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Clinical Investigation

# Modern Radiation Therapy and Cardiac Outcomes in Breast Cancer

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**Summary**

The present population-based study of women with nonmetastatic breast cancer is the first to identify that women with left-sided breast cancer and a history of cardiac disease who underwent radiation therapy from 2000 to 2010 have a small, but significantly, increased rate of percutaneous coronary intervention (PCI) compared with those with right-sided cancer. Those with left-sided cancer who underwent PCI also had a survival

**Purpose:** Adjuvant radiation therapy, which has proven benefit against breast cancer, has historically been associated with an increased incidence of ischemic heart disease. Modern techniques have reduced this risk, but a detailed evaluation has not recently been conducted. The present study evaluated the effect of current radiation practices on ischemia-related cardiac events and procedures in a population-based study of older women with nonmetastatic breast cancer.

**Methods and Materials:** A total of 29,102 patients diagnosed from 2000 to 2009 were identified from the Surveillance, Epidemiology, and End Results—Medicare database. Medicare claims were used to identify the radiation therapy and cardiac outcomes. Competing risk models were used to assess the effect of radiation on these outcomes.

**Results:** Patients with left-sided breast cancer had a small increase in their risk of percutaneous coronary intervention (PCI) after radiation therapy—the 10-year cumulative incidence for these patients was 5.5% (95% confidence interval [CI] 4.9%-6.2%) and 4.5% (95% CI 4.0%-5.0%) for right-sided patients. This risk was limited to women with previous cardiac disease. For patients who underwent PCI, those with left-sided breast cancer had a significantly increased risk of cardiac

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decrement. The results of the present study could help physicians better stratify patients for aggressive cardioprotective techniques.

mortality with a subdistribution hazard ratio of 2.02 (95% CI 1.23-3.34). No other outcome, including cardiac mortality for the entire cohort, showed a significant relationship with tumor laterality.

**Conclusions:** For women with a history of cardiac disease, those with left-sided breast cancer who underwent radiation therapy had increased rates of PCI and a survival decrement if treated with PCI. The results of the present study could help cardiologists and radiation oncologists better stratify patients who need more aggressive cardioprotective techniques. 

## Introduction

Adjuvant radiation therapy is commonly used in women with breast cancer to reduce the risk of local recurrence and breast cancer-specific mortality (1, 2). However, despite its oncologic benefit, incidental radiation to the heart, such as can occur in patients with left-sided breast cancer, can have deleterious effects. Historical studies of radiation therapy for breast cancer noted a significant increase in the risk of ischemic heart disease (3-8). Because of the potentially cardiotoxic effect of radiation therapy, research has focused on defining acceptable dose constraints for the heart (9) and developing methods that minimize the risk of cardiac radiation such as the use of computed tomography to define the treatment fields, respiratory gating, and prone positioning.

Current research has focused on evaluating the effect of these techniques on radiation-associated cardiac morbidity and mortality (10-12). Recent registry studies have found no effect from tumor laterality on cardiac-associated mortality after radiation therapy for women with nonmetastatic disease after 1980 (10). However, few studies have evaluated the risk of specific cardiac events that could affect a patient's health status and quality of life. Patt et al (12), analyzing data up to 2001, found no difference in the proportion of cardiac events between patients with right- and left-sided breast cancer. The purpose of the present study was to evaluate the effect of current radiation practices on ischemia-associated cardiac sequelae in a population-based study of women with nonmetastatic breast cancer.

## Methods and Materials

### Data source

The present research was performed using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER)−Medicare linked database. SEER pools data from cancer registries across the United States covering 28% of the population. Medicare is a federally funded insurance program for individuals aged >65 years. The SEER−Medicare linkage provides Medicare claims data for Medicare beneficiaries within the SEER database, allowing researchers to study longitudinal outcomes related to a patient's disease. The institutional review board of the University of California San Diego deemed the present study exempt from review.

### Study population

The present research focused on studying the cardiac effect of current radiation practices on older women with nonmetastatic breast cancer. An initial query of the SEER database identified 59,192 patients ≥66 years old diagnosed from 2000 to 2009 with histologically confirmed primary local or regional breast cancer with known tumor laterality who had undergone radiation therapy. Patients had to have continuous Part A and B coverage from 1 year before diagnosis until death or the end of the study period (December 2010) to allow for the ascertainment of comorbidities before diagnosis and cardiac outcomes after radiation therapy. Those covered by managed care (Part C coverage) were excluded from the study, because these organizations do not routinely bill Medicare. We included only patients with Medicare claims for radiation therapy within 1 year of diagnosis. Further refinement to the study population was based on the specifics of radiation therapy. The final study cohort consisted of 29,102 patients. The complete patient selection schema is shown in Figure 1.

