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Effect of obesity, dyslipidemia, and diabetes on trastuzumab-related cardiotoxicity in breast cancer

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ABSTRACT

Background Clinical trials have demonstrated an increased risk of cardiotoxicity in patients with breast cancer (BCA) receiving trastuzumab-based therapy. Diabetes, dyslipidemia, and obesity are known risk factors for cardiovascular disease. Studies have yielded conflicting results about whether those factors increase the risk of cardiotoxicity in patients with BCA receiving trastuzumab.

Methods In this retrospective cohort study, data were collected for 243 patients with BCA positive for HER2 (the human epidermal growth factor receptor 2) who were receiving trastuzumab and who were referred to The Ottawa Hospital Cardio-oncology Referral Clinic between 2008 and 2013. The data collected included patient demographics, reason for referral, cardiac function, chemotherapy regimen (including anthracycline use), and 3 comorbidities (diabetes, dyslipidemia, obesity). Rates of symptomatic cancer treatment–related cardiac dysfunction (SCTCD) and asymptomatic decline in left ventricular ejection fraction (ADLVEF) were calculated for patients with and without the comorbidities of interest.

Results Of the 243 identified patients, 104 had either diabetes, dyslipidemia, or obesity. In that population, the most likely reason for referral to the cardio-oncology clinic was ADLVEF. The combination of 2 or 3 comorbidities significantly increased the incidence of SCTCD in our population, reaching a rate of 67% for patients with obesity and dyslipidemia [relative risk (RR): 2.2; $p = 0.04$], 69% for patients with obesity and diabetes (RR: 2.3; $p = 0.02$), and 72% for patients with all 3 risk factors (RR: 2.4; $p = 0.08$).

Conclusions The combination of 2 or 3 comorbidities significantly increases the incidence of symptomatic cancer treatment–related cardiotoxicity. Patients with BCA experiencing cancer treatment–related cardiotoxicity who have a history of diabetes, dyslipidemia, and obesity might require more proactive strategies for prevention, detection, and treatment of cardiotoxicity while receiving trastuzumab-based treatment.

Key Words Breast cancer, trastuzumab, cardiotoxicity, diabetes, obesity, dyslipidemia, HER2 positivity

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INTRODUCTION

Clinical trials have demonstrated an increased risk of cardiotoxicity in patients with breast cancer (BCA) receiving trastuzumab-based therapy. In both the National Surgical Adjuvant Breast and Bowel Project B-31 study and the North Central Cancer Treatment Group N9831 study[1,2], women with early-stage BCA receiving trastuzumab-containing treatment experienced heart failure at a rate of about 4%, which remained stable after up to 9.2 years of follow-up. What is less well understood is the incidence of cardiotoxicity in patients treated with trastuzumab outside the setting of a clinical trial, particularly in patients who have underlying cardiovascular risk factors.

Diabetes, dyslipidemia, and obesity are known risk factors for cardiovascular disease. Thus, patients

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with those comorbidities could be at increased risk of experiencing cardiotoxicity related to cancer treatment, including trastuzumab-based therapy.

Obesity is associated with an increased risk of BCa in postmenopausal women because of aromatase activity in fat tissue and increased production of estrogens[3]. Meta-analyses demonstrate that patients with metabolic syndrome (central obesity, elevated triglycerides, diminished high-density lipoprotein cholesterol, systemic hypertension, elevated fasting glucose, and receipt of treatment for dyslipidemia, hyperglycemia, or systemic hypertension) have double the risk for cardiovascular disease and a risk for mortality that is increased by a factor of 1.5[4].

Studies of whether diabetes, obesity, hypertension, or other features of the metabolic syndrome significantly increase cardiotoxicity rates with chemotherapy have yielded conflicting results. Guenancia *et al.*[5] conducted a meta-analysis of 8745 patients with BCa receiving either or both of anthracyclines and trastuzumab. Patients with BCa and obesity (n = 2615) experienced a significantly greater risk of developing cardiotoxicity after anthracyclines, with or without trastuzumab [odds ratio: 1.47; 95% confidence interval (CI): 0.95 to 2.28; I^2 = 47%].

