Usefulness of Coronary Computed Tomographic Angiography to Evaluate Coronary Artery Disease in Radiotherapy-Treated Breast Cancer Survivors

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Breast cancer is the most commonly diagnosed cancer in women and radiotherapy is a widely used treatment approach. However, there is an increased risk of coronary artery disease and cardiac death in women treated with radiotherapy. The present study was undertaken to clarify the relation between radiotherapy and coronary disease in women with previous breast irradiation using coronary computed tomographic angiography (CCTA). We conducted a retrospective analysis of women with a history of right or left-sided breast cancer (RBC; LBC) treated with radiotherapy who subsequently underwent CCTA. RBC patients who had reduced radiation doses to the myocardium served as controls. Patients (n = 6,593) with a history of nonmetastatic breast cancer treated with radiotherapy were screened for completion of CCTA; 49 LBC and 45 RBC women were identified. Age and risk factor matched patients with LBC had higher rates of coronary disease compared with RBC patients; left anterior descending (LAD) coronary artery (76% vs 31% [p < 0.001]), left circumflex (33% vs. 6.7% [p = 0.004]), and right coronary artery (37% vs 13% [p = 0.018]). Mean LAD radiation dose and mean heart dose strongly correlated with coronary disease, with a 21% higher incidence of disease in the LAD per Gy for mean LAD dose and a 95% higher incidence of disease in the LAD per Gy for mean heart dose. In conclusion, LBC patients treated with radiotherapy have a significantly higher incidence of coronary disease when compared with a matched group of patients treated for RBC. Radiation doses correlated with the incidence of coronary disease. **(Am J Cardiol 2021;143:14−20)**

Breast cancer is the most commonly diagnosed cancer in the world in women and the second most frequent cause of cancer death in women in the United States.[1] Adjuvant radiotherapy is a widely used treatment for patients with nonmetastatic breast cancer as it reduces the risk of recurrence and improves overall survival.[2] However, there is an increased risk of cardiac death and ischemic heart disease in women treated with radiotherapy for breast cancer.[3-8] Patients treated for left-sided breast cancer (LBC) have an increased risk of radiation-induced coronary artery disease compared with patients with right-sided breast cancer (RBC) due to the proximity of the radiation beams to the coronary vasculature.[9] Coronary angiography and functional stress testing have significant limitations in evaluating the degree and extent of coronary disease and coronary plaque when compared with coronary computed tomographic angiography (CCTA).[10-12] Accordingly, the ability of CCTA to describe subclinical atherosclerosis, plaque composition, and the presence of extra-luminal plaque make it the preferred technique to evaluate patients at risk for coronary disease.[13,14] The present study describes the effects of radiotherapy on the prevalence and morphology of coronary disease using CCTA in breast cancer patients with a history of breast irradiation.

Methods

We conducted a retrospective analysis of women with a history of either right- or left-sided, nonmetastatic breast cancer who were treated with radiotherapy at a single institution from January 2006 to December 2019. Eligible patients (n = 6,593) were screened for completion of CCTA. Both asymptomatic and those performed for clinical reasons were utilized. CCTA was performed between 2.6 and 3.9 years after completing radiotherapy. Patients with a history of coronary revascularization either by percutaneous coronary intervention or coronary artery bypass grafting before radiotherapy were excluded from analysis. Patients with LBC and RBC were directly compared. Variables for multivariate analysis were chosen utilizing the Framingham Risk Score and conventional risk factors for coronary disease.[15-18]

CCTA acquisition was performed using a 128-multidetector CT scanner (Somatom Definition Flash Dual Source Scanner, Siemens Healthcare) with a detector width of 0.33 mm. The protocol for the acquisition of images differed depending on the clinical indication for CCTA. Standard coronary evaluation utilized prospective electrocardiographic gating. A trans-catheter aortic valve replacement protocol, which was used in a small number of patients who were evaluated for aortic valve replacement, employed spiral image

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acquisition, and retrospective electrocardiographic gating. Before CCTA scanning, all patients were treated with beta-blockers and sublingual nitroglycerin to achieve adequate heart rate control and vasodilation when not contraindicated per hospital protocol. Lopamidol (Isovue-M) was utilized as a contrast agent, and the dose given per CCTA protocol ranged from 70 to 120 ml. Multiphase reconstruction was used for interpretation of coronary disease.

CCTA grading and segmentation of coronary arteries employed the Society of Cardiovascular Computed Tomography guidelines criteria: grade 0 = normal, no luminal stenosis; grade 1 = minimal stenosis, 1% to 24%; grade 2 = mild stenosis, 25% to 49%; grade 3 = moderate stenosis, 50% to 69%; grade 4 = severe stenosis, 70% to 99%; and grade 5 = occluded.[19] Images were also assessed for high-risk plaque features which included the presence of spotty calcification, low attenuation plaque (< 30 Hounsfield units), or positive remodeling.[20]

We obtained the mean heart radiation dose (mean heart dose) and total left anterior descending (LAD) radiation dose from the radiation treatment plan for each patient. Contouring and segmentation of the LAD was performed using computed tomographic planning scans according to a cardiac contouring atlas as previously described.[21] The proximal LAD consists of the proximal one-fifth of the vessel from the end of the left main coronary artery, the mid segment consists of the mid two-fifths of the vessel descending anterolaterally in the anterior interventricular groove, and the distal segment consists of the distal two-fifths of the vessel running in the interventricular groove, extending to the apex. Radiation doses were converted to a radiobiological equivalent dose of 2 Gy (EQD2) using an α/β ratio of 2.

