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Breast cancer survivorship

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Breast cancer survivorship

LONG-TERM PHYSICAL AND
PSYCHOLOGICAL EFFECTS OF BREAST
CANCER AND ITS TREATMENT

Saskia W.M.C. Accord-Maass

De studie die wordt beschreven in dit proefschrift is gefinancierd door Pink Ribbon (KWF Kankerbestrijding), afdeling Huisartsgeneeskunde en Ouderengeneeskunde van het Universitair Medisch Centrum Groningen en Stichting De Friesland.



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Breast cancer survivorship
Long-term physical and psychological effects
of breast cancer and its treatment

Proefschrift

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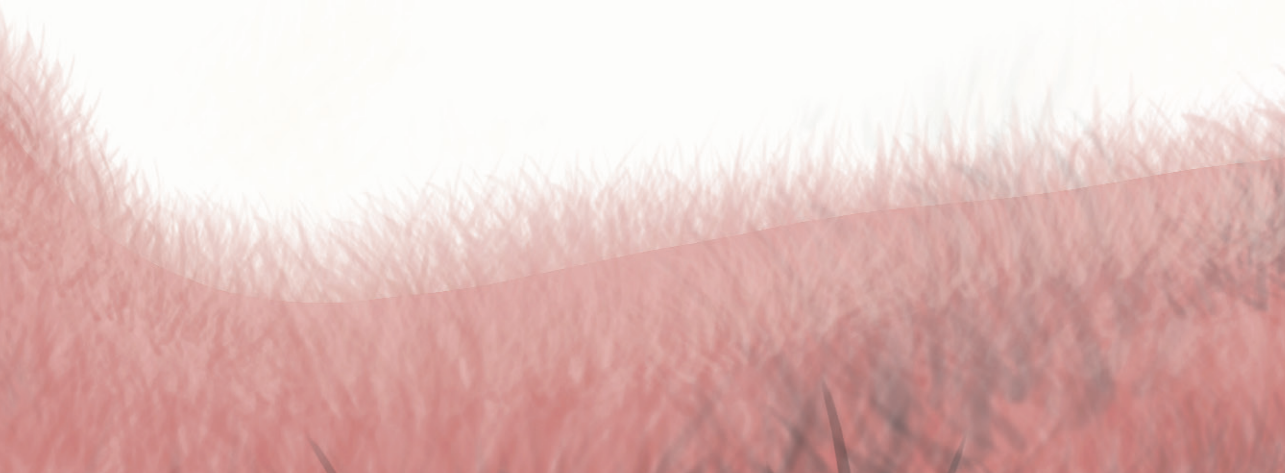
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Chapter 1

General introduction



GENERAL INTRODUCTION

Breast cancer survivors in numbers

Breast cancer is the most frequently diagnosed malignancy among women worldwide and in the Netherlands [1,2]. In 2018, there were 2.1 million women diagnosed with breast cancer worldwide [1] compared with 15,000 in the Netherlands [2]. Although these numbers have increased over the years, mainly due to the aging population, survival has also increased thanks to better treatment, staging, and screening [3]. In the Netherlands the 5-year survival is now around 88% compared to 85% in 2010 [4]. This increased incidence and improved survival have led to a growth in breast cancer survivors. In 2020, the absolute 10-year prevalence of breast cancer was 139,871 among women, as opposed to 108,741 in 2010 [5]. An average Dutch general practice will see two new cases of breast cancer per year and have 20 to 25 breast cancer survivors under their care [6].

Treatment for breast cancer

Initial curative treatment for breast cancer may include surgery, radiotherapy, chemotherapy, and/or targeted therapy. Treatment depends on stage at diagnosis, tumor characteristics, and patient characteristics. Patients with ductal carcinoma in situ or stage I-II invasive breast carcinoma will undergo either breast conserving therapy (e.g., lumpectomy and adjuvant radiotherapy) or mastectomy [7]. Adjuvant systemic therapy may be offered, with chemotherapy and/or hormonal therapy used to target possible spread beyond the breast, substantially reducing the 15-year mortality [8].

Organization of follow-up after treatment

After their initial treatment, women attend regular follow-up visits at hospital. According to several (inter)national guidelines (Nationale Huisartsen Genootschap (NHG), European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), and National Institute for Health and Care Excellence (NICE)), the goal of this follow-up is to check for locoregional recurrence and early contralateral primaries, to provide psychological support, to monitor treatment-related side effects, and to collect data for the evaluation of care [9-13]. At 5 years after diagnosis, most breast cancer survivors will return to the care of their general practitioner (GP) [13].

LONG-TERM PHYSICAL AND PSYCHOLOGICAL EFFECTS OF BREAST CANCER AND ITS TREATMENT

Breast cancer survivors want to know what they may encounter, if their experience is common, and if that experience is related to their age, physical health, or psychological health. A recent survey of 869 breast cancer survivors revealed the four most common questions about long-term effects [14]:

“What long-term effects are most common?”

“Is there something we can do as survivors to reduce the chance of long-term effects?”

“How long will these long-term effects last?”

“Will it ever pass?”

To understand these questions, it is important to realize that effective adjuvant therapies may also have negative physical and psychological effects. Some of these will be short-term, some will persist to the long-term, and some will only appear months to years after treatment ends. For example, anthracyclines have been associated with leukemia and cardiac dysfunction; radiotherapy is associated with numbness, weakness, arm swelling, pain, anxiety, and depression; hormone therapy is associated with menopausal symptoms, weight gain, ovarian failure, and with an increased risk of cerebrovascular events, thromboembolic disease, uterine cancer, and osteoporosis; and other therapies can cause neuropathy, cognitive dysfunction, sexual dysfunction, and fatigue [15-17]. These effects can have a marked impact on quality of life beyond that of the breast cancer itself.

First, we will focus on cardiotoxicity. This has been well evaluated over the first 5 years in the hospital setting, but the long-term effects have not been established (see Box 1).

Box 1. Long-term Cardiovascular Effects

Cancer and its therapy may cause vascular conditions (e.g., atherosclerosis, thrombosis), cardiac structural conditions (e.g., valvular degeneration), and most importantly in terms of late effects, cardiac dysfunction and heart failure [18]. Chemotherapy is known to be cardiotoxic [19]. Anthracycline-induced cardiotoxicity is notable for causing irreversible myocardial damage [20]. Thoracic radiotherapy may cause inflammation and oxidative damage in the coronary arteries, leading to myocardial ischemia and injury [21]. Radiotherapy also increases the risk of cardiotoxicity by anthracyclines [22].

Previous research has emphasized the importance of detecting changes in cardiac function early during therapy as a potential predictor of late cardiotoxicity [23]. The left ventricle ejection fraction on echocardiography has been suggested for this purpose, but it appears that this mainly helps to detect reversible early onset cardiotoxicity during in-hospital follow-up and not late-onset irreversible cardiotoxicity. N-terminal prohormone of brain natriuretic peptide (NT-proBNP) also has a role in the early detection of heart failure.

Cardiac dysfunction induced by chemo- and/or radiotherapy increases morbidity and mortality among cancer survivors [24]. Thus, it is essential to detect cardiac dysfunction as early as possible to prevent further progression. However, these conditions can have a subclinical onset and vague symptoms that can leave them undetected and untreated.

Long-term effects after breast cancer and related treatment are not only physical but also psychological [25], often including depression and anxiety. These are understandable given the stress of cancer (see Box 2).

Box 2. Long-term Psychological Effects

Breast cancer and its treatment have a significant impact on a woman's psychological well-being. In the first 5 years after diagnosis, 48% are diagnosed with depression, anxiety, or both [26]. This is double the prevalence in the general population. During treatment, women often receive support from loved ones, care providers, and the work environment, but after 5 years they are labeled survivors and this support can fade. Due to the lack of research beyond 5 years, the prevalence of long-term depression and/or anxiety is unknown, and these women may receive insufficient long-term support. Depression is the second-leading cause of disease burden [27], but it has very effective treatments.

Existing guidance is weak. For example, the 'Cardiovascular risk management' and 'Anxiety' guidelines do not include a medical history of cancer therapy as a risk factor. However, the 'Depression' guideline does include cancer as a risk factor for developing depressive complaints or depression. If survivors and care providers are aware of the potential for long-term psychological effects, they may be more likely to initiate a conversation or start treatment.

Fatigue is the most common and persistent symptom among breast cancer survivors, but it remains poorly understood (see Box 3). Complaints are monitored during the first 5 years of follow-up, but after this the survivor must usually seek help from her GP.

Box 3. Long-term Fatigue

The prevalence of fatigue among breast cancer survivors varies from 40% to 80% and may arise due to the breast cancer itself, the treatment, or side effects. However, only a third of survivors with fatigue report this to their physician, leaving many undetected and without proper support [28]. This is a major issue because fatigue markedly affects quality of life [29]. Chemotherapy and hormonal therapy, and to a lesser degree radiotherapy, all cause fatigue [30,31]. Fatigue is mainly reported in the short-term after treatment, usually in association with depression, anxiety, functional limitations, or physical complaints such as pain and sleep quality [31-33].

All these long-term effects (Boxes 1-3) can lead to non-specific symptoms, making it hard to identify the underlying pathology (Box 4).

Box 4. Long-term Symptoms

Long-term breast cancer survivors can present with various symptoms. Similar to fatigue, these may be related to the breast cancer, its treatment, or to long-term effects. It is important to know the most prevalent symptoms and their main causes. This can help survivors know what to expect and physicians know what to enquire about. Given that some long-term effects may have vague onsets (e.g., cardiovascular disease), it is also important to know what symptoms are associated with what diagnoses. This knowledge will bring early detection a step closer, with the ultimate goal being to improve treatment and prognostication.

THE ROLE OF GENERAL PRACTITIONERS

In the Netherlands, all inhabitants have a primary care electronic record with a GP, with an insurance that allows anyone to visit the GP free of charge. The GP has a central role in this healthcare system, serving as the gatekeeper to secondary care when patients first present with a health issue: referral only occurs when necessary and they receive details about diagnosis or treatment from medical specialists after consultation and/or treatment. On average, 90% of issues are handled by the GP and the remaining 10% are handled by secondary or tertiary care. In primary care, all contacts are coded by the International Classification for Primary Care (ICPC) and all medication is coded by the Anatomical Therapeutic Chemical (ATC) classification system.

Definitions of long-term effects vary in the literature from the period directly after treatment ends to 1-2 years after treatment or 5 years after a breast cancer diagnosis. We used the longest 5-year period to define effects as long-term, corresponding with the time when survivors are usually referred back to their GP.

Research has revealed increased primary health care use by breast cancer survivors during treatment and follow-up compared to women without breast cancer [34]. GPs have a lot to offer breast cancer survivors given their knowledge of the woman's medical history, comorbidities, and family situation, as well as their integrated approach to care [35]. However, the GP may lose oversight of patient care and the effect of cancer and its treatment when the hospital takes over their care during treatment and follow-up. Some GPs keep a list of patients with cancer, including breast cancer, and contact them on a regular basis, but this is not standard care.

Breast cancer survivors older than 60 years and treated with mastectomy will (re-)enter the National Screening program, while those treated with breast conserving therapy will receive annual physical examination and biennial mammography through their GP [36]. However, no other regular follow-up is offered, despite survivors expressing that it is needed. To know if continued follow-up should be offered as standard care, we must identify the long-term effects that persist to 5 years and beyond and know their prevalence. This information will help to clarify what to advise patients about, as well as when to intervene or refer to secondary care. Reasonable questions that can be asked by a GP include the following:

“What are the long-term effects of breast cancer treatment?”

“How common are these effects?”

“Are they specific to breast cancer survivors or merely due to aging?”

“Can we recognize women at risk of developing specific long-term effects?”

“Is treatment available?”

THIS THESIS

In this thesis, we focus on the physical and psychological long-term effects of breast cancer and its treatments, using the results of the **Breast cancer Long-term Outcome Cardiac Dysfunction (BLOC) study**. The BLOC study investigated the prevalence of different long-term outcomes in women with a history of breast cancer treated with chemotherapy and/or radiotherapy. By including only women at least 5 years after their breast cancer diagnosis, we could focus on the long-term prevalence in the population seen most often by GPs.

The BLOC study included 350 women at least 5 years after their breast cancer diagnosis, recruited by 80 GPs in the north of the Netherlands. We also included 350 women of the same age with no history of cancer at random from the same practices for comparison. Of the 350 breast cancer survivors, 175 were treated with chemotherapy (with or without radiotherapy) and 175 were treated with radiotherapy alone. GPs excluded women who could not attend hospital due to severe physical or psychological issues. All participants completed questionnaires, had a short physical exam, had blood samples taken, and underwent electrocardiography and echocardiography. From the GPs' electronic records, we retrieved all previous diagnoses (ICPC code) and prescriptions (ATC codes). By including breast cancer survivors and women with no history of cancer from the same GP, we hoped to adjust for the coding behaviors of GPs and the socioeconomic statuses of the women.

We aim to demonstrate the long-term physical and psychological consequences of breast cancer and its treatment by answering five core research questions:

1. What are the long-term cardiovascular consequences of having breast cancer? These are specified as systolic cardiac dysfunction, diastolic cardiac dysfunction, diagnosed cardiovascular disease, and NT-proBNP biomarker elevation.
2. What are the long-term cardiovascular consequences of different breast cancer treatments?
3. What are the long-term psychological consequences of breast cancer and its treatment? With focus on (symptoms of) anxiety and depression.

4. What are the long-term consequences of breast cancer and its treatment on fatigue?
5. What are long-term symptoms experienced by breast cancer survivors, and are they associated with cardiac dysfunction, depression, or anxiety?

In **chapter 2**, a systematic review of the literature to evaluate the prevalence of depression and anxiety among long-term breast cancer survivors is presented. The results of the **BLOC study** are then described in the following chapters.

In **chapter 3**, the focus is on long-term cardiovascular effects, with evaluations of systolic cardiac function, diastolic cardiac dysfunction, diagnosed cardiovascular disease, and NT-proBNP biomarker levels. Symptoms are also compared between breast cancer survivors who received chemotherapy (with or without radiotherapy) and those who received radiotherapy alone.

The presence of long-term (severe) symptoms of depression and anxiety are then reported in **chapter 4**, including the possible association with a history of depression or antidepressant use. In **chapter 5**, the focus shifts to long-term fatigue and how this highly common side effect may be associated with systolic cardiac dysfunction, cardiovascular disease, and symptoms of depression or anxiety. In **chapter 6**, a wider variety of long-term symptoms are considered, plus their possible association with systolic cardiac dysfunction, cardiovascular disease, and symptoms of depression or anxiety. Finally, in **chapter 7**, the various strands of this thesis are brought together to consider the implications for practice and research. Specifically, this chapter will discuss the knowledge and awareness of the long-term effects of breast cancer and its treatment experienced by breast cancer survivors.

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Chapter 2

The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: a systematic review

S.W.M.C. Maass, C. Roorda, A.J. Berendsen, P.F.M. Verhaak, G.H. de Bock

Maturitas. 2015 Sep; 82:100-108

ABSTRACT

Objectives: It is unclear whether breast cancer survivors have a higher risk of long-term symptoms of depression or anxiety. The aim of this study was to systematically review the evidence about long-term symptoms of depression and anxiety in breast cancer survivors.

Study design: Systematic review.

Main outcome measures: PubMed, Embase, Cochrane and PsycINFO were searched for studies with at least 100 survivors ≥ 1 year after diagnosis, and which used common questionnaires measuring symptoms of depression or anxiety, by two independent reviewers. The quality was assessed with the NIH 'Quality Assessment Tool' checklist. Prevalence of symptoms of depression and anxiety was compared to time since diagnosis, available control groups and a general female population.

Results: Seventeen articles were included in this review with an average quality score of 57% (range 38-86%). The prevalence of symptoms of depression varied from 9.4% to 66.1% and of anxiety from 17.9% to 33.3%. The results on the depression scale suggested an increase in risk of symptoms of depression for breast cancer survivors at one year after diagnosis, which decreases over the ensuing years. Symptoms of anxiety were not more prevalent among the women with early stage breast cancer.

Conclusions: This review suggests a higher prevalence of symptoms of depression among breast cancer survivors than among the general female population, persistent over more than 5 years after diagnosis. Health care providers should be aware of this. There was no indication for an increased prevalence of symptoms of anxiety among breast cancer survivors.

INTRODUCTION

Breast cancer is the most common cancer in women worldwide [1]. In the Netherlands, the incidence of breast cancer was 198 per 100,000 women in 2014 [2]. In recent years there has been an increase in the incidence of breast cancer because of an aging population [2]. On the other hand, the 5-year-survival for breast cancer has improved [3]. These changes are due to earlier detection and improvements in treatment[4]. Consequently, these developments have resulted in more and more women surviving breast cancer.

This growing group of women is experiencing the late sequelae of breast cancer and its treatment [5]. Among these possible effects are symptoms of depression and anxiety [6]. It is known that symptoms of depression and anxiety impair quality of life. This suffering can be eliminated by treatment, which has been shown to be highly effective [7,8]. However, often a patient may present vague complaints, so the depression or anxiety remains undetected.

Illustrative case

Ms. A. is a 65-year-old married woman with no family history of cancer. Four years ago she was diagnosed with ductal breast cancer after participating in a breast cancer screening program. She was treated with breast conserving therapy, including lumpectomy and adjuvant radiotherapy. She is known to have hypercholesterolemia, cardiac angina and palpitations. She has been a smoker for 50 years. She now visits her new general practitioner, for the first time, with persistent complaints of discomfort. Ms. A. states that in general she can relax and enjoy her life, however, she feels like her enjoyment is less than before. She also worries a lot, but she cannot really say why. These feelings are starting to impair her life and relationship, and she is seeking help. After the consultation the general practitioner thinks she might have a depressive disorder.

Objectives

Little is known about the prevalence of long-term symptoms of depression and anxiety as late effects after breast cancer and its treatment. Studies reporting on these symptoms are often performed during, or right after, treatment [9,10]. The aim of this systematic review was to review systematically the evidence about long-term symptoms of depression and anxiety in breast cancer survivors.

METHODS

Article selection

We systematically searched PubMed, Embase, Cochrane and PsycINFO for combinations of the following search terms: breast cancer, depression or anxiety, survivors and prevalence (See Appendix 1). Articles were included when published before January 10th 2015. Duplicates were removed. To assess the prevalence of symptoms of depression or anxiety in an unselected cohort, only observational studies were included. Further inclusion criteria were original data, adult patients (age ≥ 18), and a study group which comprised at least 100 women treated for breast cancer with curative intent, diagnosed more than one year previously. Only studies with at least one of the four most frequently used questionnaires (see Section 2.2) for symptoms of depression or anxiety were included. Excluded were studies which comprised patients with breast cancer recurrence, mixed cancer studies with no separate breast cancer data, and selected (e.g. only elderly) patient groups. Two investigators (SM and CR) independently reviewed each article. Discrepancies were discussed by the two researchers, and when necessary, with a third reviewer (PV).

Measures

Center for Epidemiological Studies Depression Scale (CES-D)

This scale is a 20-item, self-report measure for depressive symptomatology [11]. The total score range is 0-60. A score of 10 or greater indicates symptoms of depression; 16 or higher indicates severe symptoms of depression. For the 10-item CES-D, a score higher than 10 indicates severe symptoms of depression [12]. According to Ochs-Balcom et al. the mean score in an American, general female population is 7.5; the percentages for symptoms of depression and severe symptoms of depression were 24.2% and 13.8%, respectively [13].

Beck Depression Inventory (BDI)

This inventory has 21 items and measures the severity of depression. This is also a self-report scale. The range is from 0 to 63. The classification of the total score is as follows: <10, none or minimal depression; 10-18, mild to moderate symptoms of depression; 19-29, moderate to severe depression; and 30-63, severe depression [14]. Koivumaa-Honkanen et al. found a mean score of 5.1 for a European, general female population; 16.3% of the woman had symptoms of depression and 2.7% severe symptoms of depression [15].

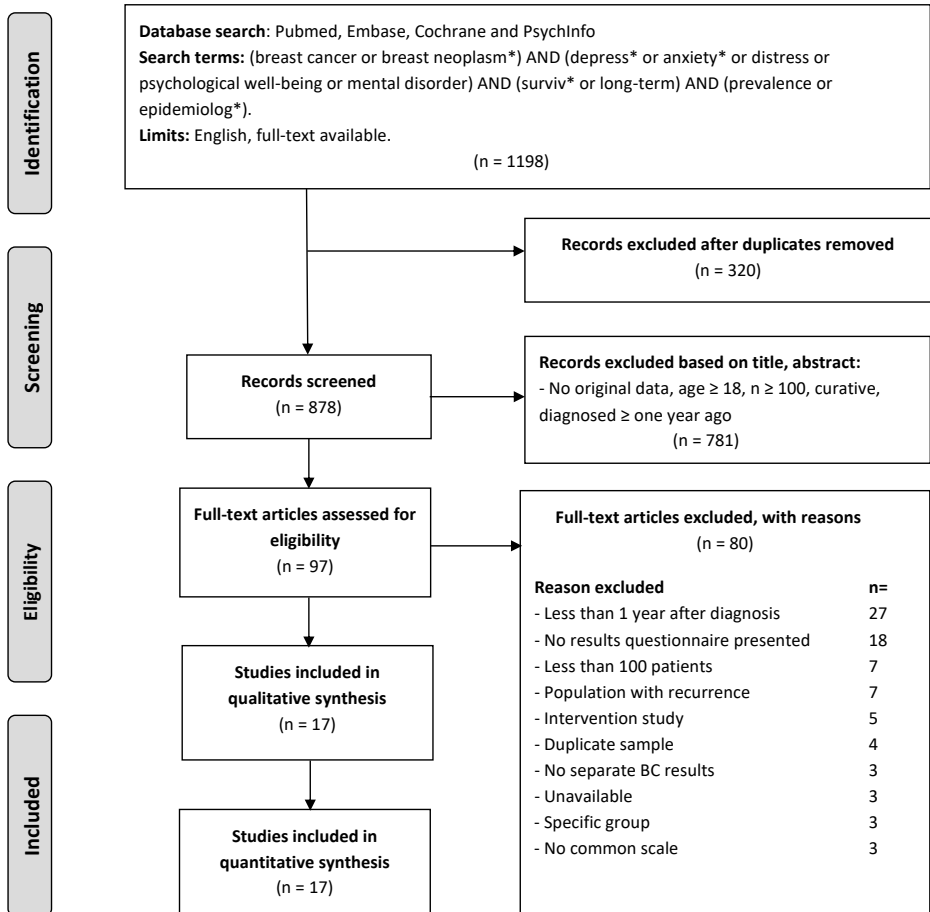


Figure 1.1. Flow diagram of the article search and selection process.

Hospital Anxiety and Depression Scale (HADS)

The HADS is a 14-item, self-report scale for symptoms of depression and anxiety, HADS-D and HADS-A, respectively [16]. The score may range between 0 and 21 per subscale. The scale distinguishes between mild symptoms (≥ 8) and severe symptoms (≥ 11) of depression or anxiety. Crawford et al. found a mean score of 3.7 and 6.1 for the HADS-D and HADS-A, respectively, in a European, general female population [17]. The percentages for the HADS-D were 10.7% for symptoms of depression and 2.9% for severe symptoms of depression. For the HADS-A, these percentages were 30.6% and 10.0%, respectively.

Table 1. Characteristics of the included breast cancer survivors (n = 10,522); controls (n=1,977); and studies (n=17). ^a

| First author year country [ref] | Ethnicity % | Age, years Mean(SD) ^b | Tumor stage % |
|--|--|---|---|
| Bower JE 2000 US [30] | White 79.5% Black 11.9% Other 8.6% | 55.0(-) | - |
| Chen X 2010 US [23] | - | 53.7(9.8) | 0-I 40.7% IIA 32.6% IIB 13.2% III 8.7% Unknown 4.7% |
| Christie KM 2010 US [31] | Hispanic 62.8% Non-Hispanic White 37.2% | 50.9(9.5) | 0 8.9% I 26.2% II 42.5% III 19.5% IV 3.1% |
| Claus EB 2006 US [20] | White 92.3% Black 5.3% Other 1.2% | 55.8(10.5) Controls 55.0(11.7) | DCIS 87.6% LCIS 12.4% |
| Crespi CM 2008 US [32] | White 83% Asian 5% Hispanic 5% Black 3% Other 4% | 66.3(10.1) | - |
| Dahl CAF 2010 NO [26] | - | 51.0(8.3) | II 86.7% III 12.1% |
| De Vries J 2013 NL [35] | - | 56.6 (11.4) | - |
| Den Oudsten BL 2009 NL [47] | - | 58.7(9.4) | 0 10.8% I 41.7% IIA 30.9% IIB 15.7% Unknown 0.9% |

| Treatment % | Study design | Questionnaire | NIH % |
|---|---------------------|----------------------|--------------|
| Surgery 99.8% Chemotherapy 40.8% Radiotherapy 59.4% Hormone therapy 47.7% | Cross-sectional | CES-D | 54 |
| Mastectomy 94.3% Chemotherapy 90.9% Radiotherapy 32.0% Immunotherapy 15.9% | Cohort | CES-D | 54 |
| Surgery 100% Chemotherapy 71.5% Radiotherapy 72.1% Hormone therapy 66.3% | Cohort | 10-item CES-D | 71 |
| - | Case-control | CES-D | 71 |
| Surgery 100% Chemotherapy 57% Hormone therapy 79% | Cohort | CES-D | 54 |
| Surgery 100% Chemotherapy 80% Radiotherapy 100% Hormone therapy 87.5% | Cross-sectional | HADS | 86 |
| - | Cross-sectional | STAI | 46 |
| Surgery 100% Adjuvant therapy 75.8% | Cohort | CES-D | 79 |

Table 1. Continued. ^a

| First author year country [ref] | Ethnicity % | Age, years Mean(SD) ^b | Tumor stage % |
|--|--|---|---|
| Ganz PA 1998 US [33] | White 77.4% African American 14.0% Other 8.6% | 55.8(-) | - |
| Härtl K 2010 DE [34] | - | 58.7(10.7) | Breast cancer 91.1% DCIS 8.9% |
| Hodgkinson K 2007 AU [27] | - | 61(14) | - |
| Karakoyun-Celik O 2010 TR [24] | - | 54.3(28.3) | - |
| Kim SH 2008 KR [25] | - | 47.4(9.5) | 0 7.9% I 34.3% II 48.8% III 8.9% |
| Klein D 2011 FR [21] | - | 64.1(-) Controls 63.3(-) | 0-I 51.2% II 22.9% III-IV 4.0% Unknown 19.3% |
| Robb C 2007 GR [22] | - | 78.2(5.0) Controls 77.6(5.0) | - |
| Tan X- 2014 CN [28] | - | 53.8(15.2) | I 18.3% II 67.8% III 13.9% |
| Thompson J 2013 UK [29] | - | 63.7(11.4) | I-II 47.9% III 36.3% |

^a National Institutes of Health - Quality Assessment Tool score (NIH); Center for Epidemiological Studies Depression Scale (CES-D), Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale - Depression (HADS-D), Hospital Anxiety and Depression Scale - Anxiety (HADS-A), State-Trait Anxiety Inventory (STAI)

| Treatment % | Study design | Questionnaire | NIH % |
|--|---------------------|----------------------|--------------|
| Surgery 100% Chemotherapy 37.9% Hormone therapy 55.8% | Cross-sectional | CES-D | 38 |
| Surgery 100% Chemotherapy 28.8% Radiotherapy 80.1% Hormone therapy 80.4% | Cohort | HADS | 57 |
| Surgery 90.8 Chemotherapy 47.9% Radiotherapy 96.6% Hormone therapy 62.2% | Cross-sectional | HADS | 54 |
| - | Cross-sectional | BDI STAI | 46 |
| Surgery 96.1% Chemotherapy 55.9% Radiotherapy 37.9% | Cross-sectional | BDI | 46 |
| Surgery 99.5% Chemotherapy 44.6% Radiotherapy 80.8% Hormone therapy 66.3% | Case-Control | STAI | 54 |
| Surgery 96.8% Chemotherapy 17.3% Radiotherapy 65.4% Hormone therapy 27.6 | Cross-sectional | STAI | 46 |
| Surgery 100% Chemotherapy 69.4% Radiotherapy 29.4% | Cross-sectional | HADS | 54 |
| Surgery 99.8% Chemotherapy 50.7% | Cross-sectional | HADS | 54 |

^bIf only the median and range were provided, we estimated the mean from the median, range and sample size.[48]

State-Trait Anxiety Inventory (STAI)

The STAI consists of a state anxiety scale and a trait anxiety scale; both have 20 items. The sum score has a range from 20-80. A total score over 60 suggests a severe anxiety [18]. The 'Manual for the State-Trait Anxiety Inventory: STAI' by Spielberger et al. provides a mean score of 35.2 for the state anxiety scale and a mean score of 34.8 for the trait scale for an American, general female population [18]. To the best of our knowledge, there are no percentages of symptoms of anxiety reported for the general female population, measured with the STAI.

