventions on emotional distress and quality of life in adult patients with cancer: systematic review and meta-analysis. *J Clin Oncol* 2013;**31**: 782-93.

50. Schneider S, Moyer A, Knapp-Oliver S, Sohl S, Cannella D, Targhetta V. Pre-intervention distress moderates the efficacy of psychosocial treatment for cancer patients: a meta-analysis. *J Behav Med* 2010;**33**: 1-14.

51. Fazel S, Wolf A, Chang Z, Larsson H, Goodwin GM, Lichtenstein P. Depression and violence: a Swedish population study. *Lancet Psychiatry* 2015;**2**: 224-32.

52. Svensson E, Lash TL, Resick PA, Hansen JG, Gradus JL. Validity of reaction to severe stress and adjustment disorder diagnoses in the Danish Psychiatric Central Research Registry. *Clin Epidemiol* 2015;**7**: 235-42.

53. National Board of Health and Welfare, Quality and Efficiency in Swedish Cancer Care: Regional Comparisons 2011. Swedish National Board of Health and Welfare, 2012.

54. National Board of Health and Welfare, National guidelines for breast, prostate, colon and rectal cancer, 2014.

Titles and legends to figures

Figure 1. Flow chart of study population selection.

Figure 2. Cumulative incidence of depression, anxiety and stress-related disorders in the nationwide cohort of invasive and in-situ breast cancer patients and the general female population.

Kaplan-Meier estimates of the cumulative risk of depression, anxiety and stress-related disorders by time since diagnosis, in invasive and in-situ breast cancer patients and age-matched individuals from the general population.

Figure 3. Time-dependent effect of comorbidity, histological grade and chemotherapy on depression and anxiety in the regional cohort of invasive breast cancer patients.

Hazard ratios by time since diagnosis are derived from flexible parametric survival models. All hazard ratios are multivariable adjusted.

Online supplementary

eTable 1. International Classification of Diseases (ICD) codes for depression, anxiety and stress-related disorders.

eTable 2. Standardized incidence ratios for psychiatric medication in the nationwide cohort of invasive and in-situ breast cancer patients, overall and stratified by age and time since diagnosis.

eTable 3. Hazard ratios of depression, anxiety and stress-related disorders according to patient, tumor and treatment characteristics in the regional cohort of breast cancer patients - grouped models.

eTable 4. Time-dependent effect of comorbidity, histological grade and chemotherapy on depression and anxiety in the regional cohort of invasive breast cancer patients.

eTable 5. Hazard ratios of depression, anxiety and stress-related disorders according to patient, tumor and treatment characteristics in the regional cohort of invasive breast cancer patients with additional censoring at recurrence or new-onset comorbidity.

Table 1. Descriptive characteristics of the nationwide and regional breast cancer cohort.

	Nationwide cohort		Regional cohort
	Invasive breast cancer (N = 40,849)	**In-situ breast cancer (N = 4,402)**	**Invasive Breast cancer (N = 7,940)**
Cohort period	2001-2010	2001-2010	2001-2013
Age at diagnosis (years)			
Mean (SD)	60.0 (11.1)	58.2 (10.3)	58.5 (11.3)
Min – Max	20-80	22-80	23-80
Duration of follow-up (years)			
Median (IQR)	4.5 (4.5)	4.7 (4.4)	7.5 (4.6)
Total no. of person years at risk	194,122	21,482	58,273
Cases of mental disorders			
Depression (% of patients)	759 (1.9%)	56 (1.3%)	335 (4.2%)
Anxiety (% of patients)	572 (1.4%)	41 (0.9%)	362 (4.6%)
Stress-related disorders (% of patients)	384 (0.9%)	26 (0.6%)	147 (1.9%)
Age at mental disorder diagnosis (years)			
Mean age at depression (SD)	58.8 (11.5)	58.1 (11.4)	55.9 (11.7)
Mean age at anxiety (SD)	58.2 (12.0)	58.4 (12.1)	55.3 (12.6)
Mean age at stress-related disorders (SD)	54.7 (10.5)	57.3 (7.0)	53.1 (10.7)

Abbreviations: SD = standard deviation; IQR = interquartile. The nationwide cohort includes women diagnosed with primary invasive or in-situ breast cancer at age 20-80 years between 2001 and 2009. In this cohort, follow-up is complete until December 31st, 2010. The regional cohort includes women diagnosed with primary invasive breast cancer at age 20-80 years between 2001 and 2008 and all patients in this cohort have complete follow-up until December 31st, 2013.

Table2. Standardized incidence ratios of depression, anxiety and stress-related disorders in the nationwide breast cancer cohort