In a retrospective study of 45 patients with BCa who were more than 70 years of age and receiving trastuzumab therapy, cardiotoxicity was more common in patients who had underlying cardiovascular risk factors such as a history of cardiac disease (33% vs. 9.1%, p = 0.017) and diabetes (33.3% vs. 6.1%, p = 0.010) than in those without those risk factors[6]. Furthermore, in another study, diabetes mellitus was associated with an increased risk of heart failure developing within 1.5 years after initiation of adjuvant chemotherapy in patients with BCa (hazard ratio: 1.47; 95% CI: 1.11 to 1.95; p = 0.008)[7]. A 2016 meta-analysis including 6527 patients with BCa receiving trastuzumab found a significant association between diabetes and cardiotoxicity (odds ratio: 1.62; p < 0.02)[8]. However, several cohort studies by Tiersten *et al.*[9], Swain *et al.*[10], and Yu *et al.*[11] failed to find associations between trastuzumab-induced cardiotoxicity and metabolic syndrome (Table I). The discrepancy in those study results might be secondary to different chemotherapy regimens, cancer stages and molecular profiles, patient demographics, and number of study recruits.

Attempts have been made to develop risk scores that will predict rates of heart failure and cardiotoxicity. One such score by Ezaz *et al.*[16], based on 1664 patients with BCa (stages I–III), used age, adjuvant chemotherapy, coronary artery disease, atrial fibrillation or flutter, diabetes, hypertension, and renal failure to determine rates of heart failure and cardiotoxicity within 3 years of diagnosis. However, those scores have not been widely adopted in clinical practice.

Multiple studies have addressed whether medical treatment of cardiovascular risk factors (that is, primary prevention) can mitigate cardiotoxicity in patients with BCa receiving chemotherapy. Those studies explored whether the prescription of statins, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, or dexrazoxane led to better cardiac outcomes (supplemental Table I). Overall, most of the studies reviewed found a lesser drop in left ventricular ejection fraction (LVEF) in patients prescribed the aforementioned medications. Current recommendations strongly advocate modification of cardiovascular risk factors in cancer patients undergoing potentially cardiotoxic treatment[17,18].

Patients with BCa receiving trastuzumab are known to have a higher risk for cancer treatment–related cardiac dysfunction (CTCD). A meta-analysis of patients with early-stage BCa receiving trastuzumab (including eight randomized controlled trials with a total of 11,991 patients) detected significantly increased rates of congestive heart failure (RR: 5.11; 90% CI: 3.00 to 8.72; p < 0.00001) and decline in LVEF (RR: 1.83; 90% CI: 1.36 to 2.47; p = 0.0008)[19]. What remains undefined is the effect of obesity, dyslipidemia, and diabetes on the risk of developing CTCD, the incidence of subclinical cardiotoxicity, and the incidence of symptomatic CTCD (SCTCD), particularly in higher-risk populations referred for further cardiac assessment.

The objective of the present study was therefore to evaluate the effect of diabetes, dyslipidemia, and obesity on the risk of developing trastuzumab-induced cardiotoxicity in women with BCa positive for HER2 (the human epidermal growth factor receptor 2). Cardiotoxicity was defined as an asymptomatic drop in LVEF (adLVEF) of more than 10 percentage points to an LVEF of less than 53%, or the appearance of SCTCD in women with BCa receiving trastuzumab-based therapy.

METHODS

This single-centre retrospective cohort study considered patients with HER2-positive BCa of all stages receiving trastuzumab-based therapy who were referred to The Ottawa Hospital Cardio-oncology Referral Clinic (CORC) between 2008 and 2013. Demographic data collected included age, weight, height, body mass index (BMI), cancer stage, estrogen (ER) and progesterone receptor (PgR) status, and lymph node positivity. We recorded whether each patient's chemotherapy regimen included an anthracycline, the number of cycles of trastuzumab received, and whether radiation was administered. The reason for referral to the CORC, the results of cardiac testing (either or both of multigated acquisition imaging and echocardiography), comorbidities [limited to diabetes, dyslipidemia, and obesity (defined as BMI > 30)], and cardiac hospitalization were also collected.

Cardiovascular endpoints included adLVEF (a decrease of >10 percentage points to an LVEF <53% according to the American Society of Echocardiography's definition for cardiac dysfunction related to cancer therapy)[20] and SCTCD (including symptoms of heart failure, such as shortness of breath, paroxysmal nocturnal dyspnea, orthopnea, and peripheral edema).

Descriptive statistics, risk ratios (RRs), and proportions were calculated. Standard statistical approaches to assess the significance of results were used: the logit transformation to compute the limits of confidence intervals; the t-test to compare means; and the chi-square test to compare proportions. A standard software application was used for the statistical analysis (Stata version 14.2: Stata Corp., College Station, TX, U.S.A.).

