Subclinical anthracycline- and trastuzumab-induced cardiotoxicity in the long-term follow-up of asymptomatic breast cancer survivors: a speckle tracking echocardiographic study

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ABSTRACT

Objective To examine the long-term effects of standard chemotherapy on myocardial function in asymptomatic breast cancer survivors using two-dimensional speckle tracking echocardiography.
Methods Seventy women (chemotherapy group) aged 54 ± 8 years who had received anthracycline treatment with (n=19) or without (n=51) adjuvant trastuzumab up to 6 years previously, and 50 female controls were studied. Left ventricular systolic (ejection fraction (EF%), peak systolic myocardial excursion, (Sm)) and diastolic (peak mitral E and A velocities, six-point average of mitral annular E′ velocities) function, 2D global and regional longitudinal and radial strain were determined using standard 2D Doppler and tissue Doppler echocardiographic methods and speckle tracking software.
Results Despite normal EF% ($62 \pm 4\%$ vs $60 \pm 3\%$, p=0.051) the chemotherapy group had reduced E/A ratios (0.9 ± 0.3 vs 1.1 ± 0.3, p=0.003), global E′ (10.2 ± 2 vs 11.2 ± 2.3, p=0.036), global Sm (9.0 ± 1.3 vs 9.6 ± 1.3, p=0.029) and global longitudinal 2D strain (-18.1 ± 2.2 vs -19.6 ± 1.8, p=0.0001) in comparison with controls. In 18 (26%) of the chemotherapy group, global longitudinal strain was below the lower limit of the control group. Cigarette smoking was a negative predictor of longitudinal strain, but only in the chemotherapy group. Radial strain did not differ significantly between the two groups. There were no significant differences in EF%, global Sm and longitudinal strain between trastuzumab-treated individuals and controls.
Conclusions Subclinical systolic and diastolic myocardial abnormalities were present in asymptomatic breast cancer survivors up to 6 years after standard chemotherapy. Cigarette smoking had a negative effect on longitudinal strain in these individuals. Adjuvant trastuzumab treatment did not appear to have an additive adverse impact on myocardial function in the medium—long term.

INTRODUCTION

Despite their well-documented cardiotoxicity, predominantly manifest as a dilated cardiomyopathy, anthracyclines remain the preferred agents for a wide variety of malignancies, including breast cancer.[1] The addition of trastuzumab, a monoclonal antibody directed against human epidermal growth factor receptor 2, to standard adjuvant chemotherapy significantly improves disease-free and overall survival[2] in the 20—30% of patients with breast cancer who overexpress this proto-oncogene. However, trastuzumab is also cardiotoxic, resulting in cardiac dysfunction in 3% to 5% of patients.[2]

In clinical practice, volumetric left ventricular ejection fraction (LVEF) is quantified as a measure of cardiac function. However, LVEF is a crude marker of myocardial function, as mechanisms are in place that ensure its maintenance despite reductions in myocardial contractility. A reduction in LVEF usually occurs in the later stages of chronic pathology, signalling an extensive loss of function beyond the compensatory capacity of the myocardium. This is followed by a course of progressive irreversible myocardial damage and LV dilatation, with its inherently poor outcomes.[3]

Anthracycline cardiotoxicity may not become clinically apparent for several years to decades after the last administered dose,[4] and long-term survival in many forms of cancer is now increasingly becoming a reality with successful anti-tumour treatment. Identifying reliable non-invasive methods for the early detection of myocardial dysfunction before the critical point of LV dysfunction is therefore crucial. Regional myocardial function, assessed by myocardial velocities and strain, is potentially a more sensitive marker of early myocardial dysfunction.[5] Developments in echocardiographic tissue Doppler imaging (TDI) and more recently, two-dimensional (2D) speckle tracking methods have allowed more accurate measurements of regional myocardial systolic and diastolic performance.

In this study we sought to determine the late effects of anthracycline and anthracycline—trastuzumab chemotherapy on global and regional myocardial function in a group of asymptomatic breast cancer survivors, using conventional, as well as more novel TDI and 2D speckle tracking echocardiographic (2DSTE) methods.

