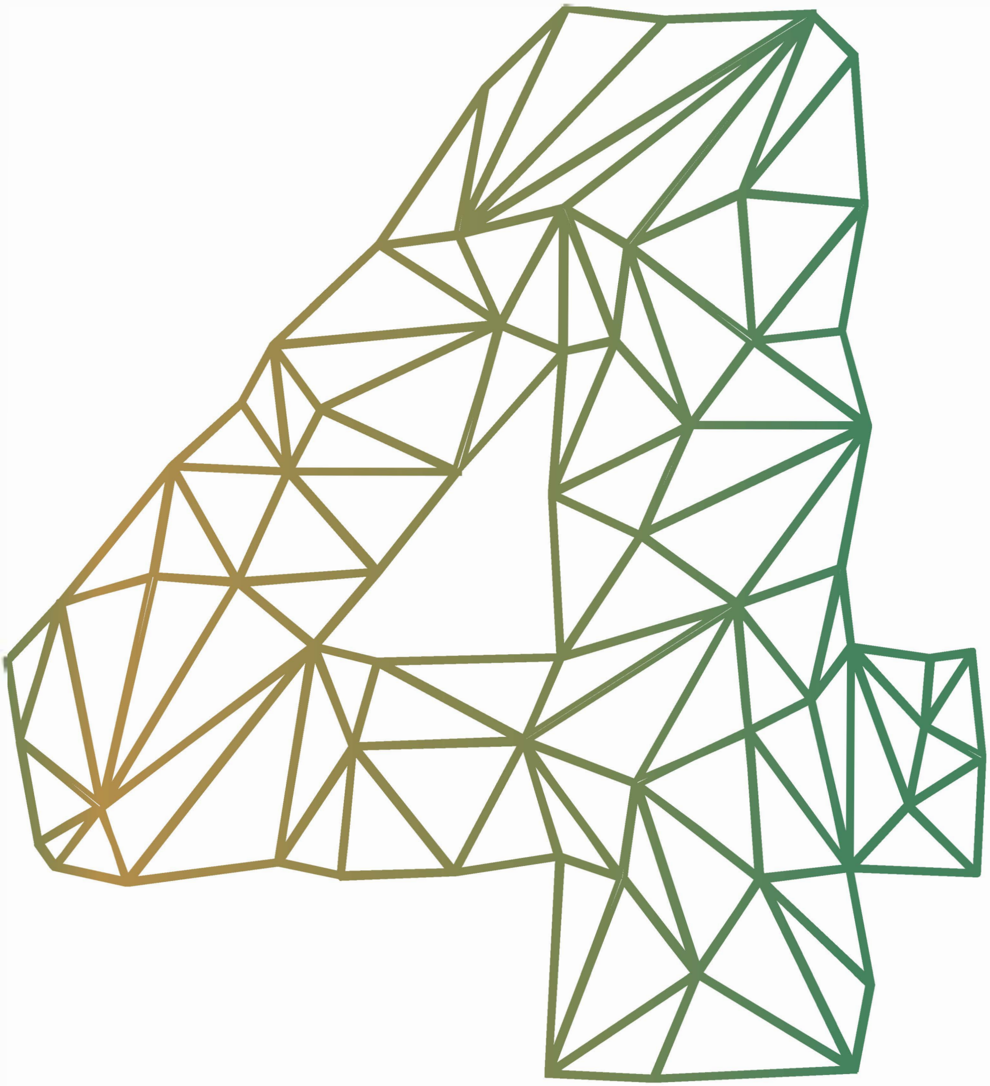
University of Groningen

Radiation-induced cardiac toxicity in breast cancer patients

van den Bogaard, Veerle

DOI:
10.33612/diss.144684776

Publication date:
2020



IS THE CORONARY ARTERY CALCIUM SCORE ASSOCIATED WITH ACUTE CORONARY EVENTS IN BREAST CANCER PATIENTS TREATED WITH RADIOTHERAPY?

C.T.G. Roos
V.A.B. van den Bogaard
M.J.W. Greuter
R. Vliegenthart
E. Schuit
J.A. Langendijk
A. van der Schaaf
A.P.G. Crijns
J.H. Maduro

Radiotherapy and Oncology. 2018;126(1):170-176.

ABSTRACT

Background and purpose

The main objective of this study was to test whether pre-treatment coronary artery calcium (CAC) was associated with the cumulative incidence of acute coronary events (ACE) among breast cancer (BC) patients treated with postoperative radiotherapy (RT).

Material and methods

The study population consisted of 939 consecutive female BC patients treated with RT. The association between CAC and ACE was tested using Cox-proportional hazard models. Known risk factors for ACE and the mean heart dose (MHD), collected from three-dimensional computed tomography planning data, were tested for confounding.

Results

CAC scores varied from 0 to 2,859 (mean 27.3). The 9-year cumulative incidence of ACE was 3.2%, this was significantly associated with the pre-treatment CAC score. After correction for confounders, age, history of ischemic heart disease, diabetes, Body Mass Index ≥30, MHD, hypercholesterolemia and hypertension, the hazard ratio for ACE for the low and the combined intermediate and high CAC score category were 1.42 (95%CI: 0.49-4.17; $p = 0.519$) and 4.95 (95%CI: 1.69-14.53; $p = 0.004$) respectively, compared to the CAC zero category.

Conclusions

High pre-treatment CAC is associated with ACE in BC patients treated with postoperative RT, even after correction for confounding factors such as MHD.

INTRODUCTION

Survival rates of breast cancer (BC) patients have gradually improved.[1] This improvement in survival is partly due to intensified treatment, such as radiotherapy (RT) and the use of more effective systemic agents.[2,3] Due to these higher survival rates, more BC patients are at risk of developing treatment-related side effects, such as radiation-induced cardiac toxicity. Although the introduction of more advanced radiation techniques has led to a substantial decrease in the radiation dose to the heart, in some cases the heart still receives a considerable radiation dose, which may contribute to the development of cardiac toxicity.[4] Recent studies showed that the risk of acute coronary events (ACE) in the first 9 years of follow-up increases by ~16% per Gray (Gy) of mean heart dose (MHD).[5,6] These studies also indicated that the absolute excess risk induced by RT strongly depends on baseline cardiovascular risk factors. Therefore, it becomes increasingly important for radiation oncologists to identify which baseline factors are important for BC patients. This will facilitate calculation of the absolute excess risk of radiation-induced ACE in individual patients. This information can be used to select BC patients for primary or secondary preventive measures.

