PREDICTION OF DISTRESS IN BREAST CANCER SURVIVORS

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ABSTRACT

According to the most recent global cancer statistics, 1.67 million new cases of breast cancer were diagnosed worldwide in 2012, accounting for an estimated 25% of new cancer cases in women. Approximately 1 in every 3 of these women will develop distress following breast cancer diagnosis.

Cancer-related distress has been recognized as an important sequela of cancer diagnosis and its treatment. To address this issue, cancer care agencies have recommended routine screening for distress at appropriate intervals throughout hospital-based treatment and survivorship. However, given the current structure of post-treatment follow-up in Canada, routine screening for already-present distress by the oncology care team may not be the most effective strategy to address cancer-related distress in survivorship. A viable alternative is risk stratification, which focuses on prevention rather than detection. This approach enables use of evidence-based resources to be targeted toward patients with an increased risk of an adverse outcome rather than applying a uniform approach across all patients regardless of risk.

The overarching goal of this Doctoral research program was to help identify breast cancer survivors at higher risk of new-onset distress to guide allocation of supportive care resources. The thesis focused on the first year after completion of hospital-based treatment (i.e., transitional survivorship), where women transition to routine follow-up care and have fewer contacts with the oncology care team. The following three objectives were completed to address this goal:

1. To synthesize the published literature around the predictors of distress in breast cancer survivors

2. To use routinely collected administrative health data to:
    a. Develop a risk stratification algorithm to identify breast cancer survivors at higher risk of new-onset distress during transitional survivorship
    b. Compare and contrast predictors of new-onset distress during transitional survivorship with predictors of new-onset distress during hospital-based treatment

3. To use gold standard electronic medical record data to:
    a. Adjust for potential outcome misclassification when including psychotropic medication dispensations as indicators of new-onset distress
    b. Assess the impact of outcome misclassification on the fit of the transitional survivorship risk stratification model

The first study identified evidence-based predictors of distress in breast cancer survivors including sociodemographic characteristics, breast cancer characteristics and treatments, treatment-related symptoms and comorbidities. These results were used to inform selection of candidate predictors in the administrative health data. The next study identified the best set of candidate predictors to identify women at higher risk of new-onset distress during transitional survivorship; the majority of the predictors were new diagnoses or events that occurred during the survivorship follow-up period. The resulting risk stratification model generated a c-statistic of 0.60 in the validation cohort. As anticipated, the predictors of new-onset distress during transitional survivorship differed

from the predictors of new-onset distress during the hospital-based treatment period. The last study demonstrated substantial outcome misclassification when using psychotropic medication dispensations as indicators of new-onset distress; the adjusted estimate of the incidence was 37% lower than the uncorrected estimate. Positively, adjustment for this misclassification in the transitional survivorship risk stratification model, generally, did not impact the statistical significance or interpretation of the predictors compared with the uncorrected model. However, the results supported the exclusion of four predictors, and placing greater weight on three of the other predictors.

In conclusion, although the transitional survivorship risk stratification model only moderately improved prediction, the findings can be used to inform development of more accurate algorithms. The results also highlighted the importance of tailoring risk stratification models to the period of the cancer care trajectory as well as consideration of newly occurring diagnoses and events as candidate predictors when developing algorithms in the future.

RÉSUMÉ

Selon les dernières statistiques mondiales sur le cancer, 1,67 million de nouveaux cas de cancer du sein ont été diagnostiqués dans le monde en 2012, ce qui représente environ 25 % des nouveaux cas de cancer chez les femmes. Parmi celles-ci, environ 1 femme sur 3 développera de la détresse à la suite d'un diagnostic de cancer du sein.

La détresse liée au cancer a été reconnue comme une séquelle importante du diagnostic du cancer et de son traitement. Afin de résoudre ce problème, les organismes de soins aux personnes atteintes de cancer ont recommandé un dépistage systématique de la détresse à des intervalles appropriés dans le cadre du traitement hospitalier et de la survie. Cependant, compte tenu de la structure actuelle du suivi post-traitement au Canada, le dépistage systématique de la détresse déjà présente par l'équipe de soins en oncologie peut ne pas être la stratégie la plus efficace afin de remédier à la détresse liée au cancer dans la survie. Une option viable est la stratification du risque, qui se concentre sur la prévention plutôt que sur la détection. Cette approche permet d'utiliser des ressources fondées sur des données probantes orientées vers les patients présentant un risque accru de répercussions néfastes plutôt que d'appliquer une approche uniforme chez tous les patients, quel que soit le risque.

L'objectif primordial de ce programme de recherche doctorale était d'aider à identifier les survivantes du cancer du sein présentant un risque plus élevé d'apparition de détresse afin d'orienter l'allocation des ressources de soins de soutien. La thèse portait sur la première année après l'achèvement du traitement hospitalier (c.-à-d. la survie transitoire), où les femmes passent vers des soins de suivi de routine et ont moins de

contacts avec l'équipe de soins oncologiques. Les trois objectifs suivants ont été complétés afin d'atteindre cet objectif :

1. synthétiser la littérature publiée portant sur les prédicteurs de la détresse chez les survivantes du cancer du sein;

2. utiliser les données de santé administratives recueillies de façon routinière pour :
    a. élaborer un algorithme de stratification des risques afin d'identifier les survivantes du cancer du sein présentant un risque plus élevé d'apparition de détresse pendant une survie transitoire;
    b. comparer et contraster les prédicteurs d'apparition de détresse pendant une survie transitoire aux prédicteurs d'apparition de détresse pendant un traitement hospitalier;

3. utiliser les données de référence standard du dossier médical informatisé pour :
    a. faire un ajustement pour une classification erronée potentielle des résultats lorsqu'on inclut les dispensations de médicaments psychotropes comme indicateurs d'apparition de détresse
    b. évaluer l'impact de la classification erronée des résultats sur l'ajustement du modèle de stratification du risque de survie transitoire.

La première étude a identifié des prédicteurs fondés sur des données probantes relatives à la détresse chez les survivantes du cancer du sein, y compris les caractéristiques sociodémographiques, les caractéristiques et les traitements du cancer du sein, les symptômes liés au traitement et les comorbidités. Ces résultats ont été utilisés

afin d'informer la sélection des prédicteurs candidats dans les données de santé administratives. L'étude suivante a identifié le meilleur ensemble de prédicteurs candidats afin d'identifier les femmes présentant un risque plus élevé d'apparition de détresse pendant une survie transitoire; la majorité des prédicteurs étaient de nouveaux diagnostics ou des événements survenus pendant la période de suivi de survie. Le modèle de stratification des risques résultant a généré une statistique C de 0,60 dans la cohorte de validation. Comme prévu, les prédicteurs d'apparition de détresse pendant la survie transitoire différaient des prédicteurs d'apparition de détresse pendant la période de traitement hospitalière. La dernière étude a démontré une classification erronée importante des résultats lors de l'utilisation des dispensations de médicaments psychotropes comme indicateurs d'apparition de détresse; l'estimation ajustée de l'incidence était 37 % inférieure à l'estimation non corrigée. Positivement, l'ajustement de cette classification erronée dans le modèle de stratification de risque de survie transitoire n'a généralement pas eu d'impact sur la signification ou l'interprétation statistique des prédicteurs par rapport au modèle non corrigé. Cependant, les résultats ont soutenu l'exclusion de quatre prédicteurs et ont mis plus de poids sur trois des autres prédicteurs.

En conclusion, bien que le modèle de stratification de risque de survie transitoire ait seulement amélioré modérément la prédiction, les résultats peuvent être utilisés afin d'informer le développement d'algorithmes plus précis. Les résultats ont également mis en évidence l'importance d'adapter les modèles de stratification du risque à la période de la trajectoire de soins du cancer, ainsi que la prise en compte des nouveaux diagnostics et d'événements comme prédicteurs candidats lors du développement d'algorithmes à l'avenir.

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CONTRIBUTIONS OF AUTHORS

This thesis was completed under the supervision of Dr. Robyn Tamblyn (primary supervisor), Dr. Ari Meguerditchian (co-supervisor), Dr. James Hanley (committee member), and Dr. William Dixon (committee member).

In collaboration with the co-authors, I conceptualized and designed this program of research. For the first study, I developed the systematic review search strategy, served as the primary reviewer, conducted the data abstraction and analyses, interpreted the results, and drafted the final manuscript. For the second and third studies, I was responsible for the database management and linkage to construct the final Régie de l'assurance maladie du Québec (RAMQ) datasets, conducted the data analyses, interpreted the results, and drafted the final manuscripts.

Dr. Robyn Tamblyn is a professor in the Department of Epidemiology, Biostatistics and Occupational Health at McGill University, and the Scientific Director of the Clinical and Health Informatics Research Group. Dr. Tamblyn provided methodological guidance and feedback, helped with interpretation of the results, and provided editorial feedback on the manuscripts for all three studies. Dr. Tamblyn also provided the data from the Medical Office of the 21st Century (MOXXI) research platform, which made the last study possible.

Dr. Ari Meguerditchian is a surgical oncologist at the McGill University Health Centre, and a member of the Clinical and Health Informatics Research Group. Dr. Meguerditchian provided substantive expertise for the design and conduct of this

program of research, helped with interpretation of the results, and provided editorial feedback on the manuscripts for all three studies. Dr. Meguerditchian also acquired the RAMQ data that was used for the second and third studies.

Dr. James Hanley is a professor in the Department of Epidemiology, Biostatistics and Occupational Health. Dr. Hanley provided statistical expertise for the design and conduct of this program of research, helped with interpretation of the results, and provided editorial feedback on the manuscripts for all three studies.

Dr. William Dixon is a rheumatologist at the Salford Royal NHS Foundation Trust, professor at the University of Manchester, and a member of the Farr Institute of Health Informatics Research. Dr. Dixon provided substantive and methodological expertise for the design and conduct of this program of research, and provided editorial feedback on the first manuscript.

Dr. Aude Motulsky was a postdoctoral fellow in the Clinical and Health Informatics Research Group. Dr. Motulsky served as the duplicate title/abstract reviewer for the first study, and provided editorial feedback on the first manuscript.

Ms. Siyana Kurteva is a graduate student in the Clinical and Health Informatics Research Group. Ms. Kurteva served as the duplicate full-text reviewer and conducted the 10% duplicate data abstraction for the first study, and provided editorial feedback on the first manuscript.

Ms. Daniala Weir is a doctoral candidate in the Clinical and Health Informatics Research Group. Ms. Weir provided methodological guidance for the data analyses conducted in the second study.

Ms. Nadyne Girard is an analyst and project coordinator in the Clinical and Health Informatics Research Group. Ms. Girard conducted the database management and linkage to construct the final Medical Office of the 21st Century (MOXXI) dataset used for the third study.

STATEMENT OF ORIGINALITY

This thesis constitutes original scholarship and distinct contributions to knowledge around the prediction of distress in breast cancer survivors. The first study provides the first synthesis of the literature around predictors of distress in breast cancer survivors. The systematic review focused on predictors of *prevalent* distress driven by the lack of published literature around *new-onset* distress in breast cancer survivors, which emphasizes the original contributions of the next two studies to this field.

To my knowledge, the second study is the first attempt to develop a risk stratification algorithm using routinely collected administrative health data to identify breast cancer patients at higher risk of new-onset distress during the transitional survivorship period. Other studies have investigated predictors of new-onset depression in breast cancer populations using administrative health data; however, the time-to-event analyses were conducted using an underlying time scale of time since breast cancer diagnosis. This approach may have obscured the estimates for predictors of new-onset depression during transitional survivorship, given that these predictors are expected to differ from predictors of new-onset depression during hospital-based treatment.

The third study contributed to the literature by measuring the extent of outcome misclassification as a result of including psychotropic medication dispensations as indicators of new-onset distress, and assessing the impact of this misclassification on the fit of the transitional survivorship risk stratification model. Other studies that have used similar outcomes have either ignored the problem of outcome misclassification or simply acknowledged it in the discussion of limitations.

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CHAPTER 1 – BACKGROUND

Incidence of and survival rates following breast cancer diagnosis

According to the most recent global cancer statistics, 1.67 million new cases of breast cancer were diagnosed worldwide in 2012, accounting for approximately 25% of new cancer cases in women.[1] More specific to the North American context, an estimated 25,700 Canadian women were diagnosed with breast cancer in 2016 representing 25.9% of new female cancer cases.[2] Currently, Canadian women have an estimated overall 11.7% lifetime risk of breast cancer, with the risk of developing breast cancer within the next 10 years reaching over 10% by the age of 60 years.[2] Given that breast cancer incidence is higher in older women, the number of new annual cases is expected to increase as a result of demographic changes in age distributions.[2] In fact, the breast cancer incidence rate has increased an estimated 3% over the last decade.[2]

Medical advances including more timely detection through screening mammography as well as treatment with better and more targeted tumor eradication therapies has dramatically improved survival after breast cancer diagnosis.[3] In fact, age-standardized breast cancer mortality rates have decreased by an estimated 44% since the mid-1980s.[4] Of the estimated 37,100 female cancer deaths in Canada in 2016, only 13.2% (~ 4,823 deaths) were attributable to breast cancer.[2] These medical advances have generated a large cohort of women living after completion of hospital-based breast cancer treatment with current five- and ten-year disease-specific survival rates of 87% and 82%, respectively.[2] Clinicians and researchers are now focusing on psychosocial and other patient-centered outcomes to improve quality as well as quantity of survivorship care.

The concept of cancer-related distress and its implications

Cancer-related distress has been recognized as an important sequela of cancer diagnosis and its treatment.[4] The National Comprehensive Cancer Network (NCCN) has developed a formal definition of this phenomenon: "Distress is a multifactorial unpleasant emotional experience of a psychological (i.e., cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis" (Figure 1-1).[4,5] The term distress was selected in an effort to reduce stigma around cancer-related mental health problems; however, the definition includes the onset or exacerbation of the following psychological conditions: (1) dementia; (2) delirium; (3) depressive disorders; (4) bipolar and related disorders; (5) schizophrenia spectrum and other psychotic disorders; (6) anxiety disorders; (7) trauma and stressor-related disorders; (8) adjustment disorders; (9) obsessive-compulsive disorders; (10) substance-related and addictive disorders; and (11) personality disorders.[4]

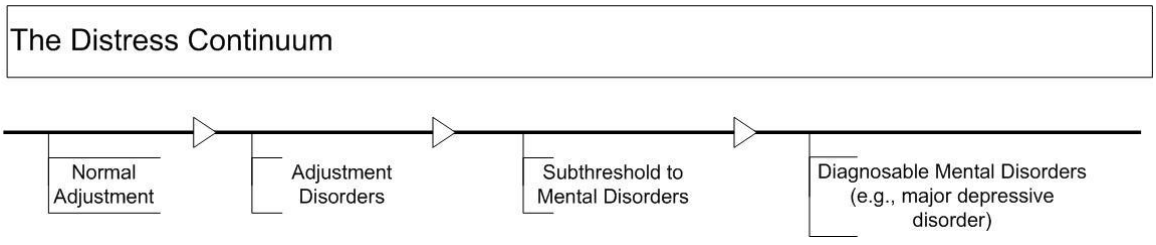

Figure 1-1. The National Cancer Institute (NCI) distress continuum[5]

Experience of significant distress, namely any distress on the continuum beyond normal adjustment can have negative implications beyond affecting breast cancer patients' quality of life; most importantly, distress and its treatment have been shown to increase all-cause and cancer-related morbidity and mortality.[6] Unmanaged distress has been shown to cause insomnia, weight loss or gain, and increased levels of stress hormones, which reduce immune function making patients more susceptible to any illness including breast cancer recurrence.[7] It can also have indirect effects on health by influencing patient behaviors. For example, depression has been associated with non-adherence to prescription medications in general[8] as well as cancer-related treatments, such as chemotherapy and anti-estrogen therapy (AET) intended to prevent cancer recurrence.[9,10]

On the other hand, pharmacological management of distress may lead to direct effects or drug-drug interactions that may also affect survival. For example, specific medications indicated for depression have been shown to reduce the efficacy of AET.[11] Commonly prescribed selective serotonin reuptake inhibitors (SSRIs) may inhibit metabolism of Tamoxifen to its active form, thereby reducing its anti-cancer properties and increasing the risk of recurrence and premature mortality. Disease-free survival time is reduced and mortality rates are higher in breast cancer populations that experience distress. In fact, women who develop new depression or bipolar disorder following breast cancer diagnosis have a 45% increased risk of all-cause mortality, as compared with breast cancer patients who did not experience this type of distress.[12]

Prevalence of distress in cancer populations

Studies have primarily focused on the prevalence of depressive and anxiety disorders in cancer patients. In general, the estimates are varied with systematic reviews reporting wide ranges. One of the first reviews reported that the prevalence of depressive disorders in cancer patients could vary from 0% to 58% with the estimated prevalence in breast cancer patients ranging from 1.5% to 46%.[13] More recently, a systematic review and meta-analysis of antidepressant use by cancer patients found that 16% (95% confidence interval [95% CI]: 13% to 18%) used antidepressants during hospital-based treatment and early survivorship with a higher prevalence of medication use in breast cancer populations at 23% (95% CI: 16% to 31%).[14] A systematic review that focused on breast cancer survivors found that the prevalence of depression varied from 1% to 56% with median values of 10% – 22% and 16% when measured using validated distress scales or clinical interviews, respectively. A different systematic review that summarized prevalence estimates for both depression and anxiety in breast cancer survivors reported averages of 40% (range: 9% to 66%) and 21% (range: 18% to 33%), respectively.[15] The wide variance in prevalence estimates can be attributed to different conceptualizations or definitions of distress, various methodological approaches to measurement as well as differences between populations under study.[13] However, these findings consistently show that breast cancer patients are more likely to experience distress as compared with other cancer populations, further highlighting the importance of addressing cancer-related distress in this higher-risk population.

Difficulty with diagnosing distress in an oncology setting

It is difficult for oncologists to identify distress and refer patients for appropriate treatment during routine cancer care. Reasons range from significant overlaps in prodromal symptoms of distress and cancer treatment-related side effects (e.g., fatigue, insomnia, cognitive impairment, or weight loss) to patients' reluctance to disclose distress due to stigma around mental health problems or the assumption that distress is a part of the cancer experience.[16,17] Oncologist-patient agreement has been shown to be low for detection of mild (33%) and moderate/severe depression (13%), corresponding to a kappa of 0.17.[18] In fact, oncologists were found to miss 61% of mild and 49% of moderate/severe cases of depression.

NCCN recommendations for the standard of care for management of distress

To address this unmet patient need, the NCCN has developed guidelines that promote routine screening of cancer patients using a 'distress thermometer' at oncology visits. Screening should be conducted at appropriate intervals throughout hospital-based treatment and post-treatment survivorship, and at important clinical time points including remission, recurrence, progression, or treatment-related complications.[4,19] However, these consensus-based guidelines are intended to be adapted to specific clinical and patient contexts, and do not provide evidence-based recommendations around appropriate or minimal screening frequency requirements. As a result, implementation of the guidelines has been pragmatic. The Commission on Cancer mandated distress screening at every oncology visit in American cancer treatment institutions starting in 2015; however, research has shown that adherence is sub-optimal, ranging from 47% to 73% of eligible

patients being screened.[20,21] Given that this screen-all approach is time and resource intensive, it may not be feasible to implement this practice across all oncology clinics.

Canadian cancer care organizations have also endorsed the NCCN guidelines and mandated routine distress screening.[22] However, 61.4% of women have low provider continuity with oncologists after completion of hospital-based treatment for breast cancer. On average, these women will attend 4.1 visits with oncologists within the first year following completion of treatment, split between a mean of 1.4, 0.8, and 1.9 visits with medical, radiation, and surgical oncologists, respectively.[23] In addition, there is substantial heterogeneity in care with approximately 37% of women attending two or fewer follow-up visits within the first year of survivorship.[23] Therefore, based on the guidelines, a substantial proportion of women will be screened less often than twice a year following completion of hospital-based treatment even with perfect adherence to distress guidelines. Furthermore, it is known that patients who suffer from distress are less likely to adhere to recommended cancer care such as attending follow-up visits,[24] suggesting that women at higher risk of experiencing distress may, in fact, be screened less often. As a result of suboptimal screening rates and inequitable adherence to recommended breast cancer follow-up care, many cases of distress may not be detected until patients manifest and seek care for more serious clinical symptoms associated with diagnosable mental health problems. Therefore, given the current structure of post-treatment follow-up in Canada, implementation of routine screening for already-present distress by oncologists may not be the most effective strategy to address cancer-related distress in survivorship.

Risk stratification as a viable alternative for optimizing management of distress

A viable alternative is risk stratification, which focuses on prevention rather than detection. This approach enables use of evidence-based resources to be targeted toward patients with an increased risk of an adverse event rather than applying a uniform approach across all patients regardless of risk.[25] Risk stratification aims to optimize integrated care in an effort to identify and intervene upon patients that are most likely to benefit from preventive interventions.

Risk stratification is particularly relevant in this context, as there are effective interventions to prevent onset of distress.[33–35] Strategies aimed to improve strength of resilience and develop effective coping strategies can prevent distress entirely, or prevent subclinical symptoms from progressing to diagnosable mental health problems.[36,37] Meta-analyses have shown that 21% to 38% of depressive disorders could be prevented with currently available interventions.[33–35] More specific to breast cancer survivors, prophylactic cognitive behavioral therapy (CBT) has been shown to be effective in reducing incidence of depression and anxiety in higher-risk cancer patients by half.[38] If breast cancer survivors could be identified as higher risk, then prevention strategies to mitigate this risk could be integrated into women's survivorship care plans. The care plans could recommend appropriate follow-up times and specify the coordinating provider responsible for preventive strategies and management of distress.[39]

There have been many successful risk stratification tools in other areas of medicine, including the Framingham risk score for developing cardiovascular disease, the Gail model for risk of breast cancer, and the Fracture Risk Assessment Tool (FRAX) for

risk of fracture occurrence.[26–28] More specific to the context of this thesis, predictive algorithms have been developed to estimate risk of new-onset distress in general practice populations.[29–32] More recently developed prognostic models, such as Hospital Admission Risk Prediction (HARP) and Patients at Risk of Readmission (PARR), have further optimized risk stratification by capitalizing on routinely collected administrative health data.[40,41] Administrative health data holds immense potential for population-based risk stratification. This type of data is increasingly available to healthcare teams and policymakers, feasible to access at the point of care, and time and resource efficient. Furthermore, if risk stratification tools for multiple conditions are to be developed and integrated into medical practice, then use of routinely collected administrative health and clinical data is the only feasible option, and represents the future of healthcare risk stratification.

Measurement of distress and its predictors in administrative health data

Incidence and prevalence of distress can be measured using administrative health databases with two complementary approaches: (a) directly using formal diagnoses of mental health problems based on documented International Classification of Diseases (ICD) diagnostic codes, and (b) indirectly using dispensations of medications that are commonly indicated for management of distress. However, both distress case ascertainment approaches have limitations.

Current reporting structures allowing only one ICD code to be documented as well as ongoing stigmatization around mental health problems and the reluctance to medicalize cancer-related distress have resulted in underreporting of relevant ICD

diagnostic codes in the administrative health data.[4,42,43] As a result, true cases of distress may not be documented in administrative medical services data. However, ICD codes for depression and anxiety have been shown to have positive predictive values of 93%, indicating that if these codes are documented then the diagnosis for distress is likely to be correct.[44]

Alternatively, measuring distress based on psychotropic medication dispensations from administrative prescription drug claims databases may include some women that are not truly distressed; thereby overestimating the incidence of new-onset distress. For example, antidepressants have been prescribed for indications other than distress, such as sleep disorders, migraine headaches, or pain.[45]

Furthermore, little is known about indicators available in administrative health data that can be used to predict onset of distress in breast cancer survivors. The published literature primarily describes predictors of prevalent distress based on relatively small sample sizes driven by the data collection methods employed for distress case ascertainment, namely validated distress scales and clinical interviews.[46]

Value of administrative health data to predict new-onset distress

Nevertheless, capitalizing on administrative health data to predict new-onset cancer-related distress can contribute to knowledge in this area and inform evidence-based decision making. A limited number of time-to-event analyses have investigated factors associated with onset of new depression in breast cancer patients.[47,48] One study reported independent associations of breast cancer recurrence, diagnosis of a new primary

cancer, higher number of tumor-positive axillary lymph nodes, being unemployed and not having children living in the home with new antidepressant use after breast cancer diagnosis.[47] Another study conducted by the same lead investigator reported independent associations of living alone, vocational or basic education levels, higher Charlson comorbidity index (CCI) score, larger breast tumor size and higher number of positive axillary lymph nodes with new antidepressant use.[48] The underlying time scales of these time-to-event studies were time since breast cancer diagnosis.

However, to date, there have not been any time-to-event analyses conducted to identify predictors of new-onset distress in women who have completed hospital-based breast cancer treatment. The survivorship period may be understudied due to the difficulty in ascertaining the date at which women complete hospital-based breast cancer treatment and transition into survivorship based on information documented in the administrative health data. Despite this difficulty, there is value in stratifying predictive algorithms by period of the cancer care trajectory to compare women faced with similar cancer-related challenges.

The breast cancer care trajectory

The cancer care trajectory outlines breast cancer patients' paths toward recovery and consists of two distinct parts that occur after definitive diagnosis: hospital-based treatment and survivorship. Figure 1-2 presents the general periods of the cancer care trajectory based on clinical experience and the literature: pre-cancer baseline (the reference period prior to the diagnostic work-up), diagnostic work-up (the 2 months prior

to definitive breast cancer diagnosis), hospital-based treatment (variable in duration), and survivorship (first-year transitional survivorship and onwards).[49]

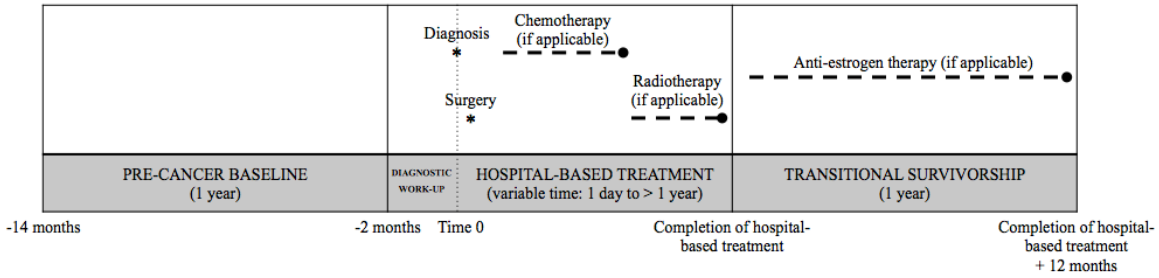

Figure 1-2. The usual breast cancer care trajectory[49]

Hospital-based treatment for breast cancer follows the diagnostic work-up period and most often begins with breast surgery.[50] In the case of non-metastatic breast disease (stages I to IIIA, which represent the majority of cases), women have the option to receive either breast-conserving surgery or total mastectomy. Breast-conserving surgery is also called lumpectomy or partial mastectomy, and consists of removing only a part of the breast surrounding the tumor. Total mastectomy results in removal of the whole breast, and in more advanced stages modified radical mastectomy may include removal of lymph nodes or lining over the chest muscles. Breast cancer surgery also includes sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND). SLNB involves examining the closest lymph node to assess regional spread of the cancer; if cancer is detected, additional lymph nodes may be removed. In ALND, lymph nodes are removed based on identification of positive lymph nodes from the SLNB as well as clinically palpable or radiologically identifiable lymph nodes.

Following surgery, women usually receive one or more of the following adjuvant treatments to prevent breast cancer recurrence: chemotherapy, radiation, or AET.[50]

Chemotherapy involves systemic cytotoxic infusions to target cancer cells that have spread beyond the breast. Infusions are administered every four weeks for three to six months. Radiotherapy uses high-energy radiation to eliminate any remaining cancer cells in the breast to optimize local cancer control. There are two main forms: external beam radiation and brachytherapy (also called accelerated partial breast irradiation). External beam radiation is the most common form for radiotherapy. Treatments are given for five days each week for a period of three to six weeks. Brachytherapy is only administered in approximately 3% of breast cancer cases.[51] The duration of treatment is much shorter, lasting between one to five days, compared with more traditional external beam radiation.

Once breast surgery and adjuvant therapy have eradicated the tumor, the cancer goes into remission and women begin the survivorship phase of the cancer care trajectory. The focus of the oncology care team during survivorship is on the monitoring and follow-up of women for routine screening and assessment for breast cancer recurrence every three to six months. If the breast cancer was hormone receptor positive, then women will be offered AET. As the name suggests, AET either serves to reduce the amount of estrogen in the body or selectively blocks estrogen receptors to prevent recurrence of estrogen-receptor-positive breast cancer. This therapy involves daily oral medication use for a duration of five to ten years.

Rationale for focus on predictors of distress in transitional survivorship

Although the most difficult part of the cancer care trajectory seems complete, women transitioning into survivorship are faced with many new and unique challenges as they re-integrate into professional, social, and family roles. Women may develop post-

treatment cancer-related distress, which may be quite different in terms of underlying causes as compared with distress that presents during hospital-based treatment. Distress in survivorship may develop as a result of fear of cancer recurrence, chronic or latent treatment-related side effects, changes in spousal relationships, or financial burden from out-of-pocket costs of cancer treatment or lost time at work.[52–55]

In time-to-event analyses, it seems counterintuitive to compare women within a few months after breast cancer diagnosis when some women are still undergoing hospital-based treatment (e.g., chemotherapy) while other women are in remission adjusting to life after completion of hospital-based treatment (e.g., after lumpectomy and radiotherapy). This type of analytic approach may dilute or obscure the estimates for predictors of new-onset distress in the survivorship period. In order to evaluate candidate predictors of new-onset distress in breast cancer survivors, it may be more appropriate to conduct a time-to-event analysis with an underlying time scale of time since completion of hospital-based treatment. Subsequently, the best set of predictors could be determined to develop a risk stratification algorithm that could be used to identify breast cancer survivors at higher risk of new-onset distress in the transitional survivorship period to provide targeted supportive care to prevent distress or mitigate its effects. This is a particularly important time, given that women will have a reduced number of contacts with the oncology care team while facing these new challenges in adjusting to life after breast cancer treatment. As a result, new cases of distress may not be detected.

Roadmap of the thesis

The overarching goal of this Doctoral research program was to help identify breast cancer patients at higher risk of new-onset distress in transitional survivorship to guide allocation of supportive care resources. The first study serves as a comprehensive review of the relevant literature, and therefore the thesis does not contain a separate review chapter. Similarly, there is no separate methods section in an effort to avoid repetition, since the methodology for each study is described in detail within the respective manuscripts.

The first manuscript describes a systematic review of the published literature around predictors of distress in breast cancer survivors. The objective was to identify evidence-based a priori predictors (or proxies) that are available in the administrative health data that could be used for the development of a transitional survivorship risk stratification model. This study focused on predictors of *prevalent* distress driven by the lack of published literature around *new-onset* distress in breast cancer survivors.

The next manuscript describes the selection of the best set of candidate predictors available in routinely collected administrative health data to help identify women at higher risk of new-onset distress during transitional survivorship. New-onset distress was ascertained using both ICD diagnostic codes and dispensations of psychotropic medications. The transitional survivorship period was defined as the first year following completion of hospital-based treatment for breast cancer. The risk stratification model was developed using a time-dependent Cox proportional hazards model and the counting process approach by week of the follow-up period.

To-date, the studies that have looked at predictors of new-onset distress (specifically, depression) in breast cancer patients have conducted time-to-event analyses with an underlying time scale of time since breast cancer diagnosis. However, the predictors of new-onset distress are expected to be different during hospital-based treatment compared with the predictors of new-onset distress during transitional survivorship. Therefore, a risk stratification model was also developed for the hospital-based treatment period in the second study. The transitional survivorship and hospital-based treatment models were then compared to investigate whether or not the predictors of new-onset distress varied based on the period of the cancer care trajectory.

The final study describes a first attempt to correct for outcome misclassification in the administrative health data when including dispensations of psychotropic medications as indicators of new-onset distress, which may have been indicated for conditions other than distress. The adjustments were informed by gold standard electronic medical record data, which includes information about indications for all psychotropic medication prescriptions. The objective was to determine the positive predictive values, and specificities of individual psychotropic medications to measure the extent of outcome misclassification and assess its impact on the fit of the transitional survivorship risk stratification model.

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CHAPTER 2 – OBJECTIVES

The overarching goal of this Doctoral research program was to help identify breast cancer survivors at higher risk of new-onset distress to guide allocation of supportive care resources. The thesis focused on the first year after completion of hospital-based treatment (i.e., transitional survivorship), where women transition to routine follow-up care and have fewer contacts with the oncology care team. The following three objectives were completed to address this goal:

1. To synthesize the published literature around the predictors of distress in breast cancer survivors

2. To use routinely collected administrative health data to:
    a. Develop a risk stratification algorithm to identify breast cancer survivors at higher risk of new-onset distress in transitional survivorship
    b. Compare and contrast predictors of new-onset distress during transitional survivorship with predictors of new-onset distress during hospital-based treatment

3. To use gold standard electronic medical record data to:
    a. Adjust for potential outcome misclassification when including psychotropic medication dispensations as indicators of new-onset distress
    b. Assess the impact of outcome misclassification on the fit of the transitional survivorship risk stratification model

CHAPTER 3 – OBJECTIVE 1

Syrowatka A, Motulsky A, Kurteva S, Hanley JA, Dixon WG, Meguerditchian AN, Tamblyn R. Predictors of distress in breast cancer survivors: a systematic review. Breast Cancer Res Treat (2017) 165:229–245. doi:10.1007/s10549-017-4290-9.

Preamble

The first manuscript presents the results of a systematic review and synthesis of the published literature around predictors of distress in breast cancer survivors. This review was conducted to inform selection of evidence-based candidate predictors for the transitional survivorship risk stratification model developed as a part of the second objective. The initial intent was to identify predictors of *new-onset* distress in breast cancer survivors; however, given the lack of published literature in this area, the systematic review was re-focused to summarize predictors of *prevalent* distress.

This study serves as a comprehensive review of the literature for this thesis. The manuscript has already been published in the journal *Breast Cancer Research and Treatment.* As a result, the terminology and referencing format are different compared with the rest of the thesis. The published article is provided as Appendix A at the end of the thesis.

Manuscript I – Title page

Predictors of distress in female breast cancer survivors: a systematic review

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Abstract

Purpose: Unmanaged distress has been shown to adversely affect survival and quality of life in breast cancer survivors. Fortunately, distress can be managed and even prevented with appropriate evidence-based interventions. Therefore, the objective of this systematic review was to synthesize the published literature around predictors of distress in female breast cancer survivors to help guide targeted intervention to prevent distress.

Methods: Relevant studies were located by searching MEDLINE, Embase, PsycINFO, and CINAHL databases. Significance and directionality of associations for commonly assessed candidate predictors ($n \geq 5$) and predictors shown to be significant ($p \leq 0.05$) by at least two studies were summarized descriptively. Predictors were evaluated based on the proportion of studies that showed a significant and positive association with the presence of distress.

Results: Forty-two studies met the target criteria and were included in the review. Breast cancer and treatment-related predictors were more advanced cancer at diagnosis, treatment with chemotherapy, longer primary treatment duration, more recent transition into survivorship, and breast cancer recurrence. Manageable treatment-related symptoms associated with distress included menopausal/vasomotor symptoms, pain, fatigue, and sleep disturbance. Sociodemographic characteristics that increased the risk of distress were younger age, non-Caucasian ethnicity, being unmarried, and lower socioeconomic status. Comorbidities, history of mental health problems, and perceived functioning limitations were also associated. Modifiable predictors of distress were lower physical activity, lower social support, and cigarette smoking.

Conclusions: This review established a set of evidence-based predictors that can be used to help identify women at higher risk of experiencing distress following completion of primary breast cancer treatment.

Introduction

Around 1.67 million new cases of breast cancer were diagnosed worldwide in 2012, accounting for an estimated 25% of new cancer cases in women [1]. Earlier detection of breast tumors through screening mammography in combination with better and more targeted therapies has dramatically improved survival [2]. Medical advances have generated a large cohort of women surviving after completion of primary breast cancer treatment.

