Risk of Heart Failure With Preserved Ejection Fraction in Older Women After Contemporary Radiotherapy for Breast Cancer

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BACKGROUND: Cardiomyocytes are resistant to radiation. However, cardiac radiation exposure causes coronary microvascular endothelial inflammation, a perturbation implicated in the pathogenesis of heart failure (HF) and particularly HF with preserved ejection fraction (HFpEF). Radiotherapy for breast cancer results in variable cardiac radiation exposure and may increase the risk of HF.

METHODS: We conducted a population-based case-control study of incident HF in 170 female residents of Olmsted County, Minnesota (59 cases and 111 controls), who underwent contemporary (1998–2013) radiotherapy for breast cancer with computed tomography–assisted radiotherapy planning. Controls were matched to cases for age, tumor side, chemotherapy use, diabetes mellitus, and hypertension. Mean cardiac radiation dose (MCRD) in each patient was calculated from the patient's computed tomography images and radiotherapy plan.

RESULTS: Mean age at radiotherapy was 69±9 years. Of HF cases, 38 (64%) had EF≥50% (HFpEF), 18 (31%) had EF<50% (HF with reduced EF), and 3 (5%) did not have EF measured. The EF was ≥40% in 50 of the 56 HF cases (89%) with an EF measurement. The mean interval from radiotherapy to HF was 5.8±3.4 years. The odds of HF was higher in patients with a history of ischemic heart disease or atrial fibrillation. The MCRD was 2.5 Gy (range, 0.2–13.1 Gy) and higher in cases (3.3±2.7 Gy) than controls (2.1±2.0 Gy; *P*=0.004). The odds ratio (95% confidence interval) for HF per log MCRD was 9.1 (3.4–24.4) for any HF, 16.9 (3.9–73.7) for HFpEF, and 3.17 (0.8–13.0) for HF with reduced EF. The increased odds of any HF or HFpEF with increasing MCRD remained significant after adjustment for HF risk factors and in sensitivity analyses matching by cancer stage rather than tumor side. Only 18.6% of patients experienced new or recurrent ischemic events between radiotherapy and the onset of HF.

CONCLUSIONS: The relative risk of HFpEF increases with increasing cardiac radiation exposure during contemporary conformal breast cancer radiotherapy. These data emphasize the importance of radiotherapy techniques that limit MCRD during breast cancer treatment. Moreover, these data provide further support for the importance of coronary microvascular compromise in the pathophysiology of HFpEF.

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Clinical Perspective

What Is New?

- In this population-based case-control study of older women with breast cancer treated with contemporary conformal radiotherapy, the odds of incident heart failure (HF) after radiotherapy increased with higher mean cardiac radiation dose.
- The predominant form of HF was HF with preserved ejection fraction (≥50%) or HF with midrange (40%–49%) ejection fraction.
- The relative risk for any HF and for HF with preserved ejection fraction increased with mean cardiac radiation dose, even after adjustment for other known risk factors and cancer stage.
- Myocardial infarction caused by epicardial coronary disease was not the predominant mediator of incident HF.

What Are the Clinical Implications?

- These data emphasize the importance of radiotherapy techniques that limit mean cardiac radiation dose during breast cancer treatment.
- Moreover, these data provide further support for the importance of coronary microvascular compromise in the pathophysiology of HF with preserved ejection fraction.

Breast-conserving surgery plus radiotherapy has emerged as the standard approach for localized breast cancer, and in more advanced disease, radiotherapy improves local control and survival.[1–4] The high doses of thoracic radiation used with thoracic tumors and older breast cancer radiotherapy techniques increase the risk of cardiac disease.[5–8] Advances in radiotherapy planning, including the use of computed tomography (CT)–assisted radiotherapy planning, can substantially reduce cardiac radiation exposure during contemporary breast cancer radiotherapy.[5] However, even low levels of cardiac radiation during breast cancer radiotherapy increase the risk of coronary events.[6]

Cardiomyocytes are resistant to radiation. However, radiation induces coronary microvascular endothelial damage and inflammation, leading to microvascular rarefaction and myocardial inflammation, oxidative stress, and fibrosis.[7–10] Comorbidity-driven coronary microvascular endothelial inflammation with similar subsequent myocardial effects has been implicated as a key factor in the pathophysiology of heart failure (HF) with preserved ejection fraction (HFpEF).[11,12] Although major cardiomyocyte loss due to infarction or other factors is the primary etiologic insult in HF with reduced ejection fraction (HFrEF), comorbidity-driven coronary microvascular endothelial inflammation can contribute to global myocardial dysfunction and HF progression.[11,12] Accordingly, we hypothesized that cardiac radiation exposure during contemporary breast cancer radiotherapy may increase the risk of HF and particularly HFpEF. We performed a population-based case-control study of patients with breast cancer treated with CT-guided radiotherapy, relating the odds of incident HF after radiotherapy to mean cardiac radiation dose (MCRD) and HF risk factors.

METHODS

Study Population

This study was restricted to appropriately consented residents of Olmsted County, Minnesota. The study was approved by the Institutional Review boards of the Mayo Clinic and the Olmsted Medical Center.

For Olmsted County residents, radiotherapy is provided solely by the Mayo Clinic. Using the resources of the Rochester Epidemiology Project and the Mayo Clinic Cancer Registry (Methods in the online-only Data Supplement), we identified all female patients >18 years of age who had undergone radiotherapy for a histologically proven diagnosis of breast cancer in the era when CT-guided radiotherapy planning was beginning to be integrated into clinical practice (January 1998–December 2013) and who resided in Olmsted County at the time of and after radiotherapy (Figure I in the online-only Data Supplement). The date of first appearance of diagnostic codes for HF and relevant comorbidities (Table I in the online-only Data Supplement) was extracted for all patients. Patients with an HF diagnosis, thoracic radiation, or chemotherapy before the breast cancer diagnosis date were excluded from consideration as cases or controls.

We manually reviewed the medical records of patients with an HF diagnostic code to further confirm the absence of preexisting HF or cardiomyopathy and to determine whether patients met the modified Framingham criteria for HF[13] (Table II in the online-only Data Supplement) or if a physician had indicated a diagnosis of HF in the medical record with supportive clinical symptoms, signs, and chest radiograph or echocardiographic evidence of HF (Table III in the online-only Data Supplement). Patients with other explanations (ie, lung metastasis) for HF symptoms were excluded. The medical records of potential controls were also reviewed with the use of free text data searches of the electronic medical record for terms consistent with HF (Methods in the online-only Data Supplement). If such terms were present, charts were manually reviewed to confirm HF as above. Assessment for incident HF included the interval from breast cancer diagnosis through December 31, 2014.

Cases and controls with bilateral tumors, distant metastases at initial diagnosis, additional radiotherapy, or chemotherapy after their initial breast cancer treatment or who did not have CT-based radiotherapy planning were excluded. At least 1 and up to 2 radiated breast cancer controls corresponding to each HF case were matched for factors known to increase HF risk, including age at the breast cancer diagnosis (within 10 years), use of anthracycline, use of trastuzumab, and history of hypertension or diabetes mellitus. Because the cardiac chambers exposed to radiation may vary by tumor side, we also matched by tumor side.[14,15] Controls were required to have follow-up (index interval) equivalent to or greater than the time from radiotherapy to HF diagnosis of the corresponding case.

Comorbid conditions, cardiovascular medications, lifestyle information, and cardiac imaging data were extracted from the

medical record. The presence of ischemic heart disease was defined as a history of myocardial infarction, coronary bypass grafting, or percutaneous coronary intervention and ascertained as previously described.[16] Availability of EF measurement at the time (30 days before or after) of HF diagnosis was assessed and used to characterize HF as HFpEF (≥50%), HFrEF (<50%), or HF with indeterminate (unavailable) EF.

Higher cancer stage often mandates more extensive radiotherapy and increases MCRD but also may result in heightened surveillance and bias HF ascertainment. Thus, we performed a sensitivity analysis rematching controls to cases using the same criteria as above except matching for cancer stage rather than tumor side (Methods in the online-only Data Supplement).

Breast Cancer Treatment and Dosimetry

Breast cancer characteristics and treatment, including the use of systemic therapy and details of radiation therapy, were extracted from Mayo Cancer Registry database and radiation oncology record and by manual record review. In each patient, MCRD was calculated with simulation software (Eclipse, Varian Medical System, Inc, Palo Alto, CA) integrating the patient's complete chest CT image set and the radiotherapy plan (Methods in the online-only Data Supplement). Dose-sparing techniques were integrated over the study period (Methods in the online-only Data Supplement).

Statistical Analyses

Conditional logistic regression, conditioning on the matching factors (age, tumor side, chemotherapy use, diabetes mellitus, and hypertension), was used to estimate incident HF odds ratios associated with clinical characteristics not used to match cases and controls. Similar models were used to calculate incident HF (overall and by HF type) odds ratios per (natural) log MCRD. Odds ratios were estimated without or with adjustment for clinical characteristics not used as matching factors but associated with HF incidence by including these adjustment factors as covariates in the conditional logistic regression models. The natural logarithm of MCRD was applied before analyses because of the skewed distribution of MCRD; this transformation improved model fit and lowered the potential of influential observations with very large values. Because the age-matching criterion was fairly broad, we also performed analysis adjusting for age as a continuous variable. Interaction terms were added to the models to test for differences in dose effects and time to HF onset.

Comparisons of crude HF frequency (HF or no HF) with increasing MCRD category were analyzed with the Cochran-Armitage test for trend. Significance tests were 2 sided. A value of $P<0.05$ was considered statistically significant. Calculations were performed with the use of SAS version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Characteristics of the Study Patients

Among 945 female Olmsted County residents with breast cancer who underwent radiotherapy during 1998 to 2013 (median age, 59 years), we identified 77 patients who developed new-onset validated HF after radiotherapy. Of these 77 potential cases, 60 met final entry criteria (Figure I in the online-only Data Supplement). No matching control was found for 1 case; only 1 matching control was found for 7 cases; and 2 matching controls were found for 52 cases. Thus, the study included 59 HF cases and 111 controls without HF. Of the HF cases, 43 fulfilled Framingham criteria, and the remaining 16 had a physician's diagnosis of HF recorded in the medical record with objective evidence of HF (Table III in the online-only Data Supplement). Of HF cases, 38 (64%) had HFpEF, 18 (31%) had HFrEF, and 3 (5%) did not have EF measured coincident with HF diagnosis. Of note, the EF was ≥40% in 50 of the 56 HF cases (89%) with an EF measurement. The majority of cases (57, 97%) and controls (105, 97%) were white. The mean interval from radiotherapy to HF diagnosis and corresponding index interval in controls was 5.8±3.4 years. Matched characteristics were similar in cases and controls (Table 1). The relative risk of HF was higher in patients with more advanced cancer stage and in those with a history of ischemic heart disease or atrial fibrillation (Table 1).

