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

S.W.M.C. Maass a,*, L.M. Boerman a, D. Brandenbarg a, P.F.M. Verhaak a, b, J.H. Maduro c, G.H. de Bock d, A.J. Berendsen a

a University of Groningen, University Medical Center Groningen, Department of General Practice and Elderly Care Medicine, PO Box 196, 9700 AD, Groningen, the Netherlands
b NIVEL, Netherlands Institute of Health Services Research, Postbus 1568, 3500 BN, Utrecht, the Netherlands
c University of Groningen, University Medical Center Groningen, Department of Radiation Oncology, PO Box 30.001, 9700 RB, Groningen, the Netherlands
d University of Groningen, University Medical Center Groningen, Department of Epidemiology, PO Box 30.001, 9700 RB, Groningen, the Netherlands

ARTICLE INFO

Article history:
Received 9 July 2020
Received in revised form 20 September 2020
Accepted 25 September 2020
Available online 30 September 2020

Keywords:
Primary health care
Breast neoplasms
Signs and symptoms
Cancer survivor

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).

© 2020 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. 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.
Table of abbreviations

- BLOC: Breast cancer Long-term Outcome Cardiac dysfunction
- CVD: Cardiovascular diseases
- HADS: Hospital Anxiety and Depression Scale
- ICPC: International Classification of Primary Care
- IQR: Interquartile range
- LVEF: Left ventricle ejection fraction
- OR: Odds ratios
- PCP: Primary care physician

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.

2. Methods

2.1. 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].

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 mg/m²) or epirubicin (>900 mg/m²) [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 was usually stopped after five years.

The BLOC study found that breast cancer survivors more often had systolic cardiac dysfunction (left ventricle 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].

2.2. 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 with 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.

2.3. 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 ICPC 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].

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 chemotherapy 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.
2.4. 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 $\geq 1.5$ 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).

### 3. Results

#### 3.1. 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 4.6%; 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).

### Table 1

|                         | Breast cancer survivors | Reference population |
|-------------------------|-------------------------|----------------------|
|                         | N = 350                 | N = 350              |
| **Years**               |                         |                      |
| 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)              | –                    |
| Anthracyline-based      | 142 (40.6)              | –                    |
| Cumulative anthracyline dose, mg/m2, median (IQR) | 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$^{c}$ |                      |                      |
| Dyslipidemia            | 54 (15.4)               | 58 (16.6)            |
| Hypertension            | 108 (30.9)              | 106 (30.3)           |
| Diabetes mellitus       | 29 (8.3)                | 16 (4.6)             |
| **Left ventricular ejection fraction (LVEF)$^{d}$** | 58 (55–61) | 59 (57–62) |
| Hospital Anxiety and Depression Scale (HADS) |                    |                      |
| HADS-Depression         | 2 (1–4)                 | 2 (1–4)              |
| HADS-Anxiety            | 5 (3–7)                 | 4 (3–6)              |

$^{a}$ Significant.
$^{b}$ IQR = interquartile range.
$^{c}$ As registered in files of the general practitioner.
$^{d}$ 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.

| Symptom                        | Breast cancer survivors (N = 350) | Reference population (N = 350) | Univariate comparison OR (95%CI) |
|--------------------------------|----------------------------------|-------------------------------|---------------------------------|
| 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)                  |

OR = Odds Ratio, unadjusted.

*Significant.

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

Table 3
Symptoms adjusted for in the multivariate analysis, comparing breast cancer survivors with an age- and PCP-matched reference population without cancer.

| Multivariate analyses, OR (95%CI)* | LVEF (continuous) | CVD (dichotomous) | HADS (continuous) | HADS-D (continuous) | HADS-A (continuous) |
|-----------------------------------|-------------------|-------------------|-------------------|---------------------|---------------------|
| Concentration difficulties        | 2.5 (1.6–3.9)*    | 2.6 (1.7–3.9)*    | 2.3 (1.5–3.6)*    | 2.3 (1.5–3.6)*      | 2.4 (1.5–3.8)*      |
| Forgetfulness                     | 1.7 (1.2–2.6)*    | 1.8 (1.2–2.6)*    | 1.6 (1.1–2.4)*    | 1.6 (1.1–2.4)*      | 1.6 (1.1–2.4)*      |
| Dizziness                         | 1.7 (1.2–2.4)*    | 1.6 (1.1–2.3)*    | 1.6 (1.1–2.3)*    | 1.6 (1.1–2.3)*      | 1.6 (1.1–2.3)*      |
| Nocturia                           | 1.5 (1.0–2.1)*    | 1.5 (1.0–2.1)*    | 1.5 (1.0–2.1)*    | 1.5 (1.0–2.1)*      | 1.5 (1.0–2.1)*      |
| Appetite loss                     | 2.5 (1.1–3.8)*    | 2.2 (0.9–4.9)     | 2.1 (0.9–4.6)     | 2.1 (0.9–4.7)       | 2.2 (0.9–4.9)       |
| Intermittent claudication         | 2.0 (0.9–4.2)     | 2.1 (0.9–4.4)     | 2.1 (1.0–4.4)*    | 2.2 (1.0–4.5)*      | 2.1 (0.9–4.4)       |
| Chest pain                        | 1.5 (0.8–2.7)     | 1.4 (0.8–2.5)     | 1.4 (0.8–2.5)     | 1.5 (0.8–2.7)       | 1.4 (0.8–2.6)       |
| Abdominal bloating                | 1.4 (0.95–2.1)    | 1.4 (0.97–2.1)    | 1.3 (0.9–2.0)     | 1.4 (0.9–2.0)       | 1.3 (0.9–2.0)       |

