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Published in:
European Journal of Heart Failure

Publication status and date:
Published: 01/02/2020

DOI (link to publisher):
10.1002/ejhf.1610

Document Version
Publisher's PDF, also known as Version of record

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Citation for the published version (APA):
Jacobse, J. N., Steggink, L. C., Sonke, G. S., Schaapveld, M., Hummel, Y. M., Steenbruggen, T. G., Lefrandt, J. D., Nuver, J., Crijns, A. P. G., Aleman, B. M. P., van der Meer, P., Gietema, J. A., & van Leeuwen, F. E. (2020). Myocardial dysfunction in long-term breast cancer survivors treated at ages 40-50 years. *European Journal of Heart Failure*, *22*(2), 338-346. https://doi.org/10.1002/ejhf.1610

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European Journal of Heart Failure (2020) **22**, 338–346
doi:10.1002/ejhf.1610

RESEARCH ARTICLE

Myocardial dysfunction in long-term breast cancer survivors treated at ages 40–50 years

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Received 3 March 2019; revised 4 July 2019; accepted 11 August 2019; online publish-ahead-of-print 6 November 2019

Aims Anthracyclines increase heart failure (HF) risk, but the long-term prevalence of myocardial dysfunction in young breast cancer (BC) survivors is unknown. Early measures of left ventricular myocardial dysfunction are needed to identify BC patients at risk of symptomatic HF.

Methods and results Within an established cohort, we studied markers for myocardial dysfunction among 569 women, who were 5–7 years ($n = 277$) or 10–12 years ($n = 292$) after BC treatment at ages 40–50 years. Left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) were assessed by echocardiography. N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured in serum. Associations between patient-related and treatment-related risk factors and myocardial dysfunction were evaluated using linear and logistic regression. Median ages at BC diagnosis and cardiac assessment were 46.7 and 55.5 years, respectively. Anthracycline-treated patients ($n = 313$), compared to the no-anthracycline group ($n = 256$), more often had decreased LVEF (10% vs. 4%), impaired GLS (34% vs. 27%) and elevated NT-proBNP (23% vs. 8%). GLS and LVEF declined in a linear fashion with increasing cumulative anthracycline dose (GLS: +0.23 and LVEF: −0.40 per cycle of 60 mg/m^2; $P < 0.001$) and GLS was worse for patients with left breast irradiation. The risk of NT-proBNP >125 ng/L was highest for patients who received 241–300 mg/m^2 anthracycline dose compared to the no-anthracycline group (odds ratio: 3.30, 95% confidence interval: 1.83–5.96).

Conclusion Impaired GLS and increased NT-proBNP levels are present in a substantial proportion of young BC survivors treated with anthracyclines. Whether this will lead to future cardiac disease needs to be evaluated by longitudinal assessment.

Keywords Cardiotoxicity • Breast cancer • Anthracyclines • Global longitudinal strain • NT-proBNP

Introduction

Anthracyclines have been the cornerstone of chemotherapy regimens for early breast cancer (BC) since the 1990s.[1] They are known, however, for their cardiotoxicity that can affect BC survivors' quality of life and life expectancy.[2] Despite awareness of anthracycline-related cardiotoxicity, no evidence-based guidelines to monitor cardiac function of long-term BC survivors are currently available.[3–5] In order to develop such guidelines it is of paramount importance to better identify survivors at high risk of developing cardiotoxicity and to evaluate methods for early detection.

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Many studies have investigated the incidence of anthracycline-related cardiotoxicity by echocardiographic measurement of left ventricular ejection fraction (LVEF) as an indicator of systolic (dys)function.[6–8] Incidence rates of systolic dysfunction range from 1–12% and are difficult to compare across studies due to lack of a uniform definition for cardiotoxicity and substantial differences in study populations in terms of age, follow-up time and prevalence of co-morbid conditions. Moreover, studies reporting on myocardial dysfunction beyond 10 years of follow-up are scarce.[9,10]

Since LVEF decline can occur as a late manifestation of cardiac injury, earlier and more sensitive markers that identify myocardial dysfunction may be valuable. A promising technique to identify left ventricular (LV) dysfunction is myocardial deformation imaging[11]; measurement of global longitudinal strain (GLS) can detect changes in contractility before LVEF decreases.[12] Additionally, serial measurements of cardiac biomarkers such as N-terminal pro-brain natriuretic peptide (NT-proBNP) – an established screening tool for heart failure in the general population[13] – may be useful to detect myocardial dysfunction in BC survivors.[14–17]

Little is known about the long-term prevalence of myocardial dysfunction in BC survivors. This study aims to determine prevalence of and risk factors for myocardial dysfunction by conventional echocardiography, strain imaging and cardiac biomarker analyses in a large cohort of young BC patients treated with and without anthracycline-based chemotherapy.

Methods

Study design

We conducted a cross-sectional study within two established hospital-based cohorts of BC survivors for which we have previously collected information on cardiovascular disease incidence through general practitioners and cardiologists.[18] Eligible women were treated for invasive BC (TNM stage I–III) or ductal carcinoma *in situ* (DCIS) at ages 40–50 years in the Netherlands Cancer Institute – Antoni van Leeuwenhoek (NKI-AVL) or University Medical Center Groningen (UMCG), and were either 5–7 or 10–12 years after initial treatment. Exclusion criteria were (i) history of radiotherapy or chemotherapy unrelated to BC/DCIS, (ii) current treatment for BC/DCIS recurrence or treatment for second malignancy (except non-melanoma skin cancer and carcinoma *in situ* of the cervix), (iii) history of cardiovascular disease (heart failure, acute coronary syndrome, coronary revascularization procedure, symptomatic valvular dysfunction, or cardiomyopathy) before BC/DCIS diagnosis. Patients who had been treated for a locoregional BC/DCIS recurrence, second BC/DCIS, or cardiovascular disease after initial BC diagnosis could participate. The study was approved by the institutional review board of the NKI-AVL and is registered with ClinicalTrials.gov, identifier NCT02485626.