### Study covariates

The patient characteristics, such as age at diagnosis, race, marital status, year of diagnosis, tumor stage, primary tumor size and grade, laterality, primary surgery, regional lymph node surgery, and median income from the 2000 US Census tract data, were extracted from SEER. Inpatient and outpatient Medicare claims from the year before the diagnosis were used to determine pre-existing comorbidity using the Deyo adaptation of the Charlson comorbidity index (13). The administration of chemotherapy was ascertained using previously described methods (14). Specific chemotherapeutic drugs with known cardiovascular toxicities were identified using Healthcare Common Procedure Coding System (HCPCS) J codes. Care at a teaching hospital was defined as any indirect medical education payment noted during a hospitalization after the patient's diagnosis of cancer. The use of breast magnetic resonance imaging after diagnosis was identified using the corresponding HCPCS codes. Patient and treatment

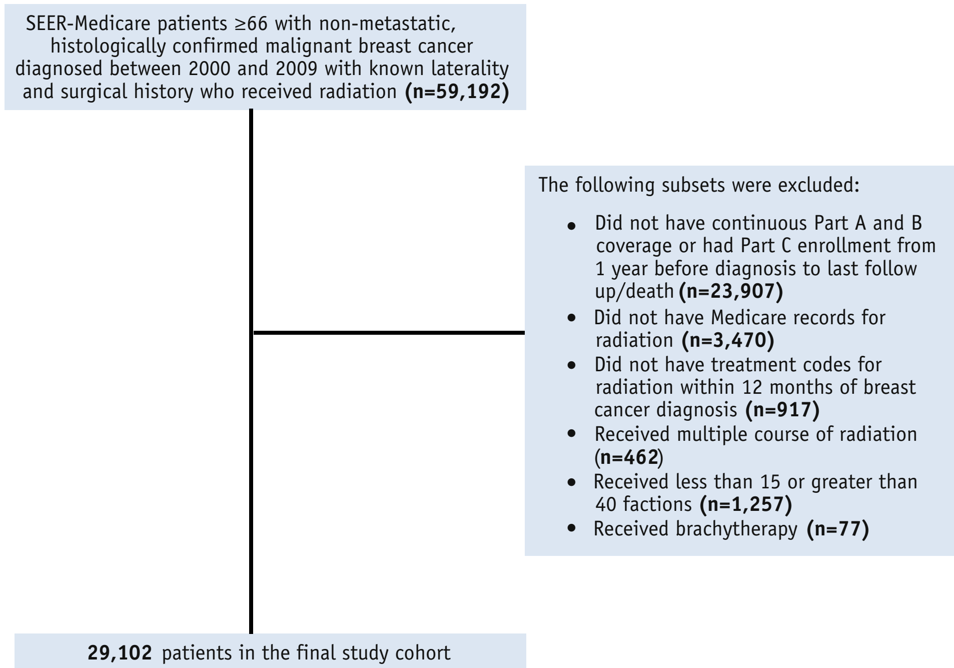



**Fig. 1.** Patient selection process.

characteristics for the entire cohort and stratified by tumor laterality are listed in Table 1.

## Radiation therapy

Radiation therapy was identified in the Carrier Claims and outpatient files using HCPCS codes (Table E1; available online at www.redjournal.org) (15). A course of radiation therapy was defined as a cluster of claims, with any break of ≥30 days between subsequent codes assumed to be indicative of a separate course of radiation therapy. Only patients who received 1 course of radiation were included to ensure that the effect of the first course of radiation was not confounded by later treatment. Patients who received brachytherapy were also excluded. Intensity modulated radiation therapy (IMRT) was identified from the specific planning or treatment codes. Only patients with a record of having received 15 to 40 days of radiation treatment, including standard and hypofractionated regimens (16) within 1 year of the breast cancer diagnosis, were included to reduce the likelihood of including patients receiving palliative courses of radiation therapy for metastatic disease.

