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REVIEW ARTICLE **CME**

Cardiovascular Events and Mortality in Patients Undergoing Adjuvant Radiotherapy for Breast Cancer: a Systematic Review

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ABSTRACT

Objective: *We performed a systematic review to quantify the cardiovascular risk of adjuvant radiotherapy (RT) for breast cancer.*

Methods: *A literature search was conducted using MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from inception to July 2020.*

Results: *The literature search produced 7363 reports, of which 76 met our inclusion criteria. In studies comparing left-sided RT with right-sided RT, 7 of 35 (20%) studies found increased cardiovascular mortality, and 8 of 28 (29%) studies found increased cardiovascular events. In studies comparing patients who received RT with those who did not, 7 of 26 (27%) studies found increased cardiovascular mortality, and 5 of 22 (23%) studies found increased cardiovascular events.*

Conclusion: *Most of the studies that found significant associations between laterality and cardiovascular risks included treatment periods that started prior to 1985, suggesting that modern RT techniques have minimised the cardiac exposure in breast cancer patients receiving RT. However, more focused studies must be conducted to investigate the long- term cardiovascular risk associated with modern RT techniques.*

Key Words: *Breast neoplasms; Heart disease risk factors; Morbidity; Mortality; Radiotherapy, adjuvant*

中文摘要

乳腺癌輔助放療患者的心血管疾病和死亡率：系統性文獻回顧

P Taylor、S Chan、AB Wan、陳俊尹、MM Rodrigues、H Lam、E Chow、林美瑩

目的：我們進行系統性文獻回顧，量化乳腺癌術後輔助放療的心血管疾病風險。

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Ethics Approval: Ethics approval was not required for this review article which does not involve patients / animal or any interventions.

方法：使用 MEDLINE、Embase和Cochrane Central Register of Controlled Trials檢索始至2020年7月刊登的文獻。

結果：文獻檢索出7363個結果，其中76個符合我們的納入標準。在比較左側乳腺癌放療與右側乳腺癌放療的研究中，35項研究中有 7 項（20%）發現心血管疾病死亡率增加，28項研究中有8項（29%）發現心血管疾病增加。在比較接受放療的患者與未接受放療的患者的研究中，26項研究中有 7項（27%）發現心血管疾病死亡率增加，22項研究中有 5項（23%）發現心血管疾病增加。

結論：大部份發現單側性乳癌與心血管疾病風險間存在顯著關聯的研究都是1985年或之前，這表明現代放療技術已將接受放療的乳腺癌患者的心臟暴露風險降至最低。然而，必須進行更有針對性的研究以檢視與現代放療技術相關的長期心血管疾病風險。

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in females worldwide.[1] It has been shown through randomised trials that adjuvant radiotherapy (RT) following breast-conserving surgery substantially reduces breast cancer recurrence and reduces the absolute breast cancer mortality rate.[2,3] RT administered to breast cancer patients usually exposes the heart, an organ at risk, to some radiation. Cheng et al[4] conducted a literature review and meta-analysis on this topic, including studies published prior to January 2015, and found that breast cancer RT was associated with an absolute increase of 76.4 cases of coronary heart disease (95% confidence interval [CI]=36.8-130.5) and 125.5 cases of cardiac death (95% CI=98.8-157.9) per 100 000 person-years, respectively. In order to create optimised and tailored treatment plans, the current relationship between adjuvant breast RT and cardiovascular risks must be studied so that physicians and patients may appropriately consider the benefits of reduced breast cancer mortality with the potential long-term cardiovascular risks. We performed a systematic review to assess the risk of cardiovascular events (CVEs) and cardiovascular mortality (CVM) and its correlation with breast/chest wall RT for women with breast cancer (including breast cancer and ductal carcinoma in situ) following breast-conserving surgery/mastectomy (for node-positive or involved resection margin disease), as well as disease laterality. This will allow radiation oncologists to better inform their patients about the risks and benefits of adjuvant RT so that patients may make a more informed decision.

METHODS

Search Strategy

A literature search was completed using MEDLINE, Embase, and Cochrane Central Register of Controlled Trials from inception through to July 2020. Search terms for breast cancer included 'breast cancer', 'breast neoplasm', 'breast carcinoma', and 'breast tumour or tumour' (online supplementary Appendix). RT terms included 'radiotherapy', 'radiation', 'irradiation', and 'radiation injury'. CVE terms included 'heart disease', 'heart infarction', 'myocardial infarction (MI) or heart attack', 'angina pectoris', 'congestive heart failure (CHF)', 'coronary artery disease (CAD)', 'coronary artery obstruction', 'heart or cardio or cardiovascular disease (CVD)', 'ischemic heart disease (IHD)', 'dosage risk', 'cardiovascular risk', and 'cardiovascular death'.