Impact of MCRD on the Relative Risk of Incident HF

The overall MCRD was 2.5 Gy (range, 0.2–13.1 Gy) and higher in cases (3.3±2.7 Gy) than controls (2.1±2.0 Gy; $P=0.004$; Figure 1). The average MCRD was higher in women with left-sided (4.1 Gy; range, 0.6–13.1 Gy) versus right-sided (1.5 Gy; range, 0.2–5.6 Gy; $P<0.001$) tumors (Figure 1, inset). The MCRD was higher in patients with higher cancer stage (Figure II in the online-only Data Supplement), likely owing to internal mammary node treatment. In the entire study population, tumor side explained 37% ($P<0.001$) of the variation and tumor side and cancer stage together explained 44% ($P<0.001$ for both) of the variation in MCRD. MCRD decreased over the study era (Figure III in the online-only Data Supplement).

The crude frequency of HF cases versus controls increased with higher MCRD (Figure 2). The odds of incident HF (any) and of HFpEF increased with higher MCRD (Table 2), even after adjustment for age, cancer stage, and history of ischemic heart disease or atrial fibrillation. The crude frequency of HF at any MCRD was numerically higher in those with versus those without a history of ischemic heart disease or atrial fibrillation, but the crude HF frequency increased with increasing MCRD in both groups (Figure 3) as in the overall conditional regression analysis (Table 2). The effect of MCRD on the odds of incident HF was apparent and statistically significant in patients with left- or right-sided tumors (Table IV in the online-only Data Supplement). Furthermore, consistent with our findings matched by use of chemotherapy (Table 2), the crude frequency of HF increased with MCRD when

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Table 1. Clinical Characteristics at Breast Cancer Diagnosis and Relative Risk of Heart Failure

	Cases (n=59)	Controls (n=111)	Odds Ratio (95% CI)	*P* Value
Matched characteristics				
Age at breast cancer diagnosis, y	69.8±9.6	68.3±8.8	NA	NA
Left-sided breast cancer, n (%)	24 (41)	43 (39)	NA	NA
Anthracycline therapy, n (%)	7 (12)	13 (12)	NA	NA
Trastuzumab therapy, n (%)	0 (0)	0 (0)	NA	NA
Hypertension, n (%)	36 (61)	68 (61)	NA	NA
Diabetes mellitus, n (%)	13 (22)	22 (20)	NA	NA
Other characteristics				
Cancer stage, n (%)				0.03
0	6 (10)	24 (21)	1.0	
1	31 (53)	62 (56)	2.14 (0.79–5.77)	
2 (A and B, n=40) or 3 (A–C, n=7)	22 (37)	25 (23)	4.63 (1.45–14.78)	
Surgical therapy, n (%)				0.67
Mastectomy	6 (10)	10 (9)	1.0	
Breast-conserving surgery	52 (88)	101 (91)	0.77 (0.22–2.65)	
None	1 (2)	0	N/A	
Adjuvant paclitaxel therapy, n (%)				0.25
No	53 (90)	104 (94)	1.0	
Yes	6 (10)	7 (6)	2.73 (0.50–15.04)	
Adjuvant hormonal therapy, n (%)				0.87
No	25 (42)	48 (43)	1.0	
Yes	34 (58)	63 (57)	1.05 (0.56–1.96)	
Obesity (body mass index ≥30 kg/m^2), n (%)	29.4±6.1	29.5±6.0		0.55
No	37 (63)	65 (59)	1.0	
Yes	22 (37)	46 (41)	0.82 (0.43–1.57)	
History of ischemic heart disease, n (%)				0.02
No	51 (86)	108 (97)	1.0	
Yes	8 (14)	3 (3)	5.06 (1.34–19.13)	
History of atrial fibrillation or flutter, n (%)				0.009
No	45 (76)	102 (92)	1.0	
Yes	14 (24)	9 (8)	3.41 (1.36–8.55)	
History of chronic lung disease, n (%)				0.11
No	53 (90)	107 (96)	1.0	
Yes	6 (10)	4 (4)	2.82 (0.79–10.03)	
Smoking, n (%)				0.11
Current	10 (17)	9 (8)	2.56 (0.89–7.37)	
Ever	12 (20)	31 (28)	0.68 (0.29–1.59)	
Never	37 (63)	71 (64)	1.0	
Medication use, n (%)				
ACE or ARB				0.32
No	38 (64)	78 (70)	1.0	

(*Continued*)

Table 1. Continued

	Cases (n=59)	Controls (n=111)	Odds Ratio (95% CI)	*P* Value
Yes	21 (36)	33 (30)	1.56 (0.65–3.72)	
β-Blocker				0.11
No	32 (54)	73 (66)	1.0	
Yes	27 (46)	38 (34)	1.76 (0.88–3.50)	

ACE indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and CI, confidence interval.

Ischemic heart disease was defined as a history of myocardial infarction, coronary bypass grafting, or percutaneous coronary intervention before breast cancer diagnosis.

the analysis was restricted to patients not receiving chemotherapy (Figure IV in the online-only Data Supplement).

The odds of incident HFrEF increased with higher MCRD, but this association was not significant (Table 2). After adjustment for age, HF risk factors, and cancer stage, there was no difference in the association between MCRD effect and odds of HF by time from radiotherapy (interaction radiation dose×time *P*=0.61; Table 3).

Sensitivity Analyses

In a cohort matched by the same factors except cancer stage rather than tumor side, clinical characteristics associated with HF incidence (Table V in the online-only Data Supplement) were similar to those in the primary analysis. The MCRD was associated with HF and HFpEF incidence (Table VI in the online-only Data Supplement), even after adjustment for pertinent covariates. The magnitude of odds per log MCRD was lower than in the primary analysis but remained substantial, particularly if the analysis was adjusted for tumor side. The effect of MCRD on the odds of incident HF was apparent and statistically significant when patients who did not fulfill Framingham criteria for HF diagnosis were excluded both in the primary analysis cohort matched by tumor side (Table VII in the online-only Data Supplement) and in the sensitivity analysis cohort matched by cancer stage (Table VIII in the online-only Data Supplement).

Factors Associated With Development of HF After Radiotherapy

Of patients who developed HF after radiotherapy, 11 (18.6%) had new or recurrent ischemic heart disease events, 15 (25.4%) had new or recurrent atrial fibrillation, and 22 (37.3%) had either of these conditions after radiotherapy but before or coincident with the HF diagnosis.

DISCUSSION

In this population-based case-control study of older women with breast cancer treated with contemporary conformal radiotherapy, the odds of incident HF after radiotherapy increased with higher MCRD. The predominant form of HF was HFpEF or HF with midrange (40%–49%) EF,[17] and the odds for any HF and for HFpEF increased with MCRD, even after adjustment for other known risk factors and cancer stage. The mean time from radiotherapy to HF was 5.8 years. A minority of women developed ischemic events between radiotherapy and HF diagnosis, suggesting that myocardial infarction due to epicardial coronary disease was not the predominant mediator of incident HF. The effect of MCRD on HF incidence was still apparent in sensitivity analyses addressing the potential for surveillance bias associated with higher cancer stage.

In 40-year-old women, the lifetime risks of both breast cancer (12%) and HF (20%) are significant.[18,19] Adjuvant

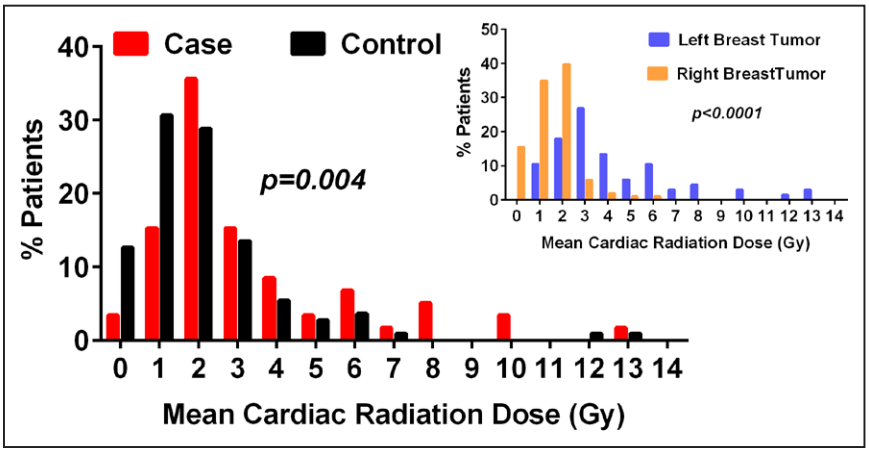

Figure 1. Distribution of mean cardiac radiation dose in study patients.
The mean cardiac radiation dose in cases and controls and in patients with right- or left-sided tumors (**inset**) is shown.

