Long-term cardiovascular mortality after radiotherapy for breast cancer: A systematic review and meta-analysis

Partha Sardar¹ | Amartya Kundu² | Saurav Chatterjee³ | Anju Nohria⁴ | Ramez Nairooz⁵ | Sripal Bangalore⁶ | Debabrata Mukherjee⁷ | Wilbert S. Aronow⁸ | Carl J Lavie⁹

¹Division of Cardiovascular Medicine, University of Utah, Salt Lake City

²Department of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts

³St Luke's-Roosevelt Hospital of the Mount Sinai Health System, New York, New York

⁴Department of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

⁵University of Arkansas for Medical Sciences, Little Rock, Arkansas

⁶New York University School of Medicine, New York, New York

⁷Texas Tech University Health Sciences Center, El Paso, Texas

⁸New York Medical College, Valhalla, New York

⁹John Ochsner Heart and Vascular Institute, Ochsner Clinical School/University of Queensland School of Medicine, New Orleans, Louisiana

Corresponding Author: Partha Sardar, MD, Division of Cardiovascular Medicine, University of Utah Health Science Center, 30 North 1900 East, Room 4A100, Salt Lake City, UT 84132 (parthasardarmd@gmail.com).

Background: Radiotherapy (RT) is frequently associated with late cardiovascular (CV) complications. The mean cardiac dose from irradiation of a left-sided breast cancer is much higher than that for a right-sided breast cancer. However, data is limited on the long-term risks of RT on CV mortality.

Hypothesis: RT for breast cancer is associated with long term CV mortality and left sided RT carries a greater mortality than right sided RT.

Methods: We searched PubMed, Cochrane Central, Embase, EBSCO, Web of Science, and CINAHL databases from inception through December 2015. Studies reporting CV mortality with RT for left- vs right-sided breast cancers were included. The principal outcome of interest was CV mortality. We calculated summary risk ratio (RR) and 95% confidence intervals (CI) with the random-effects model.

Results: The analysis included 289 109 patients from 13 observational studies. Women who had received RT for left-sided breast cancer had a higher risk of CV death than those who received RT for a right-sided breast cancer (RR: 1.12, 95% CI: 1.07-1.18, $P < 0.001$; number needed to harm: 353). Difference in CV mortality between left- vs right-sided breast RT was more apparent after 15 years of follow-up (RR: 1.23, 95% CI: 1.08-1.41, $P < 0.001$; number needed to harm: 95).

Conclusions: CV mortality from left-sided RT was significantly higher compared with right-sided RT for breast cancer and was more apparent after ≥ 15 years of follow-up.

KEYWORDS

Breast Cancer, Radiotherapy, Cardiovascular Mortality

1 | INTRODUCTION

Radiotherapy (RT) for breast cancer has been shown to reduce the risk of both breast cancer recurrence and breast cancer-related mortality.¹ However, studies have shown that RT may increase the risk of death from cardiovascular (CV) disease many years after initial treatment.²⁻⁴ The increase in CV deaths appears to be mainly due to high-volume irradiation to the heart, which was commonly used in earlier radiation protocols. However, incidental cardiac irradiation is not totally eliminated by more recent RT techniques,³⁻⁵ as the heart still receives doses of 1 to 5 Gy with modern RT regimens.⁶ Several recent studies have suggested that radiation exposure at this level

can cause coronary artery disease (CAD), thus increasing the risk of CV death in long-term survivors of breast cancer.^{6,7} Patients selected for breast cancer RT may have different mortality rates from those not selected for RT due to various reasons.^{5,8} Comparisons of RT-related outcomes should be performed in a population that avoids this selection bias. Conventionally, radiation exposure to the heart is greater for left- compared with right-sided breast cancer.⁹ Therefore, comparison of outcomes with left- vs right-sided breast RT can provide a valid indication of the extent of RT-related CV mortality.^{5,10} Extensive systematic evaluation of the association between laterality of breast cancer RT, treatment era, and follow-up duration on RT-related CV mortality has not been performed previously. We

therefore conducted a systematic review and meta-analysis to investigate the risk of the CV mortality with RT for breast cancer and its relationship to the location of breast cancer.