The amount of coronary artery calcium (CAC), as determined from Computed tomography (CT), is a well-established and reliable early predictor of ACE in the general population.[7,8,9] To establish the amount of CAC, deposits of calcium in the coronary arteries are quantified according to the Agatston score (AS).[10] Higher CAC scores correspond to a higher risk of ACE.[7,8,9,10] In general, CAC is measured using diagnostic electrocardiogram (ECG) triggered CT scans. However, CAC scores can be obtained using non-triggered CT scans as well.[11,12,13,14,15] For RT treatment planning, BC patients generally undergo a non-triggered CT scan, which can be used to determine the baseline CAC value.

The main objective of this study was to test the hypothesis that pre-treatment CAC scores, based on non-triggered planning CT scans, are associated with the cumulative incidence of ACE among BC patients treated with postoperative RT.

MATERIAL AND METHODS

Study population

The population of this retrospective study was composed of a consecutive series of female BC patients who were treated between January 2005 and December 2008 at the University Medical Center, Groningen, The Netherlands. These patients were treated for invasive BC stages I-III or ductal carcinoma in situ (DCIS). Treatment consisted of curative breast-conserving surgery followed by RT. A dose of 50.4 Gy was prescribed for the whole breast in 28 fractions, with a simultaneous integrated boost dose of 14 or 16.8 Gy in the same 28 fractions, depending on pathologic risk factors.[6] Patients were only included if their treatment planning CT scans made prior to RT were available. Patients were excluded if they had a medical history of cancer (except for non-melanoma skin cancer) or had received prior RT or prior chemotherapy treatment. Patients with a history of cardiac disease were not excluded due to the fact that our aim was to develop an association model applicable to the general BC population. In contrast to a prediction model, an association model only describes the relationship between one predictor (i.e. CAC score) and the outcome (i.e. ACE) after correction for confounding factors. Patient characteristics, follow up data, information on cardiovascular risk factors and ACE were retrospectively extracted from patient hospital records. Missing data were supplemented with information derived from the general practitioner records after obtaining written informed consent from the surviving patients. Information about deceased patients was provided by the general practitioners, as in accordance with Dutch regulations. The following baseline patient characteristics were included in the analysis: age, history of ischemic heart disease (International Classification of Diseases, 10th Revision [ICD-10] codes I20-I25), other heart diseases (ICD-10 codes I30-I52), diabetes of any type (ICD-10 E10-E14), chronic obstructive pulmonary disease (COPD) of any type (ICD-10 J44), smoking status, body mass index (BMI), hypertension (ICD-10 I10-I15), hypercholesterolemia (ICD-10 E78.0) and the MHD. Ischemic heart disease, other heart disease, diabetes and COPD were considered when the diagnosis was stated in patients' medical charts. Smoking status was stratified into currently smoking or not smoking at baseline. BMI was stratified into two categories <30 and ≥30 kg/m^2. Hypertension was considered when diagnosis was stated (systolic blood pressure ≥140 mmHg and/or when diastolic blood pressure ≥90 mmHg) or when antihypertensive medication was used. Hypercholesterolemia was considered present if identified at clinical diagnosis or when statins were used (unless they were preventively used because of present cardiovascular risk factors such as diabetes). The MHD in Gray (Gy) was collected from three-dimensional (3D) conformal RT treatment plans based on the individual planning CT scans. The primary endpoint was the occurrence of ACE defined as diagnosis of myocardial infarction (ICD-10 I21-I24), coronary revascularization or death from ischemic heart disease (ICD-10 I20-I25). The study design was approved by the medical ethics committee of the University Medical Center Groningen.

Data collection and procedures

The CT scans used in this study were non-triggered CT scans (SOMATOM Sensation Open, 40 slice, Siemens Medical Inc.) acquired for RT treatment planning. The scanning protocol for the planning CT scans was different from that used in a dedicated CAC scan procedure, mandating correction of the CAC scores. For the correction of the CAC scores, a thorax phantom with calibration inserts was scanned (QRM Thorax & QRM-CCI, QRM, Germany) according to both the diagnostic CAC protocol and the RT planning CT protocol (Supplementary material table 1). Rings of fat were placed around the phantom to represent patients of medium and large size.[16] Thereafter, the different amounts of calcium per calcium insert were determined from the multiple CT scans and quantified with the Aquarius software (iNtuition edition, v4.4.11.412.8585, Tera Recon, Inc.) according to the AS. Settings for the Aquarius software can be found in the supplementary material table 2. The correction formula was obtained by plotting the CAC scores from the calcium inserts of the QRM phantom from the planning CT scan against that of the diagnostic scan (Supplementary material: table 3 and Figs. 1-4).

To establish the CAC scores of the BC patients, the calcified lesions were selected and labeled per coronary artery by hand by a single trained technician. Subsequently, the software calculated the total CAC score. For patients with planning CT scans on which CAC was difficult to assess, experienced researchers of the Radiology department were consulted. Although patients with coronary stents and/or surgical clips due to cardiac surgery are at higher risk of ACE, these patients had to be excluded because CAC measurements were not possible due to artifacts. The CAC scores of the BC cohort were transformed using the correlation formulas described above (Supplementary material table 3). The formulas were only used for patients with a CAC score higher than zero.

Statistics

To provide clinically relevant and easily applicable results, we first classified the CAC score into widely used clinical CAC score categories: CAC zero (0), low CAC (>0-<100), intermediate CAC (100-400) and high CAC (≥400).[7,15,17,18,19,20] However, due to limited number of events in the high CAC score category we combined the intermediate and high CAC into one variable to maintain sufficient statistical power.