Methodological quality

The reviewers independently assessed the methodological quality of the articles by applying the 14 items of the NIH's 'Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies' [19]. The summary score of each study was calculated, expressed as a percentage, and could range from 0% to 100%. These were categorized into four categories: poor (0-25%), fair (25-50%), good (50-75%) or excellent (75-100%). Based on these categories, we evaluated if studies with lower quality had substantially different scores.

Data analysis

The characteristics of the study, the demographic and clinical background of the women, as well as the outcomes on the symptoms of depression and anxiety scales were summarized. Follow-up time was expressed as mean time since diagnosis. Outcomes on symptoms of depression and anxiety were provided as a mean score, or as a percentage of women with a score above the different cut-off values. Two types of cut-off values were applied. First, women with symptoms of depression or anxiety were considered as having an increased score when the scores were: CES-D ≥ 10 , BDI ≥ 10 , HADS-D or HADS-A ≥ 8 . Second, women were considered as having severe symptoms of depression or anxiety when: CES-D ≥ 16 , BDI ≥ 19 , HADS-D or HADS-A ≥ 11 , STAI ≥ 60 . To provide an overview of the symptoms of depression and anxiety over time, the study outcomes were plotted against the time since diagnosis. Outliers were identified and evaluated in relation to patient characteristics, applied questionnaires and cut-off values, sample size and the study quality. Next, the reported prevalence's were compared to those of the control group if available, or a general female population.

RESULTS

Participant and study characteristics

The search and selection process is summarized in Fig. 1. The database search generated a total of 1198 citations. The full text of 97 articles was reviewed. In total, 17 articles were included in the review. The 17 studies included data on 12,499 women, as shown in Table 1. The mean age of the women was 54.2 years (SD 16.0). The various studies had fairly similar patient groups. The mean time since diagnosis was 3.9 years (SD 2.6). Included were 10 cross-sectional studies, five cohort studies and two case-control studies. There were three studies with a control group of women without breast cancer, one study evaluated symptoms of depression, and two studies evaluated symptoms of anxiety [20-22]. Of the 17 studies, eight studies measured symptoms of depression, four studies measured symptoms of anxiety, and five studies measured both. The CES-D was applied seven times in the included studies, the BDI two times, the HADS five times, and the STAI four times. The results per questionnaire are shown in Table 2.

Methodological quality

The mean score on the NIH Quality Assessment Scale was 57% (range 38-86%). There were no studies with poor quality; five studies had fair quality; ten studies had good quality; and two studies had excellent quality (See Table 1).

Symptoms of depression

Prevalence

The percentage of women suffering from depression, ranged from 9.4% to 66.1%, with an overall percentage of 39.9% [23-29]. For severe symptoms of depression the outcomes varied from 3.0% to 41.7%, with an overall percentage of 21.2% [23,25,27,29-33].

Mean scores on the depression scales

The mean score on the CES-D was high in comparison to the general female population about one year after diagnosis, and seemed to normalize over time, see Fig. 2 (left). In one good quality study, women with a history of breast cancer were compared to women without breast cancer regarding the mean scores of depression as measured with the CES-D [20]. A statistically significant, higher mean score was found on the depression scale among women with breast cancer in comparison to their control group (8.3 versus 7.2), with a mean time of 5.6 years after diagnosis [20].

Table 2. An overview of the outcomes, per questionnaire. ^a

| First author | Time since diagnosis, years ^{b,c,d} | Scores | |
|---|--|--------|-----------|
| | mean | n | mean(SD) |
| Center for Epidemiological Studies Depression Scale (CES-D) | | | |
| Bower | 3.0 | 1957 | 10.7(9.6) |
| Chen | 1.5 | | |
| Christie ^e | 1.5 | 677 | 14.9(0.6) |
| Claus | 5.8 | 795 | 8.3(0.6) |
| Crespi | 7.4 | 1188 | 7.7(7.7) |
| Den Oudsten | 1.5 | 164 | 10.3(8.4) |
| Ganz | 3.0 | 864 | 10.3(9.4) |
| Combined | | 5,645 | 10.2(8.0) |
| Beck Depression Inventory (BDI) | | | |
| Karakoyun | 5.8 | | |
| Kim | 5.1 | 1491 | 14.0(8.4) |
| Combined | | | |
| Hospital Anxiety and Depression Scale - Depression (HADS-D) | | | |
| Dahl | 4.1 | | |
| Hodgekinson | 3.9 | | |
| Thompson | 4.6 | 168 | 3.7(3.3) |
| Tan | 2.1 | | |
| Combined | | | |
| Hospital Anxiety and Depression Scale - Anxiety (HADS-A) | | | |
| Dahl | 4.1 | | |
| Hartl | 3.0 | 236 | 6.6(3.9) |
| Hodgekinson | 3.9 | | |
| Tan | 2.1 | | |
| Thompson | 4.6 | 168 | 6.1(4.3) |
| Combined | | 404 | 6.0(3.4) |
| State-Trait Anxiety Inventory (STAI) | | | |
| De Vries | 4.5 | 139 | 35.4(9.1) |
| Karakoyun | 5.8 | | |
| Klein | 10.0 | 652 | 34.2(0.6) |
| Robb | 3.6 | 127 | 16.5(5.0) |
| Combined | | 918 | 31.7(7.4) |

^a Center for Epidemiological Studies Depression Scale (CES-D), Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale - Depression (HADS-D), Hospital Anxiety and Depression Scale - Anxiety (HADS-A), State-Trait Anxiety Inventory (STAI)

^b The mean time after treatment was made comparable to the mean time after diagnosis by adding one year.

^c Time since diagnosis for studies describing time since diagnosis as '≥ x', the mean value was estimated by adding the calculated overall SD for time since diagnosis (2.6).

| Symptoms of | | Severe symptoms of | |
|--------------------|------------|---------------------------|------------|
| total(n) | n(%) | total(n) | n(%) |
| CES-D ≥ 10 | | CES-D ≥ 16 | |
| 1399 | 363(26.0) | 1957 | 484(24.7) |
| | | 1399 | 176(12.6) |
| | | 677 | 282(41.7) |
| | | 1188 | 144(12.1) |
| | | 864 | 198(23.1) |
| | | 6,085 | 1278(21.0) |
| BDI ≥ 10 | | BDI ≥ 19 | |
| 120 | 43(35.8) | | |
| 1491 | 985(66.1) | 1491 | 372(24.9) |
| 1611 | 1028(63.8) | | |
| HADS-D ≥ 8 | | HADS-D ≥ 11 | |
| 248 | 29(11.8) | | |
| 117 | 11(9.4) | 117 | 6(5.1) |
| 168 | 23(13.7) | 168 | 5(3.0) |
| 180 | 30(16.7) | | |
| 713 | 93(13.0) | 285 | 11(3.9) |
| HADS-A ≥ 8 | | HADS-A ≥ 11 | |
| 248 | 79(31.9) | | |
| 117 | 21(18.0) | 117 | 11(9.4) |
| 180 | 38(21.1) | | |
| 168 | 56(33.3) | 168 | 17(10.1) |
| 713 | 194(27.2) | 285 | 28(19.2) |
| | | STAI ≥ 60 | |
| | | 120 | 23(19.2) |

^d If only the median and range were provided, we estimated the mean from the median, range and sample size. [48]

^e Since the cut-off of the CES-D is 1.6 times higher than the cut-off value of the 10-item CES-D, the mean score in for the CES-D was estimated by multiplying the mean score on the 10-item CES-D by 1.6. Their comparability was established by Zhang et al. [12]

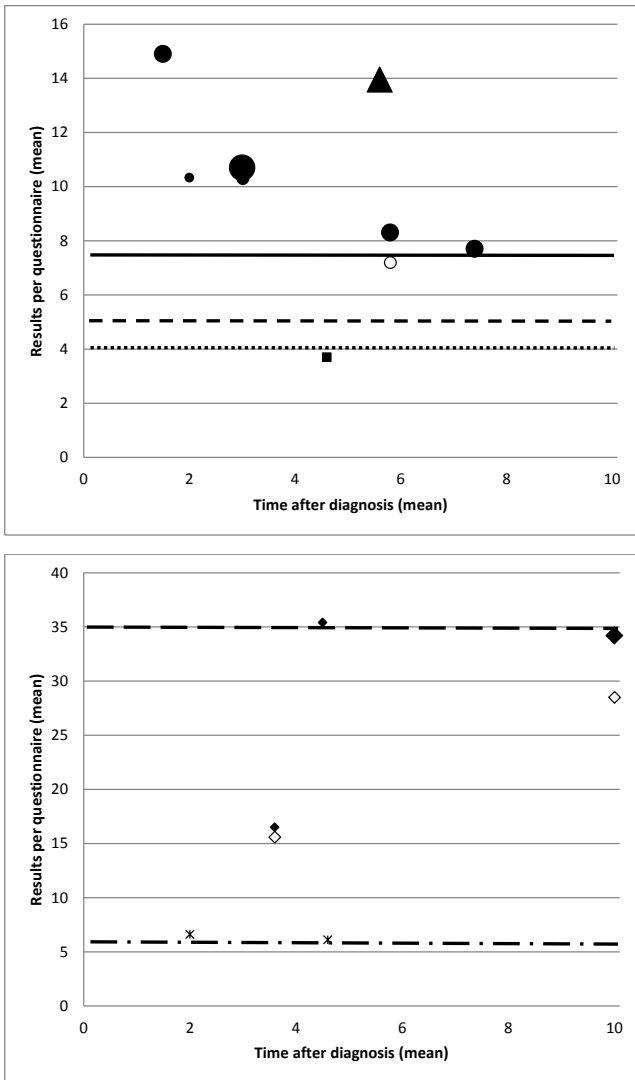


Figure 2. Mean scores on the depression (left) or anxiety (right) scales from the included studies versus time since breast cancer diagnosis, where available a control population, and a general female population.

Legend: ● CES-D, ○ CES-D control group, — CES-D general female population, ▲BDI, - - - BDI general female population, ■ HADS-D, ···· HADS-D general female population, ✕ HADS-A, - · - · HADS-A general female population, ◆ STAI, ◇ STAI control group, = = STAI general female population.

The size of the marker is dependent on sample size: ● n=100-650 women, ● n=650-1300 women, ● n=1300+ women; ▲ n=100-650 women, ▲ n=650-1300 women, ▲ n=1300+ women; ■ n=100-650 women, ■ n=650-1300 women, ■ n=1300+ women; ✕ n=100-650 women, ✕ n=650-1300 women, ✕ n=1300+ women; ◆ n=100-650 women, ◆ n=650-1300 women, ◆ n=1300+ women.

Proportions of women with symptoms of depression

The percentage of women with increased scores for symptoms of depression is shown in Fig. 3(1). There was no change over time since diagnosis for the proportion of women with symptoms or severe symptoms of depression in any questionnaire. Compared to results from the general female population, the results to the general female population, the percentage of women with symptoms of depression was higher for all studies using the CES-D and BDI scale [23-25]; however, for the HADS-D scale they were equal to the general female population [26-29]. For women treated for breast cancer compared to the general female population, the percentage of women with severe symptoms of depression was higher in four studies and equal in four studies [23,25,27,29-33].

Symptoms of anxiety*Prevalence*

For the five studies measuring the percentage of patients with symptoms of anxiety, the prevalence ranged from 17.9% to 33.3%, with an overall percentage of 27.2% [26-29]. The prevalence of severe symptoms of anxiety, the range was 9.4% to 19.2%, with an overall percentage of 12.6% [24,27,29].

Mean scores on the anxiety scales

There was no visual trend in a comparison of the mean score on the anxiety scales with the time since diagnosis, as can be seen in Fig. 2 (right). In four studies of the mean scores of the general female population the scores were equal to women more than one year after diagnosis [21,29,34,35]. One, fair quality, study found lower scores for breast cancer survivors in comparison to the general female population [22]. Two studies compared the mean scores to a control group, both using the STAI score [21,22]. Klein et al. found, for their control group, a mean score on the anxiety scale lower than in the general female population [21].

Proportions of women with symptoms of anxiety

The percentage of women with symptoms of anxiety is shown in Fig. 3(2). There was no change for the percentage of women with symptoms of anxiety or for the percentage of women with severe symptoms of anxiety. Compared to the general female population, the proportion of breast cancer survivors with symptoms of anxiety, as measured by the HADS-A, was either the same in the study group as in the general female population, or even lower.

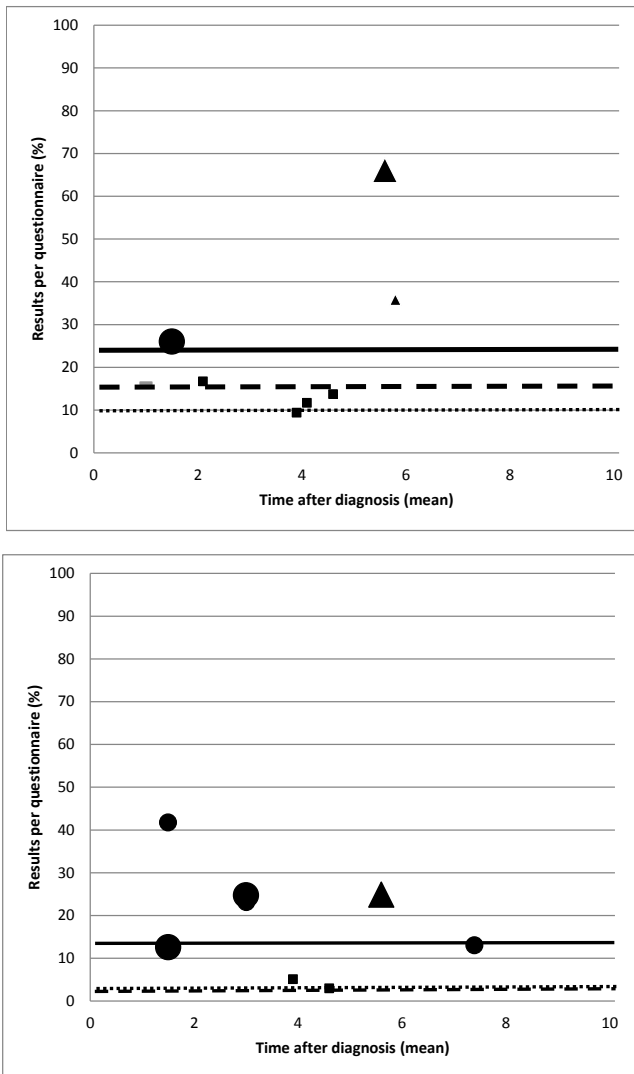


Figure 3.1. The percentage of women in the different studies with symptoms of depression (left) or severe symptoms of depression (right) found by the included studies versus the mean time since diagnosis, a control group if available, and a general female population.

Legend^a: ● CES-D, ○ CES-D control group, — CES-D general female population, ▲ BDI, - - BDI general female population, ■ HADS-D, HADS-D general female population. The size of the marker is dependent on sample size: ● n=100-650 women, ● n=650-1300 women, ● n=1300+ women; ▲ n=100-650 women, ▲ n=650-1300 women, ▲ n=1300+ women; ■ n=100-650 women, ■ n=650-1300 women, ■ n=1300+ women.

^a Center for Epidemiological Studies Depression Scale (CES-D), Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale - Depression (HADS-D).

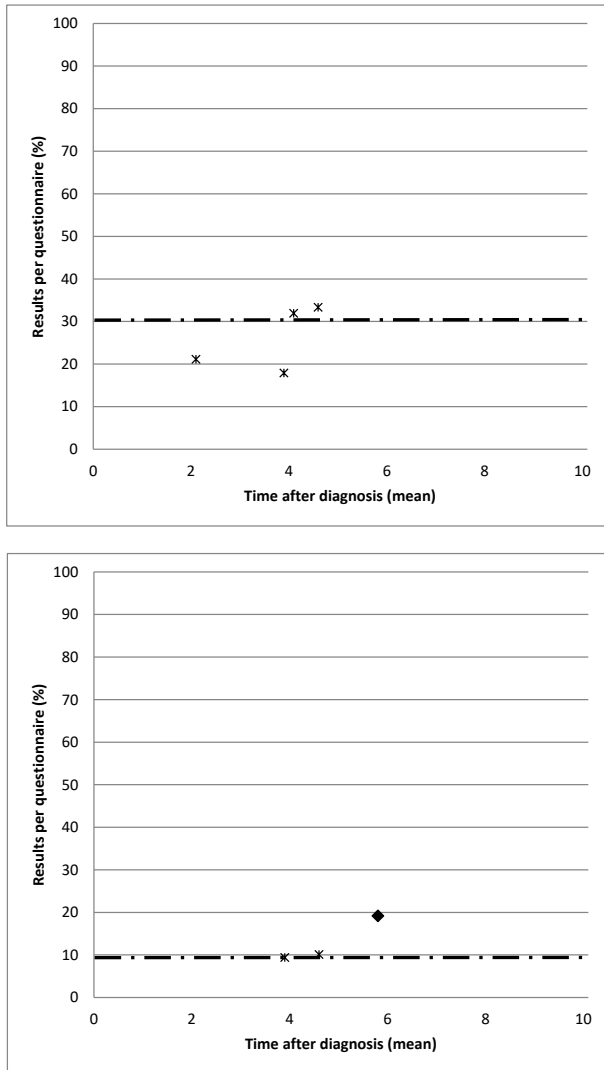


Figure 3.2. The percentage of women in the different studies with symptoms of anxiety (left) or severe symptoms of anxiety (right) found by the included studies versus the mean time since diagnosis, a control group if available, and a general female population.

Legend a: ✕ HADS-A, ■ ■ ■ HADS-A general female population, STAI, STAI control group, ■ ■ ■ STAI general female population (not available). The size of the marker is dependent on sample size: ✕ n=100-650 women, ✕ n=650-1300 women, ✕ n=1300+ women ◆ n=100-650 women, ◆ n=650-1300 women, ◆ n=1300+ women.

^a Hospital Anxiety and Depression Scale - Anxiety (HADS-A), State-Trait Anxiety Inventory (STAI).

DISCUSSION

Summary

Among the included studies, there was a wide range in prevalence of both long-term symptoms of depression and anxiety in breast cancer survivors. The combined outcomes measured with the CES-D suggest an increase in symptoms of depression one year after diagnosis, which diminishes over time. Furthermore, higher percentages of women with symptoms of depression were found for breast cancer survivors when measuring with the CES-D or BDI scale, while with the HADS-D scale, the outcomes were equal to those in the general female population. Breast cancer survivors did not appear to have more symptoms of anxiety.

Results in relation to other results

Our findings regarding the large variation in the estimates for the prevalence of depression are supported by a recent systematic review by Zainal et al., who also found a great variance in reported prevalence of depression in breast cancer patients [9]. However, their range of 1-56% prevalence of depression was wider than we found (3.0-41.7%). In Zainal's review, the three studies with the highest prevalence also included patients in their first year after diagnosis [36-38]. It is known that the prevalence of depression is high during the first year after breast cancer diagnosis [39]. Though their results also suggested a higher risk for depression for patients with a history of breast cancer, they did not distinguish between severity level (symptoms or diagnosis of depression). They also included other measurement methods (clinical interviews); which made a detailed comparison difficult.

Notably, all studies which used the CES-D combined presented a decreasing trend of symptoms of depression with breast cancer survivors. All these studies, as well as the study concerning the reference data from the general female population, were from the United States, which makes the data in principle comparable. This decreasing trend of symptoms of depression over the first eight years is similar to results reported by Deshields et al. and Hsiao et al. about the first two years after diagnosis [40,41]. A previous study described a similar positive effect of a longer time since diagnosis on psychological wellbeing [42]. Similarly Helgeson et al. examined the adjustment-process for breast cancer survivors, over the first four years, and also found improvement over time [43].

A possible explanation for the difference in outcomes between the different depression scales is provided by Cusin et al. [44]. They indicate that only the HADS is suitable for measuring depression in patients known with a medical illness; other measures might overestimate the symptoms of depression since they do not exclude somatic questions

[44]. However, there is no consensus on this topic; Hann et al. evaluated the CES-D in a breast cancer population and concluded that the CES-D is a valid and reliable measure for symptoms of depression in breast cancer survivors [45]. In a similar vein, Osborne et al. investigated the value of the HADS in breast cancer survivors, and could only find minor psychometric problems [46].

The results suggested that there was no increased prevalence of symptoms of anxiety for breast cancer survivors in comparison to the general female population. One of these studies did find a significant increase in the mean score on the STAI in comparison to their control group [21]. However, the control group was healthier than the general female population, which might be explained by the significantly lower age in the control group.

Limitations and strengths

The results showed a wide variation, even though the included studies represented a homogenous patient population, with large sized studies. A strength and a limitation to our study was the variance in the outcome measures for depression as well as for anxiety. By including different questionnaires, even though all validated, we might have compared different definitions of symptoms of depression or anxiety. This was also illustrated by the different values of the general female populations. Also, some studies presented their results with mean scores, where others presented proportions. Especially mean scores of different instruments are difficult to compare between different studies.

Conclusion and clinical perspective

The results of our review suggest that women with early staged breast cancer have a higher risk on long-term symptoms of depression than the general female population, persistent over more than 5 years after diagnosis. This increased risk seems to normalize over time. In this review we found no increased prevalence of symptoms of anxiety for breast cancer survivors. Considering the results of this review, the general practitioner in the aforementioned case, should consider that Ms. A. may have an increased risk of symptoms of depression. Since the impact of breast cancer can still be effective, many years after diagnosis, we recommend health care providers to discuss this possible relation with their patients and offer additional guidance and support.

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APPENDIX 1

Search Pubmed 10-01-2015:

Search ("Breast Neoplasms"[Mesh] OR breast cancer*[tw] OR breast neoplasm*[tw]) AND ("Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR "Anxiety"[Mesh] OR "Anxiety Disorders"[Mesh] OR "Mental Disorders"[Mesh] OR depress*[tw] OR dysthym*[tw] OR anxiety*[tw] OR distress*[tw] OR Mental Disorder*[tw]) AND ("Survivors"[Mesh] OR surviv*[tw] OR long term*[tw] OR longterm*[tw]) AND ("Prevalence"[Mesh] OR "epidemiology"[Subheading] OR "Epidemiologic Studies"[Mesh] OR "Observational Study"[Publication Type] OR prevalen*[tw] OR epidemiolog*[tw] OR cohort*[tw] OR cross sectional[tw] OR case control[tw]) Filters: Full text; English



Chapter 3

Long-term outcome of cardiac function in a population-based cohort of early breast cancer survivors: a cross-sectional study

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ABSTRACT

Background: Chemotherapy and radiotherapy for breast cancer may lead to cardiac dysfunction, but the prevalence of long-term echocardiographic evidence of cardiac dysfunction is unknown among survivors.

Methods: In a cross-sectional study in primary care, we included 350 women who survived breast cancer for at least 5 years after diagnosis (treated with chemotherapy and/or radiotherapy) and 350 matched women (age and primary care physician). The primary outcome was cardiac dysfunction, defined as a left ventricular ejection fraction (LVEF) < 54% and an age-corrected decreased left ventricular (LV) diastolic function. Secondary outcomes included serum N-terminal pro B-type natriuretic peptide (NT-proBNP) levels, newly diagnosed cardiovascular diseases and cardiovascular medication.

Results: The median age at diagnosis was 63 (interquartile range (IQR) 57-68) years for the breast cancer survivors. Median follow-up after diagnosis was 10 (IQR 7-14) years. LVEF < 54% was present in 52 (15.3%) survivors and 24 (7%) controls (OR 2.4, 95%CI 1.4-4.0), but there was no significant increased prevalence of either LVEF < 50% or LV diastolic dysfunction. Serum NT-proBNP levels were increased, cardiovascular disease was more frequently diagnosed and cardiovascular medication use was more frequent among survivors compared with controls. These associations remained after adjustment for relevant covariates at diagnosis and follow-up.