Study procedures

Eligible women received a written invitation describing the study objectives and procedures. Non-responders were sent up to two reminders. Patients who declined participation were diagnosed longer ago and were treated less often with anthracycline-based chemotherapy. Sixty-three percent of invited women provided informed consent and completed a first study visit (online supplementary *Figure S1*). Participants filled out a baseline questionnaire on current and past lifestyle factors, physical activity, family history of cardiovascular disease, and psychosocial functioning. Detailed data on tumour and treatment characteristics, medical history, previous cardiac evaluation, cardiovascular risk factors and medication use were extracted from medical records, hospital registries, and obtained through the participants' general practitioner. When detailed dosing information of chemotherapy was missing from the medical charts, we assigned standard chemotherapy doses per administered cycle according to the guidelines per hospital. At study visit, sociodemographic variables, recent medical history and current medication use were recorded. Participants underwent standardized physical examination, blood and urine sampling and electrocardiography (online supplementary *Methods S1*). NT-proBNP was measured in serum using an immuno-assay (Cobas platform, Roche Diagnostics, USA). Transthoracic tissue Doppler echocardiography was performed according to a standardized acquisition protocol, using the GE Vivid E9 machine (GE, Horten, Norway) in the UMCG and Philips iE33 machine (Philips Healthcare, DA Best, The Netherlands) in the NKI-AVL. Echocardiographic exams were centrally analysed at Groningen Imaging Core Laboratory by trained observers in accordance with the American Society of Echocardiography and the European Society of Cardiology guidelines.[19] LVEF was assessed by Simpson biplane method or, if image quality was insufficient (15.6%), an eyeballing LVEF range was reported. Other measures of LV function were also quantified (online supplementary *Methods S2*). LV GLS was measured using the Arena two-dimensional cardiac performance analysis (TomTec Imaging Systems, Unterschleissheim, Germany). Inability to track the LV wall during the full cardiac cycle precluded GLS measurements in 76 (13%) patients. GLS was measured twice for a random subset of 102 subjects. Correlation of measurements of the same individual was 0.70 [95% confidence interval (CI) 0.59–0.79].

Statistical analysis

Treatment and follow-up groups were compared using *t*-tests, Mann–Whitney tests, and Chi-square tests. No cardiotoxicity equivalence ratio for epirubicin to doxorubicin in BC survivors has been published. Therefore we used the ratio of the linear regression coefficient for cumulative epirubicin dose and LVEF and the linear regression coefficient for cumulative doxorubicin dose and LVEF from our data to calculate a doxorubicin dose equivalent. Associations between cumulative doxorubicin dose equivalent (i.e. anthracycline dose per cycle of 60 mg/m^2) and LVEF, GLS and NT-proBNP were evaluated using multivariable linear regression models to assess and control for potential confounders and test for interactions between risk factors. We tested variables of interest one by one and a potential confounder was added to the model if inclusion of this variable changed the coefficients for the other variables ≥10%. Non-linearity of the dose–response relationship was evaluated including a quadratic term for anthracycline dose. Model performance was assessed using likelihood ratio tests. We performed sensitivity analyses excluding patients with a locoregional BC recurrence and/or second BC or clinical cardiovascular disease diagnosed after BC to establish their influence on outcome measures. For clinical interpretation of the data, we conducted multivariable logistic regression to study effects of treatment-related risk factors on myocardial dysfunction prevalence, defined as a LVEF <54%, according to the range of normal LVEF values in the general female population,[19] GLS >−17%, a cut-off value indicative of impaired myocardial deformation,[20] or NT-proBNP >125 ng/L.[13] Significance tests were two-sided and $P < 0.05$ was

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considered statistically significant. Analyses were performed using Stata/SE (version 13.0; StataCorp LP, College Station, TX, USA).

Results

In total, 569 women were enrolled. Women in the 5–7 year survivor group had a median follow-up of 6.8 years [interquartile range (IQR) 6.1–7.5] vs. 11.6 years (IQR 10.9–12.2) in the 10–12 year survivor group. Median age at BC diagnosis was 47.6 years (IQR 44.9–49.5) in the no-anthracycline group ($n = 256$) and 46.0 years (IQR 43.1–49.0) in the anthracycline group ($n = 313$) (*Table 1*). Prevalence of hypertension, hypercholesterolaemia, and diabetes mellitus at BC diagnosis did not differ between patients treated with and without anthracyclines (*Table 1*), nor according to follow-up duration (data not shown). The proportion of current and former smokers was lower in the anthracycline group compared to the no-anthracycline group (current smoker: 24.9% vs. 28.5%; former smoker: 26.5% vs. 37.9%; $P = 0.001$) (*Table 1*).