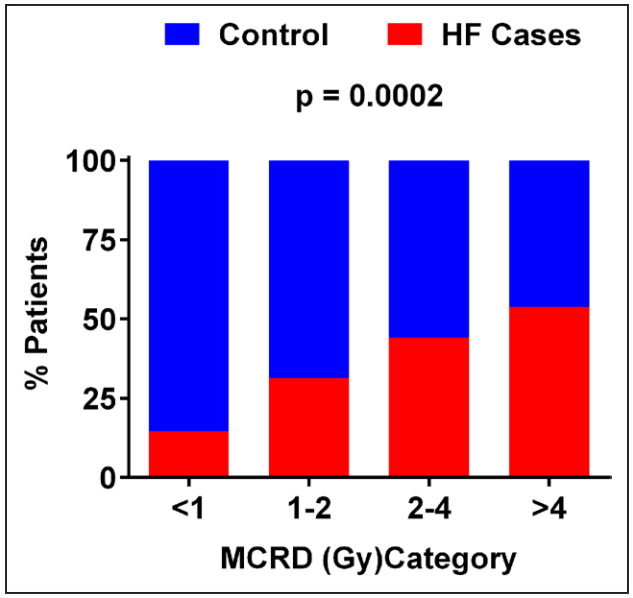

Figure 2. Crude frequency of heart failure (HF) cases vs controls according to category of mean cardiac radiation dose (MCRD).
HF cases (red) relative to controls (blue) increased with increasing MCRD.

radiotherapy reduces breast cancer loco-regional recurrence and mortality in some breast cancer subgroups.[2–4] The excellent survival after treatment for localized breast cancer mandates attention to survivorship issues, including cardiovascular complications of radiotherapy.[20] The risk of cardiac toxicity with high-dose thoracic radiotherapy is well documented.[2,7,8,10,20] Although MCRD varies with tumor side and treatment of nodal beds, individual variation in thoracic and cardiac anatomy contributes significantly to cardiac exposure, as seen here. Thus, although on average MCRD is quite low with contemporary conformal breast cancer radiotherapy, significant individual variation exists.[5,14,15] A growing number of radiotherapy techniques can reduce cardiac exposure,[5] but they are inconsistently used. Indeed, average cardiac doses and, importantly, maximal cardiac doses in a meta-analysis of contemporary breast cancer radiotherapy studies substantially exceed those observed here.[5] Furthermore, even as MCRD falls with improved techniques, our data emphasize that women treated before such advances remain at increased risk of HF. The present data also underscore the need to reduce MCRD, particularly in older women with HF risk factors.

Consistent with our findings, the ongoing study of atomic bomb survivors in Japan has demonstrated that total body radiation exposures of <2.5 Gy leads to significant increases in the incidence of HF (excess risk, 22% per 1 Gy) but not myocardial infarction.[7] Meta-analyses have suggested that cardiovascular mortality and some assessed cardiovascular morbid events are not increased in women treated with more contemporary

Table 2. Association Between Mean Cardiac Radiation Dose and Relative Risk of Incident Heart Failure

	Odds Ratio per Log MCRD	*P* Value
All HF		
Unadjusted	9.14 (3.43–24.37)	<0.001
Adjusted for age	8.57 (3.22–22.85)	<0.001
Adjusted for history of IHD	8.16 (3.05–21.83)	<0.001
Adjusted for history of AF	8.65 (3.23–23.16)	<0.001
Adjusted for cancer stage	8.66 (3.23–23.23)	<0.001
Adjusted for age/IHD/AF/ cancer stage	7.40 (2.77–19.81)	<0.001
HFpEF		
Unadjusted	16.88 (3.86–73.74)	<0.001
Adjusted for age	16.31 (3.67–72.48)	<0.001
Adjusted for history of IHD	16.45 (3.72–72.75)	<0.001
Adjusted for history of AF	20.83 (4.24–102.30)	<0.001
Adjusted for cancer stage	18.93 (4.12–87.02)	<0.001
Adjusted for age/IHD/AF/ cancer stage	22.70 (4.48–115.10)	<0.001
HFrEF		
Unadjusted	3.17 (0.77–12.96)	0.11
Adjusted for age	3.22 (0.79–13.10)	0.10
Adjusted for history of IHD	1.96 (0.48–7.95)	0.35
Adjusted for history of AF	3.33 (0.76–14.69)	0.11
Adjusted for cancer stage	2.24 (0.48–10.52)	0.31
Adjusted for age/IHD/AF/ cancer stage	2.33 (0.53–10.17)	0.26

AF indicates atrial fibrillation/flutter; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IHD, ischemic heart disease; and MCRD, mean cardiac radiation dose.

breast cancer radiotherapy techniques.[20,21] However, these studies acknowledge the limited follow-up duration, the lack of individual cardiac dose data, and importantly, the potential for interaction between preexisting clinical or subclinical cardiovascular abnormalities and the impact of cardiac radiation dose.[20,21]

Beyond differences in therapeutic era, the designs of studies assessing radiotherapy cardiac toxicity have varied, and comparisons between patients with breast cancer with or without radiotherapy and between patients receiving left- or right-sided tumor radiotherapy have significant limitations resulting from confounders[6] and the inability of tumor laterality to precisely reflect individual cardiac dose, as also demonstrated here. To address these limitations, Darby et al[6] used a case-control design with estimations of individual-patient MCRD derived from

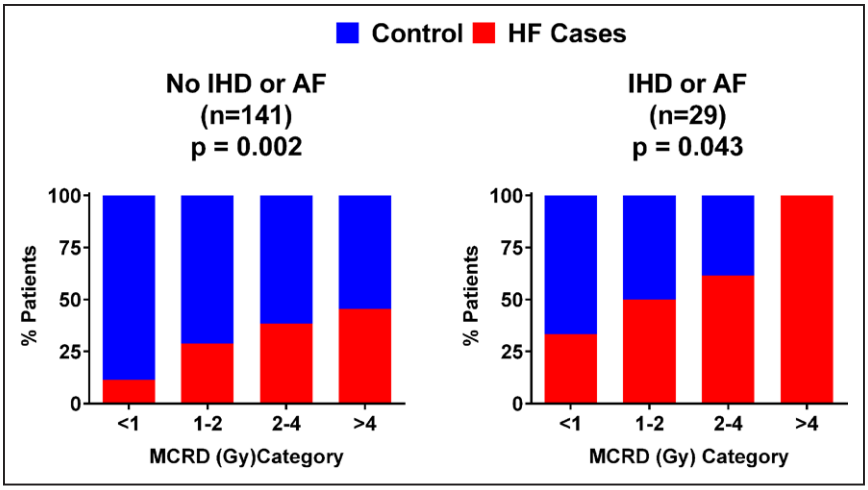

Figure 3. Crude frequency of heart failure (HF) cases vs controls according to category of mean cardiac radiation dose (MCRD) and stratified by history of HF risk factors before breast cancer diagnosis.
HF cases (red) relative to controls (blue) increased with increasing MCRD regardless of the presence or absence of atrial fibrillation (AF) or ischemic heart disease (IHD) before breast cancer diagnosis.

the radiotherapy treatment plan and a single "representative" CT scan. Even after adjustment for coronary risk factors, the risk of major coronary events increased in proportion to the MCRD (7% per 1 Gy) and over a fairly short interval after radiotherapy. The absolute risk was highest in older women with coronary risk factors.

The present study used a case-control design rather than a cohort study design. Results from previous cohort studies of the effect of breast cancer radiotherapy on HF incidence have been mixed.[22–25] No study has specifically examined the effect of individually calculated MCRD on the incidence of HFpEF and HFrEF, and study designs were subject to the limitations noted above and complexities of HF (and particularly HFpEF) case ascertainment.[26] The incidence of HF increases dramatically with age, and in the community, the mean age at HF diagnosis is 78 years for HFpEF and 72 years for HFrEF.[27] Given the average age (61 years) and low MCRD in the majority of contemporary patients with breast cancer,[5,15] the likely critical interaction between the impact of MCRD and preexisting age- and comorbidity-related myocardial abnormalities, the underuse of radiotherapy in older patients with HF risk factors,[28,29] and the challenges in HF case ascertainment, a general breast cancer cohort study may fail to detect the impact of radiation dose on HF incidence without accurate cardiac dose assessment and sensitive case ascertainment methodology.

Several studies have documented new cardiac perfusion defects (without interim myocardial infarction) after breast cancer radiotherapy consistent with microvascular rarefaction.[30] Comorbidity-driven coronary microvascular endothelial inflammation is believed to play a key role in the pathophysiology of HFpEF. Microvascular endothelial inflammation leads to microvascular dysfunction and rarefaction with a reduction in coronary flow reserve and myocardial inflammation and fibrosis, as well as oxidative stress, which may impair nitric oxide–cGMP signaling and potentiate cardiomyocyte hypertrophy and myofiber diastolic stiffness.[11,12,31] The mechanism of radiation-induced myocardial disease is well described, with microvascular damage leading to inflammatory and thrombotic changes, microvascular rarefaction, myocardial inflammation, oxidative stress, and fibrosis, as well as focal ischemia.[4,6,7,20] Thus, the present findings are consistent with and lend further support to the pivotal role of the microvasculature in the pathophysiology of HFpEF,[31,32] for which microvascular inflammation has been histologically demonstrated.[33] Studies of heart disease after higher doses of cardiac radiation in younger patients[7] suggest that HF is a late occurrence. However, older women receiving breast cancer radiotherapy have comorbidities and may already have significant but subclinical coronary microvascular and myocardial disease. Thus, even low doses of cardiac radiation may have an impact, providing the further disruption in microvascular structure and function required to precipitate overt HF.

Table 3. Association Between Mean Cardiac Radiation Dose and Relative Risk of Incident Heart Failure, by Time After Breast Cancer Diagnosis

Time Period After Breast Cancer Diagnosis (Above or Below the Median Index Interval), y	Odds Ratio per Log MCRD (95% CI)*	*P* Value
<5.9	8.47 (2.03–36.42)	0.003
≥5.9	5.65 (1.50–21.30)	0.01

CI indicates confidence interval; and MCRD, mean cardiac radiation dose. The *P* value for the interaction between radiation dose effect and time to heart failure was 0.61.

*Adjusted for age, history of ischemic heart disease, history of atrial fibrillation or flutter, and cancer stage.