2 | METHODS

We searched the PubMed, the Cochrane Library (Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials), Embase, Web of Science, and CINAHL databases from inception through December 29, 2015. The following keywords were used: breast cancer, radiotherapy, radiation therapy, cardiac death, cardiovascular mortality, cardiac toxicity, left-sided radiation, and right-sided radiation. This analysis was restricted to articles published in English, and no publication date restrictions were imposed. We also manually searched reference lists of all retrieved articles for potential additional studies. We used the published strengthening Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist to select and report the studies for this review.¹¹ We included published studies (observational studies, randomized trials, and reports from registries or databases) reporting outcomes comparing left- vs right-sided RT in patients with breast cancer. We excluded studies without a comparator group. For studies that did not report the outcome of interest, we contacted the authors via email for further information.

Two reviewers (P.S., A.K.) independently extracted the data from the eligible studies using standardized protocol (PROSPERO 2014: CRD42014008913), and disagreements were resolved by discussion with the other authors. We extracted the baseline characteristics of each study and the data related to CV mortality. The quality of the observational case-control studies was assessed by the Newcastle-Ottawa Scale,¹² and for randomized controlled trials, we used the domains suggested by the Cochrane Handbook of Systematic Reviews.¹³ The principal outcome of interest was CV mortality. We used longest available follow-up data from individual studies for our analysis.

2.1 | Statistical analysis

Statistical analysis was performed according to the recommendations from The Cochrane Collaboration. We used Review Manager version 5.2 (The Nordic Cochrane Center, The Cochrane Collaboration, 2012, Copenhagen) and Stata version 12 software (StataCorp LP, College Station, Texas). We used the random-effects model of DerSimonian and Laird and calculated the summary risk ratio (RR) with associated 95% confidence intervals (CI). Heterogeneity across studies was assessed by using the Cochrane Q statistic and the I^2 statistics. For I^2 statistics, we considered $I^2 < 25\%$ as low heterogeneity and $I^2 > 75\%$ as high heterogeneity and the Cochran Q ($P \leq 0.1$) was considered as significant heterogeneity for each outcome. "Small study effects" were evaluated using the Egger regression test and through visual inspection of asymmetry in funnel plots. A 2-tailed P value < 0.05 was considered statistically significant. The following subgroup analyses were performed: (1) analysis based on the decade of diagnosis and

therapy for breast cancer; (2) analysis based on the duration of follow-up; and (3) studies with low/intermediate risk of bias.

Sensitivity analyses were performed to identify the effect of a single study by sequential elimination of each study from the pool and assessing the overall outcomes. Conventional cumulative meta-analyses of studies are at risk for producing random errors, resulting from limited data and repetitive testing. The underlying assumption for study sequential analysis (SSA) is that significance testing and calculation of the 95% CIs are performed each time a new study is published. Study sequential analysis depends on the quantification of the required amount of information. In this context, the smaller the required amount is, the more lenient is the SSA and so are the criteria for significance. We calculated a diversity-adjusted (D^2) required information size.¹⁴ We performed the SSA with an intention to maintain an overall 5% risk of a type I error, which is the standard in most meta-analyses and systematic reviews. We calculated our monitoring boundaries according to the required information size to detect or reject an intervention effect of a 20% RR increase with a risk of a type II error of 20% (power of 80%). We used TSA version 0.9 beta (www.ctu.dk/tsa) for these analyses.¹⁵

3 | RESULTS

A total of 2792 reports were identified through the database search, out of which 13 studies were included in the final meta-analysis (see Supporting Information, Figure 1, in the online version of this article).^{5,16–27} In cases of multiple publications from a single registry, we included data from the most recent publication. The 13 selected studies reported outcome data for a total of 289 109 patients. Median age of patients ranged from 48 to 59 years, and the median duration of follow-up varied from 8 to 28 years. Most of the included studies had low risk of bias according to the Newcastle-Ottawa Scale. Further details regarding baseline characteristics of the included studies are shown in tables 1 and 2.

Women who had received RT for left-sided breast cancer had a higher risk of CV mortality than did those who received RT for right-sided breast cancer (3697 events in left-sided group [2.5%] and 3186 events in right-sided group [2.2%]; RR: 1.12, 95% CI: 1.07–1.18; number needed to harm (NNH) = 353; Figure 1). These results did not show any heterogeneity. The SSA crossed the O'Brien-Fleming boundary of harm, for cardiac mortality to indicate existing "firm evidence" of a 12% relative risk of increased CV mortality with left-sided breast RT, as available from current data (see Supporting Information, Figure 2, in the online version of this article).