We determined whether baseline demographics showed a significant difference between patients with and

TABLE I Literature review of the association of metabolic syndrome with chemotherapy (CTx)–related cardiotoxicity in patients with breast cancer (BCa)

Reference	Design	Population	Risk factors for post-CTx cardiotoxicity
Tiersten *et al.,* 2004[9]	Observational	Women with metastatic BCa (*n*=61) receiving triple-sequential high-dose cyclophosphamide-based chemotherapy	Older age (median age for developing heart failure of 59 years vs. median age for entire study population of 45 years, *p*=0.0024)
Huszno *et al.,* 2013[12]	Retrospective	Women with HER2-positive BCa (*n*=120) receiving trastuzumab	Prior radiation to the left chest (*p*=0.05) Body mass index greater than 25 (*p*=0.025) ER- or PgR-negative (*p*=0.045) Baseline LVEF 50%–60% (*p*=0.001)
Swain *et al.,* 2013[10]	Retrospective analysis of data from randomized double-blind placebo-controlled phase III trial	Patients with locally recurrent, unresectable, or metastatic HER2-positive BCa (*n*=808) randomized to receive either placebo–trastuzumab–docetaxel or pertuzumab–trastuzumab–docetaxel	Prior anthracycline therapy (HR: 2.21; 95% CI: 1.27 to 3.86; *p*=0.0053), Prior radiotherapy (HR: 2.43; 95% CI: 1.37 to 4.31; *p*=0.0025)
Goldhar *et al.,* 2015[7]	Retrospective cohort	Female patients with BCa (*n*=19,074) treated with adjuvant chemotherapy or trastuzumab, or both	Diabetes (HR: 1.47; 95% CI: 1.11 to 1.95; *p*=0.008) Age (HR: 1.28; 95% CI: 1.22 to 1.36; *p*<0.001)
Serrano *et al.,* 2015[6]	Observational	Patients receiving anthracycline for BCa (*n*=100)	Age (OR: 1.12; 95% CI: 1.03 to 1.19) Body mass index (OR: 1.19; 95% CI: 1.04 to 1.36)
Yu *et al.,* 2015[11]	Retrospective	Patients with HER2-positive BCa (*n*=573) treated with adjuvant trastuzumab	Age (*p*=0.011) Anthracycline chemotherapy (*p*=0.002) Lower pre-trastuzumab LVEF (*p*<0.001)
Advani *et al.,* 2016[2]	Randomized	Patients with HER2-positive operable BCa (*n*=1944) randomized to various treatment arms of various combinations of paclitaxel and trastuzumab	Age 60 years or older (HR: 3.2; 95% CI: 1.5 to 6.8; *p*=0.010) Registration LVEF 50%–54.9% (HR: 3.6; 95% CI: 1.2 to 10.8; *p*=0.020) Registration LVEF 55%–64.9% (HR: 2.7; 95% CI: 1.3 to 5.9; *p*=0.009) Use of antihypertensives (HR: 2.4; 95% CI: 1.2 to 4.6; *p*=0.0148)
Dang *et al.,* 2016[13]	Prospective observational	Patients with node-negative HER2-positive BCa (*n*=406) receiving paclitaxel–trastuzumab for 12 weeks, followed by 1 year of trastuzumab	Grade 3 left ventricular systolic dysfunction developed in 0.5% (2 patients, 1 on medications for high cholesterol and 1 on a beta-blocker for arrhythmogenic RV dysplasia) Of the 3.2% who developed asymptomatic decline, 6 of 13 had at least 2 cardiovascular risk factors
Guenancia *et al.,* 2016[5]	Random-effects analysis and network meta-analysis	Studies (*n*=15) including 8745 patients with BCa who were treated with anthracyclines and sequential anthracyclines and trastuzumab	Obesity (OR: 1.47; 95% CI: 0.95 to 2.28) Overweight (OR: 1.15; 95% CI: 0.83 to 1.58)
Gunaldi *et al.,* 2016[14]	Retrospective observational	Women with HER2-positive BCa (*n*=111) receiving trastuzumab as adjuvant or in cases of metastatic BCa	Postmenopausal status (*p*=0.013) Hypertension (*p*=0.002) Obesity (*p*=0.0001) Previous coronary artery disease (*p*=0.0001) History of smoking (*p*=0.03)
Jawa *et al.,* 2016[8]	Meta-analysis	Articles from MEDLINE database (*n*=17) representing 6527 patients with BCa treated with trastuzumab	Hypertension (OR: 1.61; 95% CI: 1.14 to 2.26; *p*<0.01) Diabetes (OR: 1.62; 95% CI: 1.10 to 2.38; *p*<0.02) Previous anthracycline use (OR: 2.14; 95% CI: 1.17 to 3.92; *p*<0.02) Older age (*p*=0.013)
Yu *et al.,* 2017[15]	Retrospective cohort	Patients with HER2-positive early-stage BCa (*n*=165) receiving non-anthracycline trastuzumab-based therapy	Of patients with multiple CV risk factors, 1.2% developed a cardiac event (95% CI: 0.2% to 4.3%)