Potential Limitations and Strengths

The study size was small, but the design was strengthened by the use of precise MCRD calculation using the complete set of CT images, matching or adjusting for HF risk factors, complete patient level data, rigorous case ascertainment techniques, the community-based set-

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ting, and our sensitivity analyses. Few women developed HFrEF, and even among the HFrEF group, most had mid-range EF (40%–49%),[17] often considered to be HFpEF, and thus the impact of MCRD on HFrEF incidence is uncertain. Restriction to the contemporary therapeutic era limits the ability to detect longer-term risks in younger women. Specific cardiac chamber doses were not assessed and may be important[14] because impairment in both atrial and right ventricular function contributes to the pathophysiology of HFpEF.[34,35] Although the analysis adjusted for nonmatched variables associated with HF (ischemic heart disease and atrial fibrillation), we cannot exclude residual confounding, but the effect of dose on crude HF odds ratios in patients with or without these risk factors was still apparent. Although we confined our analysis to the era when CT-guided radiotherapy planning was beginning to be integrated into clinical practice, this was an incremental practice change, and not all patients receiving radiotherapy had CT scans for MCRD calculations.

Conclusions

In older women undergoing contemporary breast cancer radiotherapy, the relative risk of HFpEF increases in proportion to calculated MCRD, begins within a few years after radiotherapy, and is not mediated solely by coronary events. These data suggest that cardiac dose and HF risk factors should be considered in decisions about breast cancer radiotherapy and underscore the importance of techniques for reducing cardiac dose. Moreover, these data provide further support for the importance of coronary microvascular compromise in the pathophysiology of HFpEF.

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DISCLOSURES

None.

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FOOTNOTES

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Risk of Heart Failure With Preserved Ejection Fraction in Older Women After Contemporary Radiotherapy for Breast Cancer

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SUPPLEMENTAL MATERIAL

Manuscript: Risk of Heart Failure with Preserved Ejection Fraction in Older Women after Contemporary Radiotherapy for Breast Cancer
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CONTENTS

SUPPLEMENTAL METHODS:

1. THE ROCHESTER EPIDEMIOLOGY PROJECT, OLMSTED COUNTY, MINNESOTA

The Rochester Epidemiology Project (REP) medical records-linkage system was established in 1966 to provide longitudinal medical data for a complete population residing in a well-defined geographic area. The primary participants in the REP include the Mayo Clinic and its two affiliated hospitals, the Olmsted Medical Center (outpatient clinics and hospital) and the Rochester Family Medicine Clinic (a private medical care practice in Olmsted County). These institutions provide virtually all medical care for Olmsted County residents. Radiotherapy is performed only by the Mayo Clinic. These organizations use a unit medical record system in which information is collected by health care clinicians in a single record, regardless of site of care. These records are easily retrievable because the Mayo Clinic has maintained extensive indices of diagnoses and procedures, which were extended through the REP to the records of other clinicians caring for county residents, resulting in the linkage of all medical records from all sources of care through a centralized system[1-3]. Beginning in 1929, Mayo physicians were required to enter patient diagnoses following each visit onto a summary "master sheet" of the unit medical record, which was then forwarded to the Department of Health Sciences Research to be indexed by trained nosologists. This diagnostic classification system was enlarged in 1935 (Berkson Coding System) to provide rapid identification of patients with 20,000 diagnostic categories. In 1975, the Hospital Adaptation of the International Classification of Diseases, Second Edition (HICDA; a modification of the International Classification of Diseases, version 8; ICD- 8) was added. In 2009, ICD-9 codes were assigned to diseases or conditions as part of the billing process.

Thus, to insure all heart failure diagnoses and comorbid conditions were identified, the diagnosis date for heart disease, cardiovascular risk factors and cardiac structural or functional abnormalities were extracted for all subjects using ICD-9 codes. Existence of prior diagnosis was double checked by referencing Berkson Dx codes (1966-1975), HICDA diagnosis codes (-1976-2005) in the REP data base.

Medication use is compiled for all Olmsted County residents using combined information from the Mayo Clinic and non-Mayo Clinic prescription systems.

2. MAYO CLINIC CANCER REGISTRY

The Mayo Clinic Cancer Registry is an information system designed for the collection, management, analysis and dissemination of data on persons with the diagnosis of malignant or neoplastic disease (cancer) and specific benign (non-cancer) conditions. The Cancer Registry at Mayo Clinic Rochester started January 1, 1972. All patients receiving the diagnosis of cancer at Mayo Clinic, Rochester are enrolled and information is obtained from their medical record and becomes part of the Mayo Clinic Cancer Registry. The registry stores the collected data for use in clinical practice, research, benchmarking of outcomes, accreditation as cancer program and fulfillment of state mandated reportable disease requirements. Cancer coding utilizes the guidelines of the American Joint Committee on Cancer Staging, the Facility Oncology Registry Data Standards and the International Classification of Disease for Oncology.
Collected data includes:

- Patient Demographics: Age, gender, race/ethnicity, residence at time of diagnosis
- Diagnostic Findings: Types, dates and results of procedures used to make the diagnosis
- Cancer Information: Primary site, cell type and extent of disease
- Treatment Information
- Follow-Up Information: Annual information concerning treatment, recurrence, and patient status is updated to maintain accurate surveillance information

3. FREE TEXT DATA SEARCHES OF THE ELECTRONIC MEDICAL RECORD

As previously described[4], Mayo Clinic has established a sophisticated data warehouse (Mayo Clinic Life Sciences [MCLSS]), which contains a near real-time normalized replicate of Mayo Clinic's electronic medical record (EMR). This warehouse is developed from multiple original clinical data sources, including highly annotated, full-text clinical notes,

laboratory tests, diagnostic findings, demographics, and related clinical data from the year 2000 onward. Mayo Clinic's EMR data are extracted, transformed, and loaded into MCLSS using IBM's WebSphere Commerce Analyzer, creating DB/2 Universal Database structures of Mayo Clinic's normalized clinical data. Clinical patient data are mapped to standard medical terminologies using LexGrid (Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN) natural language processing technology. The MCLSS provides approved users with a query-building tool called the *Data Discovery and Query Builder* (DDQB). The DDQB is a Web-based application configured for query building that is intended to help investigators interrogate data files contained in the MCLSS. The DDQB allows users to build queries without requiring programming knowledge including free text searches of the EMR.

While ICD diagnostic codes have been commonly used in epidemiology studies, they can be insensitive for heart failure diagnosis[5]. Thus, to insure that all heart failure cases were captured in this smaller case-control study, the medical records of all breast cancer radiotherapy patients without heart failure diagnostic codes were queried by free text search using non-negated terms of "heart failure", "dyspnea", "edema", "pulmonary congestion", "fatigue', "gallop", "cardiomegaly" and "jugular vein distension". If any of the terms were identified, manual medical record review to confirm non-negated terms for heart failure and determine whether the patient met modified Framingham or clinical heart failure criteria.

4. CARDIAC DOSIMETRY

Cardiac contours were done in a manner consistent with the Breast Cancer Atlas for Radiation Therapy Planning from the Radiation Treatment Oncology Group.[6]

5. RADIOTHERAPY

General methodologies employed in breast cancer radiotherapy during the study era are briefly summarized.

Partial breast: Multiple non-coplanar beams avoiding the heart with dose constraints taken from the NSABP B-39 trial protocol.

Whole breast: During 1998-2007, patients were treated with tangential beams using wedges and compensation blocks placed inferiorly and superiorly in order to minimize hot doses within the breast. Collimator angles and/or cerrobend blocks were used for posterior beam border. During 2007-2013, patients were treated using tangential beams with field-in-field compensation using multi-leaf collimation.

Whole breast with supraclavicular field with or without an axillary field: Patients were treated with a single isocenter set up with beam split technique. Tangential fields for the breast used techniques as described above for the whole breast, matched to a single slight anterior oblique field with or without a posterior axillary supplementary field.

Chest wall with supraclavicular field with or without an axillary field: Patients were treated with a single isocenter set up with beam split technique. Tangential fields for the chest wall used wedges and compensation blocks or field-in-field as described above. Depending on patient anatomy, some patients were treated with tangential fields matched to an electron field that would match the medial edge of the anterior tangent field on the skin in a manner designed to cover the skin and subcutaneous tissue but not the internal mammary nodal chain. This approach would be matched to a single slight anterior oblique field with or without a posterior axillary supplementary field.

Chest wall or whole breast with supraclavicular field with or without and axillary field or internal mammary nodal field: Patients were treated with a single isocenter set up with beam split technique matching the supraclavicular (with or without axillary) fields as described above to the breast and chest wall fields. Breast or chest wall was treated using deep tangential fields at the level of the first three intercostal spaces or photon fields laterally matched on the skin to a slight oblique electron field medially. Techniques were chosen based on which would result in lowest doses to lung and

heart. In late 2010, hybrid planning with a combination of static and rapid arc techniques were used in patients when the above technique resulted in unacceptable dose to the heart and lungs. This constitutes a minority of patients during this time era.

Reconstructed breast with supraclavicular field with or without axillary or internal mammary nodal fields: Most reconstruction patients had expanders in place at the time of the radiation. Depending on the size of the reconstructed breast and to allow for steeper tangential fields, patients often underwent deflation of the contralateral and occasional the ipsilateral expander. Patients were treated with single isocenter set up with beam split technique matching the supraclavicular with or without axillary fields with tangential fields covering the reconstructed breast. Treatment of internal mammary nodal volumes in the first three intercostal spaces was accomplished with either deep tangent fields or matching photon-electron fields as described above. Use of hybrid plans in the later time frame was occasionally utilized in this setting depending on normal tissue doses.

Integration of dose sparing measures over time: Despite having computer tomography images in all the cases being studied, the heart was not routinely contoured as part of treatment planning in the early time period. Intermittent heart contouring to capture heart dose started in 2005 with routine heart contouring as part of 3-D treatment planning integrated into practice by 2008. Determination of mean cardiac radiation dose for patients prior to this time was done retrospectively using the patient's actual CT image and treatment plans. Integration of deep inspiration breath hold techniques occurred late during the study period, only intermittently used in 2013 with more routine use after the study period. Partial breast irradiation was used in several national cooperative group trials during the study period but this accounted for a small number of patients. Proton beam therapy was not used during the study period. The MCRD declined ($r=-0.47$, $p<0.0001$) over the study period (Supplemental Figure 3).