The cumulative incidence of ACE was calculated from the date of the first RT treatment using the Kaplan Meier method. Patients were censored when receiving a new radiation treatment, at time of death or at the end of the follow-up period.

The association between the CAC score and the cumulative incidence of ACE was first tested with a univariable Cox-regression analysis. Thereafter, all cardiovascular risk factors and the MHD were examined as possible confounders in a multivariable Cox-regression association model with the CAC score category as the main determinant. This was done by iteratively adding these risk factors to the univariable Cox-regression analysis. The risk factor that caused the largest

1 2 3 4 5 6 7 8 &

change in the regression coefficients of the determinant (with a minimum of 10%) was selected as a confounder. This process was repeated with the remaining risk factors until the change in regression coefficients of the determinant was less than 10%. Data were analyzed using SPSS (IBM SPSS Statistics, Version 22, IBM Corp).

RESULTS

Patient characteristics

The consecutive BC cohort consisted of 1,032 eligible patients. Fifty-six patients were excluded because they had been scanned with a different CT scanner, 8 because of missing CT data, 23 because of deviating CT scan protocol and 6 patients were excluded because their coronary stents caused too many artifacts for reliable CAC scoring. Eventually, a total of 939 patients were included in the analysis (table 1). The mean age was 58.4 years (range: 26-84 years). The median follow-up was 7.5 years. The CAC scores were highly skewed and ranged from 0 to 2,859, with a mean CAC score of 27.3 and a median of 0. Most patients (78.9%) were in the CAC zero category, 14.5% in the low CAC category, 5.2% of the patients were in the intermediate CAC category and 1.4% were in the high CAC category (Supplementary material table 4).

Association between CAC and ACE

In total, 29 out of 939 patients developed ACE during follow-up: 13 out of 741 patients in the CAC zero category, 6 out of 136 patients in the low CAC category, 7 out of 49 patients in the intermediate CAC category and 3 out of 13 patients in the high CAC category. Due to the limited number of events, we combined the intermediate with the high CAC category, to maintain sufficient statistical power. The 9-year cumulative incidence of ACE was 3.2% (figure 1). The cumulative incidence of ACE per CAC score category is shown in figure 2. The univariable Cox-regression analysis showed a significant association between the CAC score and the cumulative incidence of ACE (table 2). This is true for all CAC categories; the comparison of the low CAC versus CAC zero category (HR: 2.75; 95%CI: 1.03-7.32, $p = 0.043$) and for the comparison of the combined intermediate and high CAC versus CAC zero category (HR: 11.57; 95%CI: 5.00-26.81, $p < 0.001$).

Multivariable analysis showed that age, history of ischemic heart disease, diabetes, BMI ≥30, MHD, hypercholesterolemia and hypertension were confounders for the association between CAC and the cumulative incidence of ACE. After correction for these confounders in the Cox-regression association model, the hazard ratios for the low and the combined intermediate and high

Table 1. Patient characteristics at baseline.

Characteristic	N	%
Total	939	100
Age in years, mean (range)	58.4 (26-84)	
History of (cardiac) comorbidity		
History of ischemic heart disease*		
Yes	36	3.8
No	903	96.2
Heart failure		
Yes	6	0.6
No	933	99.4
Cardiac valve disease(s)		
Yes	29	3.1
No	910	96.9
Arrhythmia(s)		
Yes	56	6.0
No	883	94.0
Cardiomyopathy		
Yes	5	0.5
No	934	99.5
Myocarditis, endocarditis and/or pericarditis		
Yes	0	0
No	939	100
Hypertension		
Yes	288	30.7
No	651	69.3
Hypercholesterolemia		
Yes	144	15.3
No	795	84.7
Chronic obstructive pulmonary disease[§]		
Yes	51	5.4
No	888	94.6
Pulmonary embolism		
Yes	12	1.3
No	927	98.7
Diabetes[¶]		
Yes	66	7.0
No	873	93.0
Lifestyle risk factors at baseline		
Current smoking		
Yes	205	21.8
No	734	78.2

Table 1. (continued)

Characteristic	N	%
BMI (kg/m2)		
BMI <30	852	90.7
BMI ≥30	87	9.3
Tumor characteristic		
Pathological T-stage		
T1	686	73.1
T≥2	246	26.2
Unknown	7	0.7
Pathological N-stage		
N0	628	66.9
N1	216	23.0
N2	50	5.3
N3	9	1.0
Nx / unknown	36	3.8
Laterality of the breast		
Right	476	50.7
Left	463	49.3
Systemic treatment		
Chemotherapy only	103	11.0
Endocrine therapy only	160	17.0
Chemotherapy + endocrine therapy	239	46.5
Radiotherapy		
MHD (Gy)		
Total	3.8	
Median	2.36	
Range	0.51-15.25	

Abbreviations: ACE, acute coronary events; BMI, body mass index; MHD, mean heart dose; Gy, Gray.
* History of ischemic heart disease was defined when myocardial infarction, coronary revascularisation or angina was documented in the patient record.
§ COPD with any type of GOLD-class.
¶ Any type of diabetes.

CAC categories versus the CAC zero category were 1.42 (95%CI: 0.49-4.17, p = 0.52) and 4.95 (95%CI: 1.69-14.53, p = 0.004), respectively (table 2).

