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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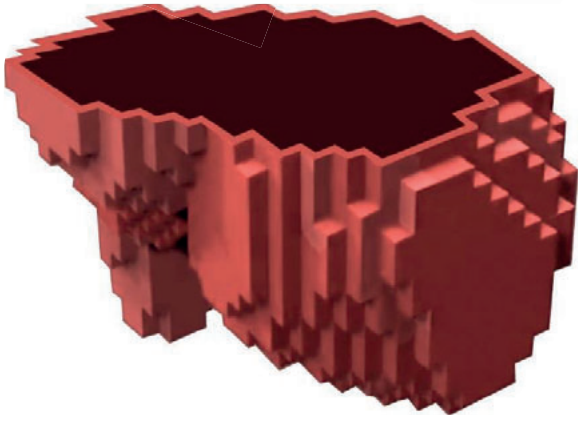

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Abstract

Purpose

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.

Patients and methods

In a cross-sectional study in primary care, we included 350 women who survived breast cancer for at least five 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 (LV) ejection fraction <54% and an age-corrected decreased LV diastolic function. Secondary outcomes included serum NT-proBNP levels, newly diagnosed cardiovascular diseases, and cardiovascular medication.

Results

Median age at diagnosis was 63 (IQR 57–68) years for the breast cancer survivors. Median follow-up after diagnosis was 10 (IQR 7–14) years. LV ejection fraction <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 LV ejection fraction <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 at follow-up.

Conclusion

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.[2, 96] Courtesy of screening programs and advances in cancer treatment, the 5-year overall survival rates have increased to 85%[12]. Although adjuvant therapies like anthracycline-based chemotherapy, trastuzumab, and radiotherapy are very effective, they may cause cardiac dysfunction decades after treatment.[32] 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.[97]

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.[32-37] By contrast, studies in selected hospital populations may have overestimated the prevalence of cardiac dysfunction in these women.[28-31] 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.[41] Therefore, we assessed the prevalence of long-term echocardiographic-based cardiac dysfunction among breast cancer survivors treated with chemotherapy (± 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 a electronical record of a primary care physician (PCP), who registers everything according to International Classification of Primary Care (ICPC)[85] and Anatomical Therapeutic Chemical (ATC) classification codes.[98]

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 five 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/loco-regional recurrence of breast cancer, they were included if they had been free of disease for at least five 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 (± one 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.

Box 1 Overview of data derived from the electronic patient files of primary care physicians

ICPC codes comprising of the presence of CV risk factors
- dyslipidaemia [ICPC: T93]
- hypertension [ICPC: K86 AND K87]
- diabetes mellitus [ICPC: T90]

ICPC codes comprising the presence of CVD

Heart failure
- acute and chronic congestive heart failure [ICPC: K77]

Ischemic cardiac disease
- stable/unstable angina pectoris [ICPC: K74]
- acute myocardial infarction [ICPC: K75]
- coronary artery sclerosis [ICPC: K91)
- transient ischemic attack [ICPC: K89]
- cerebrovascular accident [ICPC: K90])

Atrial fibrillation
- atrial fibrillation [ICPC: K78]

Other
- paroxysmal tachycardia [ICPC: K79]
- non-rheumatic valve disease [ICPC: K83]
- Wolff–Parkinson–White syndrome, atrioventricular block, cardiomyopathy, and long QT-syndrome [ICPC: K84]

Prescriptions of the following (ATC codes) CV medication
- ACE-inhibitors
- beta-blockers
- anti-platelets
- diuretics
- statins

Assessments and procedures

For all women, we collected data based on the ICPC codes for cardiovascular (CV) risk factors and CV disease (CVD), and used the ATC prescription codes for CV medications (Box 1). Hospital charts from breast cancer survivors were reviewed for detailed information on breast cancer treatment, including administered chemotherapy regimens, cumulative dosages, anti-hormone 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.[99]

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[100, 101]. A prespecified imaging protocol was used and images were digitally stored. We also performed electrocardiography (ECG) and obtained plasma in lithium-heparin stored at -80oC 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.[102]

Study endpoints

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).[100] 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/m2), LV diastolic dysfunction was considered severe.[101]

The main secondary outcomes were: clinically used LVEF cut-off points <45% and <50%, right ventricular systolic dysfunction, valve dysfunction (at least II/III insufficiency of any valve), any ECG abnormality, and increased NT-proBNP (>125 ng/ml)[103]. Right ventricular (RV) systolic function was measured through the tricuspid annular plane systolic excursion (< 17 mm) and tricuspid lateral annular systolic velocity wave (<9.5 cm/s) by Doppler imaging.[100] 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[104-106], 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 interquartile ranges (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 ± 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/m^2 or epirubicin dose > 450 mg/m^2) 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 (Figure 1). There were 22 women with a local/loco-regional 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 four years younger ($p<0.01$), and participating controls tended to be two 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 ischemic CVD (OR 0.3 [95%CI 0.3-0.6]; Table 1). 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 (Table 2).