Conclusions: In the long term, breast cancer survivors are at increased risk of mild LV systolic dysfunction, increased NT-proBNP levels, and cardiovascular disease compared with matched controls, even after adjustment for cardiovascular risk factors. Previous breast cancer treatment with chemotherapy, radiotherapy or both should be considered when assessing a patient's cardiovascular risk profile.

INTRODUCTION

Breast cancer is the most common cancer among women, with approximately 0.5 million women affected annually in Europe [1,2]. Courtesy of screening programs and advances in cancer treatment, the 5-year overall survival rates have increased to 82% [3]. Although adjuvant therapies like anthracycline-based chemotherapy, trastuzumab, and radiotherapy are very effective, they may cause cardiac dysfunction decades after treatment [4]. This late cardiac dysfunction can remain subclinical because of its gradual onset and presentation with vague symptoms.

Since the prevalence of subclinical cardiac dysfunction is unknown among long-term survivors of breast cancer, and no interventions have been established to manage it, there are no specific follow-up recommendations. Timely diagnosis of cardiac dysfunction is important because early treatment of associated risk factors may prevent further deterioration and improve prognosis [5].

Previous long-term studies among adult female breast cancer survivors have focused on the frequency of only diagnosed cardiac dysfunction, which may have underestimated the prevalence of cardiac dysfunction [4,6-10]. By contrast, studies in selected hospital populations may have overestimated the prevalence of cardiac dysfunction in these women [11-14]. This is exacerbated by the lack of controlled long-term studies assessing the incidence of undiagnosed cardiac dysfunction in adult female breast cancer survivors with echocardiographic data in non-hospital settings [15].

Therefore, we assessed the prevalence of long-term echocardiographic-based cardiac dysfunction among breast cancer survivors treated with chemotherapy (with or without radiotherapy) or radiotherapy only, and compared that with the prevalence of cardiac dysfunction among matched controls in a primary care setting.

METHODS

Study design

We performed a cross-sectional, population-based study to assess the frequency of cardiac dysfunction in a primary care setting. All inhabitants of the Netherlands are enlisted in an electronic record of a primary care physician (PCP), who registers everything according to International Classification of Primary Care (ICPC) [16] and Anatomical Therapeutic Chemical (ATC) classification codes [17].

Relevant data were retrieved from patients' medical records at primary care practices and were entered into a separate, anonymous, password-protected database. In practices contributing to data registries, we were able to retrieve information from non-respondents. The medical ethics committee of the University Medical Center Groningen (UMCG) approved this study, and all participants gave written informed consent. The study was also registered at clinicaltrials.gov [ID:NCT01904331].

Participants

Women were considered breast cancer survivors if they were diagnosed with breast cancer stage I-III, had been free of disease for at least 5 years, and were included from the electronic patient records of 80 PCPs in the north of the Netherlands. When women had been diagnosed with a local/locoregional recurrence of breast cancer, they were included if they had been free of disease for at least 5 years. The inclusion criteria were treatment for breast cancer with chemotherapy, radiotherapy or both. The exclusion criteria were metastatic disease at time of breast cancer diagnosis, breast cancer treatment after 80 years of age, and treatment for other types of cancer. For each included survivor, a randomly selected control was invited from the same PCP, from the same age (± 1 year), but without a history of cancer or cancer treatment (chemotherapy or radiotherapy). We excluded women with severe mental or physical illness from both groups when they were not able to come to the university hospital according to their PCP. Compliance with the inclusion and exclusion criteria was checked using the electronic patient records and checked with the PCP.

Assessments and procedures

For all women, we collected data based on the ICPC codes for cardiovascular (CV) risk factors and cardiovascular disease (CVD), and used the ATC prescription codes for CV medications (Box A.1). Hospital charts from breast cancer survivors were reviewed for detailed information on breast cancer treatment, including administered chemotherapy regimens, cumulative dosages, antihormone treatments, and radiotherapy site. In general, radiotherapy in the Netherlands consisted of Linac-based photon tangential fields up to a dose of 50 Gy with or without a boost [18].

We performed the following procedures at a cross-sectional follow-up assessment. Echocardiography was performed by experienced UMCG staff, using a VIVID E9 ultrasound machine (GE, Horten, Norway) according to the guidelines of the European Association of Echocardiography [19,20]. A prespecified imaging protocol was used and images were digitally stored. We also performed electrocardiography (ECG) and obtained plasma in lithium-heparin stored at -80 °C for batch analysis of N-terminal pro B-type natriuretic peptide (NT-proBNP). Finally, we assessed body mass index

(BMI) by measuring weight and length, smoking status (self-reported), and responses to the Short Questionnaire to Assess Health-Enhancing Physical Activity (SQUASH) for all participants [21].

Study end-points

The primary outcomes were left ventricular (LV) systolic and diastolic dysfunction. LV systolic cardiac dysfunction was defined as a LV ejection fraction (LVEF) $<54\%$ according to the European Association for Cardio Vascular Imaging/American Society of Echocardiography (EACVI/ASE), measured by the biplane method of disks summation (modified Simpson's rule) [19]. If image quality was too low to detect the endocardial border reliably, an estimation of the LVEF was given. LV diastolic cardiac dysfunction was defined as e' lateral or e' septal at 2.5% below the normal range for each age group, according to the EACVI/ASE recommendations. When impaired relaxation was present with an increased left atrial volume index (LAVI; defined as 34 ml/m^2), LV diastolic dysfunction was considered severe [20].

The main secondary outcomes were: clinically used LVEF cut-off points $<45\%$ and $<50\%$, right ventricular systolic dysfunction, valve dysfunction (at least grade II/ III insufficiency of any valve), any ECG abnormality and increased NT-proBNP ($>125 \text{ pg/ml}$) [22]. Right ventricular (RV) systolic function was measured through the tricuspid annular plane systolic excursion ($<17 \text{ mm}$) and tricuspid lateral annular systolic velocity wave ($<9.5 \text{ cm/s}$) by Doppler imaging [19]. Other secondary outcomes were newly diagnosed CVD and CV medication.

Power analysis

In the primary comparison, breast cancer survivors were compared with controls. Based on an event rate of 25% for cardiac dysfunction [23-25], a 5% type I error rate, a 20% type II error rate, and an anticipated difference of 6.25% (odds ratio [OR] 2.25) between survivors and controls in the proportion of cases with cardiac dysfunction, we calculated a sample size of 350 participants per group.

Statistics

Baseline characteristics were described at the date of diagnosis or at the corresponding index date for the matched controls. Age and follow-up period were reported as medians and IQR. Information on diagnosis and treatment was presented for survivors.

Besides comparing all survivors with all controls on all outcomes, we also specifically compared the chemotherapy with or without radiotherapy group with the chemotherapy control group and the radiotherapy only group with the radiotherapy control group. Logistic

regression analysis was used to compare the prevalence of long-term cardiac dysfunction and secondary outcomes between survivors and controls by estimating ORs and their 95% confidence intervals (95% CIs). To evaluate whether the association between breast cancer treatment and the prevalence of long-term cardiac dysfunction was confounded by risk factors, multivariable logistic regression was performed to give an adjusted OR for LV dysfunction, increased NT-proBNP and the occurrence of CVD after breast cancer diagnosis. We adjusted for baseline characteristics (model 1) and for characteristics at the time of echocardiography (model 2). The effect of higher-dose anthracycline therapy (e.g. doxorubicin dose > 240 mg/m² or epirubicin dose > 450 mg/m²) compared with low-dose therapy, and the effect of left-sided radiotherapy compared with right-sided therapy, were also analysed. Finally, we compared the ages and CVD diagnoses of participants and non-participants from PCPs that contributed to data registries. To evaluate the impact of potential selection bias on the prevalence of diagnosed CVD, a sensitivity analysis was performed including all eligible women who were invited. All analyses were performed with IBM SPSS, Version 23.

RESULTS

Among 741 breast cancer survivors considered eligible by 80 participating PCPs, 668 were approached for inclusion (Fig. 1). There were 22 women with a local/ locoregional recurrence in our sample. The median year of diagnosis was 2004 (IQR 2000-2007). Compared with non-participants from 58 PCPs, participating survivors tended to be 4 years younger ($p < 0.01$), and controls tended to be 2 years younger ($p < 0.01$).

Participating survivors showed no differences with regards to the prevalence of diagnosed CVD, but fewer participating controls had CVD (OR 0.5 [95%CI 0.3-0.8]), probably based on ischaemic CVD (OR 0.3 [95%CI 0.3-0.6]). In the sensitivity analysis including all eligible women, we observed no difference in diagnosed CVD, except for atrial fibrillation, which was more frequent in survivors.

Baseline data

At diagnosis, women in the 'chemotherapy with or without radiotherapy' group had a median age of 49 compared with 54 years in the 'radiotherapy only' group (Table 1). In the 'chemotherapy with or without radiotherapy' group, 81.1% were treated with anthracyclines (doxorubicin [$n = 53$] or epirubicin [$n = 89$]), and 68.6% received additional radiotherapy. The median cumulative anthracycline dose (doxorubicin isotoxic dose) was 238 mg/m², and no patient received a real high-dose doxorubicin (>400 mg/m²) or epirubicin (>900 mg/m²) [26]. Of the survivors, 97% was irradiated after 1990. At diagnosis, the rates of

dyslipidaemia, hypertension, diabetes, diagnosed CVD and use of CV medication were not statistically different between the 'chemotherapy with or without radiotherapy' group, the 'radiotherapy only' group, and their respective controls (Table 1).

Findings at the cross-sectional assessment

The median follow-up after breast cancer diagnosis was 10 years (Table 2), at which point the breast cancer survivors did not differ significantly from their controls in terms of CV risk factors.

Compared with controls, survivors had a significantly increased risk of an LVEF < 54% (OR 2.4 [95%CI 1.4-4.0]), and there was a similar but non-significant trend for the risk of an LVEF < 50% (OR 1.7 [95%CI 0.7-4.0]); however, few women had an LVEF < 45% (n = 4; Table 2). In addition, prevalence rates for LV diastolic dysfunction were also higher among survivors than among controls, but the same was not statistically significant (OR 1.2 [95%CI 0.9-1.6]; Table 2). Few women had severe diastolic dysfunction (17 survivors versus 12 controls).

Compared with controls, prevalence rates were higher among survivors for increased NT-proBNP levels (OR 1.5 [95%CI 1.1-2.1]), newly diagnosed CVD (OR 2.0 [95%CI 1.2-3.3]), and prescribed CV medication (OR 1.4 [95%CI 1.0-2.0]). Concerning CVD diagnoses, there was an increased likelihood of ischaemic CVD, with angiotensin-converting-enzyme inhibitors, anti-platelet agents, and beta-blockers being prescribed more frequently. However, there were no significant differences between survivors and controls on other outcomes.

There was a significantly increased risk of LV systolic dysfunction (LVEF < 54%) in the chemotherapy with or without radiotherapy group compared with their controls (OR 2.5 [95%CI 1.2-5.4]; Table 3). This treatment group also had a more than two-fold increased risk of being diagnosed with CVD (OR 2.3 [95%CI 1.0-4.9]), which was mainly attributable to ischemic CVD. Angiotensin-converting enzyme inhibitors and anti-platelet agents were prescribed significantly more often among survivors than controls (Table 3). Concerning anthracycline treatment, we found the same increased risk for LV systolic dysfunction as in the other groups. No differences were found between higher versus lower-dose anthracycline-treated patients.

'Radiotherapy only' mode of treatment was also associated with an increased risk of LV systolic dysfunction (LVEF < 54%; OR 2.3 [95%CI 1.1-4.6]) and raised NT-proBNP level (OR 1.6 [95%CI 1.0-2.4]); however, there was no significant increased risk of CVD in the radiotherapy group (Table 3). We found no significant differences in LV function between left-sided and right-sided radiotherapy, either before or after excluding those who received chemotherapy. However, in patients treated with left-sided therapy NT-proBNP level was raised (OR 1.6 [95%CI 1.0-2.6]).

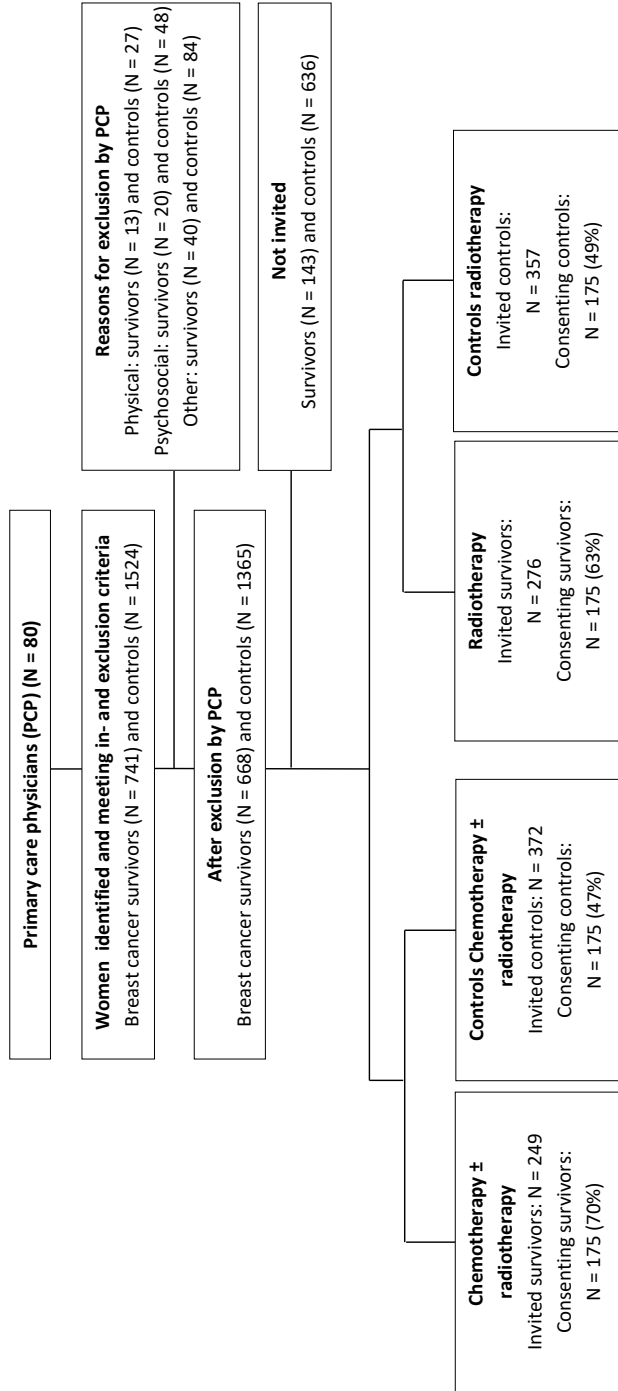


Figure 1. Flow diagram of the selection of survivors of breast cancer and their matched controls.

Table 1: Baseline characteristics at time of breast cancer diagnosis of survivors treated with chemotherapy ± radiotherapy, with radiotherapy only, and matched controls.^a

| | Chemotherapy ± radiotherapy | Controls Chemotherapy ± radiotherapy | Radio- therapy | Controls radiotherapy |
|--|--|---|---------------------------|----------------------------------|
| | (N = 175) | (N = 175) | (N = 175) | (N = 175) |
| Age at breast cancer diagnosis or index age for matched control; years, median (IQR) | 49 (42-54) | 49 (42-55) | 54 (49-59) | 53 (48-58) |
| | N (%) | N (%) | N (%) | N (%) |
| Breast cancer treatment as registered in hospital and PCP files | | | | |
| Chemotherapy | - | - | - | - |
| <i>Anthracycline-based</i> | 142 (81.1) | - | - | - |
| <i>Cumulative anthracycline dose; mg/m², median (IQR)^b</i> | 238 (228-240) | - | - | - |
| Trastuzumab | 13 (7.4) | - | - | - |
| Anti-hormonal treatment | 109 (62.3) | - | 37 (21.1) | - |
| Radiotherapy | 120 (68.6) | - | 175 (100) | - |
| <i>Side: bilateral or left</i> | 84 (48.0) | - | 89 (51.5) | - |
| Risk factors for CVD | 20 (11.4) | 18(10.3) | 25 (14.3) | 32 (18.3) |
| <i>Dyslipidemia</i> | 7 (4.0) | 8 (4.6) | 5 (2.9) | 11 (6.3) |
| <i>Hypertension</i> | 17 (9.7) | 13 (7.4) | 19 (10.9) | 27 (15.4) |
| <i>Diabetes mellitus</i> | 2 (1.1) | 2 (1.1) | 8 (4.6) | 3 (1.7) |
| Diagnosed CVD | 5 (2.9) | 2 (1.1) | 3 (1.7) | 5 (2.9) |
| <i>Heart failure</i> | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| <i>Ischemic heart disease^c</i> | 3 (1.7) | 1 (0.6) | 2 (1.1) | 0 (0) |
| <i>Atrial fibrillation</i> | 0 (0) | 0 (0) | 1 (0.6) | 2 (1.1) |
| <i>Other heart diseases^d</i> | 2 (1.1) | 1 (0.6) | 1 (0.6) | 3 (1.7) |
| Cardiovascular medication | 14 (8.0) | 10 (5.7) | 15 (8.6) | 10 (5.7) |
| <i>ACE-inhibitor</i> | 5 (2.9) | 2 (1.1) | 8 (4.6) | 5 (2.9) |
| <i>Antiplatelet agents</i> | 3 (1.7) | 0 (0) | 4 (2.3) | 0 (0) |
| <i>Beta-blockers</i> | 5 (2.9) | 3 (1.7) | 4 (2.3) | 3 (1.7) |
| <i>Diuretics</i> | 6 (3.4) | 4 (2.3) | 6 (3.4) | 2 (1.1) |
| <i>Statins</i> | 3 (1.7) | 3 (1.7) | 5 (2.9) | 1 (0.6) |

^a There were no statistical significant differences between groups, tested with Chi-square test;

^b Doxorubicin isotoxic dose, information available for 108 patients (76%);

^c Stable and unstable angina pectoris, coronary sclerosis, acute myocardial infarction, transient ischemic attack, cerebrovascular accident;

^d Paroxysmal tachycardia (supraventricular and ventricular), non-rheumatic valve dysfunction, Wolff-Parkinson-White syndrome, atrioventricular block, cardiomyopathy, long QT-syndrome.

Table 2: Comparison of outcomes at long-term follow-up echocardiography between all Northern Dutch breast cancer survivors and controls.

| | Breast cancer survivors (N = 350) | Controls breast cancer survivors (N = 350) | |
|---|--|---|------------------------|
| Follow-up duration; years, median (IQR) | 10 (7-14) | 10 (8-14) | |
| Age at cross-sectional assessment; years, median (IQR) | 63 (57-68) | 63 (57-68) | |
| | N (%) | N (%) | OR (95%CI) |
| Left ventricular dysfunction | | | |
| Systolic dysfunction ^a | | | |
| <i>LVEF < 54%</i> | 52 (15.3) | 24 (7.0) | 2.4 (1.4 - 4.0) |
| <i>LVEF < 50%</i> | 15 (4.4) | 9 (2.6) | 1.7 (0.7 - 4.0) |
| <i>LVEF < 45%</i> | 2 (0.6) | 2 (0.6) | 1.0 (0.1 - 7.2) |
| Diastolic dysfunction ^b | | | |
| Diastolic dysfunction with LAVI \geq 34 mL/m ^{2c} | 147 (43.4) | 133 (39.5) | 1.2 (0.9 - 1.6) |
| | 17 (5.5) | 12 (3.9) | 1.4 (0.7 - 3.0) |
| Right ventricular dysfunction | | | |
| Systolic dysfunction | | | |
| <i>Decreased TAPSE</i> | 4 (1.2) | 6 (1.8) | 0.7 (0.2 - 2.4) |
| <i>Decreased S'</i> | 7 (2.3) | 9 (2.8) | 0.8 (0.3 - 2.2) |
| Valve dysfunction ^d | 3 (0.9) | 5 (1.4) | 0.6 (0.4 - 2.5) |
| Any abnormality on ECG | 83 (24.1) | 68 (19.7) | 1.3 (0.9 - 1.9) |
| Increased NT-proBNP (\geq 125 pg/mL) ^e | 125 (36) | 95 (27.1) | 1.5 (1.1 - 2.1) |
| Risk factors for CVD, newly diagnosed CVD, and use of cardiovascular medication at time of echocardiography as registered in PCP files | | | |
| Risk factors for CVD - any | 139 (39.7) | 135 (38.6) | 1.0 (0.8 - 1.4) |
| <i>Dyslipidemia</i> | 54 (15.4) | 58 (16.6) | 0.9 (0.6 - 1.3) |
| <i>Hypertension</i> | 108 (30.9) | 106 (30.3) | 1.0 (0.7 - 1.4) |
| <i>Diabetes mellitus</i> | 29 (8.3) | 16 (4.6) | 1.9 (0.99 - 3.5) |
| Diagnosed CVD | 49 (14.0) | 26 (7.4) | 2.0 (1.2 - 3.3) |
| <i>Heart failure</i> | 1 (0.3) | 3 (0.9) | 0.3 (0.03 - 3.2) |
| <i>Ischemic cardiovascular diseases ^f</i> | 26 (7.4) | 13 (3.7) | 2.1 (1.1 - 4.1) |
| <i>Atrial fibrillation</i> | 11 (3.1) | 4 (1.1) | 2.8(0.9 - 8.9) |
| <i>Other cardiac diseases ^g</i> | 20 (5.7) | 9 (2.6) | 2.3 (1.0 - 5.1) |

Table 2: Continued.

| | Breast cancer survivors (N = 350) | Controls breast cancer survivors (N = 350) | |
|----------------------------------|--|---|------------------------|
| Cardiovascular medication | 132 (37.7) | 104 (29.7) | 1.4 (1.0 - 2.0) |
| <i>ACE-inhibitor</i> | 65 (18.6) | 42 (12.0) | 1.7 (1.1 - 2.5) |
| <i>Antiplatelet agents</i> | 29 (8.3) | 12 (3.4) | 2.5 (1.3 - 5.1) |
| <i>Beta-blockers</i> | 54 (15.4) | 34 (9.7) | 1.7 (1.1 - 2.7) |
| <i>Diuretics</i> | 33 (9.4) | 39 (11.1) | 0.8 (0.5 - 1.4) |
| <i>Statins</i> | 54 (15.4) | 40 (11.4) | 1.4 (0.9 - 2.2) |

Outcomes printed in bold are significant.

^a Measured by Simpson's biplane (61.8%) or BiPQ/estimate (38.2%), not available for women with atrial fibrillation during measurement (N = 6) and women with immeasurable LVEF (N = 14).

^b Decreased e' lat or e' sept, not available for women with atrial fibrillation during measurement (N = 6), valve replacement (N = 4) and women with immeasurable e' lat and e' sept (N = 14).

^c Not available for women with atrial fibrillation during measurement (N = 6), valve replacement (N = 4), and women with immeasurable e' lat and e' sept (N = 14).

^d Minimal II/III valve dysfunction from one of the 4 cardiac valves.

^e Not available for 3 women.

^f Stable and unstable angina pectoris, coronary sclerosis, acute myocardial infarction, transient ischaemic: attack, cerebrovascular accident.

^g Paroxysmal tachycardia (supraventricular and ventricular), non-rheumatic valve dysfunction, Wolff-Parkinson-White syndrome, atrioventricular block, cardiomyopathy, long QT-syndrome.

Multivariable analysis

Adjustment for CV risk factors at breast cancer diagnosis (Model 1) and at cross-sectional assessment (Model 2), did not substantially affect the ORs for the occurrence of LV systolic dysfunction (LVEF < 54%), increased NT-proBNP (cut-off \geq 125 pg/ml), or newly diagnosed CVD among survivors (Table 4).

Table 3: Comparison of outcomes at long-term follow-up echocardiography by treatment subgroup.

| | Chemotherapy ± radiotherapy (N = 175) | Controls chemotherapy (N = 175) |
|--|--|--|
| Follow-up duration; years, median (IQR) | 10 (7-13) | 10 (8-14) |
| Age at cross-sectional assessment; years, median (IQR) | 60 (53-66) | 60 (53-66) |
| | N (%) | N (%) |
| Left ventricular dysfunction | | |
| Systolic dysfunction ^a | | |
| LVEF < 54% | 25 (14.8) | 11 (6.4) |
| LVEF < 50% | 7 (4.1) | 5 (2.9) |
| LVEF < 45% | 1 (0.6) | 0 (0) |
| Diastolic dysfunction ^b | | |
| Diastolic dysfunction with LAVI ≥ 34 mL/m ^{2c} | 79 (46.7) | 65 (38.7) |
| | 10 (6.6) | 6 (4.0) |
| Right ventricular dysfunction | | |
| Systolic dysfunction | | |
| Decreased TAPSE | 2 (1.2) | 3 (1.8) |
| Decreased S' | 4 (2.5) | 6 (3.6) |
| Valve dysfunction ^d | 1 (0.6) | 3 (1.7) |
| Any abnormality on ECG | 39 (22.7) | 36 (20.8) |
| Increased NT-proBNP (≥ 125 pg/mL) ^e | 56 (32.7) | 44 (25.1) |
| Newly diagnosed CVD and use of cardiovascular medication at time of echocardiography as registered in PCP files | | |
| Diagnosed CVD | 21 (12.0) | 10 (5.7) |
| Heart failure | 1 (0.6) | 1 (0.6) |
| Ischemic cardiovascular diseases ^f | 12 (6.9) | 7 (4.0) |
| Atrial fibrillation | 4 (2.3) | 1 (0.6) |
| Other cardiac diseases ^g | 7 (4.0) | 3 (1.7) |
| Cardiovascular medication | 57 (32.6) | 44 (25.1) |
| ACE-inhibitor | 39 (22.3) | 21 (12.0) |
| Antiplatelet agents | 16 (9.1) | 6 (3.4) |
| Beta-blockers | 26 (14.9) | 17 (9.7) |
| Diuretics | 19 (10.9) | 16 (9.1) |
| Statins | 26 (14.9) | 16 (9.1) |

Outcomes printed in bold are significant.

^a Measured by Simpson's biplane (61.8%) or BiPQ/estimate (38.2%), not available for women with atrial fibrillation during measurement (N = 6) and women with immeasurable LVEF (N = 14).

^b Decreased e' lat or e' sept, not available for women with atrial fibrillation during measurement (N = 6), valve replacement (N = 4), and women with immeasurable e' lat and e' sept (N = 14).