Current 5 and 10-year survival rates following breast cancer diagnosis are 87% and 82%, respectively [3]. As a result, both clinicians and researchers are now focusing more efforts on improving quality of life and patient-centered outcomes in survivorship. The National Comprehensive Cancer Network (NCCN) has recognized distress as an important sequela of cancer diagnosis and treatment [4]. Formally, cancer-related distress is defined as ‘‘a multifactorial unpleasant emotional experience of a psychological (i.e., cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crises’’ [4]. Unmanaged distress has been shown to negatively impact all-cause and cancer-related morbidity and mortality as well as quality of life [5].

Identification of distress during survivorship still presents a challenge; it may be unclear when normal feelings of vulnerability, sadness, and fears transition to a point

requiring intervention or support. To address this issue, cancer care agencies have recommended that cancer patients be routinely screened for distress at appropriate intervals throughout primary treatment and survivorship, and at important clinical time points including remission, recurrence, progression, and treatment-related complications [4]. However, approximately 37% of breast cancer patients who have transitioned into survivorship will attend two or fewer follow-up visits with an oncologist within the first year following completion of primary treatment [6], limiting the number of opportunities for distress screening and potentially delaying necessary treatment.

An alternative approach could be to identify breast cancer patients at increased risk of developing distress following transition into survivorship. This would allow for targeted intervention to prevent distress as well as enhanced monitoring to identify prodromal symptoms and early warning signs of distress for timely intervention to mitigate the risk of progression to diagnosable mental health problems. For example, intervention with prophylactic cognitive behavioral therapy (CBT) has been shown to reduce incidence of depression and anxiety in higher-risk cancer patients by half [7]. As a first step in this direction, the objective of this systematic review is to summarize the published literature around predictors of distress in breast cancer survivors.

Methods

Study selection

Search strategy

Four databases (MEDLINE, Embase, PsycINFO, and CINAHL) were searched for relevant studies published between January 1, 2000 and March 10, 2016. Studies published prior to the year 2000 were excluded since they were not considered to be representative of the current state of distress literature, given significant improvements in breast cancer treatments and survival rates, and increased awareness of mental health challenges in survivorship. Four main concepts of breast cancer, survivorship, predictor, and distress were mapped to the most relevant controlled vocabulary using Medical Subject Headings (MeSH), and free-text terms were added where necessary. Full search strategies are provided in Appendix 3-1.

Inclusion and exclusion criteria

This systematic review identified studies that measured the presence of distress (via clinical interviews, or distress scales) and evaluated potential predictors of presence of distress in female breast cancer patients who had completed primary treatment (i.e., surgery, chemotherapy, and/or radiotherapy). Therefore, only studies that dichotomized the outcome as the presence or absence of distress were included in the review; articles that used a continuous outcome (e.g., total score on a distress scale) were not included. Distress was broadly defined based on specific mental health diagnoses (i.e., ‘depressive disorders,’ ‘anxiety disorders,’ ‘obsessive–compulsive and related disorders,’ and

'trauma- and stressor-related disorders') as well as nonspecific symptoms (e.g., 'psychological,' 'psychosocial,' 'stress,' and 'distress'). All study designs were considered (e.g., cross-sectional, prospective cohort, etc.). Studies were excluded if the article did not report original research, or was not published in the English language.

Screening and data abstraction

Screening of articles was completed in two stages. First, articles were screened for relevance based on information provided in the title and abstract, and subsequently evaluated for inclusion based on the full text. Two reviewers independently screened articles at each stage (title and abstract: AS and AM; full text: AS and SK). All articles considered eligible for inclusion by at least one reviewer based on the title and abstract screen were submitted for full-text review. Disagreements at the full-text screen were resolved by discussion and consensus between the two reviewers. Kappa scores were calculated to assess interrater reliability. Reference lists of eligible articles were searched to identify additional relevant studies for inclusion in the review.

One reviewer completed data abstraction (AS), which focused on citation information, study design, sample size and patient characteristics, type and prevalence of distress, measurement of distress (i.e., case ascertainment), timing of measurement, and predictors of distress (all predictors evaluated, and predictors significant in univariate and/or multivariable analyses). A second reviewer (SK) checked data abstracted from ten percent of the articles to assess quality of data abstraction, and one omission was identified.

Evaluation of predictors

Substantial heterogeneity in the formats of predictors (e.g., continuous, or not comparable classification approaches) limited the feasibility of meta-analysis to quantitatively synthesize results on the strength of association between predictors and the presence of distress. Consequently, significance and directionality of associations (i.e., positive, negative, or inconsistent/unspecified) for the most commonly assessed candidate predictors ($n \geq 5$) as well as predictors shown to be significant ($p \leq 0.05$) by at least two studies were summarized descriptively. Predictors were evaluated based on the proportion of studies that showed a significant and positive association (in univariate and/or multivariable analyses) with the presence of distress, in an effort to identify patterns to inform future research.

Results

Study selection

The search identified 2706 unique articles. The title and abstract screen retained 313 articles. Full-text screening with reference list searching identified 42 studies that met the target criteria and were included in the review. The kappa scores for title and abstract screen, and full-text screen were 0.43 and 0.54, respectively, indicating 'moderate' agreement [8]. The moderate kappa scores reflect the complexity around defining distress and uncertainty around the beginning of the breast cancer survivorship period as well as consideration of studies that did not focus specifically on breast cancer.

A modified Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart is presented in Figure 3-1 [9].

Characteristics of studies identified through the systematic review are presented in Table 3-1 [10–51]. Studies were published between 2001 and 2016, and were conducted in North America (19/42 studies; 45%), Asia (12/42 studies; 29%), and Europe (11/42 studies; 26%). Half of the studies collected data using a prospective cohort (21/42 studies; 50%), and the other half used a cross-sectional design (20/42 studies; 48%) or retrospective chart review (1/42 studies; 2%). Eight (8/21 studies; 38%) of the prospective cohort studies reported distress trajectories, which describe how individual women's distress can change over time from diagnosis through primary treatment and into survivorship. The remaining studies reported prevalence of distress within the survivorship period, without describing how individual women's distress changes over time.

The majority of studies measured depression (30/42 studies; 71%); anxiety, posttraumatic stress disorder (PTSD), general distress, and suicidal ideation were measured by 29% (12/42 studies), 7% (3/42 studies), 21% (9/42 studies), and 2% (1/42 studies) of studies, respectively. The median prevalence of distress was 26% (interquartile range 39–17 = 22%). The majority of studies assessed the presence of distress using validated cut-offs of the Center for Epidemiologic Studies-Depression scale (CES-D: 12/42 studies; 29%) or the Hospital Anxiety and Depression Scale (HADS: 12/42 studies; 29%). Timing of distress assessment in survivorship varied substantially. Eleven studies (26%) evaluated distress in survivorship at a specific time point following

breast cancer diagnosis (ranging from 1 to 4 years). The majority of studies based on distress trajectories (7/8 studies; 88%) followed women for periods ranging from 1 to 2 years starting from breast cancer diagnosis. The remaining studies included survivors with varying times since breast cancer diagnosis, ranging from a mean of 17.6 months following breast surgery (standard deviation (SD): 9.0 months; range 6–36 months) to 10.5 years (range 5–32 years) following breast cancer diagnosis.

Evaluation of predictors

The significance and directionality of commonly assessed candidate predictors ($n \geq 5$) as well as predictors shown to be significant ($p \leq 0.05$) by at least two studies are summarized in Table 3-2 [10–23, 25, 27–33, 35–50], and categorized based on type of predictor: sociodemographic characteristics, breast cancer characteristics and treatment, treatment-related symptoms, comorbidities and medical history, perceived functioning limitations, and behavioral and support factors. All predictors evaluated within each study, alongside predictors shown to be significant ($p \leq 0.05$) in univariate and multivariable analyses are presented in Appendix 3-2 [10–51]. Twenty-eight of the 42 studies (67%) reported on multivariable analyses conducted to estimate independent associations between candidate predictors and the presence of distress in breast cancer survivors; the remaining studies only reported data for univariate associations. Overall, studies that employed a cross-sectional design had larger sample sizes (mean: 560 women vs. 399 women for cohort and chart review studies) and were more likely to report significant associations between candidate predictors and distress.

The most commonly evaluated predictors were patient sociodemographic characteristics, breast cancer characteristics, and treatments. Sociodemographic characteristics that were associated with distress included: younger age (10/27 studies; 37%), non-Caucasian ethnicity (2/11 studies; 18%), and being unmarried (8/23 studies; 35%). Lower socioeconomic status (SES) also increased the risk of distress including: lower education (3/21 studies; 14%), lower income (4/7 studies; 57%), and experiencing financial difficulties (5/6 studies; 83%). However, unemployment did not influence the risk of distress.

Breast cancer characteristics and treatments predictive of distress were more advanced cancer at diagnosis (3/21 studies; 14%), treatment with chemotherapy (4/18 studies; 22%), and longer primary treatment duration (2/2 studies). However, type of breast surgery, treatment with radiotherapy, and treatment with hormone therapy did not influence the risk of distress. More recent transition into survivorship (3/10 studies; 30%), and breast cancer recurrence (2/4 studies; 50%) were associated with distress.

The following treatment-related symptoms were associated with distress: menopausal/vasomotor symptoms (7/10 studies; 70%), pain (9/12 studies; 75%), fatigue (6/9 studies; 67%), sleep disturbance (7/9 studies; 78%), lymphedema/arm symptoms (2/5 studies; 40%), breast symptoms (2/3 studies; 67%), appetite loss (2/5 studies; 40%), diarrhea (3/5 studies; 60%), and dyspnea (2/4 studies; 50%). Constipation, nausea, and vomiting did not influence the risk of distress. Furthermore, higher number of treatment-related complaints (3/5 studies; 60%) was associated with distress. Similarly, higher

number of comorbidities (5/9 studies; 56%) and history of mental health problems (7/7 studies) increased the risk of distress.

Lower overall quality of life (6/8 studies; 75%) and the following subscales/domains were associated with distress: lower quality of physical health (4/4 studies), lower quality of mental health (2/2 studies), physical functioning limitations (6/8 studies; 75%), role functioning limitations (6/8 studies; 75%), emotional functioning limitations (3/5 studies; 60%), cognitive functioning limitations (2/4 studies; 50%), and social functioning limitations (4/6 studies; 67%). Lower optimism (2/3 studies; 67%), lower posttraumatic growth (3/3 studies), and higher number of stressful life events (3/6 studies; 50%) also increased the risk of distress. In terms of behavioral and support factors, lower physical activity (5/8 studies; 63%), lower social support (6/8 studies; 75%), and cigarette smoking (2/6 studies; 33%) were associated with distress, whereas higher alcohol intake and higher body mass index (BMI) did not influence the risk of distress.

Discussion

This systematic review is the first synthesis of the published literature around predictors of distress in female breast cancer patients who have completed primary treatment. Breast cancer and treatment-related predictors included more advanced cancer at diagnosis, treatment with chemotherapy, longer primary treatment duration, more recent transition into survivorship, and breast cancer recurrence. Treatment-related symptoms also increased the risk of distress including menopausal/vasomotor symptoms, pain, fatigue, and sleep disturbance. A variety of factors not specific to breast cancer

survivors predicted distress. Associated sociodemographic characteristics were younger age, non-Caucasian ethnicity, being unmarried, and indicators of lower SES (specifically, lower education or income, and experiencing financial difficulties). Higher number of comorbidities and history of mental health problems also increased the risk of distress. Furthermore, lower quality of life, optimism, and posttraumatic growth as well as higher number of stressful life events predicted distress. For behavioral and support factors, lower physical activity, lower social support, and cigarette smoking were associated with distress. Informed by this systematic review, risk stratification may be a viable approach to identify women at higher risk of developing distress following completion of primary breast cancer treatment to provide targeted evidence-based interventions.

Breast cancer-specific factors were commonly evaluated as candidate predictors, given that conventional wisdom suggests that recent, traumatic experiences, such as advanced breast cancer diagnosis associated with worse prognosis and increased risk of premature mortality or more aggressive anti-cancer therapy, may increase the risk of distress. The systematic review identified initial diagnosis of more advanced breast cancer, treatment with chemotherapy, and longer primary treatment duration as predictors of distress. It is difficult to disentangle these predictors, given that they are highly correlated; women with more advanced breast cancer will undergo more aggressive anti-cancer treatment including chemotherapy, which in turn will substantially increase treatment duration. However, a potential underlying mechanism for increased distress in survivorship is that women diagnosed with more advanced breast cancer associated with higher risk of recurrence may experience more intense fears of recurrence [52], which if unmanaged could progress to diagnosable mental health problems. One study included in

this systematic review reported significant univariate associations for both breast cancer stage and treatment with chemotherapy with distress; however, only more advanced breast cancer was significant in the multivariable model [31]. Furthermore, the systematic review showed that other forms of anti-cancer therapy (i.e., type of surgery, treatment with radiotherapy, or treatment with hormone therapy) did not influence the risk of distress. These findings are supported by two large Danish cohort studies that evaluated predictors of distress following breast cancer diagnosis and identified number of tumor-positive axillary lymph nodes as an independent predictor of new antidepressant use [53, 54]. Although both studies evaluated breast cancer-related treatments as candidate predictors of distress, neither found independent associations for mastectomy, chemotherapy, or radiotherapy. The results of this systematic review suggest that more advanced breast cancer as well as its correlates could help to identify women at higher risk of experiencing distress in survivorship.

The review identified potentially modifiable breast cancer treatment-related risk factors. Timely identification and effective management of treatment-related symptoms could serve as a possible intervention to prevent distress or mitigate its effects. Symptoms commonly associated with anti-cancer therapy were predominantly assessed using standardized cancer-specific measures of health-related quality of life as well as breast cancer-specific measures [55, 56]. Other treatment-related symptoms not captured by this systematic review may also be associated with distress. Identification of additional relevant symptoms should be guided through clinical expertise and investigated to assess the relationship with distress. These findings suggest that it may not be anti-cancer therapy that directly affects distress, but rather adverse events resulting from treatment

that increase the risk of distress. Uncontrolled chronic and latent treatment-related symptoms can negatively affect health-related quality of life in survivorship and may serve as consistent reminders of the breast cancer diagnosis increasing fear of recurrence [52, 57]. Further studies are needed to assess independent contributions of more advanced breast cancer, treatments, and associated side effects on distress in survivorship.

Additional risk factors not directly related to diagnosis or treatment of breast cancer, including sociodemographic characteristics, comorbidities, medical history, and functional limitations, have also been shown to increase the risk of distress in the general population. In fact, many of these risk factors have been incorporated into predictive algorithms to estimate the risk of incident distress in general practice [58–61]. Each of the algorithms includes younger age, indicator(s) of lower SES, and indicator(s) of perceived functioning limitations as predictors. In addition, some algorithms include comorbidities, history of mental health problems, and experiences of discrimination (e.g., racial discrimination [60]). Although this may seem intuitive, the results of this systematic review indicate that risk factors for distress in the general population can also be useful in identifying breast cancer patients at higher risk of distress following completion of primary treatment. Effectively, these risk factors make breast cancer survivors inherently more susceptible to development of distress when faced with challenges in survivorship. However, it is unclear whether or not these factors have differential effects in breast cancer survivors. For example, younger survivors may have different expectations of a normal fulfilling life and experience substantially higher distress as a function of receiving a premature life-threatening diagnosis as well as coping with potential implications when raising young children. Future studies should focus on

identifying interactions between risk factors in the general population and diagnosis of breast cancer in predicting distress.

The review also highlighted modifiable behavior and support factors that could serve as interventions to prevent or mitigate the impact of distress. As expected, lower physical activity, lower social support, and cigarette smoking were associated with the presence of distress [62–64]. In fact, lifestyle and support programs that develop and promote positive coping strategies have been shown to reduce distress symptoms in breast cancer survivors [65–68]. However, contrary to results from prior studies in the general population [69, 70], alcohol intake and BMI did not influence the risk of distress. None of the studies that evaluated alcohol intake showed a significant association. There were low prevalences and absolute numbers of women who reported higher alcohol intake in these studies [10, 13, 35, 50]. Given that higher alcohol intake has been shown to increase risk of breast cancer recurrence [71], this may reflect changes in alcohol consumption due to personal choice or medical advice following breast cancer diagnosis. For studies that reported no association between BMI and distress, three studies compared mean BMI between distressed and non-distressed women, and may have been underpowered to detect significant differences due to lower sample sizes [31, 40, 41]. Another study reported a low prevalence of increased BMI from <25 to ≥ 25 with a very low number of distressed women transitioning to increased BMI [35]. Future research should focus on exploring these associations in more depth.

This systematic review highlighted an important research gap; no studies evaluated predictors of incident distress in breast cancer survivors. Instead, studies

assessed candidate predictors of prevalent distress making it unclear whether the 'predictor' or distress occurred first and introducing the possibility of reverse causation. In order to advance this field, future research should focus on establishing predictors of incident distress in breast cancer survivors with no concurrent or recent history of distress. Ideally, a large cohort of breast cancer survivors should be prospectively followed for incident distress, and evidence-based as well as clinically informed candidate predictors should be evaluated using time-to-event analysis.

Furthermore, harmonization of vocabulary around distress and survivorship periods would aid future research to develop more explicit recommendations. First, the nonspecific nature of distress makes it difficult to describe and measure. Furthermore, levels and predictors of distress are expected to change across the breast cancer survivorship life course; women who have recently transitioned into survivorship have different concerns and priorities compared with longer-term survivors. Future research should focus on predictors of distress for different intervals of the survivorship period, e.g., transitional survivorship (first year following completion of primary treatment), short-term survivorship (2–5 years after completion of primary treatment), and long-term survivorship (>5 years after completion of primary treatment).

This study has several limitations resulting from the quality and scope of articles identified through the systematic review. Publication bias and inter-study heterogeneity limited the feasibility of conducting predictor-specific meta-analyses. The majority of studies only reported measures of association for significant predictors, which would have biased pooled estimates toward significance. Furthermore, studies that evaluated the

same candidate predictor often used different measurements and classification approaches, making predictor-specific meta-analyses impossible. However, the synthesis conducted for this systematic review allowed for direct comparison of significant impact of predictors between studies assessing the same predictor.

This systematic review has established a set of evidence-based predictors that can be used to identify women at higher risk of experiencing distress following completion of primary breast cancer treatment. More advanced breast cancer and treatment-related symptoms may serve as the most practical predictors of distress in survivorship. Furthermore, findings suggest that risk factors for distress in the general population can also be used in this vulnerable population; this intuitively makes sense, given that women predisposed to distress are more likely to experience increased levels as a result of a life-altering breast cancer diagnosis. This systematic review provides preliminary evidence to address an important clinical gap. Furthermore, the results can serve to inform development of a risk stratification algorithm to identify women at higher risk of developing distress following completion of primary breast cancer treatment to provide appropriate support to prevent distress or mitigate its effects.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

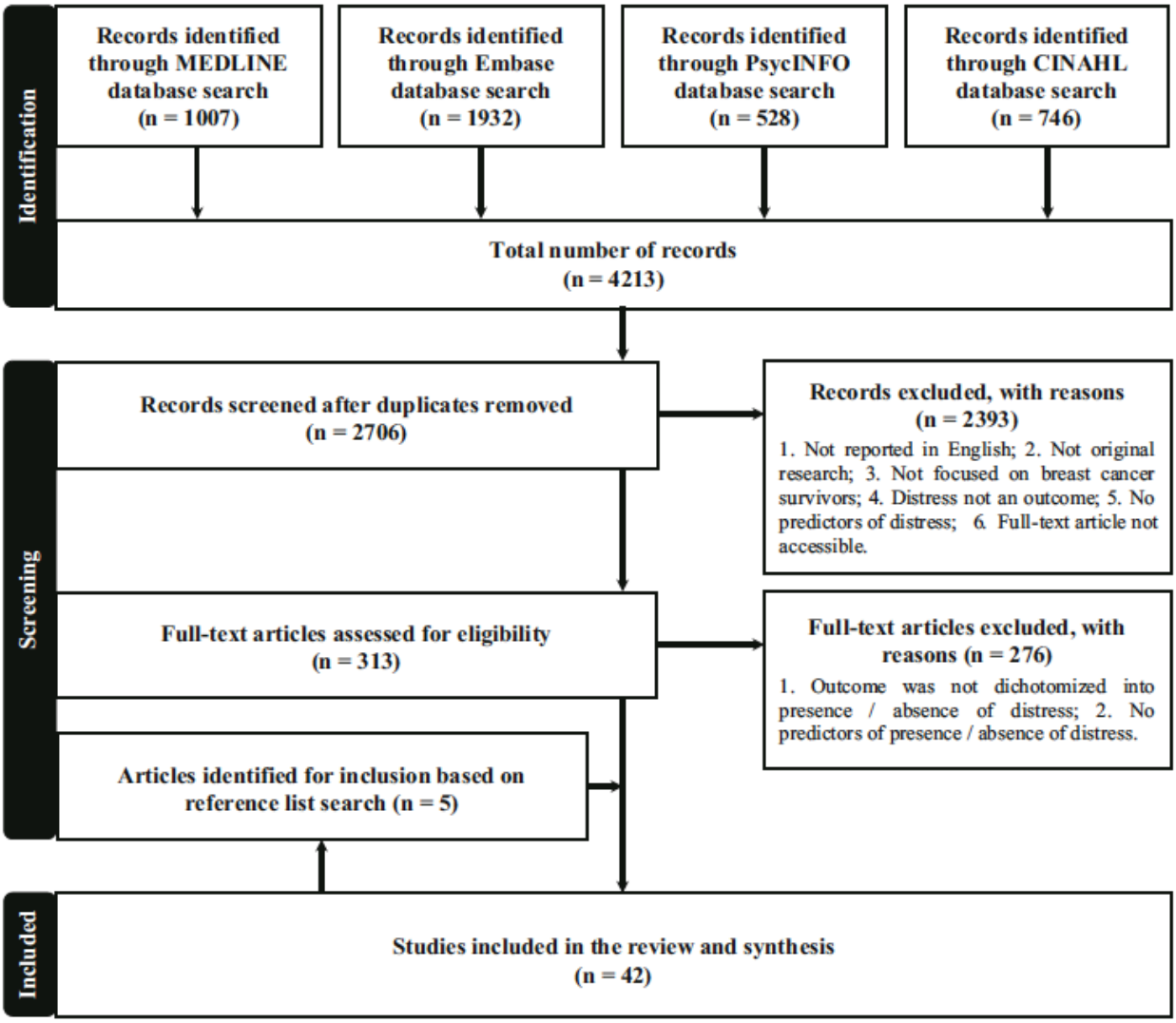

Fig. 3-1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study selection flowchart

Table 3-1 Characteristics of studies identified by the systematic review

Author, year (country) [G1 – G3: participant groups]	Study design	Sample size	Age, mean ± SD (range)[a] in years	Breast cancer stage	Outcome(s): prevalence (trajectories, if applicable)	Measurement of distress (i.e., case ascertainment)	Timing of distress measurement
Bardwell, 2006 [10] (United States)	Cross-sectional	2595	In survivorship: 53 (28 – 74)	I – III	Depression: 17%	CES-Dsf ≥ 0.06 (on the logarithmic scale)	≤ 4 years after completion of primary breast cancer treatment: ≤ 1 year: 23% 1 – 2 years: 33% 2 – 3 years: 24% 3 – 4 years: 20%
Dominick, 2014 [11] (United States)	Cross-sectional	1817	Not reported	I – III	Depression: No lymphedema – 12.2% Lymphedema without lymphedema-related distress – 12.8% Lymphedema with lymphedema-related distress – 17.6%	CES-Dsf ≥ 0.06 (on the logarithmic scale)	4 years after breast cancer diagnosis
Chen, 2009 [12] (China)	Prospective cohort	1400	At diagnosis: 53.7 ± 9.8	0 – IV	Total depression: 26.0% Mild depression: 13.4% Clinical depression: 12.6%	Mild: CES-D = 10 – 15 Clinical: CES-D ≥ 16	18 months after breast cancer diagnosis
Chen, 2010 [13] (China)	Prospective cohort	1399	At diagnosis: 53.7 ± 9.8	0 – III	Total depression: 26.0% Mild depression: 13.4% Clinical depression: 12.6%	Total: CES-D ≥ 10 Mild: CES-D = 10 – 15 Clinical: CES-D ≥ 16	18 months after breast cancer diagnosis
Kim, 2008 [14] (Korea)	Cross-sectional	1219	In survivorship: 47.4 ± 9.3	0 – III	Moderate to severe depression: 24.9%	BDI ≥ 19	Mean ± SD time after breast cancer surgery: 4.6 ± 2.4 years
Mehnert, 2008 [15] (Germany)	Cross-sectional	835	In survivorship: 61.8 ± 9.8 (31 – 81)	I – IV	Psychological distress (i.e., anxiety, depression, and/or PTSD): 42.9%	HADS ≥ 8 PCL-C = 1 intrusion + 3 avoidance + 2 arousal symptoms (rated 'moderately' or above)	Mean ± SD (range) time after breast cancer diagnosis: 46.5 ± 17.5 (18 – 77) months
Calhoun, 2015 [16] (United States)	Cross-sectional	761	In survivorship: 63.6 ± 10.5	Not reported	Depression: 15.5%	CES-D ≥ 16	Median (range) time after breast cancer diagnosis: 7 (1 – 43) years
Branstrom, 2015 [17] (Sweden)	Prospective cohort	726	At diagnosis: 51.3 ± 8.1	0 – IV	Anxiety: 20.7% Depression: 11.7%	HADS ≥ 8	24 months after breast cancer diagnosis

Table 3-1 (continued) Characteristics of studies identified by the systematic review

Author, year (country) [G1 – G3: participant groups]	Study design	Sample size	Age, mean ± SD (range)[a] in years	Breast cancer stage	Outcome(s): prevalence (trajectories, if applicable)	Measurement of distress (i.e., case ascertainment)	Timing of distress measurement
Saboonchi, 2015 [18] (Sweden)	Prospective cohort; trajectory	725	At diagnosis: 51.2 ± 8.1 (24 – 63) Median: 52	Not reported	Anxiety trajectories: High stable – 6.2% High decrease – 15.6% Mid decrease – 33.0% Low decrease – 45.0%	HADS scores (anxiety subscale): membership in 'high stable' trajectory	Over 24 month period following breast cancer surgery
Saboonchi, 2014 [19] (Sweden)	Prospective cohort	654	At diagnosis: 51.3 ± 8.1	Not reported	Anxiety: 25.1% Depression: 15.3%	Total: HADS ≥ 8 Possible: HADS = 8 – 10 Probable: HADS ≥ 11	12 months after breast cancer surgery
Avis, 2015 [20] (United States)	Prospective cohort; trajectory	653	At diagnosis: 54.9 ± 0.5	I – III	Depression trajectories: 1 consistent very low score – 3.8% 2 consistent low score – 47.3% 3 consistent borderline score – 29.2% 4 high score, declining – 11.3% 5 borderline score, increasing – 7.2% 6 consistent high score – 1.1%	BDI scores: membership in 'borderline score, increasing' trajectory	Over 24 month period following breast cancer diagnosis Mean ± SD (range) time since diagnosis at study entry: 4.5 ± 0.05 (6 – 26) months
Ganz, 2003 [21] (United States)	Cross-sectional	577	At diagnosis: 43.6 (25.2 – 51) In survivorship: 49.5 (30 – 61.6)	0 – II	Clinical depression: 25.7%	CES-D ≥ 16	Mean ± SD time after breast cancer diagnosis: 5.9 ± 1.5 years Disease-free for 2 – 10 years
Qiu, 2012 [22] (China)	Cross-sectional	505	In survivorship: 52.02 ± 4.55 (23 – 65)	0 – IV	Major depressive disorder: 20.59%	Phase 1: BDI ≥ 5 Phase 2: MINI Module A (based on DSM-IV criteria)	Mean ± SD (range) time after breast surgery: 17.6 ± 9.0 (6 – 36) months
Stanton, 2015 [23] (United States)	Prospective cohort; trajectory	457	At diagnosis: 56.4 ± 12.6 (23 – 91)	I – IV	Depression: 15.6% Depression trajectories: High – 38% Recovery – 20% Low – 32% Very low – 11%	CES-D ≥ 16 CES-D scores: membership in 'high' trajectory	Over 16 month period following breast cancer diagnosis Mean ± SD time after breast cancer diagnosis at study entry: 2.1 ± 0.8 months

Table 3-1 (continued) Characteristics of studies identified by the systematic review

Author, year (country) [G1 – G3: participant groups]	Study design	Sample size	Age, mean ± SD (range)[a] in years	Breast cancer stage	Outcome(s): prevalence (trajectories, if applicable)	Measurement of distress (i.e., case ascertainment)	Timing of distress measurement
Boehmer, 2012 [24] (United States) [G1: heterosexual women from registry; G2: sexual minority women from registry; G3: sexual minority women from convenience sample]	Cross-sectional	438 G1: 257 G2: 69 G3: 112	In survivorship: G1: 62.7 ± 11.0 G2: 55.9 ± 8.3 G3: 55.1 ± 8.7	0 – III	Anxiety: borderline/clinical G1 – 7.0% / 10.6% G2 – 6.0% / 8.9% G3 – 10.8% / 5.4% Depression: borderline/clinical G1 – 3.1% / 3.1% G2 – 3.0% / 3.0% G3 – 6.2% / 4.5%	Borderline: HADS = 8 – 10 Clinical: HADS ≥ 11	Mean ± SD time after breast cancer diagnosis: G1: 4.7 ± 1.8 years G2: 5.3 ± 1.5 years G3: 6.4 ± 1.8 years
Kim, 2013 [25] (United States)	Cross-sectional	381	Over 21 years old	0 – III	Distress (anxiety or depression): not reported	PROMIS: not reported	1 to 5 years after completion of primary breast cancer treatment
Hong, 2015 [26] (United States)	Prospective cohort	372	Not reported	0 – III	Depression: not reported	CES-D: > median	1 year after breast cancer diagnosis
Palesh, 2010 [27] (United States)	Prospective cohort	353	In survivorship: 50	Not reported	Time 1: Anxiety: 62% Depression: 15%	Hamilton Anxiety and Depression Scale ≥ 8	Time 1: 6 to 24 months after primary breast cancer treatment Time 2: 3 months after Time 1
Wang, 2015 [28] (Taiwan)	Prospective cohort; trajectory	311	Not reported	Not reported	Distress trajectories: High depression Medium depression Low depression Depression drop	HADS scores (depression subscale): membership in the 'high depression' trajectory	Over 12 month period following breast cancer surgery
Leung, 2016 [29] (Scotland)	Cross-sectional	295	In survivorship: 66.44	Not reported	Psychological distress: 16.6%	GHQ ≥ 4	At least 1 year after breast cancer diagnosis
Romito, 2012 [30] (Italy)	Cross-sectional	255	In survivorship: 58.4 (35 – 80)	Not reported	Depression: 37%	ZSDS ≥ 60	Mean (range) time since breast cancer diagnosis: 10.5 (5 – 32) years
Kim, 2013 [31] (Korea) [G1: suicidal ideation present; G2: suicidal ideation not present]	Prospective cohort	241	In survivorship: G1: 49.8 ± 9.6 G2: 50.4 ± 9.8	0 – IV	Suicidal ideation: 11.2%	BDI: question 9 about presence of suicidal ideation ≥ 1	1 year after breast cancer surgery
Reyes-Gibby, 2012 [32] (United States)	Cross-sectional	240	In survivorship: 58 ± 16	0 – III	Depression: 16.2%	PHQ-8 ≥ 10	Mean (range) time since start of primary breast cancer treatment: 7.9 (6 – 13) years Median: 8 years
Ashing-Giwa, 2013 [33] (United States)	Cross-sectional	232	In survivorship: 53 ± 10.6 (26 – 84)	0 – III	Clinical depression: 53.4%	CES-D ≥ 16	Time since breast cancer diagnosis: 1 – 6 years

Table 3-1 (continued) Characteristics of studies identified by the systematic review

Author, year (country) [G1 – G3: participant groups]	Study design	Sample size	Age, mean ± SD (range)[a] in years	Breast cancer stage	Outcome(s): prevalence (trajectories, if applicable)	Measurement of distress (i.e., case ascertainment)	Timing of distress measurement
Wang, 2011 [34] (Taiwan)	Cross-sectional	217	Not reported	Not reported	Distress: not reported	HADS ≥ 15 NCCN Distress Thermometer ≥ 4	Not reported
Lee, 2011 [35] (Korea)	Prospective cohort; trajectory	206	At diagnosis: 47 ± 10	I – III	Depression: 49.3% Deteriorated depressive mood (from breast cancer diagnosis to 1 year following diagnosis): 20.9%	Depression: ZSDS ≥ 50 Deteriorated mood: Effect size > 0.5	Over 1 year period following breast cancer diagnosis
Hsu, 2010 [36] (Taiwan)	Cross-sectional	206	Not reported	I – II	Distress (anxiety or depression): 38.6%	HADS ≥ 15	3 – 24 months after completion of primary breast cancer treatment
Burgess, 2005 [37] (England)	Prospective cohort	202	At diagnosis: 48.4 ± 7.8	III – 32% Other – 68%	Depression and/or anxiety annual prevalences: Year 2 – 25% Year 3 – 23% Year 4 – 22% Year 5 – 15%	SCID for depression and anxiety: standardized diagnostic criteria from the DSM III-R	2 – 5 years after breast cancer diagnosis
Kornblith, 2001 [38] (United States)	Cross-sectional	179	In survivorship: Median: 56 Range: 32 – 79	II	Psychological distress: 8%	MHI: ≥ 1.5 SD above the average	Median (range) time since start of chemotherapy: 6.8 (3.3 – 11.2) years
Henselmans, 2010 [39] (Netherlands)	Prospective cohort; trajectory	171	At diagnosis: 54.8 ± 9.0	0 – III	Distress trajectories: No distress – 36.3% Recovery – 33.3% Late distress – 15.2% Chronic distress – 15.2%	GHQ scores: membership in 'late distress' trajectory	Over 1 year period following breast cancer diagnosis
Accortt, 2015 [40] (United States)	Cross-sectional	163	In survivorship: 47.6 ± 5.6 (28 – 56)	I – III	Clinical depression: 39%	CES-D ≥ 16	Mean ± SD time following breast cancer diagnosis: 3.4 ± 1.5 years
Donovan, 2014 [41] (United States)	Prospective cohort; trajectory	147	At diagnosis: 51.63 ± 9.03	0 – II	Distress trajectories: Class 1 (High) – 26.5% Class 2 (Medium) – 47.6% Class 3 (Low) – 25.9%	CES-D scores: membership in 'high' trajectory	Over 12 month period following breast cancer diagnosis
Morasso, 2001 [42] (Italy)	Prospective cohort	132	In survivorship: ≤ 50: 37% 51 – 60: 35% > 60: 28%	I – III	Psychiatric disorder (major depressive disorder, adjustment disorder, anxiety disorder, dementia, hypomanic episode): 38%	SCID: standardized diagnostic criteria from the DSM III-R	First follow-up visit in first year after start of chemotherapy
Ploos van Amstel, 2013 [43] (Netherlands)	Cross-sectional	129	In survivorship: 57 ± 10	Not reported	Distress: 36%	NCCN Distress Thermometer ≥ 5	Mean ± SD time since breast cancer surgery: 5.6 ± 4.7 years

Table 3-1 (continued) Characteristics of studies identified by the systematic review