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

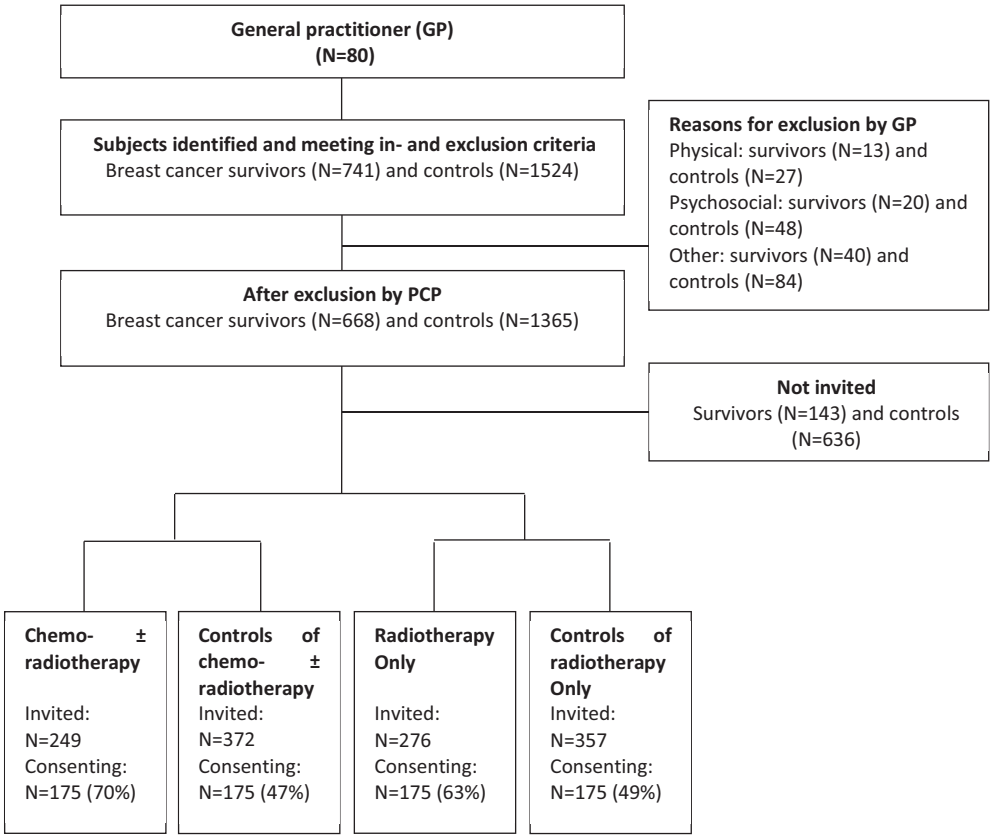

Table 1 Characteristics and the presence of CVD of eligible breast cancer patients (N = 413) and eligible controls (N = 579) who were invited to participate: participants versus non-participants *

	Eligible breast cancer patients (N = 413)			Eligible controls (N = 579)		
	Participant (N = 292)	Non-participant (N = 151)		Participant (N = 292)	Non-participant (N = 322)	
Age at invite; yr, median (IQR)ł	63 (57–68)	67 (59–74)	**P<0.001**	63 (57–68)	65 (58–71)	**P 0.002**
Follow-up; yr, median (IQR) ł	9 (7–14)	10 (6–14)	P 0.992	–	–	
	N (%)	**N (%)**	**OR (95%CI)**	**N (%)**	**N (%)**	**OR (95%CI)**
Diagnosed CVD	47 (16.1)	24 (15.9)	1.0(0.6 - 1.7)	26 (8.9)	54 (16.8)	**0.5(0.3 - 0.8)**
Heart failure	3 (1.0)	1 (0.7)	1.6(0.2 - 15.1)	2 (0.7)	4 (1.2)	0.6(0.1 - 3.0)
Ischemic CVD [a]	26 (8.9)	15 (9.9)	0.9(0.5 - 1.7)	11 (3.8)	38 (11.8)	**0.3(0.2 - 0.6)**
Atrial fibrillation	11 (3.8)	9 (6.0)	0.6(0.3 - 1.5)	5 (1.7)	8 (2.5)	0.7(0.2 - 2.1)
Other CVD [b]	16 (5.5)	7 (4.6)	1.2(0.5 - 3.0)	11 (3.8)	14 (4.3)	0.9(0.4 - 1.9)