HER2 = human epidermal growth factor receptor 2; ER = estrogen receptor; PgR = progesterone receptor; LVEF = left ventricular ejection fraction; HR = hazard ratio; CI = confidence interval; OR = odds ratio; RV = right ventricular; CV = cardiovascular.

without comorbidities included in the study. We also ascertained whether the two groups differed significantly in terms of number of patients receiving anthracycline-based therapy, total dose of anthracyclines, total number of trastuzumab cycles, use of radiation, baseline LVEF, type of cardiac imaging, and whether hospitalization for cardiac reasons had occurred before referral. We then recorded the number of patients with and without comorbidities and the reason for referral to the CORC. We determined whether referral for reasons of adLVEF, SCTCD, or pre-treatment assessment was more or less likely for patients having 1 or more comorbidities compared with patients having no comorbidities.

The study was approved by The Ottawa Hospital Research Ethics Board.

RESULTS

The analysis included 243 patients with HER2-positive BCA who were referred to the CORC between 2008 and 2015 (supplemental Figure 1). Median duration of follow-up was 5.9 years. Table II outlines the demographics and clinical characteristics of the study population. Mean age of the patients overall was 55.6 years (95% CI: 54.1 to 57.2). The patient population with comorbidities had a significantly higher mean age of 58.9 years compared with 53.2 years for patients without comorbidities (p = 0.0004). The distribution of patients by BCA stage was 19.8% stage I, 43.6% stage II, 25.9% stage III, and 8.6% stage IV. Disease stage was not specified in 5 patients (2.1%). Stages II–III BCA was observed more often in patients without comorbidities than in those with comorbidities. Mean body weight in the patients overall was 70.8 kg (95% CI: 68.9 kg to 72.7 kg), with the mean being significantly higher in women with comorbidities (80.1 kg; 95% CI: 77.2 to 83.0; p = 0.0018). Average BMI was also higher in patients with comorbidities (30.9; 95% CI: 29.9 to 32.0; p > 0.0001).

For the patients overall, ER status was positive in 63.8%, and PGR status was positive in 49.8%. Compared with patients having no comorbidities, patients with comorbidities were more likely to have a negative ER and PGR status (41.3% of patients with comorbidities and 30.2% of patients without comorbidities were ER-negative, p = 0.019; 55.8% of patients with comorbidities and 41.0% of patients without comorbidities were PGR-negative, p = 0.037). There was no significant difference in lymph node status between the two patient groups.

Of the 243 patients, 183 received anthracycline-based chemotherapy followed by trastuzumab, and 58 patients received trastuzumab without anthracycline-based chemotherapy (Table III). Whether the remaining 2 patients received therapy with anthracyclines is unknown. Patients with comorbidities were less likely to receive anthracycline-based chemotherapy (28.8% vs. 46.5% of all patients, p = 0.011). Most patients (217 of 243) received trastuzumab in the curative setting; only 21 patients (8.6%) received trastuzumab for metastatic disease. On average, patients received 24.4 cycles of trastuzumab (95% CI: 21.5 to 27.4 cycles), with no significant difference between the groups. Breast radiation was given to 42.4% of the patients (95% CI: 69.5% to 80.4%), with no significant difference between the groups, although fewer patients with comorbidities received radiation (42 vs. 61 without comorbidities).

Assessment of LVEF by echocardiography or multigated acquisition imaging showed a baseline mean LVEF of 59.2%, with no significant difference between the groups (Table IV). There was also no significant difference between the two groups in the rate of cardiac hospitalization: in all, 13.6% of the population had been hospitalized (15 patients with comorbidities and 18 patients without comorbidities).

In this study population, 3.7% of patients had a history of diabetes, 11.5% had been diagnosed with dyslipidemia, and 16.0% were obese (BMI > 30). Most patients (57.2%) had no risk factors, and almost 4% had all 3 risk factors (supplemental Figure 2).