Study Selection

Screening was first done based on the title and abstract independently by two authors (P Taylor, S Chan), with discrepancies being resolved through discussion between the two authors. Then, full-text screening was conducted independently by the two authors. Inclusion criteria were reports of the clinical cardiovascular outcomes, including CVEs and/or CVM as defined above. Specifically, studies were included if they reported comparisons in clinical cardiovascular outcomes between patients who received RT and those who did not receive RT and/or between patients who received left-sided RT and those who received right-sided RT. Exclusion criteria included any studies that investigated cancers other than breast cancer and the effects of irradiation on organ systems other than the cardiovascular system. Studies employing brachytherapy, partial breast irradiation, or boost to the tumour bed alone were excluded. Full-length papers, including cohort studies, case-control studies, and randomised controlled trials published as original papers written in English, were considered. Any case reports and non-original articles such as systematic reviews were excluded.

Data Collection and Analysis

Data extraction was conducted independently by two authors (P Taylor, S Chan). Both authors engaged in a discussion regarding any discrepancies between the extracted data and came to a consensus. The following data were extracted from the papers: publication year, geographical location, sample size, mean/median follow-up, number of CVEs, number of cardiovascular deaths, laterality, hazard ratios (HRs), incidence ratios, risk ratios (RRs), mortality ratios (MRs), and associated measures of variance for all categories of outcomes.

RESULTS

The search identified 7363 publications, of which 1063 were duplicates and excluded (Figure). A further 6132 articles were excluded because they did not meet the inclusion criteria. The remaining 168 articles underwent full-text screening. Of them, 92 were excluded for failure to meet the inclusion criteria, leaving 76 studies that were analysed in this systematic review.

Of the 76 studies, 35 investigated the risk of CVM with respect to RT laterality,[5-39] 28 studies investigated the risk of CVEs with respect to RT laterality,[7,10-12,16,18,20,22,24,33,40-57] 26 studies investigated the risk of CVM with respect to RT compared with no RT,[5,7,10,14,21,27,29,30,32,38,54,58-72] and 22 studies investigated the risk of CVEs with respect to RT compared with no RT.[7,36,44,45,48,49,54,59,61-63,67-69,73-80] Several studies overlapped between the categories and investigated the risk of CVEs and/or CVM with respect to RT and/or RT laterality. Results from the largest studies, based on study population size, will be highlighted for each of the four categories. The results for all studies are also reported in Tables 1 to 4.

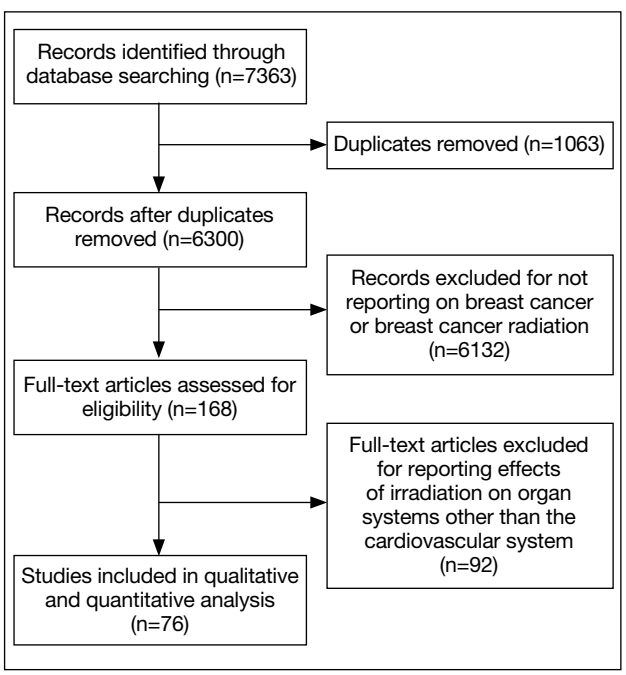

Figure. PRISMA flow diagram.