(*) Data are based on patient files of 58 (out of 80) PCPs contributing to data registries;
(ł) Tested with t-test;
(a) Stable and unstable angina pectoris, coronary sclerosis, acute myocardial infarction, transient ischemic attack, cerebrovascular accident;
(b) Paroxysmal tachycardia (supraventricular and ventricular), non-rheumatic valve dysfunction, Wolff–Parkinson–White syndrome, atrioventricular block, cardiomyopathy, long QT-syndrome.

Table 2 Sensitivity analysis: comparison of the prevalence of CVD at time of cross-sectional assessment between all invited eligible northern Dutch breast cancer survivors (N=443) and all invited eligible controls (N=614)*

	Eligible breast cancer survivors (N = 443)	Eligible controls (N = 614)		
	N (%)	**N (%)**	**OR (95% CI)**	**Age-ajusted OR (95%CI)**
Prevalence of CVD	71 (16.0)	80 (13.0)	1.3 (0.9-1.8)	1.4 (0.9-2.0)
Heart failure	4 (0.9)	6 (1.0)	0.9 (0.3-3.3)	1.0 (0.3-3.7)
Ischemic CVD [a]	41 (9.3)	49 (8.0)	1.2 (0.8-1.8)	1.2 (0.8-1.9)
Atrial fibrillation	20 (4.5)	13 (2.1)	**2.2 (1.1-4.4)**	**2.5 (1.2-5.2)**
Other cardiac diseases [b]	23 (5.2)	25 (4.1)	1.3 (0.7-2.3)	1.3 (0.7-2.4)

(*) Data are based on patient files of 58 (out of 80) PCPs contributing to data registries; (a) Stable and unstable angina pectoris, coronary sclerosis, acute myocardial infarction, transient ischemic attack, cerebrovascular accident; (b) Paroxysmal tachycardia (supraventricular and ventricular), non-rheumatic valve dysfunction, Wolff–Parkinson–White syndrome, atrioventricular block, cardiomyopathy, long QT-syndrome.

Baseline data

At diagnosis, women in the chemotherapy ± radiotherapy group had a median age of 49 compared with 54 years in the radiotherapy only group (Table 3). In the chemotherapy ± 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) (Table 4)[107]. 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 ± radiotherapy group, the radiotherapy only group, and their respective controls (Table 3).

Table 3 Baseline characteristics at time of breast cancer diagnosis of survivors treated with chemotherapy ± radiotherapy, with radiotherapy only, and matched controls*

	Chemotherapy ± radiotherapy (N = 175)	Controls Chemotherapy ± radiotherapy (N = 175)	Radiotherapy (N = 175)	Controls radiotherapy (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 (%)**
Risk factors for CVD	20 (11.4)	18(10.3)	25 (14.3)	32 (18.3)
Dyslipidemia	7 (4.0)	8 (4.6)	5 (2.9)	11 (6.3)
Hypertension	17 (9.7)	13 (7.4)	19 (10.9)	27 (15.4)
Diabetes mellitus	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)
Heart failure	0 (0)	0 (0)	0 (0)	0 (0)
Ischemic heart disease [a]	3 (1.7)	1 (0.6)	2 (1.1)	0 (0)
Atrial fibrillation	0 (0)	0 (0)	1 (0.6)	2 (1.1)
Other heart diseases [b]	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)
ACE-inhibitor	5 (2.9)	2 (1.1)	8 (4.6)	5 (2.9)
Antiplatelet agents	3 (1.7)	0 (0)	4 (2.3)	0 (0)
Beta-blockers	5 (2.9)	3 (1.7)	4 (2.3)	3 (1.7)
Diuretics	6 (3.4)	4 (2.3)	6 (3.4)	2 (1.1)
Statins	3 (1.7)	3 (1.7)	5 (2.9)	1 (0.6)

(*) There were no statistical significant differences between groups, tested with Chi-square test; (a) Stable and unstable angina pectoris, coronary sclerosis, acute myocardial infarction, transient ischemic attack, cerebrovascular accident;
(b) Paroxysmal tachycardia (supraventricular and ventricular), non-rheumatic valve dysfunction, Wolff–Parkinson–White syndrome, atrioventricular block, cardiomyopathy, long QT-syndrome.