DISCUSSION

This study showed that a high CAC score (CAC ≥ 100) assessed with a non-triggered planning CT scan is associated with ACE in a BC population treated

1
2
3
4
5
6
7
8
&

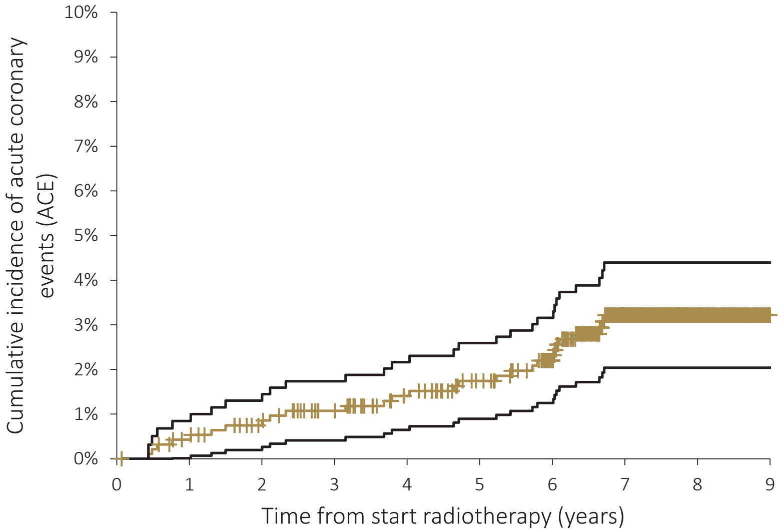
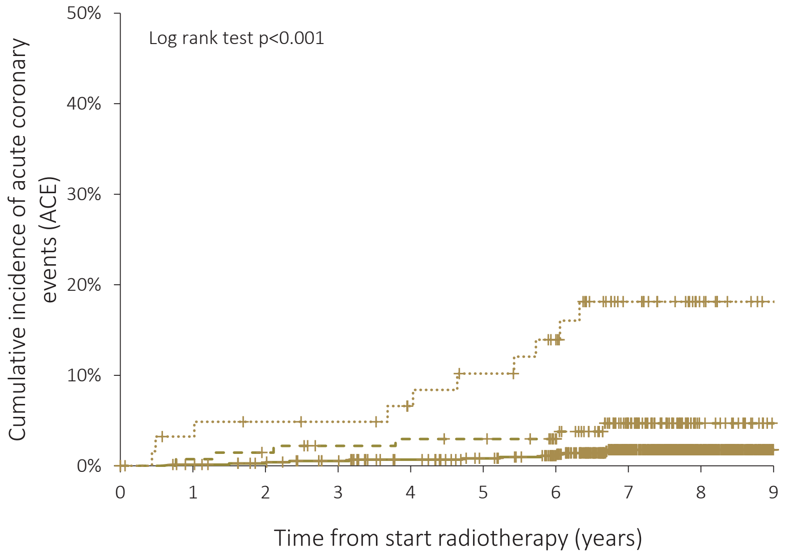


Figure 1. Cumulative incidence with 95% confidence interval of acute coronary events in the entire breast cancer population.



Number of patients at risk

Intermed + high CAC	62	59	57	56	52	49	44	27	13	4
Low CAC	136	135	133	129	128	127	120	86	30	12
CAC zero	741	736	728	718	703	688	668	499	279	73

Figure 2. Cumulative incidence of acute coronary events per coronary artery calcium (CAC) score category.

Table 2. Cox-regression association model for the cumulative incidence of acute coronary events for the different coronary artery calcium (CAC) categories, compared to the CAC zero category. Age, history of ischemic heart disease, diabetes, BMI ≥30, mean heart dose, hypercholesterolemia and hypertension were identified as confounders for the association between CAC and the cumulative incidence of acute coronary events.

Description	β	Change of β	HR	95% CI HR	*P*
Not corrected					
CAC zero (reference)			1		
Low CAC	1.01		2.75	1.03-7.32	0.043
Intermediate + high CAC	2.45		11.57	5.00-26.81	< 0.001
Corrected for age					
CAC zero (reference)			1		
Low CAC	0.5	-50.50%	1.65	0.60-4.54	0.331
Intermediate + high CAC	1.51	-38.40%	4.55	1.72-12.04	0.002
Age			1.08	1.03-1.13	0.001
Corrected for age and history of ischemic heart disease					
CAC zero (reference)			1		
Low CAC	0.37	-26.00%	1.44	0.52-4.03	0.486
Intermediate + high CAC	1.27	-15.90%	3.57	1.32-9.69	0.012
Age			1.07	1.03-1.12	0.002
History of ischemic heart disease			3.52	1.40-8.86	0.007
Corrected for age, history of ischemic heart disease and diabetes					
CAC zero (reference)			1		
Low CAC	0.27	-27.00%	1.31	0.46-3.70	0.611
Intermediate + high CAC	1.39	9.40%	4.02	1.47-10.98	0.007
Age			1.07	1.20-1.12	0.005
History of ischemic heart disease			3.32	1.31-8.40	0.011
Diabetes			2.73	1.07-6.97	0.036
Corrected for age, history of ischemic heart disease, diabetes and BMI≥30					
CAC zero (reference)			1		
Low CAC	0.36	33.30%	1.44	0.51-4.09	0.494
Intermediate + high CAC	1.48	6.50%	4.39	1.60-12.09	0.004
Age			1.07	1.02-1.12	0.004
History of ischemic heart disease			3.3	1.32-8.28	0.011
Diabetes			2.6	1.02-6.66	0.046
BMI≥30			1.99	0.66-5.99	0.219

Table 2. (continued)

	β	Change of β	HR	95% CI HR	*P*
Corrected for age, history of ischemic heart disease, diabetes, BMI≥30 and mean heart dose					
CAC zero (reference)			1		
Low CAC	0.47	30.60%	1.59	0.55-4.63	0.393
Intermediate + high CAC	1.61	8.80%	4.99	1.69-14.77	0.004
Age			1.07	1.01-1.11	0.013
History of ischemic heart disease			3.66	1.45-9.21	0.006
Diabetes			2.88	1.10-7.49	0.031
BMI≥30			2.15	0.70-6.63	0.182
Mean heart dose			1.17	1.00-1.37	0.054
Corrected for age, history of ischemic heart disease, diabetes, BMI≥30, mean heart dose and hypercholesterolemia					
CAC zero (reference)			1		
Low CAC	0.39	-17.00%	1.48	0.50-4.36	0.476
Intermediate + high CAC	1.62	0.60%	5.03	1.69-15.01	0.004
Age			1.06	1.01-1.11	0.019
History of ischemic heart disease			3.25	1.24-8.54	0.017
Diabetes			2.69	1.01-7.14	0.047
BMI≥30			2.1	0.69-6.41	0.194
Mean heart dose			1.18	1.01-1.39	0.042
Hypercholesterolemia			1.51	0.63-3.63	0.357
Corrected for age, history of ischemic heart disease, diabetes, BMI≥30, mean heart dose, hypercholesterolemia and hypertension					
CAC zero (reference)			1		
Low CAC	0.35	-10.30%	1.42	0.49-4.17	0.519
Intermediate + high CAC	1.6	-1.20%	4.95	1.69-14.53	0.004
Age			1.05	1.01-1.11	0.028
History of ischemic heart disease			3.06	1.17-8.03	0.023
Diabetes			2.49	0.93-6.67	0.07
BMI≥30			1.86	0.60-5.80	0.283
Mean heart dose			1.18	1.00-1.39	0.05
Hypercholesterolemia			1.36	0.56-3.33	0.497
Hypertension			1.57	0.66-3.74	0.308