MATERIALS AND METHODS
Study population

Seventy-five asymptomatic women who had undergone anthracycline-based chemotherapy between 2001 and 2006 were invited to participate in this cross-sectional study. Exclusion criteria were uncontrolled hypertension, significant valvular disease, a widened QRS complex on surface ECG,

other than sinus rhythm and a previous history of heart failure and/or coronary artery disease. Of the 75 women, a total of 70 subjects were studied. Five women were excluded owing to findings of uncontrolled hypertension (n=1), severe mitral regurgitation (n=2), anginal symptoms (n=1) and left bundle branch block (n=1).

Patient charts were reviewed for demographic data, past medical history, current drug use, cumulative doses of anthracycline and all other chemotherapy agents (mg/m^2), dates of anthracycline and trastuzumab administration and completion, and cumulative doses and sites of adjunctive radiation therapy. At the time of echocardiographic examination, the subject's height, weight, heart rate and systolic and diastolic blood pressures were recorded.

Fifty, healthy, normotensive women with no history of cardiovascular disease, who had never received chemotherapy and who were not receiving any drugs were recruited as control subjects. These women were randomly selected from a larger group of controls recruited from hospital staff members for other studies performed at our centre, for the age range of the chemotherapy group (34—71 years). The study was approved by the local hospital ethics review committee and informed consent was obtained from all subjects.

2D, Doppler and tissue Doppler echocardiography

Echocardiography was performed on all subjects using a commercially available ultrasound system (Vivid 7 Dimension; GE Healthcare, Norway). All images were digitally stored for offline analysis. Standard 2D images were acquired according to recommendations of the American Society of Echocardiography.[6] LV mass was determined from septal and posterior wall thickness and LV end-diastolic dimensions, and indexed to body surface area.[7] The LVEF was calculated using the modified Simpson's biplane method. Transmitral peak early (E) and peak late (A) diastolic filling velocities, E deceleration time and isovolumic relaxation time were measured using conventional Doppler ultrasound. Left ventricular outflow tract pulsed-Doppler was used to determine aortic valve opening and closure

times, and LV ejection time. The myocardial performance index was derived from the mitral valve closure to opening time, and LV ejection time.[8] Pulsed-wave TDI velocities were assessed at the basal segments of each of the three longitudinal planes in the apical four-, three- and two-chamber views. Peak systolic (Sm), peak early (E') and peak late (A') diastolic tissue velocities were measured to give regional values, and averaged to give global, basal longitudinal myocardial velocities.

2D speckle tracking echocardiography

Strain is a dimensionless parameter representing deformation of a myocardial segment relative to its original dimensions within a systolic time-frame. Although strain data may be obtained from TDI parameters, 2DSTE has been validated by cardiac MRI, the 'gold standard' for deformation analysis, with which it shows better correlation than TDI-derived strain.[9] With standard 2D echocardiographic grey-scale imaging, reflected ultrasound gives rise to speckles of bright signal within the myocardium. Frame-by-frame tracking of the movement of these natural acoustic markers throughout the cardiac cycle allows assessment of temporal displacement between neighbouring markers and quantification of myocardial deformation.

We used 2DSTE to examine 2D strain in the longitudinal and radial directions. Standard B-mode images of the left ventricle were acquired in the parasternal short-axis view at mid-papillary level and in the apical four-, two- and three-chamber views. Care was taken to ensure frame rates of between 40 and 90 MHz. Custom software (EchoPAC vBT08; GE Healthcare, Norway) was used for strain analyses. Peak longitudinal strain measurements (figure 1) were obtained from the basal, mid- and apical segments of the septal, lateral, inferior, anterior, posterior and anteroseptal walls. Regional longitudinal strain for each of these walls was obtained by averaging the three segmental strain measurements within the wall. Global longitudinal strain was derived by the software. Regional radial strain was measured in the septal, anteroseptal, anterior, lateral, posterior and inferior walls; and averaged to determine global radial strain.