Table 4 Detailed characteristics of breast cancer diagnosis and treatment for the patients treated with chemotherapy ± radiotherapy (N = 175) and radiotherapy only (N = 175)

		Chemotherapy ± radiotherapy (N = 175)	Radiotherapy (N = 175)
		N (%)	N (%)
T-size	DCIS	3 (1.7)	18 (10.3)
	T1	40 (41.1)	118 (67.4)
	T2	80 (45.7)	27 (15.4)
	T3	10 (5.7)	1 (0.6)
	T4	3 (1.7)	0 (0)
	Unknown	7 (4.0)	11 (6.3)
Lymph node involvement	N0	56 (32.0)	131 (74.9)
	N1	95 (54.3)	23 (13.1)
	N2	12 (6.9)	3 (1.7)
	N3	6 (3.4)	0 (0)
	Unknown	6 (3.4)	18 (10.3)
Type of chemotherapy*	CMF	30 (17.1)	–
	AC	47 (26.9)	–
	FEC	67 (38.3)	–
	AC + T	5 (2.9)	–
	FEC + T	21 (12.0)	–
	Other	3 (1.8)	–
	Unknown**	2 (1.1)	–
		Median (IQR)	**Median (IQR)**
Cumulative dose epirubicin (mg/m²) [a]		444.4 (300–450)	–
Cumulative dose doxorubicin (mg/m²) [b]		240 (235–240)	–
Cumulative anthracycline dose; mg/m², median (IQR) * **		238 (228–240)	**–**
		N (%)	**N (%)**
Trastuzumab		13 (7.4)	–
Anti-hormonal therapy		110 (62.9)	41 (23.4)
Tamoxifen		24 (21.8)	11 (26.8)
Aromatase-inhibitors		14 (12.7)	4 (9.8)
Tamoxifen followed by aromatase-inhibitors		62 (56.4)	23 (56.1)
Other		9 (8.2)	2 (4.9)
Unknown		1 (0.9)	1 (2.4)
Radiotherapy		120 (68.6%)	175 (100)
Side: bilateral or left		84 (48.0)	89 (51.5)

(*) C = cyclophosphamide; M = methotrexate; F = 5-fluorouracil; A = doxorubicin; E = epirubicin; T = taxanes;
(**) Other consisted of 1 patients with CMF and FEC, 1 with M and F, and 1 with M, F, A, ans vincristine;
(***) Doxorubicin isotoxic dose, information available for 108 patients (76%);

(a) This information was retrieved for 72 out 89 patients who received epirubicin;
(b) This information was retrieved for 36 out 53 patients who received doxorubicin.

Findings at the cross-sectional assessment

The median follow-up after breast cancer diagnosis was 10 years (Table 4), at which point the breast cancer survivors did not differ significantly from their controls in terms of CV risk factors (Table 5).

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 4). In addition, prevalence rates for LV diastolic dysfunction were also higher among survivors than among controls, but not statistically significant (OR 1.2 [95%CI 0.9-1.6]; Table 4). Few women had severe diastolic dysfunction (17 survivors vs 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 ischemic CVD, with angiotensin-converting-enzyme inhibitors, antiplatelet 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 ± radiotherapy group compared with their controls (OR 2.5 [95%CI 1.2-5.4]; Table 6). 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 antiplatelet agents were prescribed significantly more often among survivors than controls (Table 4). Concerning anthracycline treatment, we found the same increased risk for LV systolic dysfunction as in the other groups (Table A.5). No differences were found between higher versus low-dose anthracycline-treated patients.

Radiotherapy only 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 6). We found no significant differences in LV function between left-sided and right-sided radiotherapy, either before or after excluding those who received chemotherapy (Table 6). However, in patients treated with left-sided therapy NT-proBNP level was raised (OR1.6 ([95%CI 1.0–2.6]).