Treatment characteristics

As expected, anthracycline-treated patients received more extensive treatment, as they more often had triple negative and higher stage BC (online supplementary *Table S1*). Thirty-two percent of anthracycline-treated patients had a mastectomy compared to 5.1% in the no-anthracycline group ($P < 0.001$) (*Table 2*). Both chest wall and internal mammary lymph nodes were more often irradiated in anthracycline-treated patients (chest wall: 16.6% vs. 2.8%; internal mammary lymph nodes: 11.2% vs. 1.2%; $P < 0.001$). In the anthracycline group, 77% of patients received adjuvant endocrine therapy compared to 28.9% in the no-anthracycline group ($P < 0.001$). Most commonly prescribed chemotherapy regimens were 5-fluorouracil, epirubicin and cyclophosphamide (FEC) and doxorubicin and cyclophosphamide (AC), followed by anthracycline-taxane-based combinations (e.g. TAC, FEC-T). The number of chemotherapy cycles ranged from 1–6. Median cumulative epirubicin dose was 450 mg/m^2, median cumulative doxorubicin dose was 240 mg/m^2, and median anthracycline dose was 240 mg/m^2 (IQR 207–313). Trastuzumab was administered in 15% of anthracycline-treated patients after completion of the anthracycline part of their chemotherapy regimen. Patients in the 5–7 year follow-up group received more extensive surgery and radiotherapy, higher anthracycline doses and more endocrine therapy than patients in the 10–12 year follow-up group (online supplementary *Table S2*).

Prevalence of risk factors at study visit

Median age at study visit was 55.5 years (IQR 52.7–58.5; online supplementary *Table S3*). Overt signs of heart failure (such as pulmonary congestion and/or peripheral oedema) were absent at physical examination in all screened patients. Hypertension and hypercholesterolaemia were the most prevalent cardiovascular risk factors and their frequency did not differ between treatment groups. Anthracycline-treated patients had a higher body

Table 1 Patient characteristics at breast cancer diagnosis

	Anthracyclines	No anthracyclines	*P*-value*
Total	313 (100)	256 (100)	
Age (years)	46.0 [43.1–49.0]	47.6 [44.9–49.5]	<0.001
40–45 years	156 (49.8)	90 (35.2)	
46–50 years	157 (50.2)	166 (64.8)	<0.001
Year of breast cancer diagnosis			
2002–2007	177 (56.6)	140 (54.7)	
2008–2012	136 (43.4)	116 (45.3)	0.66
Follow-up time (years)	8.7 [7.1–11.6]	10.3 [6.6–11.5]	0.42
5–7 years	157 (50.2)	120 (46.9)	
10–12 years	156 (49.8)	136 (53.1)	0.44
Educational level			
Primary education	42 (13.4)	22 (8.6)	
Secondary education	65 (20.8)	58 (22.7)	
Vocational education	89 (28.4)	62 (24.2)	
Higher education	117 (37.4)	114 (44.5)	0.12
Cardiovascular risk factors			
Hypertension[a]	71 (22.7)	57 (22.3)	0.91
Hypercholesterolaemia[b]	7 (2.2)	7 (2.7)	0.70
Diabetes[b]	3 (1.0)	2 (0.8)	0.82
Body mass index			
<25 kg/m^2	195 (62.3)	174 (68.0)	
25–30 kg/m^2	82 (26.2)	58 (22.7)	
>30 kg/m^2	33 (10.5)	20 (7.8)	
Unknown	3 (1.0)	4 (1.6)	0.28
Smoking			
Never smoked	144 (46.0)	82 (32.0)	
Former smoker	83 (26.5)	97 (37.9)	
Current smoker	78 (24.9)	73 (28.5)	
Unknown	8 (2.6)	4 (1.6)	0.001
Menopausal status			
Premenopausal	252 (80.5)	193 (75.4)	
Postmenopausal	60 (19.2)	60 (23.4)	
Unknown	1 (0.3)	3 (1.2)	0.20
Co-morbidity[c]			
Circulatory disease[c]	18 (5.8)	20 (7.8)	0.33
Pulmonary disease[d]	26 (8.3)	26 (10.2)	0.45
Endocrine, nutritional, metabolic diseases[e]	26 (8.3)	14 (5.5)	0.19
Cardiovascular medication[f]			
Any antihypertensive drug	30 (9.6)	23 (8.9)	0.81
Any lipid-lowering drug	4 (1.3)	2 (0.8)	0.56
Any glucose-lowering drug	3 (1.0)	2 (0.8)	0.82
Any antithrombotic drug	5 (1.6)	2 (0.8)	0.38
Mutation status[g]			
BRCA1 carrier	11 (3.5)	1 (0.4)	0.01
BRCA2 carrier	9 (2.9)	3 (1.2)	0.16
Other	5 (1.6)	6 (2.3)	0.52

Values are given as *n* (%), or median [interquartile range].
[a]Hypertension was scored positive if a patient had systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, used antihypertensive drugs (medical record), or if hypertension was self-reported (patient questionnaire).
[b]Hypercholesterolaemia/diabetes mellitus were scored positive if a patient used lipid/glucose-lowering drugs (medical record), or if hypercholesterolaemia/diabetes mellitus was self-reported (patient questionnaire).
[c]Information on co-morbidity and medication use was collected from the medical record.
[d]This category includes diagnoses I00-I99, excluding I10-I15, International Classification of Diseases, 10th revision.
[e]This category includes diagnoses J00-J99, International Classification of Diseases, 10th revision.
[f]This category includes diagnoses E00-E90, excluding E10-E14 and E78, International Classification of Diseases, 10th revision.
[g]Self-reported mutation status.
*P-value for difference between treatment groups, calculated with two-sample *t*-test or Chi-square test and excluding the unknown category for categorical variables.