A history of dyslipidemia, obesity, or diabetes was present in 104 patients. For the patients with a pre-existing comorbidity of obesity or dyslipidemia, the most common reason for the CORC referral was adLVEF (63% and 60% respectively), followed by SCTCD (32% and 29% respectively). Similar findings were noted in the patients with diabetes, with 66% being referred to the clinic for adLVEF; 21%, for SCTCD; and 3%, for pre-chemotherapy assessment. Of the 139 patients with none of the 3 comorbidities, 68% were referred for adLVEF; 30%, for SCTCD; and 2%, for pre-chemotherapy assessment (Table V).

The combination of 2 or 3 pre-existing comorbidities was significantly associated with an increased incidence of SCTCD in the CORC referral population, with a rate of 67% for patients with obesity and dyslipidemia (RR: 2.2; p = 0.04), 69% for those with obesity and diabetes (RR: 2.3; p = 0.02), and 72% for those with all 3 factors (RR: 2.4; p = 0.08; Figure 1).

DISCUSSION

Cancer and heart disease are the top two causes of morbidity and mortality in North America. Epidemiology studies have identified common risk factors such as smoking, obesity, diabetes, and dyslipidemia for the development of both cancer and cardiovascular disease. For people who develop cancer, increasing evidence suggests a significant interplay between comorbidities and cancer outcomes. Patients with underlying comorbidities might not be able to complete a full course of prescribed cancer therapy and might experience more toxicities from their treatment, thus potentially compromising cancer outcomes.

In the present study, we assessed the relations between cardiotoxicity and the comorbidities of dyslipidemia, diabetes, and obesity in patients having all stages of HER2-positive BCA and receiving trastuzumab-based chemotherapy who were referred to the CORC. The combination of 2 or 3 of those comorbidities was significantly associated with an increased incidence of symptomatic cancer treatment–related cardiotoxicity.

The data presented here are consistent with data from other studies. Previous work by Goldhar *et al.*[7], Serrano *et al.*[6], Guenancia *et al.*[5], Gunaldi *et al.*[14], and Jawa *et al.*[8] linked obesity and diabetes with increased chemotherapy-related cardiotoxicity in patients with BCA (Table I). Given the increasing incidence of obesity throughout the world, the number of women at risk for developing BCA will

increase[3]. Long-term longitudinal studies indicate that obesity is not only associated with, but also independently predicts, many cardiac comorbidities[21,22]. Obesity has an indirect relation with coronary artery disease through covariates related both to obesity and to coronary artery disease risk, including hypertension, dyslipidemia (particularly reductions in high-density lipoprotein cholesterol), and impaired glucose tolerance or type 2 diabetes mellitus. Insulin resistance and accompanying hyperinsulinemia are typically associated with those comorbidities[22]. Diabetes by itself has been associated with chemotherapy-related cardiotoxicity in some studies[7,8]. In

TABLE II Demographic and clinical characteristics of patients with HER2-positive breast cancer according to comorbidity status

Characteristic	Comorbidity status group			*p* Value
	Overall	Yes	No	
Patients *(n)*	243	104	139	
Age (years)				0.0004
Mean	55.6	58.9	53.2	
95% CI	54.1 to 57.2	56.3 to 61.5	51.3 to 55.2	
Stage [*n* (%)]				0.612
I	48 (19.8)	22 (9.1)	26 (10.7)	
95% CI	15.2 to 5.3			
II	106 (43.6)	47 (19.3)	59 (24.3)	
95% CI	37.5 to 50.0			Pearson χ^2[4]: 2.68
III	63 (25.9)	22 (9.1)	41 (16.9)	
95% CI	20.8 to 31.8			
IV	21 (8.6)	11 (4.5)	10 (4.1)	
95% CI	5.7 to 12.9			
Unknown	5 (2.1)	2 (0.8)	3 (1.2)	
Estrogen receptor [*n* (%)]				0.019
Positive	155 (63.8)	58 (23.9)	97 (39.9)	
95% CI	57.5 to 69.6			Pearson χ^2[2]: 7.95
Negative	85 (34.9)	43 (17.7)	42 (17.3)	
95% CI	29.2 to 41.2			
Unknown	3 (1.2)	3 (1.2)	0	
Progesterone receptor				0.037
Positive	121 (49.8)	45 (18.5)	76 (31.3)	
95% CI	43.5 to 56.1			Pearson χ^2[2]: 6.62
Negative	115 (47.3)	58 (23.9)	57 (23.5)	
95% CI	41.1 to 53.7			
Unknown	7 (2.9)	1 (0.4)	6 (2.5)	
Lymph node status				0.397
Positive	128 (52.6)	53 (21.8)	75 (30.9)	
95% CI	46.3 to 58.9			Pearson χ^2[2]: 1.8493
Negative	113 (46.5)	51 (21.0)	62 (25.5)	
95% CI	40.3 to 52.8			
Unknown	2 (0.8)	0	2 (0.8)	
Weight (kg)				>0.0001
Mean	70.8	80.1	63.9	
95% CI	68.9 to 72.7	77.2 to 83.0	62.1 to 65.6	
Height (cm)				0.0018
Mean	162.4	160.9	163.6	
95%CI	161.5 to 163.3	159.5 to 162.2	162.5 to 164.6	
Body mass index				>0.0001
Mean	26.9	30.9	23.8	
95% CI	26.2 to 27.6	29.9 to 32.0	23.3 to 24.4	