Table 5 Comparison of outcomes at long-term follow-up echocardiography between all 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)	
Cardiac function	**N (%)**	**N (%)**	**OR (95%CI)**
Left ventricular dysfunction			
Systolic dysfunction [a]			
LVEF < 54%	52 (15.3)	24 (7.0)	**2.4 (1.4 - 4.0)**
LVEF < 50%	15 (4.4)	9 (2.6)	1.7 (0.7 - 4.0)
LVEF < 45%	2 (0.6)	2 (0.6)	1.0 (0.1 - 7.2)
Diastolic dysfunction [b]	147 (43.4)	133 (39.5)	1.2 (0.9 - 1.6)
Diastolic dysfunction with LAVI ≥ 34 mL/m^2 [c]	17 (5.5)	12 (3.9)	1.4 (0.7 - 3.0)
Right ventricular dysfunction			
Systolic dysfunction			
Decreased TAPSE	4 (1.2)	6 (1.8)	0.7 (0.2 - 2.4)
Decreased S'	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 (≥ 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)
Dyslipidemia	54 (15.4)	58 (16.6)	0.9 (0.6 - 1.3)
Hypertension	108 (30.9)	106 (30.3)	1.0 (0.7 - 1.4)
Diabetes mellitus	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)**
Heart failure	1 (0.3)	3 (0.9)	0.3 (0.03 - 3.2)
Ischemic cardiovascular diseases [f]	26 (7.4)	13 (3.7)	**2.1 (1.1 - 4.1)**
Atrial fibrillation	11 (3.1)	4 (1.1)	2.8(0.9 - 8.9)
Other cardiac diseases [g]	20 (5.7)	9 (2.6)	**2.3 (1.0 - 5.1)**
Cardiovascular medication	132 (37.7)	104 (29.7)	**1.4 (1.0 - 2.0)**
ACE-inhibitor	65 (18.6)	42 (12.0)	**1.7 (1.1 - 2.5)**
Antiplatelet agents	29 (8.3)	12 (3.4)	**2.5 (1.3 - 5.1)**
Beta-blockers	54 (15.4)	34 (9.7)	**1.7 (1.1 - 2.7)**
Diuretics	33 (9.4)	39 (11.1)	0.8 (0.5 - 1.4)
Statins	54 (15.4)	40 (11.4)	1.4 (0.9 - 2.2)

(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 ischemic attack, cerebrovascular accident;

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

Table 6 Characteristics at time of echocardiography of survivors treated with chemotherapy ± radiotherapy (N = 175) or radiotherapy only (N = 175) and their matched controls (N = 350)

	Chemo- ± radio-therapy (N = 175) N(%)	Controls chemo-therapy (N = 175) N(%)	OR (95%CI)	Radio-therapy (N = 175) N(%)	Controls radio-therapy (N = 175)	OR (95%CI)
Cardiovascular risk factors in GP files						
dyslipidemia	14 (8.0)	20 (11.4)	0.7 (0.3 - 1.4)	28 (16.0)	19 (10.9)	1.6 (0.8 - 2.9)
Hypertension	29 (16.6)	29 (16.6)	1.0 (0.6 - 1.8)	43 (24.6)	37 (21.1)	1.2 (0.7 - 2.0)
Diabetes	8 (4.6)	5 (2.9)	1.6 (0.5 - 5.1)	13 (7.4)	6 (3.4)	2.3 (0.8 - 6.1)
Measurements at time of echocardiography						
BMI above 25 kg/m2	100 (57.1)	89 (50.9)	1.3 (0.8 - 2.0)	99 (56.6)	113 (64.6)	0.7 (0.5 - 1.1)
Physical fit a	134 (76.6)	139(79.4)	0.8 (0.5 - 1.4)	128 (73.6)	142 (82.1)	0.6 (0.4 - 1.0)
Current smokers	33 (18.9)	29 (16.6)	1.2 (0.7 - 2.0)	32 (18.4)	24 (13.7)	1.4 (0.8 - 2.5)
BMI above 25 kg/m2	100 (57.1)	89 (50.9)	1.3 (0.8 - 2.0)	28 (16.0)	19 (10.9)	1.6 (0.8 - 2.9)

(a) percentage of women adhering to the Dutch guideline (≥5 days per week at least moderate exercise during 30 minutes, SQUASH questionnaire).

Table 7 Comparison of outcomes at long-term follow-up echocardiography by treatment subgroup