^c Not available for women with atrial fibrillation during measurement (N = 6), valve replacement (N = 4) and women with immeasurable e' lat and e' sept (N = 14).

| | Radiotherapy (N = 175) | Controls radiotherapy (N = 175) | |
|------------------------|-----------------------------------|--|------------------------|
| | 10 (8-15) | 10 (7-15) | |
| | 65 (61-70) | 66 (61-70) | |
| OR (95%CI) | N (%) | N (%) | OR (95%CI) |
| 2.5 (1.2 - 5.4) | 27 (15.9) | 13 (7.7) | 2.3 (1.1 - 4.6) |
| 1.4 (0.4 - 4.6) | 8 (4.7) | 4 (2.4) | 2.1 (0.6 - 6.9) |
| | 1 (0.6) | 2 (1.2) | - |
| 1.4 (0.9 - 2.1) | 68 (40.0) | 68 (40.2) | 1.0 (0.6 - 1.5) |
| 1.7 (0.6 - 4.7) | 7 (4.4) | 6 (3.8) | 1.2 (0.4 - 3.5) |
| | | | |
| 0.7 (0.1 - 4.1) | 2 (1.2) | 3 (1.8) | 0.7 (0.1 - 4.1) |
| 0.7 (0.2 - 2.5) | 3 (1.9) | 3 (1.9) | 1.0 (0.2 - 5.0) |
| 0.3 (0.03 - 3.2) | 2 (1.1) | 2 (1.1) | 1.0 (0.1 - 7.2) |
| 1.1 (0.7 - 1.9) | 48 (27.9) | 41 (23.8) | 1.2 (0.8 - 2.0) |
| 1.5 (0.9 - 2.3) | 68 (39.1) | 51 (29.1) | 1.6 (1.0 - 2.4) |
| | | | |
| 2.3 (1.0 - 4.9) | 28 (16.0) | 16 (9.1) | 1.9 (0.98 - 3.6) |
| 1.0 (0.06 - 16) | 0 (0) | 2 (1.1) | |
| 1.8 (0.7 - 4.6) | 14 (8.0) | 6 (3.4) | 2.4 (0.9 - 6.5) |
| 4.1 (0.5 - 36.8) | 7 (4.0) | 3 (1.7) | 2.4 (0.6 - 9.4) |
| 2.4 (0.6 - 9.4) | 13 (7.4) | 6 (3.4) | 2.3 (0.8 - 6.1) |
| 1.4 (0.9 - 2.3) | 75 (42.9) | 60 (34.3) | 1.4 (0.9 - 2.2) |
| 2.1 (1.2 - 3.8) | 40 (22.9) | 29 (16.6) | 1.5 (0.9 - 2.5) |
| 2.8 (1.1 - 7.4) | 13 (7.4) | 6 (3.4) | 2.3 (0.8 - 6.1) |
| 1.6 (0.8 - 3.1) | 37 (21.1) | 24 (13.7) | 1.7 (0.96 - 3.0) |
| 1.2 (0.6 - 2.4) | 26 (14.9) | 29 (16.6) | 0.9 (0.5 - 1.6) |
| 1.7 (0.9 - 3.4) | 35 (20.0) | 28 (16.0) | 1.3 (0.8 - 2.3) |

^d Minimal II/III valve dysfunction from one of the 4 cardiac valves.

^e Not available for 3 women.

^f Stable and unstable angina pectoris, coronary sclerosis, acute myocardial infarction, transient ischaemic attack, cerebrovascular accident.

^g Paroxysmal tachycardia (supraventricular and ventricular), non-rheumatic valve dysfunction, Wolff-Parkinson-White syndrome, atrioventricular block, cardiomyopathy, long QT-syndrome.

Table 4: Multivariate models, unadjusted and adjusted for measurements at time of breast cancer diagnosis (model 1) and at follow-up echocardiography (model 2).

| | Unadjusted | Adjusted model 1 ^a | Adjusted model 2 ^b |
|--|------------------------|----------------------------------|----------------------------------|
| Left ventricular systolic dysfunction (LVEF < 54%) | | | |
| All patients | | | |
| <i>Breast cancer survivors versus controls</i> | 2.4 (1.4 - 4.0) | 2.5 (1.5 - 4.1) | 2.3 (1.4 - 3.9) |
| Chemotherapy ± radiotherapy | | | |
| <i>Breast cancer survivors versus controls</i> | 2.5 (1.2 - 5.4) | 2.5 (1.2 - 5.4) | 2.5 (1.2 - 5.3) |
| Radiotherapy only | | | |
| <i>Breast cancer survivors versus controls</i> | 2.3 (1.1 - 4.6) | 2.3 (1.2 - 4.8) | 2.2 (1.1 - 4.4) |
| Increased NT-proBNP (Cut-off ≥ 125 pg/mL) | | | |
| All patients | | | |
| <i>Breast cancer survivors versus controls</i> | 1.5 (1.1 - 2.1) | 1.5 (1.1 - 2.1) | 1.5 (1.1 - 2.1) |
| Chemotherapy ± radiotherapy | | | |
| <i>Breast cancer survivors versus controls</i> | 1.5 (0.9 - 2.3) | 1.4 (0.9 - 2.3) | 1.5 (0.9 - 2.4) |
| Radiotherapy only | | | |
| <i>Breast cancer survivors versus controls</i> | 1.6 (1.0 - 2.4) | 1.6 (1.0 - 2.5) | 1.5 (0.9 - 2.3) |
| Newly diagnosed CVD (after baseline) | | | |
| All patients | | | |
| <i>Breast cancer survivors versus controls</i> | 2.0 (1.2 - 3.3) | 2.1 (1.3 - 3.4) | 1.9 (1.2 - 3.2) |
| Chemotherapy ± radiotherapy | | | |
| <i>Breast cancer survivors versus controls</i> | 2.3 (1.0 - 4.9) | 2.3 (1.0 - 5.0) | 2.3 (1.0 - 5.1) |
| Radiotherapy only | | | |
| <i>Breast cancer survivors versus controls</i> | 1.9 (0.98 - 3.6) | 2.1 (1.1 - 4.1) | 1.7 (0.9 - 3.3) |

Outcomes printed in bold are significant.

^a Model 1: Adjusted for measurements at baseline: cardiovascular risk factors (diabetes, hypertension, dyslipidaemia), prior CVD and any cardiovascular medication at time of breast cancer diagnosis.

^b Model 2: Adjusted for measurements at time of echocardiography: cardiovascular risk factors (diabetes, hypertension, dyslipidaemia) from PCP files, current smoking (yes/no), Body Mass Index (continuous), and physical fitness: percentage of women adhering to the Dutch guideline (≥5 d per week at least moderate exercise during 30 min; SQUASH).

DISCUSSION

LV systolic dysfunction

In our study, the risk of mild LV systolic dysfunction (LVEF < 54%) was higher in long-term survivors of breast cancer (15.3%) compared with age-matched controls (7.0%) (OR 2.4 [95% CI 1.4-4.0]). Notably, this increased risk remained after adjusting for CV risk factors at both breast cancer diagnosis and follow-up assessment.

Two studies of chemotherapy-treated (with or without radiotherapy) breast cancer survivors reported lower prevalence compared to our study (14.8%), with rates of 11.5% and 5% for LV systolic dysfunction (LVEF < 55%) over 6 years [27] and 14 years [13], respectively. For LVEF < 50%, six studies reported prevalence rates varying between 1.4% and 8% over 5e14 years [11,13,28-31], consistent with the 4.1% found in this study. The differences between these studies can be explained by differences in the inclusion criteria (e.g. age) and by missing data for cardiac function.

The prevalence of systolic dysfunction among survivors treated with 'radiotherapy only' was 15.9% in this study. No previous research exists, assessing LVEF by echocardiography among women who received radiotherapy without chemotherapy. When comparing survivors, who received left-sided radiotherapy with those who received right-sided radiotherapy, we observed no significant differences. This result was not in line with older studies, which did observe this left-right difference [32-34]. A potential explanation is the use of modern radiotherapy, resulting in a lower heart dose, especially in left-sided breast cancer [4]. Moreover, the older studies had different designs, including patients with cardiovascular events, and had different cardiac primary end-points. As reported by Taylor et al. the dose to the heart did not decrease much in general after the 1990s [35]. Of our patients, 97% were irradiated after 1990.

Unfortunately, dose distribution and mean heart dose were not available. In general, in the Netherlands radiotherapy for breast cancer consisted of conventional photon tangential fields up to 50 Gy.

LV diastolic dysfunction

We found no significant increased risk for LV diastolic dysfunction, with prevalence being high among both breast cancer survivors (43.4%) and controls (39.5%). This is similar to the data in two other studies [36,37]. In this last study, a systematic review, the prevalence of LV diastolic dysfunction was 36.0% (range 15.8%-52.8%) for women aged 60 years [37]. We found no increased risk for severe LV diastolic dysfunction in breast cancer survivors as compared to controls.

NT-proBNP

NT-proBNP levels were increased more often among breast cancer survivors (36%) than controls (27.1%) (OR 1.5 [95%CI 1.1-2.1]). Unfortunately, the use of different assays precluded comparison of this prevalence with another study of breast cancer survivors (mean follow-up, 6 years), in which the prevalence of increased NTproBNP was 71% [27]. In our study, patients treated with left-sided therapy had a raised NT-proBNP level compared to right-sided treated women. Earlier research showed that higher post-radiotherapy NT-proBNP levels were present among women who received radiation to a larger heart volume [38]. In the general population, it has been shown that an increased NT-proBNP level is predictive of cardiac mortality and heart failure [39].

CVD diagnosis

Survivors had an increased risk of CVD after diagnosis when compared with controls (OR 2.0 [95%CI 1.2-3.3]). Though, this risk persisted after adjusting for risk factors at diagnosis and follow-up, it was not found when all eligible women were included in the analysis, except for atrial fibrillation. Subgroup analysis showed that the higher risk applied to patients treated with chemotherapy with or without radiotherapy. Though in our study numbers were small and confidence intervals were wide we found that the increased risk was mainly seen for ischaemic cardiac diseases, whereas other studies of patients treated with chemotherapy have found an increased incidence of congestive heart failure [7,8,10,12,40]. But, those studies were notable for using high-dose chemotherapy [40] or doxorubicin [7,8,10,12].

An increased incidence of ischaemic heart disease is generally expected among patients treated by radiotherapy only [41]. Although 69% of the chemotherapy-treated women in our study also received radiotherapy, it is important to consider that the risks of CVD after radiotherapy have declined with modern radiation techniques [4].

Strengths

To our knowledge, this is the first study to compare long-term and echocardiographically correlate systolic/diastolic dysfunction between breast cancer survivors and controls in primary care. We used clear inclusion and exclusion criteria and matched the controls by age and PCP to guarantee a comparable socioeconomic status. This type of matching was considered superior to using a normal population, because it allowed for an accurate comparison. For survivors and controls, we obtained echocardiographic images and NT-proBNP levels by inviting survivors to attend a university medical centre, allowing all measurements to be performed using strict, standardized protocols. We also achieved a high participation rate (67% among survivors and 48% among controls).

Limitations

Some important limitations should be noted. As our study focused on the long-term impact of chemotherapy and/or radiotherapy in breast cancer treatment on cardiac function, we included women who survived breast cancer for at least 5 years after diagnosis. Though these women might be healthier, with less cardiac disease, we consider this as adequate. However, for this reason, our results might underestimate the absolute risk of cardiac dysfunction. After selecting cases and controls, PCP excluded some women for several reasons, and others refused participation. We observed that the non-participants were significantly older and that in the control group non-participants had more frequent CVD as compared to participating women. To estimate the impact of this bias by selection, a sensitivity analysis was performed on the relative prevalence of CVD including all eligible women. We concluded that we might have overestimated the impact of chemotherapy and/or radiotherapy on the long-term of the risk of CVD in survivors.

Conclusion

Among long-term survivors of breast cancer, there is an increased risk of mild LV systolic dysfunction and NT-proBNP elevations when compared with matched controls. They may also have an increased risk of newly diagnosed CVD. These increased risks appear to be independent of risk factors at breast cancer diagnosis and follow-up. However, the increased risks will not have clinical implications. In spite of this, it is important to enquire about previous chemotherapy or radiotherapy for breast cancer when assessing the CV risk profile of a patient.

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Chapter 4

Long-term psychological distress in breast cancer survivors and their matched controls: a cross-sectional study

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ABSTRACT

Introduction: Breast cancer survivors often experience psychological distress shortly after diagnosis. Long-term psychological effects, however, have not been clearly demonstrated.

Methods: This cross-sectional cohort study included 350 breast cancer survivors and 350 age-matched and general-practitioner-matched women. The median follow-up was 10 years. Using logistic regression we compared breast cancer survivors with controls on having (severe) symptoms of depression and/or anxiety, as measured with the Hospital Anxiety and Depression Scale. In multivariable logistic regression, we adjusted the results for a history of depression or prescription of antidepressants.

Results: Larger proportions of breast cancer survivors experienced symptoms of depression (10.6%) compared with controls (4.9%) and symptoms of anxiety (18.6%) compared with controls (16.3%). The odds of symptoms of depression (OR 2.3, 95%CI 1.3-4.2), severe symptoms of depression (OR 3.3, 95%CI 1.1-10.3) and severe symptoms of anxiety (OR 2.1, 95%CI, 1.1-4.0) were significantly higher for breast cancer survivors than for controls, even after adjusting for history of depression or prescription of antidepressants. No significant difference was seen for mild symptoms of anxiety.

Conclusions: Breast cancer survivors have an increased risk of symptoms of depression, including severe symptoms, and severe symptoms of anxiety compared with controls, for up to at least 10 years after diagnosis.

INTRODUCTION

Breast cancer is the most common cancer in women [1,2]. Fortunately, the survival of breast cancer has improved due to better screening and better treatments [3]. Numbers from the Netherlands show a 5-year survival rate of up to 88% [4]. Hence, the number of breast cancer survivors is also increasing.

The diagnosis of cancer and its treatment can have a great impact on a patient's psychological well-being [5-8]. However, both the clinicians and the patients may not be aware of possible long-term psychological impact and patients may not receive the proper support. No long-term follow up data are available with respect to the occurrence of psychological distress in breast cancer patients [9]. Therefore, it is important to know how prevalent long-term psychological distress is among breast cancer survivors. For women with breast cancer, this impact is mainly studied in the first five years after diagnosis when they still have follow-up controls with their oncologists [10]. In this period, Burgess et al. found a prevalence of 48% for depression, anxiety, or both for breast cancer survivors [11]. Which, they said, is twice as high as in the general female population. A recent systematic review of studies (2015) on symptoms of depression and anxiety among breast cancer survivors showed a widely distributed prevalence of 9.4-66.1% and 17.9-33.3%, respectively [10]. A few of the studies included women beyond the five years after diagnosis, and only two focused solely on women five years or more after their diagnosis of breast cancer [12,13]. One of these two found that 13% of women experienced severe symptoms of depression [12]. However, they did not have a control population to evaluate if this proportion is more than on average. The other study evaluated women 5, 10 or 15 years after breast cancer diagnosis on quality of life and found that they had a higher score on symptoms of anxiety than random control women [13]. Unfortunately, the patient group and the control group significantly differed on age, environment (urban/rural) and income, which might have had an influence on the comparability on psychological well-being. Studies after 2015 have only been performed within the first years of diagnosis or in a hospital setting [14,15].

For clinicians, survivors, and future guidelines, it is important to know if psychological distress is more prevalent among long-term breast cancer survivors than among women without cancer, in order to provide sufficient long-term support. Therefore in this study, we assessed symptoms of depression and anxiety at least five years after the diagnosis of breast cancer and compared with the results of women without a history of cancer, who were of the same age and general practitioner (GP).

METHODS

Context

In the Netherlands, all citizens are registered with a GP in their own residential area [16]. These GPs use electronic patient registers with coding systems of diagnosis (International Classification for Primary Care, ICPC) and medication prescriptions (Anatomical Therapeutic Chemical classification system, ATC) [17,18]. GPs are gatekeepers to secondary healthcare, which means that patients have to be referred by their GPs to medical specialists.

BLOC study design

Data for this study was derived from the Breast cancer Long-term Outcome of Cardiac dysfunction (BLOC)-study [19]. The primary outcome of the BLOC-study was the prevalence of long-term systolic and diastolic cardiac dysfunction among breast cancer survivors in comparison to matched controls. This cross-sectional cohort included 350 breast cancer survivors treated with chemo- and/or radiotherapy at least five years ago, and 350 randomly selected women from the same age and GP from the Northern part of the Netherlands (Supplementary Fig. 1), recruited from 80 GPs. The control was randomly selected from the same GP database, from all women of the same age (+/- 1 year) as the breast cancer survivor. Exclusion criteria for the control were a history of cancer or cancer treatment. In both groups, women were excluded if they were not able to come to the university hospital according to their GP due to severe mental or physical illness. At the time of the cross-sectional assessment, the GP files of both breast cancer survivors and controls were searched for the code P76 and the date of the first diagnosis of depression was extracted. Furthermore, the first prescriptions of antidepressants (ATC-code N06A), anxiolytics (ATC-code N05B), and hypnotics and sedatives (ATC-code N05C) were analysed. Since the antidepressant amitriptyline can also be prescribed as an analgesic, it was excluded when prescribed for pain. The date of diagnosis of women with breast cancer functioned as the index date for the matched women. Therefore, the time since diagnosis for the control group is the time since the index date. The median age at the time of breast cancer diagnosis was 51 years (inter-quartile range [IQR] 45-57). The median follow-up was 10 years (IQR 7-14) years. The study is registered at clinicaltrials.gov [ID:NCT01904331]. The medical ethics committee of the University Medical Center Groningen (UMCG) approved this study, and all participants gave written informed consent. The study was performed in accordance with the Declaration of Helsinki.

Current study end-points

The primary outcome was the prevalence of (severe) symptoms of depression and/or anxiety as measured by the Hospital Anxiety and Depression Scale (HADS) [20]. This questionnaire measures symptoms of both depression (HADS-D) and anxiety (HADS-A).

It is a self-reported scale with 14 items scoring each 0-3, with a maximum score of 21 for either symptoms of depression or anxiety. Cut-off values are ≥ 8 for mild symptoms of depression/anxiety and ≥ 11 for severe symptoms of depression/anxiety. The HADS has been validated for both the general population and the breast cancer population [21,22]. The secondary outcomes were the prevalence of a diagnosis of depression as registered by GPs after the diagnosis of breast cancer and/or a prescription of antidepressants after breast cancer diagnosis.

Statistical analyses

In the analysis, a diagnosis of depression and/or prescription of an antidepressant could be a determinant as well as an outcome. Survivors and controls with the first diagnosis of depression and/or first prescription of an antidepressant before the date of breast cancer diagnosis were considered as having a 'history of depression'. It is important to adjust for a history of depression, since depression is often a recurrent diagnosis. Survivors and controls with the first diagnosis of depression and/or first prescription of an antidepressant after the date of breast cancer diagnosis were considered as having an 'outcome of depression'. The diagnosis of depression and prescription of antidepressants were combined since some GPs may have the tendency to prescribe antidepressants for depression without coding a diagnosis of depression.

Table 1 describes participants' characteristics at the time of breast cancer diagnosis, including the number of survivors with a history of depression and the use of psychotropic medication before the date of breast cancer diagnosis. In Table 2, the outcomes are described. For future comparability with other studies, both the continued and dichotomous values of the HADS are reported and tested with the Mann-Whitney U test.

In univariate logistic regression analyses, breast cancer survivors were compared to controls on the odds of having (severe) symptoms of depression and (severe) symptoms of anxiety as scored with the HADS, and on having diagnosis of depression and/or first prescription of an antidepressant after the date of breast cancer diagnosis (Table 2). In this way, odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated. To adjust for having a history of depression, multivariable logistic regression analyses were performed by adding this variable (Table 3 and 4). Data is presented stratified for depression and anxiety. In univariate logistic regression analyses the time since diagnosis for breast cancer survivors with increased HADS-scores were compared to the time since diagnosis for other breast cancer survivors.

To visualize the effect of time since follow-up, a graphical overview of the course of symptoms of depression and anxiety over time was constructed. The percentage of breast cancer survivors with an increased score on the HADS was compared to the percentage of controls, grouped by time since diagnosis, per two years. The minimum of women per time-subgroup had to be 20. All analyses were performed with the use of IBM SPSS statistics 23.

RESULTS

No significant differences were found between breast cancer survivors or controls regarding patient and therapy characteristics (Table 1) [19]. Only a prescription of hypnotics/sedatives before breast cancer diagnosis was significantly higher among controls compared to breast cancer survivors, respectively 9.4% and 3.7%.

All women completed the HADS questionnaire at the time of inclusion (median 10 years after breast cancer diagnosis). At this time 3.7% of breast cancer survivors experienced severe symptoms of depression compared to 1.1% of controls; a significant difference OR 3.3 (95%CI, 1.1-10.3). Concerning severe symptoms of anxiety, there was a significant difference between breast cancer survivors (8%) compared to controls (4%; OR 2.1 [95%CI, 1.1-4.0]), (Table 2).

The proportion of women with mild symptoms of depression was significantly higher for breast cancer survivors compared to controls (10.6% versus 4.9%; OR 2.3 [95%CI, 1.3-4.2]). For mild symptoms of anxiety, the difference was not significant 18.6% versus 16.3%; OR 1.2 [95%CI, 0.8-1.7]).

The answer to the HADS-D question 'I feel as if I am slowed down' showed the largest difference; 20.3% of BC survivors responded very often/almost-all-the time compared to 9.5% of the controls.

No significant differences were seen between breast cancer survivors and controls when comparing the continuous score on the HADS-D or HADS-A, p-values 0.197 and 0.056, respectively. After the diagnosis of breast cancer, no differences were seen in the registration of GPs concerning the diagnoses of depression or prescription of medication.

Table 1. At the time of breast cancer diagnosis or index date ^a: Characteristics of breast cancer survivors and matched controls.

| | Breast cancer survivors (N = 350) ^b | Controls (N = 350) ^b |
|---|---|--|
| Age at breast cancer diagnosis or index date for matched control; years, median (IQR) | 51 (45-57) | 51 (45-57) |
| | N (%) | N (%) |
| Breast cancer treatment as registered in the hospital and general practitioners files | | |
| Chemotherapy | 175 (50.0) | |
| Anthracycline-based | 142 (81.1) | - |
| Cumulative anthracycline dose; mg/m ² , median (IQR) ^c | 238 (228-240) | - |
| Trastuzumab | 13 (3.7) | - |
| Anti-hormonal treatment | 146 (41.7) | - |
| Radiotherapy | 295 (84.3) | - |
| Diagnosis of depression or prescriptions before the time of breast cancer diagnosis or index date for matched control ^{a,d} | | |
| History of depression: diagnosis of depression or antidepressants | 36 (10.3) | 36 (10.3) |
| A diagnosis of depression | 14 (4.0) | 21 (6.0) |
| A prescription of any antidepressants | 29 (8.3) | 24 (6.9) |
| A prescription of anxiolytics | 39 (11.1) | 37 (10.6) |
| A prescription of hypnotics or sedatives | 13 (3.7) | 33 (9.4) |

^a The date of breast cancer diagnosis from the survivor was made identical for the matched control (index date);

^b There were no statistically significant differences between groups, tested with Chi-square test or Mann-Whitney U test, except for a prescription of hypnotics or sedatives; numbers in bold means significant at p <0.05 level;

^c Doxorubicin isotoxic dose, information available for 108 survivors (76%);

^d Extracted from electronic patient files of general practitioners.

Multivariable analysis

After adjusting history of depression as registered by the GPs before the date of breast cancer, all odds were significantly higher for breast cancer survivors compared to controls: severe symptoms of depression (HADS-D \geq 11; OR 3.3 [95%CI 1.1-10.3]), severe symptoms of anxiety (HADS-A \geq 11; OR 2.1 [95%CI 1.1-4.1]), mild symptoms of depression (HADS-D \geq 8; OR 2.3 [95%CI 1.3-4.2]) and mild symptoms of anxiety (OR 2.1 [95%CI 1.1-3.2]). This is shown in Table 3.

Table 2. At time of cross-sectional measurement: Univariate comparison of outcomes between breast cancer survivors and matched controls.

| | Breast cancer survivors (N = 350) | Controls breast cancer survivors (N = 350) | |
|---|--|---|--------------------------------|
| Follow-up duration ^a ; years, median (IQR) | 10 (7-14) | 10 (7-14) | |
| Age: years, median (IQR) | 63 (57-68) | 63 (57-68) | |
| | N (% , 95%CI) | N (% , 95%CI) | OR (95%CI) ^b |
| <i>Depression</i> | | | |
| HADS-Depression ^c | | | |
| HADS-D ≥ 8 | 37 (10.6, 7.3-13.9) | 17 (4.9, 2.6-7.2) | 2.3 (1.3-4.2) |
| HADS-D ≥ 11 | 13 (3.7, 1.7-5.7) | 4 (1.1, 0.0-2.3) | 3.3 (1.1-10.3) |
| Continuous median (IQR) ^d | 2 (1-4) | 2 (1-4) | 0.197 |
| <i>Anxiety</i> | | | |
| HADS-Anxiety ^c | | | |
| HADS-A ≥ 8 | 65 (18.6, 14.4-22.7) | 57 (16.3, 12.3-20.2) | 1.2 (0.8-1.7) |
| HADS-A ≥ 11 | 28 (8.0, 5.1-10.9) | 14 (4.0, 1.9-6.1) | 2.1 (1.1-4.0) |
| Continuous median (IQR) ^d | 5 (3-7) | 4 (3-6) | 0.056 |
| <i>Diagnosis of depression or prescriptions <u>after</u> time of breast cancer diagnosis or index date for matched control ^{a,e}</i> | | | |
| First diagnosis of depression | 18 (5.1, 2.8-7.5) | 13 (3.7, 1.7-5.7) | 1.4 (0.7-2.9) |
| First prescription of any antidepressant | 41 (11.7, 8.3-15.2) | 39 (11.1, 7.8-14.5) | 1.1 (0.7-1.7) |
| First prescription of any anxiolytics | 46 (13.1, 9.5-16.8) | 49 (14.0, 10.3-17.7) | 0.9 (0.6-1.4) |
| First prescription of any hypnotics or sedative | 41 (11.7, 8.3-15.2) | 34 (9.7, 6.5-12.9) | 1.2 (0.8-2.0) |

^a The date of breast cancer diagnosis from the survivor was made identical for the matched control (index date);

^b Numbers in bold means significant at p <0.05 level;

^c Explanation: HADS ≥ 8 = Symptoms of mild depression (HADS-D) or anxiety (HADS-A) and HADS ≥ 11 = symptoms of severe depression (HADS-D) or anxiety (HADS-A);

^d Tested with Mann-Whitney U test;

^e Extracted from electronic patient files of general practitioners.