Differences in CV mortality between left- vs right-breast RT were more apparent after 15 years of follow-up (5.6% vs 4.6%; RR: 1.23, 95% CI: 1.08–1.41; NNH = 95; Figure 2). There was a 23% relative increase in the risk of CV mortality with left-sided RT after 5 to 10 years of follow-up and 36% increased risk after 11 to 15 years of follow-up; however, these results did not reach statistical significance.

Breast cancer diagnosed before 1982 showed the highest risk of CV mortality with left-sided RT (13% vs 9.4%; RR: 1.38, 95% CI: 1.25–1.52; NNH = 28; Figure 3). Left-sided breast cancers diagnosed

FIGURE 1 Forest plot for cardiac mortality; left- vs right-sided RT for breast cancer. Abbreviations: CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; RT, radiotherapy.

between 1983 and 1992 had a 28% increased risk of CV death compared with right-sided cancer RT; however, the result did not reach statistical significance (RR: 1.28, 95% CI: 0.90-1.80). CV mortality with cancers diagnosed after 1992 did not differ significantly between left- and right-sided RT (RR: 0.97, 95% CI: 0.90-1.06); however, the follow-up duration was limited (<10 years).

The results of our analysis with trials showing low/intermediate risk of bias and prospective studies were consistent with our primary analysis. Sensitivity analyses by sequentially eliminating each individual study and evaluating the overall outcomes failed to identify any one individual study as having influenced the outcomes to a significant extent, and the results were concordant with the overall analyses. There was no evidence of small study effects (publication bias) by visual inspection of funnel plots (see Supporting Information, Figure 3, in the online version of this article) and by Egger test.

4 | DISCUSSION

The present study provides important insights into the risk of CV death from breast cancer RT, based on cancer location. Our analysis of data from 289 109 patients showed that RT for left-sided breast cancer is associated with a higher risk of long-term CV death compared with RT for right-sided breast cancer. Differences in CV mortality between left- and right-breast RT were more apparent after 15 years of follow-up, although a trend toward increased mortality was also seen in studies with shorter follow-up durations. Cancers diagnosed and treated before 1982 had a higher risk of CV mortality with left-sided RT; however, studies conducted after this period failed to show a difference in CV mortality, perhaps due to inadequate statistical power given the shorter duration of follow-up. Radiation exposure to the heart differs between left- and right-sided breast cancer. A study by Taylor et al had shown that in left-sided

breast cancer, average mean heart dose reported in 149 studies from 28 countries was 5.4 Gy (range, <0.1-28.6 Gy); whereas for right-sided breast cancer, the average mean heart dose was 3.3 Gy, based on 45 regimens in 23 studies.²⁸ The relationship between breast cancer laterality in women receiving RT and subsequent CV mortality may be important when assessing the long-term hazards of RT.

Previous studies have reported higher CV mortality with left-compared with right-sided breast cancer following RT.^{5,16,25} Nevertheless, other studies did not observe such an increase in CV mortality with left-sided breast irradiation.^{16,19} Our meta-analysis, which included 13 studies, showed a consistently higher CV mortality with left-sided breast RT.

Prior studies evaluating RT-related CV mortality suggested that the risk of CV death may continue for many years after initial exposure to RT.^{5,17} A recent population-based case-control study conducted in women from Sweden and Denmark showed the risk of major CAD events started within the first 5 years after therapy and continued into the third decade of follow-up.⁶ However, the length of time after which this excess risk is greater in women treated with RT for left-sided, compared with right-sided, breast cancer remains unclear. Our analysis suggests that ≥ 15 years are required to observe a significant difference in CV mortality, although a trend toward increased risk was noted in studies with a shorter duration of follow-up.

In the present study, women treated before 1982 had a significantly higher risk of CV mortality with left-sided compared with right-sided RT. However, the comparative cardiac effects of left- vs right-sided RT with modern shielding techniques are less clear. The risk of CV mortality increases with the radiation dose the heart is exposed to. A recent study by Darby et al showed the rates of major CAD events increased linearly with the mean dose to the heart by 7.4% per Gy, with no clear threshold.⁶ Unfortunately, details regarding individual cardiac radiation doses were not