Abbreviations: β, regression coefficient; HR, hazard ratio; CI, confidence interval; CAC, coronary artery calcium; BMI, body mass index.
CAC score categories: Low CAC (CAC score >0-100), intermediate + high CAC (CAC score >100).

with postoperative RT. This holds even after correction for confounding factors, such as MHD.

There are several studies on CAC scoring in BC patients. A recent study, investigating the reproducibility of automatic coronary artery calcium scoring in a BC population, found a baseline CAC score of zero in 76% of the BC patients.[15] These results are comparable to the 78,9% found in our study. In another much smaller study 53% of the BC patients had a CAC score of zero.[19] This difference could be attributed to the study size.

Accelerated coronary atherosclerosis is considered one of the mechanisms of radiation induced cardiac toxicity and can lead to serious cardiac morbidity and mortality.[21] Three studies have measured the amount of CAC in the years following RT treatment for BC. In two studies, no elevated CAC scores in BC patients were found 5 to 15.7 years after RT treatment, whereas 1 study did find an increase in CAC score depending on radiation dose to the heart.[22,23,24] Of the studies that did not find a CAC score increase, one did not include baseline CAC scores and the other only included a relatively small number of patients, which makes it difficult to draw definitive conclusions from these two studies. In young Hodgkin's lymphoma survivors (all under 55 years) elevated CAC scores have been found in the 5 to 35 years after RT.[25,26,27] A study in the general population investigated CAC scores at baseline and after 10 years of follow-up.[28] The results showed that the diagnosis of cancer and its treatments were significantly associated with the development of CAC, even after accounting for atherosclerotic risk factors. The results of these studies suggest that RT could be associated with increased CAC scores in the long term and therefore supports the hypothesis that accelerated atherosclerosis is one of the mechanisms contributing to radiotherapy induced cardiac events.

There are some studies concerning non-triggered CAC scores and the association with ACE, conducted in a general population and in lung cancer patients.[29,14] Studies concerning the general population had a median follow-up time ranging from 7.0 to 11.6 years. Overall, higher CAC scores were significantly associated with cardiovascular events. Compared to the zero CAC score group, the HRs were 1.53 (95%CI: 1.02-2.29) for the group of patients with a CAC score of >0-100 and 4.02 (95%CI: 2.62-6.19) for the group with a CAC score of >100.

A possible limitation of this study was that during planning CT scan acquisition, patients were instructed to breathe normally and no ECG triggering was used. This causes motion of the cardiac structures and calcium spots on CT images, leading to an under- or overestimation of calcium. However, several studies showed that CAC scoring can also be adequately performed with non-triggered CT scans.[11,12,13,14] A high level of agreement was found after investigating the correlations of CAC scores between non-triggered and triggered thoracic CT scans.[12] Therefore, it should be emphasized that a CAC score of zero measured on a non-triggered CT scan does not necessarily imply that there are absolutely no calcifications, but still indicates a low risk of ACE.[13,14] Yet, as shown in these studies a high CAC score is a reliable prognostic marker to identify high risk patients of ACE.[13,14]

In the current study, patients with coronary stents and/or clips that caused too many artifacts were excluded. These patients underwent cardiac interventions and can be considered as high risk patients of ACE, which could lead to an underestimation of the calcium scores in our population. As shown by recent studies the absolute risk of developing ACE is the highest in patients with cardiovascular risk factors and a higher radiation dose to the heart.[5,6] Results of the current study show that patients with high baseline CAC scores are at higher risk to develop ACE. In this respect, information on baseline risks, including the CAC score combined with the dose distribution to the heart, is useful to identify patients that may benefit from more advanced radiation techniques to reduce the heart dose.[30,31,32,33,34]

In conclusion, high pre-treatment CAC score measured on non-triggered planning CT scans is significantly associated with the cumulative incidence of ACE among BC patients treated with postoperative RT even after correction for confounding. CAC can be used to identify patients that may benefit from primary and secondary preventive measures.