Author, year (country) [G1 – G3: participant groups]	Study design	Sample size	Age, mean ± SD (range)[a] in years	Breast cancer stage	Outcome(s): prevalence (trajectories, if applicable)	Measurement of distress (i.e., case ascertainment)	Timing of distress measurement
Kornblith, 2007 [44] (United States) [G1: age ≤ 55 years; G2: age ≥ 65 years]	Prospective cohort	128 G1: 61 G2: 67	At diagnosis: G1: 43.6 ± 6.1 G2: 67.1 ± 6.8 In survivorship: G1: 47.9 ± 5.9 (IQR: 43 – 53) G2: 72.1 ± 5.4 (IQR: 67 – 76)	I – III	Depression or anxiety: G1 – 9.8% G2 – 3.0% PTSD: G1 – 4.9% G2 – 0%	Depression or anxiety: HADS ≥ 15 PTSD: PCL-C = 1 intrusion + 3 avoidance + 2 arousal symptoms (rated 'moderately' or above)	Mean ± SD time since completion of primary breast cancer treatment: G1: 3.9 ± 1.65 years G2: 4.5 ± 2.2 years
Brunault, 2013 [45] (France)	Prospective cohort	120	At completion of primary breast cancer treatment: 50.2 ± 8.1 In survivorship: 58.3 ± 8.2	0 – IV	Significant depression: 19.2% Possible depression: 12.5% Probable depression: 6.7%	Significant: HADS ≥ 8 Possible: HADS = 8 – 10 Probable: HADS ≥ 11	Mean ± SD (range) time after completion of primary breast cancer treatment: 8.1 ± 1.3 (6.1 – 11.0) years
Wang, 2013 [46] (Taiwan)	Prospective cohort; trajectory	Time 1: 248 Time 2: 118	Not reported	Early stages	Distress (anxiety or depression): Time 1 – 28.63% Time 2 – 16.10% Distress trajectories: Remained distressed – 6% Remained non-distressed – 75% Non-distressed to distressed – 8% Distressed to non-distressed – 11%	HADS ≥ 15	Over a 3-year period: Time 1: ~9 months after completion of primary breast cancer treatment Time 2: ~3 years after Time 1
Eversley, 2005 [47] (United States)	Cross-sectional	116	In survivorship: 47 (29 – 68)	I – IV	Clinical depression: 52%	CES-D ≥ 16	≤ 2 years after breast cancer diagnosis and after completion of primary breast cancer treatment
Vahdaninia, 2010 [48] (Iran)	Prospective cohort	99	In survivorship: 46.4 ± 12.5 (24 – 81)	I – IV	Anxiety: 54.5% Depression: 32.3%	HADS ≥ 8	1 year following completion of primary breast cancer treatment
Neerukonda, 2015 [49] (United States)	Retrospective chart review	81	In survivorship: 53 ± 8	I – 43% II – 41% Other – 16%	Distress: 50%	NCCN Distress Thermometer ≥ 4	First survivorship care visit

Table 3-1 (continued) Characteristics of studies identified by the systematic review

Author, year (country) [G1 – G3: participant groups]	Study design	Sample size	Age, mean ± SD (range)[a] in years	Breast cancer stage	Outcome(s): prevalence (trajectories, if applicable)	Measurement of distress (i.e., case ascertainment)	Timing of distress measurement
Shelby, 2008 [50] (United States)	Prospective cohort	74	In survivorship: Mode: 51 (31 – 84)	II – III	PTSD: 16.2% Subsyndromal PTSD: 20.3%	SCID PTSD: meet Criterion A, and 1 intrusion + 3 avoidance + 2 arousal symptoms Subsyndromal PTSD: meet Criterion A, and (a) 3 avoidance, or 2 arousal symptoms, or (b) ≥ 5 symptoms across clusters	18 months following breast cancer diagnosis
Baider, 2008 [51] (Israel) [G1: mothers were Holocaust survivors; G2: mothers not Holocaust survivors]	Cross-sectional	39 G1: 20 G2: 19	In survivorship: G1: 46.9 ± 7.1 G2: 46.3 ± 9.8	I – II	Distress: G1 – 80% G2 – 32%	GSI ≥ 63	> 6 months after completion of primary breast cancer treatment

[a]Unless otherwise specified; BDI: Beck Depression Inventory; CES-D: Center for Epidemiologic Studies – Depression scale; CES-Dsf: CES-D 8-item screening form; Criterion A: "Actual or threatened death or serious injury, or a threat to the physical integrity of the self or others and a response involving intense fear, helplessness, or horror" [50]; DSM: Diagnostic and Statistical Manual of Mental Disorders; G1 – G3: participant groups (see study-specific descriptions in first column); GHQ: General Health Questionnaire; GSI: Global Severity Index; HADS: Hospital Anxiety and Depression Scale; IQR: interquartile range; MHI: Mental Health Inventory; MINI: Mini International Neuropsychiatric Interview; NCCN: National Comprehensive Cancer Network; PCL-C: Posttraumatic Stress Disorder Checklist – Civilian Version; PHQ-8: 8-item Patient Health Questionnaire; PROMIS: Patient Reported Outcomes Measurement Information System; PTSD: posttraumatic stress disorder; SCID: Structured Clinical Interview for DSM; SD: standard deviation; ZSDS: Zung Self-Rating Depression Scale

Table 3-2 Significance and directionality of commonly assessed candidate predictors ($n \geq 5$), and predictors shown to be significant ($p \leq 0.05$) by at least two studies

Predictors (*n*)	Significant (+) association[a] ($p \leq 0.05$)	Significant association[a] ($p \leq 0.05$); direction unspecified or inconsistent	Significant (–) association[a] ($p \leq 0.05$)	No significant association or association not reported
Sociodemographic characteristics				
Younger age (*n* = 27)	**[10][11][15]**[20]**[22]**[23]**[32][37][38][49]**	[19][33]	**[42]**	[12][14][16][18]**[21][30]**[31]**[35]**[39][40][41][44][45][48]
Non-Caucasian ethnicity (*n* = 11)	[16][20]	[23][47]		[10][11]**[25]**[38][40][41][49]
Unmarried (*n* = 23)	**[10][12]**[18]**[22]**[31]**[36][37][41]**	[11][33]**[38][48]**		**[14]**[16]**[19]**[20]**[23][30]**[32]**[35]**[40][45][49]
Lower education (*n* = 21)	[10][14]**[15]**	**[12]**		[11][16][18]**[19]**[20]**[22][23][30]**[31][32]**[33][35]**[38][39][41][42][48]
Lower income (*n* = 7)	**[12][14][22]**[33]			**[23][35]**[41]
Financial difficulties (*n* = 6)	**[18]**[20][32]**[35]**[43]			[38]
Unemployment (*n* = 9)	[40]	**[23]**		**[14]**[16]**[22]**[31]**[33][35]**[38]
Breast cancer characteristics and treatment				
More advanced breast cancer at diagnosis (*n* = 21)	**[15]**[20]**[31]**		**[11]**	[10]**[12][14]**[18]**[22][23]**[32]**[33][35][36][37]**[39][41][42][45][48][50]
Mastectomy (*n* = 19)	[50]	[14]		[10][11]**[12]**[18][20]**[22][23][30]**[31]**[33][35]**[39][40][41][42][45][48]
Treatment with chemotherapy (*n* = 18)	[18]**[19]**[20][31]			[10][11]**[12][14]**[16]**[22][23][30][33][35][37]**[39][40][48]
Treatment with radiotherapy (*n* = 15)		[14]	**[12]**	[10][11][16][18]**[19]**[20]**[22][23][30][33][35]**[39][40]
Treatment with hormone therapy (*n* = 17)		[10]**[16]**	[20]	[11]**[12][14]**[18]**[19][23][30][33][35][37]**[39][40][41][45]
Longer primary treatment duration (*n* = 2)	[23][43]			
More recent transition into survivorship (*n* = 10)	**[22][32][38]**			[10]**[14][15][30]**[40][43][45]
Breast cancer recurrence (*n* = 4)	**[22]**[31]		**[38]**	[32]
Treatment-related symptoms				
Menopausal/vasomotor symptoms (*n* = 10)	**[10]**[12][14][20]**[35]**[40][42]			[11][41][45]
Pain (*n* = 12)	[10][12][14]**[16]**[20][32]**[38]**[43]**[48]**			[31]**[35]**[45]
Fatigue (*n* = 9)	[12][20]**[30]**[31][32][43]	**[48]**		**[35]**[38]
Sleep disturbance/insomnia (*n* = 9)	**[10][14][27]**[30][32][40][43]			**[35]**[38]
Lymphedema/arm symptoms (*n* = 5)	**[14]**[43]	[11]		**[35]**[45]
Breast symptoms (*n* = 3)	[14][43]			**[35]**
Appetite loss (*n* = 5)	**[14]**[32]			**[35]**[38][43]
Diarrhea (*n* = 5)	[14][32][43]			**[35]**[38]
Dyspnea (*n* = 4)	**[14]**[32]			[38][43]
Constipation (*n* = 5)	**[14]**			[32]**[35]**[38][43]
Nausea and vomiting (*n* = 5)	[32]			**[14][35]**[38][43]
Higher number of treatment-related complaints (*n* = 5)	[39][43][46]			**[35]**[45]
Comorbidities and medical history				
Higher number of comorbidities (*n* = 9)	**[11][12][23]**[30][33]	[16]		[31]**[35]**[41]
History of mental health problems (*n* = 7)	**[19][22]**[31]**[37]**[41]**[42]**[50]			
Perceived functioning limitations				
Lower quality of life/global health status (*n* = 8)	[12][14][18]**[29]**[32][43]			[35]**[38]**
Lower quality of physical health (*n* = 4)	[12]**[30]**[31][33]			
Lower quality of mental health (*n* = 2)	**[12]**[30]			

Table 3-2 (continued) Significance and directionality of commonly assessed candidate predictors ($n \geq 5$), and predictors shown to be significant ($p \leq 0.05$) by at least two studies

Predictors (*n*)	Significant (+) association[a] ($p \leq 0.05$)	Significant association[a] ($p \leq 0.05$); direction unspecified or inconsistent	Significant (–) association[a] ($p \leq 0.05$)	No significant association or association not reported
Perceived functioning limitations (continued)				
Physical functioning limitations (*n* = 8)	**[10]**[12][18][32]**[38]**[43]			[16][35]
Role functioning limitations (*n* = 8)	[12][18][32][33]**[35]**[43]			[35][38]
Emotional functioning limitations (*n* = 5)	[12][32][43]			[35][38]
Cognitive functioning limitations (*n* = 4)	[32][43]			[35][38]
Social functioning limitations (*n* = 6)	[12][32][33][43]			[35][38]
Lower optimism (n = 3)	**[10]**[29]			[39]
Lower posttraumatic growth (*n* = 3)	[28]**[36]**[46]			
Higher number of stressful life events (*n* = 6)	**[10]**[**19**][31]	**[37]**[**38**][50]		
Behavioral and support factors				
Lower physical activity (*n* = 8)	[10]**[11]****[13][17][25]**			[16][30][35]
Lower social support (*n* = 8)	**[10]****[15]**[33]**[36]**[**38**][46]	**[35]**		[20]
Cigarette smoking (*n* = 6)	[10]**[11]**			[13][16][30][35]
Higher alcohol intake (*n* = 5)				[10][13][16][35][50]
Higher BMI (*n* = 7)	[10]	[11]		[16][31][35][40][41]

Numbers in brackets are references to studies included in the review; bolded reference: predictor significant in multivariable analysis; reference in gray: study potentially underpowered (i.e., having a sample size lower than 200, or a prevalence of distress lower than 20%)

BMI body mass index

[a]Bardwell (2006) [10] multivariable analysis used significance of $p \leq 0.001$

Appendix 3-1 MEDLINE, Embase, PsycINFO, and CINAHL systematic review search strategies

Concept	MEDLINE[a] <1996 to March 10, 2016>	Embase <1996 to 2016 Week 10>	PsycINFO <1987 to March Week 2 2016>	CINAHL
Breast cancer	1. exp Breast Neoplasms/ 2. breast neoplasm*.mp. 3. breast cancer*.mp. 4. breast tumo?r*.mp. 5. or/1-4	1. exp breast tumor/ 2. breast neoplasm*.mp. 3. breast cancer*.mp. 4. breast tumo?r*.mp. 5. or/1-4	1. Breast Neoplasms/ 2. breast neoplasm*.mp. 3. breast cancer*.mp. 4. breast tumo?r*.mp. 5. or/1-4	1. (MH "Breast Neoplasms+") 2. (MH "Carcinoma, Lobular") 3. "breast neoplasm*" 4. "breast cancer*" 5. "breast tumor*" 6. "breast tumour*" 7. or/1-6
Survivorship	6. Survivors/ 7. survivor*.mp. 8. or/6-7	6. survivor/ 7. cancer survivor/ 8. survivor*.mp. 9. or/6-8	6. Survivors/ 7. survivor*.mp. 8. or/6-7	8. (MH "Survivors") 9. (MH "Cancer Survivors") 10. "survivor*" 11. or/8-10
Predictor	9. exp Risk/ 10. risk*.mp. 11. predict*.mp. 12. associat*.mp. 13. correlat*.mp. 14. beta coefficient*.mp. 15. odds ratio*.mp. 16. rate ratio*.mp. 17. hazard ratio*.mp. 18. or/9-17	10. exp risk/ 11. risk*.mp. 12. prediction/ 13. predictor variable/ 14. predict*.mp. 15. associat*.mp. 16. correlation analysis/ 17. correlat*.mp. 18. beta coefficient*.mp. 19. odds ratio*.mp. 20. rate ratio*.mp. 21. hazard ratio/ 22. hazard ratio*.mp. 23. or/10-22	9. Risk Factors/ 10. exp Risk Assessment/ 11. risk*.mp. 12. Prediction/ 13. predict*.mp. 14. associat*.mp. 15. exp Statistical Correlation/ 16. correlat*.mp. 17. beta coefficient*.mp. 18. odds ratio*.mp. 19. rate ratio*.mp. 20. hazard ratio*.mp. 21. or/9-20	12. (MH "Risk Factors") 13. (MH "Risk Assessment") 14. "risk*" 15. "predict*" 16. "associat*" 17. (MH "Correlation Coefficient+") 18. "correlat*" 19. "beta coefficient*" 20. (MH "Odds Ratio") 21. "odds ratio*" 22. (MH "Relative Risk") 23. "rate ratio*" 24. "hazard ratio*" 25. or/12-24
Distress	19. exp Mental Disorders/ 20. mental.mp. 21. mood disorder*.mp. 22. Depression/ 23. depress*.mp. 24. dysthymi*.mp. 25. Anxiety/ 26. anxi*.mp. 27. phobi*.mp. 28. panic disorder*.mp. 29. obsessive compulsive disorder*.mp. 30. OCD.mp. 31. dysmorph*.mp. 32. post-traumatic stress disorder*.mp. 33. PTSD.mp. 34. adjustment disorder*.mp. 35. Stress, Psychological/ 36. stress*.mp. 37. distress*.mp. 38. psychological.mp. 39. psychosocial.mp. 40. or/19-39	24. exp mental disease/ 25. exp mental health/ 26. mental.mp. 27. mood disorder*.mp. 28. depress*.mp. 29. dysthymi*.mp. 30. anxiety/ 31. anxi*.mp. 32. phobi*.mp. 33. panic disorder*.mp. 34. obsessive compulsive disorder*.mp. 35. OCD.mp. 36. dysmorph*.mp. 37. post-traumatic stress disorder*.mp. 38. PTSD.mp. 39. adjustment disorder*.mp. 40. exp stress/ 41. stress*.mp. 42. distress*.mp. 43. psychological.mp. 44. psychosocial.mp. 45. or/24-44	22. exp Mental Disorders/ 23. mental.mp. 24. mood disorder*.mp. 25. "Depression (Emotion)"/ 26. depress*.mp. 27. dysthymi*.mp. 28. exp Anxiety/ 29. anxi*.mp. 30. phobi*.mp 31. panic disorder*.mp. 32. obsessive compulsive disorder*.mp. 33. OCD.mp. 34. Body Dysmorphic Disorder/ 35. dysmorph*.mp. 36. post-traumatic stress disorder*.mp. 37. PTSD.mp. 38. adjustment disorder*.mp. 39. exp Stress/ 40. stress*.mp. 41. Distress/ 42. distress*.mp. 43. psychological.mp. 44. psychosocial.mp. 45. or/22-44	26. (MH "Mental Disorders+") 27. "mental" 28. "mood disorder*" 29. (MH "Depression") 30. "depress*" 31. "dysthymi*" 32. (MH "Anxiety+") 33. "anxi*" 34. "phobi*" 35. "panic disorder*" 36. "obsessive compulsive disorder*" 37. "OCD" 38. "dysmorph*" 39. "post-traumatic stress disorder*" 40. "PTSD" 41. "adjustment disorder*" 42. (MH "Stress+") 43. "stress*" 44. "distress*" 45. "psychological" 46. "psychosocial" 47. or/26-46
Overlap of all concepts	41. 5 and 8 and 18 and 40 42. limit 41 to English language 43. limit 42 to yr="2000 - Current"	46. 5 and 9 and 23 and 45 47. limit 46 to English language 48. limit 47 to yr="2000 - Current"	46. 5 and 8 and 21 and 45 47. limit 46 to English language 48. limit 47 to yr="2000 - Current"	48. 7 and 11 and 25 and 47 49. 48 (Limiters - Published Date: 20000101-20161231; English Language)

[a]Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

Appendix 3-2 Significant predictors of distress in univariate and multivariable models

Author, year	Predictors evaluated	Significant predictors of distress in univariate analysis ($p \leq 0.05$)	Significant predictors of distress in multivariable logistic analysis ($p \leq 0.05$)[a]
Bardwell, 2006 [10]	Treatment (surgery + radiotherapy, surgery + chemotherapy, surgery + both, surgery only); Tamoxifen use; breast cancer stage; time since breast cancer diagnosis; age; marital status; ethnicity; education; BMI; physical activity; alcohol intake; cigarette smoking status; number of NCI dietary guidelines met; physical functioning; pain; vasomotor symptoms; genitourinary symptoms; gastrointestinal symptoms; social support; social strain; optimism; Negative Emotional Expressiveness Questionnaire score; ambivalence over negative emotional expressiveness; hostility; stressful life events; sleep disturbance	Not currently using Tamoxifen; younger age; unmarried; lower education; higher BMI; lower physical activity; cigarette smoking; lower number of NCI dietary guidelines met; physical functioning limitations; pain; vasomotor symptoms; genitourinary symptoms; gastrointestinal symptoms; lower social support; higher social strain; lower optimism; higher ambivalence over negative emotional expressiveness; higher hostility; higher number of stressful life events; sleep disturbance	Model without psychosocial variables: younger age; unmarried; physical functioning limitations; vasomotor symptoms; gastrointestinal symptoms[b] Model with psychosocial variables: lower social support; higher social strain; lower optimism; higher ambivalence over negative emotional expressiveness; higher number of stressful life events; sleep disturbance[c]
Dominick, 2014 [11]	Age; ethnicity; education; marital status; tumor grade; tumor size; menopausal status; number of lymph nodes removed; surgery; chemotherapy; radiotherapy; hormone therapy; BMI; cigarette smoking status; physical activity; comorbidities; lymphedema; lymphedema-related distress	Lymphedema-related distress; age; marital status; BMI; number of lymph nodes removed; comorbidities; cigarette smoking status; physical activity	Younger age; lower number of lymph nodes removed; higher number of comorbidities; cigarette smoking; lower physical activity[d]
Chen, 2009 [12]	Age; education; income; marital status; menopausal status; menopausal symptoms; CCI score; ER/PR status; breast cancer stage; surgery; Tamoxifen use; chemotherapy; radiotherapy; immunotherapy; quality of life (total; physical health summary score; mental health summary score; subscale scores [physical functioning; role limitations due to physical health problems; bodily pain; general health perceptions; vitality (i.e., fatigue); social functioning; role limitations due to emotional problems; and mental health index])	Lower education; lower income; unmarried; menopausal symptoms; higher number of comorbidities; no treatment with radiotherapy; lower quality of life (lower total; lower quality of physical health; lower quality of mental health; lower subscale scores [physical functioning limitations; role limitations due to physical health problems; bodily pain; lower general health perceptions; lower vitality (i.e., fatigue); social functioning limitations; role limitations due to emotional problems; lower mental health index])	Multinomial logistic regression model[e]: Mild depression: higher education; lower income; unmarried (i.e., widowed); lower quality of mental health Clinical depression: lower income; unmarried (i.e., widowed, divorced, separated, single); higher number of comorbidities; no treatment with radiotherapy; lower quality of mental health

Appendix 3-2 (continued) Significant predictors of distress in univariate and multivariable models

Author, year	Predictors evaluated	Significant predictors of distress in univariate analysis ($p \leq 0.05$)	Significant predictors of distress in multivariable logistic analysis ($p \leq 0.05$)[a]
Chen, 2010[f] [13]	Exercise participation; duration of exercise; exercise-related MET score; type of exercise; exercise change; tea consumption post-diagnosis (yes, no); tea consumption post-diagnosis (never, former, current); tea consumption amount post-diagnosis (no, yes [≤ 100 grams/month], yes [> 100 grams/month]); lifetime tea consumption, years (no, yes [< 18 years], yes [≥ 18 years]); meat intake; cruciferous vegetable intake; soy food intake; alcohol intake; cigarette smoking status; use of Chinese herbal medicine; total supplement use; ginseng use; ganoderma lucidum capsules/sporophyte use; vitamin supplementation; use of deep sea fish oil pills	Exercise participation (categories not specified); tea consumption (categories not specified)	Shorter duration of exercise; lower exercise-related MET score; exercise change: no exercise (compared with increased exercise level and maintained high exercise level)[g] No tea consumption post-diagnosis (vs. tea consumption); never consumed tea post-diagnosis (vs. current/former tea drinker); no tea consumption post-diagnosis (compared with > 100 grams/month); no lifetime tea consumption (compared with tea consumption and < 18 years tea consumption)[h]
Kim, 2008 [14]	Age; marital status; education; employment status; income; menopausal status; breast cancer stage; time since breast cancer surgery; local treatments (breast conserving surgery, breast conserving surgery + radiotherapy, mastectomy, mastectomy + radiotherapy); adjuvant treatments (not received, chemotherapy, hormone therapy, chemotherapy + hormone therapy); cerebrovascular disease; cardiac disease; diabetes mellitus; liver disease; lung disease; hypertension; infectious disease; gastrointestinal disease; musculoskeletal disease; kidney disease; nausea and vomiting; pain; dyspnea; insomnia; appetite loss; constipation; diarrhea; breast symptoms; arm symptoms; quality of life/global health status; physical functioning; role functioning; emotional functioning; cognitive functioning; social functioning; body image; sexual functioning; sexual enjoyment; future perspectives	Lower education; lower income; menopausal; breast conserving surgery only or mastectomy + radiotherapy as local treatments; diabetes mellitus; hypertension; gastrointestinal disease; musculoskeletal disease; pain; dyspnea; insomnia; appetite loss; constipation; diarrhea; breast symptoms; arm symptoms; lower quality of life/global health status; lower for most functional domains (not specified)	Lower income; musculoskeletal disease; dyspnea; insomnia; appetite loss; constipation; arm symptoms[i]
Mehnert, 2008 [15]	Age; education; breast cancer stage; social support; detrimental interactions; time since breast cancer diagnosis	No significant difference for time since breast cancer diagnosis	Younger age; lower education; more advanced breast cancer stage; lower social support; higher level of detrimental interactions[i]
Calhoun, 2015 [16]	Age; ethnicity; marital status; BMI; education; employment status; cigarette smoking status; physical activity; alcohol intake; chemotherapy; radiotherapy; AI use; Tamoxifen use; number of chronic conditions; pain; physical functioning	Ethnicity (being black); number of chronic conditions; pain; current AI use (by black women)	Separate logistic regression models: Black women: current AI use; pain[j] White women: pain[k]
Branstrom, 2015 [17]	Physical activity	Anxiety: lower physical activity Depression: lower physical activity	Anxiety: lower physical activity[l] Depression: lower physical activity[l]
Saboonchi, 2015 [18]	Age; education; having children; living alone; living with husband/partner; born outside Sweden; financial difficulties; mastectomy; axillary clearance; T-classification; N-classification; triple negative breast cancer; chemotherapy; radiotherapy; hormone therapy; physical functioning; role functioning; quality of life/global health status	Not having children; not living with husband/partner; born outside Sweden; financial difficulties; chemotherapy; physical functioning limitations; role functioning limitations; lower quality of life/global health status	Not having children; financial difficulties[m]

Appendix 3-2 (continued) Significant predictors of distress in univariate and multivariable models

Author, year	Predictors evaluated	Significant predictors of distress in univariate analysis ($p \leq 0.05$)	Significant predictors of distress in multivariable logistic analysis ($p \leq 0.05$)[a]
Saboonchi, 2014 [19]	Age; education; marital status; radiotherapy; hormone therapy; chemotherapy; sickness absence; adverse life events; history of anxiety at baseline; history of depression at baseline	Anxiety: younger age; history of anxiety at baseline; sickness absence; chemotherapy; experienced adverse life events Depression: history of depression at baseline; sickness absence; chemotherapy; experienced adverse life events	Anxiety: history of anxiety at baseline; experienced adverse life events[n] Depression: history of depression at baseline; experienced adverse life events[n]
Avis, 2015* [20]	Age; marital status; financial difficulties; ethnicity; education; children under 18 years old in the home; first degree family history of breast cancer; breast cancer stage; chemotherapy; hormone therapy; radiotherapy; surgery; vasomotor symptoms; pain; fatigue; spirituality – role of faith; spirituality – meaning/peace; social support; illness intrusiveness	Comparing 'borderline score, increasing' (trajectory 5) vs. 'consistent low score' (trajectory 2): younger age; financial difficulties; not Caucasian; children under 18 years old in the home; more advanced breast cancer stage; chemotherapy; no hormone therapy; vasomotor symptoms; pain; fatigue; lower spirituality – meaning/peace; higher illness intrusiveness	Not reported
Ganz, 2003 [21]	Age	Not significant	Not reported
Qiu, 2012 [22]	Age; marital status; employment status; education; income; family history of mental health problems; personal history of mental health problems; time since breast cancer surgery; surgery; breast cancer stage; ER/PR status; radiotherapy; chemotherapy; immunotherapy; breast cancer recurrence	Unmarried (including separated, divorced, widowed); personal history of mental health problems; breast cancer recurrence	Younger age; unmarried (including separated, divorced, widowed); lower income; personal history of mental health problems; shorter time since breast cancer surgery; breast cancer recurrence[c]
Stanton, 2015 [23]	Age; ethnicity; marital status; income; education; employment status; subjective SES; breast cancer stage; treatment duration; surgery; chemotherapy; radiotherapy; Herceptin; hormone therapy; comorbidities; recruitment site	Comparing 'high' vs. 'low' depression trajectories: younger age; being Latina; not being retired; lower SES; longer treatment duration	Comparing 'high' vs. 'low' depression trajectories: not being retired; higher number of comorbidities
Boehmer, 2012 [24]	Sexual orientation	Not significant	Not reported
Kim, 2013 [25]	Ethnicity (Chinese-American vs. non-Hispanic white); level of acculturation in Chinese-American women; physical activity	Not reported	Lower physical activity[o]
Hong, 2015 [26]	Serum levels of 25-hydroxyvitamin D	Not reported	Lower serum levels of 25-hydroxyvitamin D[p]
Palesh, 2010 [27]	Sleep disturbance	Not reported	Anxiety: sleep disturbance[q] Depression: sleep disturbance[r]
Wang, 2015 [28]	Posttraumatic growth trajectories (i.e., stable high, medium stable, low increasing, low decreasing)	Membership in 'high depression' trajectory: least likely to be member of 'stable high' trajectory for posttraumatic growth	Not reported

Appendix 3-2 (continued) Significant predictors of distress in univariate and multivariable models

Author, year	Predictors evaluated	Significant predictors of distress in univariate analysis ($p \leq 0.05$)	Significant predictors of distress in multivariable logistic analysis ($p \leq 0.05$)[a]
Leung, 2016 [29]	Optimism; general health	Lower optimism (general health not evaluated)	Lower general health[s]
Romito, 2012 [30]	Age; education; marital status; time since breast cancer diagnosis; number of comorbidities; treatment (surgery, surgery + radiotherapy, surgery + chemotherapy, and surgery + radiotherapy + chemotherapy); hormone therapy; cigarette smoking status; physical activity; sleep disturbance; fatigue; physical health; mental health	Higher number of comorbidities; sleep disturbance; fatigue; lower physical health; lower mental health	Not reported
Kim, 2013 [31]	Age; education; employment status; marital status; religious; living alone; number of stressful life events; history of depression; HADS scores (for anxiety and depression); number of chronic physical disorders; physical disability; pain; fatigue; BMI; ER+ disease; PR+ disease; tumor size; presence of axillary lymph node; recruitment time since breast cancer diagnosis; chemotherapy; surgery; breast cancer recurrence; breast cancer stage; 5-HTTLPR s allele frequency; STin2 VNTR *10* allele frequency; 5-HTR2a 1438A allele frequency; 5-HTR2a 102C allele frequency; BDNF *met* allele frequency	Unmarried; living alone; higher number of stressful life events; history of depression; higher HADS scores (for anxiety and depression); greater physical disability; fatigue; chemotherapy; breast cancer recurrence; more advanced breast cancer stage; higher STin2 VNTR *10* allele frequency; higher BDNF *met* allele frequency	Living alone; higher HADS score (for anxiety); more advanced breast cancer stage; higher BDNF *met* allele frequency[t]
Reyes-Gibby, 2012 [32]	For inclusion in multivariable model: age; education; marital status; years since breast cancer treatment; metastasis; breast cancer recurrence; diagnosis of new primary cancer; hypertension; heart disease; lung disease; rheumatoid arthritis; osteoarthritis; diabetes; stroke Univariate assessments: cognitive functioning; emotional functioning; role functioning; physical functioning; social functioning; constipation; diarrhea; fatigue; nausea and vomiting; pain; dyspnea; insomnia; loss of appetite; financial difficulties; quality of life/global health status	Cognitive functioning limitations; emotional functioning limitations; role functioning limitations; physical functioning limitations; social functioning limitations; diarrhea; fatigue; nausea and vomiting; pain; dyspnea; insomnia; loss of appetite; financial difficulties; lower quality of life/global health status	Younger age; rheumatoid arthritis; lower number of years since breast cancer treatment[i]
Ashing-Giwa, 2013 [33]	Age; education; place of birth; income; employed prior to breast cancer diagnosis; current employment status; occupation; current marital status; change in marital/relationship status (pre to post breast cancer diagnosis); breast cancer stage; lumpectomy; mastectomy; mastectomy with immediate reconstruction; mastectomy with later reconstruction; radiotherapy; chemotherapy; hormone therapy; physical role limitations; physical well-being; number of comorbidities; neighborhood stress; social support; family stress; functional stress; social functioning limitations; ethnic identity; spirituality	Age (u-shaped association); change in marital/relationship status; lower income; physical role limitations; lower physical well-being; higher number of comorbidities; greater neighborhood stress; lower social support; higher family stress; higher functional stress; social functioning limitations	Not reported
Wang, 2011 [34]	Physical problems listed on the NCCN Distress Thermometer Problem List	18 of 21 physical problems correlated with HADS ≥ 15; 16 of 21 physical problems correlated with NCCN Distress Thermometer ≥ 4	Not reported

Appendix 3-2 (continued) Significant predictors of distress in univariate and multivariable models

Author, year	Predictors evaluated	Significant predictors of distress in univariate analysis ($p \leq 0.05$)	Significant predictors of distress in multivariable logistic analysis ($p \leq 0.05$)[a]
Lee, 2011 [35]	Age; comorbidity; living with spouse; education; religious; employment status; income; physical activity; cigarette smoking status; alcohol intake; ECOG performance status; breast cancer stage; surgery; radiotherapy; chemotherapy; hormone therapy; BMI; change to post-menopausal status; physical functioning; role functioning; emotional functioning; cognitive functioning; social functioning; quality of life/global health status; body image; sexual functioning; future perspectives; fatigue; nausea and vomiting; pain; insomnia; appetite loss; constipation; diarrhea; financial difficulties; hair loss; systemic therapy side effects; breast symptoms; arm symptoms; number of close friends or relatives; tangible support; emotional support; informational support; positive social interaction; affectionate support	Change to post-menopausal status; deteriorated financial difficulties; deteriorated emotional support; deteriorated informational support	Change to post-menopausal status; deteriorated emotional support; deteriorated financial difficulties; deteriorated role functioning[u]
Hsu, 2010 [36]	Breast cancer stage; marital status; perceived support; posttraumatic growth	Not reported	Lower perceived support; lower posttraumatic growth; unmarried (i.e., divorced or widowed)
Burgess, 2005 [37]	Lack of intimate confiding relationship (with a cohabiting partner); age; severe life events; severe non-cancer difficulties; previous episode of depression, anxiety, or both after diagnosis; number of axillary lymph nodes affected; tumor histology; tumor size; adjuvant treatment (none, hormone therapy, chemotherapy, both, or not known)	Not reported	Lack of intimate confiding relationship (with a cohabiting partner); younger age; severe non-cancer difficulties; previous episode of depression, anxiety, or both after diagnosis[v]
Kornblith, 2001 [38]	Education; ethnicity; age; employment; time since beginning of chemotherapy; breast cancer relapse; physical functioning; role functioning; cognitive functioning; emotional functioning; social functioning; quality of life/global health status; fatigue; pain; nausea and vomiting; dyspnea; loss of appetite; insomnia; constipation; diarrhea; financial difficulties; marital status; adequate social support; LES fateful negative events; LES impact of personal illness or injury (past year); LES loss of social support; LES impact of all other negative events (past year); LES impact of positive events (past year); SBI religious; SBI social support	Not reported	Model without psychosocial variables: younger age; no breast cancer relapse; pain[w] Model with psychosocial variables: younger age; shorter time since start of chemotherapy; physical functioning limitations; unmarried (i.e., divorced, separated, or widowed); less than adequate social support; LES greater impact of personal illness or injury (past year)[c]
Henselmans, 2010 [39]	Age; education; breast cancer stage; surgery; adjuvant therapy (radiotherapy only, chemotherapy only, and radiotherapy + chemotherapy); hormone therapy; complaints due to surgery; complaints due to radiotherapy, chemotherapy, and hormone therapy; mastery; optimism; neuroticism	Comparing 'late distress' vs. 'no distress' trajectories: higher number of complaints due to radiotherapy, chemotherapy, and hormone therapy	Comparing 'late distress' vs. 'no distress' trajectories: no significant differences

Appendix 3-2 (continued) Significant predictors of distress in univariate and multivariable models

Author, year	Predictors evaluated	Significant predictors of distress in univariate analysis ($p \leq 0.05$)	Significant predictors of distress in multivariable logistic analysis ($p \leq 0.05$)[a]
Accortt, 2015 [40]	Age; years since breast cancer diagnosis; BMI; marital status; employment status; ethnicity; young children in the home; breast cancer treatments received (chemotherapy only, radiotherapy only, both, or neither); surgery; current endocrine therapy; menopausal status change (pre to post after breast cancer treatment); vasomotor symptoms; sleep disturbance	Unemployed; menopausal status change (pre to post after breast cancer treatment); vasomotor symptoms; sleep disturbance	Not reported
Donovan, 2014 [41]	Age; ethnicity; education; marital status; income; menopausal status; BMI; history of depression; CCI score; surgery; breast cancer stage; number of chemotherapy cycles; number of radiation cycles; cumulative radiation dose; hormone therapy; focusing on symptoms; accommodating to illness; maintaining activity; information seeking	Membership in Class 1 (high distress) vs. Class 3 (low distress): unmarried; history of major depression; focusing on symptoms	Multinomial logistic regression: unmarried; focusing on symptoms[x]
Morasso, 2001 [42]	Age; menopausal status; education; history of mental health problems; pathological tumor size; pathological nodes; histology; estrogen receptors; progesterone receptors; surgery	Older age; post-menopausal; history of mental health problems	Older age; history of mental health problems[y]
Ploos van Amstel, 2013 [43]	Time since breast cancer surgery; treatments (surgery only, surgery + radiotherapy, surgery + chemotherapy, surgery + radiotherapy + chemotherapy); HADS scores; helplessness; acceptance; disease benefits; cognitive functioning; emotional functioning; social functioning; physical functioning; role functioning; quality of life/global health status; financial difficulties; dyspnea; pain; fatigue; sleep disturbance; appetite loss; nausea and vomiting; constipation; diarrhea; body image; sexual functioning; sexual enjoyment; future perspectives; systemic therapy side effects; breast symptoms; arm symptoms; upset by hair loss; vaginal dryness; abnormal blood loss	Treatments (surgery + radiotherapy + chemotherapy vs. surgery only); higher HADS scores; increased helplessness; lower acceptance; lower disease benefits; cognitive functioning limitations; emotional functioning limitations; social functioning limitations; physical functioning limitations; role functioning limitations; lower quality of life/global health status; financial difficulties; pain; fatigue; sleep disturbance; diarrhea; lower body image; worse future perspectives; systemic therapy side effects; breast symptoms; arm symptoms	Not reported
Kornblith, 2007* [44]	Age	No significant differences	Not reported
Brunault, 2013 [45]	Age; time since completion of breast cancer treatment; menopausal status; marital status; breast cancer stage; node status; tumor dimension; histological type; surgery; chemoradiotherapy (sequential or concurrent); hormone therapy; at least one toxicity symptom; pain; edema; fibrosis; telangiectasia; arm lymphedema; atrophy or retraction; ulcer; patient-rated breast cosmetic outcomes [overall cosmetic satisfaction; visibility of the scar; change in skin pigmentation; breast largeness; breast deformation; breast size; breast firmness; nipple displacement]; physician-rated breast cosmetic outcomes [overall cosmetic satisfaction; visibility of the scar]	No significant socio-demographic, cancer-related, or late treatment toxicity variables (breast cosmetic outcomes not reported)	Multinomial logistic regression model[z]: Probable depression vs. no depression: lower patient-rated change in skin pigmentation; patient-rated breast largeness (directionality unspecified); greater patient-rated breast deformation; lower physician-rated overall cosmetic satisfaction Probable depression vs. possible depression: no significant differences