All continuous data were assessed for normality using the Shapiro-Wilk test, along with visualization with Q-Q plots. Continuous data derived from a Gaussian distribution are reported as mean (± SD); otherwise data are reported as median (interquartile range). Normally distributed data were analyzed using the Student's *t* test; the nonparametric Mann-Whitney U (Wilcoxon rank-sum) test was used to compare distributions between groups. Categorical data were analyzed utilizing the Fisher's exact test. Mean heart dose and LAD doses were correlated with coronary disease on CCTA using univariate and multivariable logistic regression analysis. Receiver-operating-characteristic analysis with Youden index maximization was used to identify potential radiation dose constraints for mean heart dose and LAD doses. All statistical analyses were 2-sided and p-values < 0.05 were considered significant.

Results

A total of 94 women were included in the final analysis (Figure 1): 49 and 45 patients with LBC and RBC, respectively. Baseline characteristics are reported in Table 1 and no significant differences were noted between groups. Patients with LBC had significantly higher rates of coronary disease after radiotherapy compared with RBC patients (83% vs 46% respectively, [$p < 0.005$]) and per artery (Figure 2). Compared with RBC patients, the odds ratio for detecting any coronary disease following left sided radiotherapy was 5.80 (95% Confidence Interval [CI], 2.2 to 12.1), and 5.5 (95% CI, 2.2 to 13.7) for detecting LAD disease. There was more disease in the LAD (76% vs 31% [$p < 0.001$]), left circumflex (33% vs 6.7% [$p = 0.004$]), and right coronary artery (37% vs 13% [$p = 0.018$]) in the LBC cohort. When divided by segments, the proximal (70% vs 35% [$p < 0.004$]) and mid LAD (43% vs 20% [$p = 0.02$]) had a significantly higher prevalence of disease (Figure 3). Similarly, the proximal and mid right coronary artery had higher disease in the LBC patients. There was no difference in coronary disease detection in the left main artery or the left circumflex (Table 2).

Mean heart dose and mean LAD dose were calculated for both groups; mean dose to the proximal, mid, and distal LAD were calculated for LBC patients only and are reported in Table 3. Univariate and multivariable logistic regression analyses were conducted to correlate mean heart

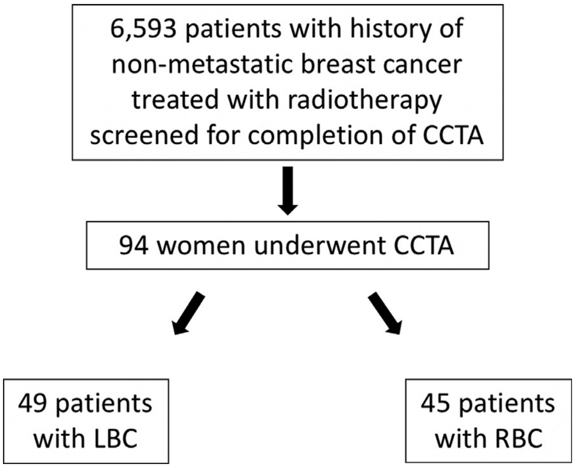

Figure 1. Flow-chart with study design and screening protocol. CCTA = coronary computed tomographic angiography; LBC = left-sided breast cancer; RBC = right-sided breast cancer.

Table 1
Baseline characteristics

Patient characteristics	Radiotherapy		
Variable	Left (n = 49)	Right (n = 45)	p Value
Age (Years)	69 (65-75)	70 (62-74)	> 0.9
Race			0.70
White	37 (76%)	37 (82%)	
Black	9 (18%)	6 (13%)	
Other	3 (6.1%)	2 (4.4%)	
BMI (kg/m^2)	29.9 (25.7-33.8)	27 (25-31)	0.07
Hyperlipidemia	26 (53%)	22 (49%)	0.80
Hypertension	31 (63%)	28 (62%)	> 0.9
Smoker	5 (10%)	4 (8.9%)	> 0.9
Aspirin use	30 (61%)	14 (31%)	< 0.05
Statin use	34 (69%)	17 (38%)	< 0.05
Beta-blocker use	26 (53%)	15 (33%)	0.08
Chemotherapy	21 (44%)	21 (49%)	0.80
Family history of premature coronary disease*	7 (14%)	9 (20%)	0.60
Time from radiotherapy to CCTA (years)	3.61 (2.25-6.27)	2.92 (1.62-5.68)	0.30

CCTA = computed tomographic angiography.
* Defined as onset before 55 years in father and 65 years in mother.