	Depression		Anxiety		Stress-related disorders	
	No.	**SIR(95%CI)**	**No.**	**SIR(95%CI)**	**No.**	**SIR(95%CI)**
Overall						
Invasive	759	**1.57 (1.46-1.69)**	572	**1.55 (1.43-1.68)**	384	**1.77 (1.60-1.95)**
In situ	56	1.03 (0.80-1.34)	41	0.99 (0.73-1.34)	26	1.02 (0.70-1.50)
Age group						
Invasive						
20-44 years	128	**1.69 (1.42-2.01)**	117	**1.84 (1.54-2.21)**	84	**1.68 (1.36-2.08)**
45-54 years	238	**1.70 (1.50-1.93)**	165	**1.56 (1.34-1.81)**	149	**1.78 (1.52-2.09)**
55-64 years	208	**1.56 (1.36-1.79)**	163	**1.58 (1.35-1.84)**	105	**1.89 (1.56-2.28)**
65-80 years	185	**1.38 (1.19-1.59)**	127	**1.31 (1.10-1.56)**	46	**1.64 (1.23-2.19)**
In-situ						
20-44 years	12	1.48 (0.84-2.61)	8	1.18 (0.59-2.36)	2	0.38 (0.09-1.51)
45-54 years	16	0.84 (0.51-1.36)	14	0.97 (0.57-1.64)	12	1.06 (0.60-1.87)
55-64 years	15	1.01 (0.61-1.68)	11	0.95 (0.53-1.72)	9	1.46 (0.76-2.81)
65-80 years	13	1.07 (0.62-1.85)	8	0.91 (0.45-1.81)	3	1.15 (0.37-3.56)
Time since diagnosis						
Invasive						
0-0.5 year	86	**1.83 (1.48-2.26)**	85	**2.53 (2.05-3.13)**	91	**4.22 (3.44-5.19)**
0.5-1 year	117	**2.48 (2.07-2.97)**	79	**2.30 (1.85-2.87)**	59	**2.73 (2.11-3.52)**
1-2 years	180	**2.04 (1.76-2.36)**	131	**2.00 (1.69-2.38)**	70	**1.72 (1.36-2.17)**
2-5 years	249	**1.29 (1.14-1.46)**	172	**1.17 (1.01-1.36)**	119	**1.36 (1.14-1.63)**
5-10 years	127	1.18 (0.99-1.41)	105	1.18 (0.97-1.42)	45	0.98 (0.73-1.32)
In situ						
0-0.5 year	4	0.77 (0.29-2.05)	2	0.53 (0.13-2.12)	7	**2.76 (1.31-5.79)**
0.5-1 year	6	1.14 (0.51-2.54)	0	-	2	0.78 (0.20-3.14)
1-2 years	9	0.91 (0.47-1.74)	12	1.62 (0.92-2.85)	5	1.04 (0.43-2.51)
2-5 years	25	1.15 (0.78-1.70)	18	1.09 (0.68-1.73)	9	0.88 (0.46-1.69)
5-10 years	12	1.00 (0.57-1.76)	9	0.90 (0.47-1.74)	3	0.57 (0.18-1.76)

Abbreviations: SIR = standardized incidence ratio; No. refers to the number of observed cases; CI = confidence interval. SIRs for depression, anxiety and stress-related disorders in the nationwide breast cancer cohort compared to the entire Swedish female population (age 20-80). The SIR is the number of observed cases divided by the number expected, and can be interpreted as measure of relative risk (i.e. a SIR of 1.5 represents a 50% increase in risk). All SIRs are standardized by calendar period (1-year categories), age (5-year categories), and region of residence (North, Stockholm-Gotland, South, Southeast, Uppsala-Örebro, West).

Table 3. Hazard ratios of depression, anxiety and stress-related disorders according to patient, tumor and treatment characteristics in the regional cohort of invasive breast cancer patients.

	Total No.	Depression			Anxiety			Stress related disorders		
		No.	HR (95%CI)		No.	HR (95%CI)		No.	HR (95%CI)	
			Model A	Model B		Model A	Model B		Model A	Model B
Patients characteristics										
Age at diagnosis										
23-44 years	1012	86	REF (1.00)	REF (1.00)	114	REF (1.00)	REF (1.00)	47	REF (1.00)	REF (1.00)
45-54 years	1913	115	**0.69 (0.52-0.92)**	0.77 (0.58-1.03)	109	**0.50 (0.38-0.65)**	**0.53 (0.41-0.69)**	64	0.71 (0.49-1.03)	0.70 (0.48-1.03)