Appendix 3-2 (continued) Significant predictors of distress in univariate and multivariable models

Author, year	Predictors evaluated	Significant predictors of distress in univariate analysis ($p \leq 0.05$)	Significant predictors of distress in multivariable logistic analysis ($p \leq 0.05$)[a]
Wang, 2013 [46]	Physical problems; social support; coping styles; posttraumatic growth	Presence of physical symptoms; lower social support; use of negative emotion or cognitive avoidance coping styles; not using positive attitude coping style; lower posttraumatic growth	Not reported
Eversley, 2005 [47]	Ethnicity	Ethnicity (being Latina)	Not reported
Vahdaninia, 2010 [48]	Age; education; marital status; breast cancer stage; fatigue; pain; initial treatment (mastectomy, conservative surgery, chemotherapy, best supportive care)	Not reported	Anxiety: pain[c] Depression: Not being single; fatigue; pain[c]
Neerukonda, 2015 [49]	Age; anxiolytic or antidepressant medication use; other demographic, psychosocial, tumor-related, and treatment characteristics (not described in detail including ethnicity and marital status); factors included in the NCCN Distress Thermometer	Not reported	Younger age[p]
Shelby, 2008 [50]	Sociodemographic variables (not listed); breast cancer stage; surgery; number of stressful life events; number of stressful life events meeting Criterion A; frequency of individual stressful life events (not all listed); physical abuse; rape; history of anxiety disorder; history of pre-cancer PTSD; history of mood disorder; history of alcohol/substance abuse; current mood disorder; current anxiety disorder; current alcohol/substance abuse	Mastectomy (vs. breast conserving surgery); higher number of Criterion A events; physical abuse; history of anxiety disorder; history of pre-cancer PTSD; history of mood disorder; history of alcohol/substance abuse; current mood disorder; current anxiety disorder	Not reported
Baider, 2008* [51]	Mothers were Holocaust survivors	Mothers were Holocaust survivors	Not reported

*Additional calculations were conducted to assess statistical significance of candidate predictors based on data provided in tables: odds ratios with associated 95% confidence intervals were calculated for categorical predictors and t-tests were conducted for continuous predictors; 5-HTR2a: serotonin 2a receptor; 5-HTTLPR: serotonin transporter gene-linked promoter region; AI: aromatase inhibitor; BDNF: brain-derived neurotrophic factor; BMI: body mass index; CCI: Charlson comorbidity index; Criterion A: "Actual or threatened death or serious injury, or a threat to the physical integrity of the self or others and a response involving intense fear, helplessness, or horror." [50]; ECOG: Eastern Cooperative Oncology Group; ER: estrogen receptor; HADS: Hospital Anxiety and Depression Scale; LES: Life Experience Survey; MET: metabolic equivalent; NCCN: National Comprehensive Cancer Network; NCI: National Cancer Institute; PR: progesterone receptor; PTSD: posttraumatic stress disorder; SBI: Systems of Belief Inventory; SES: socioeconomic status; STin2 VNTR: serotonin transporter intron 2 variable number tandem repeat; [a]Bardwell (2006) [10] multivariable analysis used significance of $p \leq 0.001$; [b]Adjusted for predictors significant in the multivariable model ($p \leq 0.001$), treatment (surgery + radiation, surgery + chemotherapy, surgery + both, surgery only), Tamoxifen use, breast cancer stage, time since breast cancer diagnosis, ethnicity, education, BMI, physical activity, alcohol intake, smoking status, number of NCI dietary guidelines met, pain, and genitourinary symptoms; [c]Adjusted for all predictors evaluated; [d]Adjusted for predictors significant in univariate analysis ($p \leq 0.05$), and marital status; [e]Adjusted for predictors significant in univariate analysis ($p \leq 0.05$); [f]Chen (2010) uses an almost identical cohort to Chen (2009). Therefore, predictors tested and reported by both Chen (2009) and Chen (2010) are only recorded under Chen (2009) to avoid double counting; [g]Adjusted for age at diagnosis, education, income, marital status, comorbidity, tea consumption, menopausal symptoms, relapse/metastasis, radiotherapy, and quality of life (short-form 36-item mental health index score); [h]Adjusted for age at diagnosis, education, income, marital status, exercise, comorbidity, menopausal symptoms, relapse/metastasis, radiotherapy, and quality of life (short-form 36-item mental health index score); [i]Adjusted for predictors significant in the multivariable model ($p \leq 0.05$); [j]Adjusted for predictors significant in the multivariable model ($p \leq 0.05$), and age; [k]Adjusted for AI use, and age; [l]Adjusted for age, education, tumor stage, body mass index, marital status, type of surgery, lymph node involvement, radiotherapy, chemotherapy, and hormonal therapy; [m]Adjusted for significant predictors in multivariable model ($p \leq 0.05$), age, not living with husband/partner, born outside Sweden, and treatment with chemotherapy; [n]Adjusted for predictors significant in the multivariable model ($p \leq 0.05$), age, sickness absence, and treatment with chemotherapy; [o]Adjusted for covariates, e.g., body mass index and comorbidity; [p]Not reported; [q]Adjusted for age; [r]Adjusted for gender, and age; [s]Adjusted for optimism, age, time since breast cancer diagnosis, survey year, socioeconomic status, education, marital status, body mass index, smoking status, and alcohol consumption; [t]Adjusted for predictors significant in multivariable model ($p \leq 0.05$), marital status, number of stressful life events, history of depression, HADS score (for depression), physical disability, pain, fatigue, recruitment time since breast cancer diagnosis, treatment with chemotherapy, breast cancer recurrence, and STin2 VNTR *10* allele frequency; [u]Adjusted for predictors significant in the

multivariable model ($p \leq 0.05$), comorbidity, age, radiotherapy, and smoking status; [v]Adjusted for predictors significant in multivariable model ($p \leq 0.05$), and severe life events; [w]Adjusted for predictors significant in multivariable model ($p \leq 0.05$), education, ethnicity, employment, time since beginning of chemotherapy, and physical function; [x]Adjusted for predictors significant in multivariable model ($p \leq 0.05$), and history of depression; [y]Adjusted for predictors significant in the multivariable model ($p \leq 0.15$); [z]Adjusted for predictors significant in the multinomial multivariable model ($p \leq 0.05$), patient-rated overall cosmetic satisfaction, patient-rated visibility of the scar, patient-rated breast size, patient-rated breast firmness, patient-rated nipple displacement, physician-rated visibility of the scar, age, tumor stage at diagnosis, time since completion of treatment, and marital status

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CHAPTER 4 – OBJECTIVE 2

Syrowatka A, Hanley JA, Weir DL, Dixon WG, Meguerditchian AN, Tamblyn R. Predicting new-onset distress following breast cancer diagnosis: development and validation of risk stratification algorithms. [Prepared for journal submission].

Preamble

The second manuscript describes the development of a transitional survivorship risk stratification model using routinely collected administrative health data. Two additional risk stratification models were developed to investigate whether or not the predictors of new-onset distress vary based on the period of the cancer care trajectory:

i. The full follow-up period (i.e., including both the hospital-based treatment and transitional survivorship periods)
ii. The hospital-based treatment period

This manuscript has been written as a standalone paper for journal submission and therefore does not focus specifically on the transitional survivorship period. Instead, the manuscript compares and contrasts the performance and significant predictors included in the three different risk stratification models.

Manuscript II – Title page

Predicting new-onset distress following breast cancer diagnosis: development and validation of risk stratification algorithms

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Abstract

Purpose: Cancer-related distress as well as its pharmacological treatment have been shown to increase all-cause and cancer-related morbidity and mortality. Fortunately, distress can be prevented with appropriate evidence-based interventions. Therefore, the primary objective of this study was to develop risk stratification models to help identify breast cancer patients at higher risk of new-onset distress. The secondary objective was to explore whether or not the predictors varied based on the period of the cancer care trajectory, specifically during hospital-based treatment and transitional survivorship.

Methods: A population-based cohort study followed 12 370 newly diagnosed female breast cancer patients who had not experienced distress during the baseline year or the diagnostic workup period to develop risk stratification models to identify women at higher risk of new-onset distress. Three different algorithms were developed using time-varying Cox proportional hazards models for: (i) the full follow-up period (i.e., including both hospital-based treatment and transitional survivorship), (ii) only the hospital-based treatment period, and (iii) only the transitional survivorship period. The predictors of new-onset distress were compared between the three models. C-statistics were used to evaluate the performance of each of the models in their respective development cohorts as well as independent validation data of 4 125 breast cancer patients.

Results: Anxiety disorders were the most common type of new-onset distress, accounting for 85.7% and 66.3% of new distress cases during hospital-based treatment and during transitional survivorship, respectively. As anticipated, the predictors of new-onset distress varied based on the period of the cancer care trajectory. In particular, more advanced

breast cancer stage at diagnosis and receipt of specific hospital-based treatments were associated with new-onset distress during the hospital-based treatment period. Whereas, newly diagnosed comorbidities and symptoms played a larger role during the transitional survivorship period. All three final models performed similarly generating Harrell's c-statistics between 0.60 and 0.62 in their respective validation cohorts.

Conclusion: These results indicate that a one-size-fits-all approach is not sufficient to predict new-onset distress in breast cancer patients and that risk stratification models should be tailored based on the period of the cancer care trajectory. Future research should focus on linking multiple administrative health and clinical databases to improve the performance of risk stratification models.

Introduction

Distress has been recognized as an important sequela of breast cancer diagnosis and its treatment.[1] Significant distress can have negative implications beyond affecting cancer patients' quality of life; most importantly, distress as well as its pharmacological treatment have been shown to increase all-cause and cancer-related morbidity and mortality.[2] Women who develop mood disorders after breast cancer diagnosis have an estimated 45% increased risk of all-cause mortality.[3]

To help identify and manage distress, the National Comprehensive Cancer Network (NCCN) has advanced a formal definition: "Distress is a multifactorial unpleasant emotional experience of a psychological (i.e., cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment."[1] This definition includes the following psychological conditions: (i) dementia; (ii) delirium; (iii) depressive disorders; (iv) bipolar and related disorders; (v) schizophrenia spectrum and other psychotic disorders; (vi) anxiety disorders; (vii) trauma and stressor-related disorders; (viii) adjustment disorders; (ix) obsessive-compulsive disorders; (x) substance-related and addictive disorders; and (xi) personality disorders.[1]

The NCCN and other cancer care agencies have released guidelines that promote routine screening of cancer patients using a distress thermometer at appropriate intervals during hospital-based treatment and post-treatment survivorship as well as at important clinical time points including remission, recurrence, progression, or treatment-related complications.[1] However, given the usual structure of cancer care, routine distress

screening by oncologists may not be the most effective strategy for several reasons, such as poor coordination of care and inadequate post-treatment follow-up with the oncology team.[4]

A viable alternative is risk stratification, which focuses on prevention rather than detection.[5] This approach can help guide responsible allocation of limited preventive resources to manage patients with an increased risk of developing distress rather than applying a uniform approach to all women regardless of risk. Risk stratification is particularly relevant in this context given that onset of distress can be prevented; for example, prophylactic cognitive behavioral therapy (CBT) has been shown to reduce the incidence of both anxiety and depression in higher-risk cancer patients by half.[6]

Ideally, the risk stratification process could be automated by capitalizing on routinely collected administrative health data. This type of data is becoming increasingly available to healthcare teams, feasible to access at the point of care, and time and resource efficient. However, little is known about risk factors available in administrative health data that can be used to predict onset of distress following breast cancer diagnosis.[7]

Therefore, the primary objective of this study was to explore the feasibility of using routinely collected administrative health data to predict new-onset distress by identifying predictors available in the administrative health data and evaluating the performance of risk stratification models based on these predictors. The secondary objective was to explore whether the predictors vary based on the period of the cancer care trajectory, specifically during hospital-based treatment and transitional survivorship.

Methods

Study design

A historical, population-based cohort of female breast cancer patients was followed from the date of initial breast cancer surgery to one year following completion of hospital-based breast cancer treatment for new-onset distress (see 'The usual breast cancer care trajectory' in Figure 4-1). The cohort included women diagnosed with a new breast cancer that received hospital-based treatment in Quebec, Canada between January 1, 1998 and March 31, 2011. Breast cancer cases were identified using International Classification of Diseases (ICD) diagnostic codes and Régie de l'assurance maladie du Québec (RAMQ) procedure codes for breast cancer surgery (Appendices 4-1 and 4-2).

To identify new cases of distress, women were excluded if they experienced the outcome of interest (i.e., distress) during the precancer baseline year or diagnostic work-up period (the two months prior to the date of admission for breast cancer surgery). Women were also excluded if they did not have a documented breast surgery, or were not continuously covered by the RAMQ health and drug insurance plans starting at least 14 months prior to the date of initial breast surgery (during the precancer baseline year and diagnostic work-up periods) until completion of transitional survivorship (i.e., one year after completion of hospital-based treatment). The date that each woman completed hospital-based treatment was estimated based on documented RAMQ procedure codes for breast cancer surgeries, chemotherapy, radiotherapy as well as consultations with medical and radio-oncologists indicating consideration of chemotherapy and radiation, respectively (see Appendix 4-2). Completion of hospital-based treatment was defined by

the start of the first six-month period without any documented hospital-based treatments for breast cancer.

Data sources

The risk stratification algorithms were developed using routinely collected administrative health data obtained from the RAMQ provincial, universal health insurance plan. The source population consists of female residents from the province of Quebec, Canada insured by the RAMQ. Data were available from January 1, 1998 to March 31, 2012. The following databases were linked to conduct the analyses: (1) RAMQ registrant database, which provides demographic data and income-indexed drug plan co-payment requirements; (2) RAMQ medical services database, which contains physician fee-for-service claims; (3) Ministry of Health hospital discharge abstract database (MED-ÉCHO), which provides administrative and clinical information on hospital discharges; and (4) RAMQ prescription drug claims database (covering all residents over 65 years of age, and selected, dynamic subgroups less than 65 years old). Ethical clearances were granted through the Institutional Review Board at McGill University and the provincial Access to Information Office.

Measurement of distress

The study outcome was time to onset of new distress. New episodes of distress were identified in the administrative medical services and hospital discharge abstract databases using documented ICD diagnostic codes for mental health problems included in the NCCN definition of cancer-related distress (see Appendix 4-3). Given that ICD

diagnostic codes for mental health problems are known to be underreported,[8,9] additional new episodes of distress were identified through the prescription drug claims database by dispensations of psychotropic medications that are commonly indicated for management of distress (see relevant American Hospital Formulary Services [AHFS] classes in Appendix 4-4).

Candidate predictors of distress

Selection of candidate predictors was informed by the published literature, particularly the systematic review of predictors of distress in breast cancer survivors conducted to address the first objective of this thesis.[7] All candidate predictors are listed in Appendix 4-6 categorized based on type of predictor: sociodemographic characteristics, breast cancer characteristics and treatments, comorbidities, symptoms, and unplanned health services use (see relevant ICD codes in Appendix 4-5). When appropriate, candidate predictors were stratified by time of first documented occurrence as either 'baseline' (i.e., present prior to the start of follow-up) or 'new' (i.e., documented for the first time during the follow-up period). This approach was taken based on evidence that side effects associated with hospital-based breast cancer treatments have been shown to increase the risk of distress.[7]

Statistical analysis

The women in the cohort of breast cancer patients were randomly assigned to either the training set for development of the risk stratification algorithms (75% of the eligible women) or the test set for validation of the algorithms (25% of the eligible

women). Incidence of distress was reported overall and by type: anxiety disorders, mood disorders, and other mental health problems. Descriptive statistics were calculated to characterize the distribution of candidate predictors by outcome for the full follow-up of the training set, and also stratified by period of the cancer care trajectory for hospital-based treatment and transitional survivorship.

The risk stratification algorithms for the full period of follow-up, hospital-based treatment period, and transitional survivorship period were developed based on model fit statistics from time-dependent Cox proportional hazards models and the counting process approach by week of the follow-up period. Age, breast cancer stage at diagnosis, breast cancer treatments (for the transitional survivorship model) as well as low income supplementation of drug insurance, comorbidities, symptoms, and unplanned health services use measurable prior to the start of follow-up were entered into the model as fixed candidate predictors. Breast cancer treatments (for models including the hospital-based treatment period), change to low income supplementation of drug insurance, comorbidities, symptoms and health services use that occurred during the follow-up period were entered into the model as time-dependent candidate predictors.

The risk stratification models were developed using a stepwise forward selection process. Best fit models were selected by constructing a full stepwise sequence using a $p \leq 0.99$ entry criteria for candidate predictors that were retained in the model at $p \leq 0.995$, and locating the model with the lowest Akaike Information Criterion (AIC) value. Best significant predictor models were developed using a $p \leq 0.15$ entry criteria for candidate predictors that were retained in the model at $p \leq 0.05$.

The performance of the risk stratification models was assessed using a modified Harrell's concordance statistic (c-statistic) that accounts for time-dependent predictors. The c-statistics and associated 95% confidence intervals (95% CI) were calculated using a publicly available SAS macro (%survcstd) from the Mayo Clinic written by Kremers (2008).[10] The best significant predictor model was compared with the best fit model using the c-statistic. If the difference between the c-statistics was less than 0.01, then the models were considered to be parsimonious and the best significant predictor model was selected as the final model.

The proportional hazards assumption was assessed for all predictors included in the final risk stratification models by testing the significance of an interaction between each of the predictors with linear time. Candidate interactions were entered into the final models using a stepwise forward selection process while retaining all original predictors in the model. The performance of the final models with interaction terms was assessed based on the c-statistic and associated 95% CIs. Similarly, the final risk stratification models were validated by calculating the c-statistics and associated 95% CIs for the respective test sets (e.g., transitional survivorship model performance was tested on the transitional survivorship test set). The performance of the model developed based on the full period of follow-up was also validated using the stratified hospital-based treatment and transitional survivorship test sets. All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Results

The study cohort consisted of 16 495 women diagnosed and treated for a new breast cancer who did not experience distress in the precancer baseline year or during the diagnostic work-up period. The training set for the development of the risk stratification algorithms included 12 370 women (75% of the cohort).

The incidence of new-onset distress in the training set was 30.1% with 1 984 cases occurring during hospital-based treatment, and the remaining 1 736 cases occurring during transitional survivorship (Table 4-1). The most common type of distress was anxiety, accounting for 76.7%, 85.7%, and 66.3% of new distress cases for the full period of follow-up, during hospital-based treatment, and during transitional survivorship, respectively.

The distributions of candidate predictors by outcome of distress are presented in Table 4-2 (for fixed candidate predictors) and Table 4-3 (for time-dependent candidate predictors). Unadjusted hazard ratios (HRs) with associated 95% CIs for associations of candidate predictors and onset of new distress are reported in Appendix 4-6. For selection of the final multivariable models, none of the best fit models improved the c-statistic by more than 0.01 compared with the best significant predictor models; therefore, the best significant predictor models were selected as the final models presented in Table 4-4.

Risk stratification model for the duration of the full follow-up period

Patient sociodemographic characteristics, breast cancer characteristics, and treatments that predicted onset of distress in the full follow-up period were: younger age,

change to low income supplementation of drug insurance during follow-up, more advanced breast cancer stage at diagnosis, receipt of axillary lymph node dissection, or chemotherapy during the hospital-based treatment period as well as receipt of additional hospital-based treatments after the start of survivorship (indicating a possible cancer recurrence). Conversely, women who had only mastectomy (vs. lumpectomy, or lumpectomy + mastectomy), or received radiotherapy had a lower risk of new-onset distress.

The risk of new-onset distress was higher in women who had pulmonary disease, rheumatologic disease, gastrointestinal symptoms, and pain (as documented through ICD codes or opioid medication dispensations), irrespective of whether it was documented in the baseline period or during follow-up. Hearing loss, menopausal symptoms, and dizziness or syncope present prior to the start of the follow-up period were associated with onset of distress. Newly diagnosed renal failure, urinary symptoms, pulmonary symptoms, and fatigue occurring in follow-up were also associated with increased risk of new-onset distress. Health services use through the emergency department and hospital contacts occurring during the follow-up period also predicted onset of distress. However, the predictors were different when the full follow-up period was stratified into hospital-based treatment and transitional survivorship periods.

Risk stratification model for the duration of the hospital-based treatment period

Onset of distress during the hospital-based treatment period was predicted by younger age, more advanced breast cancer at diagnosis as well as receipt of both lumpectomy + mastectomy, axillary lymph node dissection, or chemotherapy.

Conversely, receipt of radiotherapy was associated with a lower risk of new-onset distress. Rheumatologic disease, opioid medication dispensations (indicating pain), and emergency department health services use were associated with onset of distress whether documented in the precancer baseline or hospital-based treatment follow-up periods. Pulmonary disease or menopausal symptoms present prior to the start of follow-up also increased the risk of new-onset distress. Newly diagnosed renal failure or urinary symptoms that occurred during the hospital-based treatment follow-up period also predicted onset of distress. Conversely, baseline fluid electrolyte or acid-base imbalance was found to lower the risk.

Risk stratification model for the duration of the transitional survivorship period

In the transitional survivorship period, predictors of new-onset distress among women who did not experience distress during hospital-based treatment included: younger age, change to low income supplementation of drug insurance during follow-up, localized breast cancer stage at diagnosis, receipt of axillary lymph node dissection, shorter duration of documented hospital-based treatment, and receipt of additional hospital-based treatments after the start of survivorship (indicating a possible cancer recurrence). Rheumatologic disease and pulmonary symptoms were associated with new-onset distress whether documented prior to the start of follow-up or during the survivorship follow-up period. Gastrointestinal symptoms, menopausal symptoms, and pain (as documented by ICD codes) present prior to the start of the follow-up period were also associated with onset of distress. Newly diagnosed pulmonary disease, anemia, hypertension, urinary symptoms, and fatigue occurring during the survivorship follow-up

period were associated with an increased risk of new-onset distress. Health services use through the emergency department and hospital contacts occurring during the survivorship follow-up period also predicted onset of distress.

Risk stratification model performance and validation

Despite the different statistically significant predictors included in each model, the three final models had almost identical Harrell's c-statistics of ~ 0.62 in the development cohorts (Table 4-5). When the performance of each of the models was validated using the respective test sets (e.g., transitional survivorship model performance was tested on the transitional survivorship test set), the results were similar with each of the models generating a c-statistic between 0.60 and 0.62. The risk stratification model for the full follow-up period performed just as well as the hospital-based treatment model when validated using the hospital-based treatment test set. However, the risk stratification model for the full follow-up period performed significantly worse compared with the transitional survivorship model when validated using the transitional survivorship test set with a c-statistic of 0.542 (95% CI: 0.519 – 0.566).

Discussion

This study identified predictors of new-onset distress in female breast cancer patients available in routinely collected administrative health data in an effort to help guide allocation of supportive care resources. The unique contribution of this research was the identification of predictors of onset of distress in routinely collected administrative health data for the early survivorship period, where women transition to

follow-up care and have fewer contacts with the oncology team. Overall, anxiety disorders were the most common type of new-onset distress, accounting for 85.7% and 66.3% of new-onset distress cases during hospital-based treatment and during transitional survivorship, respectively. As anticipated, the predictors of new-onset distress varied based on the period of the cancer care trajectory. However, all three final models performed similarly, generating Harrell's c-statistics between 0.60 and 0.62 in their respective validation cohorts. Although these models only moderately improved the prediction of new-onset distress, the results of this study can be used to inform development of more comprehensive risk stratification algorithms to identify women at higher risk of new-onset distress following breast cancer diagnosis.

Breast cancer stage at diagnosis was a significant predictor of distress in both the hospital-based treatment and transitional survivorship periods; however, more advanced breast cancer was associated with new-onset distress during hospital-based treatment, whereas localized breast cancer predicted onset in the survivorship period. This difference is likely attributable to the longer duration of hospital-based treatment and more aggressive anti-cancer therapies received by women with more advanced cancer. As a result, women with more advanced cancer who are more susceptible to distress would likely develop it during the hospital-based treatment period, particularly while undergoing chemotherapy. Conversely, women with localized disease have comparatively shorter durations of hospital-based treatment, in some cases limited to only breast surgery. Under these circumstances, women may not have had adequate time to cope with the breast cancer diagnosis during hospital-based treatment, in addition to having reduced access to supportive care as a result of less frequent contacts with the

oncology care team upon transition into survivorship.[4] These results are seemingly contrary to the conclusions of the systematic review of predictors of distress in breast cancer survivors, which indicated that longer treatment duration was associated with increased risk of distress.[7] However, this inconsistency can be explained by the difference in study outcomes; the systematic review reported on predictors of prevalent distress, whereas this study investigated predictors on new-onset distress.

Newly diagnosed comorbidities or symptoms may have been related to hospital-based breast cancer treatment. Many of the predictors could have been treatment-related side effects related to breast surgery, chemotherapy, and/or radiation: pulmonary disease and related symptoms (e.g., dyspnea); renal failure and urinary symptoms (e.g., incontinence); anemia; hypertension; gastrointestinal symptoms (e.g., nausea and vomiting); menopausal symptoms; fatigue; and pain.[11–13] The results also suggest that pre-existing conditions or symptoms documented during the precancer baseline and diagnostic work-up periods may have been exacerbated by receipt of hospital-based breast cancer treatments. In particular, underlying rheumatologic disease may predict onset of distress as a result of discontinuation of disease-modifying immunosuppressant medications during hospital-based treatment, which would result in more pain and limited mobility. Additionally, hospital-based treatments and adjuvant endocrine therapy have been shown to increase the risk of joint pain, and may serve to trigger or exacerbate underlying rheumatologic symptoms. Unfortunately, ICD diagnostic codes for lymphedema were rarely documented in the administrative health data limiting their use as a predictor of distress. However, given the context, it seems that receipt of an axillary lymph node dissection may predict new-onset distress by way of increasing the risk of

lymphedema, which has been shown to occur in approximately 20% of women who receive axillary dissections based on a meta-analysis of 18 studies.[14] Furthermore, axillary lymph node dissection may also cause distress as a result of limited joint mobility and stiffness. The results of this study highlight that treatment-related conditions and symptoms do not have to be severe in order to increase the risk of new-onset distress.

Interventions focused on timely identification and effective management of treatment-related symptoms could prevent onset of distress by reducing the burden of disease. In fact, electronic monitoring of treatment-related symptoms coupled with automated alerts to the oncology care team has been shown to improve health-related quality of life in cancer patients receiving chemotherapy.[15] Furthermore, the intervention reduced the number of emergency department visits and hospitalizations. This is particularly relevant given that the results of this current study have demonstrated that emergency department visits and hospital contacts either increase the risk of new-onset distress or are early signs of new-onset distress; therefore, proactive intervention to avoid unplanned health services use may also reduce the risk of developing distress.

An important strength of this study was the development of time-dependent prognostic models that accounted for new events that occurred in the follow-up period. New treatment-related comorbidities and symptoms were significant predictors of new-onset distress, particularly in the transitional survivorship period. In addition, the time-dependent analysis helped to disentangle the independent associations of breast cancer stage and hospital-based treatments with onset of distress. Previous studies have evaluated hospital-based treatments as candidate predictors of depression following

breast cancer diagnosis using time-to-event models; however, the results may have been biased given that the analyses did not appear to account for the time-dependent nature of these predictors.[16,17] The current study also advanced the literature by stratifying the analysis by period of the cancer care trajectory, which provided more insight into the effect of duration of hospital-based treatment on risk of new-onset distress in transitional survivorship.

This study had several limitations. ICD diagnostic codes for mental health problems tend to be underreported in administrative health data. Reasons include the current RAMQ reporting structures allowing only one ICD code to be documented for physician healthcare services billing as well as ongoing stigmatization around mental health problems and reluctance to medicalize cancer-related distress.[1,8,9] As a result, a substantial number of new cases of distress may not have been documented in the administrative health databases. Similarly, comorbidities and symptoms may have been underreported weakening the predictive performance of the final models; for example, despite being relatively common following axillary lymph node dissection,[14] lymphedema was rarely documented in the administrative health data. Conversely, measuring distress based on psychotropic medication dispensations from administrative prescription drug claims databases may have overestimated the number of cases of new-onset distress, also resulting in a weaker c-statistic. Some of the new psychotropic medication dispensations may have been prescribed for other indications, such as sleep disorders, migraines, or pain.[18] Furthermore, the study did not capture new cases of distress if psychotropic medications were prescribed but never dispensed (i.e., primary

non-adherence)[19] or if women received alternative treatments for distress not covered by the universal health insurance plan, specifically psychotherapy.

Another limitation was the relatively short pre-cancer baseline period used to assess history of mental health problems, which meant that only women with a recent history were excluded from the study. However, this washout period was sufficient for the purpose of this study, which was to identify women at higher risk of experiencing a new episode of distress during hospital-based treatment or transitional survivorship to help guide allocation of supportive care resources. Women were also excluded if they were not continuously covered by the RAMQ drug insurance plan for the duration of the study, which may limit generalizability to younger women with a higher socioeconomic status since they are less likely to be covered. This exclusion criterion may have also resulted in an underestimation of the predictive value of low income supplementation of drug insurance.

This study identified predictors of new-onset distress available in routinely collected administrative health databases, and showed how the predictors change based on the period of the cancer care trajectory, specifically during hospital-based treatment and during transitional survivorship. These results indicate that a one-size-fits-all approach is not sufficient to predict new-onset distress in breast cancer patients and that risk stratification models should be tailored based on the period of the cancer care trajectory. Although the risk stratification models developed improved prediction of distress, the c-statistics were relatively low ranging from 0.60 to 0.62 in validation cohorts. However, risk stratification models with lower c-statistics are used in clinical

practice; for example, the modified Gail model for breast cancer risk assessment has a c-statistic of 0.63 (95% CI: 0.59 – 0.67).[20] Future research should focus on linking multiple administrative health and clinical databases to improve the performance of the risk stratification models. For example, candidate predictors such as the material and social deprivation index, or conditions and symptoms captured through clinical patient problem lists may substantially improve the prediction of new-onset distress in breast cancer patient populations.

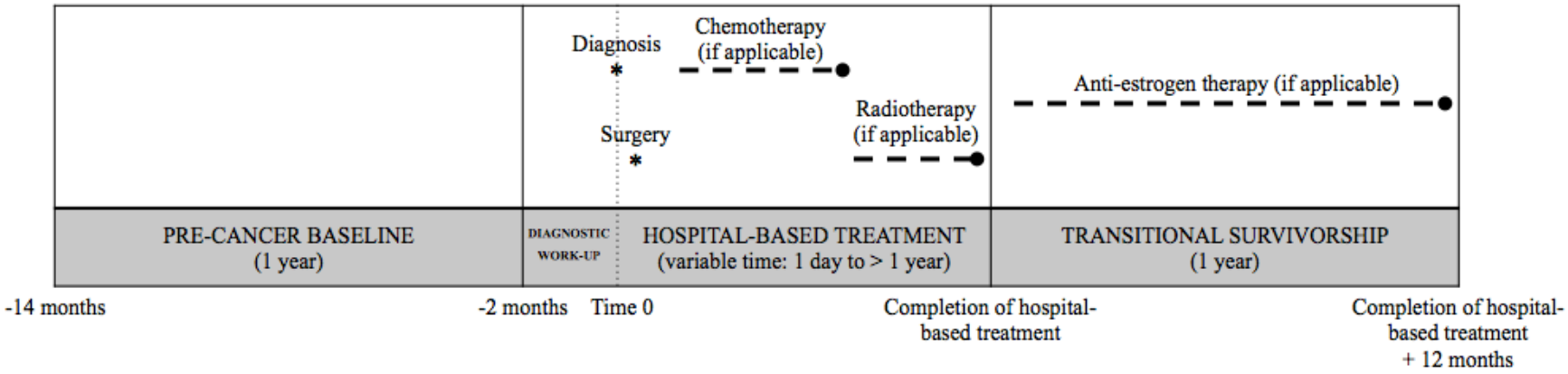

Figure 4-1. The usual breast cancer care trajectory

Table 4-1. Frequency distribution of new-onset distress by type

Type of distress	Full follow-up* (N = 12 370)	During hospital-based treatment (N = 12 370)	During transitional survivorship (N = 10 386)
Incidence of new-onset distress	% (n)	% (n)	% (n)
All distress	30.1 (3 720)	16.0 (1 984)	16.7 (1 736)
Anxiety disorders	23.1 (2 852)	13.8 (1 701)	11.1 (1 151)
Mood disorders	6.1 (755)	2.0 (250)	4.9 (505)
Other mental health disorders	1.5 (183)	0.5 (65)	1.1 (118)
Rate of new-onset distress	Per 1 000 p-y	Per 1 000 p-y	Per 1 000 p-y
All distress	293	592	185
Anxiety disorders	225	507	123
Mood disorders	60	75	54
Other mental health disorders	14	19	13

* Includes hospital-based treatment and transitional survivorship

Table 4-2. Distribution of fixed candidate predictors by outcome of new-onset distress

Fixed candidate predictors (i.e., present at the start of the follow-up period)	Full follow-up period* (N = 12 370)		During hospital-based treatment (N = 12 370)		During transitional survivorship (N = 10 386)	
	Distress (*n* = 3 720)	No distress (*n* = 8 650)	Distress (*n* = 1 984)	No distress (*n* = 10 386)	Distress (*n* = 1 736)	No distress (*n* = 8 650)
Demographic characteristics	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Age at diagnosis	63.5 ± 11.8	66.7 ± 11.6	61.2 ± 11.0	66.6 ± 11.7	66.0 ± 12.3	66.7 ± 11.6
Indicator of lower socioeconomic status	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Low income supplementation of drug insurance	26.3 (979)	31.5 (2 726)	22.0 (437)	31.5 (3 268)	32.5 (564)	32.7 (2 824)
Breast cancer characteristics and treatments	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Breast cancer stage at diagnosis						
Distant	0.7 (25)	0.5 (43)	0.8 (15)	0.5 (53)	0.6 (10)	0.5 (43)
Regional	25.5 (947)	19.2 (1 663)	32.1 (636)	19.0 (1 974)	17.9 (311)	19.2 (1 663)
Localized	63.8 (2 375)	64.5 (5 578)	60.2 (1 195)	65.1 (6 758)	68.0 (1 180)	64.5 (5 578)
Uncertain	0.3 (12)	0.8 (65)	0.2 (3)	0.7 (74)	0.5 (9)	0.8 (65)
In situ	9.7 (361)	15.0 (1 301)	6.8 (135)	14.7 (1 52)	13.0 (226)	15.0 (1 301)
Type of surgery						
Mastectomy + lumpectomy	3.6 (135)	3.5 (301)	3.3 (66)	3.6 (370)	10.8 (188)	9.5 (821)
Mastectomy only	13.2 (491)	14.7 (1 273)	10.0 (198)	15.1 (1 566)	16.4 (285)	14.6 (1 261)
Lumpectomy only	83.2 (3 904)	81.8 (7 076)	86.7 (1 720)	81.4 (8 450)	72.8 (1 263)	75.9 (6 568)
Axillary lymph node dissection	47.3 (1 760)	39.2 (3 389)	52.1 (1 033)	39.6 (4 116)	51.3 (890)	47.9 (4 145)
Receipt of adjuvant therapy						
Chemotherapy prior to first breast surgery	1.5 (54)	1.3 (114)	1.3 (25)	1.4 (143)	16.0 (278)	17.1 (1 478)
Radiotherapy prior to first breast surgery	0.0 (1)	0.2 (17)	0.1 (1)	0.2 (17)	62.4 (1 084)	66.4 (5 742)
Duration of documented hospital-based treatment					Mean ± SD	Mean ± SD
Days between breast surgery and last treatment	--	--	--	--	95.1 ± 86.0	105.6 ± 87.1
Comorbidities	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Cardiovascular disease	18.7 (696)	19.0 (1 642)	15.9 (315)	19.5 (2 023)	26.2 (455)	22.9 (1 984)
Pulmonary disease	13.2 (489)	11.0 (949)	13.2 (262)	11.3 (1 176)	14.7 (255)	12.4 (1 075)
Gastrointestinal disease	1.7 (62)	1.5 (128)	1.5 (29)	1.6 (161)	2.1 (37)	1.8 (151)
Rheumatologic disease	28.3 (1 052)	24.3 (2 105)	27.2 (540)	25.2 (2 617)	32.9 (571)	27.0 (2 337)
Renal failure	1.5 (56)	1.6 (136)	1.2 (23)	1.6 (169)	2.2 (38)	1.8 (159)
Anemia	3.8 (143)	3.4 (292)	3.3 (65)	3.6 (370)	6.2 (108)	5.0 (435)
Diabetes	10.7 (397)	12.5 (1 080)	9.8 (195)	12.3 (1 282)	12.4 (216)	13.0 (1 124)
Hypothyroidism	9.5 (352)	10.0 (864)	8.7 (173)	10.0 (1 043)	11.1 (193)	10.7 (928)

