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

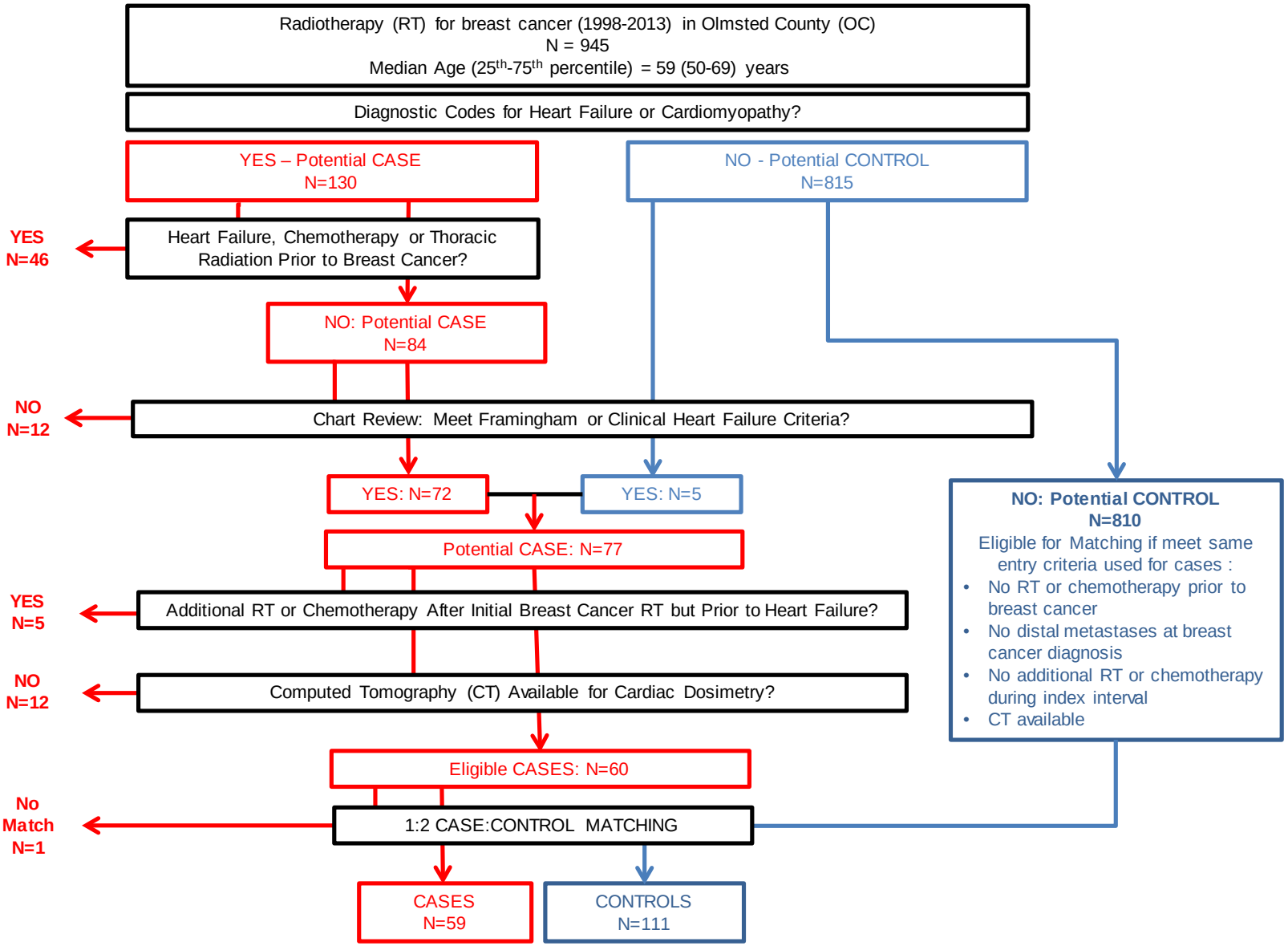
Table S8. Association between mean cardiac radiation dose and odds of incident heart failure in the sensitivity analysis cohort (matched by cancer stage rather than tumor side) after exclusion of the 16 HF cases not meeting Framingham Criteria and their matched controls[†]