REFERENCES

1. Forouzanfar MH, Foreman KJ, Delossantos AM, et al. Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. *Lancet*. 2011;378(9801):1461-1484. doi:10.1016/S0140-6736(11)61351-2
2. Wöckel A, Wolters R, Wiegel T, et al. The impact of adjuvant radiotherapy on the survival of primary breast cancer patients: a retrospective multicenter cohort study of 8935 subjects. *Ann Oncol Off J Eur Soc Med Oncol*. 2014;25(3):628-632. doi:10.1093/annonc/mdt584
3. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;366(9503):2087-2106. doi:10.1016/S0140-6736(05)67887-7
4. Taylor CW, Povall JM, McGale P, et al. Cardiac Dose From Tangential Breast Cancer Radiotherapy in the Year 2006. *Int J Radiat Oncol*. 2008;72(2):501-507. doi:10.1016/j.ijrobp.2007.12.058
5. Darby SC, Ewertz M, McGale P, et al. Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer. *N Engl J Med*. 2013;368(11):987-998. doi:10.1056/NEJMoa1209825
6. van den Bogaard VAB, Ta BDP, van der Schaaf A, et al. Validation and Modification of a Prediction Model for Acute Cardiac Events in Patients With Breast Cancer Treated With Radiotherapy Based on Three-Dimensional Dose Distributions to Cardiac Substructures. *J Clin Oncol*. 2017;35(11):1171-1178. doi:10.1200/JCO.2016.69.8480
7. Pletcher MJ, Tice JA, Pignone M, Browner WS. Using the Coronary Artery Calcium Score to Predict Coronary Heart Disease Events. *Arch Intern Med*. 2004;164(12):1285. doi:10.1001/archinte.164.12.1285
8. Kavousi M, Elias-Smale S, Rutten JHW, et al. Evaluation of Newer Risk Markers for Coronary Heart Disease Risk Classification. *Ann Intern Med*. 2012;156(6):438. doi:10.7326/0003-4819-156-6-201203200-00006
9. Lakoski SG, Greenland P, Wong ND, et al. Coronary Artery Calcium Scores and Risk for Cardiovascular Events in Women Classified as "Low Risk" Based on Framingham Risk Score. *Arch Intern Med*. 2007;167(22):2437. doi:10.1001/archinte.167.22.2437
10. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990;15(4):827-832. doi:10.1016/0735-1097(90)90282-t
11. Takx RAP, de Jong PA, Leiner T, et al. Automated Coronary Artery Calcification Scoring in Non-Gated Chest CT: Agreement and Reliability. *PLoS One*. 2014;9(3):e91239. doi:10.1371/journal.pone.0091239
12. Budoff MJ, Nasir K, Kinney GL, et al. Coronary artery and thoracic calcium on noncontrast thoracic CT scans: Comparison of ungated and gated examinations in patients from the COPD Gene cohort. *J Cardiovasc Comput Tomogr*. 2011;5(2):113-118. doi:10.1016/j.jcct.2010.11.002
13. Xie X, Greuter MJW, Groen JM, et al. Can nontriggered thoracic CT be used for coronary artery calcium scoring? A phantom study. *Med Phys*. 2013;40(8):081915. doi:10.1118/1.4813904
14. Xie X, Zhao Y, de Bock GH, et al. Validation and Prognosis of Coronary Artery Calcium Scoring in Nontriggered Thoracic Computed Tomography. *Circ Cardiovasc Imaging*. 2013;6(4):514-521. doi:10.1161/circimaging.113.000092
15. Gernaat SAM, Išgum I, de Vos BD, et al. Automatic Coronary Artery Calcium Scoring on Radiotherapy Planning CT Scans of Breast Cancer Patients: Reproducibility and Association with Traditional Cardiovascular Risk Factors. *PLoS One*. 2016;11(12):e0167925. doi:10.1371/journal.pone.0167925

16. McCollough CH, Ulzheimer S, Halliburton SS, Shanneik K, White RD, Kalender WA. Coronary Artery Calcium: A Multi-institutional, Multimanufacturer International Standard for Quantification at Cardiac CT. *Radiology*. 2007;243(2):527-538. doi:10.1148/radiol.2432050808
17. Bax JJ, Schuijf JD. Can Coronary Calcification Define the Warranty Period of a Normal Myocardial Perfusion Study? *Mayo Clin Proc*. 2008;83(1):10-12. doi:10.4065/83.1.10
18. Nucifora G, Bax JJ, van Werkhoven JM, Boogers MJ, Schuijf JD. Coronary Artery Calcium Scoring in Cardiovascular Risk Assessment. *Cardiovasc Ther*. 2011;29(6):e43-e53. doi:10.1111/j.1755-5922.2010.00172.x
19. Mast ME, Heijenbrok MW, Petoukhova AL, Scholten AN, Schreur JHM, Struikmans H. Preradiotherapy Calcium Scores of the Coronary Arteries in a Cohort of Women With Early-Stage Breast Cancer: A Comparison With a Cohort of Healthy Women. *Int J Radiat Oncol*. 2012;83(3):853-858. doi:10.1016/j.ijrobp.2011.08.012
20. Raggi P, Callister TQ, Cooil B, et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation*. 2000;101(8):850-855. doi:10.1161/01.cir.101.8.850
21. Stewart FA, Hoving S, Russell NS. Vascular Damage as an Underlying Mechanism of Cardiac and Cerebral Toxicity in Irradiated Cancer Patients. *Radiat Res*. 2010;174(6):865-869. doi:10.1667/RR1862.1
22. Tjessem KH, Bosse G, Fosså K, et al. Coronary calcium score in 12-year breast cancer survivors after adjuvant radiotherapy with low to moderate heart exposure – Relationship to cardiac radiation dose and cardiovascular risk factors. *Radiother Oncol*. 2015;114(3):328-334. doi:10.1016/j.radonc.2015.01.006
23. Chang M, Suh J, Kirtani V, et al. Coronary Calcium Scanning in Patients after Adjuvant Radiation for Early Breast Cancer and Ductal Carcinoma In situ. *Front Oncol*. 2013;3:253. doi:10.3389/fonc.2013.00253
24. Mast ME, Heijenbrok MW, van Kempen-Harteveld ML, et al. Less increase of CT-based calcium scores of the coronary arteries. *Strahlentherapie und Onkol*. 2016;192(10):696-704. doi:10.1007/s00066-016-1026-4
25. Andersen R, Wethal T, Günther A, et al. Relation of Coronary Artery Calcium Score to Premature Coronary Artery Disease in Survivors >15 Years of Hodgkin's Lymphoma. *Am J Cardiol*. 2010;105(2):149-152. doi:10.1016/j.amjcard.2009.09.005
26. Apter S, Shemesh J, Raanani P, et al. Cardiovascular calcifications after radiation therapy for Hodgkin lymphoma: computed tomography detection and clinical correlation. *Coron Artery Dis*. 2006;17(2):145-151. doi:10.1097/00019501-200603000-00008
27. Rademaker J, Schöder H, Ariaratnam NS, et al. Coronary Artery Disease After Radiation Therapy for Hodgkin's Lymphoma: Coronary CT Angiography Findings and Calcium Scores in Nine Asymptomatic Patients. *Am J Roentgenol*. 2008;191(1):32-37. doi:10.2214/AJR.07.3112
28. Whitlock MC, Yeboah J, Burke GL, Chen H, Klepin HD, Hundley WG. Cancer and Its Association With the Development of Coronary Artery Calcification: An Assessment From the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc*. 2015;4(11). doi:10.1161/JAHA.115.002533
29. Kavousi M, Desai CS, Ayers C, et al. Prevalence and Prognostic Implications of Coronary Artery Calcification in Low-Risk Women. *JAMA*. 2016;316(20):2126. doi:10.1001/jama.2016.17020
30. Bradley JA, Dagan R, Ho MW, et al. Initial Report of a Prospective Dosimetric and Clinical Feasibility Trial Demonstrates the Potential of Protons to Increase the Therapeutic Ratio in Breast Cancer Compared With Photons. *Int J Radiat Oncol*. 2016;95(1):411-421. doi:10.1016/j.ijrobp.2015.09.018