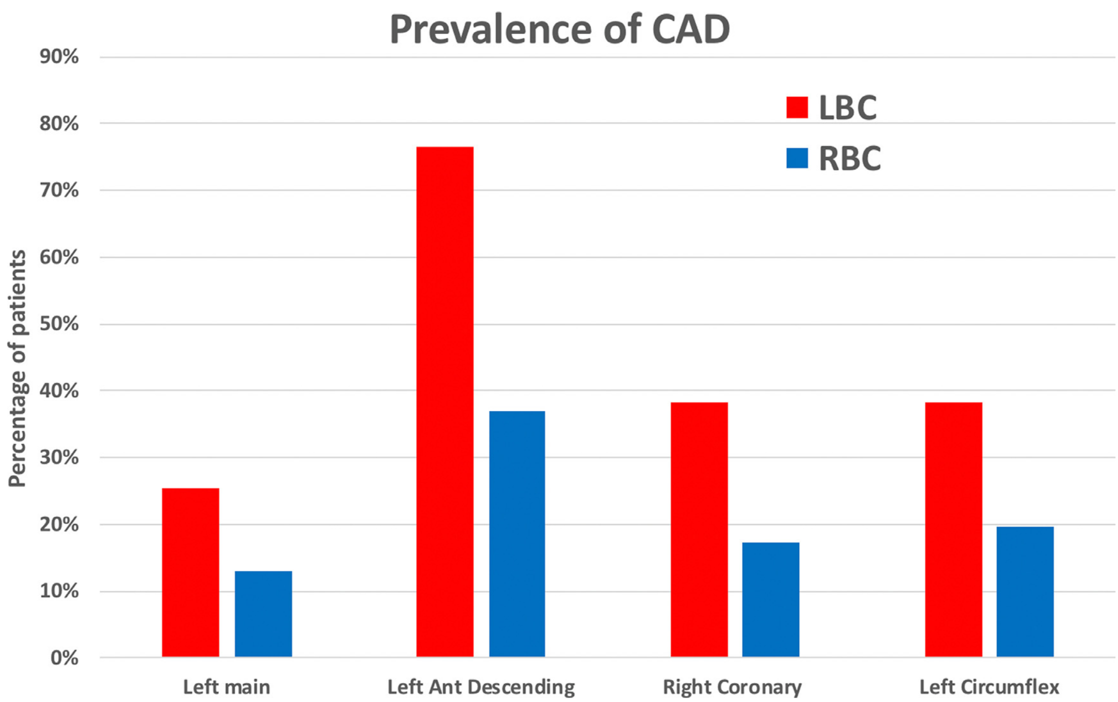

Figure 2. Prevalence of coronary disease by coronary artery, comparing right-sided breast cancer (RBC) patients and left-sided breast cancer (LBC) patients previously treated with radiation therapy. Ant = anterior.