55-64 years	2629	80	**0.35 (0.26-0.48)**	**0.40 (0.30-0.55)**	86	**0.28 (0.21-0.38)**	**0.32 (0.24-0.43)**	26	**0.21 (0.13-0.34)**	**0.20 (0.12-0.33)**
65-80 years	2386	54	**0.28 (0.20-0.39)**	**0.33 (0.23-0.47)**	53	**0.20 (0.15-0.28)**	**0.22 (0.16-0.32)**	10	**0.10 (0.05-0.19)**	**0.09 (0.04-0.18)**
Comorbidities †										
No	6797	287	REF (1.00)	REF (1.00)	304	REF (1.00)	REF (1.00)	128	REF (1.00)	REF (1.00)
Yes	1143	48	**1.43 (1.04-1.94)**	**1.44 (1.05-1.97)**	58	**1.72 (1.30-2.29)**	**1.67 (1.25-2.23)**	19	1.50 (0.92-2.44)	1.49 (0.91-2.44)
Tumor characteristics										
Size in mm										
<10	1867	71	REF (1.00)	REF (1.00)	69	REF (1.00)	REF (1.00)	37	REF (1.00)	REF (1.00)
10-20	3320	145	1.12 (0.85-1.49)	0.95 (0.70-1.27)	149	1.17 (0.88-1.55)	0.94 (0.70-1.26)	70	0.99 (0.66-1.47)	1.06 (0.70-1.62)
>20	2348	104	1.18 (0.87-1.60)	0.83 (0.60-1.16)	121	**1.40 (1.04-1.88)**	0.96 (0.69-1.33)	35	0.70 (0.44-1.12)	0.79 (0.47-1.33)
Histological grade (Elston) †										
Low	899	26	REF (1.00)	REF (1.00)	26	REF (1.00)	REF (1.00)	22	REF (1.00)	REF (1.00)
Moderate	2390	111	**1.62 (1.06-2.49)**	1.52 (0.98-2.34)	120	**1.78 (1.16-2.72)**	**1.65 (1.07-2.54)**	44	0.72 (0.43-1.20)	0.77 (0.45-1.29)
High	1476	91	**1.90 (1.22-2.95)**	1.53 (0.95-2.47)	98	**2.00 (1.29-3.09)**	**1.73 (1.08-2.77)**	36	0.70 (0.41-1.20)	0.77 (0.42-1.42)
Lymph nodes										
Negative	4702	177	REF (1.00)	REF (1.00)	183	REF (1.00)	REF (1.00)	87	REF (1.00)	REF (1.00)
Positive	2750	149	**1.43 (1.15-1.78)**	**1.30 (1.00-1.70)**	162	**1.51 (1.22-1.86)**	1.22 (0.95-1.59)	54	0.97 (0.69-1.37)	1.20 (0.79-1.80)
ER status										
Positive	5952	236	REF (1.00)	REF (1.00)	276	REF (1.00)	REF (1.00)	111	REF (1.00)	REF (1.00)
Negative	1271	73	**1.36 (1.04-1.77)**	1.33 (0.82-2.15)	62	0.95 (0.72-1.26)	0.95 (0.58-1.57)	28	0.96 (0.63-1.46)	0.76 (0.37-1.58)
Distant Metastasis										
Negative	7654	328	REF (1.00)	REF (1.00)	342	REF (1.00)	REF (1.00)	145	REF (1.00)	REF (1.00)
Positive	136	4	1.51 (0.56-4.06)	--	11	**4.25 (2.33-7.78)**	--	1	0.95 (0.13-6.78)	--
Treatment characteristics										
Endocrine therapy										
No	1346	75	REF (1.00)	REF (1.00)	64	REF (1.00)	REF (1.00)	33	REF (1.00)	REF (1.00)
Yes	6303	252	0.77 (0.60-1.00)	1.04 (0.65-1.68)	283	1.07 (0.81-1.41)	1.22 (0.75-2.00)	112	0.90 (0.60-1.33)	0.62 (0.31-1.23)
Chemotherapy †										
No	4912	158	REF (1.00)	REF (1.00)	159	REF (1.00)	REF (1.00)	80	REF (1.00)	REF (1.00)
Yes	2720	167	**1.46 (1.16-1.84)**	1.16 (0.86-1.55)	186	**1.56 (1.25-1.94)**	**1.36 (1.02-1.81)**	64	0.82 (0.58-1.17)	0.82 (0.51-1.29)
Radiotherapy										
No	1810	72	REF (1.00)	REF (1.00)	81	REF (1.00)	REF (1.00)	31	REF (1.00)	REF (1.00)
Yes	5839	254	1.01 (0.77-1.31)	1.11 (0.80-1.53)	267	0.92 (0.72-1.19)	1.02 (0.75-1.38)	114	1.06 (0.71-1.57)	0.91 (0.55-1.50)
Surgery										
Partial mastectomy	4627	181	REF (1.00)	REF (1.00)	188	REF (1.00)	REF (1.00)	92	REF (1.00)	REF (1.00)
Total mastectomy	3048	147	1.24 (0.99-1.54)	1.18 (0.89-1.57)	160	**1.29 (1.04-1.60)**	1.13 (0.86-1.49)	53	0.80 (0.57-1.12)	0.83 (0.53-1.31)