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Table 2 Treatment characteristics

	Anthracyclines	No anthracyclines	*P*-value*
Total	313 (100	256 (100	
Surgery			
Lumpectomy	212 (67.7)	243 (94.9)	
Mastectomy	99 (31.6)	13 (5.1)	
Other[a]	2 (0.6)	0 (0)	<0.001
Radiotherapy fields			
No radiotherapy	23 (7.4)	6 (2.3)	
Right breast	107 (34.2)	126 (49.2)	
Left breast	96 (30.7)	114 (44.5)	
Right chest wall	23 (7.4)	3 (1.2)	
Left chest wall	29 (9.2)	4 (1.6)	
IMN[b]	35 (11.2)	3 (1.2)	<0.001
Chemotherapy regimen[c]			
FEC	105 (33.6)	NA	
FAC	17 (5.4)	NA	
AC	70 (22.4)	NA	
FEC + T	35 (11.2)	NA	
AC + T	37 (11.8)	NA	
TAC	44 (14.1)	NA	
Other, with anthracyclines[d]	5 (1.6)	NA	
Cumulative epirubicin dose (mg/m^2)	450 [360–500]	NA	
≤270 mg/m^2	31 (21.8)	NA	
271–450 mg/m^2	72 (50.7)	NA	
>450 mg/m^2	39 (27.5)	NA	
Cumulative doxorubicin dose (mg/m^2)	240 [240–300]	NA	
≤240 mg/m^2	88 (51.5)	NA	
241–300 mg/m^2	58 (33.9)	NA	
>300 mg/m^2	25 (14.6)	NA	
Cumulative anthracycline dose[e,f] (mg/m^2)	240 [207–313]	NA	
≤180 mg/m^2	52 (16.6)	NA	
181–240 mg/m^2	148 (47.3)	NA	
241–300 mg/m^2	88 (28.1)	NA	
>300 mg/m^2	25 (8.0)	NA	
Trastuzumab			
No	266 (85.0)	253 (98.8)	
Yes	47 (15.0)	3 (1.2)	<0.001
Endocrine treatment[g]			
No	72 (23.0)	182 (71.1)	
Tamoxifen only	59 (18.9)	34 (13.3)	
Tamoxifen, switch to aromatase inhibitor	146 (44.7)	26 (10.2)	
Aromatase inhibitor only	35 (11.2)	14 (5.5)	
Unknown	1 (0.3)	0 (0)	<0.001

Values are given as *n* (%), or median [interquartile range].
A, doxorubicin; C, cyclophosphamide; E, epirubicin; F, 5-fluorouracil; IMN, internal mammary lymph nodes; NA, not applicable; T, taxane.
[a]One patient had an occult breast cancer for which she had an axillary lymph node dissection. One patient refused surgery.
[b]Eleven patients received IMN irradiation combined with breast irradiation (seven left-sided/four right-sided) and 27 patients received IMN irradiation combined with chest wall irradiation (12 left-sided/15 right-sided).
[c]Sixteen percent of anthracycline-treated patients received neo-adjuvant chemotherapy.
[d]One patient received four cycles of EC, one patient received six cycles of A + docetaxel, one patient received three cycles of AC, followed by three cycles of docetaxel + capecitabin, one patient received three cycles of AC followed by paclitaxel + carboplatin + trastuzumab, one patient received four cycles of FEC, followed by two cycles of high dose C + thiotepa + carboplatin.
[e]For epirubicin a conversion factor of 0.45 was used to calculate a doxorubicin dose equivalent in relation to cardiotoxicity.
[f]For 61% of patients standard chemotherapy doses per administered cycle were assigned according to the guidelines per hospital.
[g]In 22% of anthracycline-treated patients and in 35% of no-anthracycline patients, tamoxifen/aromatase inhibitor was combined with a gonadotropin-releasing hormone agonist.
*P-value for difference between treatment groups, calculated with Chi-square test and, if applicable, excluding the unknown category.

mass index at study visit, smoked less and were more often postmenopausal. Thirteen women (five anthracycline-treated and eight no-anthracycline patients) had been diagnosed with a cardiovascular disease after BC for which they received treatment (online supplementary *Table S3*). Hypertension and hypercholesterolaemia were more prevalent among 10–12 year survivors than among 5–7 year survivors (online supplementary *Table S4*).

Markers of myocardial dysfunction

Mean LVEF values were 58.3% [standard deviation (SD) ±4.3%] and 59.9% (SD ±4.9%) in the anthracycline- and no-anthracycline group, respectively. LVEF decreased with increasing cumulative anthracycline dose (LVEF 59.9–0.40% per cycle of 60 mg/m^2 anthracycline dose; $P < 0.001$), with no evidence for non-linearity (*Figure 1A*; online supplementary *Figure S2*). No confounding effects of patient or treatment variables were identified (*Table 3*). Other risk factors that were associated with decreased LVEF were history of cardiovascular disease ($\beta = -2.96$, $P = 0.02$), postmenopausal status ($\beta = -1.11$, $P = 0.05$) and a known BRCA mutation ($\beta = -1.94$, $P = 0.05$; online supplementary *Table S5*). In a multivariable model, only a history of cardiovascular disease after BC in addition to anthracycline dose remained associated with a decreased LVEF ($\beta = -3.10$, $P = 0.02$) (*Table 3*). Interaction analyses showed that an increasing cumulative anthracycline dose was associated with a larger decrease in LVEF in patients without hypertension (*Table 4*). LVEF <54% was found in 32/312 (10%) of anthracycline-treated patients compared to 11/255 (4%) of no-anthracycline patients. In a logistic model, the highest risk of decreased LVEF was seen in those who received >300 mg/m^2 anthracycline dose vs. no anthracyclines [odds ratio (OR) 14.98, 95% CI 4.03–55.67, adjusted for radiotherapy field, endocrine treatment and trastuzumab] (*Table 5*).