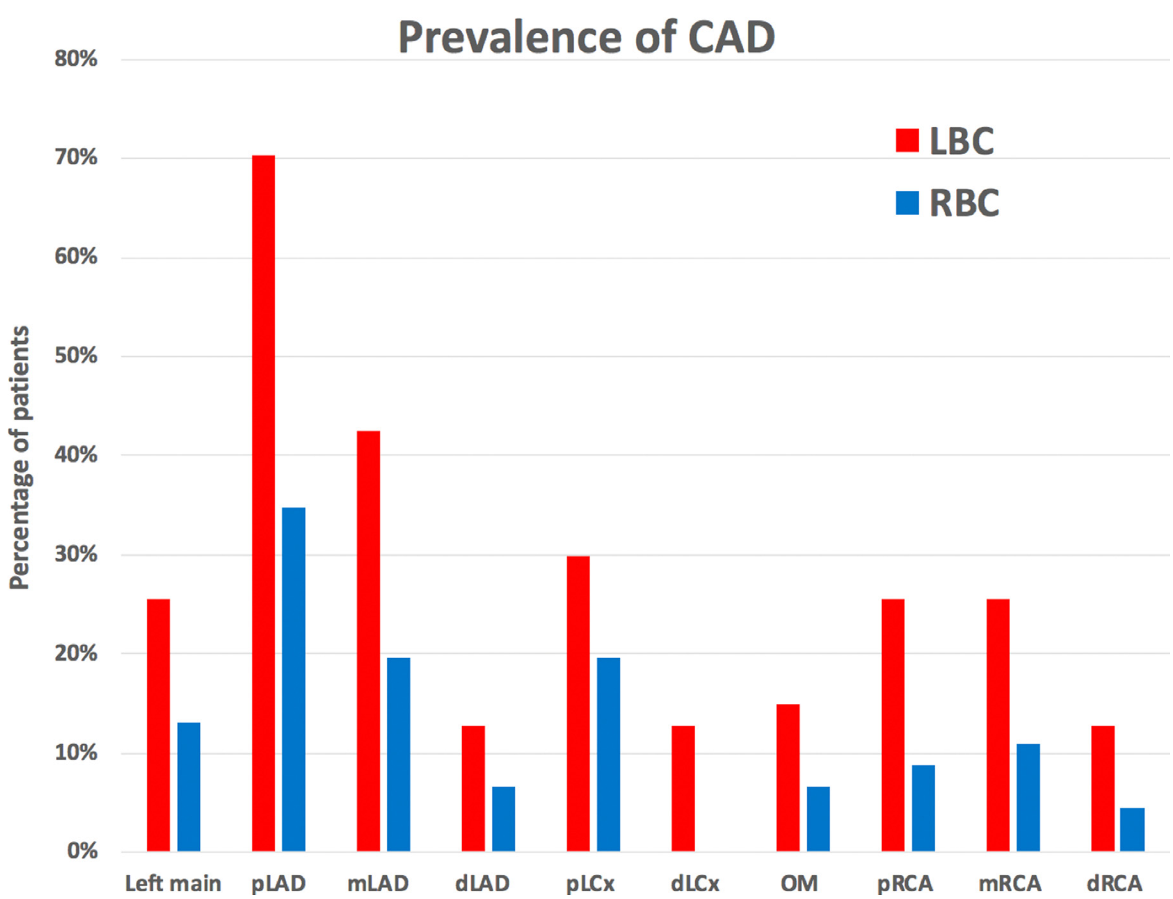

Figure 3. Prevalence of coronary disease by segment of coronary arteries in right-sided breast cancer (RBC) versus left-sided breast cancer (LBC) patients. pLAD = proximal left anterior descending; mLAD = mid left anterior descending; dLAD = distal left anterior descending; pLCx proximal left circumflex; dLCx = distal left circumflex; OM = obtuse marginal; pRCA = proximal right coronary artery; mRCA = mid right coronary artery; dRCA = distal right coronary artery.

Table 2
Coronary artery disease in right and left sided breast cancer patients

Coronary Disease by Segment	Radiotherapy		
Segments	Left (n = 49)	Right (n = 45)	p Value
Left main	26%	13%	0.13
Left anterior descending	77%	37%	0.005
Right coronary	38%	17%	0.025
Left circumflex	38%	20%	0.05
Proximal left anterior descending	70%	35%	0.004
Mid left anterior descending	43%	20%	0.02
Distal left anterior descending	13%	7%	0.31
Proximal circumflex	30%	20%	0.25
Distal circumflex	13%	0%	NA
Obtuse marginal	15%	7%	0.19
Proximal right	26%	9%	0.03
Mid right	26%	11%	0.07
Distal right	13%	4%	0.15

dose and LAD doses with ≥ grade 3 disease (≥ 50% stenosis) and for the presence of any LAD disease. Chemotherapy use, BMI ≥35 kg/m^2, family history (cardiovascular disease with onset before 55 and 65 years in the father and mother, respectively), diabetes, age ≥60 years, hypertension, hyperlipidemia, chronic kidney disease, and smoking history were included in the multivariate analysis. Mean LAD dose and mean heart dose strongly correlated with the presence of any coronary disease with and ≥ 3 grade stenosis (Tables 4 and 5).

Receiver operator curves were generated to determine potential radiation dose constraints to minimize the development of ≥ grade 3 stenosis. The analysis showed excellent specificity and sensitivity as shown in Figure 4. Apparent thresholds were ≥ 1.6 (C-index 0.81 [p = 0.03]), and ≥ 2.9 Gy (C-index 0.79 [p = 0.04]) for mean heart dose and mean LAD dose for ≥ grade 3 stenosis, respectively.

In LBC patients with LAD disease (n = 37), the proximal LAD was involved in 34 patients (92%), mid LAD in 20 patients (52%), and distal LAD in 6 patients (17%). Mixed calcified lesions were present in 16 patients (43%) compared with 21 patients with non-calcified lesions only (57%). There was no difference in the presence of calcified plaque compared with RBC patients, 58% vs 76%, respectively, p = 0.22. High-risk plaque features, as defined previously, were present in the LAD in 6 patients. The mean age of this high-risk cohort was 66.6 years. The median mean heart dose was 1.97 (1.64 to 2.59) Gy and median time from radiotherapy to CCTA was 2.7 (1.2 to 3.4) years. One of these patients underwent percutaneous coronary intervention.

Table 5
Logistics regression correlating radiation dose per Gy to ≥ grade 3 LAD disease

	Univariate analysis		
	OR	95% CI	p Value
Mean LAD Dose	1.08	1.00, 1.17	0.049
Mean Heart Dose	1.49	1.03, 2.17	0.029

CI = Confidence interval; Gy = Gray; LAD = left anterior descending; OR = Odds Ratio.

[1]Multivariable analysis included age ≥ 60 years, BMI ≥ 30 kg/m^2, family history of coronary disease defined as having at least 1 parent with premature cardiovascular disease with onset before 55 and 65 years in the father and/or mother respectively, use of chemotherapy and history of diabetes, hypertension, hyperlipidemia, chronic kidney disease, and smoking history.