TABLE 1 Baseline characteristics of included studies

Studies	Total Patients, L/R	Median Age, y, L/R	Study Design	Cardiac Mortality	Median Follow-up, y	Therapy Duration	CVD Before BC Diagnosis, % L/R	HTN, L/R	DM, L/R	Current Smoking, L/R	Hyperlipidemia, L/R	Study Quality NOS
Borger, 2007	870/731	48/49	Observational study	MI, IHD, CVD	16	1980–1993	1.0/2.2	21.5/23.9	8.3/5.4	11/7.9	15.2/13.6	8
Bouillon, 2011	1472/1388	55 ¹	Hospital-based cohort	IHD, valvular HD, myocarditis, arrhythmias, HF	28	1954–1984	NA	NA	NA	NA	NA	8
Gustavsson, 1999	34/33	59/57	Analysis from randomized trial	Cardiac deaths	10	1978–1983	NA	11.7/15.1	0/0	23.5/39.3	26.4/27.2	8
Harris, 2006	484/477	53/52	Retrospective observational study	MI, IHD, CHF	12	1977–1994	NA	NA	NA	NA	NA	9
Højris, 1999	755/770	NA	Randomized trials	MI and IHD mortality	10	1982–1990	NA	NA	NA	NA	NA	Randomized trial
Nixon, 1998	365/380	50/50.1	Retrospective observational study	NA	12	1968–1986	NA	NA	NA	NA	NA	6
Park, 2011	59/70	55/55.6	Medical records reviewed	MI, CHF, CAD, IHD, arrhythmia, valvular HD, cardiomyopathy	8	1986–2002	NA	NA	NA	NA	NA	7
Vallis, 2002	1074/1054	54	Hospital-based retrospective cohort linkage study	MI	10.2	1982–1988	8/8	27/26	NA	37/38	NA	6
Registry/database												
Henson, 2012	130285/126691	NA	Population-based tumor registry	Cardiac death	20	1973–2008	NA	NA	NA	NA	NA	6
Marhin, 2007	3781/3666	57.3/57.1	Population-based retrospective study	MI, CHF, CAD, arrhythmia, IHD	7.9	1084–2000	NA	NA	NA	NA	NA	7
Paszat, 1999	1555/1451	55.7	Population-based cohort study	MI mortality	8	1982–1987	NA	NA	NA	NA	NA	6
Roychoudhuri, 2007	5704/5441	54.8/54.5	Cancer registry database	IHD/CVD mortality	17.9	1971–1988	NA	NA	NA	NA	NA	8
Wang, 2011	274/245	56.9	Cancer registry	MI, IHD, CHF, valvular HD	10	1995	NA	NA	NA	NA	NA	6

Abbreviations: BC, breast cancer; CHF, congestive heart failure; CVD, cardiovascular disease; DM, diabetes mellitus; HD, heart disease; HF, heart failure; HTN, hypertension; IHD, ischemic heart disease; L, left; MI, myocardial infarction; NA, not available; NOS, Newcastle-Ottawa Scale; R, right; RT, radiotherapy.

¹ Mean values.