OR = Odds Ratio, unadjusted.

*Significant.

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 (N = 175) | Breast cancer survivors treated with radiotherapy (N = 175) |
|------------------------------------------------------------|-----------------------------------------------------------|
| N (%)                                                      | N (%)                                                     |
| 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.

OR = Odds Ratio.

4. 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 [34]. 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.

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.

5. Conclusion

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).

Ethical approval

This study has been approved by the Medical Ethical Committee of the University Medical Center Groningen.

Funding

This study was supported by unrestricted grants from Pink Ribbon (grant no. 2011.WO18.C118); Stichting de Friesland (“BLOC-studie” DS 20); the University of Groningen, and the University Medical Center Groningen. They had no involvement in the study, writing or publication process.

Declaration of competing interest

Nothing to disclose.

Acknowledgments

We would like to thank all the women and PCPs who participated. Also, we want to thank the medical students who helped to obtain the data. Finally, we thank Dr Robert Sykes (www.doctored.org.uk) for providing editorial services.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2020.09.013.

References

[1] Otten JD, Broeders MJ, Fracheboud J, Otto SJ, de Koning HJ, Verheek AL.
Impressive time-related influence of the Dutch screening programme on breast cancer incidence and mortality, 1975–2006. Int J Canc 2008;123: 1529–34.

[2] Vervoort MM, Draisma G, Fracheboud J, van de Poli-Franse LV, de Koning HJ. Trends in the usage of adjuvant systemic therapy for breast cancer in The Netherlands and its effect on mortality. Br J Canc 2004;91:242–7.

[3] Caram ME, Guo C, Leja M, et al. Doxorubicin-induced cardiac dysfunction in selected patients with a history of early-stage breast cancer. Breast Canc Res Treat 2015;152:163–72.

[4] Zambetti M, Molfetta A, Materazzo C, et al. Long-term cardiac sequelae in operable breast cancer patients given adjuvant chemotherapy with or without doxorubicin and breast irradiation. J Clin Oncol 2001;19:37–43.

[5] Boerman LM, Maass SWMC, van der Meer P, et al. Long-term outcome of cardiac function in a population-based cohort of breast cancer survivors: a cross-sectional study. Eur J Canc 2017;81:56–65.

[6] Taylor C, Correa C, Duane FK, et al. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. J Clin Oncol 2017;35:1641–9.

[7] Lenihan DJ, Cardinale DM. Late cardiac effects of cancer treatment. J Clin Oncol 2012;30:3657–64.

[8] Ketepe-Arachi T, Sharma S. Cardiovascular disease in women: understanding symptoms and risk Factors 2017;12:10.

[9] Crespi CM, Ganz PA, Petersen L, Castillo A, Caan B. Refinement and psychometric evaluation of the impact of cancer scale. J Natl Cancer Inst 2008;100: 1539–41.

[10] Klein D, Mercier M, Abelard E, et al. Long-term quality of life after breast cancer: a French registry-based controlled study. Breast Canc Res Treat 2011:129:125–34.

[11] Suppli NP, Johansen C, Christensen J, Kessing LV, Kroman N, Dalton SO. Increased risk for depression after breast cancer: a nationwide population-based cohort study of associated factors in Denmark, 1998-2011, vol. 32, p. 3831–9.

[12] Maass S, Boereman L, Verhaak P, Du J, de Bock G, Berendsen A. Long-term psychological distress in breast cancer survivors and their matched controls: a cross-sectional study. Maturitas 2019;130:6–12.

[13] Ahles TA, Root JC, Ryan EL. Cancer- and cancer treatment–associated cognitive change: an update on the state of the Science 2012;30:3675–80.

[14] Brewden CB, Phillips K, Abdolett M, Bunston T, Tannock IF. Cognitive function in breast cancer patients receiving adjuvant Chemotherapy 2000;18: 2695–701.

[15] Zamorano JL, Lancellotti P, Rodriguez Munoz D, et al. ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J 2016;37:2768–801.