LVEF and GLS were moderately correlated [Pearson correlation coefficient (r) 0.34; online supplementary *Figure S3*] and this correlation was stronger in the no-anthracycline group (r = 0.43). Mean GLS was −17.9% (SD ±2.9%) in the anthracycline group and −18.8% (SD ±3.2%) in the no-anthracycline group. GLS linearly declined with increasing cumulative anthracycline dose in a model accounting for age at BC diagnosis and radiotherapy field (GLS = −18.7% + 0.23% per cycle of 60 mg/m^2 anthracycline dose; $P < 0.001$) (*Figure 1B*). The association between GLS and anthracycline dose did not change when excluding patients with LVEF <54%. In the 5–7 year group, the effect of dose on GLS was more pronounced than in the 10–12 year group ($\beta = 0.70$ vs. $\beta = 0.38$, $P_{interaction} = 0.01$) (*Table 4*). Irradiation of the left breast was associated with worse GLS ($\beta = 0.96$, $P = 0.002$) (*Table 3*). Impaired GLS (>−17%) was found in 34% of the anthracycline group and in 27% of the no-anthracycline group; risk was highest in patients who received 240–300 mg/m^2 anthracycline dose (OR 1.83, 95% CI 1.05–3.17, adjusted for age at BC diagnosis and trastuzumab) (*Table 5*). The prevalence of cardiovascular risk factors stratified by GLS is shown in the online supplementary *Table S5*.

Median NT-proBNP was 75 ng/L (IQR 50–122) in the anthracycline group and 58 ng/L (IQR 37–92) in the no-anthracycline group. A linear association between NT-proBNP and cumulative anthracycline dose was found (NT-proBNP 72 ng/L + 7.2 ng/L per cycle

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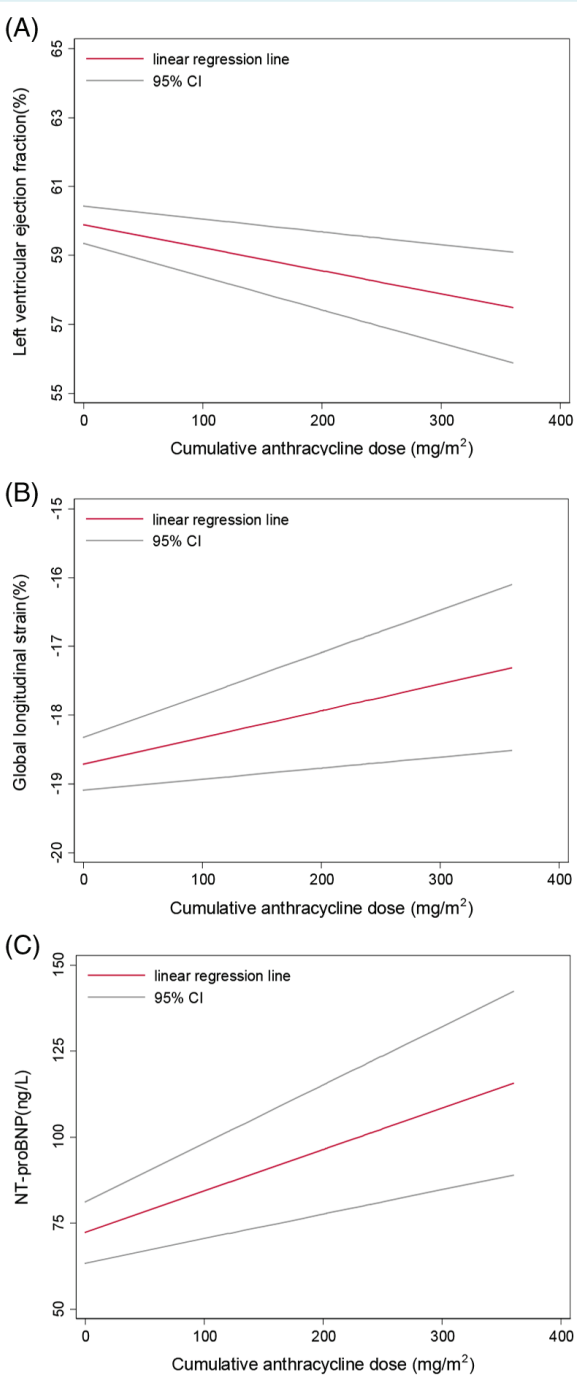

Figure 1 Associations between cumulative anthracycline dose and left ventricular ejection fraction (LVEF) (*A*), global longitudinal strain (GLS) (*B*) and N-terminal pro-brain natriuretic peptide (NT-proBNP) (*C*). Red lines depict linear associations and grey lines depict 95% confidence intervals (CI). Associations can be described by LVEF = 59.9−0.40 per cycle of 60 mg/m^2 anthracycline dose; GLS = -18.7 + 0.23 per cycle of 60 mg/m^2 anthracycline dose; NT-proBNP = 72 + 7.2 per cycle of 60 mg/m^2 anthracycline dose (all $P < 0.001$).