Discussion

To our knowledge this is the first study to evaluate coronary disease using CCTA in women previously treated with radiotherapy for breast cancer. We detected a higher incidence of coronary disease in patients treated for LBC compared with a matched group of patients treated for RBC who served as controls. RBC is an appropriate comparator

Table 3
Radiation dose in right and left sided breast cancer patients

Mean Radiation Doses	Radiotherapy		
Dose	Left (n = 49)	Right (n = 45)	p Value
Mean Heart Dose (Gy)	1.93 (1.56-2.64)	0.99 (0.69-1.25)	< 0.001
Mean LAD Dose (Gy)	5.2 (2.8-12.8)	0.7 (0.5-1.0)	< 0.001
Mean Proximal LAD Dose (Gy)	2.30 (1.86-3.35)	-	
Mean Mid LAD Dose (Gy)	6 (4-16)	-	
Mean Distal LAD Dose (Gy)	6 (3-22)	-	

Gy = Gray; LAD = left anterior descending.

Table 4
Logistics regression correlating radiation dose per GY to > grade 0 LAD disease

	Univariate analysis			Multivariate analysis*		
	OR	95% CI	p Value	OR	95% CI	p Value
Mean LAD Dose	1.21	1.08, 1.40	0.005	1.08	0.99, 1.20	0.07
Mean Heart Dose	1.95	1.22, 3.62	0.017	1.45	0.98, 2.24	0.06

CI = Confidence interval; Gy = Gray; LAD = left anterior descending; OR = Odds Ratio.

* Multivariable analysis included use of chemotherapy, history of diabetes, hypertension, hyperlipidemia, kidney disease, and smoking.

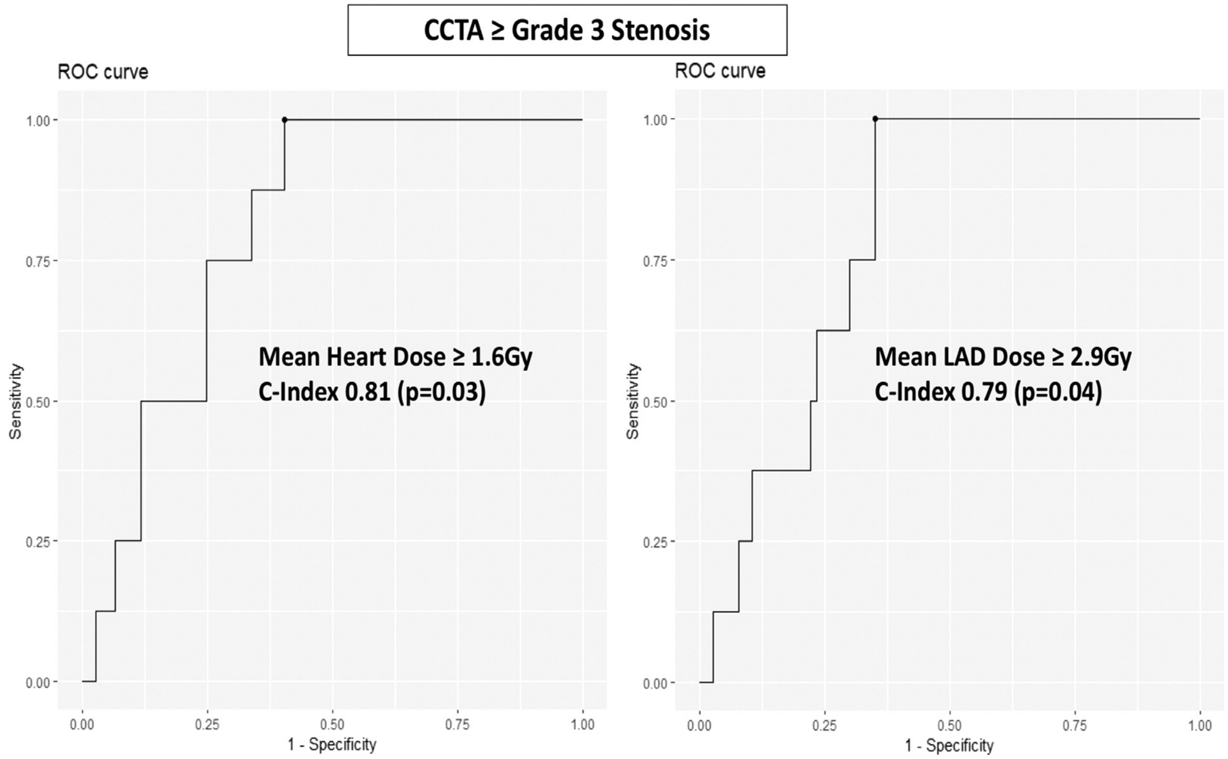

Figure 4. Receiver-operating-characteristic curves with suggested constraints of 1.6, and 2.9 Gy for mean heart dose and mean LAD dose for ≥ grade 3 stenosis, respectively. Gy = gray; LAD = left anterior descending.