Total no. refers to the total number of patients. No. refers to the number of observed cases. In model A, hazard ratios were estimated with adjustment for age and calendar period only. In model B, hazard ratios are adjusted for all variables listed in the table. Missingness on individual variables < 5 %, except for histological grade (39.0%, N = 3,042), which was included in the Stockholm-Gotland Breast Cancer Register from 2004 onward and ER status (7.6%, N = 590). Patients with distant metastases at diagnosis are not included in model B (because of missing values on tumor characteristics) as these patients do not undergo routine surgery. † The proportional hazards assumption was met for all variables, except for comorbidities, histological grade and chemotherapy.

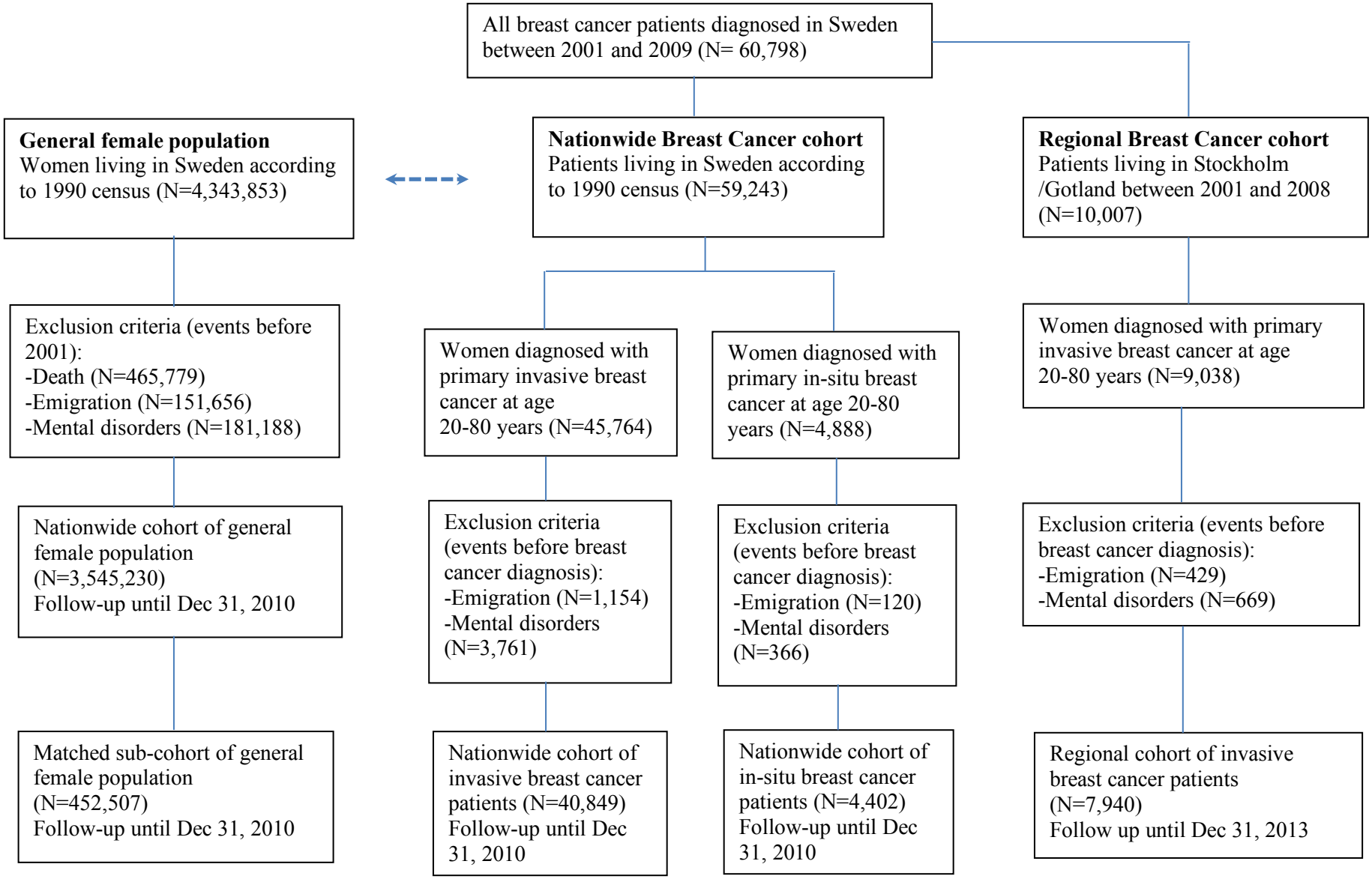

All breast cancer patients diagnosed in Sweden between 2001 and 2009 (N= 60,798)
General female population
Women living in Sweden according to 1990 census (N=4,343,853)
Nationwide Breast Cancer cohort
Patients living in Sweden according to 1990 census (N=59,243)
Regional Breast Cancer cohort
Patients living in Stockholm /Gotland between 2001 and 2008 (N=10,007)
Exclusion criteria (events before 2001):
-Death (N=465,779)
-Emigration (N=151,656)
-Mental disorders (N=181,188)
Women diagnosed with primary invasive breast cancer at age 20-80 years (N=45,764)
Women diagnosed with primary in-situ breast cancer at age 20-80 years (N=4,888)
Women diagnosed with primary invasive breast cancer at age 20-80 years (N=9,038)
Nationwide cohort of general female population (N=3,545,230)
Follow-up until Dec 31, 2010
Exclusion criteria (events before breast cancer diagnosis):
-Emigration (N=1,154)
-Mental disorders (N=3,761)
Exclusion criteria (events before breast cancer diagnosis):
-Emigration (N=120)
-Mental disorders (N=366)
Exclusion criteria (events before breast cancer diagnosis):
-Emigration (N=429)
-Mental disorders (N=669)
Matched sub-cohort of general female population (N=452,507)
Follow-up until Dec 31, 2010
Nationwide cohort of invasive breast cancer patients (N=40,849)
Follow-up until Dec 31, 2010
Nationwide cohort of in-situ breast cancer patients (N=4,402)
Follow-up until Dec 31, 2010
Regional cohort of invasive breast cancer patients (N=7,940)
Follow up until Dec 31, 2013

Figure 2.