6. SENSITIVITY ANALYSIS ADDRESSING POTENTIAL FOR SURVEILLANCE BIAS IN PATIENTS WITH HIGHER CANCER STAGE

The 60 eligible heart failure cases (Figure 1) were re-matched to non-heart failure controls from the pool of potential controls (including those used in the primary analysis). Matching criteria were the same as for the primary analysis (age at the breast cancer diagnosis (within 10 years), use of anthracycline, use of trastuzumab and prior history of hypertension or diabetes), except that patients were not matched by tumor side but rather matched by cancer stage to account for the potential for surveillance bias (increased ascertainment of heart failure due to closer medical follow-up of more advanced cancer patients). Matching was possible in 59 of 60 eligible cases and the cases were identical to the primary analysis cases except for one patient. The re-matched control group (n=109) included 39 of control patients from the primary analysis (29 matched to a different case) and 70 new controls from the potential pool of controls (Figure 1). The baseline characteristics in the re-matched cases and controls (Table S5), analysis of conditions associated with heart failure incidence (Table S5) and analysis of association between mean cardiac radiation dose (MCRD) and heart failure incidence (Table S6) were performed as for the primary analysis.

As in the primary analysis, a history of ischemic heart disease or atrial fibrillation was associated with HF incidence in the sensitivity analysis cohort. In the primary analysis, there was a trend towards an association between beta blocker use and HF incidence ($p=0.11$) which was significant in the sensitivity analysis cohort ($p=0.02$) and likely related to the use of beta blockers for treatment of ischemic heart disease and atrial fibrillation rather than a primary effect of beta blockers on HF incidence. In this entire cohort, tumor side explained 34% ($p<0.001$) of the variation and tumor side and cancer stage explained 45% ($p<0.001$ for both) of the variation in MCRD.

As in the primary analysis, MCRD was associated with HF and HFpEF incidence (Table S6). The odds ratios were for HF per log MCRD were lower than in the primary analysis but higher when adjusting for tumor side, indicating an effect of

MCRD on HF incidence irrespective of tumor side and potentially indicative of differences in cardiac substructures affected by treatment of right vs left sided tumors.

Supplemental Table 1. Heart failure and comorbidity diagnostic codes.

	ICD-9 Diagnostic Codes or Procedure Codes
Heart failure	402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.93, 428-xx
Cardiomyopathy	425-xx
Diabetes Mellitus	250.X
Hypertension	401.X-405.X
Ischemic heart disease	
Acute Myocardial infarction*_or_	410.x1, 411.1, 411.8, 411.81, 411.89
History of CABG _or_	36.10-19
History of PCI	00.66, 36.01, 36.02, 36.05, 36.06, 36.07, 36.09
Atrial Fibrillation / Flutter	427.3x
Chronic pulmonary diseases	490-492.8, 493-493.91, 494, 495.0-505, 506.1

*Acute myocardial infarction was also verified by review of medical record for the presence of chest pain and cardiac biomarker and electrocardiographic evidence of myocardial infarction as previously described[7].

Abbreviations: CABG, coronary artery bypass grafting; ICD, International Classification of Disease; PCI, percutaneous coronary intervention

Supplemental Table 2. Modified Framingham Heart Failure Criteria.

Framingham Heart Failure Criteria
Major Criteria
Paroxysmal nocturnal dyspnea or orthopnea
Cardiomegaly
Acute pulmonary edema
Jugular venous distention
Central venous pressure ≥ 16 cm H_2O
Hepatojugular reflex
Rales
S3 gallop
Weight loss of 4.5 kg in 5 days during HF treatment
Minor Criteria
Nocturnal cough
Dyspnea on exertion
Edema
Hepatomegaly
Pleural effusion
Tachycardia
Weight loss of 4.5 kg in 5 days not during HF treatment

Patients are considered to meet Framingham criteria if at least two major or one major and at least two minor criteria are met.

Supplemental Table 3. Clinical Heart Failure Criteria.

Clinical Criteria for Heart Failure	N with finding documented
Physician diagnosis of heart failure	16
Symptoms	
Dyspnea at rest	5
Paroxysmal nocturnal dyspnea or orthopnea	2
Dyspnea on exertion	14
Signs	
Edema	12
Jugular venous distension or hepatojugular reflex	0
Rales	0
S3 gallop	1
Tachycardia	4
Chest radiography	
Cardiomegaly	8
Pulmonary venous hypertension or edema	5
Pleural effusion (without non-cardiac etiology)	3
Cardiac imaging after radiotherapy and prior to or coincident with heart failure diagnosis	
Ejection fraction < 50%	7
E/e' ≥ 15 or > Grade I diastolic dysfunction	6
Left atrial enlargement	11
Pulmonary artery systolic pressure > 40 mmHg	8
Response to diuretics	
Improved dyspnea	1
Weight loss > 5 lbs	0
Biomarker	
BNP ≥ 100 or NT-proBNP ≥ 400 pg/ml	4

Patients are considered to meet clinical heart failure criteria if a physician has documented a diagnosis of heart failure in the medical record and if objective evidence of heart failure was documented in the medical record. Of the 59 heart failure cases, 16 did not meet Framingham criteria. The objective evidence present in those 16 patients are shown.

Supplemental Table 4. Mean cardiac radiation dose and odds of heart failure in analysis stratified by tumor side.

	Right Side (N=35 Cases and 68 Controls)		Left Side (N=24 Cases and 43 Controls)	
	Odds Ratio Per Log MCRD	**p value**	**Odds Ratio Per Log MCRD**	**p value**
All Heart Failure				
Unadjusted	10.90 (2.82, 42.18)	<0.001	7.32 (1.76, 30.37)	<0.001
Adjusted for Age	9.27 (2.42, 35.46)	0.001	7.30 (1.75, 30.38)	0.006
Adjusted for History of Ischemic Heart Disease (IHD)	9.67 (2.49, 37.61)	0.001	6.56 (1.55, 27.69)	0.01
Adjusted for History of Atrial Fibrillation/Flutter (AF)	10.68 (2.74, 41.58)	<0.001	6.55 (1.54, 27.91)	0.01
Adjusted for Cancer Stage	11.02 (2.72, 44.68)	<0.001	6.57 (1.62, 26.61)	0.008
Adjusted for Age/IHD/AF/cancer stage	8.27 (2.10, 32.55)	0.002	5.98 (1.38, 25.80)	0.02

Supplemental Table 5. Clinical characteristics at breast cancer diagnosis and risk of heart failure in cohort matched by cancer stage rather than tumor side.

	Cases (n=59)	Controls (n=109)	Odds Ratio	p-value
Matched characteristics				
Age at breast cancer diagnosis, year	69.9±9.6	67.9±9.9	NA	NA
Anthracycline therapy, n(%)	7 (11.9)	13(11.9)	NA	NA
Trastuzumab therapy, n(%)	1 (1.7)	1 (0.92)	NA	NA
Hypertension, n(%)	39 (66.1)	70 (64.2)	NA	NA
Diabetes, n(%)	13(22.0)	24(22.0)	NA	NA
Cancer stage, n(%)			NA	NA
Stage 0	6 (10.2)	12(11.0)		
Stage 1	31 (52.5)	62 (56.9)		
Stage 2 (A and B , n=44) or 3 (A-C, n=13)	22 (37.3)	35 (32.1)		
Left sided breast cancer, n (%)	25 (42.4)	50 (45.9)	0.90 (0.48, 1.69)	0.75
Surgical therapy				0.79
Mastectomy	7 (11.9)	11 (10.1)	1.0	
Breast-conserving surgery	52 (88.1)	98 (89.1)	0.81 (0.17,3.86)	
None	0(0)	0(0)	N/A	
Adjuvant Paclitaxel therapy, n(%)				0.75
No	52(88.1)	97 (89.0)	1.0	
Yes	7 (11.9)	12 (11.0)	1.36 (0.20, 9.00)	
Adjuvant hormonal therapy, n(%)				0.44
No	24(40.7)	41(37.6)	1.0	
Yes	35(59.3)	68 (62.4)	0.74 (0.35, 1.59)	
Obesity (Body Mass Index ≥ 30 kg/m^2)				0.47
No	37 (62.7)	62 (56.9)	1.0	
Yes	22 (37.3)	47 (43.1)	0.78 (0.40, 1.52)	
History of ischemic heart disease, n(%)				0.03
No	51(86.4)	106 (97.3)	1.0	
Yes	8(13.6)	3(2.8)	4.52 (1.19, 17.20)	
History of atrial fibrillation or flutter, n(%)				0.01
No	46 (78.0)	101 (92.7)	1.0	
Yes	13 (22.0)	8 (7.3)	3.21 (1.26, 8.19)	
History of chronic lung disease, n(%)				0.21
No	53 (90.0)	103 (94.5)	1.0	
Yes	6 (10.2)	6 (5.5)	2.16 (0.65, 7.19)	
Medication use				
ACE or ARB, n(%)				0.35
No	38 (64.4)	76 (69.7)	1.0	
Yes	21 (35.6)	33 (30.3)	1.48 (0.66, 3.32)	
Beta blocker, n(%)				0.02
No	32 (54.2)	81 (74.3)	1.0	
Yes	27 (45.8)	28 (25.7)	2.29 (1.14, 4.60)	

Supplemental Table 6. Association between mean cardiac radiation dose and odds of incident heart failure in cohort matched by cancer stage rather than tumor side.