group as these patients have a much lower mean heart dose and have similar co-morbidities as well as concomitant chemotherapy. LBC patients had a 5-fold higher incidence of coronary disease compared with RBC patients. This was primarily driven by LAD disease with an odds ratio of 5.5 (95% CI, 2.2 to 13.7), and is consistent with previous studies which demonstrated higher LAD disease in patients treated with left sided radiation. However, in these studies, the effects were seen late (>10 years) after treatment compared with our results with a median time from radiotherapy to detected coronary disease of 3.6 years.[9,22] This difference may be due to the coronary disease detection methods employed, as CCTA is more sensitive in detecting coronary disease as compared with coronary angiography and functional stress testing.[12]

This is also the earliest investigation to correlate radiation dose to coronary disease detection by CCTA. Logistic regression analysis showed a strong correlation between mean LAD dose and mean heart dose with the detection of disease in the LAD. For each mean Gy increase in LAD dose, the odds of detecting any disease increased by 21% and increased 8% for detecting ≥ grade 3 stenosis. For each mean Gy increase in mean heart dose the odds of detecting any disease increased 95% and increased 49% for detecting ≥ grade 3 stenosis.

Our analysis supports the notion that the radiation dose to the heart should be as low as reasonably achievable for breast cancer patients. The receiver operator curve analysis suggests ~ 1.5 Gy and ~3 Gy as potential constraints for mean heart dose and mean LAD dose to minimize the risk of developing ≥ grade 3 LAD stenosis. These values are suggested as a general frame to consider when developing radiation treatment plans and must be individualized according to each patient's risk of disease recurrence and treatment fields. For example, such constraints are generally achievable for RBC patients, even with inclusion of internal mammary lymph nodes in the treatment fields. For LBC, the delineated constraints are realistic for most patients who underwent whole breast radiotherapy. However, for patients with tumors in the lower inner quadrant of the breast, or those for whom internal mammary lymphatics are targeted, one may have to accept a higher mean heart dose or LAD dose.

Interestingly, we detected more plaque in the right coronary artery in LBC patients than in RBC patients. This is counterintuitive as RBC patients receive higher doses of radiation to the right coronary artery than LBC patients. One possible explanation is that mean heart dose is more closely correlated with disease formation than dose to each individual artery. Alternatively, via the abscopal effect, the effects of radiation may extend beyond the area of treatment. This is presumably due to activation of immune cells which in turn have effects on neighboring tissues to create an inflammatory response.[23] The absolute numbers of patients with right coronary artery disease was low, 18 vs 8 in the LBC and RBC groups, respectively, and additional studies with larger numbers of patients are needed to verify these results.

CCTA offers advantages over conventional exercise stress testing and coronary angiography in that it characterizes plaque composition and detects the presence of high-risk plaque features. The presence of spotty calcification, low-attenuation plaque, or positive remodeling (Figure 5) have been shown to increase the risk of acute coronary syndrome by 9-fold.[24] In the LBC cohort, there was a higher incidence of patients with high-risk plaque features.