## Cardiac events

Given that previous research has shown an association between ischemic heart disease and breast radiation (4, 10, 12, 17, 18), we focused on studying cardiac ischemia and its sequelae. The diagnoses evaluated included myocardial infarction, coronary artery disease (CAD), congestive heart failure, and electrical abnormalities, which can be caused by ischemic disease (19, 20). Associated procedures (eg, percutaneous coronary intervention [PCI], coronary artery bypass graft surgery, pacemaker or implantable cardiac defibrillator placement) were also identified to better understand the association between radiation and the severity of ischemic heart disease. The diagnoses were ascertained using the "International Classification of Diseases, revision 9" (ICD-9) diagnosis codes. Procedures were determined using the ICD-9 procedure codes, Common Procedural Terminology, version 4, codes, and Berenson-Eggers type of service codes (Table E1; available online at www.redjournal.org). Cardiac-related mortality was identified from SEER. Cardiac endpoints were evaluated from the start of radiation through death or the last follow-up visit (December 2010).

Because previous research has indicated that the risk of adverse cardiac events after radiation therapy might be linked to the patient's underlying cardiac risk (17), the presence of one of the aforementioned cardiac diagnosis codes in the year before the breast cancer diagnosis was used to adjust the multivariate analysis for pre-existing cardiac morbidity. Only the year before diagnosis was assessed to ensure that all patients were evaluated equally for pre-existing cardiac conditions, regardless of their diagnosis date. If a cardiac diagnosis was present, patients were classified as having a high risk of a cardiac event. Those without any cardiac events in the year before the breast cancer diagnosis were assumed to have a low risk of a cardiac events.

**Table 1** Descriptive characteristics of study patients with stratification by tumor laterality

| Variable | Patients (n) | Left-sided breast cancer | Right-sided breast cancer | *P* value[*] |
|---|---|---|---|---|
| Total (n) | 29,102 | 14,702 | 14,440 | .08 |
| Age at diagnosis (y) | | | | .84 |
| 66-74 | 14,559 (50.0) | 7332 | 7227 | |
| 75-79 | 7695 (26.5) | 3907 | 3788 | |
| ≥80 | 6848 (23.5) | 3463 | 3385 | |
| Metropolitan area | 25,293 (86.9) | 12,767 | 12,526 | .71 |
| Teaching hospital | 10,956 (37.6) | 5586 | 5370 | .22 |
| Region | | | | .06 |
| East | 7003 (24.0) | 3628 | 3375 | |
| Midwest | 3979 (13.7) | 1984 | 1995 | |
| South | 4744 (16.3) | 2348 | 2396 | |
| West | 13,376 (46.0) | 6742 | 6634 | |
| Race | | | | .64 |
| White | 26,285 (90.3) | 13,256 | 13,029 | |
| Black | 1403 (4.8) | 717 | 686 | |
| Other | 1414 (4.9) | 729 | 685 | |
| Marital status | | | | .27 |
| Married | 14,627 (50.3) | 7369 | 7258 | |
| Divorced | 2091 (7.2) | 1092 | 999 | |
| Single | 1749 (6.0) | 859 | 890 | |
| Other | 10,635 (36.5) | 5328 | 5253 | |
| Charlson comorbidity score | | | | .49 |
| 0 | 20,149 (69.3) | 10,234 | 9915 | |
| 1 | 6238 (21.4) | 3108 | 3130 | |
| 2 | 1811 (6.2) | 899 | 912 | |
| ≥3 | 904 (3.1) | 461 | 443 | |
| High cardiac risk[†] | 14,331 (49.2) | 7216 | 7115 | .57 |
| Year of diagnosis | | | | .85 |
| 2000-2003 | 11,431 (39.2) | 5756 | 5665 | |
| 2004-2006 | 8500 (29.2) | 4285 | 4215 | |
| 2007-2009 | 9181 (31.6) | 4661 | 4520 | |
| Primary tumor size (cm) | | | | .44 |
| 0-2 | 20,817 (71.5) | 10,475 | 10,342 | |
| 2-5 | 6319 (21.7) | 3200 | 3119 | |
| >5 | 1438 (5.0) | 752 | 686 | |
| Unknown | 528 (1.8) | 275 | 253 | |
| Positive nodes (n) | | | | .37 |
| None | 19,360 (66.5) | 9723 | 9637 | |
| 1-3 | 4579 (15.8) | 2356 | 2223 | |
| 4-9 | 1201 (4.1) | 630 | 571 | |
| ≥10 | 700 (2.4) | 349 | 351 | |
| Unknown | 3262 (11.2) | 1644 | 1618 | |
| Stage | | | | .05 |
| Localized | 21,119 (72.6) | 10,595 | 10,524 | |
| Regional | 7983 (27.4) | 4107 | 3876 | |
| Grade | | | | .01 |
| Well or moderately differentiated | 20,108 (69.1) | 10,034 | 10,074 | |
| Poorly or undifferentiated | 7155 (24.6) | 3701 | 3454 | |
| Unknown | 1839 (6.3) | 967 | 872 | |
| Breast MRI | 3328 (11.4) | 1691 | 1637 | .72 |
| Primary surgery | | | | .46 |
| Partial mastectomy | 24,977 (85.8) | 12,601 | 12,376 | |
| Mastectomy | 3867 (13.3) | 1961 | 1906 | |
| None | 258 (0.9) | 140 | 118 | |
| Lymph node surgery | | | | .66 |
| None | 2637 (9.1) | 1323 | 1314 | |
| Sentinel | 11,068 (38.0) | 5643 | 5425 | |