Table 4-2 (continued). Distribution of fixed candidate predictors by outcome of new-onset distress

Fixed candidate predictors (i.e., present at the start of the follow-up period)	Full follow-up period* (N = 12 370)		During hospital-based treatment (N = 12 370)		During transitional survivorship (N = 10 386)	
	Distress (*n* = 3 720)	No distress (*n* = 8 650)	Distress (*n* = 1 984)	No distress (*n* = 10 386)	Distress (*n* = 1 736)	No distress (*n* = 8 650)
Comorbidities (continued)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Hypertension	36.4 (1 353)	38.4 (3 325)	33.3 (660)	38.7 (4 018)	41.5 (721)	40.3 (3 488)
Hearing loss	3.6 (134)	3.3 (281)	3.2 (64)	3.4 (351)	4.4 (76)	3.8 (327)
Equilibrium problems	1.5 (57)	1.1 (96)	3.3 (65)	3.3 (346)	1.7 (29)	1.3 (109)
Cataract	7.3 (273)	9.0 (774)	6.0 (118)	8.9 (929)	9.5 (165)	9.6 (826)
Glaucoma	5.5 (204)	6.6 (574)	4.6 (91)	6.6 (687)	6.8 (118)	7.1 (614)
Other vision problems	11.0 (410)	11.7 (1 012)	10.1 (202)	11.8 (1 220)	13.4 (233)	13.1 (1 133)
Osteoporosis	10.0 (370)	10.9 (944)	8.7 (173)	11.1 (1 141)	16.1 (280)	15.2 (1 313)
Fracture	2.34 (87)	2.6 (222)	2.0 (39)	2.6 (270)	3.4 (59)	3.0 (257)
Cellulitis	2.0 (74)	1.8 (152)	2.1 (42)	1.8 (184)	5.2 (91)	4.5 (390)
Breast wound	0.2 (8)	0.2 (19)	0.2 (4)	0.2 (23)	0.8 (14)	0.8 (67)
Gynecologic disorders	8.8 (328)	7.4 (638)	9.0 (178)	7.6 (788)	10.5 (183)	9.2 (798)
Symptoms	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Pulmonary symptoms	17.2 (639)	15.7 (1 355)	16.0 (317)	16.2 (1 677)	21.7 (377)	18.6 (1 605)
Gastrointestinal symptoms	14.4 (535)	11.5 (997)	13.5 (268)	12.2 (1 264)	19.0 (329)	14.8 (1 283)
Urinary symptoms	1.9 (70)	1.9 (165)	2.1 (41)	1.9 (194)	2.0 (35)	2.2 (192)
Menopausal symptoms	16.1 (598)	12.5 (1 080)	16.8 (334)	12.9 (1 344)	16.9 (294)	14.0 (1 213)
Fatigue	2.3 (85)	2.1 (183)	2.2 (43)	2.2 (225)	3.0 (52)	2.6 (226)
Dizziness or syncope	3.6 (135)	3.0 (258)	3.4 (68)	3.1 (325)	4.7 (82)	3.8 (327)
Fluid electrolyte or acid-base imbalance	1.3 (48)	1.5 (128)	0.8 (15)	1.6 (161)	2.5 (44)	2.0 (175)
Pain	11.6 (431)	9.5 (823)	10.9 (216)	10.0 (1 038)	14.9 (258)	11.4 (986)
Opioid medication dispensation (indicating pain)	15.7 (582)	13.8 (1 195)	17.2 (341)	13.8 (1 436)	22.4 (388)	20.8 (1 803)
Health services use	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Number of emergency department visits	0.5 ± 1.1	0.5 ± 1.0	0.6 ± 1.1	0.5 ± 1.1	0.9 ± 1.5	0.8 ± 1.4
Number of hospital contacts	0.2 ± 0.5	0.2 ± 0.5	0.1 ± 0.4	0.2 ± 0.5	0.5 ± 0.8	0.5 ± 0.7

* Includes hospital-based treatment and transitional survivorship; P-y = person-years

Table 4-3. Distribution of time-dependent candidate predictors by outcome of new-onset distress

Time-dependent candidate predictors (i.e., occurring during the follow-up period)	Full follow-up* (N = 12 370)		During hospital-based treatment (N = 12 370)		During transitional survivorship (N = 10 386)	
	Distress (*n* = 3 720)	No distress (*n* = 8 650)	Distress (*n* = 1 984)	No distress (*n* = 10 386)	Distress (*n* = 1 736)	No distress (*n* = 8 650)
Indicator of lower socioeconomic status	Per 1 000 p-y (n)	Per 1 000 p-y (n)	Per 1 000 p-y (n)	Per 1 000 p-y (n)	Per 1 000 p-y (n)	Per 1 000 p-y (n)
Low income supplementation of drug insurance	65 (71)	40 (303)	57 (16)	56 (120)	71 (33)	36 (205)
Breast cancer treatments	% (n)	% (n)	% (n)	% (n)		
Receipt of both mastectomy and lumpectomy	9.5 (352)	9.5 (821)	8.3 (164)	9.7 (1 009)	--	--
Axillary lymph node dissection	57.7 (2 146)	47.9 (4 145)	63.3 (1 256)	48.5 (5 035)	--	--
Receipt of adjuvant therapy						
Chemotherapy	21.0 (782)	17.1 (1 478)	25.4 (504)	16.9 (1 756)	--	--
Radiotherapy	35.6 (1 324)	66.4 (5 742)	12.1 (240)	65.7 (6 826)	--	--
Possible cancer recurrence	Per 1 000 p-y (n)	Per 1 000 p-y (n)			Per 1 000 p-y (n)	Per 1 000 p-y (n)
Receipt of additional treatments in survivorship	190 (30)	68 (286)	--	--	190 (30)	68 (286)
Comorbidities	Per 1 000 p-y (n)	Per 1 000 p-y (n)	Per 1 000 p-y (n)	Per 1 000 p-y (n)	Per 1 000 p-y (n)	Per 1 000 p-y (n)
Cardiovascular disease	197 (229)	94 (791)	273 (82)	176 (416)	143 (73)	70 (449)
Pulmonary disease	96 (124)	46 (442)	103 (32)	58 (154)	108 (64)	43 (316)
Gastrointestinal disease	13 (19)	8 (87)	14 (5)	9 (27)	14 (10)	8 (64)
Rheumatologic disease	201 (207)	125 (977)	216 (57)	132 (291)	204 (91)	125 (745)
Renal failure	20 (30)	7 (81)	22 (8)	10 (28)	25 (17)	7 (58)
Anemia	78 (112)	30 (313)	103 (36)	61 (173)	70 (46)	21 (170)
Diabetes	33 (44)	23 (222)	40 (13)	22 (58)	28 (17)	24 (178)
Hypothyroidism	41 (56)	20 (197)	41 (14)	29 (78)	45 (28)	17 (133)
Hypertension	382 (352)	81 (526)	107 (26)	103 (191)	147 (58)	73 (363)
Hearing loss	23 (33)	22 (231)	17 (6)	18 (52)	31 (21)	22 (185)
Equilibrium problems	11 (16)	8 (93)	20 (7)	18 (53)	11 (8)	9 (80)
Cataract	37 (51)	41 (406)	17 (6)	23 (62)	55 (35)	46 (354)
Glaucoma	19 (28)	19 (191)	14 (5)	16 (45)	27 (18)	19 (151)
Other vision problems	65 (86)	63 (596)	64 (21)	55 (146)	67 (40)	65 (475)
Osteoporosis	145 (188)	115 (1 054)	111 (37)	173 (452)	119 (68)	99 (685)
Fracture	29 (43)	20 (210)	22 (8)	16 (46)	35 (24)	21 (175)
Cellulitis	122 (174)	41 (432)	209 (73)	105 (297)	64 (42)	24 (194)
Breast wound	19 (29)	7 (79)	41 (15)	20 (58)	6 (4)	4 (31)
Gynecologic disorder	95 (128)	61 (599)	120 (39)	72 (193)	89 (56)	58 (439)

Table 4-3 (continued). Distribution of time-dependent candidate predictors by outcome of new-onset distress

Time-dependent candidate predictors (i.e., occurring during the follow-up period)	Full follow-up* (N = 12 370)		During hospital-based treatment (N = 12 370)		During transitional survivorship (N = 10 386)	
	Distress (*n* = 3 720)	No distress (*n* = 8 650)	Distress (*n* = 1 984)	No distress (*n* = 10 386)	Distress (*n* = 1 736)	No distress (*n* = 8 650)
Symptoms	Per 1 000 p-y (n)	Per 1 000 p-y (n)	Per 1 000 p-y (n)	Per 1 000 p-y (n)	Per 1 000 p-y (n)	Per 1 000 p-y (n)
Pulmonary symptoms	169 (200)	75 (665)	221 (66)	128 (305)	148 (79)	61 (415)
Gastrointestinal symptoms	189 (233)	92 (846)	292 (90)	152 (384)	145 (81)	79 (560)
Urinary symptoms	27 (41)	12 (134)	36 (13)	11 (33)	32 (22)	13 (107)
Menopausal symptoms	70 (89)	55 (515)	49 (15)	64 (163)	75 (44)	53 (382)
Fatigue	36 (53)	16 (174)	33 (12)	18 (53)	46 (31)	16 (131)
Dizziness or syncope	43 (62)	23 (248)	48 (17)	29 (84)	45 (30)	22 (179)
Fluid electrolyte or acid-base imbalance	26 (39)	10 (110)	36 (13)	20 (58)	22 (15)	7 (63)
Pain	119 (155)	76 (731)	126 (41)	78 (206)	121 (71)	77 (568)
Opioid medication dispensation (indicating pain)	407 (460)	113 (962)	927 (239)	328 (755)	139 (74)	54 (354)
Health services use	Per 1 000 p-y (n)	Per 1 000 p-y (n)	Per 1 000 p-y (n)	Per 1 000 p-y (n)	Per 1 000 p-y (n)	Per 1 000 p-y (n)
New emergency department visit	892 (1 042)	355 (2 960)	1 476 (442)	740 (1 798)	584 (362)	260 (1 944)
New hospital contact	1 029 (1 139)	386 (3 055)	1 885 (525)	1 164 (2 637)	354 (233)	154 (1 232)

* Includes hospital-based treatment and transitional survivorship; P-y = person-years

Table 4-4. Hazard ratios (HR) for the best significant predictor risk stratification models

Candidate predictors	Full follow-up* (N = 12 370)	During hospital-based treatment (N = 12 370)	During transitional survivorship (N = 10 386)
Sociodemographic characteristics			
Age (per 5-year increase)	0.900 (0.882, 0.918)[a]	0.911 (0.894, 0.929)	0.945 (0.925, 0.965)
Low income supplementation of drug insurance			
New supplementation	1.321 (1.042, 1.676)	--	1.657 (1.172, 2.345)
Prior to start of follow-up	--	--	--
Breast cancer characteristics and treatments			
Breast cancer stage			
Distant	2.554 (1.454, 4.487)[b]	2.637 (1.533, 4.538)	1.072 (0.565, 2.031)
Regional	1.625 (1.325, 1.993)[c]	1.542 (1.250, 1.902)	1.028 (0.843, 1.253)
Localized	1.460 (1.224, 1.740)[d]	1.453 (1.207, 1.750)	1.201 (1.032, 1.397)
Uncertain	0.849 (0.373, 1.932)[e]	1.590 (0.505, 5.008)	0.688 (0.353, 1.343)
In situ	Reference	Reference	Reference
Type of surgery			
Mastectomy + lumpectomy	0.995 (0.883, 1.121)	1.204 (1.020, 1.422)	--
Mastectomy only	0.882 (0.796, 0.978)	0.903 (0.774, 1.054)	--
Lumpectomy only	Reference	Reference	--
Axillary lymph node dissection	1.344 (1.204, 1.500)[f]	1.200 (1.077, 1.338)	1.535 (1.298, 1.816)[h]
Receipt of adjuvant therapy			
Chemotherapy	1.298 (1.185, 1.423)	1.172 (1.033, 1.330)	--
Radiotherapy	0.886 (0.810, 0.970)	0.607 (0.521, 0.707)	--
Duration of documented hospital-based treatment (per additional 30 days)	N/A	N/A	0.874 (0.845, 0.903)[i]
Receipt of additional hospital-based treatments in survivorship (indicating possible recurrence)	2.042 (1.402, 2.973)	N/A	1.776 (1.218, 2.588)
Comorbidities			
Pulmonary disease			
New diagnosis	1.384 (1.148, 1.668)	--	1.538 (1.182, 2.001)
Prior to start of follow-up	1.167 (1.060, 1.285)	1.219 (1.069, 1.390)	--
Rheumatologic disease			
New diagnosis	1.374 (1.188, 1.591)	1.468 (1.123, 1.918)	1.308 (1.050, 1.630)
Prior to start of follow-up	1.210 (1.123, 1.303)	1.219 (1.102, 1.348)	1.246 (1.123, 1.382)
Renal failure			
New diagnosis	1.836 (1.274, 2.647)	2.837 (1.404, 5.730)	--
Prior to start of follow-up	--	--	--
Anemia			
New diagnosis	--	--	1.646 (1.204, 2.251)
Prior to start of follow-up	--	--	--
Hypertension			
New diagnosis	--	--	1.384 (1.055, 1.817)
Prior to start of follow-up	--	--	--
Hearing loss			
New diagnosis	--	--	--
Prior to start of follow-up	1.246 (1.047, 1.482)	--	--

Table 4-4 (continued). Hazard ratios (HR) for the best significant predictor risk stratification models

Candidate predictors	Full follow-up* (N = 12 370)	During hospital-based treatment (N = 12 370)	During transitional survivorship (N = 10 386)
Symptoms			
Pulmonary symptoms			
New diagnosis	1.228 (1.058, 1.425)	--	2.535 (1.523, 4.219)[j]
Prior to start of follow-up	--	--	1.171 (1.042, 1.316)
Gastrointestinal symptoms			
New diagnosis	1.186 (1.031, 1.364)	--	--
Prior to start of follow-up	1.161 (1.058, 1.274)	--	1.234 (1.093, 1.393)
Urinary symptoms			
New diagnosis	1.772 (1.297, 2.421)	1.868 (1.074, 3.247)	5.259 (2.065, 13.392)[k]
Prior to start of follow-up		--	--
Menopausal symptoms			
New diagnosis	--	--	--
Prior to start of follow-up	1.250 (1.144, 1.365)	1.240 (1.101, 1.395)	1.553 (1.268, 1.902)[l]
Fatigue			
New diagnosis	1.430 (1.083, 1.889)	--	1.963 (1.369, 2.813)
Prior to start of follow-up	--	--	--
Dizziness or syncope			
New diagnosis	--	--	--
Prior to start of follow-up	1.197 (1.007, 1.423)	--	--
Fluid electrolyte or acid-base imbalance			
New diagnosis	--	--	--
Prior to start of follow-up	--	0.553 (0.332, 0.921)	--
Pain			
New diagnosis	1.203 (1.018, 1.422)	--	--
Prior to start of follow-up	1.133 (1.022, 1.255)	--	1.241 (1.085, 1.420)
Opioid medication dispensation (indicating pain)	1.270 (1.148, 1.406)	1.132 (0.924, 1.388)[g]	--
New dispensation	1.145 (1.046, 1.253)	1.213 (1.076, 1.368)	--
Prior to start of follow-up			
Health services use			
Emergency department visits			
New visit in follow-up	1.286 (1.185, 1.395)	1.278 (1.141, 1.433)	1.445 (1.263, 1.653)
Per additional baseline visit	--	1.046 (1.005, 1.090)	--
Hospital contacts			
New contact in follow-up	1.189 (1.096, 1.289)	--	1.600 (1.359, 1.883)
Per additional baseline contact	--	--	--

* Includes hospital-based treatment and transitional survivorship; [a] Significant age x time beta coefficient: 0.0001869; [b] Significant distant breast cancer stage x time beta coefficient: -0.00382; [c] Significant regional breast cancer stage x time beta coefficient: -0.00135; [d] Localized breast cancer stage x time beta coefficient: -0.0006937; [c] Uncertain breast cancer stage x time beta coefficient: -0.00179; [f] Significant axillary lymph node dissection x time beta coefficient: -0.0009739; [g] Significant new opioid dispensation x time beta coefficient: 0.00214; [h] Significant axillary lymph node dissection x time beta coefficient: -0.00186; [i] Significant duration of hospital-based treatment x time beta coefficient: 0.0004489; [j] Significant new pulmonary symptoms x time beta coefficient: -0.00248; [k] Significant new urinary symptoms x time beta coefficient: -0.00562; [l] Significant baseline menopausal symptoms x time beta coefficient: -0.00155

Table 4-5. Harrell's concordance statistics (c-statistic) for development and validation cohorts

	Full follow-up algorithm*	Hospital-based treatment algorithm	Transitional survivorship algorithm
Development cohorts	C-statistic (95% CI)	C-statistic (95% CI)	C-statistic (95% CI)
Respective development set	0.629 (0.620, 0.638)	0.622 (0.610, 0.635)	0.629 (0.616, 0.643)
Validation cohorts	C-statistic (95% CI)	C-statistic (95% CI)	C-statistic (95% CI)
Full follow-up test set*	0.620 (0.604, 0.635)	--	--
Hospital-based treatment test set	0.616 (0.594, 0.638)	0.616 (0.594, 0.637)	--
Transitional survivorship test set	0.542 (0.519, 0.566)	--	0.603 (0.579, 0.627)

* Includes hospital-based treatment and transitional survivorship

Appendix 4-1. International Classification of Diseases (ICD) diagnostic codes used to identify women with breast cancer in the administrative health databases

Breast cancer stage	ICD-9 codes	ICD-10 codes
No breast cancer	No 174.x, 233.0, 238.3, 239.3	No C50.x, D05.x, D48.6
Carcinoma in situ	233.0	D05.x
Uncertain	238.3 or 239.3 with no 233.0, 174.x, 196.0-199.1	D48.6 with no C50.x, D05.x, C77.x-C80.x
Localized (breast cancer with no documented lymph node involvement or metastasis)	174.x with no 196.0-199.1	C50.x with no C77.x-C80.x
Regional (breast cancer with lymph node involvement but no metastasis)	196.0-196.9 with no 197.0-199.1	C77.x with no C78.x-C80.x
Distant (breast cancer with metastasis beyond lymph nodes)	197.0-199.1	C78.x-C80.x

Appendix 4-2. Régie de l'assurance maladie du Québec (RAMQ) procedure codes used to estimate completion of hospital-based breast cancer treatment in the administrative health databases

Hospital-based treatment event	RAMQ procedure codes
Lumpectomy	01174; 01175; 01201; 01202; 01203; 01204; 01205; 01228; 01229; 01250; 01251; 01252
Mastectomy	01230; 01231; 01232
Axillary lymph node dissection	01231; 01232; 01228; 04240
Sentinel lymph node biopsy	04161; 04199; 01252
Chemotherapy	00734
External beam radiotherapy	08507; 08508; 08509; 08511; 08518; 08519; 08520; 08553; 08564
Brachytherapy	08522; 08538; 08545; 08547; 08548; 08550; 08562; 08563
First medical oncologist consult (indicating consideration of chemotherapy)	09127[a]; 09150[a]; 09160[a]; 09162[a]; 09165[a]; 09170[a]; 15000; 15001; 15005; 15007; 15020; 15021
First radio-oncologist consult (indicating consideration of radiation)	09127[b]; 09150[b]; 09160[b]; 09162[b]; 09165[b]; 09170[b]

[a] Restricted to RAMQ specialty codes for hematologists and medical oncologists; [b] Restricted to RAMQ specialty code for radio-oncologists

Appendix 4-3. International Classification of Diseases (ICD) codes used to identify distress in the administrative health databases

Type of distress	ICD-9 codes	ICD-10 codes
Organic disorders: Senile and pre-senile psychotic conditions (i.e., dementias)	2900; 2901; 2902; 2903; 2904; 2908; 2909	F000; F001; F002; F009; F010; F011; F012; F013; F018; F019; F020; F021; F022; F023; F024; F028; F03; F04; F050; F051; F058; F059; F060; F061; F062; F063; F064; F065; F066; F067; F068; F069; F070; F071; F072; F078; F079; F09; G300; G301; G308; G309
Organic disorders: Transient organic psychotic conditions	2930; 2931; 2938; 2939	
Organic disorders: Other organic psychotic conditions	2940; 2941; 2942; 2948; 2949	
Substance-related disorders: Alcoholic psychoses	2910; 2911; 2912; 2913; 2914; 2915; 2918; 2919	F100-9; F110-9; F120-9; F130-9; F140-9; F150-9; F160-9; F170-9; F180-9; F190-9; F55
Substance-related disorders: Drug psychoses	2920; 2921; 2922; 2928; 2929	
Substance-related disorders: Alcohol dependence	3030; 3039	
Substance-related disorders: Drug dependence	3040; 3041; 3042; 3043; 3044; 3045; 3046; 3047; 3048; 3049	
Substance-related disorders: Non-dependent abuse of drugs	3050; 3051; 3052; 3053; 3054; 3055; 3056; 3057; 3058; 3059	
Schizophrenic and psychotic disorders: Schizophrenia	2950; 2951; 2952; 2953; 2954; 2955; 2956; 2957; 2958; 2959	F200; F201; F202; F203; F204; F205; F206; F208; F209; F21; F220; F228; F229; F230; F231; F232; F233; F238; F239; F24; F250; F251; F252; F258; F259; F28; F29
Schizophrenic and psychotic disorders: Psychotic	2988; 2989	
Schizophrenic and psychotic disorders: Paranoia, delusional disorders, other psychoses	2970; 2971; 2972; 2973; 2978; 2979; 2980; 2981; 2982; 2983; 2984	
Mood disorders: Bipolar	2960; 2961; 2964; 2965; 2966; 2967; 2968	F300; F301; F302; F308; F309; F310; F311; F312; F313; F314; F315; F316; F317; F318; F319; F340
Mood disorders: Depression	2962; 2963; 3004; 311	F320; F321; F322; F323; F328; F329; F330; F331; F332; F333; F334; F338; F339; F341; F381
Mood disorder: Other	2969	F348; F349; F380; F388; F39
Anxiety disorders: Anxiety	3000; 3002; 3003; 3098	F400; F401; F402; F408; F409; F410; F411; F412; F413; F418; F419; F420; F421; F422; F428; F429; F930; F931; F932
Anxiety disorders: Acute stress	3083	F430; F431; F438; F439
Personality disorders: Personality disorders	3010; 3011; 3012; 3013; 3014; 3015; 3016; 3017; 3018; 3019	F600; F601; F602; F603; F604; F605; F606; F607; F608; F609; F61; F620; F621; F628; F629; F680; F681; F688; F69
Other disorders: Adjustment disorders	3090; 3091; 3092; 3093; 3094; 3099	F432; F99

Appendix 4-4. American Hospital Formulary Service (AHFS) classes used to identify distress and pain in the administrative health databases

Markers of distress or pain	AHFS classes
Anticonvulsants, anxiolytics, sedatives, and hypnotics	281204; 281208; 282404; 282408; 282492
Antidepressants	281604
Antipsychotics	281608[a]; 282800
Cholinesterase inhibitors	120400
Opioids	280808; 280812

[a] Excluding Prochlorperazine, which has been re-classified as an anti-emetic (AHFS class: 562208)

Appendix 4-5. International Classification of Diseases (ICD) codes used to identify comorbid diseases and symptoms in the administrative health databases

Diseases and symptoms	ICD-9 codes	ICD-10 codes
Comorbidities		
Cardiovascular disease and related symptoms	3623; 402; 404; 410; 411; 412; 413; 414; 425; 426; 427; 428; 4292; 4299; 430; 431; 432; 433; 434; 435; 436; 437; 438; 440; 441; 442; 443; 4471; 451; 452; 453; 4599; 7852; 7853; 7854; 7855; 7859	G45; H34; I11; I13; I20; I21; I22; I23; I24; I25; I42; I43; I44; I45; I46; I47; I48; I49; I50; I519; I60; I61; I62; I63; I65; I66; I67; I68; I69; I70; I71; I72; I73; I771; I80; I81; I82; I96; I999; R011; R012; R570
Pulmonary disease	415; 416; 417; 490; 491; 492; 493; 494; 496; 5080; 5081; 511; 5184; 5185; 5188; 7991	I26; I27; I28; J40; J41; J42; J43; J44; J45; J47; J700; J701; J80; J81; J90; J91; J94; J951; J952; J953; J958; J96; J98; J99; R091; R092
Gastrointestinal disease	4560; 4561; 4562; 531; 532; 533; 534; 570; 571; 572; 573	I85; K25; K26; K27; K28; K70; K71; K72; K73; K74; K75; K76; K77
Rheumatologic disease	714; 715; 716; 7193; 7199; 720; 721; 722; 723; 724; 725; 726; 727; 728; 7290	M05; M06; M12; M13; M14; M15; M16; M17; M18; M19; M259; M353; M43; M45; M46; M47; M48; M49; M50; M51; M53; M54; M60; M61; M62; M63; M65; M66; M67; M70; M71; M72; M75; M76; M77; M790
Renal failure	403; 404; 584; 585; 586; 588	I12; I13; N17; N18; N19; N25
Anemia	280; 281; 282; 283; 284; 285	D50; D51; D52; D53; D55; D56; D57; D58; D59; D60; D61; D62; D63; D64
Diabetes	250	E10; E11; E12; E13; E14
Hypothyroidism	244	E02; E03; E890
Hypertension	401	I10
Hearing loss	389	H90; H91
Equilibrium problems	386; 3883	H81; H82; H83; H931; H93A
Cataract	366	H25; H26; H28
Glaucoma	365	H40; H42
Other vision problems	360; 361; 362; 363; 364; 367; 368; 369; 370; 371; 372; 373; 374; 375; 376; 377; 378; 379	H00; H01; H02; H04; H05; H10; H11; H15; H16; H17; H18; H20; H21; H22; H27; H30; H31; H32; H33; H34; H35; H36; H43; H44; H46; H47; H49; H50; H51; H52; H53; H54; H55; H57; H59
Osteoporosis	7330	M81
Fracture	7331; 800; 801; 802; 803; 804; 805; 806; 807; 808; 809; 810; 811; 812; 813; 814; 815; 816; 817; 818; 819; 820; 821; 822; 823; 824; 825; 826; 827; 828; 829	M80; M84; S02; S12; S22; S32; S42; S52; S62; S72; S82; S92
Cellulitis	6822; 6829	L033; L039

Appendix 4-5 (continued). International Classification of Diseases (ICD) codes used to identify comorbid diseases and symptoms in the administrative health databases

Diseases and symptoms	ICD-9 codes	ICD-10 codes
Comorbidities (cont'd)		
Breast wound	8790; 8791	S210
Gynecologic disorders	614; 615; 616; 617; 618; 619; 620; 621; 622; 623; 624; 625; 626; 628; 629	N70; N71; N72; N73; N74; N75; N76; N77; N80; N81; N82; N83; N84; N85; N86; N87; N88; N89; N90; N91; N92; N93; N94; N96; N97; N98; R37
Symptoms		
Pulmonary symptoms	7860; 7863; 7865; 7869	R04; R06; R071; R072; R078; R079
Gastrointestinal symptoms	558; 5603; 5609; 562; 5640; 7870; 7879; 789	K52; K564; K565; K566; K567; K57; K590; R10; R11; R18; R19
Urinary symptoms	788	N23; N39; R30; R31; R32; R33; R34; R35; R36; R39
Menopausal symptoms	627	N95
Fatigue	7807	R53
Dizziness or syncope	7802; 7804	R42; R55
Fluid electrolyte or acid-base imbalance	276	E87
Pain	053; 338; 353; 354; 355; 7194; 7291; 7292; 7295; 7809	B02; G54; G56; G57; G58; G59; G89; M255; M791; M792; M796; M797; R52

Appendix 4-6. Univariate hazard ratios (HR) with associated 95% confidence intervals (95% CI) for candidate predictors

Candidate predictors	Full follow-up* (N = 12 370)	During hospital-based treatment (N = 12 370)	During transitional survivorship (N = 10 386)
Sociodemographic characteristics	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age (per 5-year increase)	0.915 (0.903, 0.927)[a]	0.900 (0.884, 0.917)	0.977 (0.958, 0.997)
Low income supplementation of drug insurance			
New supplementation	1.374 (1.084, 1.740)	0.849 (0.518, 1.392)	1.757 (1.243, 2.484)
Prior to start of follow-up	0.819 (0.761, 0.881)[a]	0.772 (0.694, 0.859)[a]	0.992 (0.898, 1.097)
Breast cancer characteristics and treatments	HR (95% CI)	HR (95% CI)	HR (95% CI)
Breast cancer stage at diagnosis			
Distant	1.947 (1.298, 2.920)	3.070 (1.800, 5.236)	1.327 (0.705, 2.501)
Regional	1.753 (1.552, 1.979)[a]	2.067 (1.715, 2.492)	1.074 (0.905, 1.274)
Localized	1.427 (1.277, 1.594)[a]	1.619 (1.355, 1.935)	1.201 (1.042, 1.385)
Uncertain	0.753 (0.424, 1.338)	1.654 (0.526, 5.195)	0.818 (0.420, 1.591)
In situ	Reference	Reference	Reference
Type of surgery			
Lumpectomy and mastectomy	1.224 (1.095, 1.368)	1.489 (1.266, 1.750)	1.174 (1.033, 1.335)
Mastectomy only	0.956 (0.868, 1.053)[a]	1.086 (0.936, 1.260)	1.173 (1.006, 1.367)[a]
Lumpectomy only	Reference	Reference	Reference
Axillary lymph node dissection	1.456 (1.364, 1.554)[a]	1.512 (1.378, 1.660)	1.139 (1.036, 1.251)[a]
Receipt of adjuvant therapy			
Chemotherapy	1.635 (1.505, 1.777)[a]	1.569 (1.392, 1.768)[a]	0.924 (0.813, 1.051)[a]
Radiotherapy	0.827 (0.761, 0.899)[a]	0.502 (0.433, 0.582)	0.849 (0.770, 0.935)[a]
Duration of documented hospital-based treatment (per additional 30 days)	N/A	N/A	0.956 (0.939, 0.974)[a]
Receipt of additional hospital-based treatments in survivorship (indicating possible recurrence)	2.422 (1.668, 3.517)	N/A	2.466 (1.706, 3.564)
Comorbidities	HR (95% CI)	HR (95% CI)	HR (95% CI)
Cardiovascular disease			
New diagnosis	1.472 (1.285, 1.686)	1.277 (1.020, 1.599)	1.823 (1.439, 2.310)
Prior to start of follow-up	0.996 (0.917, 1.082)	0.940 (0.834, 1.061)	1.177 (1.057, 1.309)
Pulmonary disease			
New diagnosis	1.781 (1.486, 2.135)	1.469 (1.033, 2.088)	2.343 (1.822, 3.015)
Prior to start of follow-up	1.191 (1.083, 1.310)	1.243 (1.091, 1.415)[a]	1.190 (1.042, 1.359)
Gastrointestinal disease			
New diagnosis	1.334 (0.850, 2.095)	1.165 (0.484, 2.805)[a]	1.695 (0.910, 3.158)
Prior to start of follow-up	1.121 (0.872, 1.440)	1.045 (0.724, 1.508)	1.210 (0.874, 1.676)
Rheumatologic disease			
New diagnosis	1.444 (1.252, 1.666)	1.412 (1.083, 1.841)	1.485 (1.199, 1.840)
Prior to start of follow-up	1.192 (1.110, 1.280)	1.171 (1.061, 1.293)	1.287 (1.165, 1.423)
Renal failure			
New diagnosis	2.291 (1.599, 3.284)	2.646 (1.317, 5.314)	3.007 (1.863, 4.853)
Prior to start of follow-up	0.984 (0.756, 1.281)	0.931 (0.617, 1.403)	1.185 (0.859, 1.634)

Appendix 4-6 (continued). Unadjusted hazard ratios (HR) with associated 95% confidence intervals (95% CI) for candidate predictors

Candidate predictors	Full follow-up* (N = 12 370)	During hospital-based treatment (N = 12 370)	During transitional survivorship (N = 10 386)
Comorbidities (cont'd)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Anemia			
New diagnosis	1.867 (1.544, 2.257)	1.543 (1.105, 2.154)	3.112 (2.319, 4.178)
Prior to start of follow-up	1.117 (0.945, 1.320)	1.011 (0.789, 1.295)	1.227 (1.010, 1.491)
Diabetes			
New diagnosis	1.396 (1.036, 1.881)	1.504 (0.871, 2.598)	1.158 (0.717, 1.869)
Prior to start of follow-up	0.856 (0.772, 0.950)	0.809 (0.698, 0.938)	0.954 (0.828, 1.100)
Hypothyroidism			
New diagnosis	1.666 (1.278, 2.171)	1.497 (0.884, 2.535)	2.272 (1.561, 3.305)
Prior to start of follow-up	0.952 (0.853, 1.063)	0.916 (0.783, 1.070)	1.038 (0.893, 1.205)
Essential hypertension			
New diagnosis	1.262 (1.043, 1.527)	1.000 (0.678, 1.475)	1.854 (1.424, 2.414)
Prior to start of follow-up	0.933 (0.873, 0.997)	0.880 (0.801, 0.966)	1.045 (0.950, 1.150)
Hearing loss			
New diagnosis	1.095 (0.777, 1.545)	1.044 (0.468, 2.326)	1.373 (0.892, 2.114)[a]
Prior to start of follow-up	1.105 (0.930, 1.313)	1.116 (0.870, 1.432)	1.142 (0.907, 1.437)
Equilibrium problems			
New diagnosis	1.304 (0.797, 2.132)	1.207 (0.574, 2.536)	1.154 (0.576, 2.313)
Prior to start of follow-up	1.326 (1.021, 1.722)	1.140 (0.890, 1.459)	1.288 (0.892, 1.859)
Cataract			
New diagnosis	1.050 (0.795, 1.386)	0.864 (0.387, 1.926)	1.185 (0.847, 1.660)
Prior to start of follow-up	0.843 (0.745, 0.954)	0.793 (0.659, 0.956)	0.995 (0.848, 1.168)
Glaucoma			
New diagnosis	1.105 (0.761, 1.605)	1.192 (0.495, 2.871)	1.399 (0.879, 2.228)
Prior to start of follow-up	0.844 (0.733, 0.972)	0.757 (0.614, 0.935)	0.962 (0.798, 1.160)
Other vision problems			
New diagnosis	1.069 (0.862, 1.326)	1.046 (0.678, 1.611)	1.034 (0.754, 1.417)
Prior to start of follow-up	0.949 (0.856, 1.051)	0.961 (0.830, 1.111)	1.018 (0.887, 1.168)[a]
Osteoporosis			
New diagnosis	1.039 (0.895, 1.207)	0.916 (0.661, 1.270)	1.008 (0.790, 1.287)
Prior to start of follow-up	0.918 (0.825, 1.022)	0.844 (0.722, 0.986)	1.067 (0.939, 1.212)
Fracture			
New diagnosis	1.658 (1.226, 2.244)	1.480 (0.738, 2.970)	1.691 (1.129, 2.534)
Prior to start of follow-up	0.908 (0.734, 1.123)	0.797 (0.580, 1.094)	1.126 (0.869, 1.460)
Cellulitis			
New diagnosis	1.500 (1.287, 1.748)	1.398 (1.105, 1.769)	2.017 (1.483, 2.741)
Prior to start of follow-up	1.111 (0.883, 1.399)	1.121 (0.826, 1.522)	1.137 (0.921, 1.404)[a]
Breast wound			
New diagnosis	1.089 (0.755, 1.569)	1.217 (0.732, 2.023)[a]	0.882 (0.331, 2.353)
Prior to start of follow-up	0.975 (0.488, 1.952)	0.955 (0.358, 2.545)	1.047 (0.619, 1.771)
Gynecologic disorders			
New diagnosis	1.411 (1.180, 1.687)	1.407 (1.022, 1.937)	1.483 (1.134, 1.940)
Prior to start of follow-up	1.159 (1.035, 1.298)	1.092 (0.936, 1.273)	1.149 (0.986, 1.339)

Appendix 4-6 (continued). Unadjusted hazard ratios (HR) with associated 95% confidence intervals (95% CI) for candidate predictors

Candidate predictors	Full follow-up* (N = 12 370)	During hospital-based treatment (N = 12 370)	During transitional survivorship (N = 10 386)
Symptoms	HR (95% CI)	HR (95% CI)	HR (95% CI)
Pulmonary symptoms			
New diagnosis	1.641 (1.420, 1.897)	1.354 (1.056, 1.737)	2.215 (1.763, 2.782)[a]
Prior to start of follow-up	1.074 (0.986, 1.170)[a]	0.954 (0.846, 1.076)	1.192 (1.064, 1.336)
Gastrointestinal symptoms			
New diagnosis	1.537 (1.343, 1.759)	1.563 (1.261, 1.937)	1.659 (1.324, 2.078)
Prior to start of follow-up	1.229 (1.121, 1.347)	1.138 (1.000, 1.294)	1.306 (1.158, 1.472)
Urinary symptoms			
New diagnosis	2.251 (1.652, 3.067)[a]	2.308 (1.334, 3.993)	2.457 (1.611, 3.747)[a]
Prior to start of follow-up	1.005 (0.793, 1.273)	1.183 (0.868, 1.612)	0.912 (0.652, 1.274)
Menopausal symptoms			
New diagnosis	1.129 (0.913, 1.396)	0.742 (0.446, 1.235)	1.252 (0.926, 1.691)
Prior to start of follow-up	1.273 (1.166, 1.389)	1.214 (1.079, 1.365)	1.236 (1.091, 1.402)[a]
Fatigue			
New diagnosis	1.898 (1.442, 2.500)	1.471 (0.832, 2.600)	2.559 (1.791, 3.655)
Prior to start of follow-up	1.068 (0.861, 1.324)	1.041 (0.770, 1.409)	1.133 (0.860, 1.493)
Dizziness or syncope			
New diagnosis	1.571 (1.221, 2.022)[a]	1.586 (0.982, 2.560)	1.947 (1.355, 2.798)
Prior to start of follow-up	1.208 (1.017, 1.435)	1.231 (0.966, 1.567)	1.234 (0.989, 1.540)
Fluid electrolyte or acid-base imbalance			
New diagnosis	1.854 (1.351, 2.545)	1.470 (0.851, 2.539)	2.867 (1.723, 4.771)
Prior to start of follow-up	0.880 (0.662, 1.170)	0.560 (0.337, 0.931)	1.239 (0.918, 1.671)
Pain			
New diagnosis	1.486 (1.262, 1.750)	1.458 (1.068, 1.993)	1.482 (1.166, 1.885)
Prior to start of follow-up	1.193 (1.079, 1.319)	1.085 (0.942, 1.250)	1.316 (1.153, 1.502)
Opioid medication dispensation (indicating pain)			
New dispensation	1.476 (1.339, 1.628)	1.498 (1.308, 1.716)[a]	1.692 (1.340, 2.137)
Prior to start of follow-up	1.125 (1.030, 1.229)	1.168 (1.040, 1.313)	1.086 (0.970, 1.216)
Health services use	HR (95% CI)	HR (95% CI)	HR (95% CI)
Emergency department visits			
New visit in follow-up	1.645 (1.527, 1.773)	1.513 (1.354, 1.690)	2.021 (1.793, 2.278)
Per additional baseline visit	1.048 (1.019, 1.077)	1.070 (1.030, 1.112)	1.032 (1.001, 1.063)
Hospital contacts			
New contact in follow-up	1.515 (1.408, 1.631)	1.383 (1.241, 1.541)	2.375 (2.060, 2.738)[a]
Per additional baseline contact	1.003 (0.935, 1.076)[a]	0.959 (0.862, 1.066)	1.038 (0.976, 1.104)[a]

* Includes hospital-based treatment and transitional survivorship

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CHAPTER 5 – OBJECTIVE 3

Syrowatka A, Hanley JA, Girard N, Dixon WG, Meguerditchian AN, Tamblyn R. Predicting new-onset distress in breast cancer survivors: adjustment for outcome misclassification. [Prepared for journal submission].