HER2 = human epidermal growth factor receptor 2; CI = confidence interval.

a study by Gunaldi *et al.*[14], dyslipidemia by itself was not associated with increased cardiotoxicity.

Our findings demonstrate that, compared with either risk factor alone, the combination of multiple risk factors

TABLE III Therapy for HER2-positive breast cancer in patients stratified by comorbidities

Characteristic	Comorbidity status group			*p* Value
	Overall	Yes	No	
Patients *(n)*	243	104	139	
Anthracycline-based therapy [*n* (%)]				0.011
Yes	183 (75.3)	70 (28.8)	113 (46.5)	
95% CI	69.5 to 80.4			Pearson χ^2[2]: 8.97
No	58 (23.9)	34 (14.0)	24 (9.9)	
95% CI	18.9 to 29.7			
Unknown	2 (0.8)	0	2 (0.8)	
Total dose of anthracyclines	(*n*=199)	(*n*=81)	(*n*=118)	0.978
Mean	452.0	451.5	452.4	
95%CI	419.9 to 484.1	394.4 to 508.5	414.3 to 490.5	
Total trastuzumab cycles	(*n*=241)	(*n*=103)	(*n*=138)	0.16
Mean	24.4	22.0	26.2	
95%CI	21.5 to 27.4	17.8 to 26.3	22.2 to 30.3	
Radiation therapy [*n* (%)]				0.562
Yes	103 (42.4)	42 (17.3)	61 (25.1)	
95% CI	69.5 to 80.4			Pearson χ^2[2]: 1.1525
No	37 (15.2)	23 (9.5)	14 (5.7)	
95% CI	18.9 to 29.7			
Unknown	103 (42.4)	48 (19.8)	55 (22.6)	

HER2 = human epidermal growth factor receptor 2; CI = confidence interval.

TABLE IV Initial cardiac assessment in patients with HER2-positive breast cancer

Characteristic	Comorbidity status group			*p* Value
	Overall	Yes	No	
Patients *(n)*	243	104	139	
Baseline LVEF (%)	(*n*=221)	(*n*=97)	(*n*=124)	0.116
Mean	59.2	58.2	60.0	
95% CI	58.1 to 60.3	56.4 to 60.1	58.6 to 61.4	
Baseline cardiac imaging [*n* (%)]				0.475
Echocardiography	152 (62.6)	65 (26.8)	87 (35.8)	
95% CI	56.3 to 68.5			Pearson χ^2[2]: 1.4876
MUGA	85 (35.0)	35 (14.4)	50 (20.6)	
95% CI	29.2 to 41.2			
Unknown	6 (2.5)	4 (1.7)	2 (0.8)	
Cardiac hospitalization [*n* (%)]				0.479
No	209 (86.0)	88 (36.2)	121 (49.8)	
95% CI	81.0 to 89.9			Pearson χ^2[2]: 1.4727
Yes	33 (13.6)	15 (6.2)	18 (7.4)	
95% CI	9.8 to 18.5			
Unknown	1 (0.4)	1 (0.4)	0	

HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; CI = confidence interval; MUGA = multigated acquisition imaging.