31. Cuaron JJ, Chon B, Tsai H, et al. Early Toxicity in Patients Treated With Postoperative Proton Therapy for Locally Advanced Breast Cancer. *Int J Radiat Oncol*. 2015;92(2):284-291. doi:10.1016/j.ijrobp.2015.01.005
32. Kozak KR, Katz A, Adams J, et al. Dosimetric comparison of proton and photon three-dimensional, conformal, external beam accelerated partial breast irradiation techniques. *Int J Radiat Oncol.* 2006;65(5):1572-1578. doi:10.1016/j.ijrobp.2006.04.025
33. Mast ME, Vredeveld EJ, Credoe HM, et al. Whole breast proton irradiation for maximal reduction of heart dose in breast cancer patients. *Breast Cancer Res Treat*. 2014;148(1):33-39. doi:10.1007/s10549-014-3149-6
34. Moon SH, Shin KH, Kim TH, et al. Dosimetric comparison of four different external beam partial breast irradiation techniques: Three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, helical tomotherapy, and proton beam therapy. *Radiother Oncol.* 2009;90(1):66-73. doi:10.1016/j.radonc.2008.09.027

APPENDIX

Table 1. CT scan protocols

	kV	mA	Slice (mm)	Increment (mm)
Planning CT scan protocol				
2005 - September 2007	140	100	5	5
September 2007- 2008	140	100	3	3
Diagnostic CAC score CT scan protocol				
	120	200	3	3

Abbreviations: kV, kilovoltage; mA, mili ampere; CAC, coronary artery calcium.

Table 2. Aquarius options for calcium detection

Options	Setting
Lay-Over (Hounsfield Units)	130 -1300
Isotropically interpolated volumes	Yes
Noise rejection – connected pixels	2
Connectivity	Diagonally and laterally

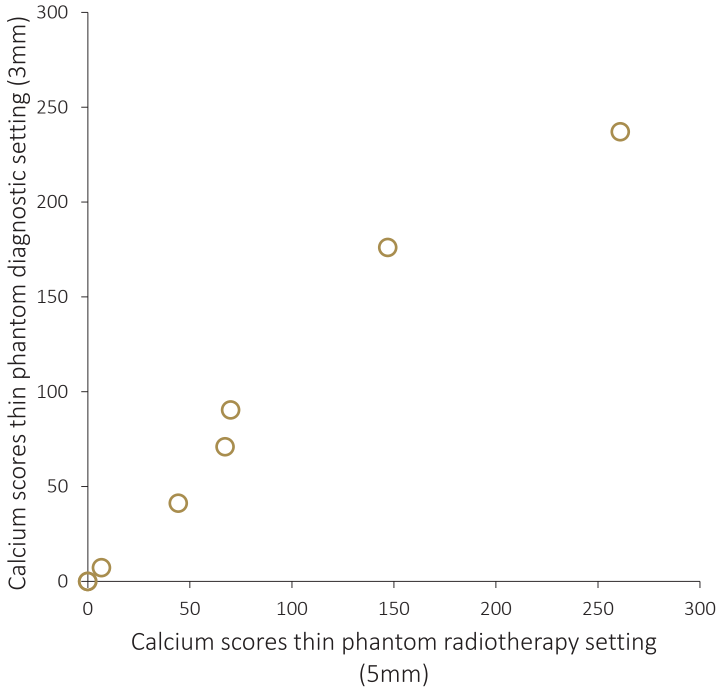
Table 3. Calibration factors and correlation formulas. (X=patient coronary artery calcium (CAC) score, Y=related diagnostic CAC score)

Planning scan protocol	Patient size	Correlation formula
5mm slices & increment	Thin	y=0.964x + 5.317
	Thick	y=1.094x – 0.791
3mm slices & increment	Thin	y=1.037x + 1.912
	Thick	y=0.924x + 3.086

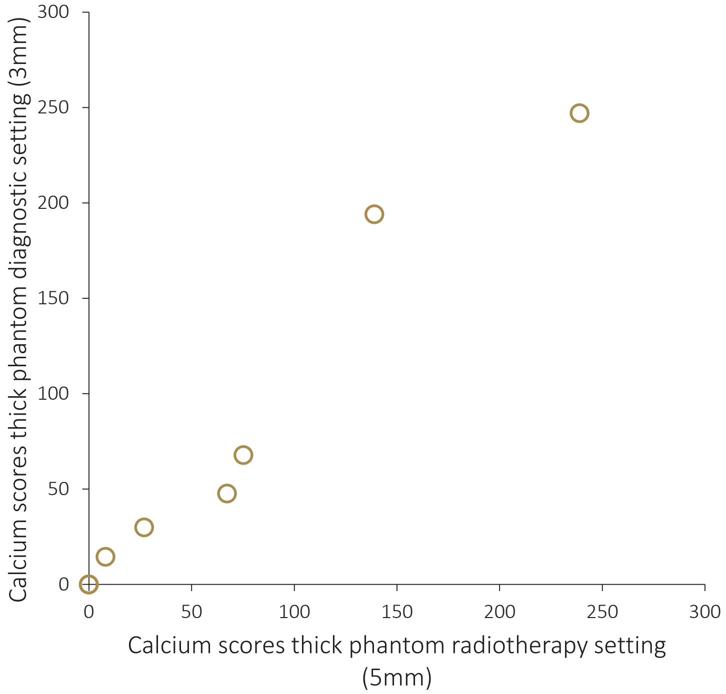
Table 4. Coronary calcium scores divided in age categories