[16] Taylor CW, Nisbet A, McGale P, et al. Cardiac doses from Swedish breast cancer radiotherapy since the 1950s. Radiother Oncol 2009;90:3675–7.

[17] Vliet A. Protocollair CVRM 2013;3:95–6.

[18] Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28(1):39. e14.

[19] Zignond A, Smith AP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.

[20] Herrmann C. International experiences with the Hospital Anxiety and Depression Scale–a review of validation data and clinical results. J Psychosom Res 1997;42:17–41.

[21] Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: an updated literature review. J Psychosom Res 2002;52:60–77.

[22] Ahles TA, Saykin AJ, Furstenberg CT, et al. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. J Clin Oncol 2002;20:485–93.

[23] Nguyen CM, Yamada TH, Beglinger LJ, Cavanaugh JE, Denburg NL, Schultz SK. Cognitive features 10 or more years after successful breast cancer survival: comparisons across types of cancer interventions 2013;22:862–8.

[24] Silverman DH, Dy CJ, Castelion SA, et al. Altered frontocortical, cerebellar, and basal ganglia activity in adjuvant-treated breast cancer survivors 5–10 years after chemotherapy. Breast Canc Res Treat 2007;103:303–11.

[25] Stouen-Kemperman MM, de Ruiter MB, Boogerd W, Veltman DJ, Reneman L, Schagen SB. Very late treatment–related alterations in brain function of breast cancer survivors 2015;21:50–61.

[26] de Ruiter MB, Reneman L, Boogerd W, et al. Late effects of high-dose adjuvant chemotherapy on white and gray matter in breast cancer survivors: converging results from multimodal magnetic resonance imaging. Hum Brain Mapp 2012;33:2971–83.

[27] Conde DM, Pinto-Neto AM, Cabello C, Santos-Sá D, Costa-Paiva L, Martinez E. Quality of life in Brazilian breast cancer survivors age 45–65 years: associated factors. Breast 2005;11:425–32.

[28] Post RE, Dickeren IM. Dizziness: a diagnostic approach. Am Fam Physician 2010;82:361–8.

[29] Bruno D, Feeney KJ. Management of postmenopausal symptoms in breast cancer survivors 2006;33:969–707.

[30] Demling AA, Sarni T, Baker KS, et al. Survivorship, version 2.2018. NCN clinical practice guidelines in oncology 2018;16:1216–47.

[31] Andersen BL, Rowland JH, Somerfield MR. Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation 2014;11:133–4.

[32] Khatcheressian JL, Hurley P, Bantug E, et al. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2013;31:961–5.

[33] Buips C, de Vries EG, Mourits MJ, Willems PH. The influence of endocrine treatments for breast cancer on health-related quality of life. Cancer Treat Rev 2008;34:640–55.

[34] Runowicz CD, Leach CR, Henry NL, et al. American cancer society/American society of clinical oncology breast cancer survivorship care guideline 2016: 66–73.

[35] Hwang H, Tsai W, Chou W, et al. Quality of life of breast and cervical cancer survivors. BMC Wom Health 2017;17:30.

[36] Arraras JI, Mantero A, Illarremendi JJ, et al. Quality of life evolution in elderly survivors with localized breast cancer treated with radiotherapy over a three-year follow-up 2018;41:74–81.

[37] Roorda C, Berendse AJ, Groenhof F, van der Meer K, de Bock GH. Increased primary healthcare utilisation among women with a history of breast cancer. Support Care Canc 2013;21:941–9.

[38] Von Ah D, Hubermann B, Carpenter JS, Schneider BL. Impact of perceived cognitive impairment in breast cancer survivors, vol. 17; 2013. p. 3831.

[39] Ashley Henneghan M. When do I get my brain back? Breast cancer survivors’ experiences of cognitive problems. Clin J Oncol Nurs 2015;19:180.

[40] Thomas KB. General practice consultations: is there any point in being positive? Br Med J 1987;294:1200–2.

[41] Bail JR, Ivankova N, Heaton K, Vance DE, Triebel K, Meneses K. Cancer-related symptoms and cognitive intervention adherence among breast cancer survivors treated with chemotherapy. Canc Nurs 2013;36:22–30.

[42] Bail JR, Ivanikova N, Heaton K, Vance DE, Tribel K, Menses K. Cancer-related symptoms and cognitive intervention adherence among breast cancer survivors: a mixed-methods study. Cancer Nurs 2019.

[43] Vanz DE, Frank JS, Bail J, et al. Interventions for cognitive deficits in breast cancer survivors treated with chemotherapy, Canc Nurs 2017;40:E11–27.

[44] Cifu G, Power MC, Shomstein S, Arem H. Mindfulness-based interventions and psychological distress in breast cancer survivors: a systematic review. J Psychosom Res 2018;11:138.

[45] Lambert H, Woods M. The International Classification of Primary Care (ICPC). 1987.