TABLE V Reason for referral to the cardio-oncology clinic

Comorbidity	Patients			Cardiology assessment before cancer therapy		Asymptomatic decrease in LVEF		Symptoms of CTCD	
	(n)	Proportion	95% CI	*(n)*	(%)	*(n)*	(%)	*(n)*	(%)
None[a]	139	0.57	0.51 to 0.63	3	2	94	68	42	30
Diabetes	29	0.12	0.08 to 0.17	4	13	19	66	6	21
Obesity	60	0.25	0.20 to 0.31	3	5	40	63	20	32
Dyslipidemia	52	0.21	0.17 to 0.27	6	11	31	60	15	29

[a] Of diabetes, obesity, or dyslipidemia.
CI = confidence interval; LVEF = left ventricle ejection fraction; CTCD = cancer treatment–induced cardiac dysfunction

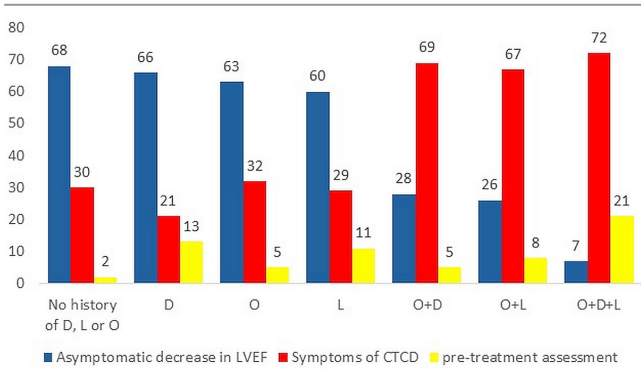

FIGURE 1 Reason for referral to cardio-oncology clinic. D = diabetes; L = dyslipidemia; O = obesity; LVEF = left ventricle ejection fraction; CTCD = cancer treatment–induced cardiac dysfunction.

(obesity, dyslipidemia, diabetes) has a significant effect on SCTCD.

Our study is different from other works in the field because it focuses on a cohort of patients referred to a cardio-oncology clinic for assessment before the initiation of trastuzumab or after the detection of ADLVEF or SCTCD during use of trastuzumab. Other studies investigated patients recruited from general medical centres. The patients in the present study had been identified either as being at risk for or as already having experienced chemotherapy-related cardiotoxicity. Thus, it might provide some insight about the risks for SCTCD and ADLVEF in patients referred for specialized cardio-oncologic care.

Our study has limitations. It is single-centre retrospective study of patients with BCa referred to a dedicated multidisciplinary cardio-oncology clinic at a tertiary care centre. Patients were referred to the clinic at the discretion of the oncologists, and thus our data likely underestimate the risk posed by comorbidities in the population with BCa. That being said, closer cardiac surveillance of patients referred to the CORC could also have led to bias in favour of identifying additional cases of ADLVEF and SCTCD.

A substantial portion of patients had been treated with anthracyclines, which might have confounded the association between patients with metabolic risk factors receiving trastuzumab and cardiotoxicity. Global longitudinal strain was not being measured by our centre at the time that the study was conducted. We limited our study to an assessment of 3 risk factors only: obesity, dyslipidemia, and diabetes.

The small difference in the RRS for the incidence of cardiotoxicity in patients having all 3 risk factors compared with those having 2 risk factors might reflect an underestimation of the cumulative effect of the risk factors given the small number of patients in former study group. It is also possible that cardiotoxicity rates increase slightly with longer follow-up time.

Patients with no comorbidities referred to the clinic were typically referred for cardiac dysfunction and thus had rates of ADLVEF and SCTCD that were comparable to rates in patients with 1 comorbidity. Notably, patients without comorbidities were significantly more likely to have received anthracycline-based chemotherapy, which likely contributed to the cardiac dysfunction that led to their referral to the clinic. Patients with comorbidities also were more likely to be ER- and PGR-negative, and to be older, which might have favoured more negative outcomes.

The present study provides further evidence that obesity, dyslipidemia, and diabetes are risk factors for both heart disease and BCa. Patients with BCa and multiple comorbidities in this study experienced a significantly higher risk for symptomatic cardiotoxicity during cancer treatment. The management of comorbidities in patients with BCa requires a multidisciplinary approach to optimize cardiac risk factors at the initiation of cancer therapy. Referral to health care providers with expertise in cardio-oncology and discussion of primary prevention strategies (for example, beta-blockers) should be considered to facilitate delivery of optimal cancer therapy.

CONCLUSIONS

The combination of 2 or 3 comorbidities (diabetes, dyslipidemia, obesity) is associated with a significant increase the incidence of symptomatic cancer treatment–related cardiotoxicity in patients with BCa receiving cancer therapy. Patients with BCa experiencing cancer treatment–related cardiotoxicity with a pre-existing history of diabetes, dyslipidemia, and obesity could require more proactive strategies for prevention, detection, and treatment of cardiotoxicity during trastuzumab-based treatment.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: SD has received honoraria from Amgen, Celgene, and Roche; fees for consulting or an advisory role from Amgen and Roche; and funds for travel, accommodations, or expenses from Celgene, Novartis, and Roche. The remaining authors have no conflicts to disclose.