Table 3. Regression analyses: Comparison of outcomes at the time of cross-sectional measurement from the Hospital Anxiety Depression Scale (HADS) - Depression and Anxiety, between breast cancer survivors and matched controls. ^a

| | | HADS-D ≥ 8 | HADS-D ≥ 11 | HADS-A ≥ 8 | HADS-A ≥ 11 |
|---|-----|----------------------|-----------------------|----------------------|----------------------|
| | | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) |
| Univariate regression analyses ^b | | | | | |
| History of breast cancer | No | 1 | 1 | 1 | 1 |
| | Yes | 2.3 (1.3-4.2) | 3.3 (1.1-10.3) | 1.2 (0.8-1.7) | 2.1 (1.1-4.0) |
| History of depression ^c | No | 1 | 1 | 1 | 1 |
| | Yes | 1.3 (0.6-2.1) | 1.9 (0.5-6.8) | 1.8 (1.0-3.2) | 2.2 (0.97-4.9) |
| Multivariable regression analyses ^b (adjusted for each other) | | | | | |
| History of breast cancer | No | 1 | 1 | 1 | 1 |
| | Yes | 2.3 (1.3-4.2) | 3.3 (1.1-10.3) | 1.2 (0.8-1.7) | 2.1 (1.1-4.1) |
| History of depression ^c | No | 1 | 1 | 1 | 1 |
| | Yes | 1.3 (0.6-3.1) | 1.9 (0.5-6.9) | 1.8 (1.0-3.2) | 2.2 (0.97-5.0) |

^a Explanation: HADS-D (Depression) ≥ 8 = mild symptoms of depression and HADS-D ≥ 11 = severe symptoms of depression, HADS-A (Anxiety) ≥ 8 = mild symptoms of anxiety and HADS-A ≥ 11 = severe symptoms of anxiety;

^b Numbers in bold means significant at p <0.05 level;

^c The determinant 'history of depression' was defined as a diagnosis of depression and/or prescription of an antidepressant before the date of breast cancer diagnosis or index date.

Time since diagnosis

Time since diagnosis was not associated with symptoms of (severe) depression or anxiety among breast cancer survivors. The figures visualize the proportion of women (breast cancer survivors and controls) with (severe) symptoms of depression (Fig. 1) or anxiety (Fig. 2) with a specific follow-up duration. The proportion of women with severe or mild symptoms of depression and severe symptoms of anxiety is higher among the breast cancer survivors than among the controls for every time-subgroup.

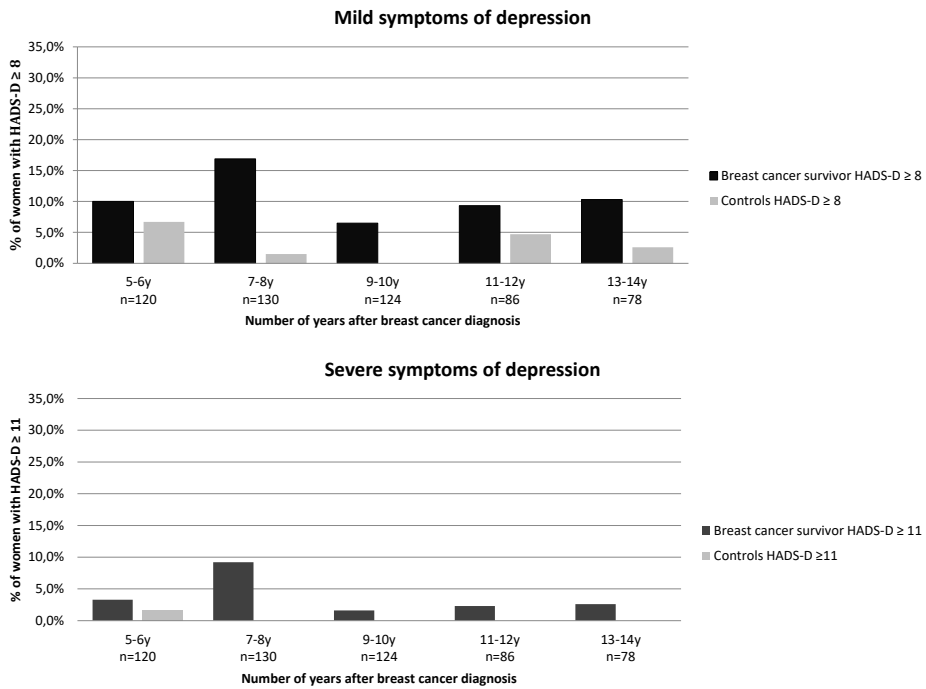


Figure 1. Percentage of breast cancer survivors and controls with symptoms of depression, per two years after breast cancer diagnosis. ^a

^a Since the minimum of women per time-subgroup was 20, the subgroup goes up to 13-14 years after breast cancer diagnosis.

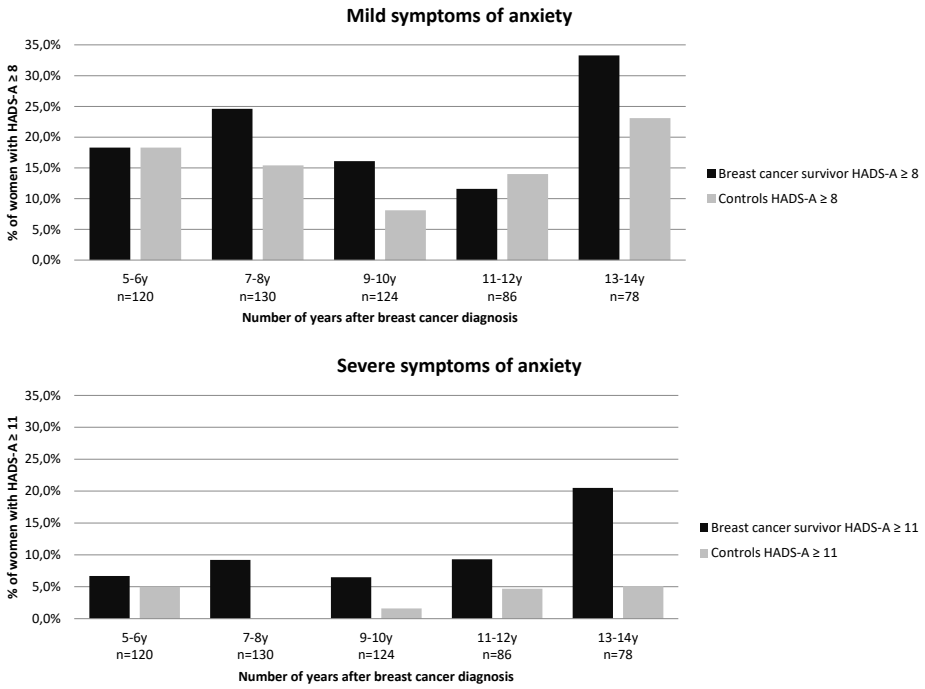


Figure 2. Percentage of breast cancer survivors and controls with symptoms of anxiety, per two years after breast cancer diagnosis.^a

^a Since the minimum of women per time-subgroup was 20, the subgroup goes up to 13-14 years after breast cancer diagnosis.

DISCUSSION

To our knowledge, no other study included women at least five years after breast cancer diagnosis from the general population and compared their symptoms of depression and anxiety with women of the same age without any cancer. When discussing the findings, it is important to realize that a large proportion of the long-term breast cancer survivors in our study did not experience symptoms of depression or anxiety (89.4% and 81.4%, respectively) at the moment of measurement. This does not exclude the possibility that they have experienced symptoms of depression or anxiety at an earlier stage, that might have recovered since then.

Assessing proportions of symptoms

There is some discrepancy in literature regarding the proportions of breast cancer survivors with symptoms of depression and anxiety [10]. Some studies report comparable results, while others report different figures [12,23,24]. The prevalence of women with symptoms of depression and anxiety found in this study is low in comparison to other studies [25,26]. The main explanations for these differences are the differences in follow-up time, differences in age of the included women, and the differences in applied questionnaires. The controls from our study had a lower proportion of women with severe symptoms of depression or anxiety compared to a European female population [27]. However, these proportions were within the confidence intervals of our control population: 2.9% severe symptoms of depression and 10.0% severe symptoms of anxiety, respectively. The European population was selected at random and might have included women with (a history of) cancer. In addition, the difference might be due to the younger age of the participants in the European population, which is associated with an increased score on the HADS questionnaire for symptoms of depression and anxiety [28-30].

Comparison symptoms with controls

We found an increased odds of severe symptoms of depression and anxiety among long-term breast cancer survivors compared to controls. The mean scores in this study did not significantly differ. Claus et al. found significant higher mean scores for severe symptoms of depression among breast cancer survivors than among controls, measured with the CES-D questionnaire (mean follow-up 5.8 years) [31]. Klein et al. compared mean scores for severe symptoms of anxiety among long-term breast cancer survivors and controls and found significantly higher mean scores for survivors, measured with the STAI questionnaire (5, 10 or 15 years after breast cancer diagnosis) [13]. We found an increased odds of mild symptoms of depression among long-term breast cancer survivors compared to controls. None of the studies compared mild symptoms of depression or anxiety among breast cancer survivors and controls. Hoffman et al. evaluated psychological distress in a long-

term cancer survivors cohort (22.9% breast cancer, ≥ 5 years after diagnosis) and found significantly more psychological distress among cancer survivors than among controls without cancer, measured with the self-reporting K6 scale, designed to assess nonspecific psychological distress [32].

History of depression

A previous diagnosis of depression or prescription of antidepressants before the cancer diagnosis had no effect on the odds of having (severe) symptoms of depression or severe symptoms of anxiety for breast cancer survivors in comparison to controls in our population. In contrast, other research defined a history of depression as a risk factor for depression after breast cancer, but in that study the outcome measure was a diagnosis of depression and not symptoms of depression [11]. Interestingly, in our study all women (survivors and controls) with a history of depression had significantly more mild symptoms of anxiety. One could hypothesize that women with a history of depression are more anxious than others, perhaps by nature or they might fear recurrence of psychological distress. However, this was not the aim of this study and not evaluated further.

Time since diagnosis

Time since diagnosis was not associated with having (severe) symptoms of depression and severe symptoms of anxiety for breast cancer survivors. These results are in-line with the results of another study among survivors two to ten years after diagnosis [33]. Additionally, in a large long-term cancer survivors cohort more than five years after cancer diagnosis, no association was found with time since diagnosis [32]. A significant difference of symptoms of depression one year after diagnosis compared to women in the general population appeared to decline in the following years [10]. A complete decline was not supported by the results of our study, as the time since diagnosis had no significant effect on the elevated odds of breast cancer survivors having symptoms of depression.

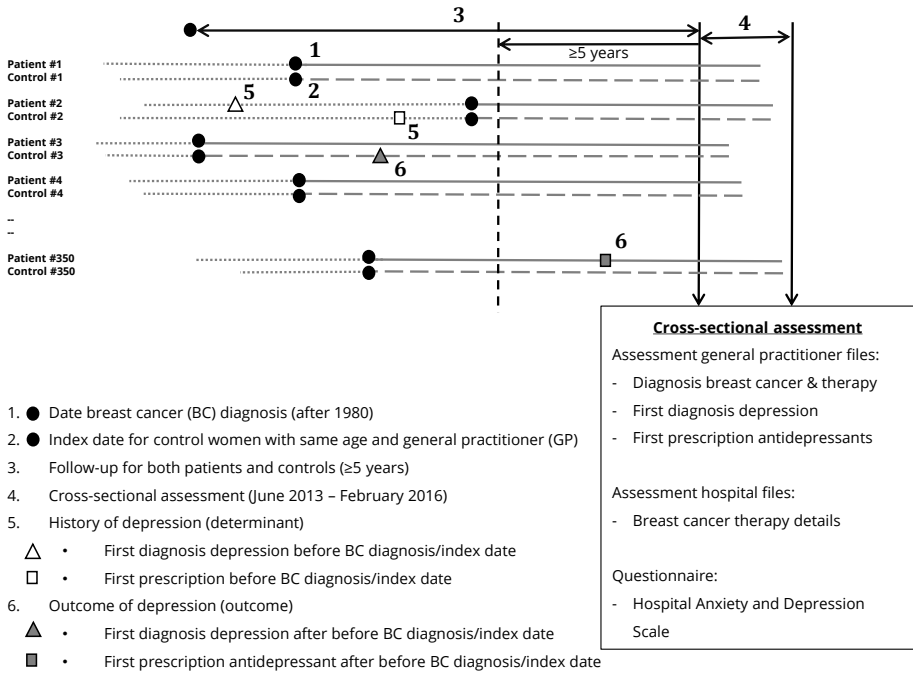
Strengths and limitations

The main strength of this study is that we have included a random sample of women from the general population. Although no other study included this unselected population, it can be argued that our population still does not include the mean breast cancer patient. Which is true, because the included patients were slightly younger and a higher percentage received radiotherapy. Therefore, we might underestimate the occurrence of anxiety and depression. Also, breast cancer survivors are more likely to be underdiagnosed than controls, because signs of depression or anxiety might be interpreted as "natural" consequences of cancer [7]. The median follow-up of 10 years is a strength, because it focusses exclusively on the long-term effects. In order to achieve a uniform outcome, we let all the participants complete the HADS questionnaire, hereby relying on the symptoms

the women are experiencing at that point in time, rather than on patients' help-seeking or doctors' coding behaviour. It is important to realize that the HADS questionnaire only measures symptoms of depression; for an actual diagnosis of depression a clinical interview has to be performed. However, the HADS-D and HADS-A have a sensitivity and specificity of approximately 0.80 for depression and anxiety [34]. Furthermore, we adjusted for a history of depression before breast cancer as registered by GPs to ensure that an already psychologically delicate group did not influence the results. In both groups, women with depression or depressive symptoms might be less inclined to participate, making the comparison equal. Missing from our data is the diagnosis of anxiety disorder; unfortunately, this data was not retrieved from the GP databases. Notable, controls had more prescriptions of hypnotics/sedatives at the time of breast cancer diagnosis than the breast cancer survivors. However, the effect on the results is expected to be minimal since the number was comparable at the time of cross-sectional assessment. It should be taken into account that socioeconomic (SES), occupational and marital status were not assessed in this study.

Conclusions

At least five years after breast cancer, breast cancer survivors have a higher prevalence of (severe) symptoms of depression and severe symptoms of anxiety, even after adjusting for a history of depression prior to breast cancer. Future studies should take into account factors such as fatigue and SES. However, in our study more than 80% of long-term breast cancer survivors did not have mild or severe symptoms of depression or anxiety.



Supplementary figure 1. Design of the study.

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Chapter 5

Fatigue among long-term breast cancer survivors: a controlled cross-sectional study

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ABSTRACT

Background: Fatigue is the most common and persistent symptom among women in the first five years after a breast cancer diagnosis. However, long-term prevalence of fatigue, among breast cancer survivors, needs further investigation.

Aim: To compare fatigue experienced by long-term breast cancer survivors with that in a reference population and to evaluate the determinants of that fatigue.

Design and Setting: A cross-sectional cohort study of 350 breast cancer survivors ≥ 5 years after diagnosis and a reference population of 350 women matched by age and general practitioner.

Method: Fatigue was measured using the Multidimensional Fatigue Inventory (MFI-20), and a sum score of >60 (multidimensional fatigue) was the primary outcome. Logistic regression was applied to compare the prevalence of multidimensional fatigue between the survivor and reference populations, adjusted for body mass index (BMI) and for cardiovascular and psychological variables. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated. Logistic regression was applied to evaluate the determinants of multidimensional fatigue among the survivors.

Results: Breast cancer survivors (median 10 years after diagnosis), more often experienced multidimensional fatigue than the reference population (26.6% versus 15.4%; OR, 2.0 [95%CI, 1.4-2.9]), even after adjusting for confounders. The odds of multidimensional fatigue were also higher among survivors with symptoms of depression (32.2% versus 2.7%; OR, 17.0 [95%CI, 7.1-40.5]) or anxiety (41.9% versus 10.1%; OR, 6.4 [95%CI, 3.6-11.4]).

Conclusion: One in four breast cancer survivors experience multidimensional fatigue and fatigue occurs more frequently than in women of the same age and general practitioner. This fatigue appears to be associated with symptoms of depression and anxiety.

INTRODUCTION

Breast cancer is the most common cancer among women [1], and due to an ageing population, its incidence is increasing in Western countries [2]. Fortunately, better treatment regimens mean that survival has also increased over recent decades, leading to a growth in the number of long-term survivors [3]. A downside of this has been that a growing population of women are experiencing the negative long-term effects of breast cancer therapy [4]. Among these effects, fatigue is the most common complaint among survivors, with a prevalence of 40%-80% [5,6]. Fatigue can be distressing and can severely affect daily life, potentially persisting into the long term [7]. Several mechanisms have been described to explain fatigue in survivors. It may be related to the disease itself, to the treatment, or to the physical or psychological side effects [8], having known associations with anxiety, depression, and cardiac dysfunction [9,10]. Fatigue also appears to be multidimensional, with different subtypes described, including general, physical, or mental fatigue, as well as reduced activity and reduced motivation [11]. Despite being studied extensively among breast cancer survivors, little is known about the long-term prevalence of fatigue in this population. Indeed, most studies have only reported data up to 5 years after diagnosis, and they have not compared fatigue among survivors to that among women with no cancer [12-16]. Given that fatigue is common in the general population, and the prevalence varies between studies (10.8%-21.6%) [17,18], such a comparison is necessary to enable the accurate interpretation of the data.

In this study, we evaluated the prevalence of multidimensional fatigue, and its persistence over time, among long-term breast cancer survivors compared to a reference population. We also evaluated the association of multidimensional fatigue with factors such as breast cancer treatment, cardiac dysfunction, depression, and anxiety.

METHODS

Context

In the Netherlands, almost all inhabitants are registered with a general practitioner (GP). All GPs record clinical contacts in electronic databases in which they assign codes according to the International Classification for Primary Care, and prescribed medication is coded using the Anatomical Therapeutic Chemical classification system [19,20].

BLOC Study

This present study was embedded in the previously published cross-sectional BLOC study [21,22], which was designed to explore the long-term effects of breast cancer treatment on cardiac dysfunction and psychological distress. Between 2013 and 2016, we compared 350 women treated for breast cancer 5 or more years previously to 350 women with no history of cancer matched by age and GP. Women with a local/locoregional recurrence were included if the recurrence was diagnosed more than five years ago. Half of the breast cancer survivors were treated with chemotherapy (with or without radiotherapy) and the other half were treated with radiotherapy alone. After receiving written informed consent, all participants completed questionnaires, underwent echocardiography, and had their BMI calculated. Details of cancer treatment and cardiovascular diagnoses were extracted from hospital files and GP medical records. The study was registered at ClinicalTrials.gov (accessed on 25 January 2021) (ID: NCT01904331) and approved by the medical ethics committee of the University Medical Center Groningen (UMCG).

Current Study

For the current study, we compared multidimensional fatigue between the two cohorts and explored the factors associated with multidimensional fatigue in breast cancer survivors. These factors included age, time since breast cancer diagnosis, type of cancer treatment, systolic cardiac dysfunction, cardiovascular disease (CVD), depression, and anxiety.

Primary Outcome

Multidimensional fatigue was measured with the Dutch version of the 20-item Multidimensional Fatigue Inventory (MFI-20) questionnaire [23]. This measures five subtypes of fatigue: general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation. In turn, each subtype has four questions that are each scored on a five-point Likert-scale to give subtypes scores of 4-20. Fatigue was considered present for a subtype if the subtype score was >12 [24], and multidimensional fatigue was considered present if the total score was >60 [25]. Participants were also classified as having severe multidimensional fatigue if they scored >12 on all subtypes.

Variables

Information on CVD was obtained from the electronic medical records of the participants' GPs. All CVD diagnoses up to the time of the cross-sectional study were included. A list of CVD codes that were included is provided in Supplementary Data S1. The presence of any of these codes in the participant's file was taken to indicate a diagnosis. Echocardiography was also performed to measure systolic cardiac function,

which we defined as a left ventricle ejection fraction (LVEF) <54%, using the biplane method of disk summation (modified Simpson's rule) recommended by the European Association for Cardiovascular Imaging/American Society of Echocardiography (EACVI/ASE) [26].

Depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS), a self-reporting questionnaire that comprises subscales for symptoms of depression (HADS-D) and anxiety (HADS-A). Each subtype consists of seven items, with scores ranging from 0 to 3 per item. For this study, we used a cut-off of ≥ 8 per subscale to indicate the presence of depression or anxiety symptoms (includes both mild and severe). The HADS performs well in recognizing depression and anxiety disorders [27]. Contrasting with other questionnaires to identify depression or anxiety symptoms, the HADS does not include a question about tiredness or sleeping difficulties [23].

Statistics

Medians and interquartile ranges (IQRs) are reported to describe continuous variables, whereas numbers and percentages are reported to describe categorical variables. For the purpose of analyses, the date of breast cancer diagnosis, functioned as the index date for the matched control. Hereby, we could make a comparison between the breast cancer survivors and matched controls, including adjusting for time since diagnosis. Univariate logistic regression was used to evaluate the prevalence of multidimensional fatigue (sum score >60), and its persistence over time, among long-term survivors compared to the reference population. We set the presence of multidimensional fatigue (yes or no) as the outcome of interest and stratified the analyses according to time since diagnosis for women <10 years and those at ≥ 10 years after diagnosis. In multivariable logistic regression, the results were adjusted for time since diagnosis ≥ 10 years, BMI >30, LVEF <54%, CVD ≥ 1 , HADS-D ≥ 8 , and HADS-A ≥ 8 . The presence of severe multidimensional fatigue and the fatigue subtypes were evaluated in the same way. In addition, an independent-samples t-test was conducted to compare the mean sum MFI score for breast cancer survivors to the mean sum MFI of the reference population. This analysis was repeated, stratified for time since diagnosis for women <10 years versus ≥ 10 years after breast cancer diagnosis.

We performed further univariate logistic regression analyses to evaluate the associations between being a breast cancer survivor with or without multidimensional fatigue (the outcome) and the various factors of interest (the determinants). The following factors were considered: age > 30, LVEF $\geq 54\%$ at assessment, ≥ 10 years since diagnosis, BMI > 30, treatment (chemo- and or radiotherapy), hormonal therapy, CVD ≥ 1 , LVEF < 54%, HADS-D ≥ 8 , and HADS-A ≥ 8 . We applied a full model in the multivariable logistic regression, adjusting for all variables and describing the absolute effects of statistically significant

associations between the factors and multidimensional fatigue. This was repeated for severe multidimensional fatigue and all fatigue subtypes. All analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA)

RESULTS

Participants had a median age of 63 (IQR 57-68) years and breast cancer survivors had a median follow-up duration of 10 (IQR 7-14) years after diagnosis (Table 1). A total of 22 breast cancer survivors were included (≥ 5 years) after a local/locoregional recurrence.

Fatigue among Survivors and Reference Population

Breast cancer survivors experienced multidimensional fatigue significantly more often than the reference population (26.6% vs. 15.4%; OR, 2.0 [95%CI, 1.4-2.9]; Table 2). This remained for survivors 10 years after diagnosis (24.3% vs. 16.9%; OR, 1.6 [95%CI, 0.95-2.6]). The mean sum score of the MFI was significantly higher for breast cancer survivors in comparison to the reference population. Moreover, breast cancer survivors in both stratified groups (time since diagnosis < 10 years or ≥ 10 years) had significantly higher mean sum scores on the MFI than the reference population.

Severe multidimensional fatigue was significantly more prevalent among survivors than in the reference population, (6.6% vs. 1.7%; OR, 4.0 [95%CI, 1.6-10.1]), as was each fatigue subtype: general fatigue (40.7% vs. 25.4%; OR, 2.0 [95%CI, 1.5-2.8]), physical fatigue (32.6% vs. 20.9%; OR, 1.8 [95%CI, 1.3-2.6]), reduced activity (24.0% vs. 14.0%; OR, 1.9 [95%CI, 1.3-2.9]), reduced motivation (17.8% vs. 11.7%; OR, 1.6 [95%CI, 1.1-2.5]), and mental fatigue (26.3% vs. 14.3%; OR, 2.1 [95%CI, 1.5-3.1]). After adjusting for time since diagnosis (≥ 10 years), BMI > 30 , systolic cardiac dysfunction, CVD, depression, and anxiety, the odds remained significant for all fatigue subtypes except for reduced motivation.

Fatigue among Breast Cancer Survivors

As shown in Table 3, symptoms of depression or anxiety were significantly more common among breast cancer survivors with (OR, 17.0 [95%CI, 7.1-40.5]) than without (OR, 6.4 [95%CI, 3.6-11.4]) multidimensional fatigue. These odds remained significant after adjusting for age, time since diagnosis (≥ 10 years), BMI > 30 , chemo- and or radiotherapy, hormonal therapy, systolic cardiac dysfunction, CVD, depression, and anxiety. Multidimensional fatigue among breast cancer survivors was not significantly associated with cardiac dysfunction (OR, 1.3 [95%CI, 0.7-2.5]) or CVD (OR, 1.8 [95%CI, 0.97-3.3]). Finally, multidimensional fatigue was experienced by 81.1% of the survivors with symptoms of depression and by 60.0% of those with symptoms of anxiety, with both

being considerably higher than the 26.6% (95%CI, 22.0-31.5%) observed among all breast cancer survivors (Table 4). Comparable data were observed for severe multidimensional fatigue and all subtypes of fatigue.