Cardiovascular Mortality in Patients with Left-sided or Right-sided Radiotherapy

Of 35 studies investigating the risk of CVM with respect to RT laterality, seven (20%) found a significant increased risk of CVM in patients who received left-sided RT compared with patients who received right-sided RT, all of which included study periods that started prior to 1985 (Table 1).[8,10,21,26,28,30,39] An additional six studies found a significant association between laterality and CVM only in subgroup analysis.[5,11,23,32,34,36] Of these six studies, three had subgroup analyses based on time period stratification, where in general older study periods before 1980-1990 were significant while more recent time periods were not (Table 1).[5,23,34]

Cardiovascular Events in Patients with Left-sided Radiotherapy or Right-sided Radiotherapy

Of 28 studies investigating the risk of CVEs with respect to RT laterality, eight (29%) found a significant increased risk of CVEs in patients who received left-sided RT compared with patients who received right-sided RT (Table 2).[11,18,40,41,46,49,51,56] Of these eight studies, five included study periods that started prior to 1985.[11,18,40,41,46] An additional three studies found a significant association between laterality and CVEs only in subgroup analysis.[22,47,55] These subgroup analyses were based on different treatment types and differences in types of CVEs.

Cardiovascular Mortality in Patients with Radiotherapy or without Radiotherapy

Of 26 studies investigating the risk of CVM for patients that received RT compared with those who did not receive RT, seven (27%) found a significant increase in CVM (Table 3).[29,30,32,63,64,71,72] Of these seven studies, six included study periods that started prior to 1985. An additional five studies found a significant association between RT and CVM only in subgroup analysis.[5,10,21,68,70] These subgroup analyses were based on different treatment types and differences in specific causes of CVM, such as death from cardiac diseases compared with death from vascular diseases.

Table 1. Studies assessing the risk of cardiovascular mortality in patients who received left-sided RT compared with those who received right-sided RT.

Study (first author)	Study population	Country	Treatment period	Study design	Median or mean follow-up time, y	Endpoint(s)	Endpoint criteria	Significant increased risk of cardiovascular death
Henson (2020)[5]	1,018,505	Multinational	1987-2002	Population-based cohort	6.7	Cardiac mortality	Did not specify	Yes for women diagnosed before 1990 (RR=1.134, 95% CI=1.09-1.17), but not for women diagnosed after 1990 (RR=0.98, 95% CI=0.93-1.02)
Beaton (2019)[6]	5249	Canada	2002-2006	Population-based case-control	10-year cardiac mortality	Cardiovascular deaths (CAD, MI, CHF, cardiomyopathy, arrhythmias, pericardial disease and 'other' heart disease)	ICD-10	No (1.7% for left-sided vs. 1.3% for right-sided, log rank p = 0.30) No for CAD (p = 0.26), cardiac arrest (p = 0.34), CHF and cardiomyopathy (0.75), conduction disorders and arrhythmias (p = 0.66), valvular heart disease (0.1), or other heart diseases (p = 0.18)
Li (2018)[17]	168,761	United States	2000-2008	Population-based cohort	8.8	Cardiac mortality	Did not specify	No (right-sided vs. left-sided RT, HR=1.025, 95% CI=0.856-1.099; p = 0.481)
Obi (2018)[27]	2439	Germany	2001-2005	Population-based case-control	11.9	Cardiac mortality	ICD-10	No (HR=0.96, 95% CI=0.54-1.71)
Chang (2017)[33]	2577 for 1 institution which was used for acute coronary event (YCCR) and 24,235 for nationwide registry analysis used for cardiac mortality (KBCR)	Korea	1990-2012	Population-based cohort	7 for YCCR and 7.9 for KBCR	Acute coronary event (death resulting from heart disease, or newly diagnosed IHD)	ICD-10	No in the KBCR (HR=1.52, 95% CI=0.37-6.25) and YCCR (p = 0.347)
Haque (2017)[34]	140,914	United States	1973-2002	Population-based cohort	11.5	Cardiac mortality	Not specified	Yes from 1973-1982 (HR=1.295, 95% CI=1.182-1.420) No from 1983-1992 (HR=1.022, 95% CI=0.949-1.100) or 1993-2002 (HR=0.989, 95% CI=0.935-1.046)
Merzenich (2017)[35]	9058	Germany	1998-2008	Multicentre cohort	6.5	Death due to MI, chronic IHD, acute IHD, CHF, angina, cardiac arrest, conduction disorder or vitium cordis	ICD-10	No (HR=0.94, 95% CI=0.64-1.38)
Boekel (2016)[36]	27,380	Netherlands	1989-2005	Population-based cohort	9	Cardiovascular event (a cardiovascular hospital discharge diagnosis, cardiosurgical intervention, or death due to CVD)	ICD-10	Yes for RT after mastectomy (HR=1.19, 95% CI=1.04-1.36) No for RT after WLE (HR=1.07, 95% CI=0.98-1.16)
Paul Wright (2016)[37]	66,687	United States	1990-1999	Population-based cohort	15.5	Cardiac mortality	SEER cause-specific death classification	No difference in 5-, 10- and 15-year cardiac mortality (p = 0.435)
Ye (2015)[38]	2796	United States	1990-1997	Population-based cohort	15	Cardiac mortality	Cause of death codes	No. There was a lower cardiac mortality rate for left-sided RT than for right-sided RT (4.6% vs. 6.0%, respectively; p = 0.04)