	Odds Ratio Per Log MCRD	p value
All Heart Failure		
Unadjusted	1.81 (1.16, 2.82)	0.009
Adjusted for Age	1.89 (1.18, 3.02)	0.008
Adjusted for History of Ischemic Heart Disease (IHD)	1.62 (1.02, 2.58)	0.04
Adjusted for History of Atrial Fibrillation/Flutter (AF)	1.68 (1.06, 2.69)	0.03
Adjusted for Age/IHD/AF	1.63 (0.98, 2.71)	0.06
Adjusted for Laterality	3.28 (1.68, 6.39)	<0.001
Adjusted for Age/IHD/AF/laterality	3.21 (1.48, 6.96)	0.003
Heart Failure with Preserved Ejection Fraction		
Unadjusted	1.96 (1.09, 3.54)	0.03
Adjusted for Age	2.00 (1.08, 3.70)	0.03
Adjusted for History of Ischemic Heart Disease (IHD)	1.89 (1.04, 3.45)	0.04
Adjusted for History of Atrial Fibrillation/Flutter (AF)	1.94 (1.05, 3.58)	0.04
Adjusted for Age/IHD/AF	1.90 (0.98, 3.68)	0.06
Adjusted for Laterality	5.40 (1.96, 14.90)	0.001
Adjusted for Age/IHD/AF/laterality	8.05 (2.21, 29.33)	0.002
Heart Failure with Reduced Ejection Fraction		
Unadjusted	1.61 (0.75, 3.46)	0.22
Adjusted for Age	1.83 (0.80, 4.15)	0.15
Adjusted for History of Ischemic Heart Disease (IHD)	NA*	
Adjusted for History of Atrial Fibrillation/Flutter (AF)	1.56 (0.69, 3.57)	0.29
Adjusted for Age/AF	1.73 (0.72, 4.15)	0.22
Adjusted for Laterality	1.44 (0.53, 3.89)	0.47
Adjusted for Age/IHD/AF/laterality	1.39 (0.46, 4.25)	0.56

* No controls matched to those cases of heart failure and reduced ejection fraction had a history of ischemic heart disease

Supplemental Table 7. Association between mean cardiac radiation dose and odds of incident heart failure in Primary Analysis Cohort (matched by tumor side) after exclusion of the 16 HF cases not meeting Framingham Criteria and their matched controls*

	Odds Ratio Per Log MCRD	p value
All Heart Failure		
Unadjusted	9.52 (2.94, 30.90)	<0.001
Adjusted for Age	8.86 (2.70, 29.10)	<0.001
Adjusted for History of Ischemic Heart Disease (IHD)	7.97 (2.49, 25.48)	<0.001
Adjusted for History of Atrial Fibrillation/Flutter (AF)	9.75 (2.92, 32.61)	<0.001
Adjusted for Cancer Stage	9.15 (2.79, 30.05)	<0.001
Adjusted for Age/IHD/AF/cancer stage	9.13 (2.50, 33.37)	<0.001
Heart Failure with Preserved Ejection Fraction		
Unadjusted	11.03 (2.59, 46.92)	0.001
Adjusted for Age	9.86 (2.30, 42.25)	0.002
Adjusted for History of Ischemic Heart Disease (IHD)	10.26 (2.41, 43.70)	0.002
Adjusted for History of Atrial Fibrillation/Flutter (AF)	13.40 (2.74, 65.55)	0.001
Adjusted for cancer stage	12.23 (2.69, 55.54)	0.001
Adjusted for Age/IHD/AF/cancer stage	16.14 (2.73, 95.56)	0.002
Heart Failure with Reduced Ejection Fraction		
Unadjusted	5.60 (0.72, 43.54)	0.10
Adjusted for Age	6.61 (0.75, 58.50)	0.09
Adjusted for History of Ischemic Heart Disease (IHD)	2.52 (0.36, 17.49)	0.35
Adjusted for History of Atrial Fibrillation/Flutter (AF)	5.35 (0.68, 41.92)	0.11
Adjusted for cancer stage	5.18 (0.59, 45.12)	0.14
Adjusted for Age/IHD/AF/cancer stage	2.13 (0.31, 14.65)	0.44

*Final N=43 cases and 82 matched controls

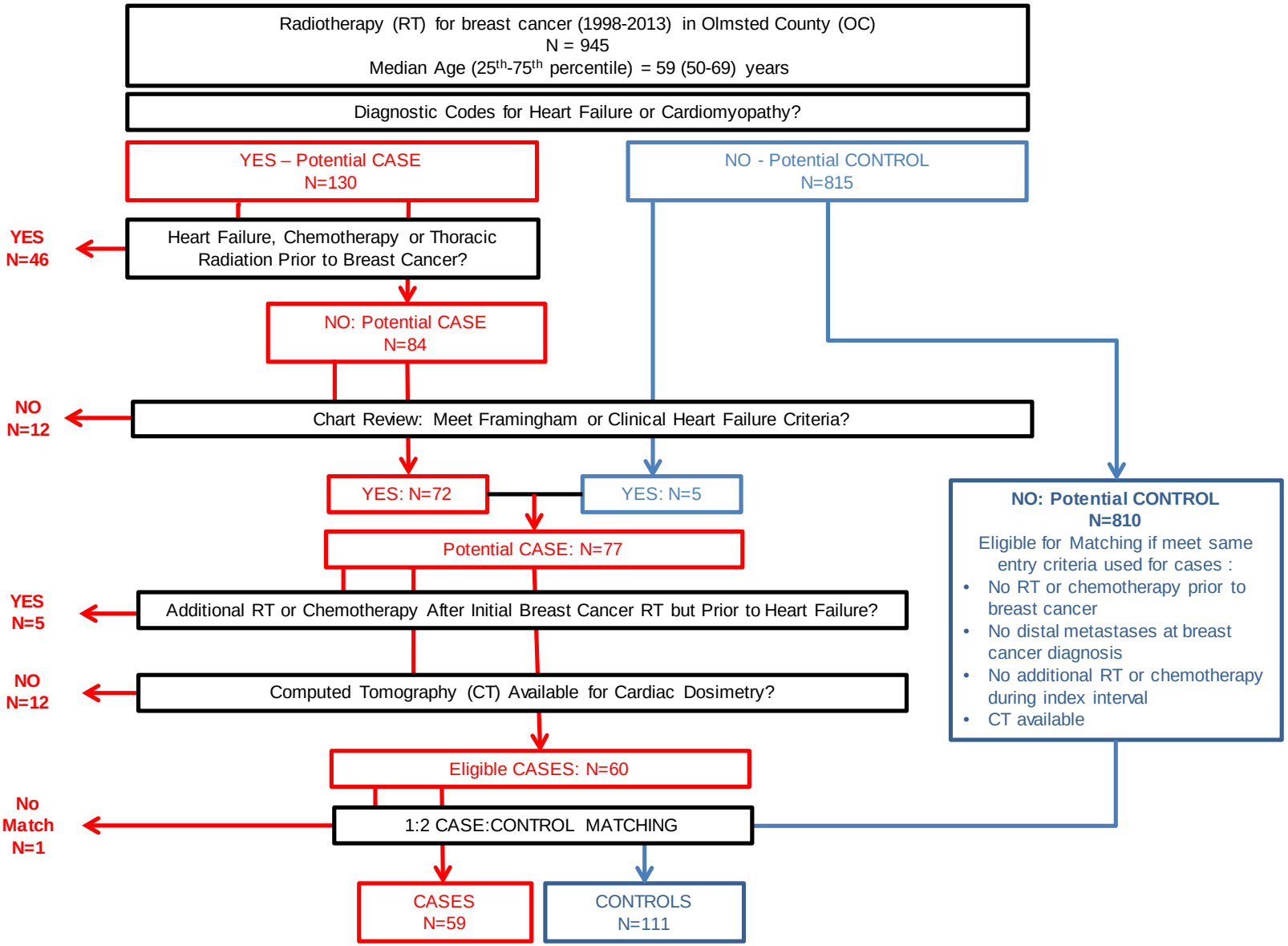
Table S8. Association between mean cardiac radiation dose and odds of incident heart failure in the sensitivity analysis cohort (matched by cancer stage rather than tumor side) after exclusion of the 16 HF cases not meeting Framingham Criteria and their matched controls[†]

	Odds Ratio Per Log MCRD	p value
All Heart Failure		
Unadjusted	2.02 (1.16, 3.52)	0.01
Adjusted for Age	2.09 (1.18, 3.72)	0.01
Adjusted for History of Ischemic Heart Disease (IHD)	1.81 (1.01, 3.24)	0.05
Adjusted for History of Atrial Fibrillation/Flutter (AF)	1.90 (1.04, 3.45)	0.02
Adjusted for Age/IHD/AF	1.77 (0.94, 3.33)	0.07
Adjusted for Laterality	3.16 (1.46, 6.82)	0.003
Adjusted for Age/IHD/AF/laterality	2.71 (1.10, 6.67)	0.03
Heart Failure with Preserved Ejection Fraction		
Unadjusted	2.27 (1.13, 4.56)	0.02
Adjusted for Age	2.30 (1.12, 4.71)	0.02
Adjusted for History of Ischemic Heart Disease (IHD)	2.16 (1.07, 4.37)	0.03
Adjusted for History of Atrial Fibrillation/Flutter (AF)	2.20 (1.06, 4.58)	0.04
Adjusted for Age/IHD/AF	2.07 (0.97, 4.40)	0.06
Adjusted for Laterality	4.33 (1.50, 12.48)	0.007
Adjusted for Age/IHD/AF/laterality	5.17 (1.40, 19.12)	0.01
Heart Failure with Reduced Ejection Fraction		
Unadjusted	2.07 (0.70, 6.06)	0.19
Adjusted for Age	2.20 (0.71, 1.44)	0.17
Adjusted for History of Ischemic Heart Disease (IHD)	NA*	
Adjusted for History of Atrial Fibrillation/Flutter (AF)	1.56 (0.40, 6.01)	0.52
Adjusted for Age/AF	1.68 (0.40, 7.08)	0.49
Adjusted for Laterality	1.80 (0.50, 6.44)	0.36
Adjusted for Age/IHD/AF/laterality	1.16 (0.22, 6.03)	0.86