Table 1. Characteristics of breast cancer survivors and a reference population at the time of assessment [21,22].^a

| | Breast Cancer Survivors^f (n = 350) | Controls (n = 350) |
|--|--|-------------------------------------|
| Age; years, median (IQR) | 63 (57-68) | 63 (57-68) |
| Time since diagnosis of breast cancer or index date; years, median (IQR) | 10 (7-14) | 10 (7-14) |
| BMI > 30, n (%) | 69 (19.7%) | 70 (20%) |
| | n (%) | n (%) |
| Breast cancer stage | | |
| Stage 0 | 13 (3.7%) | |
| Stage I | 123 (35.1%) | |
| Stage II | 161 (46%) | |
| Stage III | 28 (8%) | |
| Unknown | 25 (7.1%) | |
| Breast cancer treatment^b | | |
| Chemotherapy ^c | 175 (50.0%) | - |
| Radiotherapy ^d | 295 (84.3%) | - |
| Hormonal therapy | 146 (41.7%) | - |
| Variables | | |
| LVEF < 54% | 52 (15.3%) | 24 (7.0%) |
| CVD ≥ 1 | 54 (15.4%) | 31 (8.9%) |
| Cardiac risk factor ^e | 139 (39.7%) | 135 (38.6%) |
| HADS-D ≥ 8 | 37 (10.6%) | 17 (4.9%) |
| HADS-A ≥ 8 | 65 (18.6%) | 57 (16.3%) |

^a IQR = interquartile range; BMI = body mass index; LVEF = left ventricle ejection fraction; CVD = cardiovascular diseases; HADS = Hospital Anxiety and Depression Scale.

^b As registered in the hospital and general practitioners' files.

^c Including breast cancer survivors who have received chemo- and radiotherapy n = 120 (68.6%), and breast cancer survivors who have received chemotherapy and hormonal therapy n = 109 (62.3%).

^d Including breast cancer survivors who have received radiotherapy and hormonal therapy, n = 37 (21.1%).

^e Cardiac risk factors: diabetes, hypertension, or dyslipidemia.

^f Including 22 breast cancer survivors ≥ 5 years after a local/locoregional recurrence.

Table 2. Scores on fatigue amongst breast cancer survivors (n = 350) in comparison to a reference population (n = 350), measured with the MFI-20 questionnaire. ^a

| | Breast Cancer Survivors n = 350 | Reference Population n = 350 |
|---|--|---|
| Multidimensional fatigue | | |
| All women (n = 350) | | |
| Sum score >60, n (%) | 93 (26.6%) | 54 (15.4%) |
| Sum score, mean (SD) ^d | 49.0 (17.9) | 42.7 (15.7) |
| Time since diagnosis < 10 yrs (n = 161) | | |
| Sum score, mean (SD) | 50.9 (19.1) | 41.3 (14.6) |
| Age: median 61 (IQR 55-67) years | | |
| FU: median 7 (IQR 6-8) years | | |
| Time since diagnosis ≥ 10 yrs (n = 189) | | |
| Sum score, mean (SD) | 47.3 (16.8) | 43.8 (16.5) |
| Age: median 65 (IQR 58-69) years | | |
| FU: median 14 (IQR 11-17) years | | |
| Severe multidimensional fatigue | | |
| All 5 subtypes scores >12, n (%) | 23 (6.6%) | 6 (1.7%) |
| Fatigue, subtypes | | |
| General fatigue | | |
| n (% >12) ^e | 142 (40.7%) | 89 (25.4%) |
| Median (25-75%) | 11 (7-15) | 9 (5-13) |
| Physical fatigue | | |
| n (% >12) | 114 (32.6%) | 73 (20.9%) |
| Median (25-75%) | 10 (6-14) | 10 (6-14) |
| Reduced activity | | |
| n (% >12) | 84 (24.0%) | 49 (14.0%) |
| Median (25-75%) | 9 (6-12) | 9 (6-12) |
| Reduced motivation | | |
| n (% >12) | 62 (17.8%) | 41 (11.7%) |
| Median (25-75%) | 8 (5-11.5) | 8 (5-11.5) |
| Mental fatigue | | |
| n (% >12) | 92 (26.3%) | 50 (14.3%) |
| Median (25-75%) | 8 (5-13) | 8 (5-13) |

^a MFI = Multidimensional Fatigue Inventory; IQR = interquartile range; FU = follow-up; BMI = body mass index; LVEF = left ventricle ejection fraction; CVD = cardiovascular diseases; HADS = Hospital Anxiety and Depression Scale; OR = odds ratio; CI = confidence intervals.

^b Significant results are in bold.

^c Multivariable analysis for breast cancer adjusted for time since diagnosis ≥10 years, BMI > 30, LVEF > 54%, CVD ≥ 1, HADS-D ≥ 8, HADS-A ≥ 8.

| Univariate Analyses | Multivariable Analyses |
|--------------------------------|----------------------------------|
| OR (95%CI) ^b | OR (95%CI) ^{b,c} |
| 2.0 (1.4-2.9) | 1.7 (1.1-2.6) |
| 2.6 (1.5-4.5) | 2.0 (1.0-3.7) |
| 1.6 (0.95-2.6) | 1.5 (0.8-2.7) |
| 4.0 (1.6-10.1) | 3.1 (1.2-8.3) |
| 2.0 (1.5-2.8) | 1.9 (1.4-2.8) |
| 1.8 (1.3-2.6) | 1.6 (1.1-2.3) |
| 1.9 (1.3-2.9) | 1.7 (1.1-2.6) |
| 1.6 (1.1-2.5) | 1.3 (0.8-2.1) |
| 2.1 (1.5-3.1) | 2.0 (1.3-3.1) |

^d Tested with the independent-samples t-test, significant p < 0.05.

^e Definitions: fatigue, subtype score >12; multidimensional fatigue, overall score >60; severe multidimensional fatigue, all subtypes score >12.

Table 3. Comparison of breast cancer survivors with (n = 93) and without (n = 257) multidimensional fatigue. ^a

| | | Survivors with Multidimensional Fatigue n = 93 |
|--|-----|---|
| | | n (%) |
| Age at time of assessment >65 years | No | 54 (58.1%) |
| | Yes | 39 (41.9%) |
| Time since diagnosis breast cancer ≥10 years | No | 47 (50.5%) |
| | Yes | 46 (49.5%) |
| BMI > 30 | No | 80 (86.0%) |
| | Yes | 13 (14.0%) |
| CT (+/-RT) | No | 44 (47.3%) |
| | Yes | 49 (52.7%) |
| Hormonal therapy | No | 47 (50.5%) |
| | Yes | 46 (49.5%) |
| LVEF < 54% | No | 72 (77.4%) |
| | Yes | 16 (17.2%) |
| CVD ≥ 1 | No | 73 (78.5%) |
| | Yes | 18 (19.4%) |
| HADS-Depression ≥ 8 | No | 63 (67.7%) |
| | Yes | 30 (32.3%) |
| HADS-Anxiety ≥ 8 | No | 54 (58.1%) |
| | Yes | 39 (41.9%) |

^a Definition: multidimensional fatigue, overall score >60.

^b BMI = body mass index; RT = radiotherapy; CT = chemotherapy; LVEF = left ventricle ejection fraction; CVD = cardiovascular diseases; HADS = Hospital Anxiety and Depression Scale; OR = odds ratio; CI = confidence intervals.

| Survivors without Multidimensional Fatigue <i>n</i> = 257 | Univariate Analyses | Multivariable Analyses |
|---|-------------------------|---------------------------|
| <i>n</i> (%) | OR (95%CI) ^c | OR (95%CI) ^{c,d} |
| 162 (63.0%) | 1 | 1 |
| 95 (37.0%) | 1.2 (0.8-2.0) | 1.2 (0.6-2.2) |
| 114 (44.4%) | 1 | 1 |
| 143 (55.6%) | 0.8 (0.5-1.3) | 0.8 (0.5-1.5) |
| 201 (78.2%) | 1 | 1 |
| 56 (21.8%) | 0.6 (0.3-1.1) | 0.5 (0.2-1.2) |
| 131 (51.0%) | 1 | 1 |
| 126 (49.0%) | 1.2 (0.7-1.9) | 1.0 (0.6-2.0) |
| 152 (59.1%) | 1 | 1 |
| 105 (40.9%) | 1.4 (0.9-2.3) | 1.3 (0.7-2.4) |
| 215 (83.7%) | 1 | 1 |
| 36 (14.0%) | 1.3 (0.7-2.5) | 0.9 (0.4-1.9) |
| 223 (86.8%) | 1 | 1 |
| 34 (13.2%) | 1.8 (0.97-3.3) | 1.9 (0.9-4.0) |
| 250 (97.3%) | 1 | 1 |
| 7 (2.7%) | 17.0 (7.1-40.5) | 8.9 (3.4-23.5) |
| 231 (89.9%) | 1 | 1 |
| 26 (10.1%) | 6.4 (3.6-11.4) | 3.7 (1.9-7.3) |

^c Significant results are in bold.

^d Adjusted for: age at the time of assessment > 65 years, time since diagnosis ≥10 years, BMI > 30, treatment (chemo- and or radiotherapy), hormonal therapy, LVEF > 54%, a diagnosis of CVD, HADS-D ≥ 8, HADS-A ≥ 8.

Table 4. Fatigue among breast cancer survivors (n = 350) overall and stratified for women with symptoms of depression (n = 37) or anxiety (n = 65).^a

| | All Breast Cancer Survivors n = 350 | HADS-Depression ≥ 8 n = 37 | HADS-Anxiety ≥ 8 n = 65 |
|---------------------------------|--|---------------------------------------|------------------------------------|
| | n (%; 95%CI's)^b | n (%) | n (%) |
| Multidimensional fatigue | 93 (26.6%; 22.0-31.5) | 30 (81.1%) | 39 (60.0%) |
| Severe multidimensional fatigue | 23 (6.6%; 4.2-9.7) | 10 (27.8%) | 13 (20.3%) |
| Fatigue, subtypes | | | |
| General fatigue | 142 (40.7%; 35.4-45.9%) | 30 (83.3%) | 45 (70.3%) |
| Physical fatigue | 114 (32.6%; 27.7-37.8) | 28 (75.7%) | 39 (60.0%) |
| Mental fatigue | 92 (26.3%; 21.7-31.2) | 27 (73.0%) | 44 (67.7%) |
| Reduced activity | 84 (24.0%; 19.6-28.8) | 22 (59.5%) | 28 (43.1%) |
| Reduced motivation | 62 (17.8%; 13.9-22.1) | 23 (62.2%) | 26 (40.0%) |

^aHADS = Hospital Anxiety and Depression Scale; CI = confidence intervals.

^b Bold if the percentage with fatigue is higher than the upper bound of the 95%CI for the group 'All breast cancer survivors'.

DISCUSSION

Summary

A quarter of the long-term breast cancer survivors in our cohort experienced multidimensional fatigue, and this occurred significantly more often than in a reference population of the same age. After considering the time since diagnosis, survivors experienced more fatigue than the reference population. Multidimensional fatigue among survivors was significantly associated with symptoms of depression and anxiety, but not with cardiac dysfunction or CVD. Indeed, breast cancer survivors with symptoms of depression or anxiety had higher levels of all fatigue subtypes. There is a need for greater awareness of persistent multidimensional fatigue and psychological problems in these women.

Comparison with Existing Literature

Fatigue is known to be a persistent symptom after treatment for breast cancer [28]. In our study, we additionally confirmed that this fatigue persists for a longer period than has previously been reported. Indeed, after a median follow-up of 10 years, 26.6% of breast cancer survivors experienced multidimensional fatigue, which is consistent with previous estimates from studies with shorter follow-up periods. A meta-analysis of patients with several types of cancer, reported a pooled prevalence of fatigue of 26.9% with a maximum follow-up of 10 years [29]. Studies of breast cancer survivors ≥5 years after diagnosis report prevalence rates of 16%-35% [13,30-32]. These estimates are particularly

noteworthy given that we included survivors with a median of 10 years' follow-up (IQR 7-14 years), whereas other researchers have included survivors up to 7 years after diagnosis, except for Bower et al., who included patients up to 10 years after diagnosis (mean 6.3 ± 1.0 years). In addition, Cella et al. reported that, ≥ 5 years after diagnosis, 33% of breast cancer survivors experienced at least 2 weeks of fatigue in the month before they were interviewed [28]. The wide range of estimates can be explained by the use of different questionnaires and contrasting time periods from diagnosis.

Overall, we showed that the differences in multidimensional fatigue between breast cancer survivors and controls were statistically significant up to 10 years after diagnosis, supporting the results of studies with different methodologies [33,34]. However, in this study, also breast cancer survivors 10 or more years after diagnosis scored significantly higher on fatigue than the reference population. The relatively older age of our long-term breast cancer survivors may contribute both to their symptom burden and to the persistence of fatigue, similar to the results of a study amongst older breast cancer survivors questioned 3 years after diagnosis [35]. After 10 years of follow-up, however, any differences become less significant because of the increase in the prevalence of fatigue among the reference population. This finding was also reported in a study comparing cancer patients of different ages with the general population [36].

In the present study, symptoms of depression and anxiety were significantly associated with multidimensional fatigue among long-term breast cancer survivors. Similarly, other researchers have established an association between fatigue, depression, and anxiety in studies of breast cancer survivors over 2 years [37]. Bower et al., for example, found an association between psychological factors and adverse fatigue trajectories up to 6 years after diagnosis [38].

Strengths and Limitations

A strength of this study is that we performed the comparison with a reference population matched by age and GP. This approach allowed us to separate the effects of breast cancer and its treatment from the effects of ageing over the long study duration. By including a random sample of breast cancer survivors and then enquiring about fatigue, we are also able to provide a more accurate prevalence measure than had we relied on women visiting a clinic. Another strength is that we only included breast cancer survivors at least 5 years after diagnosis, which resulted in a cohort median of 10 years since diagnosis. Although previous studies have reported that fatigue is persistent, none has used such a long follow-up period. Given the increasing number of long-term breast cancer survivors, it is important to know if fatigue persists this long after diagnosis. Measuring fatigue with the MFI-20 was also beneficial because it includes multiple fatigue subtypes, allowing for these to be stratified and for key issues to be identified.

Despite the strengths of our research, it is important to note that using strict cut-offs for the fatigue and severe fatigue subtypes may have resulted in an underestimation of the true prevalence [39]. Another limitation is that GPs may have coded inconsistently, which could have led to cases of CVD being missed and an underestimation of CVD diagnoses. By matching survivors and controls by the same GP, we anticipate that the impact on the comparison should be minimized. However, absolute numbers could have been underestimated and resulted in an underpowered analysis of the association with multidimensional fatigue. In addition, we did not adjust for all known determinants for fatigue [29,40]. We also measured cardiac function by echocardiography rather than the gold standard of cardiovascular MRI [41], although this should be tempered with knowledge that measuring the ejection fraction by Simpson's 2D echo has been shown to produce comparable results [42]. Finally, the cross-sectional design precludes any comment on the course and causality related to fatigue among breast cancer survivors.

Implications for Research and/or Practice

Of note, approximately a quarter of breast cancer survivors still experienced multidimensional fatigue after more than 10 years of follow-up. However, because more women in the reference population also experienced multidimensional fatigue as women aged, the statistical significance of the difference was lost over time. Future research should explore this finding and the course of fatigue in a longitudinal study.

Regarding the clinical implications, our findings indicate that GPs should be vigilant for long-term (multidimensional) fatigue. Other research has shown that physical activity and exercise improve cancer-related fatigue, depression, and overall quality of life [43]. If fatigue is related to depression or anxiety, these could be modifiable factors that could improve fatigue if targeted appropriately. Fortunately, treatment options for depression and anxiety have proven to be as effective in cancer survivors as in the general population [44]; for example, cognitive behavioural therapy has been proven effective in breast cancer survivors [45]. It was also evident that depression and anxiety were associated with reduced motivation among breast cancer survivors, possibly implying that survivors with fatigue and reduced motivation may have depression or anxiety, or that stimulating motivation may be a necessary first step towards improvement.

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Chapter 6

Symptoms in long-term breast cancer survivors: a cross-sectional study in primary care

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ABSTRACT

Purpose: Various long-term symptoms can manifest after breast cancer treatment, but we wanted to clarify whether these are more frequent among long-term breast cancer survivors than matched controls and if they are associated with certain diagnoses.

Methods: This was a cross-sectional, population-based study of 350 breast cancer survivors treated with chemo- and/or radiotherapy ≥ 5 years (median 10) after diagnosis and 350 women without cancer matched by age and primary care physician. All women completed a questionnaire enquiring about symptoms, underwent echocardiography to assess the left ventricle ejection fraction, and completed the Hospital Anxiety and Depression Scale. Cardiovascular diseases were diagnosed from primary care records. In a multivariable logistic regression analysis, symptoms were adjusted for the long-term effects and compared between cohorts and within the survivor group.

Results: Concentration difficulties, forgetfulness, dizziness, and nocturia were more frequent among breast cancer survivors compared with controls, but differences could not be explained by cardiac dysfunction, cardiovascular diseases, depression, or anxiety. Intermittent claudication and appetite loss were more frequent among breast cancer survivors than controls and associated with cardiac dysfunction, depression, and anxiety. Breast cancer survivors treated with chemotherapy with/without radiotherapy were at significantly higher odds of forgetfulness and nocturia, but significantly lower odds of dizziness, compared with breast cancer survivors treated with radiotherapy alone.

Conclusions: Intermittent claudication and appetite loss are common among breast cancer survivors and are associated with cardiac dysfunction and mood disorders. Other symptoms varied by whether the patient underwent chemotherapy with/without radiotherapy (forgetfulness and nocturia) radiotherapy alone (dizziness).

INTRODUCTION

The incidence of breast cancer has increased over recent decades [1], but thanks to better staging and treatment, there has been a marked increase in the number of long-term survivors [2]. Most women are treated with chemo- and/or radiotherapy, and although highly effective, these may cause long-term effects, such as cardiac dysfunction, depression, anxiety, concentration difficulties, and forgetfulness. Indeed, previous studies have showed that breast cancer survivors treated with chemo- and/or radiotherapy may develop systolic cardiac dysfunction or cardiovascular disease (CVD) up to 10 years after diagnosis [3-7]. In women, such dysfunction often has a vague onset that can lead to undertreatment [8]. Long-term breast cancer survivors are also at a higher odds of depressive and anxiety symptoms than their peers with no history of cancer [9-12]. Cognitive effects, such as concentration difficulties and forgetfulness, are known effects of chemotherapy [13,14]. Overall, timely diagnosis and treatment can lessen the impact on quality of life of these long-term sequelae.

Women often experience symptoms that have low predictive value, making it hard to match the correct diagnosis and therapy. In addition, the same symptoms are often reported to primary care physicians (PCPs) by women without cancer, making it unclear if the incidence is truly increased in breast cancer survivors (see Box 1). It is essential that PCPs have a clear understanding of this issue because all inhabitants of the Netherlands are registered with a PCP, and for most long-term survivors, hospital follow-up is discontinued after 5 years. Given that the PCP is responsible for long-term care and that their electronic patient records include all diagnoses by International Classification of Primary Care (ICPC) code [45], their practices offer an ideal setting to assess long-term effects.

In this study, we aimed to identify which symptoms are more prevalent among long-term breast cancer survivors compared with a reference population with no history of cancer. Furthermore, we wanted to determine if symptoms are associated with cardiac dysfunction, CVD, depression, anxiety, or a history of breast cancer treatment with chemotherapy and/or radiotherapy.

METHODS

Study design and sample

The present analysis is based on data derived in the cross-sectional BLOC study (Breast cancer Long-term Outcome Cardiac dysfunction). In brief, the BLOC study compared the prevalence of cardiac dysfunction between women in two groups: 350 treated for breast

cancer with chemo- and/or radiotherapy >5 years after diagnosis (the breast cancer survivor group); and 350 with no history of cancer or chemotherapy (the control group). Additional details have been described elsewhere [5].

Box 1. Illustrative Case

A 56-year-old woman presented with fatigue, palpitations, and loss of concentration 7 years after treatment for breast cancer (including chemo- and radiotherapy). These symptoms were affecting her daily functioning, so she sought treatment or reassurance from a primary care physician. The physician was uncertain whether the presenting symptoms were due to the well-known long-term effects of breast cancer (e.g., cardiac dysfunction, CVD, depression or anxiety), the history of breast cancer treatment, or some other etiology.

Women were included from the electronic patient records of 80 PCPs in the north of the Netherlands if they had been free of disease for at least 5 years. ICPC code X78, for breast cancer, was the primary inclusion criterion (668 invited, 350 responded; response rate, 52%). The exclusion criteria were treatment for other types of cancer or for rheumatic arthritis, age >80 years, or metastasis at the time of diagnosis. For each included survivor, we randomly selected a control woman of the same age from the same PCP records if they had no history of cancer or chemotherapy (1365 invited, 350 responded; response rate, 26%). All participants filled out a written consent form.

Of the breast cancer survivor group, 175 received chemotherapy (with or without radiotherapy) and 175 received radiotherapy alone. In the chemotherapy (with or without radiotherapy) subgroup, 81.1% were treated with anthracyclines (doxorubicin [$n = 53$] or epirubicin [$n = 89$]) and 68.6% received additional radiotherapy. No patient received high-dose doxorubicin ($>400 \text{ mg/m}^2$) or epirubicin ($>900 \text{ mg/m}^2$) [15]. In general, radiotherapy in the Netherlands in this cohort consisted of LINAC-based photon tangential fields to a dose of 50 Grey with or without a boost up to 66 Grey [16], and 97% of the survivors were irradiated after 1990. Hormonal therapy was given to 146 breast cancer survivors, and this usually stopped after five years.

The BLOC study found that breast cancer survivors more often had systolic cardiac dysfunction (left ventricular ejection fraction [LVEF] $<54\%$) and more diagnoses of CVD compared with controls. Crucially, these associations remained after adjustment for

relevant covariates at diagnosis and at the time of the cross-sectional assessment [5]. In addition, breast cancer survivors more often had (severe) symptoms of depression and anxiety, even after adjusting for a diagnosis of depression and/or antidepressant use at the time of breast cancer diagnosis and for the time since diagnosis [12].

Current study

In the current analysis, all 700 women from the BLOC study were included and interviewed by trained medical students about the occurrence of 18 specific symptoms during the previous 3 weeks, following a structured anamnestic questionnaire (single item scale) [17]. The primary outcome was the prevalence of these symptoms compared between breast cancer survivors and controls. The secondary outcome was the prevalence of symptoms among breast cancer survivors treated with chemotherapy (with or without radiotherapy) compared with those who received radiotherapy alone.

Instruments

Outcomes for cardiac dysfunction, CVD, depression, or anxiety were included to assess the possible association with symptoms. Systolic cardiac dysfunction was defined as an LVEF <54%, according to the European Association of Echocardiography/American Society of Echocardiography guideline [18]. CVD was diagnosed based on the presence of certain ICD codes in the electronic patient record (Supplement 1). Symptoms of depression and anxiety were measured with the Hospital Anxiety and Depression Scale (HADS) that has depression (HADS-D) and anxiety (HADS-A) subscales. Each subscale has seven items that are scored 0-3, giving a maximum score of 21 [19,20]. Both subscales have acceptable specificities and sensitivities (0.80) and perform well when assessing symptom severity and the presence of anxiety disorders and depression in primary care patients [21].

Analyses/statistics

Descriptive data are reported as medians and interquartile ranges (IQRs) for continuous variables and as numbers with percentages for discrete variables. In univariate logistic regression analysis, the presence of each symptom was compared between breast cancer survivors and the reference population, reporting estimated odds ratios (ORs) and 95% confidence intervals (95% CIs). Any symptoms with ORs ≥ 1.5 were adjusted by the LVEF value, presence/absence of CVD, and HADS scores (total, HADS-D, and HADS-A) and the adjusted ORs were considered stable if they remained unchanged or changed by <10% from baseline. Analysis of these symptoms was stratified to compare breast cancer survivors who received chemotherapy with/without radiotherapy and those who received radiotherapy alone. Given that women who received radiotherapy alone were older, analysis was adjusted for age at assessment. A P-value of <0.05 was considered statistically significant. All analyses were performed using IBM SPSS for Windows, Version 23.0 (IBM Corp., Armonk, NY).

RESULTS

Symptoms among breast cancer survivors versus the reference population

Table 1 shows the characteristics of the 700 women included in the cross-sectional BLOC study. The median time since breast cancer diagnosis was 10 (IQR 7-14) years and the median age at assessment was 63 (IQR 57-68) years. More breast cancer survivors were diagnosed with diabetes mellitus than controls (8.3% versus 4.3%). Table 2 shows that six of the eighteen included symptoms were experienced more by breast cancer survivors than by the reference population. Breast cancer survivors experienced the following significantly more often than the reference population: concentration difficulties (22.9% versus 10.6%; OR 2.5 [95%CI, 1.6-3.8]), forgetfulness (22.9% versus 14.6%; OR 1.7 [95%CI, 1.2-2.6]), dizziness (27.1% versus 18.0%; OR 1.7 [95%CI, 1.2-2.4]), and nocturia (25.7% versus 18.6%; OR 1.5 [95%CI, 1.1-2.2]) (Table 2).

Symptoms with ORs ≥ 1.5 were entered into multivariate analysis and adjusted for LVEF, CVD, HADS-total, HADS-D, and HADS-A (Table 3). Of note, the ORs for concentration difficulties, forgetfulness, dizziness, and nocturia remained significant and changed minimally after adjustment. However, although breast cancer survivors were at a significantly higher odds than the reference population for experiencing appetite loss in the univariate analysis (6% versus 2.6%; OR 2.4 [95%CI, 1.1-5.4]; Table 2), this did not remain significant after adjusting for CVD, HADS, HADS-D, and HADS-A (Table 3). Breast cancer survivors were also at significantly increased odds of experiencing intermittent claudication in the univariate analysis (7.3% versus 3.5%; OR 2.2 [95%CI, 1.1-4.6]; Table 2), but this did not remain after adjustment for LVEF, CVD, or HADS-A (Table 3).

Symptoms in breast cancer survivors: chemotherapy versus radiotherapy only

We analyzed the eight symptoms with ORs ≥ 1.5 and found that three were significantly different between the two groups (Table 4). Compared with breast cancer survivors who received radiotherapy alone, those who received chemotherapy (with/without radiotherapy) had a higher odds of forgetfulness (OR 1.8 [95%CI, 1.0e3.0]) and nocturia (OR 1.9 [95%CI, 1.1-3.2]), whereas the odds of dizziness was lower (OR 0.6 [95%CI, 0.4-0.97]). These results remained significant after adjusting for LVEF, CVD, HADS, HADS-D, and HADS-A.