Table 3 Multivariable linear regression analyses for left ventricular ejection fraction, global longitudinal strain and N-terminal pro-brain natriuretic peptide

Variable	Multivariable model[a]		Final model[b]	
	β[c]	*P*-value	*β*[c]	*P*-value
LVEF[d]				
Anthracycline dose (60 mg/m^2)	−0.41	<0.001	−0.40	<0.001
Age (years)[e]	−0.04	0.50		
Diastolic blood pressure (mmHg)[f]	−0.00	0.94		
BMI (kg/m^2)[f]	0.05	0.34		
Glucose (mmol/L)[f]	−0.26	0.16		
Radiotherapy field				
Right breast	ref.			
Left breast	−0.50	0.25		
Right chest wall	−0.85	0.38		
Left chest wall	0.10	0.91		
IMN	−0.83	0.32		
No radiotherapy	−0.41	0.66		
Trastuzumab	0.43	0.54		
History of CVD	−3.10	0.02		
GLS				
Anthracycline dose (60 mg/m^2)	0.21	0.004	0.23	0.001
Age (years)	0.02	0.59	0.06	0.21
Diastolic blood pressure (mmHg)	0.04	0.006		
BMI (kg/m^2)	0.01	0.77		
Glucose (mmol/L)	0.37	0.02		
Radiotherapy field				
Right breast	ref.		ref.	
Left breast	1.00	0.001	0.96	0.002
Right chest wall	0.05	0.94	−0.06	0.93
Left chest wall	−0.24	0.69	−0.26	0.67
IMN	0.06	0.92	0.13	0.83
No radiotherapy	−0.06	0.93	−0.18	0.79
Trastuzumab	−0.42	0.41		
History of CVD	1.72	0.11		
NT-proBNP				
Anthracycline dose (60 mg/m^2)	9.4	<0.001	7.2	<0.001
Age (years)	0.5	0.63		
Diastolic blood pressure (mmHg)	0.6	0.05		
BMI (kg/m^2)	−1.8	0.02		
Glucose (mmol/L)	−6.7	0.03		
Radiotherapy field				
Right breast	ref.			
Left breast	11.4	0.11		
Right chest wall	−20.3	0.19		
Left chest wall	−4.0	0.77		
IMN	0.4	0.98		
No radiotherapy	4.7	0.75		
Trastuzumab	−21.0	0.07		
History of CVD	104.6	<0.001		

BMI, body mass index; CVD, cardiovascular disease; GLS, global longitudinal strain; IMN, internal mammary lymph nodes; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.

[a]Model including other potential cardiotoxic treatments and cardiovascular risk factors of interest. Since systolic and diastolic blood pressure were correlated and stronger associations between diastolic blood pressure and outcome variables were seen, estimates for diastolic blood pressure are presented.

[b]Model including variables that changed the regression coefficient for anthracycline dose (and, if applicable, other variables) ≥10%.

[c]*β* describes the linear change in LVEF (%), GLS (%), or NT-proBNP (ng/L) per unit increase of the variable of interest.

[d]For 88 patients (15.6%), mean LVEF of an eyeballing LVEF range was used for the analyses.

[e]Age at breast cancer diagnosis.

[f]Factor measured at study visit.

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Table 4 Association between left ventricular ejection fraction, global longitudinal strain and N-terminal pro-brain natriuretic peptide and cumulative anthracycline dose for subgroups

	β^a LVEF	*P*-value[b]	β^a GLS	*P*-value[b]	β^a NT-proBNP	*P*-value[b]
Age at BC diagnosis						
40–45 years	−0.61		0.14		1.1	
46–50 years	−0.48	0.49	0.20	0.66	5.2	0.18
Follow-up time						
5–7 years	−0.81		0.70		11.5	
10–12 years	−0.54	0.13	0.38	0.01	8.7	0.35
Trastuzumab						
No	−0.41		0.26		7.7	
Yes	−0.73	0.53	−0.06	0.41	11.0	0.69
Hypertension at BC diagnosis						
No	−0.50		0.26		7.5	
Yes	−0.06	0.04	0.07	0.22	6.3	0.73
Hypertension at study visit						
No	−0.59		0.26		7.7	
Yes	−0.06	<0.01	0.16	0.44	6.2	0.64

BC, breast cancer; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.
[a] β describes the linear change in LVEF (%), GLS (%), or NT-proBNP (ng/L) per anthracycline cycle (60 mg/m^2).
[b] $P_{interaction}$.

Table 5 Multivariable logistic regression analyses of decreased left ventricular ejection fraction, impaired global longitudinal strain and elevated N-terminal pro-brain natriuretic peptide by treatment

	LVEF <54%			GLS >−17%			NT-proBNP >125 ng/L			≥1 parameter of myocardial dysfunction		
	n/N[a]	OR	95% CI	n/N[b]	OR	95% CI	n/N[c]	OR	95% CI	n/N[d]	OR	95% CI
Model 1												
No anthracyclines	11/255	1.00	ref.	60/226	1.00	ref.	31/256	1.00	ref.	76/226	1.00	ref.
Anthracyclines	32/312	2.54	1.25–5.14	91/267	1.43	0.97–2.11	71/313	2.13	1.35–3.37	138/267	2.11	1.46–3.04
Model 2[e]												
Chemotherapy												
No anthracyclines	11/255	1.00	ref.	60/226	1.00	ref.	31/256	1.00	ref.	76/226	1.00	ref.
≤180 mg/m^2	4/52	3.66	0.99–13.71	13/41	1.38	0.66–2.85	4/52	0.66	0.22–1.95	18/40	1.60	0.81–3.17
181–240 mg/m^2	12/148	2.83	1.11–7.22	41/125	1.53	0.93–2.52	34/148	2.35	1.36–4.08	61/125	1.98	1.25–3.15
241–300 mg/m^2	10/88	4.05	1.54–10.66	30/79	1.83	1.05–3.17	27/88	3.30	1.83–5.96	49/79	3.27	1.92–5.58
>300 mg/m^2	6/24	14.98	4.03–55.67	7/22	1.45	0.56–3.78	6/25	2.41	0.89–6.53	10/22	1.68	0.69–4.07
Trastuzumab												
No	40/518	1.00	ref.	141/453	1.00	ref.	95/519	1.00	ref.	197/453	1.00	ref.
Yes	3/49	0.67	0.19–2.37	10/40	0.68	0.32–1.49	7/50	0.59	0.25–1.39	17/40	0.75	0.38–1.49