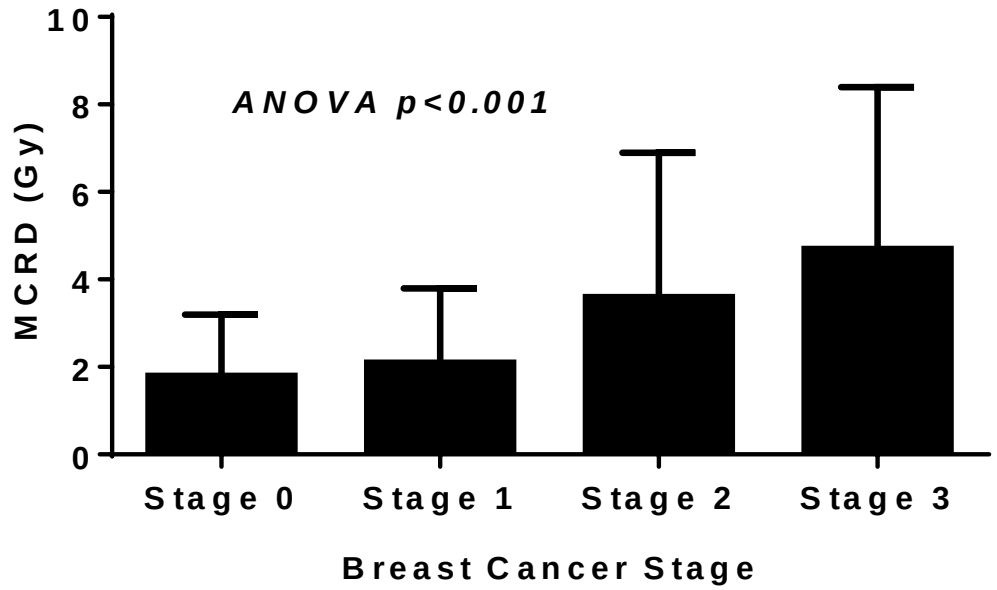
[†]Final N=43 cases and 78 matched Controls; * No controls matched to those cases of heart failure and reduced ejection fraction had a history of ischemic heart disease

Supplemental Figure 1. Study population

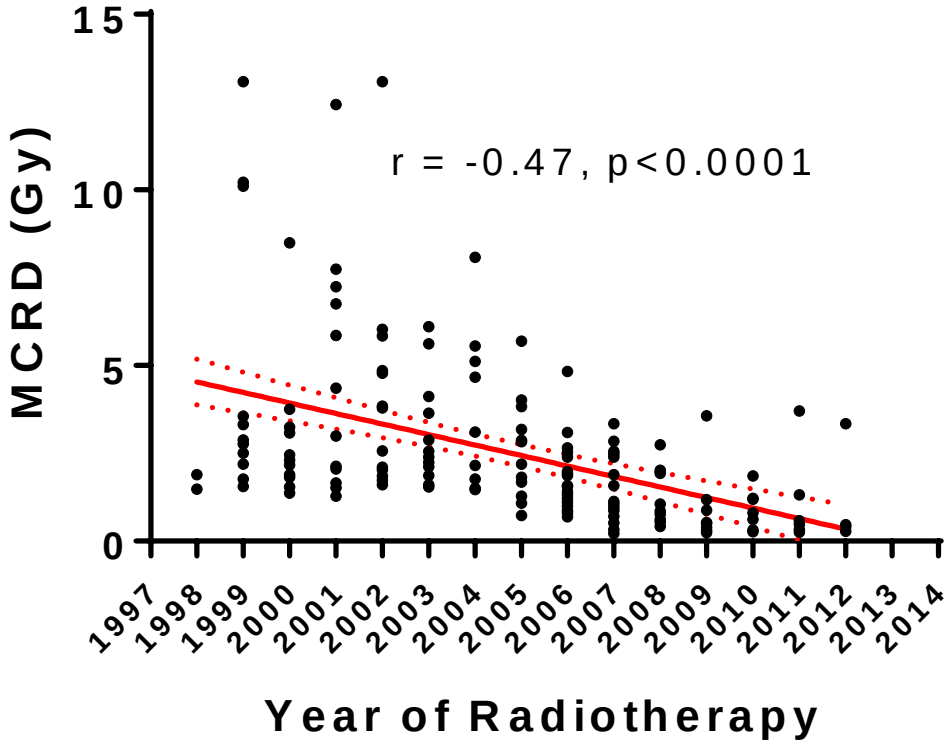
Only subjects (cases or controls) who were residents of Olmsted County, MN were eligible for inclusion.



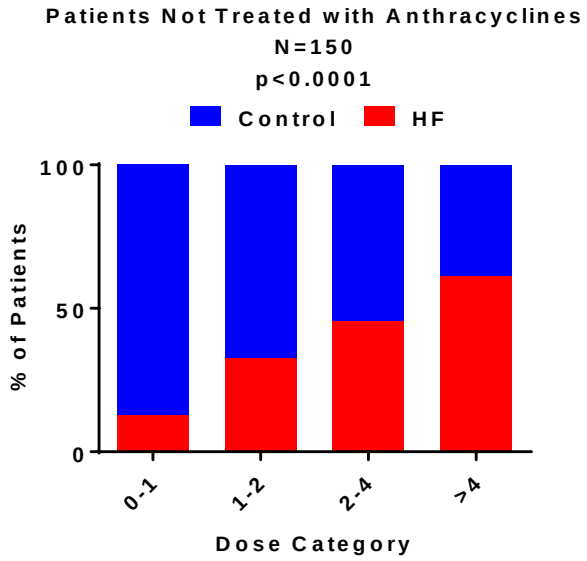
Supplemental Figure 2. Mean cardiac radiation dose (MCRD) according to cancer stage: The mean and standard deviation MCRD for patients with Stage 0-3 breast cancer are shown.



Supplemental Figure 3. Mean cardiac radiation dose (MCRD) according to calendar year of radiotherapy.



Supplemental Figure 4. MCRD and crude frequency of heart failure excluding cases and controls that also were treated with chemotherapy



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Dr Carolyn Lam: Welcome to Circulation on the Run, your weekly podcast summary and backstage pass to The Journal and its editors. I'm Dr. Carolyn Lam, associate editor from the National Heart Center and Duke National University of Singapore.

Today's issue features two exciting papers regarding heart failure in patients with breast cancer. We will be discussing this right after these summaries.

Are we any closer to improving survival in Eisenmenger syndrome? Well, today's first original paper looks at contemporary trends and presents a multivariable mortality risk stratification model based on five simple noninvasive predictors of death in this population. Dr. Kempny and colleagues from Royal Brompton Hospital in London in the United Kingdom preform a large multicenter study in 1098 patients with Eisenmenger syndrome followed up between years 2000 and 2015.

At the end of the study almost two-thirds of patients were on advance therapy for pulmonary arterial hypertension, while only six patients underwent lung or heart and lung transplantation. The study showed that despite advances in management, there was significant mortality amongst contemporary adults with Eisenmenger syndrome and 25.3% of patients died over a median follow up period of 3.1 years. Mortality was higher in older patients, those with a pre-tricuspid shunt, lower oxygen saturation, absence of sinus rhythm, or with a pericardial effusion.

This important study is accompanied by an editorial by Drs. Lange, from Texas Tech University Health Sciences Center El Paso and Dr. Brickner from UT Southwest Medical Center in Dallas, Texas. The editorialists call for a prospective randomized control trials of the effect of current, or future pulmonary vasoactive disease targeting therapies on mortality in Eisenmenger syndrome patients, and say it's time to direct our efforts from improving risk-stratification towards improving survival.

The next study provides experimental evidence of tolerogenic dendritic cell therapy as a novel anti-remodeling therapy in myocardial infarction. Tolerogenic dendritic cells are promising, potent, beneficial regulators of the post-infarct healing process via their control of T-regulatory cells and M1 M2 macrophages. Plus they have the advantage of the ease of administration and feasibility of a heart specific tolero-dendritic cell production.

In the current paper by co-first authors, Drs. Choo and Lee, and co-corresponding authors, Drs. Chang and Lim, from Catholic University Korea and Chai University in Korea, authors generated tolerogenic dendritic cells by treating bone marrow-derived dendritic cells with TNF-alpha and cardiac lysate from mice with myocardial infarction. They then injected myocardial infarction mice twice with tolerogenic dendritic cells within 24 hours and at 7 days after LAD ligation. In treated animals, in vivo cardiac magnetic resonance imaging and

ex vivo histology confirm the beneficial effects on post-infarct LV remodeling. Furthermore, subcutaneously administered tolerogenic dendritic cells near the inguinal lymph node migrated to the regional lymph nodes and induced infarct tissue specific T-regulatory T-cell populations in the inguinal and mediastinal lymph nodes, spleen, and infarcted myocardium, all of which elicited an inflammatory to reparative macrophage shift. The altered immune environment in the infarcted heart resulted in better wound remodeling, preserved left ventricular systolic function, and an improved survival following myocardial infarction. Thus, this study shows that tolerogenic dendritic cell therapy in a preclinical model of myocardial infarction may be potentially translatable into an anti-remodeling therapy for ischemic repair.

The final paper reports results of cell therapy on exercise performance and limb perfusion in peripheral artery disease from the PACE trial, which is an NHLBI-sponsored randomized double-blind placebo-controlled phase two clinical trial, designed to assess the safety and efficacy of autologous bone marrow-derived aldehyde dehydrogenase bright cells in peripheral artery disease, and to explore associated claudication physiological mechanisms. In this paper from corresponding author Dr. Moye from UT School of Public Health in Houston, Texas and colleagues of the Cardiovascular Cell Therapy Research Network, a total of 82 patients with claudication and infrainguinal peripheral artery disease were randomized at nine sites to receive alcohol dehydrogenase bright cells or placebo. All patients underwent bone marrow aspiration and isolation of aldehyde dehydrogenase bright cells followed by 10 injections into the thigh and calf of the index leg. Results showed that there were no significant differences in the change over six months between study groups for the co-primary endpoint of peak walking time, collateral count, peak hyperemic popliteal flow, and capillary profusion measured by magnetic resonance imaging.

Additionally, there were no significant differences for the secondary endpoints including quality of life measures. There were no adverse safety outcomes. Interestingly, a post-hoc exploratory analysis suggested that aldehyde dehydrogenase bright cell administration might be associated with an increase in the number of collateral arteries in participants with completely occluded femoral arteries.

In summary, cell therapy did not improve peak walk time or magnetic resonance outcomes, and the changes in peak walk time were not associated with the anatomic or physiologic MRI endpoints. However, future peripheral artery disease cell therapy trial design may be informed by new anatomic and perfusion insights. These and other issues are discussed in an accompanying editorial by Drs. Breton-Romero and Hamburg from Boston University School of Medicine. Well, that wraps it up for our summaries, now for our feature discussion.

We are really in the grove here in Washington, D.C. and I am borrowing the words of my very special, star associate editor, guest, Dr. Gregory Hundley, and he's from Wakefield University School of Medicine. We're discussing two very important papers and they deal with the risk of heart failure following breast cancer. Why they're so important? Well, first of all, it's about time we looked at this problem in detail, and secondly, they actually represent papers in a new section of the journal called "Bridging Disciplines," and in this case cardio-oncology. Very, very important topics.