Figure 1 Apical four-chamber two-dimensional, speckle tracking-derived longitudinal strain. Custom software calculates longitudinal strain by tracking multiple acoustic speckles in the myocardium over a cardiac cycle. These are then averaged for each of six standard segments to generate time-strain plots, which are colour-coded according to the individual segment represented. Peak average strain values for each segment are displayed in the bottom left panel.
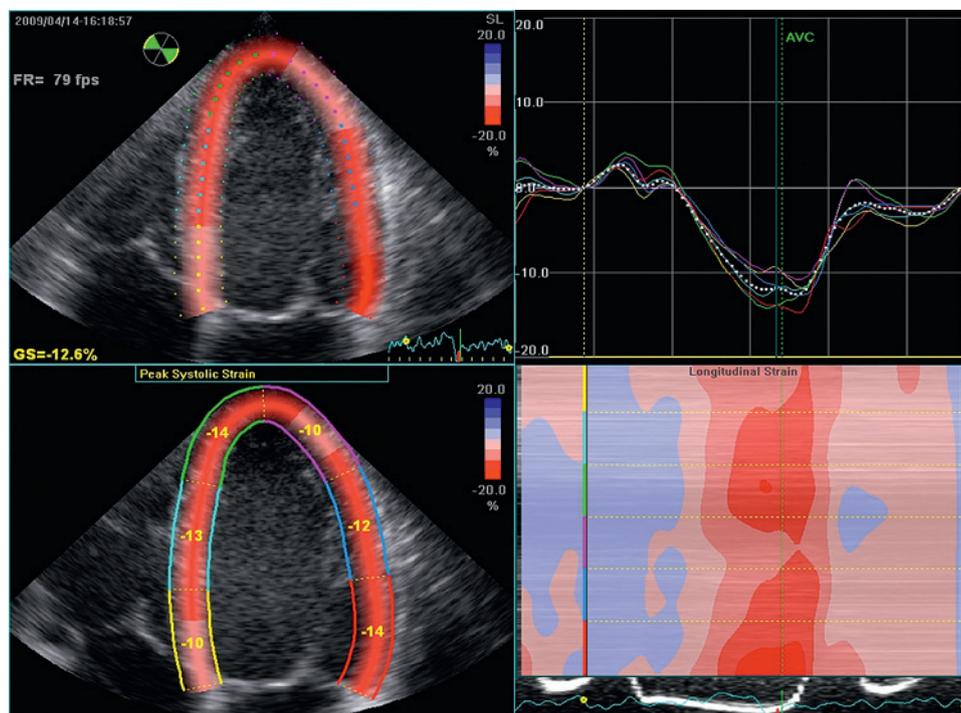
To assess intraobserver and interobserver variability, longitudinal and radial strain measurements were repeated in the same datasets from 20 randomly selected subjects by the same investigator (EH), and by an independent observer (RBM).

Statistics

Data are expressed as mean±SD. Differences between groups were determined using the unpaired t test for continuous variables and Fisher's exact test for categorical data. Multiple linear regression analyses to determine the predictors of longitudinal strain were carried out in two separate models. First, the whole population was examined with age, cigarette smoking, systolic blood pressure, body mass index and previous chemotherapy exposure entered into the model. As anthracycline dose and time from last dose, paclitaxel use, adjuvant trastuzumab treatment and radiotherapy have been known to have detrimental effects on cardiac function, the effects of these predictors were entered into a second model examining the chemotherapy group alone, adjusting for the cardiovascular risk covariates above. Owing to collinearity with anthracycline (r=0.6, p<0.0001), cyclophosphamide was not included in the model. We also tested for an interaction effect between significant independent predictors of longitudinal strain by introducing an interaction term for these predictors into the respective regression models. Intraobserver and interobserver variability were measured by the intraclass correlation coefficient and by the coefficient of variation (CV) using the root-mean-square method. A p value of <0.05 was considered statistically significant. Corrections for multiple comparisons were not made. All statistical analyses were performed using Stata/IC software (v10, StatCorp).

RESULTS

Population demographics

Differences in age, cigarette smoking, body surface area, body mass index, systolic or diastolic blood pressure between controls and the whole chemotherapy group, and between trastuzumab-treated and trastuzumab-naïve patients were not statistically significant (table 1). Six of the chemotherapy group had a history of hypertension, which was well-controlled by medication. All of the chemotherapy group had received anthracy-

cline treatment a mean of 4.2±1.8 years previously. Of these, 56 individuals (80%) also received cyclophosphamide and 36 (51%) individuals received paclitaxel. Nineteen (27%) individuals had received trastuzumab 3.1±1.9 years previously. Fifty-six patients (80%) received adjuvant chest wall radiotherapy, which was applied to the right side in 36 patients (56±8 Grays), left side in 19 patients (52±4 Grays) and to both sides (right 45 Grays, left 55 Grays) in one patient. There were no statistically significant differences in the chemotherapy regimens, including total anthracycline dose and time from last administered anthracycline dose, between the two trastuzumab-based chemotherapy subgroups.