(*continued on next page*)

**Table 1** (*continued*)

| Variable | Patients (n) | Left-sided breast cancer | Right-sided breast cancer | *P* value* |
|---|---|---|---|---|
| Regional | 15,364 (52.8) | 7719 | 7645 | |
| Unknown | 33 (0.1) | 17 | 16 | |
| Fractions delivered (n) | | | | .18 |
| 15-20 | 1053 (3.6) | 518 | 535 | |
| 21-25 | 1337 (4.6) | 572 | 665 | |
| 26-30 | 6011 (20.6) | 2975 | 3036 | |
| 31-35 | 18,767 (64.5) | 9525 | 9242 | |
| 36-40 | 1934 (6.7) | 1012 | 992 | |
| Intensity modulated radiation therapy | 3328 (9.9) | 1678 | 1212 | <.001 |
| Chemotherapy | | | | |
| Anthracyclines | 3830 (13.2) | 1982 | 1848 | .10 |
| Cyclophosphamide | 5312 (18.3) | 2722 | 2590 | .24 |
| Trastuzumab | 980 (3.4) | 523 | 457 | .07 |
| Taxanes | 2386 (8.2) | 1244 | 1142 | .10 |
| 5-Fluorouracil | 1617 (5.6) | 815 | 802 | .92 |
| Other | 690 (2.4) | 346 | 344 | .84 |

*Abbreviations:* CAD = coronary artery disease; MRI = magnetic resonance imaging.

* $\chi^2$ Tests were used to compare the proportions between patients with right- and left-sided breast cancer.

† Patients with a diagnosis of myocardial infarction, CAD, congestive heart failure, or electrical abnormalities in the year before the breast cancer diagnosis.

## Statistical analysis

We assessed the difference in the incidence of individual cardiac events between right- and left-sided breast cancers as a proxy for the effect of radiation. We evaluated the incidence of these cardiac-associated morbidities and mortality as the primary outcomes of the study. For cardiac diagnoses and procedures, the patients were allowed to experience multiple distinct events; however, only the time to the first event was evaluated. For each endpoint, we used competing risk analyses (21) for cumulative incidence analyses and multivariable regression models to account for

**Table 2** Cardiac outcomes observed in the study cohort from 2000 to 2010*

| Cardiac outcome | Events (n) | Median time (y) | 10-y Cumulative incidence (%; 95% CI) | Adjusted SDHR of left-sided breast cancer†‡ (95% CI) | Adjusted *P* value§ |
|---|---|---|---|---|---|
| Conditions | | | | | |
| Myocardial infarction | 3217 | 4.2 | 17.9 (17.1-18.7) | 1.05 (0.98-1.13) | .22 |
| Coronary artery disease | 12,163 | 2.7 | 56.0 (55.0-57.0) | 1.04 (1.00-1.08) | .07 |
| Conduction abnormalities/ dysrhythmias | 13,539 | 2.7 | 64.1 (63.1-65.0) | 1.01 (0.98-1.04) | .91 |
| Congestive heart failure | 7789 | 3.7 | 41.3 (40.2-42.3) | 0.97 (0.92-1.01) | .26 |
| Procedures | | | | | |
| PCI | 920 | 4.5 | 5.4 (4.9-5.9) | 1.21 (1.06-1.38) | .01‖ |
| CABG | 316 | 4.6 | 1.8 (1.6-2.1) | 0.98 (0.79-1.22) | .97 |
| Pacemaker/ICD placement | 1084 | 4.5 | 6.8 (6.3-7.4) | 1.01 (0.90-1.14) | .95 |
| Cardiac-associated mortality | 1191 | 4.6 | 8.4 (7.8-9.1) | 1.08 (0.96-1.21) | .32 |