TABLE 2 Baseline characteristics

Studies	Cardiotoxic Drugs, %	Interventions	Radiation Doses	Stage of Cancer	Median Year of First Treatment	Source
Borger, 2007	None	Post-lumpectomy irradiation with breast tangentials	50 Gy in 25 fractions of 2 Gy in all patients	T1-2 N0	NA	5 institution in the Netherlands
Bouillon, 2011	6% received chemotherapy (non-anthracycline)	RT combined with surgery; internal mammary chain included at times in tangential fields	45 Gy in 18 fractions (4 fractions per week) or 50 Gy in 25 fractions (5 fractions per week)	NA	1976	Institut Gustave Roussy, Sweden
Gustavsson, 1999	NA	Adjuvant postoperative RT $\pm$ cyclophosphamide	38–48 Gy, administered in daily fractions of 1.9–2.4 Gy, 5 days per week	Stage II breast cancer	NA	South Sweden Breast Cancer Trial
Harris, 2006	6%/7% (doxorubicin)	BCS followed by whole breast contemporary irradiation techniques via tangential fields	Tangential coplanar fields using 6–15 MV photons, followed by a boost to the tumor bed to a median total tumor bed dose of 64 Gy (range, 59.75–71.60 Gy). In both groups, 74% of patients were treated with tangents alone, and 26% were also treated with regional nodal fields (a supraclavicular photon field with or without a posterior axillary field).	Stage I or II breast cancer	NA	University of Pennsylvania
Højris, 1999	NA	Postmastectomy chemotherapy with RT	The intended dose was 48–50 Gy in 22–25 fractions, at 4 to 5 fractions per week.	Nonmetastatic disease	NA	DBC82b and 82c randomized trials, Danish Breast Cancer Cooperative Group
Marhin, 2007	NA	BCS or mastectomy plus adjuvant RT; tangential irradiation with or without breast boost	Median RT dose delivered was 4400 cGy, with a median of 16 fractions and median fraction size of 275 cGy.	pTis-2, pNO-1, M0	NA	British Columbia Cancer Agency database
Nixon, 1998	Adjuvant chemotherapy was relatively uncommon (25% of patients); cyclophosphamide, methotrexate, and fluorouracil in combination. Doxorubicin was used in only 12 patients (1.6%). Only 15 patients (2%) were treated with adjuvant tamoxifen.	BCS that consisted of complete gross excision and ≥ 60 Gy to the tumor bed.	45 to 50 Gy to the whole breast delivered with megavoltage irradiation (4–8 MV) by tangential technique over a period of approximately 5 weeks, using a daily fraction size of 180 cGy.	Stage I or II breast cancer	NA	Harvard Medical School, Boston, Massachusetts
Park, 2011	1/1 (adriamycin)	BCS; in all cases, radiation using 2D planning techniques was delivered to the whole breast via tangential coplanar fields using 6- to 18-MV photons.	The median radiation dose was 60 Gy. Sixty-four percent of patients received a boost ranging from 14 to 20 Gy. Internal mammary nodes were not electively covered in the radiation field.	NA	NA	Moffitt Cancer Center, Florida
Vallis, 2002	10 (1%) / 13 (2%) (adriamycin)	BCS and RT to the breast using a pair of coplanar, tangential	Treatment to the breast and the regional nodes was 40.0 Gy in 16 fractions of 2.5 Gy each,	All stages	NA	Hospital-based retrospective cohort linkage study, Canada

TABLE 2 Continued

Studies	Cardiotoxic Drugs, %	Interventions	Radiation Doses	Stage of Cancer	Median Year of First Treatment	Source
Registry/ database						
Henson, 2012	NA	NA	NA	NA	NA	SEER cancer registries
Marhin, 2007	NA	BCS or mastectomy plus adjuvant RT; tangential irradiation with or without breast boost	Median RT dose delivered was 4400 cGy, with a median of 16 fractions and median fraction size of 275 cGy.	pTis-2, pNO-1, M0	NA	British Columbia Cancer Agency database
Paszat, 1999	NA	Post-lumpectomy radiotherapy	Mean radiation dose to the breast was 42,975 Gy divided into a mean number of 18.4 fractions.	NA	NA	Population-based cohort study, Ontario Cancer Registry
Roychoudhuri, 2007	NA	RT	NA	All stages	NA	Thames Cancer Registry database, England
Wang, 2011	8.4/2.9 (5.8%)	RT to breast as well as postmastectomy RT; tangential, megavoltage, linear accelerator-based RT	The most common dose fractionation utilized was 50 Gy in 25 fractions to the whole breast with 10 Gy in 5 fractions; boost to the tumor bed for patients undergoing BCS, and 50 Gy in 25 fractions without boost for patients undergoing postmastectomy RT.	Stage I–III invasive breast cancer	NA	New South Wales Central Cancer Registry, Australia

Abbreviations: 2D, 2-dimensional; BCS, breast-conserving surgery; L, left; NA, not available; R, right; RT, radiotherapy; SEER, Surveillance, Epidemiology and End Results.

FIGURE 2 Forest plot for cardiac mortality with left- vs right-sided RT for breast cancer. Analysis according to duration of follow-up. Abbreviations: CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; RT, radiotherapy.

available from all studies included in this meta-analysis; therefore, we could not evaluate whether cardiac doses were higher in patients treated before 1982 compared to earlier.^{5,29} However, RT to the internal mammary nodes, regardless of laterality, remains one of the major determinants of cardiac toxicity. The use of internal mammary RT has declined in the United States since the 1980s,⁵ and this could explain the reductions in left-sided radiation-related CV mortality.