2D, Doppler and tissue Doppler echocardiography

Although the LVEF did not significantly differ between chemotherapy and controls, or between trastuzumab subgroups (table 2), global Sm was significantly lower in the whole chemotherapy group and the trastuzumab-naïve subgroup than in controls, as were transmitral Doppler E velocities and E/A ratios. Global E′ velocities were lower in the chemotherapy group and trastuzumab-naïve subgroup than in controls; but in all groups differences in E/E′ ratio, and global A′ velocities did not reach statistical significance. While the absolute mean differences in LV end-diastolic diameter and global E′/A′ ratio were lower, and myocardial performance index higher, in the chemotherapy group in comparison with controls, these differences were small and did not reach statistical significance. Differences in systolic and diastolic function parameters between the trastuzumab-treated subgroup and controls were also not statistically significant.

Speckle tracking and 2D longitudinal and radial strain

The intraobserver intraclass coefficients for global longitudinal strain and global radial strain were 0.97 (CV 3.1%) and 0.97 (CV 2.9%), respectively. Interobserver global longitudinal strain and global radial strain intraclass coefficients were 0.95 (CV 4.8%) and 0.97 (CV 5%), respectively. The intraobserver and interobserver coefficients of variation for regional longitudinal and radial strain were between 2.3% and 10% (data not shown).

Table 1 Demographic, clinical parameters and breast cancer treatment in the study population

Variable	Control group (n=50)	Chemotherapy groups Whole (n=70)	p Value*	Trastuzumab-naïve (n=51)	Trastuzumab-treated (n=19)	p Value†
Demographics and clinical parameters						
Age, years	52±5	54±8	0.10	53±8	56±8	0.23
Cigarette smoker, n (%)	9 (18)	9 (13)	0.52	6 (12)	3 (16)	1.00
Hypertension, n (%)	0	6 (8)	**0.023**	4 (8)	2 (10)	1.00
Heart rate, bpm	74±12	75±12	0.79	76±13	70±10	0.20
Systolic blood pressure, mm Hg	126±12	130±14	0.10	133±13	125±15	0.10
Diastolic blood pressure, mm Hg	77±8	78±10	0.76	79±9	75±10	0.14
Body surface area, m^2	1.73±0.14	1.77±0.17	0.16	1.78±0.18	1.75±0.16	0.49
Body mass index, kg/m^2	26±4	27±6	0.12	27±7	27±5	0.69
Chemotherapy and radiotherapy						
Anthracycline dose, mg/m^2	—	402 (312, 580)	—	413 (312, 580)	405 (376, 448)	0.60
Last anthracycline dose, months	—	50±22	—	56±21	48±24	0.20
Cyclophosphamide dose, mg/m^2	—	4235 (3120, 9312)	—	4196 (3120, 9312)	4351 (3760, 6760)	0.59
Paclitaxel dose, mg/m^2	—	861 (508,1620)	—	912 (508, 1620)	778 (598, 1208)	0.13
Adjuvant radiotherapy, Gy	—	55±9	—	56±9	55±7	0.67

Values are mean±SD, total number (%) or mean (range).
*Denotes statistical difference between the whole chemotherapy group and controls.
†Denotes statistical difference between the two chemotherapy subgroups.

Drug-induced cardiotoxicity

Table 2 Two-dimensional left ventricular dimensions, and systolic and diastolic function in the study population