*Abbreviations:* CABG = coronary artery bypass grafting surgery; CI = confidence interval; ICD = implantable cardiac defibrillator; IMRT = intensity modulated radiation therapy; MRI = magnetic resonance imaging; PCI = percutaneous coronary intervention; SDHR = subdistribution hazard ratio; SEER = Surveillance, Epidemiology, and End Results.

* Including median time to occurrence, cumulative incidence of each outcome, adjusted SDHR for left-sided breast cancer, and adjusted significance of this value.

† Right-sided breast cancer used as reference.

‡ Adjusted competing risk model controlled for age, marital status, race, metropolitan area, SEER region, treatment at a teaching hospital, median income, Charlson comorbidity index, year of diagnosis, tumor size, tumor stage, tumor grade, nodal status, primary and secondary surgeries, length of radiation treatment, delivery of IMRT, breast MRI before radiation, receipt of cardiotoxic chemotherapeutic drugs (anthracyclines, trastuzumab, taxanes, cyclophosphamide, 5-fluorouracil) or other chemotherapeutic agents, and cardiac risk status.

§ Adjusted *P* values using the Dubey/Armitage-Parmar procedure, which takes into account the mean correlation between outcomes, the number of primary outcomes, and original *P* values to correct for multiple comparisons.

‖ Significant with the Dubey/Armitage-Parmar adjusted threshold of significance according to original level of significance ($\alpha = 0.05$), the number of endpoints evaluated, and mean correlation between outcomes.

the competing risk of death. These multivariable regression models produced subdistribution hazard ratios (SDHRs), with a SDHR >1 implying increased risk. Patients were censored for each outcome if they were still alive at the end of the study period (December 2010) and had not experienced the specific cardiac outcome.

For these multivariable analyses, main effects models for each cardiac event were created using a standard set of covariates (Table 2). These covariates were defined a priori based on factors that could affect patients' health status and the likelihood of developing cardiac toxicities. All covariates examined were categorical with the subgroups shown in Table 1. All statistical tests performed were 2-sided; $P<.05$ was considered significant. Because our study evaluated 8ight primary, but correlated, outcomes, the Dubey/Armitage-Parmar procedure, which considers correlations between outcomes, was used to adjust the $P$ values ($P_{adj}$) and the threshold of significance ($\alpha_{adj}$) for multiple comparisons (22). The analyses were conducted using SAS, version 9.4 (SAS Institute Inc, Cary, NC).

## Results

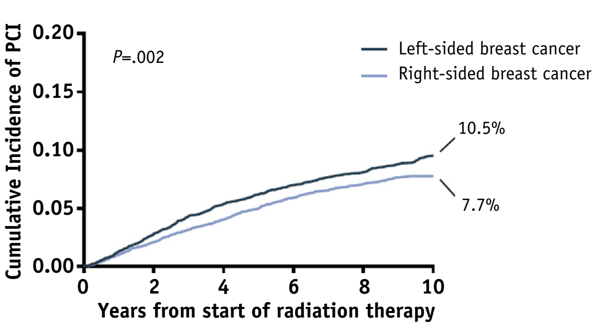
The incidence of cardiac events after radiation therapy for the study cohort between 2000 and 2010 is presented in Table 2. CAD and conduction abnormalities/dysrhythmias were the most commonly diagnosed events, with a cumulative incidence of 56.0% (95% confidence interval [CI] 55.0%-57.0%) and 64.1% (95% CI 63.1%-65.0%), respectively. PCI and pacemaker/implantable cardiac defibrillator placement were the most frequently noted procedures, with a cumulative incidence of 5.4% (95% CI 4.9%-5.9%) and 6.8% (95% CI 6.3%-7.4%). The cumulative incidence of cardiac-related mortality was 8.4% (95% CI 7.8%-9.1%). The median time to the diagnosis of any cardiac condition, the occurrence of a cardiac procedure, and cardiac-associated death was 3.3, 4.5, and 4.6 years, respectively.