	Chemo- ± radio-therapy (N = 175)	Controls chemo-therapy (N = 175)		Radio-therapy (N = 175)	Controls radio-therapy (N = 175)	
Follow-up; years, median (IQR)	10 (7–13)	10 (8–14)		10 (8–15)	10 (7–15)	
Age at assessment; yr, median (IQR)	60 (53–66)	60 (53–66)		65 (61–70)	66 (61–70)	
	N (%)	**N (%)**	**OR (95%CI)**	**N (%)**	**N(%)**	**OR (95%CI)**
LV dysfuntion						
Systolic[a]						
LVEF<54%	25 (14.8)	11 (6.4)	**2.5 (1.2 - 5.4)**	27 (15.9)	13 (7.7)	**2.3 (1.1 - 4.6)**
LVEF < 50%	7 (4.1)	5 (2.9)	1.4 (0.4 - 4.6)	8 (4.7)	4 (2.4)	2.1 (0.6 - 6.9)
LVEF < 45%	1 (0.6)	0 (0)	-	1 (0.6)	2 (1.2)	-
Diastolic[b]	79 (46.7)	65 (38.7)	1.4 (0.9 - 2.1)	68 (40.0)	68 (40.2)	1.0 (0.6 - 1.5)
Diastolic with LAVI ≥ 34 mL/m^2 [c]	10 (6.6)	6 (4.0)	1.7 (0.6 - 4.7)	7 (4.4)	6 (3.8)	1.2 (0.4 - 3.5)
RV systolic dysfunction						
Decreased TAPSE	2 (1.2)	3 (1.8)	0.7 (0.1 - 4.1)	2 (1.2)	3 (1.8)	0.7 (0.1 - 4.1)
Decreased S'	4 (2.5)	6 (3.6)	0.7 (0.2 - 2.5)	3 (1.9)	3 (1.9)	1.0 (0.2 - 5.0)
Valve dysfunction	1 (0.6)	3 (1.7)	0.3 (0.03 - 3.2)	2 (1.1)	2 (1.1)	1.0 (0.1 - 7.2)
ECG abnormalities	39 (22.7)	36 (20.8)	1.1 (0.7 - 1.9)	48 (27.9)	41 (23.8)	1.2 (0.8 - 2.0)
Increased NT-proBNP[e]	56 (32.7)	44 (25.1)	1.5 (0.9 - 2.3)	68 (39.1)	51 (29.1)	**1.6 (1.0 - 2.4)**
Diagnosed CVD	21 (12.0)	10 (5.7)	**2.3 (1.0 - 4.9)**	28 (16.0)	16 (9.1)	1.9 (0.98 - 3.6)
Heart failure	1 (0.6)	1 (0.6)	1.0 (0.06 - 16)	0 (0)	2 (1.1)	-
Ischemic CVD [f]	12 (6.9)	7 (4.0)	1.8 (0.7 - 4.6)	14 (8.0)	6 (3.4)	2.4 (0.9 - 6.5)
Atrial fibrillation	4 (2.3)	1 (0.6)	4.1 (0.5 - 36.8)	7 (4.0)	3 (1.7)	2.4 (0.6 - 9.4)
Other CD [g]	7 (4.0)	3 (1.7)	2.4 (0.6 - 9.4)	13 (7.4)	6 (3.4)	2.3 (0.8 - 6.1)
Cardiovascular medication	57 (32.6)	44 (25.1)	1.4 (0.9 - 2.3)	75 (42.9)	60 (34.3)	1.4 (0.9 - 2.2)
ACE-inhibitor	39 (22.3)	21 (12.0)	**2.1 (1.2 - 3.8)**	40 (22.9)	29 (16.6)	1.5 (0.9 - 2.5)
Antiplatelets	16 (9.1)	6 (3.4)	**2.8 (1.1 - 7.4)**	13 (7.4)	6 (3.4)	2.3 (0.8 - 6.1)
Beta-blockers	26 (14.9)	17 (9.7)	1.6 (0.8 - 3.1)	37 (21.1)	24 (13.7)	1.7 (0.96 - 3.0)
Diuretics	19 (10.9)	16 (9.1)	1.2 (0.6 - 2.4)	26 (14.9)	29 (16.6)	0.9 (0.5 - 1.6)
Statins	26 (14.9)	16 (9.1)	1.7 (0.9 - 3.4)	35 (20.0)	28 (16.0)	1.3 (0.8 - 2.3)

(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) cut-off ≥ 125 pg/mL), Not available for 3 women;
(f) Stable and unstable angina pectoris, coronary sclerosis, acute myocardial infarction, transient ischemic attack, cerebrovascular accident;
(g) Paroxysmal tachycardia (supraventricular and ventricular), non-rheumatic valve dysfunction, Wolff–Parkinson–White syndrome, atrioventricular block, cardiomyopathy, long QT-syndrome.