Table 1. BLOC study: Characteristics of breast cancer survivors and the reference population. [5,12]

| | Breast cancer survivors N = 350 | Reference population N = 350 |
|--|--|---|
| | Years Median (IQR)^a | Years Median (IQR) |
| Time since breast cancer diagnosis | 10 (7-14) | - |
| Age at cross-sectional assessment | 63 (57-68) | 63 (57-68) |
| | N (%) | N (%) |
| Adjuvant therapy | | |
| Chemotherapy | 175 (50.0) | - |
| <i>Anthracycline-base</i> | 142 (40.6) | - |
| <i>Cumulative anthracycline dose; mg/m², median (IQR)</i> | 238 (228-240) | - |
| Radiotherapy | 295 (84.3) | - |
| Hormonal therapy | 146 (41.7) | - |
| Comorbidity^b | | |
| Cardiovascular diseases | 49 (14.0) | 26 (7.4) |
| Risk factors for CVD^b | | |
| Dyslipidemia | 54 (15.4) | 58 (16.6) |
| Hypertension | 108 (30.9) | 106 (30.3) |
| Diabetes mellitus | 29 (8.3) | 16 (4.6) |
| | Median (IQR) | Median (IQR) |
| Left ventricular ejection fraction (LVEF)^c | 58 (55-61) | 59 (57-62) |
| Hospital Anxiety and Depression Scale (HADS) | | |
| HADS-Depression | 7 (4-11) | 6 (4-10) |
| HADS-Anxiety | 2 (1-4) | 2 (1-4) |
| | 5 (3-7) | 4 (3-6) |

Significant results are in bold.

^a IQR = interquartile range.

^b As registered in files of the general practitioner.

^c Measured by Simpson's biplane (61.8%) or BiPQ/estimate (38.2%), not available for women with atrial fibrillation during measurement (N = 6) and women with immeasurable LVEF (N = 14).

Table 2. Symptom comparison between breast cancer survivors and the reference population.

| | Breast cancer survivors (N = 350) | Reference population (N = 350) | Univariate comparison OR (95%CI) ^a |
|------------------------------------|--|---|--|
| | N (%) | N (%) | OR (95%CI) ^a |
| Concentration difficulties | 80 (22.9) | 37 (10.6) | 2.5 (1.6-3.8) |
| Forgetfulness | 80 (22.9) | 51 (14.6) | 1.7 (1.2-2.6) |
| Dizziness | 95 (27.1) | 63 (18.0) | 1.7 (1.2-2.4) |
| Nocturia | 90 (25.7) | 65 (18.6) | 1.5 (1.1-2.2) |
| Appetite loss | 21 (6.0) | 9 (2.6) | 2.4 (1.1-5.4) |
| Intermittent claudication | 23 (7.3) | 11 (3.5) | 2.2 (1.1-4.6) |
| Chest pain | 32 (9.1) | 21 (6.0) | 1.6 (0.9-2.8) |
| Abdominal bloating | 72 (20.6) | 53 (15.1) | 1.5 (0.98-2.1) |
| Cough when lying down | 47 (13.4) | 34 (9.7) | 1.4 (0.9-2.3) |
| Shortness of breath after exertion | 106 (30.3) | 87 (24.9) | 1.3 (0.9-1.8) |
| Fatigue after exertion | 97 (27.7) | 79 (22.6) | 1.3 (0.9-1.9) |
| Palpitations | 82 (23.4) | 66 (18.9) | 1.3 (0.9-1.9) |
| Edema ankles | 65 (18.6) | 51 (14.6) | 1.3 (0.9-2.0) |
| Radiating chest pain | 10 (3.0) | 8 (2.4) | 1.2 (0.5-3.2) |
| Cold extremities | 130 (37.1) | 121 (34.6) | 1.1 (0.8-1.5) |
| Constipation | 64 (18.3) | 57 (16.3) | 1.1 (0.8-1.7) |
| Weight gain | 33 (9.4) | 30 (8.6) | 1.1 (0.7-1.9) |
| Sleeping difficulty | 140 (40.0) | 140 (40.0) | 1.0 (0.7-1.4) |

Significant results are in bold.

^a OR = Odds Ratio, unadjusted.

^b The multivariate analysis only performed when the odds ratio is 1.5 or higher.

DISCUSSION

The aim of this study was to investigate which symptoms are more prevalent among breast cancer survivors in comparison to women with no history of cancer. And, to assess the association with several diagnoses associated with breast cancer and its therapy. We found that breast cancer survivors experienced concentration difficulties, dizziness, forgetfulness, and nocturia more often than a reference population. Given that we found no association with systolic cardiac dysfunction, CVD, depression, or anxiety, it is plausible that these symptoms were associated with the chemotherapy or radiotherapy given during breast cancer treatment. Survivors also experienced more intermittent claudication and appetite loss: the former was associated with breast cancer treatment, systolic dysfunction, CVD, and anxiety; and the latter was associated with breast cancer treatment, CVD, depression, and anxiety. Among the survivors who received chemotherapy (with/ without radiotherapy), forgetfulness and nocturia were more frequent and dizziness was less frequent compared with the breast cancer survivors who received radiotherapy alone. Notably, most of the symptoms were not significantly more present among breast cancer survivors.

Consistent with our results, several studies have found that long-term breast cancer survivors treated with chemotherapy experienced more cognitive impairment (i.e., forgetfulness and concentration difficulties) than reference populations [23-27]. However, the methods used in these studies were heterogeneous, making comparison difficult. Dizziness has been associated with breast cancer survivors in previous studies and has been shown to have a negative effect on quality of life [28], but this symptom can result for other reasons [29]. Only one other study has mentioned nocturia as a symptom of breast cancer survivors [30], but that was done in the context of discussing the control of postmenopausal symptoms and did not compare the frequency of nocturia between cases and controls. However, given that hormone replacement therapy is not recommended for breast cancer survivors, this might explain the high incidence of nocturia in this group. Another explanation could be the high prevalence of diabetes mellitus among the breast cancer survivors in this study, since nocturia is associated with uncontrolled blood glucose levels. Some guidelines do include symptom-specific advice, but these mainly cover disorders instead of individual symptoms, except for fatigue [31-33]. To our knowledge, there is no available literature on the prevalence of intermittent claudication or appetite loss in long-term survivors of breast cancer.

Table 3. Symptoms adjusted for in the multivariate analysis, comparing breast cancer survivors with an age- and PCP-matched reference population.

| Multivariate analyses, OR (95%CI) ^a | | |
|--|----------------------|----------------------|
| | LVEF (continuous) | CVD (dichotomous) |
| Concentration difficulties | 2.5 (1.6-3.9) | 2.6 (1.7-3.9) |
| Forgetfulness | 1.7 (1.2-2.6) | 1.8 (1.2-2.6) |
| Dizziness | 1.7 (1.2-2.4) | 1.6 (1.1-2.3) |
| Nocturia | 1.5 (1.0-2.1) | 1.5 (1.0-2.1) |
| Appetite loss | 2.5 (1.1-5.8) | 2.2 (0.99-4.9) |
| Intermittent claudication | 2.0 (0.9-4.2) | 2.1 (0.99-4.4) |
| Chest pain | 1.5 (0.8-2.7) | 1.4 (0.8-2.5) |
| Abdominal bloating | 1.4 (0.95-2.1) | 1.4 (0.97-2.1) |

Significant results are in bold.

^a The multivariate analysis only performed when the odds ratio is 1.5 or higher. Data were adjusted for left ventricular ejection fraction (LVEF), cardiovascular disease (CVD), and for scores on the HADS, HADS-D (depression subscale), and HADS-A (anxiety subscale).

Table 4. Symptoms reported by breast cancer survivors after adjusting for age at time of assessment.

| | Breast cancer survivors treated with chemotherapy | Breast cancer survivors treated with radiotherapy | |
|----------------------------|---|---|-----------------------|
| | (N = 175) | (N = 175) | |
| | N (%) | N (%) | OR (95%CI) |
| Nocturia | 52 (29.7) | 38 (21.7) | 1.9 (1.1-3.2) |
| Forgetfulness | 50 (28.6) | 30 (17.1) | 1.8 (1.0-3.0) |
| Concentration difficulties | 48 (27.4) | 32 (18.3) | 1.3 (0.7-2.2) |
| Abdominal bloating | 40 (22.9) | 32 (18.3) | 0.99 (0.6-1.7) |
| Appetite loss | 11 (6.3) | 10 (5.7) | 0.99 (0.4-2.5) |
| Chest pain | 14 (8.0) | 18 (10.3) | 0.8 (0.4-1.8) |
| Intermittent claudication | 9 (5.1) | 14 (8.0) | 0.6 (0.3-1.6) |
| Dizziness | 38 (21.7) | 57 (32.6) | 0.6 (0.4-0.97) |

Significant results are in bold.

| Multivariate analyses, OR (95%CI) ^a | | |
|--|----------------------|----------------------|
| HADS (continuous) | HADS-D (continuous) | HADS-A (continuous) |
| 2.3 (1.5-3.6) | 2.3 (1.5-3.6) | 2.4 (1.5-3.8) |
| 1.6 (1.1-2.4) | 1.6 (1.1-2.4) | 1.6 (1.1-2.4) |
| 1.6 (1.1-2.3) | 1.6 (1.1-2.3) | 1.6 (1.1-2.3) |
| 1.5 (1.0-2.1) | 1.5 (1.0-2.1) | 1.5 (1.0-2.1) |
| 2.1 (0.9-4.6) | 2.1 (0.9-4.7) | 2.2 (0.98-4.9) |
| 2.1 (1.0-4.4) | 2.2 (1.0-4.5) | 2.1 (0.99-4.4) |
| 1.4 (0.8-2.5) | 1.5 (0.8-2.7) | 1.4 (0.8-2.6) |
| 1.3 (0.9-2.0) | 1.4 (0.9-2.0) | 1.3 (0.9-2.0) |

A major strength of this study is that we used an unselected population of breast cancer survivors from primary care, which helps to increase the generalizability of our data. Comparing these with a reference population matched by age and PCP further improved the rigor of our analysis. Another strength is that the median follow-up for the included breast cancer survivors was 10 years, which contrasts favorably with most other studies that have only focused on the first 5 years after diagnosis; as such, ours includes the increasingly important population of long-term survivors. Our assumption was that hormonal therapy will have the greatest effects during treatment, and not in the long term [34]. As a consequence, we hypothesize that the observed effects are not caused by hormonal treatment. We also compared the relationship between various symptoms and both cardiovascular problems and psychological distress in long-term breast cancer survivors. Other studies have reported on the quality of life for survivors, but it must be noted that experiencing symptoms themselves may ultimately have a negative effect on the quality of life [35-37]. One might argue that using the HADS to define depression or anxiety is inferior to a structured psychological interview, despite having excellent psychometric properties, and that this may have led to an underestimation of the association of symptoms to depression or anxiety. In order to rule out results based on chance future research should confirm our results. Finally, because of the cross-sectional design, it is only possible to draw conclusions about associations and not about causality.

Research has indicated that there is increased primary healthcare utilization among breast cancer survivors [38]. The PCP has a key role in managing symptoms among this growing population that is at risk of long-term sequelae. It is therefore important that PCPs pay attention to these symptoms to manage their negative impact on quality of life [39,40].

This must start by recognizing symptoms and knowing if they are associated with previous breast cancer treatment. In this study, we confirmed that this association existed, even after adjusting for well-known long-term effects with overlapping symptomatology (e.g., cardiac dysfunction, CVD, depression, and anxiety). When breast cancer survivors consult their PCP with vague symptoms, the differential diagnosis should include all long-term effects of breast cancer treatment, even if more than 10 years has elapsed since diagnosis [5,12]. When these have been excluded, positive reassurance could be provided through awareness that these symptoms are common among breast cancer survivors, even though the etiology is not known [41]. Possible treatments for symptoms include cognitive therapy or mindfulness, which have been proven to improve long-term symptoms of forgetfulness and concentration difficulty in breast cancer survivors [42-44]. The possibility of these symptoms and treatments should also be included in the information given to patients at the time of a breast cancer diagnosis to keep the patient informed and to help them pre-empt and deal with their symptoms.

Conclusions

Up to 10 years after diagnosis, breast cancer survivors experience intermittent claudication, appetite loss, concentration difficulties, forgetfulness, dizziness, and nocturia significantly more often than peers matched by age and PCP, without cancer. Intermittent claudication and appetite loss are associated with cardiovascular dysfunction, depression, and anxiety. Concentration difficulties, forgetfulness, dizziness, and nocturia are significantly associated with a history of breast cancer (therapy).

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Chapter 7

Summary and general discussion

SUMMARY AND GENERAL DISCUSSION

Introduction

Over the course of this thesis (2014-2021), I noticed a change in awareness of the presence of long-term effects in survivors after completing breast cancer treatment. At the start, colleagues and friends usually rejected my hypothesis that long-term breast cancer survivors still experience the effects of breast cancer and its treatment. This contrasted with the experience of survivors, who recognized this as a problem, regularly thanked us for choosing this topic, and expressed their hope for the recognition that treatment-related symptoms are persistent. Nowadays, when I talk about our findings with colleagues and friends, the first response is “this is already known.” Indeed, awareness has now been raised by the Dutch Breast Cancer Society, the Dutch Cancer Society, the Dutch Heart Foundation, and by our presentations. This increased awareness and recognition of long-term effects experienced by breast cancer survivors is a positive development. An illustrative case is shown below.

Illustrative case

A 63-year-old woman presents to her general practitioner (GP) with vague complaints. She was diagnosed with breast cancer and treated with surgery, chemotherapy, and radiotherapy 11 years ago. She feels less motivated to take on new challenges, feels dizzy, and has difficulty concentrating during long conversations. Because these symptoms affect her daily life, she seeks help from her GP. Together, they wonder if the presenting complaints could be traced back to the breast cancer diagnosis and its treatment.

Aim of this thesis

The main objective of this thesis and of the BLOC study was to gain insight into the prevalence of long-term physical and psychological effects among long-term survivors of breast cancer. More specifically, we explored the prevalence of, and the relationships between, various disorders and symptoms in breast cancer survivors, including cardiovascular disease, systolic cardiac function, depression, anxiety, fatigue, forgetfulness, and dizziness.

SUMMARY OF MAIN FINDINGS

We found that, beyond 5 years after breast cancer treatment, women have more left ventricle cardiac dysfunction, cardiovascular disease, and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) elevation, than matched controls without cancer. Women in this group also experience more anxiety, depression, and fatigue. Breast cancer survivors also experience more dizziness, concentration problems, forgetfulness, and nocturia.

In **chapter 2**, we performed a systematic review of the current literature on long-term symptoms of depression or anxiety in breast cancer survivors (>1 year after breast cancer diagnosis), which revealed a wide range in prevalence. Survivors were shown to be at higher risk of long-term symptoms of depression than the general female population, with this risk persisting beyond 5 years after diagnosis and normalizing over time. However, we found no increased prevalence of anxiety symptoms among breast cancer survivors.

Chapters 3 to 6 concerned the *Breast cancer Long-term Outcome Cardiac dysfunction (BLOC) study*. In this study, we compared 350 long-term breast cancer survivors against a reference population of 350 women who had no history of cancer (matched by age and GP). The breast cancer survivors received either chemotherapy (with or without radiotherapy) or radiotherapy alone (175 per group), and they were followed up for a median of 10 years from diagnosis.

In **chapter 3**, the first article arising from the BLOC study, we explored the prevalence of long-term cardiovascular effects. The main finding was that breast cancer survivors are at increased risk of mild left ventricular systolic dysfunction (LVEF <54%), with dysfunction present in 15.3% of all survivors compared with 7.0% in the reference population. At the clinically relevant LVEF cut-off of <50%, however, we found no significant difference in prevalence when comparing the survivor and reference groups. Overall, left ventricular diastolic dysfunction was high in both the breast cancer survivor (43.4%) and the reference (39.5%) groups. Breast cancer survivors more often had increased NT-proBNP levels (36.0%) than the reference group (27.1%), and those treated with chemotherapy (with or without radiotherapy) more often had cardiovascular disease than the reference population.

In **chapter 4**, the BLOC study focused on long-term depression and/or anxiety symptoms. We found that long-term breast cancer survivors more often experienced symptoms of mild depression, severe depression, and severe anxiety than the reference population. There was also a significant association between symptoms of anxiety and a history of

diagnosed depression or antidepressant prescribing before the cancer diagnosis, but this association was lacking for (severe) symptoms of depression and severe symptoms of anxiety.

Chapter 5 focused on multidimensional fatigue, revealing that it was experienced by a quarter of breast cancer survivors, which was significantly more often than in the reference population. This fatigue was associated with symptoms of depression and anxiety. Irrespective of the time since diagnosis (median 10 years), breast cancer survivors experienced significantly more fatigue than the reference population.

In **chapter 6**, the emphasis was on various symptoms and their possible association with the long-term effects of breast cancer and its treatment. Breast cancer survivors more often experienced concentration difficulties, dizziness, forgetfulness, and nocturia than the reference population. These symptoms did not seem to be associated with systolic cardiac dysfunction, cardiovascular disease, depression, or anxiety. Survivors also experienced more intermittent claudication and appetite loss than the reference population. On the one hand, intermittent claudication was associated with systolic cardiac function, cardiovascular disease, and anxiety symptoms. On the other hand, appetite loss was associated with cardiovascular disease, depression symptoms, and anxiety symptoms. Finally, when we compared breast cancer survivors by the treatment received, it was shown that those treated with chemotherapy (with or without radiotherapy) experienced more nocturia and forgetfulness while those treated with radiotherapy alone experienced more dizziness.

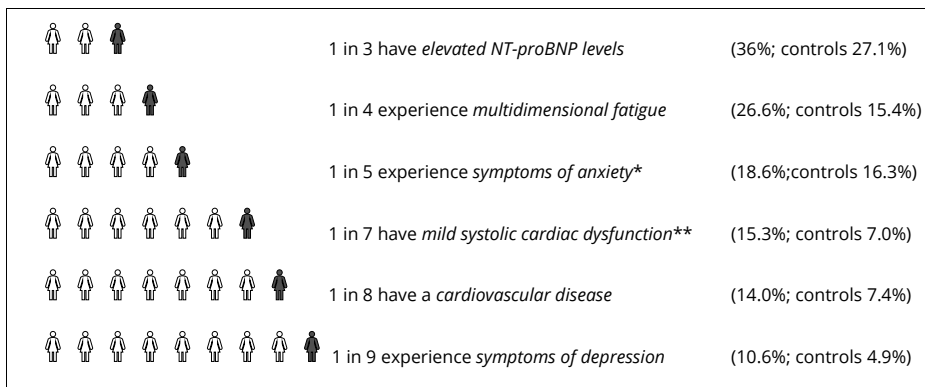


Figure 1. Outcomes for 350 breast cancer survivors and the reference population, included in the BLOC-study.

Abbreviations: BLOC, Breast Cancer Long-term Outcome Cardiac Dysfunction study; NT-proBNP, N-terminal prohormone of brain natriuretic peptide. *Non-significant. **Mild dysfunction was defined by a left-ventricular ejection fraction <54%.

COMPARISON WITH CURRENT LITERATURE

Cardiovascular effects

Other research looking at cardiovascular effects in breast cancer survivors treated with chemotherapy (with or without radiotherapy) for periods >5 years after diagnosis have found a lower prevalence of systolic cardiac dysfunction (LVEF <54%), with rates of 5.1%-11.5% versus our 14.8% [1,2]. However, they have found a comparable prevalence of LVEF<50%, with rates of 1.9%-8.0% compared to the 4.1% in this study [2-5]. These studies were limited by not comparing their results with a reference group [1-5], including only hospital-based populations (which makes comparison difficult) [1-5], and by having a maximum follow-up of 10 years [1,3]. Thus, the present thesis adds value in four ways. First, we performed comparison with a reference group. Second, we included a population-based cohort instead of a hospital-based cohort. Third, we followed women for a median of 10 years after diagnosis (interquartile range, 7-14 years). Fourth, all women underwent echocardiography, regardless of the presence of symptoms, which allowed us to include cases of asymptomatic systolic cardiac dysfunction.

We included 175 breast cancer survivors treated with radiotherapy alone. Although prior studies have evaluated other cardiac outcomes, such as comparing left- and right-sided breast irradiation [6-10], ours was the first study to evaluate long-term systolic cardiac dysfunction in this important cohort. We found no difference in outcomes between left- and right-sided radiotherapy, possibly due to the more refined radiotherapy protocol that is less spread, and therefore, less harmful to the heart and coronary arteries [11].

There were high rates of left ventricular diastolic dysfunction in both the breast cancer survivor (43.4%) and the reference (39.5%) groups, which corresponds to rates mentioned in the literature (15.8%-52.8%) [12]. Although breast cancer survivors had the same increased risk as the reference population, GPs should be aware that the prevalence of LV diastolic is high in women aged >60 years and may require different treatment to LV systolic dysfunction.

In line with our study, a high prevalence of increased NT-proBNP has been reported among breast cancer survivors. We reported an increase in 36.0% of cases while Caram et al. reported an increase in 46.0% with a shorter follow-up (6 years) [1]. Given that a raised NT-pro BNP is related to cardiac mortality and heart failure, it is important to be aware of this risk, and if necessary, monitor these women [13]. NT-proBNP is an easy and affordable tool that has a high negative predictive value for excluding chronic heart failure [14].

Psychological effects

At least 1 year after breast cancer diagnosis

Studies included in the systematic review by Zainal et al. [15] showed prevalence rates ranging from 1% to 56% for depression in survivors of breast cancer, consistent with our systematic review. The wide range in both reviews was due, in part, to the use of different questionnaires with varied definitions of depression. For example, Zainal et al. found a higher prevalence of depression with the Center for Epidemiological Studies-Depression (CES-D) questionnaire and Beck Depression Inventory (BDI) than with the Hospital Anxiety and Depression Scale (HADS). Overall, our numbers were lower than those reported by Zainal et al., probably because we excluded studies evaluating the first year after a breast cancer diagnosis.

When focusing on the results for the CED-D questionnaire only, we saw that the prevalence of depression decreased after the first year from diagnosis. Although all three questionnaires are valid and reliable tools for evaluating depression, diagnosis requires a formal diagnostic interview. Therefore, we have taken care to write about symptoms of depression or anxiety rather than diagnoses. The HADS offers the best approach to the outcome of a diagnostic interview, which was one of the main reasons we included it in the BLOC study [16].

A more recent systematic review (2018) evaluated mental health outcomes among breast cancer survivors and compared the results of women beyond 1 year after diagnosis to those with no history of cancer [17]. They found a higher risk for anxiety and depression among breast cancer survivors, but as in our systematic review, they produced wide confidence intervals [17]. The prevalence of anxiety symptoms among breast cancer patients ranged from 10% to 50% in that study, whereas we found a range from 17.9% to 33.3%. The diversity in questionnaires may again explain the wide range in prevalence.

Beyond 5 years after diagnosis (BLOC study)

The prevalence rates for mild symptoms of depression (measured with the HADS-D) among breast cancer survivors were 10.6% in the BLOC study and 13.0% in the systematic review, with severe symptoms present in 3.7% and 3.9%, respectively. Concerning anxiety (measured with the HADS-A) mild symptoms were present in 18.6% in the BLOC study and 27.2% in the systematic review, whereas severe symptoms were present in 8.0% and 9.8%, respectively. Overall, the percentages reported in the review were slightly higher than those reported in the BLOC study because of the shorter mean follow-up of 4 years in the systematic review.

In the BLOC study, we confirmed the hypothesis that (severe) symptoms of depression and severe symptoms of anxiety are associated with the presence of a history of breast cancer. Similarly, a nationwide study in Denmark, with a follow-up period of up to 8 years, concluded that long-term breast cancer survivors are at increased risk for depression [18].

We did not find a significant association between a history of diagnosed depression or of antidepressant prescription before the breast cancer diagnosis and (severe) symptoms of depression or severe symptoms of anxiety after the breast cancer diagnosis. However, women with symptoms of depression before the breast cancer diagnosis were found to be at increased risk of anxiety symptoms after their diagnosis. A recent systematic review of breast cancer survivors with and without a history of mental disorders found that an increased risk of depression or anxiety after the breast cancer diagnosis was unrelated to a history of mental problems [17].

Fatigue

The 26.6% prevalence of multidimensional fatigue in long-term breast cancer survivors is comparable with that reported in other studies of fatigue in this cohort (range, 16%–35%) [19–22]. This is remarkable given that we used a longer median follow-up of 10 years after breast cancer diagnosis, while other studies have had a median follow-up of approximately 5 years (range, 1 month to 10 years). In the BLOC study, comparison with a reference population also revealed that breast cancer survivors experienced multidimensional fatigue more often, consistent with the results of other studies with different methodologies [23,24]. Supporting our study, a systematic review by Abrahams et al. found a strong relation between fatigue and symptoms of depression or anxiety [25]. Our findings add to their systematic review by including a long median time from diagnosis and by performing comparison to a reference population with no history of cancer.

Symptoms

We evaluated the symptoms experienced long-term after treatment for breast cancer. These do not always reflect a specific disease or condition, often resulting in vague presentations, but they do reflect a patient burden that may prompt contact with a GP. Previous research has revealed that this symptom burden can be high [26] and results in more GP visits [27], requiring the GP to search for the underlying pathology. However, as shown in our study, there is an inter-relationship between these symptoms in breast cancer survivors with not only cardiac dysfunction but also with symptoms of depression or anxiety.

IMPLICATIONS OF OUR FINDINGS

Key message

The key message of this thesis is that long-term effects occur after the successful treatment of breast cancer and that these may persist for more than a decade after diagnosis. By increasing awareness of long-term effects, patients and health care practitioners alike will be better placed to recognize and acknowledge them, which is imperative for breast cancer survivors.

GPs need to know about the long-term effects because they provide most long-term health care for breast cancer survivors. As in the illustrative case, women might present to the GP with symptoms that are not always explained by defined diseases, and it is up to GPs to consider whether these might be long-term effects of breast cancer or its treatment. However, other health care providers should also be aware of these long-term effects. Oncologists should discuss their possibility when outlining treatment options to newly diagnosed women of how they can affect physical and psychological wellbeing. Psychologists treating women for depression (either newly diagnosed or with a history of breast cancer over 10 years ago) will need to consider the potential association with a history of breast cancer and its treatment. Perhaps of even greater importance, the survivor should know that symptoms may persist or occur up to 10 years after diagnosis so that she is better placed to seek help or guidance.