Significant differences between patients with right- and left-sided breast cancer included the use of IMRT, which was more common for left-sided tumors (Table 1) and a small increase in regional disease distribution for left-sided compared with right-sided breast cancer (28% vs 27%). Otherwise, these patients were similar in terms of tumor size, lymph node involvement, pre-existing cardiac status, number of radiation fractions delivered, and treatment with cardiotoxic chemotherapeutic agents, key factors that could affect the aggressiveness of the radiation plan and the rate of cardiac outcomes.

We noted an increased incidence of CAD diagnosis codes after radiation for left-sided breast cancer, with an adjusted SDHR of 1.04 (95% CI 1.00-1.08). With adjustment for multiple comparisons, however, the effect of tumor laterality was not statistically significant ($P_{adj} = .03$, $\alpha_{adj} = 0.07$). No other diagnosis codes had a statistically significant association with tumor laterality. For procedures, the incidence of PCI was significantly greater in women with left-sided breast cancer, with an adjusted SDHR of 1.21 (95% CI 1.06-1.38). This outcome was statistically significant when adjusting for multiple comparisons ($P_{adj} = .01$, $\alpha_{adj} = 0.03$). The incidence of other procedures was not associated with tumor laterality. We also found no significant difference in cardiac survival between patients with left- and right-sided breast cancer, with an SDHR of 1.08 (95% CI 0.96-1.21) for cardiac-related mortality. Complete results for all primary outcomes are presented in Table 2. The complete multivariate regression analysis for PCI is presented in Table E2 (available online at www.redjournal.org).

The cumulative incidence of PCI for patients with left- and right-sided breast cancer was 5.5% (95% CI 4.9%-6.2%) and 4.5% (95% CI 4.0%-5.0%), respectively, with adjustment for competing risks. When stratifying the incidence of PCI by pre-existing cardiac risk status, the effect of tumor laterality was limited to the high cardiac risk subgroup. In that group, the cumulative incidence of PCI was 10.5% (95% CI 9.3%-11.7%) for left-sided breast cancer and 7.7% (95% CI 7.0%-8.5%) for right-sided breast cancer (Fig. 2).

Although the trend of increased CAD diagnoses observed with left-sided breast cancer supports the finding of an increased incidence of PCI, to better understand the greater rate of PCI, we looked for correlations in the cardiac diagnosis associated with the procedure (Table E3; available online at www.redjournal.org). For both left- and right-sided breast cancer, CAD was the main accompanying diagnosis. We found no statistically significant difference in the distribution of specific cardiac conditions between those with right- and left-sided breast cancer, except for conduction abnormalities, which were more common in those with right-sided disease ($P=.04$).




| Group | Number at risk 0 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|
| Left-sided | 7,216 | 5,921 | 4,215 | 2,700 | 1,364 | 316 |
| Right-sided | 7,115 | 5,937 | 4,268 | 2,743 | 1,421 | 315 |

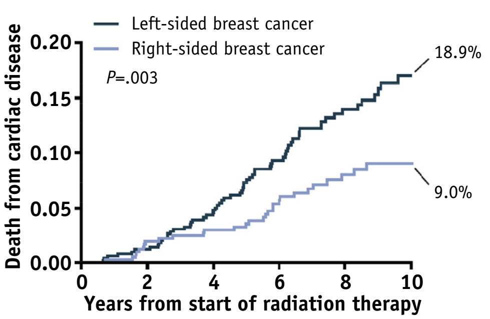
**Fig. 2.** Cumulative incidence of percutaneous coronary intervention (PCI) for left- and right-sided breast cancer after radiation therapy for patients with high cardiac risk. The number of patients at risk is shown below. Gray's test of equality was used to evaluate a significant difference between groups.

To further explore the association between radiation and the patency of the coronary vasculature, for patients who underwent an initial and then a repeat PCI after a breast cancer diagnosis (n = 155), a trend was observed for repeat intervention for patients with left-sided breast cancer (*P* = .06). The mean time to reintervention, however, was significantly shorter for left-sided breast cancer patients at 379 days compared with 582 days for right-sided breast cancer patients (*P* = .03), suggesting a possible acceleration of CAD associated with radiation.