CI, confidence interval; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; OR, odds ratio.
[a] Patients included in the analyses: $n = 567$. For two patients, LVEF could not be measured.
[b] Patients included in the analyses: $n = 493$. For 76 patients, GLS could not be measured.
[c] Patients included in the analyses: $n = 569$.
[d] Patients included in the analyses: $n = 493$.
[e] ORs for LVEF <54% were calculated in a multivariable model including radiotherapy field and endocrine treatment in addition to trastuzumab. ORs for GLS >−17% were calculated in a multivariable model including age at breast cancer diagnosis in addition to trastuzumab.

of 60 mg/m^2 anthracycline dose; $P < 0.001$) (*Table 3*, *Figure 1C*); risk of NT-proBNP >125 ng/L was 2.13-fold increased (95% CI 1.35–3.37) in patients who received anthracyclines (71/313; 23%) compared to no anthracyclines (31/256; 12%) (*Table 5*). When combining LVEF, GLS and NT-proBNP in one model, we obtained similar results for the risk of having ≥1 abnormal marker increasing with anthracycline dose (*P*-trend <0.001) (*Table 5*).

Sensitivity analyses excluding (i) patients with a recurrence and/or second BC/DCIS ($n = 32$), (ii) patients who developed cardiovascular disease during follow-up, and (iii) patients who used

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angiotensin-converting enzyme inhibitors, did not change results for any of the outcome parameters (data not shown).

Discussion

This study represents one of the largest comprehensive assessments of cardiac function by echocardiography, strain imaging and biomarker analysis in young, long-term BC survivors. Other studies in this research area were smaller, included older BC patients and reported results on fewer outcomes.[21,22] A substantial proportion of survivors in our cohort presented with myocardial dysfunction; in the anthracycline group, LVEF <54%, GLS >−17% and NT-proBNP >125 ng/L were observed in 10%, 34%, and 23% of patients, respectively. More than half of anthracycline-treated women (54%) had at least one indicator of myocardial dysfunction. The observed linear relationship between cumulative anthracycline dose and LVEF is consistent with previous findings,[2] indicating that there is no safe anthracycline dose below which there is no increased risk of cardiac damage. A novel result is the observed linear association between anthracycline dose and GLS. Furthermore, patients who received left breast irradiation had significant worse GLS values.

Prior large epidemiological studies have provided much information on risk of cardiac disease after BC treatment, but lacked data from an in-depth cardiac assessment that includes evaluation of early cardiotoxicity.[23,24] The use of registry data in such studies increases misclassification of exposure and event status compared to our study.[23] Qin *et al.*[24] abstracted cardiac imaging information from medical records, which may have led to higher risk estimates, since outcome data were likely only available for patients with signs and/or symptoms of cardiac disease.

Caram *et al.*[25] did evaluate the prevalence of cardiac dysfunction by a biomarker assay and an echocardiogram. They found that LVEF <55% was present in 11.5% of doxorubicin-treated BC survivors (median age: 56 years, median follow-up: 6 years) with an elevated cardiac biomarker at first screening (71% of included patients). Another Dutch study ($n = 350$, median follow-up: 10 years) found a LVEF <54% in 15.3% of patients, possibly due to the higher prevalence of cardiovascular risk factors. Almost 38% of participants were prescribed cardiovascular medication at study visit,[22] compared to 19.7% in our study. Interestingly, these previous studies showed no clear effect of cumulative anthracycline dose and may be the result of lower patient numbers and limited dose ranges.

Somewhat surprisingly, we observed no association between trastuzumab and either LVEF, GLS or NT-proBNP. Trastuzumab is known to increase the risk of LVEF decline, but this decline is often reversible.[26] Long-term cardiotoxicity data of trastuzumab-treated patients in a population-based setting are, however, limited.[27] In this cohort, the prevalence of LVEF <54% among trastuzumab-treated patients was only 6% (*Table 5*), suggesting that the cardiotoxic effect of trastuzumab may indeed be transient, but strong conclusions about the combined effects of anthracyclines and trastuzumab cannot be drawn from our data, since only 47 patients received both agents.

We found that about a third of screened patients had impaired GLS. In a cohort of 549 healthy European subjects, mean GLS was −23.3% (±3.1%) in females aged 40–60 years,[20] compared to mean GLS in our total cohort of −18.3% (±3.1%): −17.9% (±2.9%) in anthracycline-treated patients and −18.8% (±3.2%) in the no-anthracycline group. It should be noted that part of this ∼5% difference may be explained by differences in the prevalence of cardiovascular risk factors associated with worse GLS. Since previous studies have shown that GLS is a promising predictor for subsequent cardiotoxicity in BC patients,[12,28] we expect some of the women with impaired GLS to develop clinical cardiotoxicity.