We're here with the corresponding authors of both papers, Bonnie Ky from University of Pennsylvania School of Medicine and Dr. Margaret Redfield from Mayo Clinic.

Dr Gregory Hundley: Thank you, Carolyn. I really appreciate that wonderful introduction and also the chance to talk with Bonnie about this exciting topic.

So, Bonnie, you've got a paper here, now, where you did a study in patients with breast cancer, and it sounds like you acquired echocardiograms over a period of time. Can you tell us a little bit about that?

Dr Bonnie Ky: Correct. So this is longitudinal prospective cohort study, it's an NIH-funded R01, whereby we are enrolling patients from the breast cancer clinic who are receiving doxorubicin or trastuzumab or a combination of the two therapies. And we're performing very careful cardiovascular phenotyping, from the time at which they initiate chemotherapy through their chemotherapy and then annually once a year we have them come back, for a total follow up time of 10 years.

We took a subcohort, 277 patients, and from their echocardiograms, we analyze them very carefully for various measures of left ventricular size, function, not only systolic function but also diastolic function. We also looked at measures of contractility such as strain in multiple dimensions, and then also measures of ventricular arterial coupling, as well as arterial loads, so how the ventricle interacts with the arterial system. And what we found was that over a 3.2 period time period, on population average, these modest declines in left ventricular ejection fraction, and even across all three treatment groups, and even at three years there were persistent LVF declines.

Dr Gregory Hundley: So, I understand, Bonnie, that you also collected some information as to whether or not these patients were experiencing symptoms associated with heart failure. How did the imaging markers relate to the symptomatology associated with heart failure?

Dr Bonnie Ky: What we found was that early changes in arterial stiffness or total arterial load, as well as early changes in EF were associated with worse heart failure symptoms at one year. A lot of our other analysis was focused on defining what

echo parameters of remodeling, size, function are driving or associated most strongly with LVF decline, as well as LVF recovery.

Dr Gregory Hundley: And then at two years, what happened? Did the echo parameters, were they still associated with heart failure or was there a little discrepancy there?

Dr Bonnie Ky: Interestingly, at two years ... no, there was no significant association with changes in arterial load and heart failure symptoms at two years.

Dr Gregory Hundley: So there might be something transient that's occurring that is associated with heart failure early, and then the patients still had heart failure late, so maybe something else is operative. What do you think we need to do next? What's the next step in your research and then other investigators around the world; what do we need to do to design studies to look at these issues further?

Dr Bonnie Ky: Yeah. What does the field need, the field of cardio-oncology that's really growing and developing at rapid paces. Some of the major findings from the study was that changes in total arterial load were very strongly associated with both LVF decline and LVF recovery. So total arterial load is the measure of blood pressure or total arterial stiffness, it's derived from blood pressure. And to me, that begs the question, or begs the next step is that changes in blood pressure are associated with decline as well as recovery. I think, oh, as cardiologists we've also always recognized the importance of afterload reduction. And to me, this study suggests that we need a study, a randomized clinical trial, looking at blood pressure lowering in this population to help mitigate LVF declines.

Dr Carolyn Lam: I'd actually like to turn it back to you. You are world-renowned for your work in cardio-oncology. Where do you think this fits in, and where do you think we need to address most urgently?

Dr Gregory Hundley: I think where this fits in wonderfully is a lot of individuals around the world are collecting echocardiographic measures, and all different types. And what Bonnie has helped do is clarify what we would expect to see in this particular patient population. How those measures change over time and that feeds into another block of data, when the measurements head south, do we change therapy, do we add protective agents, and things of that nature. So I think Bonnie's work really contributes on that front. What she has also pointed out is that more research needs to be performed, not necessarily because the patients had heart failure symptomatology at two years, but not necessarily associated with the decline in EF; are there other systems in the cardiovascular realm that are being affected? The vascular system-

Dr Carolyn Lam: Yeah.

Dr Gregory Hundley: Skeletal muscle, many other areas. So as cardiologists start to work more with oncologists in this space, and we're all working together to make sure that not only patients survive their cancer, but they have an excellent quality of life, I

think we'll see, as we have in other heart failure syndromes, a look toward other aspects of the cardiovascular system, body in general, to reduce the overall morbidity associated with the disease.

I think what we need to recognize as cardiovascular medicine specialists is that now for many forms of cancer, cardiovascular events, and certainly morbidity are becoming the primary issue that folks have to deal with with survivors. It's not necessarily the cancer recurrence, it's not necessarily a new cancer, it's cardiovascular. So we've got to integrate cardiology earlier in working with oncologists to improve overall survival and create an excellent quality of life from our different perspectives.

Dr Carolyn Lam: So, Maggie, let's move on to your paper now. You looked at radiotherapy's effect, whereas Bonnie looked at chemotherapy's effect. Could you tell us what you did and what you found?

Dr Margaret Redfield: The rationale for doing this study was, of course, seeing a lot of patients with HFpEF who had had radiation therapy for breast cancer, and I always just sort of assumed that that was because 12% of women over the age of 40 get breast cancer and 20% of women over the age of 40 get heart failure, but it seemed to be somehow more common than that. The other rationale was that radiation therapy does not actually affect the cardiomyocytes; they are very radiation resistant. And what radiation does is cause microvascular endothelial cells damage and inflammation, and that is felt to be fundamental in the pathophysiology for HFpEF.

So we thought we should look at this. I collaborated with a radiation oncologist and oncologists, and they were interested in looking at this because there's a lot of techniques now to reduce cardiac radiation exposure during radiation therapy, including proton beam therapy, and they're trying to prioritize who they use this new technology on. So what we did was start with a population-based study, all women who lived in Olmsted county who received radiation therapy for breast cancer in the contemporary era, where they're already using these dose reducing techniques. So we wanted to make it relevant to what's going on today. And so we started with a base cohort of all women. We matched patients' cases, it was a case-control study, so we matched cases and controls according to their age at the time of breast cancer, whether they had heart failure risk factors, like hypertension or diabetes, whether they got adjuvant chemotherapy, and tumor size, because we felt it was important that radiation could affect different parts of the heart, depending on whether it was right- or left-sided tumor.

And what we found is that the risk of heart failure increased with the mean cardiac radiation dose. We measured the mean cardiac radiation dose in every case and every control from their CT scans and their radiation plants. And as the radiation dose went up, the risk of heart failure went up, even matching or controlling for chemotherapy, which wasn't used that often in this group, or

heart failure risk factors. And the vast majority of these cases were indeed HFpEF.

So we then looked at factors that happened in-between the radiotherapy and the onset of heart failure, making sure that this all wasn't just coronary artery disease, 'cause we know radiation can increase the risk of coronary artery disease. And indeed there were, only in about 18% of cases was there a new episode of coronary disease in the interim between the radiotherapy and the breast cancer. So, basically found that the mean cardiac radiation dose, even in today's era, does increase the risk of heart failure with preserved ejection fractions.

Dr Carolyn Lam: The things that stuck out to me ... it's population based. You did such a comprehensive study to really answer very key questions: dose of radiation, is it really just mediated by age and age-related risk factors, is it just about MI or could it be more microvascular disease? Congratulations, I really appreciated this paper. Some of the take-home messages are directly related to the treatment of breast cancer, isn't it? And about the importance of minimizing radiation dose if possible. I suppose one of the take-homes is, as well, for screening and watching out for heart failure. One thing though: how were these woman diagnosed with HEpEF? I mean, this is always the questions I get. How do you get diagnosed with HEpEF?

Dr Margaret Redfield: Right, well, first we started with looking to see if they had a ICD code for heart failure, and then we looked at each case of heart failure and determined if they either met Framingham criteria at the time of the diagnosis and the majority of them did. If they didn't actually meet the Framingham criteria, we looked to be sure there was a physician diagnosis of heart failure in the record and that they had supportive evidence of heart failure: echocardiographic findings, natriuretic peptide findings, and other clinical characteristics of heart failure.

And importantly, in the large control group from where we, you know, got our controls, people, a very large group of patients who did not get heart failure, we'd use natural language processing to look at all those records to make sure we weren't missing anybody who didn't have an ICD diagnosis or code for heart failure to make sure we weren't missing any cases of heart failure. So, we really tried to use very stringent methods to make sure we had true cases and control groups.

Dr Carolyn Lam: Indeed, and it actually goes back to Bonnie's paper as well, where we have to remind everyone that the diagnosis of HEpEF really starts with the symptomatology of heart failure in particular, that you so rigorously determined. I think just one last thing, Maggie: what do you think this implies now, for HEpEF? What do we do in general so the non-radiation-associated, do we believe more the Walter Paulus-Carsten Tschope hypothesis, and if so, what do we do?

Dr Margaret Redfield: Yes, well I think it really does support that hypothesis. We know that radiation therapy, again, we know what it does to the coronary microvascular endothelial cells and that's been elegantly worked out both in patients and in animal models. I think this really supports the Paulus hypothesis because this microvascular damage was able to produce heart failure, so I think that really supports that hypothesis. And there's been some studies showing decreased coronary flow reserve in HEpEF patients; it's very common. So I think indeed it does support that hypothesis and that the coronary microvasculature is key in the pathophysiology of HEpEF.

However it's a little scary to me because that sort of damage, once it's established, may be very hard to treat. You know, proangiogenic strategies in peripheral vascular disease have not yet yielded the benefits that we hoped for, so I think it's a tough therapeutic challenge that'll be very important to try to address in pre-clinical studies to try and figure out once the microvasculature is so damaged how do we treat that? How do we reverse that process?

Dr Carolyn Lam: Yeah. Words of wisdom. Maggie, thanks so much for inspiring, just all of us in this field. I just had to say that. You know, you are the reason that I am totally in love with HEpEF. (laughter)

Dr Margaret Redfield: (laughter)

Dr Carolyn Lam: So thank you so much for joining me today on the show. In fact, thank you to all my three guests.

You've been listening to Circulation on the Run. You must tell everyone about this episode, it is full of gems.

Thank you, and tune in next week.