Our analysis showed a clear association of RT for left-sided breast cancer with an increased risk of CV death in long-term survivors. Although more modern RT techniques might have attenuated this risk, the long-term safety of RT for breast cancer remains uncertain. Continued efforts to minimize cardiac exposure in patients undergoing RT for breast cancer, especially for left-sided disease, are warranted. Although efforts have been focused on reducing cardiac irradiation, it would be interesting to see whether reducing internal mammary node involvement in the RT field would further reduce the difference between left- and right-sided outcomes. Future studies are required to evaluate the long-term effects of modern RT on CV morbidity and mortality. Newer techniques that specifically reduce left-sided radiation-related cardiac doses and risks, such as prone position radiotherapy,³⁰ need to be explored further. Adjuvant RT is associated with a statistically definite reduction in the annual death rate from cancer. Although the absolute gains from RT might seem to be small, proportional gain may be larger because of more effective modern RT.

There is still a lack of knowledge for early cardiotoxicity induced by breast RT that can appear long before the onset of clinically significant cardiac events. Different diagnostic methods—including measurements of functional myocardial dysfunction, including strain and strain rate based on 2D-speckle tracking echocardiography;

anatomical coronary lesions including description of plaques in segments of coronary arteries based on coronary computed tomography angiography; and a wide panel of circulating biomarkers—might be useful options to detect early cardiotoxicity related to RT. Although modern RT has decreased the risk of cardiac mortality, the risk still exists even if mean doses have decreased, and it is important to continue efforts in radiation protection of healthy tissues neighboring RT-treated organs.³¹

4.1 | Study limitations

Our study had several limitations. This analysis was based on published studies reporting aggregate data and not on individual patient-level data. The vast majority of the data were from observational studies, without any randomization or propensity matching. The optimal method to assess the impact of heart irradiation on outcomes would include cardiac dose-volume information. Most of the included studies did not report the percentage of patients with prior CV disease, which might influence subsequent CV mortality. Along with RT, a few women also received other treatment modalities (such as cardiotoxic chemotherapy) that may have influenced the outcome and were not controlled for in the present analysis.

5 | CONCLUSION

Our analysis showed that late CV mortality with left-sided RT was significantly higher compared with right-sided RT for breast cancer. This difference was more apparent after ≥ 15 years of follow-up. Additional follow-up data are needed to evaluate whether modern

FIGURE 3 Forest plot for cardiac mortality with left- vs right-sided RT for breast cancer. Analysis according to calendar year of diagnosis and RT. Abbreviations: CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; RT, radiotherapy.

methods effectively reduce the cardiac adverse effects of radiation therapy.

Conflicts of Interest

The authors declare no potential conflicts of interest.

REFERENCES

- McGale P, Taylor C, Correa C, et al; Early Breast Cancer Trialists' Collaborative Group. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials [published correction appears in *Lancet*. 2014;384:1848]. *Lancet*. 2014;383:2127-2135.
- Giordano SH, Kuo YF, Freeman JL, et al. Risk of cardiac death after adjuvant radiotherapy for breast cancer. *J Natl Cancer Inst*. 2005;97:419-424.
- Demirci S, Nam J, Hubbs JL, et al. Radiation-induced cardiac toxicity after therapy for breast cancer: interaction between treatment era and follow-up duration. *Int J Radiat Oncol Biol Phys*. 2009;73:980-987.
- Darby SC, McGale P, Taylor CW, et al. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300 000 women in US SEER cancer registries. *Lancet Oncol*. 2005;6:557-565.
- Henson KE, McGale P, Taylor C, et al. Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer. *Br J Cancer*. 2013;108:179-182.
- Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*. 2013;368:987-998.
- Carr ZA, Land CE, Kleinerman RA, et al. Coronary heart disease after radiotherapy for peptic ulcer disease. *Int J Radiat Oncol Biol Phys*. 2005;61:842-850.
- McGale P, Darby SC. Commentary: a dose-response relationship for radiation-induced heart disease—current issues and future prospects. *Int J Epidemiol*. 2008;37:518-523.
- Taylor CW, Nisbet A, McGale P, et al. Cardiac exposures in breast cancer radiotherapy: 1950s-1990s. *Int J Radiat Oncol Biol Phys*. 2007;69:1484-1495.
- Vandenbroucke JP. When are observational studies as credible as randomised trials? *Lancet*. 2004;363:1728-1731.