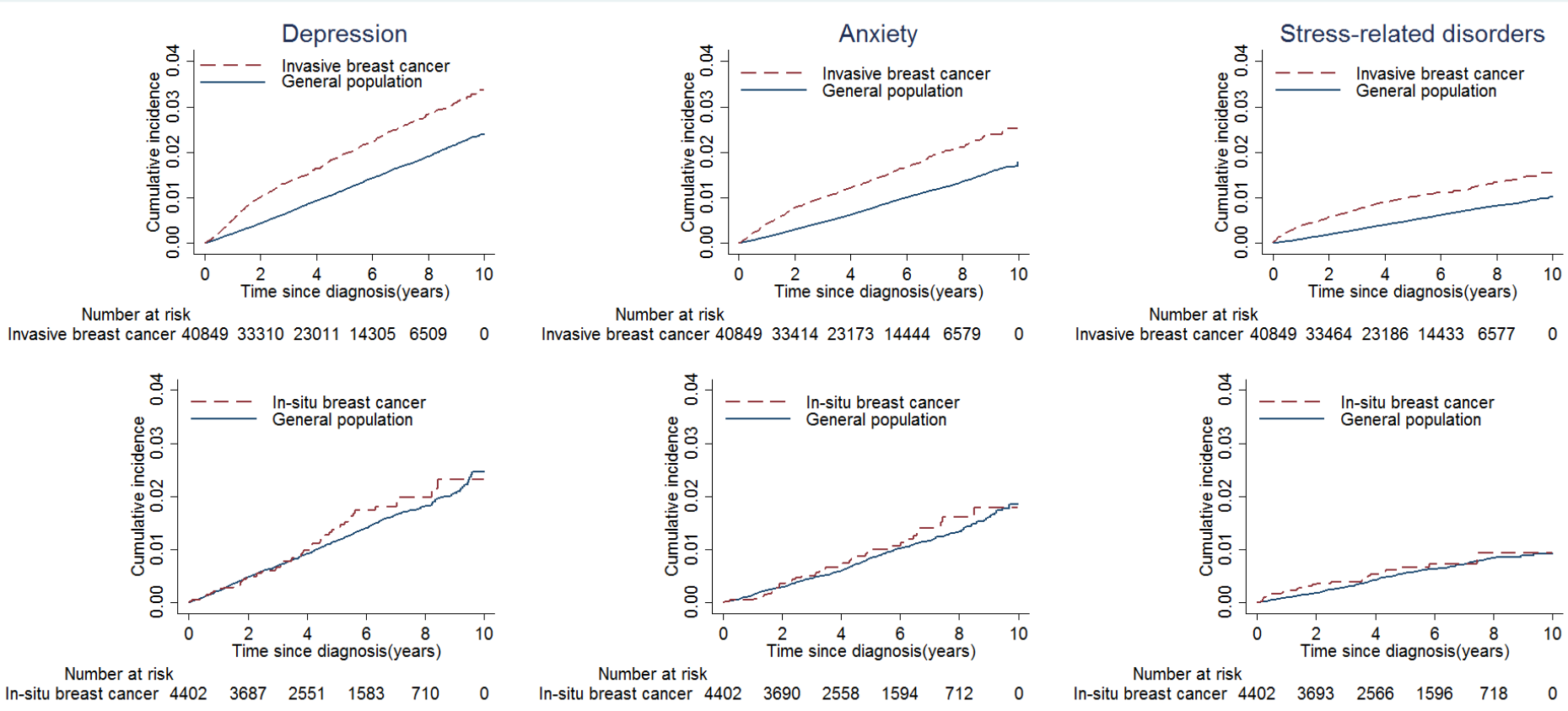
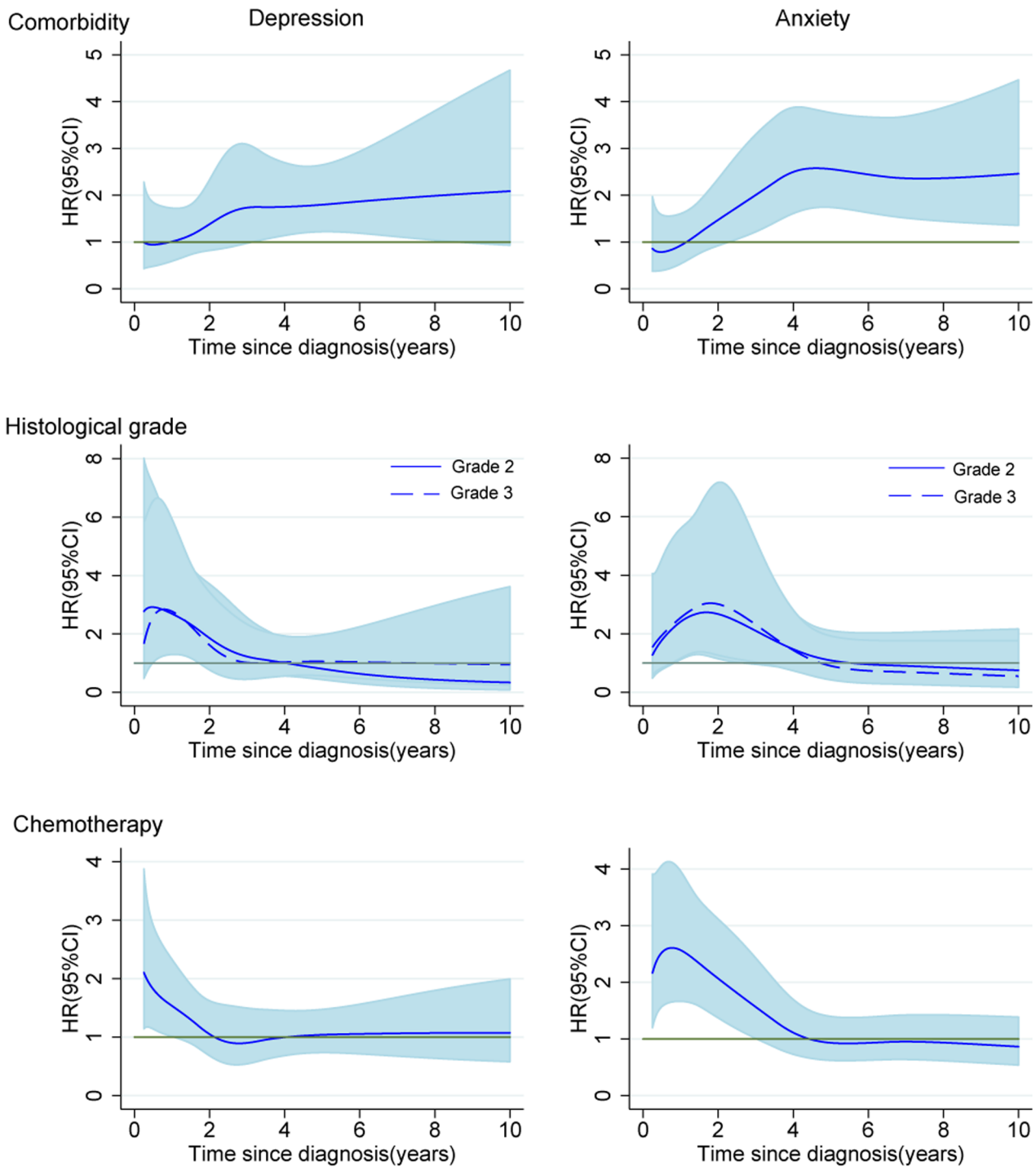