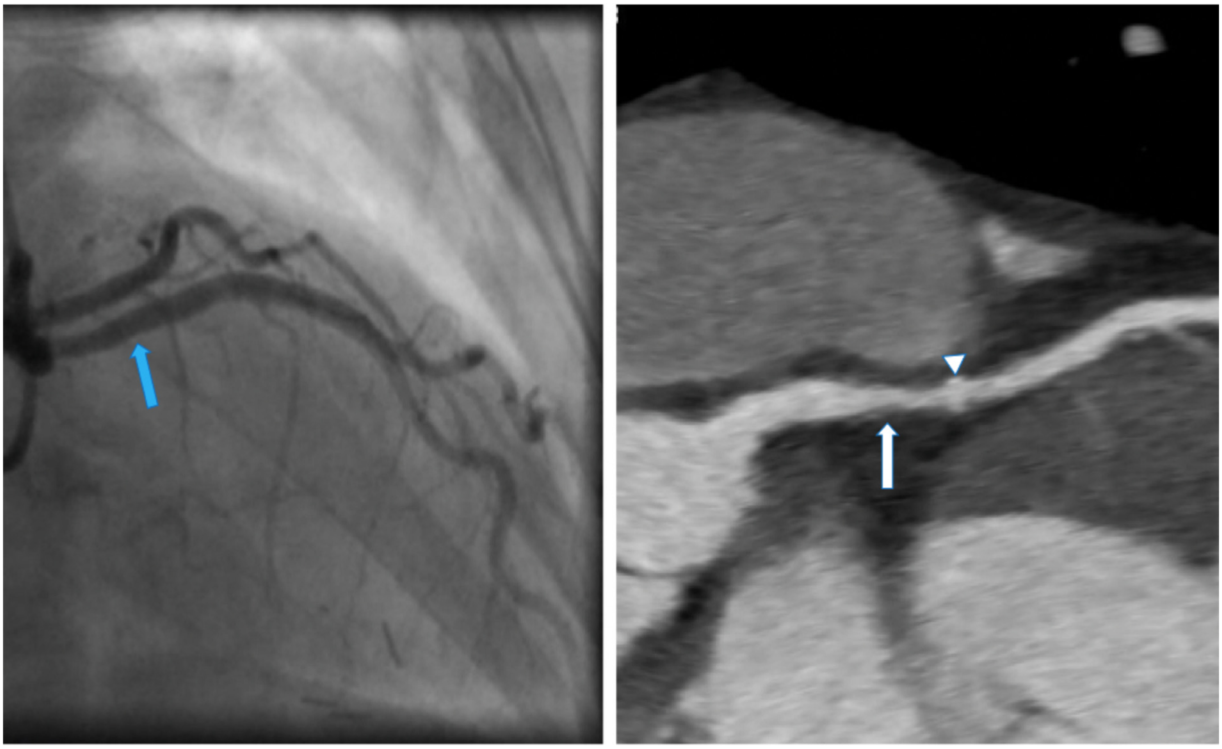

Figure 5. Coronary angiography compared to CCTA in the same patient. CCTA demonstrates high risk plaque features of positive remodeling (white arrow), spotty calcification (arrowhead), compared to same segment in LAD that appears normal using coronary angiography (blue arrow). CCTA = coronary computed tomographic angiography.

Although there was not a defined mortality end point for this study, previous studies have shown that increased coronary disease burden can lead to higher mortality rates.[25,26] Thus, localization and detection of coronary disease may prove to be of clinical utility, particularly in patients receiving higher radiation doses to potentially improve survival. Additionally, aggressive lifestyle modification and adjunctive medical therapy can be initiated earlier if coronary disease is detected by CCTA. Further study in larger numbers of patients will be needed to test this hypothesis.

We acknowledge several methodological limitations to our study. The indication for ordering the CCTA was not adjudicated and this may have led to selection bias of patients with coronary disease presenting with chest pain or other anginal equivalents. To counter this potential confounder, RBC patients were chosen as controls as they had CCTAs ordered in likely the same manner as LBC patients. Another potential limiting factor is the comparison of contrast enhanced CCTA disease to noncontrast radiation planning computed tomographic scans, which are unable to delineate vascular structures. The use of a standardized, previously validated protocol was utilized to address this issue. Lastly, this was a retrospective analysis and prospective studies will be needed to validate these findings.

In summary, patients treated with radiotherapy for LBC have a higher incidence of coronary disease when compared with a matched cohort of patients treated for RBC and these differences occurred earlier (~3.5 years post-treatment) than previously reported. Mean LAD radiation dose and mean heart dose strongly correlated with coronary disease, with a 21% higher incidence of disease in the LAD per Gy for mean LAD dose and a 95% higher incidence of disease in the LAD per Gy for mean heart dose. Early identification of coronary disease is critical as these findings may accelerate proactive prevention interventions and improve long-term cardiovascular outcomes in breast cancer survivors.

Authors contribution

Travis Tagami: Conceptualization, Methodology, Data collection, Writing. **Muayad F. Almahariq:** Conceptualization, Data collection, Statistical analysis. **Dinu V. Balanescu:** Data collection. **Thomas J. Quinn:** Statistical analysis. **Joshua T. Dilworth:** Conceptualization, Methodology. **Barry A. Franklin:** Supervision, Writing - Reviewing and Editing **Abhay Bilolikar:** Supervision, Writing - Reviewing, and Editing.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020;70:7–30.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, Cutter D, Davies C, Ewertz M, Godwin J, Gray R, Pierce L, Whelan T, Wang Y, Peto R. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378:1707–1716.