Moreover, when examining the survival of the 920 patients who underwent PCI, those with left-sided tumors had a greater risk of death. Of the 257 patients who died, the most common cause of death was cardiac related (n = 94). The cumulative incidence curves for cardiac-associated mortality in this subgroup are presented in Figure 3. In a 10-year period, for the PCI cohort, 18.9% (95% CI 14.4%-24.0%) of women with left-sided breast cancer died of cardiac causes compared with 9.0% (95% CI 6.1%-12.9%) for women with right-sided breast cancer. Correspondingly, the patients with left-sided breast cancer in this subgroup had an adjusted SDHR of 2.02 (95% CI 1.23-3.34) for cardiac mortality relative to patients with right-sided breast cancer. These results suggest that radiation could be contributing to the worsening of severe disease. The main findings of the present study for the cumulative incidence of key events stratified by laterality and cardiac risk status are listed in Table 3.

## Discussion

Breast radiation therapy techniques have evolved in the era of 3-dimensional planning, motivated in part by historical studies linking increased rates of cardiac mortality to radiation treatment for left-sided breast cancer. Understanding the effect of current techniques on cardiac toxicity is critical to adequately capturing the risks associated with modern radiation therapy. Our population-based analysis offers a holistic update on the specific cardiac risks women face when undergoing radiation therapy for breast cancer. The key finding of our study is that for women with a history of cardiac disease, those with left-sided breast cancer had a significantly greater rate of PCI after radiation therapy and a trend toward a greater incidence of CAD diagnoses relative to patients with right-sided disease. Additionally, cardiac survival in patients who underwent PCI was significantly lower for patients with left-sided breast cancer, identifying a potentially high-risk patient subgroup that could warrant additional cardiac monitoring. However, this result must be contextualized by the small absolute increase in the incidence of PCI.




Number at risk

| Group | 0 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|
| Left-sided | 504 | 482 | 400 | 281 | 165 | 54 |
| Right-sided | 416 | 398 | 339 | 253 | 142 | 47 |

**Fig. 3.** The incidence of cardiac-associated mortality for left- and right-sided breast cancer patients who received percutaneous coronary intervention (PCI) after radiation therapy (n = 920). The number of patients at risk is shown below. Gray's test of equality was used to evaluate a significant difference between groups.

Furthermore, this observation did not translate into an increase in cardiac-related mortality when examining all patients with left-sided breast cancer. This result aligns with findings from more recent studies and stands in contrast to older studies, which reported increased rates of cardiac-specific mortality for women with left-sided breast cancer (1, 4). Giordano et al (10) investigated long-term mortality due to ischemic heart disease and found no effect of tumor laterality on survival after 1980 in analyzing 12 years of follow-up data. Our current study yielded comparable results, suggesting that the use of modern techniques is adequately preventing significant cardiotoxicity for most patients.

Similarly, Patt et al (12), who adopted a more granular approach for cardiac outcomes by assessing hospitalizations for specific cardiac diagnoses and procedures, including PCI, found no difference in the frequency of events between patients with right and left breast cancer. Our research reached a different conclusion only with regard to the rate of PCI. The discordant findings could have been because we studied a different period. Patt et al (12) evaluated Medicare records from 1986 to 2001, and our study used records from 2000 to 2010, when access to PCI had generally increased (23), resulting in a greater number of events to evaluate.

Most recently, Onwudiwe et al (17) found that women with left-sided tumors had greater rates of death or hospitalization for a cardiac event after radiation therapy in a high-risk cardiac population. Our analyses found a similar pattern for PCI. This finding could help guide physicians when counseling patients about the risk of cardiotoxicity, because women with previous cardiac disease appear to have a greater risk of cardiac sequelae. One might also wonder whether initiation of atheroprotective medical therapy, including antiplatelet therapy, angiotensin-converting enzyme inhibitors, or 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (HMG CoA), might alter this increased risk.