Table 8 Outcomes of breast cancer patients treated with anthracyclines based (N = 142) compared to their controls (N = 142)

	Anthracycline-treated vs. controls			Higher vs. low-dose		
	Anthracycline treated patients (N = 142)	Controls (N = 142)		Higher dose [f] (N = 21)	Low-dose [f] (N = 87)	
Follow-up; yr, median (IQR)ł	9 (7–12)	9 (7–12)		9 (7–12)	8 (7–12)	
Age at echo; yr, median (IQR) ł	59 (53–66)	60 (53–66)		61 (52–64)	60 (53–66)	
	N (%)	**N (%)**	**OR (95%CI)**	**N (%)**	**N (%)**	**OR (95%CI)**
Radiotherapy	98 (69.0)	–	-	15 (71.4)	64 (73.6)	**-**
LV dysfunction						
LVEF <54%	22 (16.2)	11 (7.9)	**2.2 (1.0 - 4.8)**	1 (4.8)	16 (19.8)	0.2(0.03 - 1.6)
LVEF<50%	7 (5.1)	5 (3.6)	1.5 (0.5 - 4.7)	0 (0)	6 (7.4)	–
LVEF<45%	0 (0)	1 (0.7)	–	0 (0)	0 (0)	–
Diastolic dysf.[a]	62 (45.3)	51 (37.2)	1.4 (0.9 - 2.3)	8 (38.1)	41 (50.0)	0.6 (0.2 - 1.6)
Diastolic dysf + LAVI ≥ 34 mL/m2 [b]	9 (7.2)	5 (4.1)	1.8 (0.6 - 5.5)	1 (5.3)	7 (9.5)	0.5(0.06 - 4.6)
RV dysfunction						
Decr.TAPSE	1 (0.8)	1 (0.7)	1.0(0.1 - 16.6)	0 (0)	0 (0)	–
Decr. S'	3 (2.4)	5 (3.7)	0.6(0.1 - 2.7)	0 (0)	2 (2.6)	–
Valve dysf.	1 (0.7)	2 (1.4)	0.5(0.04 - 5.5)	0 (0)	0 (0)	
Abnormal ECG	31 (22.3)	29 (20.7)	1.1(0.6 - 1.9)	5 (25.0)	19 (22.4)	1.2 (0.4 - 3.6)
Incr. NT-pro BNP	47 (33.6)	35 (24.6)	1.5(0.9 - 2.6)	7 (36.8)	25 (28.7)	1.5 (0.5 - 4.1)

(*a) Measured by Simpson's biplane (72.5%) or BiPQ/estimate (28.5%), not available for women with atrial fibrillation (N = 2) during measurement and women with immeasurable LVEF (n = 5);*

(b) Not available for women with atrial fibrillation (N = 2) during measurement, valve replacement (N = 0) and women with immeasurable e' lat and e' sept (N = 7);

(c) Minimal II/III valve dysfunction from one of the 4 cardiac valves;

(e) Not available for 2 women;

(f) Available for 108 patients: higher dose defined as doxorubicin dose>240 mg/m^2 or epirubicin dose 450 mg/m^2.

Table 9 Outcomes of breast cancer patients who received bilateral or left-sided radiotherapy compared to patients who received right-sided radiotherapy: for all patients and those who received radiotherapy only*

	All patients with radiotherapy			Patients who received radiotherapy only		
	Bilateral or left sided radiation (N = 152)	Right-sided radiation (N = 141)		Bilateral or left-sided radiation (N = 90)	Right-sided radiation (N = 83)	
Follow-up; yr, median (IQR)ł	10 (7–14)	10 (7–15)		10 (7–14)	10 (8–15)	
Age at echo; yr, median (IQR) ł	64 (58–69)	64 (57–68)		65 (61–70)	66 (61–70)	
	N (%)	**N (%)**	**OR (95%CI)**	**N (%)**	**N (%)**	**OR (95%CI)**
Radiotherapy						
LV dysfunction						
LVEF <54%	21 (14.3)	23 (16.7)	0.8 (0.4 - 1.6)	12 (14.0)	15 (18.3)	0.7 (0.3 - 1.7)
LVEF<50%	5 (3.4)	10 (7.2)	0.5 (0.1 - 1.4)	3 (3.5)	5 (6.1)	0.6 (0.1 - 2.4)
LVEF<45%	0 (0)	2 (1.4)	–	0 (0)	2 (2.4)	–
Diastolic dysf.[a]	66 (45.2)	57 (41.0)	1.2 (0.7 - 1.9)	33 (38.4)	35 (42.7)	0.8 (0.5 - 1.5)
Diastolic dysf + LAVI ≥ 34 mL/m2 [b]	6 (4.5)	7 (5.3)	0.8 (0.3 - 2.6)	2 (2.5)	5 (6.5)	0.4 (0.1 - 2.0)
RV dysfunction						
Decr.TAPSE	2 (1.4)	1 (0.7)	1.9 (0.2 - 21.7)	1 (1.1)	1 (1.3)	1.0(0.1 - 15.9)
Decr. S'	2 (1.5)	3 (2.3)	0.6 (0.1 - 3.9)	1 (1.3)	2 (2.7)	0.5(0.04 - 5.4)
Valve dysf.	2 (1.3)	0 (0)	–	2 (2.2)	0 (0)	–
Abnormal ECG	40 (26.8)	33 (23.6)	1.2 (0.7 - 2.0)	24 (27.3)	23 (27.7)	1.0 (0.5 - 1.9)
Incr. NT-pro BNP	65 (43.0)	45 (32.4)	1.6(0.98 - 2.6)	40 (44.4)	28 (34.1)	1.5 (0.8 - 2.9)