Preamble

The third manuscript describes a first attempt to adjust for new-onset distress outcome misclassification and assess its impact on the fit of the transitional survivorship risk stratification model developed as a part of the second objective of this thesis. The second manuscript used a composite outcome for new-onset distress, which included relevant International Classification of Diseases (ICD) diagnostic codes as well as dispensations of psychotropic medications. However, the psychotropic medications may have been prescribed for indications other than distress. This study aims to correct for potential outcome misclassification during transitional survivorship using an auxiliary gold-standard clinical database that contains information about indications for psychotropic medication prescriptions.

Manuscript III – Title Page

Predicting new-onset distress in breast cancer survivors: adjustment for outcome misclassification

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Abstract

Purpose: Inclusion of psychotropic medication dispensations as indicators of new-onset distress may introduce unintended outcome misclassification, given that the medications may have been indicated for conditions other than distress. Therefore, the objective of this study was to use gold-standard clinical data to adjust for distress outcome misclassification and assess its effect on the fit of the transitional survivorship risk stratification model developed in the previous study.

Methods: A historical cohort of 2 929 female cancer patients was selected from a clinical research platform and followed to identify prescriptions for psychotropic medications. The indications for each prescription documented in the clinical database were used to calculate the positive predictive values and specificities for each unique psychotropic medication. The positive predictive values were used to correct the naïve estimate of the incidence of new-onset distress in a population-based cohort of 10 386 breast cancer survivors. Two multiple imputation approaches were then applied to assess the impact of outcome misclassification on the fit of the risk stratification model: (i) using the positive predictive values of the psychotropic medications, and (ii) using predictor information in combination with the specificities of the psychotropic medications.

Results: The adjusted estimate of the incidence of new-onset distress in the cohort of breast cancer survivors was 37% lower than the uncorrected estimate. Generally, adjustment for this misclassification in the transitional survivorship risk stratification model did not impact the statistical significance or interpretation of the predictors compared with the uncorrected model. However, both adjustment approaches supported

the exclusion of four predictors: change to lower income supplementation of drug insurance, localized breast cancer at diagnosis, receipt of additional hospital-based treatments after the start of survivorship, and baseline pain. Furthermore, both approaches also supported placing additional weight on three predictors: new urinary symptoms, fatigue, and emergency department visits occurring during the survivorship follow-up period. However, the adjustment approaches had opposing effects on the parameter estimates for newly diagnosed hypertension and hospital contacts as well as baseline gastrointestinal and menopausal symptoms.

Conclusion: The results show that ignoring distress outcome misclassification will negatively impact the fit of the transitional survivorship risk stratification model. However, it is not clear which adjustment approach provided the more accurate corrected parameter estimates and better model fit.

Introduction

In the study conducted to address the second objective of this thesis, dispensations of psychotropic medications were included as indicators of new-onset cancer-related distress in female breast cancer survivors.[1] The purpose of the study was to develop a risk stratification algorithm to help identify predictors of onset of distress in this vulnerable population. However, the results may have been biased due to the potential for outcome misclassification when counting all psychotropic medication dispensations as true episodes of distress.

Imperfectly documented outcomes are a common challenge when using administrative health databases for research. Formal mental health diagnoses based on the International Classification of Diseases (ICD) codes are underreported in these databases. Reasons include current reporting structures limiting documentation to one ICD code per physician visit as well as ongoing stigmatization around mental health problems and reluctance to medicalize distress.[2,3] Despite this limitation, administrative health databases hold a vast amount of information that can be used to evaluate as well as improve quality of mental health care, for example, through risk stratification.[4]

As a result, investigators have sought indirect ways to measure mental health problems using these data sources, namely through the dispensation of psychotropic medications that are commonly indicated for management of mental health problems: anxiolytics, antidepressants, antimanics, antipsychotics, and cholinesterase inhibitors. Although using psychotropic medication dispensations improves sensitivity by identifying a higher number of true distress cases, this approach may also introduce

unintended misclassification if these medications were indicated for management of other conditions. For example, certain types of antidepressants may have been prescribed to manage sleep disorders, migraines, or pain.[5] Nevertheless, use of psychotropic medication dispensations as indicators of mental health problems is common practice in health services research.[4] However, the potential impact of outcome misclassification on study results is often simply acknowledged in the discussion as a limitation, or entirely ignored.

We had a unique opportunity to use an auxiliary database with information about indications for psychotropic medication prescriptions to try to correct for potential outcome misclassification. Therefore, the first objective of this study was to use gold-standard clinical data to measure the extent of outcome misclassification as a result of including psychotropic medication dispensations as indicators of new-onset distress in breast cancer survivors. Second, this study aimed to assess the impact of outcome misclassification on the fit of the transitional survivorship risk stratification model developed as a part of the second objective of this thesis.

Methods

Study design – estimation of misclassification

A historical cohort of female cancer patients was selected from the Medical Office of the 21st Century (MOXXI) clinical research platform and followed for three years, starting from the first cancer-related hospitalization. Although the purpose of this study was to measure and adjust for distress outcome misclassification in breast cancer

survivors, additional women diagnosed with other higher-survival cancers were also included in the MOXXI cohort to increase the sample size and the precision of the misclassification estimates. Higher-survival cancers were defined as those with an estimated five-year net survival greater than 50% as reported in the Canadian Cancer Statistics, and included breast, cervical, uterine, colorectal, bladder, kidney/renal pelvis, oral, laryngeal, and thyroid cancers as well as melanoma, leukemia, Hodgkin lymphoma and non-Hodgkin lymphoma.[6] Cancer cases were identified using ICD diagnostic codes documented in the Quebec Ministry of Health hospital discharge abstract database (MED-ÉCHO), which is integrated with the MOXXI clinical research platform (see Appendix 5-1). The cohort included women diagnosed with cancer in Quebec, Canada between January 1, 2002 and March 31, 2014 who provided consent for their medical information to be used for research. Women were followed to identify the first prescription written by a MOXXI physician for unique psychotropic medications (based on generic drug name).

Study design – adjustment for misclassification

A historical, population-based cohort of female breast cancer survivors was followed for one year after completion of hospital-based treatment (i.e., breast surgery, chemotherapy, and radiation) for new-onset distress. The cohort included women diagnosed with a new breast cancer that received hospital-based treatment in Quebec, Canada between January 1, 1998 and March 31, 2011. Breast cancer cases were identified using ICD diagnostic codes and Régie de l'assurance maladie du Québec (RAMQ) procedure codes for breast cancer surgery (see Appendices 4-1 and 4-2). To

identify new cases of distress, women were excluded if they had experienced the outcome of interest (i.e., distress) during the pre-cancer baseline year, diagnostic work-up period, or hospital-based treatment period. Women were also excluded if they did not have a documented breast surgery, or were not continuously covered by the RAMQ health and drug insurance plans starting at least 14 months prior to the date of initial breast surgery until completion of transitional survivorship.

Data source – estimation of misclassification

The MOXXI is an integrated electronic prescription and drug management system developed by the Clinical and Health Informatics Research Group at McGill University and used by a select group of primary care physicians in community-based, fee-for-service practices. The source population consists of female patients cared for by MOXXI primary care physicians in Quebec, Canada from 2002 to present. The MOXXI has a unique e-prescribing tool that requires physicians to document an indication for every prescription given to a patient using either a dropdown menu or a free-text field. Indications documented within the MOXXI system have been shown to have 99% sensitivity and 97% positive predictive value.[7] Ethical clearances were granted through the Institutional Review Board at McGill University.

Data sources – adjustment for misclassification

Cases of new-onset distress in breast cancer survivors were identified using routinely collected administrative health data obtained from the RAMQ provincial, universal health insurance plan. The source population consists of female residents from

the province of Quebec, Canada insured by the RAMQ. Data were available from January 1, 1998 to March 31, 2012. The following databases were linked to conduct the analyses: (1) RAMQ registrant database, which provides demographic data and income-indexed drug plan co-payment requirements; (2) RAMQ medical services database, which contains physician fee-for-service claims; (3) Ministry of Health hospital discharge abstract database (MED-ÉCHO), which provides administrative and clinical information on hospital discharges; and (4) RAMQ prescription drug claims database (covering all residents over 65 years of age, and selected, dynamic subgroups less than 65 years old). Ethical clearances were granted through the Institutional Review Board at McGill University and the provincial Access to Information Office.

Measurement of outcome – estimation of misclassification

The therapeutic indication for each MOXXI prescription was classified based on the National Comprehensive Cancer Network (NCCN) definition of distress, which includes: (i) dementia; (ii) delirium; (iii) depressive disorders; (iv) bipolar and related disorders; (v) schizophrenia spectrum and other psychotic disorders; (vi) anxiety disorders; (vii) trauma and stressor-related disorders; (viii) adjustment disorders; (ix) obsessive-compulsive disorders; (x) substance-related and addictive disorders; and (xi) personality disorders.[8] If the documented indication met this definition then the prescription was classified as 'indicated for distress' (Y=1). Otherwise, the prescription was classified as 'not indicated for distress' (Y=0).

Measurement of outcome – adjustment for misclassification

New episodes of distress in the breast cancer survivorship cohort were identified in the administrative medical services and hospital discharge abstract databases using documented ICD diagnostic codes for mental health problems included in the NCCN definition of cancer-related distress (see Appendix 4-3).[8] Given that ICD diagnostic codes for mental health problems are known to be underreported,[2,3] additional new episodes of distress were identified through the prescription drug claims database by dispensations of psychotropic medications that are commonly indicated for management of distress (see relevant American Hospital Formulary Services [AHFS] classes in Appendix 4-4).

Statistical analysis – estimation of misclassification

Descriptive statistics were calculated for the MOXXI cohort of women to provide the frequencies of type of cancer as well as the number of women who received at least one prescription for a psychotropic medication from a MOXXI physician within the three years of follow-up. For each woman, the first prescription for each unique psychotropic medication (as determined by the generic drug name) was identified. Only the first prescription was selected since the documented indication very rarely changed between prescriptions for the same psychotropic medication for a specific woman. Therefore, including all prescriptions would not have added much new information, while complicating the statistical analysis with near perfect correlations. Under the same rationale, both new and ongoing prescriptions were included in the analysis to increase the sample size and number of eligible prescriptions.

All prescriptions for a given psychotropic medication were used to calculate the probability that the medication was indicated for distress (i.e., the positive predictive value). Given the lack of information to estimate the sensitivity of the distress outcome measures, the sensitivity was assumed to be 100% (i.e., no missed cases) for the purpose of adjustment for misclassification. The specificity of each psychotropic medication was estimated using the equation: number of true negatives / [number of false positives + number of true negatives]. The number of false positives was the number of prescriptions for the specific psychotropic medication that were indicated for a condition other than distress. The number of true negatives was the number of women who did not receive any prescriptions for psychotropic medications from a MOXXI physician over the period of the study.

Statistical analysis – adjustment for misclassification

For the purposes of estimating risk, the probabilities that specific psychotropic medications were indicated for distress (i.e., the positive predictive values) estimated using the MOXXI prescribing data were used to adjust the naïve (or uncorrected) estimates of the incidence of distress in the cohort of breast cancer survivors. The adjustment for outcome misclassification was applied to both the 'first' and the 'strongest' indicators of possible new-onset distress to generate better-informed estimates. The 'first' indicator refers to the timing and was the first documented ICD code or psychotropic medication dispensation that occurred during the survivorship follow-up period. The 'strongest' indicator refers to the best evidence of true distress and

was the indicator with the highest probability of representing new-onset distress documented during the survivorship follow-up period.

For the purposes of risk stratification, the positive predictive values and specificities of the psychotropic medications were used to assess the impact of misclassification of distress on the fit of the transitional survivorship risk stratification model developed as a part of the second objective of this thesis. To recap, the transitional survivorship risk stratification algorithm was developed using a time-dependent Cox proportional hazards model and the counting process approach by week of the follow-up period. Candidate predictors are listed in Appendix 4-6. The risk stratification model was developed using a stepwise forward selection process using a $p \leq 0.15$ entry criteria for candidate predictors that were retained in the model at $p \leq 0.05$.

Two different approaches were used to adjust for misclassification of the distress outcome and assess its impact on the fit of the transitional survivorship risk stratification model. The first approach incorporated information on all indicators of possible distress and used global estimates (i.e., uninformed by predictors) of the probability that the medication was indicated for distress (i.e., positive predictive values) to impute if a woman was distressed and if so, at what point during the follow-up period. In contrast, the second approach used profile-specific imputations (i.e., based on predictors) but was limited to using only the first indicator of possible new-onset distress given the complexity of the adjustment. Furthermore, this approach used the specificities of the medications rather than the positive predictive values. The two approaches for adjustment of outcome misclassification were:

1) Multiple imputation based on global probabilities (or positive predictive values)

An algorithm was created to impute whether or not each breast cancer survivor in the RAMQ cohort experienced new-onset distress, and if so, at what point in time during the follow-up period. In order to set up the data, all indicators of possible new-onset distress and associated times were identified for each woman and linked with the positive predictive value of the indicator. ICD diagnostic codes for mental health problems have been shown to have positive predictive values around 93%, indicating that if the codes are documented then the diagnosis is likely to be correct;[9] therefore, all ICD diagnostic codes were assigned a 100% global probability of distress. The positive predictive values for dispensations of psychotropic medications were estimated based on the indication information provided in the MOXXI gold standard prescribing data. If multiple indicators of possible distress occurred on one day (e.g., co-occurring ICD diagnosis and psychotropic medication dispensation), then the indicator with the highest probability of being indicated for distress was used for the purpose of multiple imputation.

For each breast cancer survivor, the algorithm moved forward through time to identify the first indicator of possible new-onset distress (i.e., y=1). At the first indicator, the algorithm imputed a value of Y=1 (distressed) or Y=0 (not distressed) using the positive predictive value of the indicator. If the woman was imputed as 'distressed' at this point in time then her follow-up ended. However, if the woman was imputed as 'not distressed' then her follow-up continued, and the imputation process was repeated for subsequent indicators of possible new-onset distress until the woman either became 'distressed' or the one-year study follow-up period ended.

Once imputation of the cohort was complete, the predictors included in the transitional survivorship risk stratification model developed for the second objective of this thesis were re-evaluated with the adjusted distress outcome using a time-dependent Cox proportional hazards model. The imputation and model fit process was then repeated 500 times to generate 500 "copies" of the dataset and associated model fit statistics. The averages of the beta estimates were used to calculate summary hazard ratios (HR) for each of the predictors. The associated 95% confidence intervals (95% CI) were calculated using Rubin's formula.[10] These results were then compared with the HRs and 95% CIs of the naïve (i.e., uncorrected) model to assess the impact of outcome misclassification on the fit of the transitional survivorship risk stratification model.

2) Profile-specific multiple imputation as proposed by Magder and Hughes[11]

An approach to recalibrate the transitional survivorship risk stratification model was undertaken by accounting for the predictor information to further inform adjustment for misclassification of distress. Magder and Hughes offer a working example with almost perfect sensitivity but lower specificity, where pregnant women were asked to self-report whether or not they had quit smoking.[11] The purpose of the study was to identify predictors of smoking cessation in this vulnerable population. Sensitivity was expected to be around 100% with most women who had successfully quit reporting to have done so. However, specificity was expected to be lower at 90% with some women self-reporting that they had quit even if they had not. The predictors were then used to impute which of the women had successfully quit smoking. After adjustment, the odds ratio (OR) for the strongest predictor in the naïve logistic model (i.e., previous smoking

history [pack/day]) increased from 4.31 to 13.11 in the adjusted model. In the context of our study, this approach will be used to impute which of the breast cancer survivors who filled a prescription for a psychotropic medication were truly distressed based on the predictors in the transitional survivorship risk stratification model.

In contrast to the first adjustment approach, this approach only used the first indicator of possible distress due to the complexity around accounting for multiple time points. Furthermore, for the purpose of this adjustment, the naïve (i.e., uncorrected) time-dependent Cox proportional hazards model was fitted using pooled logistic regression, which has been shown to approximate the time-dependent Cox model.[12]

Each of the recalibrations consisted of two parts: the 'expectation' step and the 'maximization' step. The first expectation step took the fitted probabilities from the naïve (i.e., uncorrected) risk stratification model and applied Bayes' Theorem to incorporate information about the specificity of the outcome measure from the MOXXI data to estimate the probability that each of the breast cancer survivors was truly distressed (see Figure 5-1). Given the lack of information to estimate the sensitivity of the outcome measure, sensitivity was assumed to be 100% (i.e., no missed cases).

The revised probabilities were then applied as weights in the maximization step to recalibrate the logistic regression model. Each possible distress case was entered into the logistic model as both 'distressed' (Y=1) and 'not distressed' (Y=0) weighted by the current probability that the particular woman was truly distressed based on the indicator of distress and predictors. For example, if a woman had a 65% probability of truly being distressed in the previous iteration, then a new dataset was created that included one line

with a positive outcome for new-onset distress (Y=1) weighted at 0.65 and a second line with a negative outcome for new-onset distress (Y=0) weighted at 0.35. The logistic regression model was then re-fit using the new data to generate updated parameter estimates resulting in new fitted probabilities for each woman. This expectation-maximization algorithm was repeated until the parameter estimates were stable. These results were then compared with the ORs and 95% CIs of the naïve (i.e., uncorrected) pooled logistic regression model to assess the impact of outcome misclassification on the fit of the transitional survivorship risk stratification model.

Results

The MOXXI study cohort consisted of 2 929 women diagnosed with higher-survival cancers, with breast cancer patients representing almost half of the cohort (Table 5-1). Approximately one quarter of all women received at least one prescription for a psychotropic medication from a MOXXI primary care physician.

The probabilities that specific psychotropic medications were indicated for distress estimated using the MOXXI prescribing data are presented in Table 5-2. The probabilities varied considerably and ranged from 0% (e.g., Amitriptyline) to 100% (e.g., Citalopram). In general, with the exception of one medication (i.e., Alprazolam, which was 84.1%), the probabilities that anxiolytics were indicated for distress were 65% or lower. These medications were also indicated for management of insomnia, skin conditions, and nervous system disorders. Antidepressants had higher probabilities of being indicated for distress, except for Amitriptyline, Nortriptyline, and Trazodone, which were commonly prescribed for management of insomnia or pain. Likewise,

antipsychotics were mostly indicated for distress with the exception of Haloperidol, which was also indicated for nausea and vomiting. Cholinesterase inhibitors were always indicated for distress.

The RAMQ study cohort consisted of 10 386 breast cancer survivors. Based on naïve estimates that counted all psychotropic medication dispensations as new-onset distress, 1 736 women (16.7% of the cohort) were considered to have developed distress over the one-year transitional survivorship period. When this naïve (i.e., uncorrected) estimate was adjusted based on the positive predictive value of each woman's first indicator of possible distress, the incidence of new-onset distress became 10.6% – a 37% reduction (Table 5-2). Using Alprazolam as a working example: In 84.1% of prescriptions (i.e., 37/44) the indication was distress. This probability was used to adjust the naïve estimates of new-onset distress. For example, in the RAMQ-only estimates based on the first indicator, the naïve estimate was 24 cases (representing 1.38% of all distress cases) and the adjusted estimate was 20 cases [24 cases * 84.1%] (representing 1.82% of all distress cases). In fact, 233 women were prescribed a psychotropic medication with a positive predictive value of 0% (i.e., never indicated for distress), accounting for 13.4% of the naïve distress cases. The same approach was applied to calculate adjusted estimates based on the strongest indicator. Even when the estimate was adjusted based on each woman's strongest indicator of distress during the follow-up period, the incidence remained low at 11.3%. The greatest contributors to outcome misclassification based on higher dispensation rates and lower probabilities of being indicated for distress were: Hydroxyzine (0%), Lorazepam (50%), Oxazepam (32%), Temazepam (0%), Amitriptyline (0%), and Trazodone (7%). For example, when

Trazodone was dispensed (y=1) then the woman was distressed (Y=1) only in 7% of possible cases of new-onset distress, and was not distressed (Y=0) for the remaining 93% of possible cases.

Despite the considerable amount of distress outcome misclassification, the 'global' and 'profile-specific' adjustments, generally, did not impact the statistical significance or interpretation of the parameter estimates compared with the naïve (i.e., uncorrected) transitional survivorship risk stratification model (Table 5-3). Only four of the 20 original predictors were no longer significant after accounting for misclassification using both adjustment approaches (flagged with an asterisk in Table 5-3): change to low income supplementation of drug insurance, localized breast cancer at diagnosis, receipt of hospital-based treatments after start of survivorship (indicating a possible cancer recurrence), and pain documented prior to the start of the follow-up period.

There were negligible changes in the parameter estimates for age, duration of documented hospital-based treatment, and new pulmonary symptoms irrespective of the adjustment approach. Both adjustment approaches increased the parameter estimates for new urinary symptoms, fatigue, and emergency department visits occurring during the follow-up period. Conversely, both approaches decreased the parameter estimate for newly pulmonary disease diagnosed during the survivorship follow-up period.

In some cases, only one of the adjustment approaches affected the parameter estimates. The 'global' approach generated lower estimates for both receipt of axillary lymph node dissection and new anemia diagnosis, whereas the 'profile-specific' approach provided higher parameter estimates for rheumatologic disease present prior to the start

of the follow-up period. Interestingly, the adjustment approaches had opposing effects on the parameter estimates for newly diagnosed hypertension and hospital contacts that occurred during the survivorship follow-up period as well as gastrointestinal symptoms or menopausal symptoms that were present prior to the start of the follow-up period.

Discussion

This study aimed to correct for outcome misclassification when including psychotropic medication dispensations as indicators of new-onset distress in a cohort of 10 386 breast cancer survivors. The naïve estimate of the incidence was 16.7% when all psychotropic medication dispensations were counted as new-onset distress. This uncorrected estimate was adjusted using the positive predictive values from the MOXXI gold standard clinical data where each prescription had a documented indication. The adjusted estimate was 10.6% after accounting for the fact that some psychotropic medications were likely indicated for other conditions. The positive predictive values varied widely, with Hydroxyzine, Lorazepam, Oxazepam, Temazepam, Amitriptyline, and Trazodone responsible for a large proportion of distress misclassification.

The study then evaluated the impact of this misclassification on the fit of the transitional survivorship risk stratification model developed as a part of the second objective of this thesis. Four of the 20 original predictors were no longer significant after accounting for distress misclassification. Both adjustments increased the parameter estimates for new urinary symptoms, fatigue, and emergency department visits as well as decreased the parameter estimates for baseline pulmonary disease. However, the adjustment approaches had opposing effects on the parameter estimates for newly

diagnosed hypertension and hospital contacts as well as baseline gastrointestinal or menopausal symptoms.

Outcome misclassification was substantial when new-onset distress was measured based on dispensations of psychotropic medications, overestimating the incidence by approximately 37%. However, based on the estimates adjusted for distress misclassification, inclusion of medication dispensations led to increased sensitivity by doubling the number of detected cases of true distress. This trade-off increased the power to develop predictive models at the cost of including numerous false positives as true outcomes; more than half of the additional possible distress cases identified through psychotropic medication dispensations were likely indicated for other disorders. Therefore, adjustment for this magnitude of misclassification is critical.

To briefly summarize to aid in the interpretation, the two adjustment methods had important differences. The 'global' imputation approach incorporated information on all indicators of possible new-onset distress and used global estimates (i.e., uninformed by predictors) of the probability that a psychotropic medication was indicated for distress to impute if and when a woman was distressed. In contrast, the 'profile-specific' imputation approach incorporated additional predictor information in combination with the specificities of psychotropic medications to inform identification of true distress cases. However, this approach only used the first indicator of possible new-onset distress due to the complexity around including multiple time points.

Four of the original predictors from the naïve (i.e., uncorrected) transitional survivorship risk stratification model were no longer significant after adjustment for

outcome misclassification using both of these approaches. This indicates that these predictors were more likely to be associated with dispensations of psychotropic medications with lower probabilities of being indicated for distress. In effect, these predictors may be associated with alternate indications of these psychotropic medications and represent two models for two different processes. For example, dispensation of certain psychotropic medications following receipt of additional hospital-based treatments after start of the survivorship period (indicating a possible cancer recurrence) could be associated with treatment-related insomnia or pain rather then distress. Likewise, if pain was documented prior to the start of the follow-up period, psychotropic medications could have been prescribed for its ongoing management if other strategies had proven ineffective or for pain-related insomnia. Therefore, these predictors should be considered for exclusion from the transitional survivorship risk stratification model for new-onset distress.

Conversely, in cases where both adjustment approaches served to increase the parameter estimates, it would indicate that the predictors were more likely to be associated with dispensations of psychotropic medications that had a higher likelihood of being indicated for distress. Therefore, new urinary symptoms, fatigue, and emergency department visits occurring during the follow-up period should be given more weight in this transitional survivorship risk stratification model.

For some predictors, the two adjustment approaches had different effects on the parameter estimates. In most cases, the differences were not substantial. However, the adjustment approaches had opposing effects on the parameter estimates for newly

diagnosed hypertension and hospital contacts as well as baseline gastrointestinal or menopausal symptoms. Even though the confidence intervals overlaped, these differences were likely a result of updating the time-varying predictors following the first possible indicator of new-onset distress using the 'global' imputation method. This was not done with the 'profile-specific' approach, since it was based only on the first possible indicator of new-onset distress due to the complexity of the adjustment. It is not clear which approach provided the more accurate parameter estimates and better model. Ideally, a hybrid approach incorporating the strengths of both the 'global' method (i.e., consideration of multiple indicators) and the 'profile-specific' method (i.e., consideration of predictors) could be developed to generate more accurate parameter estimates to inform model recalibration. Alternatively, a simulation study could help to determine which of the two adjustment approaches is more appropriate to account for distress outcome misclassification.

One limitation of this study was that it focused on the correction of uncertainty around possible new-onset distress cases that were documented during transitional survivorship. The study did not account for breast cancer patients that were incorrectly excluded from the study due to distress outcome misclassification in the pre-cancer baseline or during hospital-based treatment. Another limitation was that the sensitivity of distress was assumed to be 100% for both adjustment methods, which is not correct. Many cases of new-onset distress were likely not documented in the health administrative data, particularly if cases were not detected by the physician, if psychotropic medications were prescribed but never dispensed (i.e., primary non-adherence),[13] or if women received alternative treatments for distress not covered by the universal health insurance

plan. Additional data would be required to estimate the sensitivity of distress and incorporate this information to account for false negatives. One approach to adjust for misclassification of missed cases could be to impute a random time for the outcome as done by Li et al; however, in their study the adjustment was applied to a standard Cox proportional hazards model.[14] More information would be needed to guide imputation of missed cases in the context of time-varying covariates.

Another limitation was that the MOXXI data did not include information to estimate the probability of distress for seven of the psychotropic medications dispensed in the RAMQ cohort. These medications were assigned a 100% probability of being indicated for distress. It is unlikely that this had a significant impact on the study results given that these medications accounted for only 8 (0.7%) of the first indicators of possible new-onset distress. Finally, the MOXXI dataset provided information for all *prescriptions* written by MOXXI physicians, whereas the RAMQ dataset only provided *dispensation* information. Therefore, applying the estimated positive predictive values and specificities from the MOXXI dataset may not be accurate if there was differential filling of prescriptions based on indication. Nevertheless, this approach is an improvement on the prevailing practice of either ignoring the problem of outcome misclassification or simply acknowledging it in the discussion of limitations.