Variable	Control group (n=50)	Chemotherapy groups Whole (n=70)	Trastuzumab-naive (n=51)	Trastuzumab-treated (n=19)	Whole versus controls	Trastuzumab-naive versus controls	Trastuzumab-treated versus controls	Trastuzumab-treated versus naive
Two-dimensional LV dimensions								
LVEDD, cm	4.3±0.4	4.2±0.5	4.2±0.5	4.2±0.5	−0.1 (−0.3 to 0.1)	−0.1 (−0.3 to 0.1)	−0.1 (−0.3 to 0.1)	0.01 (−0.2 to 0.2)
LVMI	53.0±1.1	51.5±1.4	51.2±1.5	52.2±9.3	−1.5 (−6.3 to 3.3)	−1.8 (−7.3 to 3.7)	−0.8 (−6.4 to 4.8)	1.0 (−7.0 to 9.0)
Systolic function								
Ejection fraction, %	61.7±3.9	60.4±3.1	59.8±2.6	62.0±3.7	−1.3 (−2.6 to 0.01)	**−1.9 (−3.3 to −0.5)**	0.3 (−1.8 to 2.4)	2.2 (−0.1 to 2.5)
Global Sm, cm/s	9.6±1.3	9.0±1.3	8.7±1.30	9.7±1.2	**−0.6 (−1.1 to −0.1)**	**−0.9 (−1.5 to −0.3)**	0.1 (−0.8 to 1.0)	**1.0 (0.2 to 1.8)**
Diastolic function								
Doppler indices								
E velocity, m/s	75.9±14.1	69.3±15.5	67.5±16.3	73.9±12.3	**−6.6 (−12.2 to −1.0)**	**−8.4 (−14.5 to −2.3)**	−2.0 (−9.3 to 5.3)	6.4 (−1.8 to 14.6)
A velocity, m/s	70.2±14.8	74.8±13.1	74.3±11.8	76.1±16.3	4.6 (−0.5 to 9.7)	4.1 (−0.5 to 8.7)	5.9 (−2.3 to 14.1)	1.8 (−5.3 to 8.9)
E/A ratio	1.1±0.3	0.9±0.3	0.9±0.3	1.0±0.3	**−0.2 (−0.3 to −0.1)**	**−0.2 (−0.3 to −0.1)**	−0.1 (−0.3 to 0.1)	0.1 (−0.1 to 0.3)
Deceleration time, ms	176.6±29.7	190.0±40.8	186.7±41.4	198.5±38.8	13.4 (−0.2 to 27.0)	10.1 (−4.3 to 24.5)	21.9 (−4.4 to 48.2)	11.8 (−10.2 to 33.8)
IVRT, ms	78.9±8.5	82.1±12.3	81.6±11.9	83.2±13.2	3.2 (−1.1 to 7.5)	2.7 (−1.7 to 7.1)	4.3 (−1.3 to 9.9)	1.6 (−5.4 to 8.6)
MPI	0.42±0.10	0.43±0.10	0.44±0.10	0.40±0.10	0.01 (−0.02 to 0.04)	0.02 (−0.02 to 0.06)	−0.02 (−0.08 to 0.04)	−0.04 (−0.1 to 0.02)
Tissue Doppler indices								
Global E′ velocity, cm/s	11.2±2.3	10.2±2	9.8±2.2	11.4±2.4	**−1.0 (−1.9 to −0.1)**	**−1.4 (−2.4 to −0.4)**	0.2 (−1.2 to 1.6)	**1.6 (0.2 to 3.0)**
E/E′ ratio	6.9±1.4	7.0±1.2	7.0±1.3	6.8±0.8	0.1 (−0.4 to 0.6)	0.1 (−0.5 to 0.7)	−0.1 (−0.8 to 0.6)	−0.2 (−0.9 to 0.5)
Global A′ velocity, cm/s	10.7±1.7	10.9±2.2	10.8±2.3	11.4±2.0	0.2 (−0.6 to 1.0)	0.1 (−0.8 to 1.0)	0.7 (−0.4 to 1.8)	0.6 (−0.7 to 1.9)
E′/A′ ratio	1.08±0.29	0.99±0.35	0.97±0.36	1.04±0.33	−0.09 (−0.22 to 0.04)	−0.11 (−0.25 to 0.03)	−0.04 (−0.22 to 0.14)	0.07 (−0.14 to 0.28)

Values are mean±SD or mean difference (95% CI). Values in bold are significant at the 5% level.
IVRT, intraventricular relaxation time; LVEDD, left ventricular end-diastolic diameter; LVMI, left ventricular mass index; MPI, myocardial performance index.

Longitudinal strain in the whole chemotherapy group and trastuzumab-naïve subgroup was reduced globally in comparison with controls (table 3). Eighteen (26%) individuals in the chemotherapy group had global longitudinal strain values below the lower limit of the control group (minimum global longitudinal strain=16.6). Regional reductions in longitudinal strain were found in the septal, lateral, anterior walls in the trastuzumab-naïve subgroup, and additionally, in the posterior wall in the whole chemotherapy group, in comparison with controls. There were no statistically significant differences in radial strain in all groups. Differences in global longitudinal and radial strain measurements between the trastuzumab-treated subgroup and controls did not reach statistical significance.