Abbreviations: 95% CI = 95% confidence interval; AMI = acute myocardial infarction; CAD = coronary artery disease; CHF = congestive heart failure; CVD = cardiovascular disease; DCIS = ductal carcinoma in situ; HR = hazard ratio; ICD = International Classification of Diseases; IHD = ischaemic heart disease; KBCR = Korean Breast Cancer Society; MI = myocardial infarction; N/A = not available; RCT = randomised controlled trial; RR = risk ratio; RT = radiotherapy; SEER = Surveillance, Epidemiology, and End Results Program; SMR = standardised mortality ratio; WLE = wide local excision; YCCR = Yonsei Cancer Center.

Table 1. (cont'd)

Study (first author)	Study population	Country	Treatment period	Study design	Median or mean follow-up time, y	Endpoint(s)	Endpoint criteria	Significant increased risk of cardiovascular death
Boekel (2014)[7]	2899 (DCIS patients only)	Netherlands	1989-2004	Population-based cohort	10	Death due to MI, other IHDs, other heart disease, pericarditis, valvular dysfunction, cardiomyopathy, arrhythmia, CHF, and/or cerebrovascular disease	ICD-10	No (HR=0.70, 95% CI=0.31-1.56)
Henson (2013)[8]	256,976	United States	1973-2008	Population-based cohort	Not specified. Studied up to 20+ years of follow-up	Death due to heart disease	ICD-10	Overall, yes (HR=1.08, 95% CI=1.03-1.14; 2p = 0.002) Yes from 1973-1982 <10 years after diagnosis (HR=1.19, 95% CI= 1.02-1.38), 10-14 years after diagnosis (HR=1.35, 95% CI=1.05-1.73), 15-19 years after diagnosis (HR=1.64, 95% CI= 1.26-2.14) and 20+ years after diagnosis (HR=1.90, 95% CI=1.52-2.37) No after 1982
Tjessem (2013)[9]	1107 in 4.3-Gy group and 459 in 2.5-Gy group	Norway	1975-1991	Population-based case-control	20	Cardiovascular death (death due to IHD or CVD)	ICD-9 and ICD-10	No (HR=0.93, 95% CI=0.52-1.66; p = 0.812)
Bouillon (2011)[10]	3038	France	1954-1984	Single-centre cohort	28	Death due to cardiac diseases (pericarditis, myocarditis, valvular heart diseases, IHD, heart failure)	ICD-8, ICD-9, ICD-10	Yes, 1.56-fold (95% CI=1.27-1.90) higher risk of dying of cardiac disease
McGale (2011)[11]	34,825	Sweden and Denmark	1976-2006	Population-based cohort	Not specified	Death due to heart disease	ICD-8, ICD-9, ICD-10	Overall, no for all IHDs (HR=1.00, 95% CI= 0.86-1.15) or for heart disease other than IHD (HR=1.00, 95% CI= 0.81-1.22) Yes for death due to AMI (HR=1.23, 95% CI= 1.01-1.49; p = 0.04)
Park (2011)[12]	129 (DCIS patients only)	United States	1986-2002	Single-centre cohort	8.2	Death due to CAD, MI, CHF, chronic IHD, arrhythmia, valvular disease, and cardiomyopathy	Did not specify	No (p = 0.64)
Stokes (2011)[13]	4929	Canada	1990-1996	Population-based cohort	11.7	Cardiac and cerebrovascular deaths	Did not specify	No (RR=1.02, 95% CI=0.77-1.35; p = 0.89)
Wang (2011)[14]	519	Australia	1 Apr-30 Sep 1995	Population-based cohort	Not specified	10-year cardiac mortality	Death certificates codes by the Australian Bureau of Statistics	No (p = 0.63)
Bouchardy (2010)[15]	1245	Switzerland	1980-2004	Population-based cohort	7.7	Cardiovascular mortality	ICD-10	No (HR=0.5, 95% CI=0.2-1.1)
Gutt (2008)[16]	41	United States	1980-1994	Single-centre cohort	7.9 for left-sided, 11.3 for right-sided	Cardiovascular mortality following MI, CHF and/or CAD	Not specified	No (HR=4.2; p = 0.08)
Borger (2007)[18]	1601	Netherlands	1980-1993	Multicentre cohort	16	CVD (including IHD and other heart diseases)	ICD-9	No for CVD (HR=1.57, 95% CI=0.83-3.00) and IHD (HR=1.99, 95% CI=0.71-5.59)