In conclusion, this study provided a first attempt at improving the transitional survivorship risk stratification model fit to account for distress misclassification. Most of the predictors remained significant, which suggests that they are robust despite the substantial amount of distress outcome misclassification. Both adjustments for

misclassification supported the exclusion of four predictors: change to low income supplementation of drug insurance, localized breast cancer at diagnosis, receipt of hospital-based treatments after start of survivorship, and baseline pain. Both adjustment approaches also supported giving additional weight to three predictors: urinary symptoms, fatigue, and emergency department visits. Future research should focus on determining which approach to adjustment for misclassification provides more accurate parameter estimates for prediction of distress as well as adjustment for false negatives not captured in the administrative health databases.

$$\hat{Y}_i = \frac{Prob(Y_i = 1|X_{1i}, \ldots X_{ki}, \beta_0, \ldots \beta_k)sens}{Prob(Y_i = 1|X_{1i}, \ldots X_{ki}, \beta_0, \ldots \beta_k)sens + Prob(Y_i = 0|X_{1i}, \ldots X_{ki}, \beta_0, \ldots \beta_k)(1 - spec)}.$$

Figure 5-1. Bayes' Theorem used to estimate the probability that a specific breast cancer survivor who filled a prescription for a psychotropic medication was truly distressed[11]

Table 5-1. Characteristics of the Medical Office of the 21st Century (MOXXI) cohort of women diagnosed with a higher-survival cancer

	MOXXI cohort (N = 2 929)	
Type of cancer	n	% of cohort
Breast	1 324	45.20
Colorectal	471	16.08
Uterine	220	7.51
Thyroid	176	6.01
Non-Hodgkin lymphoma	159	5.43
Bladder	132	4.51
Leukemia	103	3.52
Kidney and renal pelvis	92	3.14
Cervical	85	2.90
Melanoma	75	2.56
Oral	52	1.78
Laryngeal	25	0.85
Hodgkin lymphoma	15	0.51
Prescriptions for psychotropic medications from MOXXI physicians	n	% of cohort
Number of women who received at least one prescription	707	24.1

Table 5-2. Probabilities that International Classification of Diseases (ICD) diagnoses and psychotropic medications were indicated for distress, and adjustment of the naïve estimates of new-onset distress in breast cancer survivors based on these probabilities [see worked example for Alprazolam in footnote]

Medication	MOXXI (N = 2 929)	RAMQ (N = 10 386)			
		First indicator[b]		Strongest indicator[c]	
	Probability of distress (i.e., positive predictive value)	**Naïve** estimate of new-onset distress	**Adjusted** estimate of new-onset distress	**Naïve** estimate of new-onset distress	**Adjusted** estimate of new-onset distress
Total distress	% (n / total rx)	% of cohort (n)	% of cohort (n)	% of cohort (n)	% of cohort (n)
Any indicators	55.7 (674/1 211)	16.71 (1 736)	10.60 (1 101)	16.71 (1 736)	11.31 (1 175)
ICD codes	%	% of distressed (n)	% of distressed (n)	% of distressed (n)	% of distressed (n)
Mental health disorder	100.0	30.76 (534)	48.50 (534)	37.67 (654)	55.66 (654)
Anxiolytics	% (n / total rx)	% of distressed (n)	% of distressed (n)	% of distressed (n)	% of distressed (n)
Alprazolam[a]	84.1 (37/44)	1.38 (24)	1.82 (20)	1.44 (25)	1.79 (21)
Bromazepam	62.1 (18/29)	0.86 (15)	0.82 (9)	0.98 (17)	0.94 (11)
Clobazam	N/E	0.06 (1)	0.09 (1*)	0.00 (0)	0.00 (0)
Clonazepam	65.0 (39/60)	2.59 (45)	2.63 (29)	2.59 (45)	2.47 (29)
Diazepam	61.5 (8/13)	1.09 (19)	1.09 (12)	1.09 (19)	1.02 (12)
Flurazepam	0.0 (0/15)	0.75 (13)	0.00 (0)	0.52 (9)	0.00 (0)
Hydroxyzine	0.0 (0/21)	6.57 (114)	0.00 (0)	5.93 (103)	0.00 (0)
Lorazepam	49.7 (92/185)	20.62 (358)	16.17 (178)	18.32 (318)	13.45 (158)
Midazolam	N/E	0.00 (0)	0.00 (0)	0.06 (1)	0.09 (1*)
Nitrazepam	0.0 (0/10)	0.06 (1)	0.00 (0)	0.06 (1)	0.00 (0)
Oxazepam	32.1 (34/106)	10.20 (177)	5.18 (57)	8.58 (149)	4.09 (48)
Phenobarbital	0.0 (0/2)	0.06 (1)	0.00 (0)	0.06 (1)	0.00 (0)
Primidone	0.0 (0/1)	0.12 (2)	0.00 (0)	0.06 (1)	0.00 (0)
Temazepam	0.0 (0/38)	1.32 (23)	0.00 (0)	1.27 (22)	0.00 (0)
Triazolam	N/E	0.06 (1)	0.09 (1*)	0.06 (1)	0.09 (1*)
Antidepressants	% (n / total rx)	% of distressed (n)	% of distressed (n)	% of distressed (n)	% of distressed (n)
Amitriptyline	0.0 (0/47)	4.55 (79)	0.00 (0)	4.03 (70)	0.00 (0)
Citalopram	100.0 (125/125)	2.30 (40)	3.63 (40)	1.90 (33)	2.81 (33)
Desipramine	100.0 (2/2)	0.06 (1)	0.09 (1)	0.06 (1)	0.09 (1)
Doxepin	50.0 (1/2)	0.23 (4)	0.18 (2)	0.23 (4)	0.17 (2)

Table 5-2 (continued). Probabilities that International Classification of Diseases (ICD) diagnoses and psychotropic medications were indicated for distress, and adjustment of the naïve estimates of new-onset distress in breast cancer survivors based on these probabilities [see worked example for Alprazolam in footnote]

Medication	MOXXI (N = 2 929)	RAMQ (N = 10 386)			
		First indicator[b]		Strongest indicator[c]	
	Probability of distress (i.e., positive predictive value)	**Naïve** estimate of new-onset distress	**Adjusted** estimate of new-onset distress	**Naïve** estimate of new-onset distress	**Adjusted** estimate of new-onset distress
Antidepressants (cont'd)	% (n / total rx)	% of distressed (n)	% of distressed (n)	% of distressed (n)	% of distressed (n)
Fluoxetine	100.0 (3/3)	0.23 (4)	0.36 (4)	0.23 (4)	0.34 (4)
Fluvoxamine	100.0 (1/1)	0.06 (1)	0.09 (1)	0.12 (2)	0.17 (2)
Imipramine	N/E	0.06 (1)	0.09 (1*)	0.06 (1)	0.09 (1*)
Mirtazapine	100.0 (34/34)	0.12 (2)	0.18 (2)	0.17 (3)	0.26 (3)
Nortriptyline	33.3 (2/6)	0.29 (5)	0.18 (2)	0.23 (4)	0.09 (1)
Paroxetine	100.0 (34/34)	0.98 (17)	1.54 (17)	0.63 (11)	0.94 (11)
Sertraline	94.4 (17/18)	0.46 (8)	0.73 (8)	0.23 (4)	0.34 (4)
Trazodone	7.27 (4/55)	1.73 (30)	0.18 (2)	1.27 (22)	0.17 (2)
Trimipramine	100.0 (5/5)	0.06 (1)	0.09 (1)	0.06 (1)	0.09 (1)
Venlafaxine	82.4 (70/85)	11.00 (191)	14.26 (157)	10.94 (190)	13.36 (157)
Antipsychotics	% (n / total rx)	% of distressed (n)	% of distressed (n)	% of distressed (n)	% of distressed (n)
Haloperidol	28.6 (2/7)	0.12 (2)	0.09 (1)	0.06 (1)	0.00 (0)
Loxapine	100.0 (1/1)	0.06 (1)	0.09 (1)	0.06 (1)	0.09 (1)
Methotrimeprazine	100.0 (1/1)	0.06 (1)	0.09 (1)	0.12 (2)	0.17 (2)
Olanzapine	87.5 (7/8)	0.06 (1)	0.09 (1)	0.06 (1)	0.09 (1)
Perphenazine	N/E	0.06 (1)	0.09 (1*)	0.06 (1)	0.09 (1*)
Quetiapine	82.9 (29/35)	0.17 (3)	0.18 (2)	0.23 (4)	0.26 (3)
Risperidone	100.0 (14/14)	0.23 (4)	0.36 (4)	0.06 (1)	0.09 (1)
Cholinesterase inhibitors	% (n / total rx)	% of distressed (n)	% of distressed (n)	% of distressed (n)	% of distressed (n)
Bethanechol	N/E	0.17 (3)	0.27 (3*)	0.17 (3)	0.26 (3*)
Donepezil	100.0 (8/8)	0.23 (4)	0.36 (4)	0.23 (4)	0.34 (4)
Galantamine	N/E	0.06 (1)	0.09 (1*)	0.00 (0)	0.00 (0)
Rivastigmine	100.0 (6/6)	0.18 (3)	0.27 (3)	0.12 (2)	0.17 (2)

[a] Worked example using Alprazolam: In 84.1% of prescriptions (i.e, 37/44) the indication was distress. This probability was used to adjust the naïve estimates of new-onset distress. For example, in the RAMQ-only estimates based on the first indicator, the naïve estimate was 24 cases (representing 1.38% of all distress cases) and the adjusted estimate was 20 cases [24 cases * 84.1%] (representing 1.82% of all distress cases). The same approach was applied to calculate adjusted estimates based on the strongest indicator; [b] First indicator: the first indicator of possible new-onset distress documented during the survivorship follow-up period; [c] Strongest indicator: the indicator with the highest probability of representing new-onset distress (i.e., best evidence of true distress) documented during the survivorship follow-up period; N/E = no estimate: there were 15 psychotropic medication dispensations where estimates of the probability of being indicated for distress were not available from the MOXXI prescribing data. In these cases, the psychotropic medications were assigned a distress probability of 100%, and the adjusted estimates are denoted by * No antimanic medications were dispensed as the first or strongest indicators of possible new-onset distress

Table 5-3. Assessment of the impact of adjustments for new-onset distress outcome misclassification by comparison of hazard ratios (HR) and odds ratios (OR) from naïve and adjusted transitional survivorship risk stratification models

Predictors	Multiple imputation based on global probabilities		Profile-specific multiple imputation	
	COMPARATOR 1: Naïve multivariable Cox proportional hazards model	ADJUSTMENT 1: Multiple imputation based on global probabilities	COMPARATOR 2:[k] Naïve multivariable pooled logistic regression model	ADJUSTMENT 2:[q] Profile-specific multiple imputation
Sociodemographic characteristics	HR (95% CI)	HR (95% CI)	OR (95% CI)	OR (95% CI)
Age (per 5-year increase)	0.945 (0.925, 0.965)	0.941 (0.919, 0.963)	0.945 (0.925, 0.965)	0.948 (0.918, 0.980)
Low income supplementation of drug insurance				
New supplementation*	1.657 (1.172, 2.345)	1.334 (0.895, 1.989)	1.655 (1.169, 2.344)	1.077 (0.568, 2.041)
Prior to start of follow-up	--	--	--	--
Breast cancer and treatments	HR (95% CI)	HR (95% CI)	OR (95% CI)	OR (95% CI)
Breast cancer stage				
Distant	1.072 (0.565, 2.031)	0.639 (0.241, 1.697)	1.064 (0.560, 2.021)	0.254 (0.039, 1.648)
Regional	1.028 (0.843, 1.253)	0.896 (0.714, 1.123)	1.028 (0.843, 1.254)	0.907 (0.670, 1.229)
Localized*	1.201 (1.032, 1.397)	1.074 (0.905, 1.276)	1.201 (1.032, 1.397)	1.063 (0.845, 1.336)
Uncertain	0.688 (0.353, 1.343)	0.686 (0.340, 1.385)	0.687 (0.352, 1.342)	0.872 (0.356, 2.135)
In situ	Reference	Reference	Reference	Reference
Axillary lymph node dissection	1.535 (1.298, 1.816)[a]	1.458 (1.177, 1.806)[f]	1.587 (1.334, 1.887)[l]	1.576 (1.188, 2.090)[r]
Duration of documented hospital-based treatment (per additional 30 days)	0.874 (0.845, 0.903)[b]	0.902 (0.865, 0.941)[g]	0.867 (0.838, 0.897)[m]	0.883 (0.835, 0.933)[s]
Receipt of additional hospital-based treatments in survivorship (indicating possible recurrence)*	1.776 (1.218, 2.588)	1.331 (0.889, 1.995)	1.953 (1.338, 2.849)	1.335 (0.688, 2.590)
Comorbidities	HR (95% CI)	HR (95% CI)	OR (95% CI)	OR (95% CI)
Pulmonary disease				
New diagnosis	1.538 (1.182, 2.001)	1.482 (1.147, 1.917)	1.546 (1.187, 2.014)	1.442 (0.959, 2.169)
Prior to start of follow-up	--	--	--	--
Rheumatologic disease				
New diagnosis	1.308 (1.050, 1.630)	1.335 (1.062, 1.677)	1.308 (1.049, 1.631)	1.301 (0.928, 1.824)
Prior to start of follow-up	1.246 (1.123, 1.382)	1.256 (1.113, 1.416)	1.247 (1.124, 1.384)	1.368 (1.166, 1.605)

Table 5-3 (continued). Assessment of the impact of adjustments for new-onset distress outcome misclassification by comparison of hazard ratios (HR) and odds ratios (OR) from naïve and adjusted transitional survivorship risk stratification models

Predictors	Multiple imputation based on global probabilities		Profile-specific multiple imputation	
	COMPARATOR 1: Naïve multivariable Cox proportional hazards model	ADJUSTMENT 1: Multiple imputation based on global probabilities	COMPARATOR 2:[k] Naïve multivariable pooled logistic regression model	ADJUSTMENT 2:[q] Profile-specific multiple imputation
Comorbidities	HR (95% CI)	HR (95% CI)	OR (95% CI)	OR (95% CI)
Anemia				
New diagnosis	1.646 (1.204, 2.251)	1.508 (1.131, 2.010)	1.643 (1.200, 2.251)	1.642 (1.016, 2.653)
Prior to start of follow-up	--	--	--	--
Hypertension				
New diagnosis	1.384 (1.055, 1.817)	1.245 (0.932, 1.663)	1.385 (1.054, 1.819)	1.612 (1.092, 2.379)
Prior to start of follow-up	--	--	--	--
Symptoms	HR (95% CI)	HR (95% CI)	OR (95% CI)	OR (95% CI)
Pulmonary symptoms				
New diagnosis	2.535 (1.523, 4.219)[c]	2.489 (1.414, 4.380)[h]	2.181 (1.297, 3.667)[n]	2.188 (0.960, 4.985)[t]
Prior to start of follow-up	1.171 (1.042, 1.316)	1.110 (0.968, 1.273)	1.173 (1.044, 1.318)	1.300 (1.090, 1.551)
Gastrointestinal symptoms				
New diagnosis	--	--	--	--
Prior to start of follow-up	1.234 (1.093, 1.393)	1.185 (1.030, 1.363)	1.237 (1.095, 1.397)	1.353 (1.126, 1.625)
Urinary symptoms				
New diagnosis	5.259 (2.065, 13.392)[d]	6.211 (2.913, 13.244)[i]	4.484 (1.713, 11.735)[o]	5.739 (1.299, 25.362)[u]
Prior to start of follow-up	--	--	--	--
Menopausal symptoms				
New diagnosis	--	--	--	--
Prior to start of follow-up	1.553 (1.268, 1.902)[e]	1.591 (1.223, 2.068)[j]	1.601 (1.297, 1.976)[p]	1.297 (0.900, 1.870)[v]
Fatigue				
New diagnosis	1.963 (1.369, 2.813)	2.292 (1.656, 3.171)	1.973 (1.374, 2.832)	2.037 (1.199, 3.461)
Prior to start of follow-up	--	--	--	--
Pain				
New diagnosis	--	--	--	--
Prior to start of follow-up*	1.241 (1.085, 1.420)	1.104 (0.940, 1.297)	1.242 (1.085, 1.422)	1.225 (0.994, 1.510)

Table 5-3 (continued). Assessment of the impact of adjustments for new-onset distress outcome misclassification by comparison of hazard ratios (HR) and odds ratios (OR) from naïve and adjusted transitional survivorship risk stratification models

Predictors	Multiple imputation based on global probabilities		Profile-specific multiple imputation	
	COMPARATOR 1: Naïve multivariable Cox proportional hazards model	ADJUSTMENT 1: Multiple imputation based on global probabilities	COMPARATOR 2:[k] Naïve multivariable pooled logistic regression model	ADJUSTMENT 2:[q] Profile-specific multiple imputation
Health services use	HR (95% CI)	HR (95% CI)	OR (95% CI)	OR (95% CI)
Emergency department visits				
New visit in follow-up	1.445 (1.263, 1.653)	1.648 (1.428, 1.902)	1.420 (1.242, 1.624)	1.622 (1.331, 1.978)
Per additional baseline visit	--	--	--	--
Hospital contacts				
New contact in follow-up	1.600 (1.359, 1.883)	1.935 (1.640, 2.283)	1.593 (1.353, 1.876)	1.385 (1.075, 1.783)
Per additional baseline contact	--	--	--	--

* Predictors that were no longer significant after accounting for new-onset distress outcome misclassification using both adjustment approaches; [a] Significant axillary lymph node dissection x time beta coefficient: -0.00186; [b] Significant duration of hospital-based treatment x time beta coefficient: 0.0004489; [c] Significant new pulmonary symptoms x time beta coefficient: -0.00248; [d] Significant new urinary symptoms x time beta coefficient: -0.00562; [e] Significant baseline menopausal symptoms x time beta coefficient: -0.00155; [f] Significant axillary lymph node dissection x time beta coefficient: -0.00131; [g] Significant duration of hospital-based treatment x time beta coefficient: 0.0002500; [h] New pulmonary symptoms x time beta coefficient: -0.00181; [i] Significant new urinary symptoms x time beta coefficient: -0.00531; [j] Significant baseline menopausal symptoms x time beta coefficient: -0.00171; [k] Model intercept: -4.6588 and significant time beta coefficient: -0.00396; [l] Significant axillary lymph node dissection x time beta coefficient: -0.00207; [m] Significant duration of hospital-based treatment x time beta coefficient: 0.000493; [n] New pulmonary symptoms x time beta coefficient: -0.00175; [o] Significant new urinary symptoms x time beta coefficient: -0.00488; [p] Significant baseline menopausal symptoms x time beta coefficient: -0.00175; [q] Model intercept: -6.0503 and significant time beta coefficient: -0.00255; [r] Significant axillary lymph node dissection x time beta coefficient: -0.00180; [s] Significant duration of hospital-based treatment x time beta coefficient: 0.000394; [t] New pulmonary symptoms x time beta coefficient: -0.00180; [u] New urinary symptoms x time beta coefficient: -0.00690; [v] Baseline menopausal symptoms x time beta coefficient: -0.00180

Appendix 5-1. International Classification of Diseases (ICD) codes used to identify women diagnosed with higher-survival cancers in the Medical Office of the 21st Century (MOXXI) clinical research platform

Type of cancer	ICD-9	ICD-10
Breast	174; 2330; 2383; 2393	C50; D05; D486
Colorectal	153; 154; 2303; 2304; 2305; 2306	C18; C19; C20; C21; D010; D011; D012; D013
Uterine	179; 182	C54; C55
Thyroid	193	C73
Non-Hodgkin lymphoma	200; 202	C82; C83; C84; C85; C963
Bladder	188; 2337	C67; D090
Leukemia	204; 205; 206; 207; 208	C91; C92; C93; C94; C95; C901
Kidney and renal pelvis	189; 2339	C64; C65; C66; C68; D091
Cervical	180; 2331	C53; D06
Melanoma	172	C43; D03
Oral	140; 141; 142; 143; 144; 145; 146; 147; 148; 149; 2300	C00; C01; C02; C03; C04; C05; C06; C07; C08; C09; C10; C11; C12; C13; C14
Laryngeal	161; 2310	C32; D020
Hodgkin lymphoma	201	C81

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DISCUSSION

The purpose of this Doctoral research program was to help identify breast cancer survivors at higher risk of new-onset distress to inform allocation of supportive care resources. The thesis focused on the transitional survivorship period where women face new, unexpected challenges and experience a higher incidence of distress compared with longer-term survivors.[1]

Summary of research findings

The first manuscript, titled "*Predictors of distress in female breast cancer survivors: a systematic review*," describes a synthesis of the published literature around predictors of prevalent distress in women who had completed hospital-based treatment for breast cancer. The systematic review established a set of evidence-based predictors that could be used to help identify breast cancer patients at higher risk of experiencing distress in the survivorship period. Important breast cancer and treatment predictors were more advanced breast cancer at diagnosis, treatment with chemotherapy, longer duration of hospital-based treatment, more recent transition into survivorship, and breast cancer recurrence. Treatment-related symptoms associated with distress included: menopausal/vasomotor symptoms, pain, fatigue, and sleep disturbance. Factors not specific to breast cancer patients also predicted distress. Younger age, non-Caucasian ethnicity, being unmarried, and lower socioeconomic status increased the risk of distress. Furthermore, higher numbers of comorbidities and history of mental health problems were associated with distress. Lower quality of life, optimism, and posttraumatic growth as well as higher numbers of stressful life events also predicted distress. In terms of

behavioral and support factors, lower physical activity, lower social support, and cigarette smoking increased the risk of distress. The results from this systematic review were used to inform the selection of candidate predictors for the risk stratification models developed to address the second objective of this thesis.

The second manuscript, titled "*Predicting new-onset distress following breast cancer diagnosis: development and validation of risk stratification algorithms*," explores the feasibility of using routinely collected administrative health data to predict onset of new distress in women diagnosed with breast cancer. Several risk stratification algorithms were developed to investigate whether predictors varied based on the period of the cancer care trajectory, specifically comparing predictors during hospital-based treatment with those during transitional survivorship. Predictors of new-onset distress during transitional survivorship included younger age, change to lower income supplementation of drug insurance, localized breast cancer stage at diagnosis, receipt of axillary lymph node dissection, shorter duration of hospital-based treatment, and receipt of additional hospital-based treatments after the start of survivorship. Baseline rheumatologic disease, pain as well as pulmonary, gastrointestinal and menopausal symptoms were also associated with onset of distress. Newly diagnosed rheumatologic disease, pulmonary disease, anemia, hypertension, and fatigue as well as pulmonary and urinary symptoms increased the risk of new-onset distress. Emergency department visits and hospital contacts during the survivorship follow-up period also predicted distress. As anticipated, the predictors of new-onset distress varied based on the period of the cancer care trajectory. In particular, more advanced breast cancer stage at diagnosis and receipt of specific hospital-based treatments were associated with new-onset distress during the

hospital-based treatment period. These results indicate that a one-size-fits-all approach is not sufficient to predict new-onset distress in breast cancer patients and that risk stratification models should be tailored based on the period of the cancer care trajectory.

The third manuscript, titled "*Predicting new-onset distress in breast cancer survivors: adjustment for outcome misclassification*," describes a first attempt to adjust for distress misclassification and assess its effect on the fit of the transitional survivorship risk stratification model developed as a part of the second objective of this thesis. The estimated incidence of new-onset distress decreased from 16.7% to 10.6% after adjustment for possible distress misclassification using a unique, gold standard clinical database. Most of the predictors remained significant, indicating that they were robust despite the substantial amount of outcome misclassification. However, both adjustment approaches supported the exclusion of four predictors: change to lower income supplementation of drug insurance, localized breast cancer at diagnosis, receipt of additional hospital-based treatments after the start of survivorship, and baseline pain. Furthermore, both approaches also supported placing additional weight on three predictors: new urinary symptoms, fatigue, and emergency department visits occurring during the survivorship follow-up period. However, the adjustment approaches had opposing effects on the parameter estimates for newly diagnosed hypertension and hospital contacts as well as baseline gastrointestinal and menopausal symptoms. The results show that ignoring distress outcome misclassification will negatively impact the fit of the transitional survivorship risk stratification model. However, it is not clear which adjustment approach provided the more accurate corrected parameter estimates and better model fit.

Implications for patients, physicians, and healthcare decision makers

Patients and physicians

Considering the current structure of cancer care, breast cancer survivors as well as the physicians providing post-treatment care should be made aware of the increased risk of new-onset distress associated with new symptoms and comorbidities that present in survivorship. This knowledge is particularly relevant as women transition to routine follow-up care and have fewer contacts with the oncology care team. In fact, this education could be included as a part of survivorship care plans. Timely identification and effective management of treatment-related symptoms and conditions could prevent the onset of distress or mitigate its effects by reducing the burden of breast disease. For example, electronic monitoring of treatment-related symptoms coupled with automated alerts to the oncology care team has been shown to improve health-related quality of life in cancer patients receiving chemotherapy.[2] In particular, women should be attentive to and seek care for new pulmonary or urinary symptoms as well as fatigue and treatment-related side effects of axillary lymph node dissection (e.g., lymphedema or limited joint mobility) as identified in the transitional survivorship risk stratification model. Similarly, women should be diligent in seeking appropriate management for health conditions that can present with distressing symptoms, such as pulmonary disease, rheumatologic disease, anemia, and hypertension. These recommendations could be generalized to other treatment-related symptoms or comorbidities that affect women's quality of life. Furthermore, as the second manuscript of the thesis has shown, treatment-related symptoms and conditions do not have to be severe in order to increase the risk of new-

onset distress. Therefore, women should be encouraged to seek care even for seemingly minor symptoms and conditions.

In the future, the quality of supportive cancer care could be improved through integration of risk stratification algorithms into routine follow-up care. Risk stratification algorithms could be integrated into electronic medical record (EMR) systems in cancer treatment centers alongside real-time access to relevant administrative health services and pharmaceutical data. Such algorithms could be configured to run automatically in the background of the EMR to prevent interference with physician workflow. Patient risk estimates could be updated at each follow-up visit, or more often if requested. This information could help guide physician decision making around referral of higher-risk women for targeted interventions to prevent distress as well as enhanced monitoring for early identification and timely intervention. The results of this thesis could be used to inform development of more accurate risk stratification algorithms that could be implemented in clinical practice.

Healthcare decision makers

This thesis provides a proof-of-concept that distress can be predicted in breast cancer populations. In order to make it possible for risk stratification algorithms to be used in routine cancer care, policies would need to be put in place to provide oncologists with real-time access to administrative health services and pharmaceutical data. The data could then be used in combination with information in the local EMR to risk stratify breast cancer survivors for targeted interventions to prevent distress or mitigate its effects.

The next phase would be to identify effective evidence-based preventive interventions that could be integrated into supportive cancer care. For example, electronic monitoring of treatment-related symptoms coupled with automated alerts to the oncology care team for timely identification and management.[2] More broadly, psychological interventions aimed to improve strength of resilience and development of positive coping strategies can also prevent distress entirely, or prevent subclinical levels from progressing to diagnosable mental health problems. Meta-analyses have reported that 21% to 38% of depressive disorders could be prevented with currently available interventions.[3,4] More specific to breast cancer survivors, prophylactic cognitive behavioral therapy (CBT) has been shown to reduce the incidence of anxiety and depression in higher-risk cancer patients by half.[5] Once the preventive interventions have been identified, allocation of mental health professionals and the level of resources will need to be aligned with the expected incidence of distress during survivorship, which will likely vary by geographic area. One of the benefits of developing a risk stratification algorithm using historical population-based data is that the data could also be used to guide the level of resource allocation, with a greater number of resources allocated to areas of higher risk. Following implementation, the impact of providing targeted preventive resources for breast cancer survivors at higher risk of new-onset distress would need to be evaluated.

Successful implementation of an accurate risk stratification algorithm alongside appropriate referral to effective supportive cancer care would address the 'triple aim' of providing higher quality patient care, improving patient health outcomes, and reducing overall costs to the healthcare system.[6] This approach would provide integrated supportive care resources for breast cancer survivors, which would have a positive impact

on all-cause and cancer-related morbidity and mortality as well as quality of life.[7] Furthermore, despite initial investments for implementing the preventive supportive care programs, this approach could reduce overall healthcare utilization resulting in significant cost savings. If this approach is shown to be effective in reducing new-onset distress in breast cancer survivors, similar risk stratification algorithms and supportive care programs could be offered for other cancer populations.

Directions for future research

The findings from this Doctoral research program suggest a few new directions for future work. First, the performance of the risk stratification algorithms could be improved by linking the administrative health data with more comprehensive datasets (e.g., clinical health records) to generate more accurate risk predictions. In particular, access to candidate predictors such as the material and social deprivation index as well as symptoms, comorbidities, and medical history (e.g., past mental health problems) documented in clinical patient problem lists could substantially improve the prediction of new-onset distress in breast cancer survivors.

Second, the risk stratification algorithms could be improved by accounting for missed distress cases. The thesis focused on documented indicators of possible new-onset distress and assumed 100% sensitivity, which is not correct. Many cases of true distress were likely not documented in the administrative health services and pharmaceutical data, particularly in cases where psychotropic medications were prescribed but never dispensed (i.e., primary non-adherence)[8] or if women received alternative treatments for distress not covered by the universal health insurance plan. These cases would likely be documented

in clinical health records and could be used to adjust for imperfect sensitivity. However, the greater challenge will be to obtain accurate estimates of and adjust for true cases of distress that were entirely missed by a physician.

Last, prediction of new-onset distress could be improved by creating risk stratification algorithms for specific types of distress. The thesis used a composite outcome based on the broad the National Comprehensive Cancer Network (NCCN) definition of distress.[9] However, the types of distress are heterogeneous in terms of both presentation and time to onset. For example, depression and dementia take time to develop, whereas anxiety (e.g., panic attacks) and delirium can present suddenly. As a result, different types of distress may be associated with different sets of predictors. Given that the risk stratification algorithms would be automated in clinical practice, integration of separate algorithms for each type of distress would not require additional resources at the point of care.

Conclusion

This Doctoral research program provides the first attempt to predict new-onset distress in breast cancer patients as women transition to routine follow-up care and have fewer contacts with the oncology care team. Although the risk stratification models only moderately improved prediction, the results can be used to inform development of more accurate algorithms to identify women at higher risk of new-onset distress after completion of hospital-based treatment. Furthermore, the results of this thesis highlight the importance of developing risk stratification algorithms that are tailored to the period of the cancer care trajectory as well as inclusion of new treatment-related symptoms and

conditions that occur during the survivorship period as candidate predictors of new-onset distress when developing algorithms in the future.

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REVIEW

Predictors of distress in female breast cancer survivors: a systematic review

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Abstract

Purpose Unmanaged distress has been shown to adversely affect survival and quality of life in breast cancer survivors. Fortunately, distress can be managed and even prevented with appropriate evidence-based interventions. Therefore, the objective of this systematic review was to synthesize the published literature around predictors of distress in female breast cancer survivors to help guide targeted intervention to prevent distress.

Methods Relevant studies were located by searching MEDLINE, Embase, PsycINFO, and CINAHL databases. Significance and directionality of associations for commonly assessed candidate predictors ($n \geq 5$) and predictors shown to be significant ($p \leq 0.05$) by at least two studies were summarized descriptively. Predictors were evaluated based on the proportion of studies that showed a significant and positive association with the presence of distress.

Results Forty-two studies met the target criteria and were included in the review. Breast cancer and treatment-related predictors were more advanced cancer at diagnosis, treatment with chemotherapy, longer primary treatment duration, more recent transition into survivorship, and breast cancer recurrence. Manageable treatment-related symptoms associated with distress included menopausal/vasomotor symptoms, pain, fatigue, and sleep disturbance. Sociodemographic characteristics that increased the risk of distress were younger age, non-Caucasian ethnicity, being unmarried, and lower socioeconomic status. Comorbidities, history of mental health problems, and perceived functioning limitations were also associated. Modifiable predictors of distress were lower physical activity, lower social support, and cigarette smoking.

Conclusions This review established a set of evidence-based predictors that can be used to help identify women at higher risk of experiencing distress following completion of primary breast cancer treatment.

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Keywords Breast cancer · Survivorship · Predictor · Distress · Systematic review

Introduction

Around 1.67 million new cases of breast cancer were diagnosed worldwide in 2012, accounting for an estimated 25% of new cancer cases in women [1]. Earlier detection of breast tumors through screening mammography in combination with better and more targeted therapies has dramatically improved survival [2]. Medical advances have generated a large cohort of women surviving after completion of primary breast cancer treatment.

Current 5 and 10-year survival rates following breast cancer diagnosis are 87 and 82%, respectively [3]. As a result, both clinicians and researchers are now focusing more efforts on improving quality of life and patient-centered outcomes in survivorship. The National Comprehensive Cancer Network (NCCN) has recognized distress as an important sequela of cancer diagnosis and treatment [4]. Formally, cancer-related distress is defined as "a multifactorial unpleasant emotional experience of a psychological (i.e., cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crises" [4]. Unmanaged distress has been shown to negatively impact all-cause and cancer-related morbidity and mortality, as well as quality of life [5].

Identification of distress during survivorship still presents a challenge; it may be unclear when normal feelings of vulnerability, sadness, and fears transition to a point requiring intervention or support. To address this issue, cancer care agencies have recommended that cancer patients be routinely screened for distress at appropriate intervals throughout primary treatment and survivorship, and at important clinical time points including remission, recurrence, progression, and treatment-related complications [4]. However, approximately 37% of breast cancer patients who have transitioned into survivorship will attend two or fewer follow-up visits with an oncologist within the first year following completion of primary treatment [6], limiting the number of opportunities for distress screening and potentially delaying necessary treatment.

An alternative approach could be to identify breast cancer patients at increased risk of developing distress following transition into survivorship. This would allow for targeted intervention to prevent distress, as well as enhanced monitoring to identify prodromal symptoms and early warning signs of distress for timely intervention to mitigate the risk of progression to diagnosable mental health problems. For example, intervention with prophylactic cognitive behavioral therapy (CBT) has been shown to reduce incidence of depression and anxiety in higher-risk cancer patients by half [7]. As a first step in this direction, the objective of this systematic review is to summarize the published literature around predictors of distress in breast cancer survivors.

Methods

Study selection

Search strategy

Four databases (MEDLINE, Embase, PsycINFO, and CINAHL) were searched for relevant studies published between January 1, 2000 and March 10, 2016. Studies published prior to the year 2000 were excluded since they were not considered to be representative of the current state of distress literature, given significant improvements in breast cancer treatments and survival rates, and increased awareness of mental health challenges in survivorship. Four main concepts of breast cancer, survivorship, predictor, and distress were mapped to the most relevant controlled vocabulary using Medical Subject Headings (MeSH), and free-text terms were added where necessary. Full search strategies are provided in Appendix 1 in electronic supplementary material.

Inclusion and exclusion criteria

This systematic review identified studies that measured the presence of distress (via clinical interviews, or distress scales) and evaluated potential predictors of presence of distress in female breast cancer patients who had completed primary treatment (i.e., surgery, chemotherapy, and/or radiotherapy). Therefore, only studies that dichotomized the outcome as the presence or absence of distress were included in the review; articles that used a continuous outcome (e.g., total score on a distress scale) were not included. Distress was broadly defined based on specific mental health diagnoses (i.e., depressive disorders, anxiety disorders, obsessive–compulsive and related disorders, and trauma- and stressor-related disorders), as well as non-specific symptoms (e.g., 'psychological,' 'psychosocial,' 'stress,' and 'distress'). All study designs were considered (e.g., cross-sectional, prospective cohort, etc.). Studies were excluded if the article did not report original research, or was not published in the English language.

Screening and data abstraction

Screening of articles was completed in two stages. First, articles were screened for relevance based on information provided in the title and abstract, and subsequently evaluated for inclusion based on the full text. Two reviewers independently screened articles at each stage (title and abstract: AS and AM; full text: AS and SK). All articles considered eligible for inclusion by at least one reviewer based on the title and abstract screen were submitted for full-text review. Disagreements at the full-text screen were resolved by discussion and consensus between the two reviewers. Kappa scores were calculated to assess interrater reliability. Reference lists of eligible articles were searched to identify additional relevant studies for inclusion in the review.

One reviewer completed data abstraction (AS), which focused on citation information, study design, sample size and patient characteristics, type and prevalence of distress, measurement of distress (i.e., case ascertainment), timing of measurement, and predictors of distress (all predictors evaluated, and predictors significant in univariate and/or multivariate analyses). A second reviewer (SK) checked data abstracted from ten percent of the articles to assess quality of data abstraction, and one omission was identified.

Evaluation of predictors

Substantial heterogeneity in the formats of predictors (e.g., continuous, or not comparable classification approaches) limited the feasibility of meta-analysis to quantitatively synthesize results on the strength of association between predictors and the presence of distress. Consequently, significance and directionality of associations (i.e., positive, negative, or inconsistent/unspecified) for the most commonly assessed candidate predictors ($n \geq 5$) as well as predictors shown to be significant ($p \leq 0.05$) by at least two studies were summarized descriptively. Predictors were evaluated based on the proportion of studies that showed a significant and positive association (in univariate and/or multivariate analyses) with the presence of distress, in an effort to identify patterns to inform future research.

Results

Study selection

The search identified 2706 unique articles. The title and abstract screen retained 313 articles. Full-text screening with reference list searching identified 42 studies that met the target criteria and were included in the review. The kappa scores for title and abstract screen, and full-text screen were 0.43 and 0.54, respectively, indicating 'moderate' agreement [8]. The moderate kappa scores reflect the complexity around defining distress and uncertainty around the beginning of the breast cancer survivorship period, as well as consideration of studies that did not focus specifically on breast cancer. A modified Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart is presented in Fig. 1 [9].

Characteristics of studies identified through the systematic review are presented in Table 1 [10–51]. Studies were published between 2001 and 2016, and were conducted in North America (19/42 studies; 45%), Asia (12/42 studies; 29%), and Europe (11/42 studies; 26%). Half of the studies collected data using a prospective cohort (21/42 studies; 50%), and the other half used a cross-sectional design (20/42 studies; 48%) or retrospective chart review (1/42 studies; 2%). Eight (8/21 studies; 38%) of the prospective cohort studies reported distress trajectories, which describe how individual women's distress can change over time from diagnosis through primary treatment and into survivorship. The remaining studies reported prevalence of distress within the survivorship period, without describing how individual women's distress changes over time.

The majority of studies measured depression (30/42 studies; 71%); anxiety, posttraumatic stress disorder (PTSD), general distress, and suicidal ideation were measured by 29% (12/42 studies), 7% (3/42 studies), 21% (9/42 studies), and 2% (1/42 studies) of studies, respectively. The median prevalence of distress was 26% (interquartile range 39–17 = 22%). The majority of studies assessed the presence of distress using validated cut-offs of the Center for Epidemiologic Studies-Depression scale (CES-D: 12/42 studies; 29%) or the Hospital Anxiety and Depression Scale (HADS: 12/42 studies; 29%). Timing of distress assessment in survivorship varied substantially. Eleven studies (26%) evaluated distress in survivorship at a specific time point following breast cancer diagnosis (ranging from 1 to 4 years). The majority of studies based on distress trajectories (7/8 studies; 88%) followed women for periods ranging from 1 to 2 years starting from breast cancer diagnosis. The remaining studies included survivors with varying times since breast cancer diagnosis, ranging from a mean of 17.6 months following breast surgery (standard deviation (SD): 9.0 months; range 6–36 months) to 10.5 years (range 5–32 years) following breast cancer diagnosis.