(*) For 2 patients this information was missing

(**) Right-sided treated patients served as reference

(a) Measured by Simpson's biplane (70.1%) or BiPQ/estimate (29.9%), not available for patients with atrial fibrillation (N = 3) during measurement and patients with immeasurable LVEF (N = 5);

(b) Not available for patients with atrial fibrillation (N = 3) during measurement, valve replacement (N = 2) and women with immeasurable e' lat and e' sept (N = 3);

(c) Minimal II/III valve dysfunction from one of the 4 cardiac valves;

(d) Not available for 3 women.

Multivariate 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 ≥ 125 pg/mL), or newly diagnosed CVD among survivors (Table 9).

Table 10 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			
Breast cancer survivors vs. controls	**2.4 (1.4 - 4.0)**	**2.5 (1.5 - 4.1)**	**2.3 (1.4 - 3.9)**
Chemotherapy ± radiotherapy			
Breast cancer survivors vs. controls	**2.5 (1.2 - 5.4)**	**2.5 (1.2 - 5.4)**	**2.5 (1.2 - 5.3)**
Radiotherapy only			
Breast cancer survivors vs. controls	**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			
Breast cancer survivors vs. controls	**1.5 (1.1 - 2.1)**	**1.5 (1.1 - 2.1)**	**1.5 (1.1 - 2.1)**
Chemotherapy ± radiotherapy			
Breast cancer survivors vs. controls	1.5 (0.9 - 2.3)	1.4 (0.9 - 2.3)	1.5 (0.9 - 2.4)
Radiotherapy only			
Breast cancer survivors vs. controls	**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			
Breast cancer survivors vs. controls	**2.0 (1.2 - 3.3)**	**2.1 (1.3 - 3.4)**	**1.9 (1.2 - 3.2)**
Chemotherapy ± radiotherapy			
Breast cancer survivors vs. controls	**2.3 (1.0 - 4.9)**	**2.3 (1.0 - 5.0)**	**2.3 (1.0 - 5.1)**
Radiotherapy only			
Breast cancer survivors vs.controls	1.9 (0.98 - 3.6)	**2.1 (1.1 - 4.1)**	1.7 (0.9 - 3.3)

(a) Model 1: Adjusted for measurements at baseline: cardiovascular risk factors (diabetes, hypertension, dyslipidemia), 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, dyslipidemia) from PCP files, current smoking (yes/no), Body Mass Index (continuous), and physical fitness: percentage of women adhering to the Dutch guideline (≥5 days per week at least moderate exercise during 30 minutes; SQUASH questionnaire).

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 (± 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[108] and 14 years[30], respectively. For LVEF <50%, six studies reported prevalence rates varying between 1.4% and 8% over 5–14 years[28, 30,

[59, 82, 109, 110], 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.[49, 76, 111] A potential explanation is the use of modern radiotherapy, resulting in a lower heart dose, especially in left-sided breast cancer.[32, 112] Of our patients 97% was 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.[113, 114] 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.[114] 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 NT-proBNP was 71%.[108] 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.[115] In the general population, it has been shown that an increased NT-proBNP level is predictive of cardiac mortality and heart failure.[116]

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 ± radiotherapy. Though in our study numbers were small and confidence intervals were wide we found that the increased risk was mainly seen for ischemic cardiac diseases, whereas other studies of patients treated with chemotherapy have found an increased incidence of congestive heart failure.[29, 34, 35, 37, 83] But, those studies were notable for using high-dose chemotherapy[83] or doxorubicin.[29, 34, 35, 37] An increased incidence of ischemic heart disease is generally expected among patients treated by radiotherapy only.[46] 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.[32]

Strengths

To our knowledge, this is the first study to compare long-term echocardiographic 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 focussed 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 five 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, GPs 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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