The underlying mechanism driving the difference in PCI between left- and right-sided breast cancer patients deserves further consideration. Although the indications for

**Table 3** Cumulative incidence of key cardiac outcomes observed stratified by breast cancer laterality and cardiac risk status

| | Left-sided breast cancer | | | | Right-sided breast cancer | | | |
|---|---|---|---|---|---|---|---|---|
| | | 10-y Cumulative incidence | | | | 10-y Cumulative incidence | | |
| Cardiac outcome | Events (n)* | All (95% CI) | Low cardiac risk (95% CI) | High cardiac risk (95% CI) | Events (n)* | All (95% CI) | Low cardiac risk (95% CI) | High cardiac risk (95% CI) |
| CAD | 6194 (4976) | 56.15 (54.80-57.47) | 26.26 (24.50-28.04) | 79.17 (77.83-80.44) | 5969 (4802) | 55.86 (54.44-57.27) | 26.37 (24.22-28.55) | 77.53 (76.16-78.82) |
| PCI | 504 (502) | 6.24 (5.41-7.14) | 0.11 (0.02-0.47) | 10.51 (9.29-11.77) | 416 (411) | 4.52 (4.05-5.02) | 0.19 (0.06-0.55) | 7.76 (7.01-8.56) |
| Cardiac mortality | | | | | | | | |
| All | 619 (546) | 8.63 (7.75-9.57) | 2.10 (1.57-2.74) | 12.89 (11.63-14.21) | 572 (507) | 8.21 (7.29-9.19) | 2.79 (1.60-4.50) | 11.77 (10.58-13.03) |
| PCI cohort | 65 (64) | 18.97 (14.43-24.00) | 50.00 (0.00-95.98) | 18.83 (14.29-23.86) | 29 (29) | 9.07 (6.13-12.71) | — | 9.17 (6.20-12.83) |

*Abbreviations:* CAD = coronary artery disease; CI = confidence interval; PCI = percutaneous coronary intervention.

* Data in parentheses are number of patients in high-risk group.

PCI have evolved, and previous research found that the ≤12% of all PCI procedures might be inappropriate (24), the decreased survival of patients with left-sided breast cancer after PCI, with the most common cause of death being cardiac related, suggests a component of radiation-induced toxicity. Radiation is likely worsening already present disease, which aligns with previous research showing radiation-induced cardiac damage causes vascular changes such as accelerated coronary artery disease and an increased likelihood of vulnerable plaques (25, 26). This acceleration of ischemic disease could also contribute to the increased need for PCI.

Furthermore, previous studies of small cohorts of early-stage breast cancer found a significantly greater frequency of abnormal stress test findings for patients with left-sided breast cancer patients who had undergone radiation therapy (27) and an increased number of perfusion abnormalities observed with myocardial perfusion scanning (28). Our finding of shorter times to repeat PCI among those with left-sided breast cancer also supports the hypothesis that current radiation practices are still affecting the behavior of the cardiac vasculature and could alter the time course of the vascular response to mechanical injury from the index PCI.

Just as with other studies derived from administrative data sets, our analyses were limited by the lack of patient records. We could not ascertain specifics relating to radiation therapy (including dose, technique, or target) the physician rationale in diagnosing CAD, or the details of PCI. Also, the present research focused on patients who were ≥66 years old; therefore, our findings might not be generalizable to a younger population. This administrative data set also did not provide insight into important cardiac risk factors, such as smoking status, activity level, or body habitus, which could affect the cardiac outcomes. We also could not assess the use of hormonal therapy or the receipt of cardioprotective drugs such as antiplatelet therapies or HMG CoA reductase inhibitors, which could affect the rate of cardiac events. Furthermore, cardiologists might have a lower threshold for diagnosis and intervention in women with left-sided breast cancer who have undergone radiation, resulting in the greater number of CAD diagnosis codes and procedures observed in this patient subgroup without necessarily representing a true increase in CAD prevalence or severity. A final limitation relates to the follow-up time for our patients. Because our study aimed to understand radiation therapy in the modern era, our follow-up period was at most a decade, with most patients having shorter follow-up times based on their diagnosis date. Although reports have varied in the onset of cardiovascular toxicity, the full manifestations of radiation to the heart likely take several years to develop; therefore, with further follow-up, additional events might occur that could result in different conclusions from those presented in the present report. Darby et al (29) reported mortality from heart disease was observed to increase 10 to 20 years after radiation. Thus, ongoing research evaluating the interplay of radiation therapy and cardiotoxicity in breast cancer is warranted.

## Conclusions

The results from the present study complement existing data focusing on cardiac outcomes after adjuvant radiation therapy for breast cancer patients. Our research found that women with a history of cardiac disease and left-sided breast cancer treated with radiation had greater rates of PCI, a previously unreported association, with higher mortality for left-sided patients who underwent PCI. Although additional research is needed to clarify the effect of radiation dose, overall, our findings could help cardiologists and radiation oncologists better stratify higher risk patients and consider more aggressive cardioprotective techniques.

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