11. Stroup DF, Berlin JA, Morton SC, et al; Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA*. 2000;283:2008–2012.
12. Wells GA, Shea B, O'Connell D, et al; The Ottawa Hospital Research Institute. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed online, January 21, 2016.
13. Higgins J, Altman D, Sterne J. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. <http://handbook.cochrane.org/>. Accessed online, January 15, 2016.
14. Wetterslev J, Thorlund K, Brok J, et al. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Med Res Methodol*. 2009;9:86.
15. Brok J, Thorlund K, Gluud C, et al. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *J Clin Epidemiol*. 2008;61:763–769.
16. Borger JH, Hoening MJ, Boersma LJ, et al. Cardiotoxic effects of tangential breast irradiation in early breast cancer patients: the role of irradiated heart volume. *Int J Radiat Oncol Biol Phys*. 2007;69:1131–1138.
17. Bouillon K, Haddy N, Delaloge S, et al. Long-term cardiovascular mortality after radiotherapy for breast cancer. *J Am Coll Cardiol*. 2011;57:445–452.
18. Gustavsson A, Bendahl PO, Cwikiel M, et al. No serious late cardiac effects after adjuvant radiotherapy following mastectomy in premenopausal women with early breast cancer. *Int J Radiat Oncol Biol Phys*. 1999;43:745–754.
19. Harris EE, Correa C, Hwang WT, et al. Late cardiac mortality and morbidity in early-stage breast cancer patients after breast-conservation treatment. *J Clin Oncol*. 2006;24:4100–4106.
20. Højris I, Overgaard M, Christensen JJ, et al; Radiotherapy Committee of the Danish Breast Cancer Cooperative Group. Morbidity and mortality of ischaemic heart disease in high-risk breast-cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: analysis of DBCG 82b and 82c randomised trials. *Lancet*. 1999;354:1425–1430.
21. Marhin W, Wai E, Tyldesley S. Impact of fraction size on cardiac mortality in women treated with tangential radiotherapy for localized breast cancer. *Int J Radiat Oncol Biol Phys*. 2007;69:483–489.
22. Nixon AJ, Manola J, Gelman R, et al. No long-term increase in cardiac-related mortality after breast-conserving surgery and radiation therapy using modern techniques. *J Clin Oncol*. 1998;16:1374–1379.
23. Park CK, Li X, Starr J, et al. Cardiac morbidity and mortality in women with ductal carcinoma in situ of the breast treated with breast conservation therapy. *Breast J*. 2011;17:470–476.
24. Paszat LF, Mackillop WJ, Groome PA, et al. Mortality from myocardial infarction following postlumpectomy radiotherapy for breast cancer: a population-based study in Ontario, Canada. *Int J Radiat Oncol Biol Phys*. 1999;43:755–762.
25. Roychoudhuri R, Robinson D, Putcha V, et al. Increased cardiovascular mortality more than fifteen years after radiotherapy for breast cancer: a population-based study. *BMC Cancer*. 2007;7:9.
26. Vallis KA, Pintilie M, Chong N, et al. Assessment of coronary heart disease morbidity and mortality after radiation therapy for early breast cancer. *J Clin Oncol*. 2002;20:1036–1042.
27. Wang W, O'Connell D, Stuart K, et al. Analysis of 10-year cause-specific mortality of patients with breast cancer treated in New South Wales in 1995. *J Med Imaging Radiat Oncol*. 2011;55:516–525.
28. Taylor CW, Wang Z, Macaulay E, et al. Exposure of the heart in breast cancer radiation therapy: a systematic review of heart doses. *Int J Radiat Oncol Biol Phys*. 2015;93:845–853.
29. Shank B, Moughan J, Owen J, et al. The 1993-94 patterns of care process survey for breast irradiation after breast-conserving surgery-comparison with the 1992 standard for breast conservation treatment. The Patterns of Care Study, American College of Radiology. *Int J Radiat Oncol Biol Phys*. 2000;48:1291–1299.
30. Formenti SC, DeWyngaert JK, Jozsef G, et al. Prone vs supine positioning for breast cancer radiotherapy. *JAMA*. 2012;308:861–863.
31. Jacob S, Pathak A, Franck D, et al. Early detection and prediction of cardiotoxicity after radiation therapy for breast cancer: the BACCARAT prospective cohort study. *Radiat Oncol*. 2016;11:54.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Sardar P, Kundu A, Chatterjee S, Nohria A, Nairooz R, Bangalore S, Mukherjee D, Aronow WS and Lavie CJ. Long-term cardiovascular mortality after radiotherapy for breast cancer: A systematic review and meta-analysis. *Clin Cardiol*, 2017;40(2):73–81.