	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

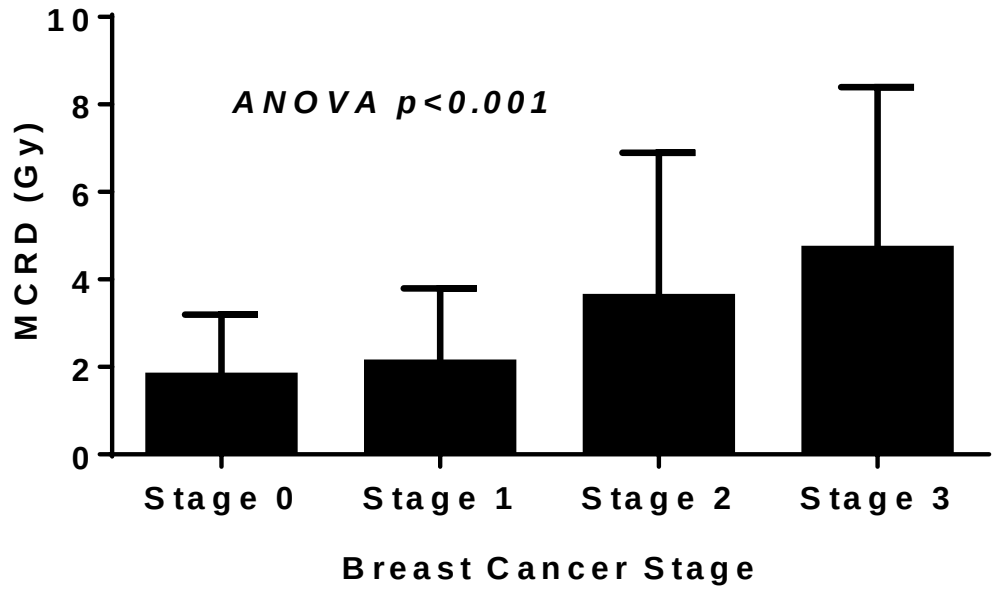
[†]Final N=43 cases and 78 matched Controls; * No controls matched to those cases of heart failure and reduced ejection fraction had a history of ischemic heart disease

Supplemental Figure 1. Study population

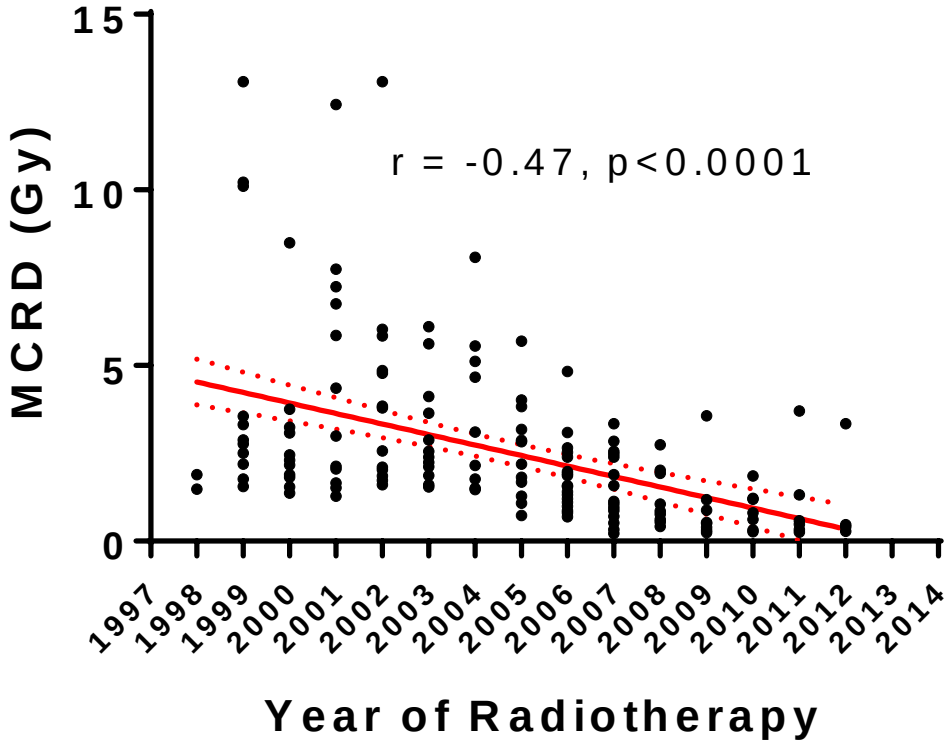
Only subjects (cases or controls) who were residents of Olmsted County, MN were eligible for inclusion.



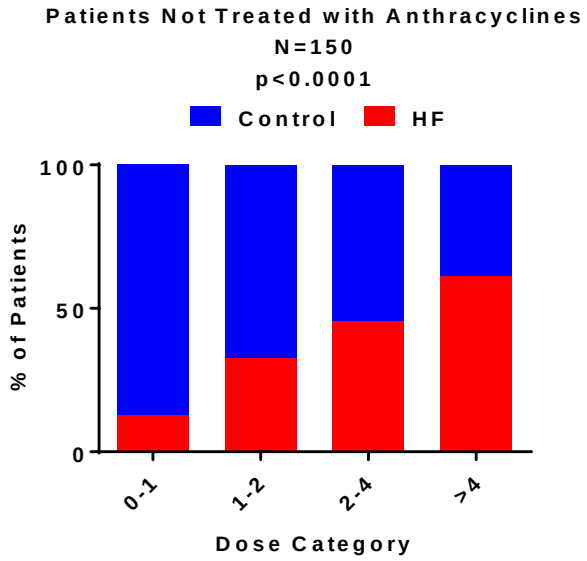
Supplemental Figure 2. Mean cardiac radiation dose (MCRD) according to cancer stage: The mean and standard deviation MCRD for patients with Stage 0-3 breast cancer are shown.



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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