Determinants of 2D longitudinal strain

Cigarette smoking ($p=0.039$; 95% CI 0.1 to 2.1) and chemotherapy use ($p<0.0001$; 95% CI 1.0 to 2.6) were the only independent predictors of global longitudinal strain in the whole population. There was a significant interaction between cigarette smoking and chemotherapy (table 4), where the effect of smoking was only evident in the chemotherapy group (figure 2). In the chemotherapy group, trastuzumab use was associated with an increase in longitudinal strain, but anthracycline dose and time from last dose, paclitaxel use and adjuvant radiotherapy use did not predict the magnitude of longitudinal strain. There was no significant interaction between cigarette smoking and trastuzumab use in the chemotherapy group ($p=0.791$).

DISCUSSION

In keeping with an extensive body of evidence,[10–12] we found evidence of diastolic dysfunction in the chemotherapy group, who had lower transmitral E velocities and E/A ratios, and global E′ velocities than control subjects. Transmitral E/E′ ratio was similar and within normal limits in all groups, indicating normal LV filling pressures. This was consistent with our findings of normal LV dimensions and LVEF.

We found the chemotherapy group to have reduced global peak myocardial excursion velocities Sm. Reduced TDI parameters of myocardial systolic function both acutely and in chronic follow-up of anthracycline treatment, have previously been reported.[10 13] Nevertheless TDI-derived strain and strain rate measurements are subject to a number of limitations, including angle dependency, tethering and translational motion artefacts which result in a low signal-to-noise ratio. This in turn results in high intraobserver and interobserver variability,[14] limiting its widespread use in clinical practice. 2DSTE-derived strain is free of these limitations and allows quantification of myocardial deformation in three dimensions, requiring only B-mode images from a standard echocardiographic examination. Its ease of use and reproducibility make it a potentially useful method for detecting subclinical myocardial abnormalities in the long-term follow-up of chemotherapy patients. The intra- and interobserver reproducibility of longitudinal and radial 2D strain in our study was comparable to that in other studies,[9 15] where intra- and interobserver variability from 3.6% to 5.3% and 7% to 11.8%, respectively, were reported.

This is the first study demonstrating evidence of reduced 2DSTE-derived global and regional longitudinal strain in asymptomatic individuals previously treated with anthracyclines with normal systolic function. Just over one-quarter of the chemotherapy group had longitudinal strain values below the lower limits of the control group. We found regional reductions in longitudinal strain in the septal, lateral, anterior and posterior

Table 3 Two-dimensional longitudinal and radial strain in the study population

Variable	Control group (n=50)	Chemotherapy groups			Whole versus controls	Trastuzumab–naïve versus controls	Trastuzumab–treated versus controls	Trastuzumab–treated versus naïve
		Whole (n=70)	Trastuzumab–naïve (n=51)	Trastuzumab–treated (n=19)				
Longitudinal strain								
Global	−19.6±1.8	−18.1±2.2	−17.7±2.1	−19.2±2.1	**−1.5 (−2.2 to −0.8)**	**−1.9 (−2.7 to −1.1)**	−0.4 (−1.4 to 0.6)	**1.5 (0.3 to 2.7)**
Septal wall	−18.3±2.3	−16.7±2.6	−16.7±2.5	−16.7±2.9	**−1.6 (−2.5 to −0.7)**	**−1.6 (−2.5 to −1.7)**	**−1.6 (−2.9 to −0.3)**	0.04 (−1.4 to 1.5)
Lateral wall	−20.1±2.3	−18.2±4.4	−17.5±4.6	−20.0±3.3	**−1.9 (−3.3 to −0.5)**	**−2.6 (−4.1 to −1.1)**	−0.1 (−1.5 to 1.3)	**2.5 (0.1 to 4.9)**
Inferior wall	−20.4±2.2	−19.6±6.7	−18.5±2.8	−22.6±11.6	−0.8 (−2.8 to 1.2)	**−1.9 (−2.9 to −0.9)**	2.2 (−1.2 to 5.6)	**4.1 (0.6 to 7.6)**
Anterior wall	−20.0±3.0	−18.5±3.4	−18.0±2.8	−19.8±4.4	**−1.5 (−2.7 to −0.3)**	**−2.0 (−3.2 to −0.8)**	−0.2 (−2.0 to 1.6)	1.8 (−0.1 to 3.7)
Posterior wall	−20.7±2.8	−19.4±2.6	−19.3±3	−19.9±2.8	**−1.3 (−2.4 to −0.2)**	**−1.4 (−2.6 to −0.2)**	−0.8 (−3.2 to 1.6)	0.6 (−1.7 to 2.9)
Anteroseptal wall	−18.7±3.4	−17.9±2.0	−17.8±2.1	−18.5±3.0	−0.8 (−2.1 to 0.5)	−0.9 (−2.2 to 0.4)	−0.2 (−2.9 to 2.5)	0.7 (−1.1 to 2.5)
Radial strain								
Global	44.7±18.0	45.8±18.9	45.2±22.0	46.3±17.8	1.1 (−9.5 to 11.7)	0.5 (−10.8 to 11.8)	1.6 (−6.3 to 9.5)	1.1 (−12.0 to 14.2)