Depression
Invasive breast cancer
General population
Cumulative incidence
0.00 0.01 0.02 0.03 0.04
0 2 4 6 8 10
Time since diagnosis(years)
Number at risk
Invasive breast cancer 40849 33310 23011 14305 6509 0
Anxiety
Invasive breast cancer
General population
Cumulative incidence
0.00 0.01 0.02 0.03 0.04
0 2 4 6 8 10
Time since diagnosis(years)
Number at risk
Invasive breast cancer 40849 33414 23173 14444 6579 0
Stress-related disorders
Invasive breast cancer
General population
Cumulative incidence
0.00 0.01 0.02 0.03 0.04
0 2 4 6 8 10
Time since diagnosis(years)
Number at risk
Invasive breast cancer 40849 33464 23186 14433 6577 0
In-situ breast cancer
General population
Cumulative incidence
0.00 0.01 0.02 0.03 0.04
0 2 4 6 8 10
Time since diagnosis(years)
Number at risk
In-situ breast cancer 4402 3687 2551 1583 710 0
In-situ breast cancer
General population
Cumulative incidence
0.00 0.01 0.02 0.03 0.04
0 2 4 6 8 10
Time since diagnosis(years)
Number at risk
In-situ breast cancer 4402 3690 2558 1594 712 0
In-situ breast cancer
General population
Cumulative incidence
0.00 0.01 0.02 0.03 0.04
0 2 4 6 8 10
Time since diagnosis(years)
Number at risk
In-situ breast cancer 4402 3693 2566 1596 718 0

Figure 3.


Comorbidity
Depression
Anxiety
HR(95%CI)
Time since diagnosis(years)
Histological grade
Grade 2
Grade 3
Chemotherapy

eTable 1. International Classification of Diseases (ICD) codes for depression, anxiety and stress-related disorders.

ICD code	Description	No. of cases in nationwide cohort
Depression		
F320	Mild depressive episode	64
F321	Moderate depressive episode	205
F322	Severe depressive episode without psychotic symptoms	100
F323	Severe depressive episode with psychotic symptoms	19
F328	Other depressive episodes	15
F329	Depressive episode, unspecified	272
F330	Recurrent depressive disorder, current episode mild	20
F331	Recurrent depressive disorder, current episode moderate	52
F332	Recurrent depressive disorder, current episode severe without psychotic symptoms	18
F333	Recurrent depressive disorder, current episode severe with psychotic symptoms	4
F334	Recurrent depressive disorder, currently in remission	19
F338	Other recurrent depressive disorders	2
F339	Recurrent depressive disorder, unspecified	25
Anxiety		
F400	Agoraphobia	13
F401	Social phobias	16
F402	Specific (isolated) phobias	7
F410	Panic disorder (episodic paroxysmal anxiety)	54
F411	Generalized anxiety disorder	43
F412	Mixed anxiety and depressive disorder	287
F413	Other mixed anxiety disorders	3
F418	Other specified anxiety disorders	2
F419	Anxiety disorder, unspecified	188
Stress related disorders		
F430	Acute stress reaction	185
F431	Post-traumatic stress disorder	31
F432	Adjustment disorders	88
F438	Other reactions to severe stress	34
F439	Reaction to severe stress, unspecified	72

eTable 2. Standardized incidence ratios for psychiatric medications in the nationwide cohort of invasive and in-situ breast cancer patients, overall and stratified by age and time since diagnosis

	Antidepressant		Anxiolytics		Hypnotics and sedatives	
	No.	**SIR(95%CI)**	**No.**	**SIR(95%CI)**	**No.**	**SIR(95%CI)**
Overall						
Invasive	1758	**1.95 (1.86-2.04)**	2610	**2.52 (2.43-2.62)**	3578	**3.55 (3.43-3.66)**
In-situ	160	**1.58 (1.36-1.85)**	200	**1.64 (1.43-1.88)**	252	**2.05 (1.81-2.32)**
Age group						
Invasive						
20-44 years	238	**2.43 (2.14-2.76)**	342	**3.96 (3.56-4.40)**	479	**6.31 (5.77-6.90)**
45-54 years	428	**2.23 (2.02-2.45)**	588	**3.04 (2.81-3.30)**	899	**4.63 (4.33-4.94)**
55-64 years	501	**2.00 (1.83-2.18)**	766	**2.50 (2.33-2.68)**	1104	**3.55 (3.35-3.77)**
65-80 years	591	**1.64 (1.51-1.77)**	914	**2.04 (1.91-2.17)**	1096	**2.56 (2.41-2.72)**
In-situ						
20-44 years	16	1.36 (0.84-2.23)	18	1.52 (0.96-2.42)	23	**2.09 (1.39-3.15)**
45-54 years	53	**1.93 (1.48-2.53)**	51	**1.69 (1.28-2.22)**	71	**2.21 (1.75-2.79)**
55-64 years	45	**1.54 (1.15-2.07)**	60	**1.57 (1.22-2.02)**	71	**1.84 (1.46-2.32)**
65-80 years	46	**1.40 (1.05-1.87)**	71	**1.69 (1.34-2.14)**	87	**2.12 (1.72-2.62)**
Time since diagnosis						
Invasive						
0-0.5	427	**2.14 (1.95-2.36)**	1349	**6.13 (5.81-6.47)**	2133	**9.19 (8.81-9.59)**
0.5-1	472	**2.62 (2.40-2.87)**	384	**1.90 (1.72-2.10)**	525	**2.62 (2.41-2.85)**
1-2	527	**1.92 (1.76-2.09)**	470	**1.47 (1.35-1.61)**	541	**1.77 (1.63-1.93)**
2-4.5	332	**1.34 (1.20-1.49)**	407	**1.38 (1.26-1.52)**	379	**1.40 (1.27-1.55)**
In-situ						
0-0.5	46	**2.09 (1.57-2.79)**	97	**3.86 (3.17-4.71)**	131	**4.93 (4.15-5.85)**
0.5-1	30	**1.49 (1.04-2.13)**	22	0.93 (0.61-1.41)	37	**1.53 (1.11-2.11)**
1-2	53	**1.70 (1.30-2.22)**	49	1.28 (0.97-1.70)	48	1.26 (0.95-1.68)
2-4.5	31	1.12 (0.79-1.59)	32	0.91 (0.64-1.28)	36	1.06 (0.76-1.47)

* Abbreviations: SIR = standardized incidence ratio; No. refers to the number of observed cases; CI = confidence interval. SIRs for first use of antidepressant (ATC code: N06A), anxiolytics (ATC: N05B), hypnotics and sedatives (ATC: N05C) in the nationwide breast cancer cohort compared to the general female population (age 20-80 years). SIRs are standardized by calendar period (1-year categories), age (5-year categories), and region of residence (North, Stockholm-Gotland, South, Southeast, Uppsala-Örebro, West).

eTable 3. Hazard ratios of depression, anxiety and stress-related disorders in the regional cohort of invasive breast cancer patients - grouped models.