Age (years)	CAC zero (n) (0)	Low CAC (n) (>0 - 100)	Intermediate CAC (n) (100 - 400)	High CAC (n) (≥400)
Mean age	56.3	64.3	69.4	73.5
<45	102 (97.1%)	3 (2.9%)	0 (0%)	0 (0%)
45-54	226 (93.8%)	13 (5.4%)	2 (0.8%)	0 (0%)
55-64	251 (80.2%)	49 (15.6%)	10 (3.2%)	3 (1.0%)
65-74	138 (61.0%)	58 (25.7%)	26 (11.5%)	4 (1.8%)
75-84	24 (44.4%)	13 (24.1%)	11 (20.4%)	6 (11.1%)
Total	741 (78.9%)	136 (14.5%)	49 (5.2%)	13 (1.4%)

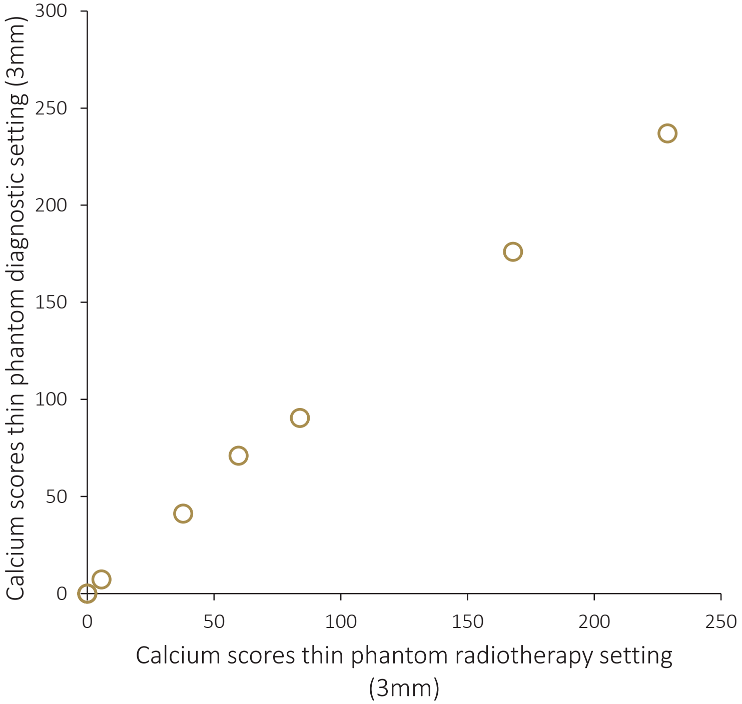
Abbreviations: CAC, Coronary Artery Calcium.



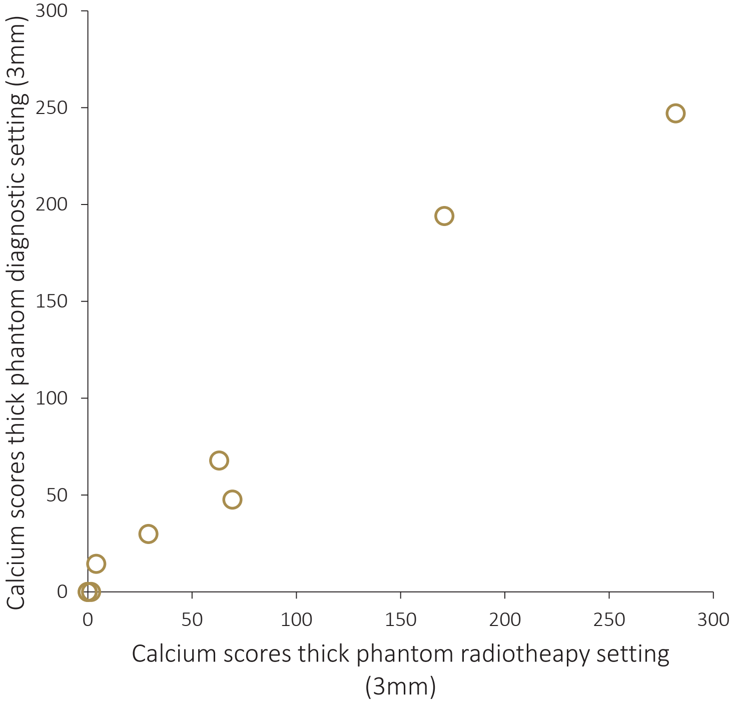
Appendix Figure 1. The coronary artery calcium scores of the calcium inserts from the QRM phantom scanned with the diagnostic coronary artery calcium scanning protocol and radiotherapy planning scanning protocol. Used for the correlation formula: 5 millimetre slices and increment, thin patient.



Appendix Figure 2. The coronary artery calcium scores of the calcium inserts from the QRM phantom scanned with the diagnostic coronary artery calcium scanning protocol and radiotherapy planning scanning protocol. Used for the correlation formula: 5 millimetre slices and increment, thick patient.



Appendix Figure 3. The coronary artery calcium scores of the calcium inserts from the QRM phantom scanned with the diagnostic coronary artery calcium scanning protocol and radiotherapy planning scanning protocol. Used for the correlation formula: 3 millimetre slices and increment, thin patient.



Appendix Figure 4. The coronary artery calcium scores of the calcium inserts from the QRM phantom scanned with the diagnostic coronary artery calcium scanning protocol and radiotherapy planning scanning protocol. Used for the correlation formula: 3 millimetre slices and increment, thick patient.