Values are mean±SD or mean difference (95% CIs). Values in bold are significant at the 5% level.

Table 4 Multiple linear regression of independent predictors of longitudinal strain

Variable	Regression coefficient	95% CI	p Value
Whole population (n=120)*			
Cigarette smoking×previous chemotherapy	2.3	0.2 to 4.3	**0.029**
Previous chemotherapy	1.5	0.7 to 2.3	**0.001**
Whole chemotherapy group (n=70)†			
Cigarette smoking	1.8	0.1 to 3.4	**0.030**
Trastuzumab use	−1.5	−2.9 to −0.4	**0.042**

Cigarette smoking×previous chemotherapy denotes the interaction term between these two significant independent predictors.
*Adjusting for age, cigarette smoking, systolic blood pressure, body mass index and previous chemotherapy use and cigarette smoking×previous chemotherapy use.
†Adjusting for age, cigarette smoking, systolic blood pressure, body mass index, anthracycline dose and time from last dose, paclitaxel use, trastuzumab treatment, cigarette smoking×trastuzumab treatment and radiotherapy.

walls in our anthracycline group. Ganame et al[10] also demonstrated regional reductions in TDI-derived longitudinal strain in the interventricular septum and LV lateral wall in their cohort of 56 children who had received anthracycline treatment up to 15 years previously. The reasons for this heterogeneous pattern of strain reduction have not yet been elucidated, but may be related to differences in regional wall stress, or to local differences in activation of signalling pathways involved in apoptosis or fibrosis.[16] Interestingly, in a case report of two patients with anthracycline-induced cardiomyopathy,[17] late gadolinium enhancement cardiac MRI showed subendocardial enhancement of the anterior, inferior and septal walls of one patient, and a more diffuse pattern of subendocardial enhancement in the second patient.

In contradistinction to some previous studies,[10 12] we did not find any significant difference in 2D radial strain between the chemotherapy and control groups. These studies used TDI-derived parameters of deformation, where radial strain can only be assessed in a single segment of the inferolateral wall. Indeed, Ganame et al[10] found that although TDI-derived peak systolic strain in the inferolateral wall was reduced, global radial cardiac performance as assessed by fractional shortening was normal.
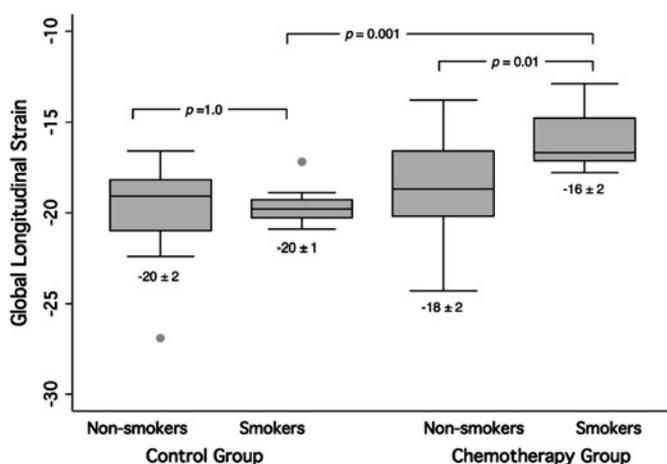
Figure 2 Box and whisker plots showing global two-dimensional, longitudinal strain according to chemotherapy group and smoking status. Values are mean±SD. Longitudinal strain was significantly lower in smokers in the chemotherapy group (n=9) than those in the control group (n=9); but no different between smokers and non-smokers (n=41) in the control group.