		Depression		Anxiety		Stress-related disorders	
	Total No.	**No.**	**Grouped model HR (95%CI)**	**No.**	**Grouped model HR (95%CI)**	**No.**	**Grouped model HR (95%CI)**
Patients characteristics							
Age at diagnosis							
23-44 years	1012	86	REF (1.00)	114	REF (1.00)	47	REF (1.00)
45-54 years	1913	115	**0.69 (0.52-0.91)**	109	**0.49 (0.38-0.64)**	64	0.70 (0.48-1.02)
55-64 years	2629	80	**0.34 (0.25-0.47)**	86	**0.27 (0.21-0.36)**	26	**0.20 (0.13-0.33)**
65-80 years	2386	54	**0.27 (0.19-0.38)**	53	**0.19 (0.13-0.26)**	10	**0.09 (0.05-0.18)**
Comorbidities†							
No	6797	287	REF (1.00)	304	REF (1.00)	128	REF (1.00)
Yes	1143	48	**1.38 (1.01-1.89)**	58	**1.66 (1.25-2.22)**	19	1.48 (0.91-2.41)
Tumor characteristics							
Size in mm							
<10	1867	71	REF (1.00)	69	REF (1.00)	37	REF (1.00)
10-20	3320	145	0.99 (0.74-1.32)	149	1.05 (0.78-1.41)	70	1.03 (0.68-1.56)
>20	2348	104	0.92 (0.67-1.27)	121	1.14 (0.83-1.57)	35	0.74 (0.45-1.21)
Histological grade (Elston) †							
Low	899	26	REF (1.00)	26	REF (1.00)	22	REF (1.00)
Moderate	2390	111	1.53 (0.99-2.36)	120	**1.64 (1.07-2.52)**	44	0.74 (0.44-1.25)
High	1476	91	**1.62 (1.02-2.58)**	98	**1.89 (1.20-2.99)**	36	0.73 (0.41-1.31)
Lymph nodes							
Negative	4702	177	REF (1.00)	183	REF (1.00)	87	REF (1.00)
Positive	2750	149	**1.42 (1.13-1.79)**	162	**1.40 (1.12-1.75)**	54	1.07 (0.75-1.52)
ER status							
Positive	5952	236	REF (1.00)	276	REF (1.00)	111	REF (1.00)
Negative	1271	73	1.31 (0.98-1.74)	62	0.85 (0.63-1.14)	28	1.06 (0.67-1.68)
Treatment characteristics							
Endocrine therapy							
No	1346	75	REF (1.00)	64	REF (1.00)	33	REF (1.00)
Yes	6303	252	0.87 (0.66-1.14)	283	1.27 (0.96-1.69)	112	0.83 (0.55-1.26)
Chemotherapy†							
No	4912	158	REF (1.00)	159	REF (1.00)	80	REF (1.00)
Yes	2720	167	**1.36 (1.07-1.73)**	186	**1.59 (1.26-2.01)**	64	0.81 (0.56-1.18)
Radiotherapy							
No	1810	72	REF (1.00)	81	REF (1.00)	31	REF (1.00)
Yes	5839	254	1.20 (0.88-1.63)	267	1.09 (0.81-1.46)	114	0.89 (0.55-1.44)
Surgery							
Partial mastectomy	4627	181	REF (1.00)	188	REF (1.00)	92	REF (1.00)
Total mastectomy	3048	147	1.28 (0.98-1.66)	160	1.27 (0.98-1.64)	53	0.77 (0.51-1.17)

Abbreviations: HR = hazard ratio; CI = confidence interval. Hazard ratios were estimated from flexible parametric survival models with time since diagnosis as underlying time scale. Grouped models include respectively all patient, tumor or treatment characteristics with additional adjustment for age and calendar period. Missingness on individual variables < 5 %, except for histological grade (39.0%, N = 3,042), which was included in the Stockholm-Gotland Breast Cancer Register from 2004 onward and ER status (7.6%, N = 590). Patients with distant metastases at diagnosis are not included in this model (because of missing values on tumor characteristics) as these patients do not undergo routine surgery. † The proportional hazards assumption was met for all variables, except for comorbidities, histological grade and chemotherapy.

eTable 4. Time-dependent effects of comorbidity, histological grade and chemotherapy in the regional cohort of invasive breast cancer patients, with hazard ratios at specific time points following diagnosis.