In addition, we showed that GLS may not only detect anthracycline-related cardiotoxicity, but also radiotherapy-related cardiac injury, as left-sided breast irradiation was associated with worse GLS in a model including anthracycline dose ($\beta = 0.96$, $P = 0.002$). We believe that this finding does not reflect the use of older radiation techniques that expose the heart to higher radiation doses, as stratification by follow-up period yielded similar results. Although efforts have been made to reduce cardiac radiation exposure, the heart may still be exposed to ∼4 Gy when left-sided radiotherapy is given. Only a few small studies have investigated the potential of strain imaging as a screening tool for radiotherapy-related cardiotoxicity and showed promising results.[29,30] Patients in these studies were assessed, however, <6 weeks after radiotherapy and did not receive chemotherapy. Data on the long-term combined effects of anthracyclines and radiotherapy on GLS are limited and this finding requires further investigation.

Remarkably, the effect of anthracycline dose on GLS was more pronounced in patients diagnosed more recently. Similar trends were seen for LVEF and NT-proBNP (*Table 4*). Patients diagnosed 5–7 years ago more often received chest wall irradiation, adjuvant endocrine therapy and taxanes in addition to anthracycline-based chemotherapy. Inclusion of these treatment factors to our statistical model, however, did not change the relationship between anthracycline dose and GLS in the two follow-up groups. Although we tried to eliminate the influence of other (cardiovascular) risk factors on GLS, residual confounding cannot be ruled out. Confirmation of this result is therefore necessary and will be possible when prospective measurements for this cohort become available.

We also observed a linear association for anthracycline dose and NT-proBNP. Furthermore, 23% of patients in the anthracycline group had NT-proBNP >125 ng/L vs. 12% in the no-anthracycline group. Sandri *et al.*[16] showed that early, persistent increases in NT-proBNP may predict subsequent clinical cardiotoxicity. Also, in the European Society of Cardiology position paper it was reported that abnormal NT-proBNP is indicative of an increased risk of cardiotoxicity among patients treated with anthracyclines.[4] Evidence-based strategies to prevent progression to overt cardiac disease in this particular patient group should be further investigated. We were unable to identify patients with LVEF <54% using NT-proBNP >125 ng/L (online supplementary *Figure S2*) and the question remains whether the cut-off value for ruling out heart failure in the general population[13] is appropriate for detecting cardiotoxicity in BC survivors.

When interpreting our results, some limitations of our study should be considered. Included patients had no cardiovascular assessment at BC diagnosis and we were therefore unable to

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investigate changes in outcome measures from baseline. However, we believe that the influence of subclinical cardiovascular disease at BC diagnosis was minimal, since we studied BC patients diagnosed at age 40–50 years, who had a low prevalence of cardiovascular risk factors. Second, inability to track the LV wall during the full cardiac cycle precluded GLS measurements in 13% of screened patients. We explored patient and treatment characteristics of women for whom GLS was not available. They received more extensive treatment in terms of anthracycline dose and radiotherapy fields compared to patients with GLS measurement (data not shown) and this could have led to an underestimation of the association reported. Finally, our study was cross-sectional and patients who developed cardiovascular disease prior to study invitation might have been over- or under-represented. However, the study was embedded within established BC cohorts and for the NKI-AVL cohort we have information on cardiovascular disease incidence and mortality,[18] enabling us to explore selection bias. We found no evidence for patient selection by comparing cardiovascular disease incidence rates of responders and non-responders, and since only seven patients died of cardiovascular disease before study initiation, we believe that survival bias is negligible.

Several task forces have made great efforts to set up guidelines for prevention and monitoring of cardiotoxicity among (breast) cancer survivors.[3–5] However, these guidelines are not broadly used in clinical practice, since the quality of evidence supporting those guidelines is still insufficient. We believe that results of the current analyses do not yet allow us to recommend a specific strategy for monitoring BC survivors, since follow-up data are crucial and are expected to contribute to knowledge about the course of cardiac (dys)function over time, identification of patients at high risk of developing overt cardiac disease, and adaptation of new methods for early detection of cardiotoxicity in cancer survivors.

In conclusion, we found that 5–12 years after treatment with anthracycline-based chemotherapy, a substantial proportion of young BC survivors showed signs of myocardial dysfunction based on GLS measurements and NT-proBNP levels, whereas the number of women with a decreased LVEF was much smaller. Longitudinal assessment is essential to determine the prognostic value of strain and cardiac biomarkers in the development of overt cardiotoxicity and identify high-risk BC survivors who may benefit from cardiac surveillance.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Methods S1. Overview of data collected by questionnaires, blood and urine sampling and physical examination.

Methods S2. Overview of echocardiography parameters.

Figure S1. Flow diagram of included patients.

Table S1. Tumour characteristics.

Table S2. Treatment characteristics by follow-up group.

Table S3. Prevalence of (cardiovascular) risk factors at study visit by treatment group.

Table S4. Prevalence of (cardiovascular) risk factors at study visit by follow-up group.

Table S5. Prevalence of (cardiovascular) risk factors at study visit by global longitudinal strain.

Figure S2. Associations between cumulative anthracycline dose and left ventricular ejection fraction (LVEF) (*A*), global longitudinal strain (GLS) (*B*) and N-terminal pro-brain natriuretic peptide (NT-proBNP) (*C*).

Figure S3. (*A*) Scatter plot of left ventricular ejection fraction (LVEF) (%) and global longitudinal strain (GLS) (%) and linear regression line. (*B*) Scatter plot of LVEF (%) and N-terminal pro-brain natriuretic peptide (NT-proBNP) (ng/L) and linear regression line. (*C*) Scatter plot of GLS (%) and NT-proBNP (ng/L) and linear regression line.

Acknowledgements

The authors thank Sandra Fase, Gerrie Steursma and Manon Eising for assistance in data collection.

Funding

This work was financially supported by Pink Ribbon/Dutch Cancer Society (grant 2012.WO39.C143).

Conflict of interest: none declared.

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