Evaluation of predictors

The significance and directionality of commonly assessed candidate predictors ($n \geq 5$), as well as predictors shown to

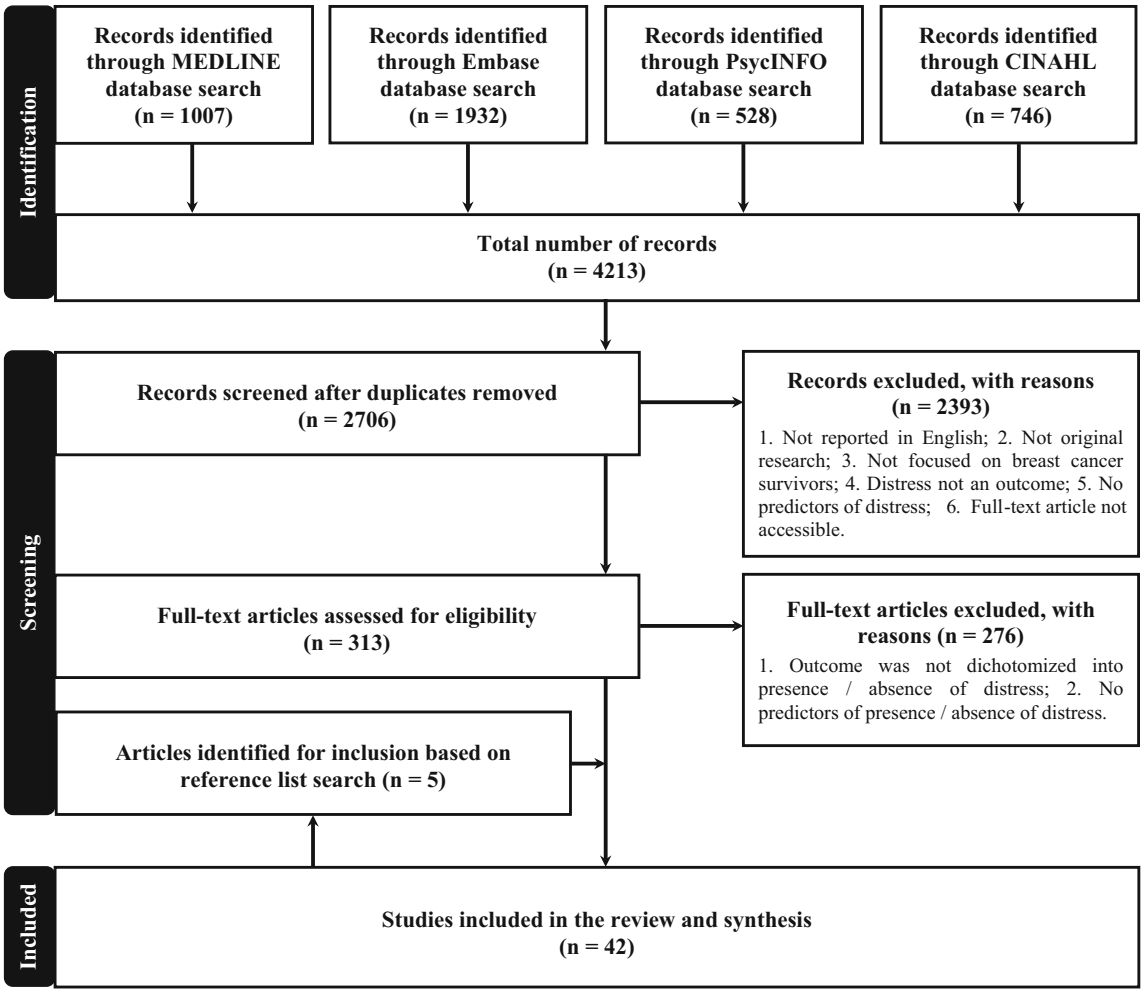

Fig. 1 PRISMA study selection flowchart

be significant ($p \leq 0.05$) by at least two studies are summarized in Table 2 [10–23, 25, 27–33, 35–50], and categorized based on type of predictor: sociodemographic characteristics, breast cancer characteristics and treatment, treatment-related symptoms, comorbidities and medical history, perceived functioning limitations, and behavioral and support factors. All predictors evaluated within each study, alongside predictors shown to be significant ($p \leq 0.05$) in univariate and multivariate analyses are presented in Appendix 2 in electronic supplementary material [10–51]. Twenty-eight of the 42 studies (67%) reported on multivariate analyses conducted to estimate independent associations between candidate predictors and the presence of distress in breast cancer survivors; the remaining studies only reported data for univariate associations. Overall, studies that employed a cross-sectional design had larger sample sizes (mean: 560 women vs. 399 women for cohort and chart review studies) and were more likely to report significant associations between candidate predictors and distress.

The most commonly evaluated predictors were patient sociodemographic characteristics, breast cancer characteristics, and treatments. Sociodemographic characteristics that were associated with distress included: younger age (10/27 studies; 37%), non-Caucasian ethnicity (2/11 studies; 18%), and being unmarried (8/23 studies; 35%). Lower socioeconomic status (SES) also increased the risk of distress including: lower education (3/21 studies; 14%), lower income (4/7 studies; 57%), and experiencing financial difficulties (5/6 studies; 83%). However, unemployment did not influence the risk of distress.

Breast cancer characteristics and treatments predictive of distress were more advanced cancer at diagnosis (3/21 studies; 14%), treatment with chemotherapy (4/18 studies; 22%), and longer primary treatment duration (2/2 studies). However, type of breast surgery, treatment with radiotherapy, and treatment with hormone therapy did not influence the risk of distress. More recent transition into survivorship (3/10 studies; 30%), and breast cancer recurrence (2/4 studies; 50%) were associated with distress.

Table 1 Characteristics of studies identified by the systematic review

Author, year (country) [G1–G3: participant groups]	Study design	Sample size	Age, mean ± SD (range) in years[a]	Breast cancer stage	Outcome(s): prevalence (trajectories, if applicable)	Measurement of distress (i.e., case ascertainment)	Timing of distress measurement
Bardwell, 2006 [10] (United States)	Cross-sectional	2595	In survivorship: 53 (28–74)	I–III	Depression: 17%	CES-Dsf ≥ 0.06 (on the logarithmic scale)	≤4 years after completion of primary breast cancer treatment: ≤1 year: 23% 1–2 years: 33% 2–3 years: 24% 3–4 years: 20%
Dominick, 2014 [11] (United States)	Cross-sectional	1817	Not reported	I–III	Depression: No lymphedema—12.2% Lymphedema without lymphedema-related distress—12.8% Lymphedema with lymphedema-related distress—17.6%	CES-Dsf ≥ 0.06 (on the logarithmic scale)	4 years after breast cancer diagnosis
Chen, 2009 [12] (China)	Prospective cohort	1400	At diagnosis: 53.7 ± 9.8	0–IV	Total depression: 26.0% Mild depression: 13.4% Clinical depression: 12.6%	Mild: CES-D = 10–15 Clinical: CES-D ≥ 16	18 months after breast cancer diagnosis
Chen, 2010 [13] (China)	Prospective cohort	1399	At diagnosis: 53.7 ± 9.8	0–III	Total depression: 26.0% Mild depression: 13.4% Clinical depression: 12.6%	Total: CES-D ≥ 10 Mild: CES-D = 10–15 Clinical: CES-D ≥ 16	18 months after breast cancer diagnosis
Kim, 2008 [14] (Korea)	Cross-sectional	1219	In survivorship: 47.4 ± 9.3	0–III	Moderate to severe depression: 24.9%	BDI ≥ 19	Mean ± SD time after breast cancer surgery: 4.6 ± 2.4 years
Mehnert, 2008 [15] (Germany)	Cross-sectional	835	In survivorship: 61.8 ± 9.8 (31–81)	I–IV	Psychological distress (i.e., anxiety, depression, and/or PTSD): 42.9%	HADS ≥ 8 PCL-C = 1 intrusion + 3 avoidance + 2 arousal symptoms (rated 'moderately' or above)	Mean ± SD (range) time after breast cancer diagnosis: 46.5 ± 17.5 (18–77) months
Calhoun, 2015 [16] (United States)	Cross-sectional	761	In survivorship: 63.6 ± 10.5	Not reported	Depression: 15.5%	CES-D ≥ 16	Median (range) time after breast cancer diagnosis: 7 (1–43) years
Branstrom, 2015 [17] (Sweden)	Prospective cohort	726	At diagnosis: 51.3 ± 8.1	0–IV	Anxiety: 20.7% Depression: 11.7%	HADS ≥ 8	24 months after breast cancer diagnosis

Table 1 continued

Author, year (country) [G1–G3: participant groups]	Study design	Sample size	Age, mean ± SD (range) in years[a]	Breast cancer stage	Outcome(s): prevalence (trajectories, if applicable)	Measurement of distress (i.e., case ascertainment)	Timing of distress measurement
Saboonchi, 2015 [18] (Sweden)	Prospective cohort; trajectory	725	At diagnosis: 51.2 ± 8.1 (24–63) Median: 52	Not reported	Anxiety trajectories: High stable—6.2% High decrease—15.6% Mid decrease—33.0% Low decrease—45.0%	HADS scores (anxiety subscale): membership in 'high stable' trajectory	Over 24 month period following breast cancer surgery
Saboonchi, 2014 [19] (Sweden)	Prospective cohort	654	At diagnosis: 51.3 ± 8.1	Not reported	Anxiety: 25.1% Depression: 15.3%	Total: HADS ≥ 8 Possible: HADS = 8–10 Probable: HADS ≥ 11	12 months after breast cancer surgery
Avis, 2015 [20] (United States)	Prospective cohort; trajectory	653	At diagnosis: 54.9 ± 0.5	I–III	Depression trajectories: 1 consistent very low score—3.8% 2 consistent low score—47.3% 3 consistent borderline score—29.2% 4 high score, declining—11.3% 5 borderline score, increasing—7.2% 6 consistent high score—1.1%	BDI scores: membership in 'borderline score, increasing' trajectory	Over 24 month period following breast cancer diagnosis Mean ± SD (range) time since diagnosis at study entry: 4.5 ± 0.05 (6–26) months
Ganz, 2003 [21] (United States)	Cross-sectional	577	At diagnosis: 43.6 (25.2–51) In survivorship: 49.5 (30–61.6)	0–II	Clinical depression: 25.7%	CES-D ≥ 16	Mean ± SD time after breast cancer diagnosis: 5.9 ± 1.5 years Disease-free for 2–10 years
Qiu, 2012 [22] (China)	Cross-sectional	505	In survivorship: 52.02 ± 4.55 (23–65)	0–IV	Major depressive disorder: 20.59%	Phase 1: BDI ≥ 5 Phase 2: MINI Module A (based on DSM-IV criteria)	Mean ± SD (range) time after breast surgery: 17.6 ± 9.0 (6–36) months
Stanton, 2015 [23] (United States)	Prospective cohort; trajectory	457	At diagnosis: 56.4 ± 12.6 (23–91)	I–IV	Depression: 15.6% Depression trajectories: High—38% Recovery—20% Low—32% Very low—11%	CES-D ≥ 16 CES-D scores: membership in 'high' trajectory	Over 16 month period following breast cancer diagnosis Mean ± SD time after breast cancer diagnosis at study entry: 2.1 ± 0.8 months

Table 1 continued

Author, year (country) [G1–G3: participant groups]	Study design	Sample size	Age, mean ± SD (range) in years[a]	Breast cancer stage	Outcome(s): prevalence (trajectories, if applicable)	Measurement of distress (i.e., case ascertainment)	Timing of distress measurement
Boehmer, 2012 [24] (United States) [G1: heterosexual women from registry; G2: sexual minority women from registry; G3: sexual minority women from convenience sample]	Cross-sectional	438 G1: 257 G2: 69 G3: 112	In survivorship: G1: 62.7 ± 11.0 G2: 55.9 ± 8.3 G3: 55.1 ± 8.7	0–III	Anxiety: borderline/clinical G1—7.0 / 10.6% G2—6.0 / 8.9% G3—10.8 / 5.4% Depression: borderline/clinical G1—3.1 / 3.1% G2—3.0 / 3.0% G3—6.2 / 4.5%	Borderline: HADS = 8–10 Clinical: HADS ≥ 11	Mean ± SD time after breast cancer diagnosis: G1: 4.7 ± 1.8 years G2: 5.3 ± 1.5 years G3: 6.4 ± 1.8 years
Kim, 2013 [25] (United States)	Cross-sectional	381	Over 21 years old	0–III	Distress (anxiety or depression): not reported	PROMIS: not reported	1–5 years after completion of primary breast cancer treatment
Hong, 2015 [26] (United States)	Prospective cohort	372	Not reported	0–III	Depression: not reported	CES-D > median	1 year after breast cancer diagnosis
Palesh, 2010 [27] (United States)	Prospective cohort	353	In survivorship: 50	Not reported	Time 1: Anxiety: 62% Depression: 15%	Hamilton Anxiety and Depression Scale ≥ 8	Time 1: 6–24 months after primary breast cancer treatment Time 2: 3 months after Time 1
Wang, 2015 [28] (Taiwan)	Prospective cohort; trajectory	311	Not reported	Not reported	Distress trajectories: High depression Medium depression Low depression Depression drop	HADS scores (depression subscale): membership in the 'high depression' trajectory	Over 12 month period following breast cancer surgery
Leung, 2016 [29] (Scotland)	Cross-sectional	295	In survivorship: 66.44	Not reported	Psychological distress: 16.6%	GHQ ≥ 4	At least 1 year after breast cancer diagnosis
Romito, 2012 [30] (Italy)	Cross-sectional	255	In survivorship: 58.4 (35–80)	Not reported	Depression: 37%	ZSDS ≥ 60	Mean (range) time since breast cancer diagnosis: 10.5 (5–32) years
Kim, 2013 [31] (Korea) [G1: suicidal ideation present; G2: suicidal ideation not present]	Prospective cohort	241	In survivorship: G1: 49.8 ± 9.6 G2: 50.4 ± 9.8	0–IV	Suicidal ideation: 11.2%	BDI: question about presence of suicidal ideation ≥ 1	1 year after breast cancer surgery

Table 1 continued

Author, year (country) [G1–G3: participant groups]	Study design	Sample size	Age, mean ± SD (range) in years[a]	Breast cancer stage	Outcome(s): prevalence (trajectories, if applicable)	Measurement of distress (i.e., case ascertainment)	Timing of distress measurement
Reyes-Gibby, 2012 [32] (United States)	Cross-sectional	240	In survivorship: 58 ± 16	0–III	Depression: 16.2%	PHQ-8 ≥ 10	Mean (range) time since start of primary breast cancer treatment: 7.9 (6–13) years Median: 8 years
Ashing-Giwa, 2013 [33] (United States)	Cross-sectional	232	In survivorship: 53 ± 10.6 (26–84)	0–III	Clinical depression: 53.4%	CES-D ≥ 16	Time since breast cancer diagnosis: 1–6 years
Wang, 2011 [34] (Taiwan)	Cross-sectional	217	Not reported	Not reported	Distress: not reported	HADS ≥ 15 NCCN Distress Thermometer ≥ 4	Not reported
Lee, 2011 [35] (Korea)	Prospective cohort; trajectory	206	At diagnosis: 47 ± 10	I–III	Depression: 49.3% Deteriorated depressive mood (from breast cancer diagnosis to 1 year following diagnosis): 20.9%	Depression: ZSDS ≥ 50 Deteriorated mood: Effect size > 0.5	Over 1 year period following breast cancer diagnosis
Hsu, 2010 [36] (Taiwan)	Cross-sectional	206	Not reported	I–II	Distress (anxiety or depression): 38.6%	HADS ≥ 15	3–24 months after completion of primary breast cancer treatment
Burgess, 2005 [37] (England)	Prospective cohort	202	At diagnosis: 48.4 ± 7.8	III—32% Other—68%	Depression and/or anxiety annual prevalences: Year 2—25% Year 3—23% Year 4—22% Year 5—15%	SCID for depression and anxiety: standardized diagnostic criteria from the DSM III-R	2–5 years after breast cancer diagnosis
Kornblith, 2001 [38] (United States)	Cross-sectional	179	In survivorship: Median: 56 (32–79)	II	Psychological distress: 8%	MHI ≥ 1.5 SD above the average	Median (range) time since start of chemotherapy: 6.8 (3.3–11.2) years
Henselmans, 2010 [39] (Netherlands)	Prospective cohort; trajectory	171	At diagnosis: 54.8 ± 9.0	0–III	Distress trajectories: No distress—36.3% Recovery—33.3% Late distress—15.2% Chronic distress—15.2%	GHQ scores: membership in 'late distress' trajectory	Over 1 year period following breast cancer diagnosis

Table 1 continued

Author, year (country) [G1–G3: participant groups]	Study design	Sample size	Age, mean ± SD (range) in years[a]	Breast cancer stage	Outcome(s): prevalence (trajectories, if applicable)	Measurement of distress (i.e., case ascertainment)	Timing of distress measurement
Accortt, 2015 [40] (United States)	Cross-sectional	163	In survivorship: 47.6 ± 5.6 (28–56)	I–III	Clinical depression: 39%	CES-D ≥ 16	Mean ± SD time following breast cancer diagnosis: 3.4 ± 1.5 years
Donovan, 2014 [41] (United States)	Prospective cohort; trajectory	147	At diagnosis: 51.63 ± 9.03	0–II	Distress trajectories: Class 1 (High)—26.5% Class 2 (Medium)—47.6% Class 3 (Low)—25.9%	CES-D scores: membership in 'high' trajectory	Over 12 month period following breast cancer diagnosis
Morasso, 2001 [42] (Italy)	Prospective cohort	132	In survivorship: ≤ 50: 37% 51–60: 35% > 60: 28%	I–III	Psychiatric disorder (major depressive disorder, adjustment disorder, anxiety disorder, dementia, hypomanic episode): 38%	SCID: standardized diagnostic criteria from the DSM III-R	First follow-up visit in first year after start of chemotherapy
Ploos van Amstel, 2013 [43] (Netherlands)	Cross-sectional	129	In survivorship: 57 ± 10	Not reported	Distress: 36%	NCCN Distress Thermometer ≥ 5	Mean ± SD time since breast cancer surgery: 5.6 ± 4.7 years
Kornblith, 2007 [44] (United States) [G1: age ≤55 years; G2: age ≥65 years]	Prospective cohort	128 G1: 61 G2: 67	At diagnosis: G1: 43.6 ± 6.1 G2: 67.1 ± 6.8 In survivorship: G1: 47.9 ± 5.9 (IQR: 43–53) G2: 72.1 ± 5.4 (IQR: 67–76)	I–III	Depression or anxiety: G1—9.8% G2—3.0% PTSD: G1—4.9% G2—0%	HADS ≥ 15 PCL-C = 1 intrusion + 3 avoidance + 2 arousal symptoms (rated 'moderately' or above)	Mean ± SD time since completion of primary breast cancer treatment: G1: 3.9 ± 1.65 years G2: 4.5 ± 2.2 years
Brunault, 2013 [45] (France)	Prospective cohort	120	At completion of primary breast cancer treatment: 50.2 ± 8.1 In survivorship: 58.3 ± 8.2	0–IV	Significant depression: 19.2% Possible depression: 12.5% Probable depression: 6.7%	Significant: HADS ≥ 8 Possible: HADS = 8–10 Probable: HADS ≥ 11	Mean ± SD (range) time after completion of primary breast cancer treatment: 8.1 ± 1.3 (6.1–11.0) years

Table 1 continued

Author, year (country) [G1–G3: participant groups]	Study design	Sample size	Age, mean ± SD (range) in years[a]	Breast cancer stage	Outcome(s): prevalence (trajectories, if applicable)	Measurement of distress (i.e., case ascertainment)	Timing of distress measurement
Wang, 2013 [46] (Taiwan)	Prospective cohort; trajectory	Time 1: 248 Time 2: 118	Not reported	Early stages	Distress (anxiety or depression): Time 1—28.63% Time 2—16.10% Distress trajectories: Remained distressed—6% Remained non-distressed—75% Non-distressed to distressed—8% Distressed to non-distressed—11%	HADS ≥ 15	Over a 3 year period: Time 1: ~9 months after completion of primary breast cancer treatment Time 2: ~3 years after Time 1
Eversley, 2005 [47] (United States)	Cross-sectional	116	In survivorship: 47 (29–68)	I–IV	Clinical depression: 52%	CES-D ≥ 16	≤2 years after breast cancer diagnosis and after completion of primary breast cancer treatment
Vahdaninia, 2010 [48] (Iran)	Prospective cohort	99	In survivorship: 46.4 ± 12.5 (24–81)	I–IV	Anxiety: 54.5% Depression: 32.3%	HADS ≥ 8	1 year following completion of primary breast cancer treatment
Neerukonda, 2015 [49] (United States)	Retrospective chart review	81	In survivorship: 53 ± 8	I—43% II—41% Other—16%	Distress: 50%	NCCN Distress Thermometer ≥ 4	First survivorship care visit
Shelby, 2008 [50] (United States)	Prospective cohort	74	In survivorship: Mode: 51 (31–84)	II–III	PTSD: 16.2% Subsyndromal PTSD: 20.3%	SCID PTSD: meet Criterion A, and 1 intrusion + 3 avoidance + 2 arousal symptoms Subsyndromal PTSD: meet Criterion A, and (a) 3 avoidance, or 2 arousal symptoms, or (b) ≥ 5 symptoms across clusters	18 months following breast cancer diagnosis

Table 1 continued

Author, year (country) [G1–G3: participant groups]	Study design	Sample size	Age, mean ± SD (range) in years[a]	Breast cancer stage	Outcome(s): prevalence (trajectories, if applicable)	Measurement of distress (i.e., case ascertainment)	Timing of distress measurement
Baider, 2008 [51] (Israel) [G1: mothers were Holocaust survivors; G2: mothers not Holocaust survivors]	Cross-sectional	39 G1: 20 G2: 19	In survivorship: G1: 46.9 ± 7.1 G2: 46.3 ± 9.8	I–II	Distress: G1—80% G2—32%	GSI ≥ 63	> 6 months after completion of primary breast cancer treatment

BDI Beck Depression Inventory, *CES-D* Center for Epidemiologic Studies—Depression scale, *CES-Dsf* CES-D 8-item screening form, *Criterion A* "Actual or threatened death or serious injury, or a threat to the physical integrity of the self or others and a response involving intense fear, helplessness, or horror" [50], *DSM* Diagnostic and Statistical Manual of Mental Disorders, *G1–G3* participant groups (see study-specific descriptions in first column), *GHQ* General Health Questionnaire, *GSI* Global Severity Index, *HADS* Hospital Anxiety and Depression Scale, *IQR* interquartile range, *MHI* Mental Health Inventory, *MINI* Mini International Neuropsychiatric Interview, *NCCN* National Comprehensive Cancer Network, *PCL-C* Posttraumatic Stress Disorder Checklist—Civilian version, *PHQ-8* 8-item Patient Health Questionnaire, *PROMIS* Patient Reported Outcomes Measurement Information System, *PTSD* posttraumatic stress disorder, *SCID* Structured Clinical Interview for DSM, *SD* standard deviation, *ZSDS* Zung Self-rating Depression Scale

[a] Unless otherwise specified

The following treatment-related symptoms were associated with distress: menopausal/vasomotor symptoms (7/10 studies; 70%), pain (9/12 studies; 75%), fatigue (6/9 studies; 67%), sleep disturbance (7/9 studies; 78%), lymphedema/arm symptoms (2/5 studies; 40%), breast symptoms (2/3 studies; 67%), appetite loss (2/5 studies; 40%), diarrhea (3/5 studies; 60%), and dyspnea (2/4 studies; 50%). Constipation, nausea, and vomiting did not influence the risk of distress. Furthermore, higher number of treatment-related complaints (3/5 studies; 60%) was associated with distress. Similarly, higher number of comorbidities (5/9 studies; 56%) and history of mental health problems (7/7 studies) increased the risk of distress.

Lower overall quality of life (6/8 studies; 75%) and the following subscales/domains were associated with distress: lower quality of physical health (4/4 studies), lower quality of mental health (2/2 studies), physical functioning limitations (6/8 studies; 75%), role functioning limitations (6/8 studies; 75%), emotional functioning limitations (3/5 studies; 60%), cognitive functioning limitations (2/4 studies; 50%), and social functioning limitations (4/6 studies; 67%). Lower optimism (2/3 studies; 67%), lower posttraumatic growth (3/3 studies), and higher number of stressful life events (3/6 studies; 50%) also increased the risk of distress. In terms of behavioral and support factors, lower physical activity (5/8 studies; 63%), lower social support (6/8 studies; 75%), and cigarette smoking (2/6 studies; 33%) were associated with distress, whereas higher alcohol intake and higher body mass index (BMI) did not influence the risk of distress.

Discussion

This systematic review is the first synthesis of the published literature around predictors of distress in female breast cancer patients who have completed primary treatment. Breast cancer and treatment-related predictors included more advanced cancer at diagnosis, treatment with chemotherapy, longer primary treatment duration, more recent transition into survivorship, and breast cancer recurrence. Treatment-related symptoms also increased the risk of distress including menopausal/vasomotor symptoms, pain, fatigue, and sleep disturbance. A variety of factors not specific to breast cancer survivors predicted distress. Associated sociodemographic characteristics were younger age, non-Caucasian ethnicity, being unmarried, and indicators of lower SES (specifically, lower education or income, and experiencing financial difficulties). Higher number of comorbidities and history of mental health problems also increased the risk of distress. Furthermore, lower quality of life, optimism, and posttraumatic growth, as well as higher number of stressful life events predicted

Table 2 Significance and directionality of commonly assessed candidate predictors ($n \geq 5$), and predictors shown to be significant ($p \leq 0.05$) by at least two studies

Predictors (*n*)	Significant (+) association[a] ($p \leq 0.05$)	Significant association[a] ($p \leq 0.05$); direction unspecified or inconsistent	Significant (–) association[a] ($p \leq 0.05$)	No significant association or association not reported
Sociodemographic characteristics				
Younger age (*n* = 27)	[10][11][15][20][22][23][32][37][38][49]	[19][33]	[42]	[12][14][16][18][21][30][31][35][39][40][41][44][45][48]
Non-Caucasian ethnicity (*n* = 11)	[16][20]	[23][47]		[10][11][25][38][40][41][49]
Unmarried (*n* = 23)	[10][12][18][22][31][36][37][41]	[11][33][38][48]		[14][16][19][20][23][30][32][35][40][45][49]
Lower education (*n* = 21)	[10][14][15]	[12]		[11][16][18][19][20][22][23][30][31][32][33][35][38][39][41][42][48]
Lower income (*n* = 7)	[12][14][22][33]			[23][35][41]
Financial difficulties (*n* = 6)	[18][20][32][35][43]			[38]
Unemployment (*n* = 9)	[40]	[23]		[14][16][22][31][33][35][38]
Breast cancer characteristics and treatment				
More advanced breast cancer at diagnosis (*n* = 21)	[15][20][31]		[11]	[10][12][14][18][22][23][32][33][35][36][37][39][41][42][45][48][50]
Mastectomy (*n* = 19)	[50]	[14]		[10][11][12][18][20][22][23][30][31][33][35][39][40][41][42][45][48]
Treatment with chemotherapy (*n* = 18)	[18][19][20][31]			[10][11][12][14][16][22][23][30][33][35][37][39][40][48]
Treatment with radiotherapy (*n* = 15)		[14]	[12]	[10][11][16][18][19][20][22][23][30][33][35][39][40]
Treatment with hormone therapy (*n* = 17)		[10][16]	[20]	[11][12][14][18][19][23][30][33][35][37][39][40][41][45]
Longer primary treatment duration (*n* = 2)	[23][43]			
More recent transition into survivorship (*n* = 10)	[22][32][38]			[10][14][15][30][40][43][45]
Breast cancer recurrence (*n* = 4)	[22][31]		[38]	[32]
Treatment-related symptoms				
Menopausal/vasomotor symptoms (*n* = 10)	[10][12][14][20][35][40][42]			[11][41][45]
Pain (*n* = 12)	[10][12][14][16][20][32][38][43][48]			[31][35][45]
Fatigue (*n* = 9)	[12][20][30][31][32][43]	[48]		[35][38]
Sleep disturbance/insomnia (*n* = 9)	[10][14][27][30][32][40][43]			[35][38]
Lymphedema/arm symptoms (*n* = 5)	[14][43]	[11]		[35][45]
Breast symptoms (*n* = 3)	[14][43]			[35]
Appetite loss (*n* = 5)	[14][32]			[35][38][43]
Diarrhea (*n* = 5)	[14][32][43]			[35][38]
Dyspnea (*n* = 4)	[14][32]			[38][43]
Constipation (*n* = 5)	[14]			[32][35][38][43]
Nausea and vomiting (*n* = 5)	[32]			[14][35][38][43]
Higher number of treatment-related complaints (*n* = 5)	[39][43][46]			[35][45]
Comorbidities and medical history				
Higher number of comorbidities (*n* = 9)	[11][12][23][30][33]	[16]		[31][35][41]
History of mental health problems (*n* = 7)	[19][22][31][37][41][42][50]			
Perceived functioning limitations				
Lower quality of life/global health status (*n* = 8)	[12][14][18][29][32][43]			[35][38]
Lower quality of physical health (*n* = 4)	[12][30][31][33]			
Lower quality of mental health (*n* = 2)	[12][30]			
Physical functioning limitations (*n* = 8)	[10][12][18][32][38][43]			[16][35]
Role functioning limitations (*n* = 8)	[12][18][32][33][35][43]			[35][38]
Emotional functioning limitations (*n* = 5)	[12][32][43]			[35][38]
Cognitive functioning limitations (*n* = 4)	[32][43]			[35][38]
Social functioning limitations (*n* = 6)	[12][32][33][43]			[35][38]
Lower optimism (n = 3)	[10][29]			[39]
Lower posttraumatic growth (*n* = 3)	[28][36][46]			
Higher number of stressful life events (*n* = 6)	[10][19][31]	[37][38][50]		
Behavioral and support factors				
Lower physical activity (*n* = 8)	[10][11][13][17][25]			[16][30][35]
Lower social support (*n* = 8)	[10][15][33][36][38][46]	[35]		[20]
Cigarette smoking (*n* = 6)	[10][11]			[13][16][30][35]
Higher alcohol intake (*n* = 5)				[10][13][16][35][50]
Higher BMI (*n* = 7)	[10]	[11]		[16][31][35][40][41]

Numbers in brackets are references to studies included in the review; bolded reference: predictor significant in multivariate analysis; reference in gray: study potentially underpowered (i.e., having a sample size lower than 200, or a prevalence of distress lower than 20%)

BMI body mass index

[a] Bardwell (2006) [10] multivariate analysis used significance of $p \leq 0.001$

distress. For behavioral and support factors, lower physical activity, lower social support, and cigarette smoking were associated with distress. Informed by this systematic review, risk stratification may be a viable approach to identify women at higher risk of developing distress following completion of primary breast cancer treatment to provide targeted evidence-based interventions.

Breast cancer-specific factors were commonly evaluated as candidate predictors, given that conventional wisdom suggests that recent, traumatic experiences, such as advanced breast cancer diagnosis associated with worse prognosis and increased risk of premature mortality or more aggressive anti-cancer therapy, may increase the risk of distress. The systematic review identified initial diagnosis of more advanced breast cancer, treatment with chemotherapy, and longer primary treatment duration as predictors of distress. It is difficult to disentangle these predictors, given that they are highly correlated; women with more advanced breast cancer will undergo more aggressive anti-cancer treatment including chemotherapy, which in turn will substantially increase treatment duration. However, a potential underlying mechanism for increased distress in survivorship is that women diagnosed with more advanced breast cancer associated with higher risk of recurrence may experience more intense fears of recurrence [52], which if unmanaged could progress to diagnosable mental health problems. One study included in this systematic review reported significant univariate associations for both breast cancer stage and treatment with chemotherapy with distress; however, only more advanced breast cancer was significant in the multivariate model [31]. Furthermore, the systematic review showed that other forms of anti-cancer therapy (i.e., type of surgery, treatment with radiotherapy, or treatment with hormone

therapy) did not influence the risk of distress. These findings are supported by two large Danish cohort studies that evaluated predictors of distress following breast cancer diagnosis and identified number of tumor-positive axillary lymph nodes as an independent predictor of new antidepressant use [53, 54]. Although both studies evaluated breast cancer-related treatments as candidate predictors of distress, neither found independent associations for mastectomy, chemotherapy, or radiotherapy. The results of this systematic review suggest that more advanced breast cancer, as well as its correlates could help to identify women at higher risk of experiencing distress in survivorship.

The review identified potentially modifiable breast cancer treatment-related risk factors. Timely identification and effective management of treatment-related symptoms could serve as a possible intervention to prevent distress or mitigate its effects. Symptoms commonly associated with anti-cancer therapy were predominantly assessed using standardized cancer-specific measures of health-related quality of life as well as breast cancer-specific measures [55, 56]. Other treatment-related symptoms not captured by this systematic review may also be associated with distress. Identification of additional relevant symptoms should be guided through clinical expertise and investigated to assess the relationship with distress. These findings suggest that it may not be anti-cancer therapy that directly affects distress, but rather adverse events resulting from treatment that increase the risk of distress. Uncontrolled chronic and latent treatment-related symptoms can negatively affect health-related quality of life in survivorship and may serve as consistent reminders of the breast cancer diagnosis increasing fear of recurrence [52, 57]. Further studies are needed to assess independent contributions of more advanced breast cancer, treatments, and associated side effects on distress in survivorship.

Additional risk factors not directly related to diagnosis or treatment of breast cancer, including sociodemographic characteristics, comorbidities, medical history, and functional limitations, have also been shown to increase the risk of distress in the general population. In fact, many of these risk factors have been incorporated into predictive algorithms to estimate risk of incident distress in general practice [58–61]. Each of the algorithms includes younger age, indicator(s) of lower SES, and indicator(s) of perceived functioning limitations as predictors. In addition, some algorithms include comorbidities, history of mental health problems, and experiences of discrimination (e.g., racial discrimination [60]). Although this may seem intuitive, the results of this systematic review indicate that risk factors for distress in the general population can also be useful in identifying breast cancer patients at higher risk of distress following completion of primary treatment. Effectively, these risk factors make breast cancer survivors inherently more susceptible to development of distress when faced with challenges in survivorship. However, it is unclear whether or not these factors have differential effects in breast cancer survivors. For example, younger survivors may have different expectations of a normal fulfilling life and experience substantially higher distress as a function of receiving a premature life-threatening diagnosis, as well as coping with potential implications when raising young children. Future studies should focus on identifying interactions between risk factors in the general population and diagnosis of breast cancer in predicting distress.

The review also highlighted modifiable behavior and support factors that could serve as interventions to prevent or mitigate the impact of distress. As expected, lower physical activity, lower social support, and cigarette smoking were associated with the presence of distress [62–64]. In fact, lifestyle and support programs that develop and promote positive coping strategies have been shown to reduce distress symptoms in breast cancer survivors [65–68]. However, contrary to results from prior studies in the general population [69, 70], alcohol intake and BMI did not influence the risk of distress. None of the studies that evaluated alcohol intake showed a significant association. There were low prevalences and absolute numbers of women who reported higher alcohol intake in these studies [10, 13, 35, 50]. Given that higher alcohol intake has been shown to increase risk of breast cancer recurrence [71], this may reflect changes in alcohol consumption due to personal choice or medical advice following breast cancer diagnosis. For studies that reported no association between BMI and distress, three studies compared mean BMI between distressed and non-distressed women, and may have been underpowered to detect significant differences due to lower sample sizes [31, 40, 41]. Another study reported a low prevalence of increased BMI from <25 to ≥ 25 with a very low number of distressed women transitioning to increased BMI [35]. Future research should focus on exploring these associations in more depth.

This systematic review highlighted an important research gap; no studies evaluated predictors of incident distress in breast cancer survivors. Instead, studies assessed candidate predictors of prevalent distress making it unclear whether the 'predictor' or distress occurred first and introducing the possibility of reverse causation. In order to advance this field, future research should focus on establishing predictors of incident distress in breast cancer survivors with no concurrent or recent history of distress. Ideally, a large cohort of breast cancer survivors should be prospectively followed for incident distress, and evidence-based as well as clinically informed candidate predictors should be evaluated using time-to-event analysis.

Furthermore, harmonization of vocabulary around distress and survivorship periods would aid future research to develop more explicit recommendations. First, the non-specific nature of distress makes it difficult to describe and measure. Furthermore, levels and predictors of distress are expected to change across the breast cancer survivorship life course; women who have recently transitioned into survivorship have different concerns and priorities compared to longer-term survivors. Future research should focus on predictors of distress for different intervals of the survivorship period, e.g., transitional survivorship (first year following completion of primary treatment), short-term survivorship (2–5 years after completion of primary treatment), and long-term survivorship (>5 years after completion of primary treatment).

This study has several limitations resulting from the quality and scope of articles identified through the systematic review. Publication bias and inter-study heterogeneity limited the feasibility of conducting predictor-specific meta-analyses. The majority of studies only reported measures of association for significant predictors, which would have biased pooled estimates toward significance. Furthermore, studies that evaluated the same candidate predictor often used different measurements and classification approaches, making predictor-specific meta-analyses impossible. However, the synthesis conducted for this systematic review allowed for direct comparison of significant impact of predictors between studies assessing the same predictor.

This systematic review has established a set of evidence-based predictors that can be used to identify women at higher risk of experiencing distress following completion of primary breast cancer treatment. More advanced breast cancer and treatment-related symptoms may serve as the most practical predictors of distress in survivorship. Furthermore, findings suggest that risk factors for distress in the general population can also be used in this vulnerable population; this intuitively makes sense, given that women predisposed to distress are more likely to experience increased levels as a result of a life-altering breast cancer diagnosis. This systematic review provides preliminary evidence to address an important clinical gap. Furthermore, the results can serve to inform development of a risk stratification algorithm to identify women at higher risk of developing distress following completion of primary breast cancer treatment to provide appropriate support to prevent distress or mitigate its effects.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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