Cardiac dysfunction

Long-term symptoms may be caused by (mild) systolic cardiac dysfunction, cardiovascular disease, or heart failure. Given this, GPs should consider taking a cardiac history and perform a physical examination or blood tests. Testing may need to be ordered earlier for women with a history of breast cancer than for women without a history of cancer.

If one or more tests are abnormal, the GP may need to consider a check-up by the cardiologist. By contrast, if a result is only slightly abnormal or the patient has comorbidity, the GP can include the patient in their preventive program for cardiovascular risk management. Standard blood tests for cardiac risk assessment include lipid profile (e.g., LDL cholesterol, HDL cholesterol, total cholesterol, triglycerides), glucose, creatinine/eGFR, and the albumin-creatinine ratio. Based on our findings, we would then recommend including an NT-proBNP blood test for breast cancer survivors. Although one might consider including all breast cancer survivors in such a program, our study data do not support the general position that having a history of breast cancer is an independent risk factor for cardiovascular disease. However, for women with a history of chronic comorbidity or cardiac risk factors, we recommend that careful consideration should be given to including them in a cardiovascular risk management program.

Psychological effects, fatigue, and other symptoms

Depression or anxiety can also occur in the long-term effect among breast cancer survivors. The GP or other health care worker should include this in their differential diagnoses when a breast cancer survivor visits the practice. Survivors may be direct in stating that they are feeling depressed or anxious, or indirect by expressing vague, even physical, symptoms. It is important to explore these symptoms further because they can severely affect quality of life and may increase morbidity and mortality. GPs should also consider the association between depression or anxiety and symptoms such as fatigue, appetite loss, intermittent claudication, chest pain, or abdominal bloating. Multiple treatments have been shown to be effective at treating depression or anxiety among cancer survivors [28].

Fatigue was already known to be the most prevalent and persistent complaint in women treated for breast cancer. In this research, we demonstrated that it can persist for a long time. Given the potential for fatigue to have a severe effect on daily life, GPs should be especially aware of this as a potential long-term effect. Physical activity programs may help to alleviate fatigue [29].

It's not over when it's over

Acknowledgment was a recurring topic in discussions with breast cancer survivors. Many women indicated that they received a lot of attention from family and friends, at work, in the hospital, and from the GP during the first 5 years. Beyond that, however, when they received a "clean bill of health," they reported that people around them seemed to forget about their breast cancer or paid it no more attention. A substantial proportion of survivors were unable to forget, partly because having breast cancer is such a life event and partly because some are still experiencing the effects of breast cancer diagnosis and treatment. It is important for this group that these long-term symptoms after breast cancer and its therapy be acknowledged.

Mention should also be given to the definition of the term "survivor," which is currently being debated. The National Cancer Institute considers a person a survivor from the day of diagnosis, whereas others only use the term after 5 years of survival. However, some breast cancer survivors themselves disagree with the use of this term entirely, and elsewhere, the National Health Service in England speaks of "people living with or beyond cancer", while in Italy, oncologists have used the terms "cured" or "cancer-free." However, oncology practitioners tend to be hesitant to use the term "cured" because they cannot know for certain that a cancer will not return.

A systematic review of long-term symptoms in cancer survivors, entitled "It's not over when it is over" [26], accurately captures the feeling of many breast cancer survivors. Therefore, should we consider breast cancer a chronic disease? I would disagree because

most survivors will not experience long-term effects and because labeling breast cancer a chronic disease may result in unnecessary medicalization. Indeed, we found that symptoms persisted beyond 10 years in only a small group of survivors. Awareness could be better accomplished in other ways, such as existing campaigns by different cancer societies or by including the need to consider long-term effects in guidelines.

In conclusion, I recommend that women should be made aware of the potential for long-term effects from breast cancer and its treatment in a small group of survivors. This approach will facilitate recognition, acknowledgment, and treatment. However, I would stop short of labeling breast cancer a chronic disease.

Future research

The BLOC study was a cross-sectional cohort study of 350 women with a history of breast cancer from different databases in the north of the Netherlands, including 350 randomly selected women of the same age and from the same GP practice. This helped not only to evaluate the number of women having long-term physical or psychological problems but also to compare these data with the general population. In turn, this made it possible to assess the risks for breast cancer survivors. Although we evaluated the codes for diagnosis and medication before and after the breast cancer diagnosis based on longitudinal data from GP records, the echocardiography, blood test, and questionnaire results were evaluated based on cross-sectional data. This represents an important limitation because we could only describe one point in time, limiting our conclusions to associations rather than causality. A fully longitudinal study would provide much more useful information about the course of the physical and psychological problems. Therefore, we are in the process of setting up the BLOC2 study, which will include follow-up of the same breast cancer survivors and reference population after a minimum of 8 years later. Each participant will undergo repeat echocardiography and blood testing. In the BLOC study, we focused on women with complaints (especially psychological distress, fatigue, and other symptoms) who were seeking acknowledgment. In the BLOC2 study, we hope to predict beforehand who will develop these complaints so that we can better target care and support. For the GP, this might help to clarify those women at risk and who should be included in a cardiovascular risk management program, who should undergo regular check-up, or who should be referred to a cardiologist or psychologist.

CONCLUSIONS / TAKE HOME MESSAGE

Breast cancer survivors more often have mild systolic dysfunction and/or experience more symptoms of depression, anxiety, multidimensional fatigue, and other symptoms than women of the same age and GP with no history of cancer. By understanding which long-term effects are associated with breast cancer and its treatment, and by knowing which determinants are associated with them, we can improve awareness among physicians, emphasizing the role of the GP. There is a need to acknowledge that breast cancer survivors could have symptoms associated with breast cancer and its treatment for up to 10 years after diagnosis. We must also improve the information provided to patients and survivors about these long-term effects. Even though symptoms are often mild, they may significantly affect day-to-day lives. By seeking an association with symptoms of anxiety and depression, we considered modifiable determinants that could be improved. We hope this information can be used to improve future guidelines and increase awareness of long-term symptoms experienced by breast cancer survivors.

Highlights

- Concerning long-term effects: knowledge leads to recognition, which leads to acknowledgement.
- Fortunately, most breast cancer survivors will not experience long-term effects; however, we must recognize those who do.
- When in doubt, cardiac dysfunction must be excluded, followed by an assessment of psychological needs.
- Psychological needs are underestimated and undertreated, causing distress and reduced quality of life among breast cancer survivors.
- Long-term effects should receive appropriate attention in breast cancer guidelines.

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Appendices

Nederlandse samenvatting

Dankwoord

Over de auteur

Publications

NEDERLANDSE WETENSCHAPPELIJKE SAMENVATTING

Borstkanker treft 1 op de 8 vrouwen in Nederland en de incidentie neemt toe. Gelukkig is de vijfjaarsoverleving gestegen tot 88% dankzij continue verbetering in behandelingen, screening en stadiëring. Dit betekent dat de populatie van vrouwen met borstkanker in de voorgeschiedenis, steeds groter wordt. Ook deze vrouwen kunnen negatieve effecten van borstkanker en de behandeling ervan ervaren. Onderzoek heeft zich voorheen met name gericht op vrouwen in de eerste vijf jaar na de diagnose borstkanker en nog onder behandeling in het ziekenhuis. De studie beschreven in dit proefschrift richt zich op vrouwen bij wie de diagnose tenminste vijf jaar geleden is gesteld. Zij vallen vaak weer onder de zorg van de huisarts.

In **hoofdstuk 1** staat een introductie over de huidige behandelingen voor borstkanker, de organisatie van zorg en de huidige kennis van de langetermijneffecten van borstkanker en de behandelingen. Vanuit het oogpunt van de vrouwen met borstkanker in de voorgeschiedenis wordt het belang van deze kennis voor hen belicht. Deze vrouwen willen weten wat ze op de lange termijn kunnen verwachten. Vanuit het oogpunt van de huisartsen wordt hun rol ten aanzien van de langetermijnzorg voor vrouwen met borstkanker in de voorgeschiedenis besproken, zoals welke langetermijneffecten zijn te verwachten, hoe vaak het voorkomt en hoe deze vrouwen het beste te begeleiden of behandelen.

Hoofdstuk 2 beschrijft de systematische review waarin symptomen van depressie en angst op de lange termijn na borstkanker worden beschreven. Gezien de beperkte literatuur over de langetermijneffecten, zijn studies geïnccludeerd vanaf 1 jaar na de diagnose borstkanker. De verschillende studies laten uiteenlopende prevalenties zien voor zowel symptomen van depressie als angst. Bij het samenvoegen van de verschillende resultaten wordt gezien dat vrouwen met borstkanker in de voorgeschiedenis vaker symptomen van depressie hebben dan vrouwen uit de referentie populatie, ook vijf jaar na diagnose. Dit verschil lijkt in de loop van de tijd te normaliseren. Symptomen van angst komen niet vaker voor bij vrouwen met borstkanker in de voorgeschiedenis dan bij vrouwen in de algehele populatie.

Hoofdstuk 3 tot en met 6 beschrijven de resultaten uit de Breast cancer Long-term Outcome Cardiac dysfunction (BLOC)-studie. In deze cross-sectionele studie worden 350 vrouwen die meer dan vijf jaar geleden werden gediagnostiseerd en behandeld voor borstkanker vergeleken met 350 vrouwen, van dezelfde leeftijd en huisartspraktijk, zonder kanker in de voorgeschiedenis. De helft van de vrouwen met borstkanker in de voorgeschiedenis is behandeld met chemotherapie (met of zonder radiotherapie) en de andere helft alleen met radiotherapie. De diagnose borstkanker was gemiddeld tien jaar geleden.

Hoofdstuk 3, het bronartikel van de BLOC-studie, kijkt naar de prevalentie van langetermijn-cardiovasculaire-effecten. De primaire uitkomst is dat vrouwen met borstkanker in de voorgeschiedenis vaker milde linker ventrikel systolische disfunctie (LVEF <54%) hebben, namelijk 15.3% in vergelijking met 7.0% in de referentie groep. Bij de klinisch relevante afkappaarde van LVEF <50%, is dit verschil niet langer significant. De prevalentie van linker ventrikel diastolische disfunctie is in beide groepen vrijwel gelijk, bij vrouwen met borstkanker in de voorgeschiedenis 43.4% en 39.5% bij de referentiegroep. De vrouwen met borstkanker in de voorgeschiedenis hebben vaker een verhoogde NT-proBNP waarde (36.0%) dan de referentie groep (27.1%). Vrouwen met borstkanker in de voorgeschiedenis behandeld met chemotherapie (met of zonder radiotherapie) hebben vaker hart- en vaatziekten (12.0%) dan de referentie groep (5.7%).

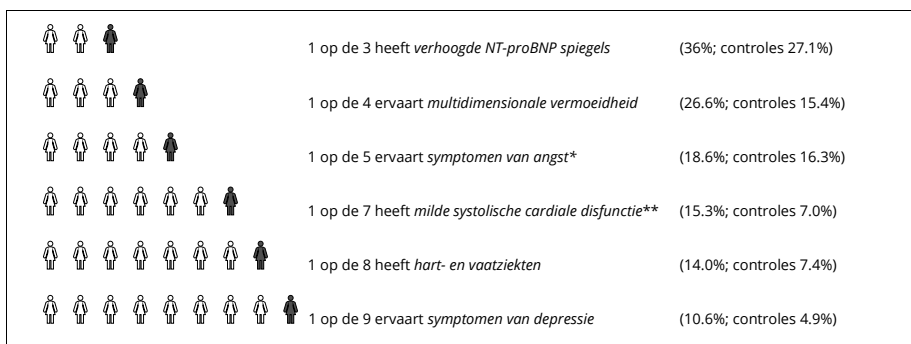
Hoofdstuk 4 gaat over symptomen van depressie en angst op de lange termijn na borstkanker. Er blijkt dat de vrouwen met borstkanker in de voorgeschiedenis, gemiddeld tien jaar na diagnose, vaker symptomen van depressie (10.6%) en ook ernstige depressie (3.7%) ervaren dan de referentie populatie (respectievelijk 4.9% en 1.1%). Symptomen van angst worden niet significant vaker ervaren door vrouwen met borstkanker in de voorgeschiedenis (18.6%) dan door de referentie populatie (16.3%). Daarentegen komen ernstige symptomen van angst wel vaker voor bij vrouwen met borstkanker in de voorgeschiedenis (8.0%), dan bij de referentie populatie (4.0%). De resultaten blijken geen associatie te hebben met de tijd sinds diagnose.

Hoofdstuk 5 gaat over multidimensionale vermoeidheid (algemeen, fysiek, activiteit, motivationeel en mentaal). Dit hoofdstuk laat zien dat een kwart van de vrouwen met borstkanker in de voorgeschiedenis multidimensionale vermoeidheid ervaart (26.6%) gemiddeld tien jaar na diagnose. Dit is significant meer dan de referentie populatie (15.4%). Daarnaast blijkt een associatie tussen vermoeidheid bij vrouwen met borstkanker in de voorgeschiedenis en met symptomen van depressie of angst. Al blijkt geen associatie met o.a. type behandeling voor borstkanker, cardiale disfunctie, hart- en vaatziekten of tijd sinds diagnose.

In **hoofdstuk 6** wordt gekeken naar een variatie van klachten en hun mogelijke associatie met de eerder onderzochte fysieke en psychische langetermijneffecten na (de behandeling voor) borstkanker. Vrouwen met in de voorgeschiedenis borstkanker ervaren vaker concentratieproblemen, duizeligheid, vergeetachtigheid en nycturie, dan vrouwen in de referentie populatie. Deze klachten hebben geen associatie met systolische cardiale disfunctie, hart- en vaatziekten, symptomen van depressie of angst. Vrouwen met in de voorgeschiedenis borstkanker ervaren ook vaker claudicatio intermittens en een verminderde eetlust. De claudicatio intermittens klachten hebben een associatie

met systolische cardiale disfunctie, hart- en vaatziekten en symptomen van angst. De verminderde eetlust is geassocieerd met hart- en vaatziekten en symptomen van depressie en angst. Daarnaast is gekeken naar het verschil tussen het type behandeling voor borstkanker. Vrouwen die werden behandeld met chemotherapie (met of zonder radiotherapie) voor borstkanker hebben vaker klachten van nycturie en vergeetachtigheid. Vrouwen die alleen met radiotherapie werden behandeld voor borstkanker ervaren vaker duizeligheid.

Hoofdstuk 7 geeft een samenvatting van de resultaten en aanbevelingen. De resultaten zijn gespiegeld aan de huidige literatuur. De belangrijkste boodschap is dat vrouwen ook na een succesvolle behandeling van borstkanker op de lange termijn nog fysieke en psychische klachten kunnen ervaren als gevolg van borstkanker of de behandeling daarvan. Het is belangrijk dat hier kennis over is, zodat de patiënten en zorgverleners het kunnen herkennen, erkennen en eventueel een behandeling kunnen starten. Gelukkig ervaren de meeste vrouwen geen langetermijneffecten. Op basis van de resultaten uit de BLOC-studie wordt niet geadviseerd om alle vrouwen die behandeld zijn voor borstkanker preventief naar de cardioloog te verwijzen of op te nemen in het cardiovasculair risicomanagement (CVRM) programma. Dit omdat de systolische cardiale disfunctie meestal mild is en niet klinisch relevant. Maar als er meerdere risicofactoren aanwezig zijn, specifieke klachten of onderzoek aanwijzingen geeft voor cardiale disfunctie, is dit wel te overwegen. Psychische klachten na borstkanker worden onderschat en onderbehandeld. Gedurende de behandeling is hier gelukkig steeds meer aandacht voor, maar uit dit onderzoek blijkt dat ook na de eerste vijf jaar deze klachten een grote rol kunnen spelen en er aandacht voor moet zijn. Vermoeidheid blijkt de meest voorkomende klacht. Gezien de grote impact op het dagelijks leven zou deze klacht meer aandacht moeten krijgen en verder uitgediept moeten worden, zodat er eventueel een gerichte behandeling gezocht kan worden om de klachten te verlichten. In de (huisartsgeneeskundige) richtlijnen voor borstkanker zou meer aandacht moeten komen voor het herkennen, begeleiden en behandelen van de langetermijneffecten na borstkanker.



Figuur 1. Uitkomsten van de 350 vrouwen met in de voorgeschiedenis borstkanker en de referentiegroep, uit de BLOC-studie.

Afkortingen: BLOC, Breast Cancer Long-term Outcome Cardiac Dysfunction study; NT-proBNP, N-terminal breinnatriuretisch peptide. *Niet-significant. **Milde disfunctie werd gedefinieerd als een linker ventrikel ejectie fractie van <54%.

DANKWOORD

Allereerst wil ik alle 700 **deelnemers** bedanken. Dankzij jullie hebben we dit onderzoek kunnen uitvoeren, conclusies kunnen trekken en kunnen zorgen voor verbetering in de zorg voor vrouwen met borstkanker in de voorgeschiedenis.

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OVER DE AUTEUR



Saskia is geboren op 4 maart 1986 in Geleen, waar ze samen met haar broers, Marc en Jeroen, en ouders, Carel en Nanny, opgroeide. In 2005 behaalde ze haar atheneumdiploma aan het Graaf Huyn College in Geleen. Vervolgens studeerde ze geneeskunde in Maastricht en behaalde ze in 2011 haar artsdiploma. Het laatste jaar werkte Saskia op de intensive care in het MUMC+ en deed ze onderzoek, waar later haar eerste publicatie uit voort kwam. Daarna heeft ze een jaar gewerkt bij de chirurgie in het Orbis Medisch Centrum in Sittard-Geleen. In 2013 vertrok ze samen met haar echtgenoot Ryan naar Toronto, Canada. In het Toronto General Hospital deed Saskia onderzoek naar mamma-reconstructies na borstkanker in samenwerking met dr. Toni Zhong van de afdeling Plastic and Reconstructive Surgery. Na terugkomst werkte ze enkele maanden bij de geestelijke gezondheidszorg in Groningen.

In 2014 werd Saskia door dr. Annette Berendsen aangenomen voor de Breast cancer Long-term Outcome of Cardiac dysfunction (BLOC)-studie, bij de afdeling Huisartsgeneeskunde van het UMCG. Dit promotietraject werd begeleid door prof. Truuske de Bock en prof. Peter Verhaak. Dit onderzoek sloot mooi aan op de eerder opgedane ervaring van onderzoek bij borstkankerpatiënten en de ervaring in de GGZ. De promotie was onderdeel van een aioto-traject waarbij de promotie werd gecombineerd met de opleiding tot huisarts en de opleiding tot epidemioloog. De huisartsopleiding werd begeleid door huisarts Henk Wielinga en in het laatste jaar door Sonja Dorgelo. In 2021 werd de opleiding tot huisarts succesvol afgerond. Daarna is Saskia bij haar laatste opleidingspraktijk, huisartspraktijk van Bracht en Dorgelo, in Drachten in dienst gegaan. Van Mark van Bracht leerde ze onder andere het uitvoeren van bovenooglidcorrecties. De opleiding tot Epidemioloog B is met het behalen van de promotie tevens voltooid.

Naast het werk in de huisartspraktijk begeleidt Saskia als post-doc de vervolgstudie van de BLOC-studie, BLOC-II, bij de afdeling Huisartsgeneeskunde en Ouderengeneeskunde van het UMCG.

Saskia is getrouwd met Ryan Accord, stiefmoeder van Jaden en Gillian, en moeder van Mason en Colin. Haar hobby's zijn o.a. fotografie, handbal en wielrennen, maar het liefst gaat ze op pad met het hele gezin.

INTERNATIONAL PUBLICATIONS

*This thesis

1. **Fatigue among Long-Term Breast Cancer Survivors: A Controlled Cross-Sectional Study.**
S.W.M.C. Maass, D. Brandenburg, L.M. Boerman, P.F.M. Verhaak, G.H. de Bock, A.J. Berendsen.
Cancers (Basel). 2021 Mar 15;13(6):1301. *
2. **Symptoms in long-term breast cancer survivors: A cross-sectional study in primary care.**
S.W.M.C. Maass, L.M. Boerman, D. Brandenburg, P.F.M. Verhaak, J.H. Maduro, G.H. de Bock, A.J. Berendsen.
Breast. 2020 Dec;54:133-138. *
3. **Long-term survivors of early breast cancer treated with chemotherapy are characterized by a pro-inflammatory biomarker profile compared to matched controls.**
 J. Tromp, L.M. Boerman, I.E. Sama, S.W.M.C. Maass, J.H. Maduro, Y.M. Hummel, M.Y. Berger, G.H. de Bock, J.A. Gietema, A.J. Berendsen, P. van der Meer.
Eur J Heart Fail. 2020 Jul;22(7):1239-1246.
4. **Long-term psychological distress in breast cancer survivors and their matched controls: A cross-sectional study.**
S.W.M.C. Maass, L.M. Boerman, P.F.M. Verhaak, J. Du, G.H. de Bock, A.J. Berendsen.
Maturitas. 2019 Dec;130:6-12. *
5. **Cardiac Function After Radiation Therapy for Breast Cancer.**
 V. vd. Bogaard, P. v. Luijk, Y. Hummel, P. vd. Meer, E. Schuit, L. Boerman, S.W.M.C. Maass et al.
International Journal of Radiation Oncology Biology* Physics* 104 (2), 392-400, 2019.
6. **A systematic review on the prevalence of symptoms of depression, anxiety and distress in long-term cancer survivors: Implications for primary care.**
 D. Brandenburg, S.W.M.C. Maass, O.P. Geerse, M.E. Stegmann, C. Handberg, M.J. Schroevers, S.F.A. Duijts.
European journal of cancer care, e13086, 2019.
7. **Long-term outcome of cardiac function in a population-based cohort of breast cancer survivors: A cross-sectional study.**
 L.M. Boerman¹, S.W.M.C. Maass¹, P. van der Meer, J.A. Gietema, J.H. Maduro, Y.M. Hummel, M.Y. Berger, G.H. de Bock, A.J. Berendsen. ¹Shared first author.
Eur J Cancer. 2017 Aug;81:56-65. doi: 10.1016/j.ejca.2017.05.013. Epub 2017 Jun 8. *

8. **The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: a systematic review.**
S.W.M.C. Maass, C. Roorda, A.J. Berendsen, P.F.M. Verhaak, G.H. de Bock.
Maturitas. 2015 Sep;82(1):100-8.*
9. **Systematic Review: Aesthetic Assessment of Breast Reconstruction Outcomes by Healthcare Professionals.**
S.W.M.C. Maass, T. Zhong, A. O'Neill, S.O.P. Hofer.
Ann Surg Oncol. 2015 Dec;22(13):4305-16.
10. **A single pre-operative antibiotic dose is as effective as continued antibiotic prophylaxis in implant-based breast reconstruction: A matched cohort study.**
W.A. Townley, N. Baluch, S. Bagher, S.W.M.C. Maass, A. O'Neill, T. Zhong, S.O.P. Hofer.
J Plast Reconstr Aesthet Surg. 2015 May;68(5):673-8.
11. **Using propensity score analysis to compare major complications between DIEP and free muscle-sparing TRAM flap breast reconstructions.**
T. Zhong, C. Novak, S. Bagher, S.W.M.C. Maass, J. Zhang, U. Arad, A. O'Neill, K. Metcalfe, S.O.P. Hofer.
Plast Reconstr Surg. 2014 Apr;133(4):774-82.
12. **Cardiac output measurement by bioimpedance and noninvasive pulse contour analysis compared with the continuous pulmonary artery thermodilution technique.**
S.W.M.C. Maass, P.M. Roekaerts, M.D. Lancé.
J Cardiothorac Vasc Anesth. 2014 Jun;28(3):534-9.

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1. **Wel of geen echogeleide injectie in het AC-gewricht?**
E. Reitsma, S.W.M.C. Accord-Maass
Huisarts en wetenschap, 1-2, 2021.
2. **Late effecten borstkanker op de hartfunctie**
S. Accord-Maass, A. Berendsen
TPO-De Praktijk 15 (1), 30-31, 2020.
3. **Langetermijneffecten van de behandeling voor borstkanker op de hartfunctie.**
S.W.M.C. Accord-Maass, L.M. Boerman, D. Brandenburg, P. van der Meer, J.A. Gietema, J.H. Maduro, Y.M. Hummel, M.Y. Berger, G.H. de Bock, A.J. Berendsen.
Nederlands Tijdschrift voor Oncologie, 2019;16;3-12;2019. (Dubbelpublicatie)
4. **Late effecten van borstkankerbehandeling op het hart.**
S.W.M.C. Accord-Maass, L.M. Boerman, D. Brandenburg, M.Y. Berger, G.H. de Bock, A.J. Berendsen.
Huisarts en wetenschap 62 (4), 26-29, 2019. (Dubbelpublicatie)
5. **Langetermijneffecten behandeling borstkanker.**
S.W.M.C. Accord-Maass.
Huisarts en wetenschap. Juli 2017, 60 (7), 357-357.
6. **Psychologische distress en vermoeidheid.**
M. Deveugele, P. Pype, S.W.M.C. Accord-Maass.
Praktische huisartsgeneeskunde: Oncologie. 2017, 79-86.

SPECIAL ACHIEVEMENTS

Late Breaking Abstract, European Breast Cancer Conference, 2020.

Fatigue among long-term breast cancer survivors: a controlled cross-sectional study

People's Choice Award, 3-Minute Thesis Competition, 2020.

University Medical Center Groningen, University of Groningen.

Late Breaking Abstract, European Breast Cancer Conference, 2018.

Long-term psychological distress in breast cancer survivors and their matched controls:

A cross-sectional study

Top Publication Award, awarded by Research Institute SHARE, 2015.

University Medical Center Groningen, University of Groningen.

MULTIMEDIA

Three Minute Thesis (3MT®) competition: Saskia Accord-Maass

<https://www.youtube.com/watch?v=O3cvhSpcByg>

Saskia Accord-Maass: The long-term psychological effects of breast cancer

https://www.youtube.com/watch?v=VK55Mhr6e_w

ECancer.org: Fatigue among long-term breast cancer survivors: a controlled cross-sectional study

<https://ecancer.org/en/video/9240-dr-saskia-maass-university-of-groningen-groningen-netherlands>

Podcast: Research Round-up - December 2020 - Saskia Maass and Dr Annette Berendsen

<https://soundcloud.com/user-120631541-263641781/december-2020-saskia-maass-and-dr-annette-berendsen>

“Erken en herken angst en depressie na borstkankerbehandeling”

<https://kennisinzicht.umcg.nl/Paginas/Erken-en-herken-angst-en-depressie-na-borstkankerbehandeling.aspx>