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REFERENCES

1. Romond EH, Jeong JH, Rastogi P, *et al.* Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2–positive breast cancer. *J Clin Oncol* 2012;30:3792–9.
2. Advani PP, Ballman KV, Dockter TJ, Colon-Otero G, Perez EA. Long-term cardiac safety analysis of NCCTG N9831 (Alliance) adjuvant trastuzumab trial. *J Clin Oncol* 2016;34:581–7.
3. Cleary MP, Grossmann ME. Minireview: Obesity and breast cancer: the estrogen connection. *Endocrinology* 2009;150:2537–42.
4. Mottillo S, Filion KB, Genest J, *et al.* The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol* 2010;56:1113–32.
5. Guenancia C, Lefebvre A, Cardinale D, *et al.* Obesity as a risk factor for anthracyclines and trastuzumab cardiotoxicity in breast cancer: a systematic review and meta-analysis. *J Clin Oncol* 2016;34:3157–65.
6. Serrano JM, González I, Del Castillo S, *et al.* Diastolic dysfunction following anthracycline-based chemotherapy in breast cancer patients: incidence and predictors. *Oncologist* 2015;20:864–72.
7. Goldhar HA, Yan AT, Ko DT, *et al.* The temporal risk of heart failure associated with adjuvant trastuzumab in breast cancer patients: a population study. *J Natl Cancer Inst* 2015;108:djv301.
8. Jawa Z, Perez RM, Garlie L, *et al.* Risk factors of trastuzumab-induced cardiotoxicity in breast cancer: a meta-analysis. *Medicine (Baltimore)* 2016;95:e5195.
9. Tiersten A, Wo J, Jacobson C, *et al.* Cardiac toxicity observed in association with high-dose cyclophosphamide-based chemotherapy for metastatic breast cancer. *Breast* 2004;13:341–6.
10. Swain SM, Ewer MS, Cortes J, *et al.* Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in CLEOPATRA: a randomized, double-blind, placebo-controlled phase III study. *Oncologist* 2013;18:257–64.
11. Yu AF, Yadav NU, Eaton AA, *et al.* Continuous trastuzumab therapy in breast cancer patients with asymptomatic left ventricular dysfunction. *Oncologist* 2015;20:1105–10.
12. Huszno J, Les D, Sarczyny-Slota D, Nowarta E. Cardiac side effects of trastuzumab in breast cancer patients—single center experiences. *Contemp Oncol (Pozn)* 2013;17:190–5.
13. Dang C, Guo H, Najita J, *et al.* Cardiac outcomes of patients on adjuvant weekly paclitaxel and trastuzumab for node negative, HER2 positive breast cancer. *JAMA Oncol* 2016;2:29–36.
14. Gunaldi M, Duman BB, Afsar CU, *et al.* Risk factors for developing cardiotoxicity of trastuzumab in breast cancer patients: an observational single-centre study. *J Oncol Pharm Practice* 2016;22:242–7.
15. Yu A, Mukku R, Verma S, *et al.* Cardiac safety of non-anthracycline trastuzumab-based therapy for HER2-positive breast cancer. *Breast Cancer Res Treat* 2017;166:241–7.
16. Ezaz G, Long JB, Gross CP, Chen J. Risk prediction model for heart failure and cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. *J Am Heart Assoc* 2014;3:e000472.
17. Zamorano JS, Lancellotti P, Munoz DR, *et al.* on behalf of the ESC Scientific Document Group. 2016 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.
18. Curigliano G, Cardinale D, Suter T, *et al.* Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO clinical practice guidelines. *Ann Oncol* 2012;23(suppl 7):vii155–66.
19. Moja L, Tagliabue L, Balduzzi S, *et al.* Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev* 2012;18:CD006243.
20. Plana JC, Galderisi M, Barac A, *et al.* Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2014;15:1063–93.
21. Manson JE, Willett W, Stampfer M, *et al.* Body weight and mortality among women. *N Engl J Med* 1995;333:677–85.
22. Kramer FM, Jeffery RW, Forster JL, Snell MK. Long-term follow-up of behavioral treatment for obesity: patterns of weight regain among men and women. *Int J Obes* 1989;13:123–36.