3. Darby S, McGale P, Peto R, Granath F, Hall P, Ekbom A. Mortality from cardiovascular disease more than 10 years after radiotherapy for breast cancer: nationwide cohort study of 90 000 Swedish women. *BMJ* 2003;326:256–257.
4. Hooning MJ, Botma A, Aleman BMP, Baaijens MHA, Bartelink H, Klijn JGM, Taylor CW, van Leeuwen FE. Long-term risk of cardiovascular disease in 10−year survivors of breast cancer. *J Natl Cancer Inst* 2007;99:365–375.
5. Bouillon K, Haddy N, Delaloge S, Garbay J-R, Garsi J-P, Brindel P, Mousannif A, Lê MG, Labbe M, Arriagada R, Jougla E, Chavaudra J, Diallo I, Rubino C, de Vathaire F. Long-term cardiovascular mortality after radiotherapy for breast cancer. *J Am Coll Cardiol* 2011;57:445–452.
6. McGale P, Darby SC. Commentary: A dose−response relationship for radiation-induced heart disease—current issues and future prospects. *Int J Epidemiol* 2008;37:518–523.
7. Wennstig AK, Garmo H, Isacsson U, Gagliardi G, Rintelä N, Lagerqvist B, Holmberg L, Blomqvist C, Sund M, Nilsson G. The relationship between radiation doses to coronary arteries and location of coronary stenosis requiring intervention in breast cancer survivors. *Radiat Oncol* 2019;14:40.
8. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, Correa C, Cutler D, Gagliardi G, Gigante B, Jensen M-B, Nisbet A, Peto R, Rahimi K, Taylor C, Hall P. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987–998.
9. Nilsson G, Holmberg L, Garmo H, Duvernoy O, Sjögren I, Lagerqvist B, Blomqvist C. Distribution of coronary artery stenosis after radiation for breast cancer. *J Clin Oncol* 2012;30:380–386.
10. Kolossváry M, Szilveszter B, Édes IF, Nardai S, Voros V, Hartyánszky I, Merkely B, Voros S, Maurovich-Horvat P. Comparison of quantity of coronary atherosclerotic plaques detected by computed tomography versus angiography. Am J *Cardiol* 2016;117:1863–1867.
11. Butler J, Shapiro M, Reiber J, Sheth T, Ferencik M, Kurtz EG, Nichols J, Pena A, Cury RC, Brady TJ, Hoffman U. Extent and distribution of coronary artery disease: a comparative study of invasive versus noninvasive angiography with computed angiography. *Am Heart J* 2007;153:378–384.
12. Foy AJ, Dhruva SS, Peterson B, Mandrola JM, Morgan DJ, Redberg RF. Coronary computed tomography angiography vs functional stress testing for patients with suspected coronary artery disease: a systematic review and meta-analysis. *JAMA Internal Medicine* 2017;177:1623–1631.
13. Motoyama S, Ito H, Sarai M, Kondo T, Kawai H, Nagahara Y, Harigaya H, Kan S, Anno H, Takahashi H, Naruse H, Ishii J, Hecht H, Shaw LJ, Ozaki Y, Narula J. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. *J Am Coll Cardiol* 2015;66:337–346.
14. Rademaker J, Schoder H, Ariaratnam NS, Strauss HW, Yahalom J, Steingart R, Oeffinger KC. Coronary artery disease after radiation therapy for Hodgkin's lymphoma: coronary CT angiography findings and calcium scores in nine asymptomatic patients. *AJR Am J Roentgenol* 2008;191:32–37.
15. Lloyd-Jones DM, Nam B-H, D'Agostino RB, Sr Levy D, Murabito JM, Wang TJ, Wilson PWF, O'Donnell CJ. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. *JAMA* 2004;291:2204–2211.
16. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cogain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117:743–753.
17. Alkhawam H, Nguyen J, Sayanlar J, Sogomonian R, Desai R, Jolly J, Vyas N, Syed U, Homsi M, Rubinstein D. Coronary artery disease in patients with body mass index ≥ 30 kg/m^2: a retrospective chart analysis. *J Community Hosp Intern Med Perspect* 2016;6:31483.
18. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després J-P, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, NIchol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB, American Heart Association Statistics Committee and Stroke Subcommittee. Heart disease and stroke statistics □2015 update: a report from the American Heart Association. *Circulation* 2015;131:e29–e322.
19. Leipsic J, Abbara S, Achenbach S, Cury R, Earls JP, Mancini GJ, Nieman K, Pontone G, Raff GL. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr* 2014;8:342–358.
20. Hecht HS, Achenbach S, Kondo T, Narula J. High-risk plaque features on coronary CT angiography. *JACC: Cardiovasc Imaging* 2015;8:1336–1339.
21. Duane F, Aznar MC, Bartlett F, Cutter DJ, Darby SC, Jagsi R, Lorenzen EL, Mc Ardle O, McGale P, Myerson S, Rahimi K, Vivekanandan S, Warren S, Taylor CW. A cardiac contouring atlas for radiotherapy. *Radiother Oncol* 2017;122:416–422.
22. Correa CR, Litt HI, Hwang W-T, Ferrari VA, Solin LJ, Harris EE. Coronary artery findings after left-sided compared with right-sided radiation treatment for early-stage breast cancer. *J Clin Oncol* 2007;25:3031–3037.
23. Bonanno L, Pavan A, Attili I, Pasello G, Guarneri V. Immunotherapy in SCLC: exceptional clinical benefit and abscopal pneumonitis after radiotherapy. *J Thorac Oncol* 2019;14:e5–e7.
24. Puchner SB, Liu T, Mayrhofer T, Truong QA, Lee H, Fleg JL, Nagurney JT, Udelson JE, Hoffmann U, Ferencik M. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. *J Am Coll Cardiol* 2014;64:684–692.
25. Lin FY, Shaw LJ, Dunning AM, Labounty TM, Choi J-H, Weinsaft JW, Koduru S, Gomez MJ, Delago AJ, Callister TQ, Berman DS, Min JK. Mortality risk in symptomatic patients with nonobstructive coronary artery disease: a prospective 2-center study of 2,583 patients undergoing 64-detector row coronary computed tomographic angiography. *J Am Coll Cardiol* 2011;58:510–519.
26. Nowbar AN, Gitto M, Howard JP, Francis DP, Al-Lamee R. Mortality from ischemic heart disease. *Circ Cardiovasc Qual Outcomes* 2019;12:e005375.