Furthermore, reduced contractility in the longitudinal plane has been shown to precede radial dysfunction in other conditions of LV dysfunction.[18 19] In a 2DSTE study of hypertensive subjects with heart failure,[20] longitudinal fibre dysfunction progressively deteriorated with an increasing severity of symptoms; whereas radial and circumferential strain were preserved in less advanced stages of heart failure. Indeed these subjects had supranormal radial function, a finding also reported in other hypertensive cohorts.[21 22] This suggests that radial and circumferential contractility may compensate for early longitudinal dysfunction, thus initially maintaining normal overall LV function.

Cigarette smoking, which has been associated with left ventricular remodelling and dysfunction in a number of large population-based studies,[23] was an independent predictor of longitudinal strain in our chemotherapy group. Although the exact mechanistic pathways of anthracycline-induced cardiotoxicity have not yet been fully elucidated, oxidative stress is thought to have a central role.[24] Anthracyclines induce the formation of reactive oxygen species, which in excess can result in DNA and cytosolic damage, with subsequent loss of cellular integrity and apoptosis. It is well established that cigarette smoking is associated with increased levels of oxidative stress[25] and thus could potentially augment anthracycline-induced myocyte damage. However, there is surprisingly little information on the impact of cigarette smoking on anthracycline-induced cardiomyopathy in epidemiological studies, owing to the difficulty in determining its incidence from the disease-coding databases used in these studies.[26] Although further confirmation in larger populations is required, our finding that cigarette smoking had a negative impact on longitudinal strain in the chemotherapy group emphasises the importance of lifestyle modification in long-term cancer survivors.

As the detrimental effects of anthracycline—trastuzumab cardiotoxicity are known to be additive in the short-term,[27] we would expect to see a greater reduction in myocardial contractility and/or a greater impairment of diastolic function in the trastuzumab-treated group than in those treated with anthracyclines alone. Interestingly, in our medium- to long-term study, this was not the case.

There is now increasing evidence that trastuzumab-induced cardiomyopathy differs from that induced by anthracyclines, in that trastuzumab-induced cardiomyopathy is less severe, with no apparent ultrastructural abnormalities, and has a high likelihood of reversibility.[28 29]

However, the trastuzumab-treated group in our study was small, reflecting the relatively low incidence of HER2-positive tumours, and these findings may have been due to chance. Also, the time from the last administered dose of trastuzumab was relatively short, and longer follow-up will be required to determine the true chronic sequelae of the drug. Even so, we feel that our findings add to the current knowledge of the natural history of trastuzumab-induced cardiotoxicity, and warrant further investigation.

Limitations
A limitation of our study is its cross-sectional design, with the inherent drawbacks of selection bias and a lack of prognostic data. In addition, corrections for multiple comparisons were not included in the analyses, which may increase the likelihood for type I error or false-positive findings. Long-term, large-scale outcome studies with hard clinical end points will be required to determine the clinical significance of our findings.

CONCLUSIONS

Despite a normal LVEF, subtle abnormalities in myocardial diastolic and systolic function were present in patients with asymptomatic breast cancer previously exposed to anthracycline treatment. Global longitudinal strain in 26% of the chemotherapy group was below the lower limit of this parameter in age-matched controls. Cigarette smoking had a negative impact on myocardial function, and is a modifiable target in risk reduction in chemotherapy survivors. Adjuvant trastuzumab treatment in this group did not appear to add to myocardial dysfunction in the medium—long term. Speckle tracking echocardiography, with its greater ease of use and reproducibility over TDI, is a potential non-invasive tool for the early detection of subclinical myocardial abnormalities in these patients. The detection of early systolic dysfunction in this group has potential therapeutic implications, and may provide a rationale for the early implementation of antifailure medication in individuals with anthracycline-induced cardiotoxicity before the onset of irreversible functional LV changes.

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Heart

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