	HR of depression (95% CI)				HR of anxiety (95% CI)			
	Year 1	**Year 2**	**Year 5**	**Year 10**	**Year 1**	**Year 2**	**Year 5**	**Year 10**
Patient characteristics								
Comorbidity								
No	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Yes	1.01 (0.59-1.73)	1.38 (0.82-2.33)	**1.80 (1.22-2.65)**	2.09 (0.93-4.67)	0.93 (0.54-1.61)	1.47 (0.92-2.35)	**2.56 (1.74-3.76)**	**2.46 (1.36-4.46)**
Tumor characteristics								
Histological grade (Elston)								
Low	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Moderate	**2.69 (1.31-5.51)**	1.86 (0.93-3.71)	0.80 (0.43-1.49)	0.34 (0.08-1.43)	**2.41 (1.12-5.21)**	**2.67 (1.14-6.25)**	1.09 (0.56-2.11)	0.75 (0.26-2.17)
High	**2.77 (1.29-5.94)**	1.62 (0.76-3.43)	1.06 (0.57-1.97)	0.95 (0.25-3.62)	**2.55 (1.16-5.60)**	**3.01 (1.27-7.17)**	0.90 (0.42-1.93)	0.55 (0.17-1.76)
Treatment characteristics								
Chemotherapy								
No	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Yes	1.45 (0.96-2.19)	0.99 (0.65-1.52)	0.99 (0.70-1.39)	1.03 (0.56-1.92)	**2.28 (1.48-3.50)**	**1.82 (1.21-2.72)**	0.85 (0.57-1.27)	0.80 (0.50-1.28)

Abbreviations: HR = hazard ratio; CI = confidence interval. Time-dependent hazard ratios as estimated from flexible parametric survival models with time since diagnosis as underlying time scale, allowing the effect of each characteristic to vary over time. Hazard ratios are from multivariable adjusted models, including all patient, tumor and treatment characteristics and calendar period of diagnosis.

eTable 5. Hazard ratios of depression, anxiety and stress-related disorders by patient, tumor and treatment characteristics in the regional cohort of invasive breast cancer patients with additional censoring at recurrent events and new-onset comorbidity.

	HR (95%CI) of depression		HR (95%CI) of anxiety		HR(95%CI) of stress-related disorder	
	Censoring at recurrence	**Censor at comorbidity**	**Censoring at recurrence**	**Censoring at comorbidity**	**Censoring at recurrence**	**Censoring at comorbidity**
Patients characteristics						
Age at diagnosis						
23-44 years	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
45-54 years	0.79 (0.58-1.07)	0.82 (0.60-1.12)	**0.61 (0.45-0.81)**	**0.61 (0.45-0.81)**	0.77 (0.51-1.19)	0.79 (0.50-1.26)
55-64 years	**0.44 (0.32-0.61)**	**0.43 (0.30-0.60)**	**0.34 (0.25-0.47)**	**0.32 (0.23-0.45)**	**0.23 (0.14-0.40)**	**0.21 (0.12-0.40)**
65-80 years	**0.37 (0.25-0.54)**	**0.32 (0.21-0.50)**	**0.28 (0.19-0.41)**	**0.16 (0.10-0.27)**	**0.11 (0.05-0.23)**	**0.13 (0.06-0.30)**
Tumor characteristics						
Size in mm						
<10	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
10-20	0.93 (0.69-1.26)	0.88 (0.64-1.22)	0.89 (0.65-1.22)	0.74 (0.53-1.05)	1.04 (0.66-1.63)	1.05 (0.63-1.76)
>20	0.82 (0.58-1.15)	0.69 (0.48-1.01)	0.90 (0.63-1.27)	0.94 (0.65-1.35)	0.81 (0.47-1.41)	0.85 (0.46-1.59)
Histological grade (Elston)						
Low	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Moderate	1.51 (0.97-2.33)	1.42 (0.88-2.29)	**1.56 (1.00-2.43)**	**2.07 (1.19-3.60)**	0.79 (0.46-1.36)	0.86 (0.46-1.60)
High	1.50 (0.92-2.43)	1.46 (0.86-2.46)	1.60 (0.98-2.61)	**2.18 (1.20-3.95)**	0.69 (0.36-1.33)	0.78 (0.37-1.65)
Lymph nodes						
Negative	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Positive	1.30 (0.98-1.71)	1.25 (0.93-1.69)	1.09 (0.82-1.44)	**1.40 (1.04-1.90)**	1.05 (0.68-1.64)	1.14 (0.69-1.87)
ER status						
Positive	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Negative	1.40 (0.84-2.33)	0.95 (0.55-1.66)	0.75 (0.43-1.29)	0.75 (0.42-1.36)	0.89 (0.41-1.95)	0.62 (0.25-1.51)
Treatment characteristics						
Endocrine therapy						
No	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Yes	1.11 (0.67-1.84)	0.77 (0.45-1.31)	1.02 (0.60-1.73)	1.01 (0.57-1.77)	0.68 (0.33-1.44)	0.51 (0.22-1.16)
Chemotherapy						
No	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Yes	1.19 (0.87-1.61)	1.28 (0.92-1.79)	**1.62 (1.19-2.21)**	**1.40 (1.01-1.96)**	0.93 (0.56-1.53)	0.94 (0.53-1.65)
Radiotherapy						
No	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Yes	1.12 (0.80-1.57)	0.99 (0.69-1.43)	0.96 (0.69-1.33)	0.96 (0.67-1.37)	0.93 (0.54-1.59)	0.66 (0.36-1.22)
Surgery						
Partial mastectomy	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)	REF (1.00)
Total mastectomy	1.15 (0.85-1.55)	1.09 (0.79-1.51)	1.13 (0.83-1.52)	1.01 (0.74-1.38)	0.84 (0.52-1.37)	0.58 (0.33-1.03)

*All hazard ratios are multivariable adjusted and refer to analyses with either additional censoring at current events or new-onset comorbidity. Missingness on individual variables < 5%, except for histological grade (39.0%, N = 3,042), which was included in the Stockholm-Gotland Breast Cancer Register from 2004 onward and ER status (7.6%, N = 590).). Patients with distant metastases at diagnosis are not analyzed in the models (because of missing values on tumor characteristics) as these patients do not undergo routine surgery.