Table 1. (cont'd)

Study (first author)	Study population	Country	Treatment period	Study design	Median or mean follow-up time, y	Endpoint(s)	Endpoint criteria	Significant increased risk of cardiovascular death
Marhin (2007)[19]	7477	Canada	1984-2000	Population-based cohort	7.9	Death due to AMI, aortic stenosis, CHF, atherosclerotic CVD, atherosclerotic heart disease, arrhythmia, cardiac arrest, CVD, IHD, chronic IHD, coronary atherosclerosis, endocarditis, or essential primary hypertension	Oncology Reporting System database death certificates	No (p = 0.69)
Paszat (2007)[20]	619	Canada	1982-1988	Population-based cohort	13.5 minimum	AMI and death due to AMI	Chart review	No (HR=1.07, 95% CI=0.65-1.72)
Roychoudhuri (2007)[21]	20,871	South East England	1971-1988	Population-based cohort	18.5	Death due to IHD and other CVDs	ICD-9, 10	Yes for overall CVD mortality (HR=1.25, 95% CI=1.05-1.49; p = 0.014) No for IHD mortality specifically (HR=1.23, 95% CI=0.95-1.60; p = 0.114)
Harris (2006)[22]	961	United States	1977-1994	Single-centre cohort	12	Freedom from cardiac death (death due to MI or CHF) at 5, 10, 15, and 20 years	Not specified	No for cardiac death overall (p = 0.25) No for MI (p = 0.22) and CHF (p = 0.82)
Darby (2005)[39]	115,165	United States	1973-2001	Population-based cohort	N/A	5-, 10-, and 15-year death rates due to AMI, IHD and other heart disease	ICD-9	Overall, yes (HR=1.16, 95% CI=1.08-1.24; 2p = 0.00004) Yes for patients diagnosed during 1973-1982 <10 years after diagnosis (HR=1.20, 95% CI= 1.04-1.38), 10-14 years after diagnosis (HR=1.42, 95% CI=1.11-1.82) and ≥15 years after diagnosis (HR=1.58, 95% CI= 1.29-1.95) No, during 1983-1992 <10 years after diagnosis (HR=1.04, 95% CI= 0.91-1.18) or >10 years after diagnosis (HR=1.27, 95% CI=0.99-1.63) or during 1993-2001 (HR=0.96, 95% CI= 0.82-1.12)
Giordano (2005)[23]	27,283	United States	1973-1989	Population-based cohort	10.1 (1973-1979), 11.1 (1980-1984), and 11 (1985-1989)	Death due to IHD	ICD-9, ICD-10	Overall, no (p = 0.07) Yes for patients diagnosed between 1973 and 1979 (p = 0.02). No between 1980 and 1984 (p = 0.64) and 1985-1989 (p = 0.98)
Vallis (2002)[24]	2128	Canada	1982-1988	Single-centre cohort	10.2	Death due to MI	ICD-9	No
Nixon (1998)[25]	745	United States	1968-1986	Single-centre cohort	Not specified. Studied 12 years of follow-up	Cardiac mortality	Not specified	No (RR=1.3; p = 0.29)
Paszat (1999)[26]	3006	Canada	1982-1987	Population-based cohort	8.8	Death due to MI	ICD-9	Yes (RR=2.10, 95% CI=1.11-3.95)
Paszat (1998)[28]	47,948	United States	1973-1992	Population-based cohort	74 mo	Death due to MI	ICD-9	Yes (RR=1.17, 95% CI=1.01-1.36)
Cuzick (1994)[29]	3970	Multinational	1949-1974	Multiple RCTs	>10	Cardiac mortality	ICD-9	No (SMR=1.34; p = 0.9)

Table 1. (cont'd)

Study (first author)	Study population	Country	Treatment period	Study design	Median or mean follow-up time, y	Endpoint(s)	Endpoint criteria	Significant increased risk of cardiovascular death
Houghton (1994)[30]	1376	United Kingdom	1970-1975	RCT	19	Cardiac death (death due to heart failure, myocardial infarct, or coronary thrombosis)	Did not specify	Yes (x2(int)=5.08; p = 0.02)
Rutqvist (1990)[31]	54,617	Sweden	1970-1985	Population-based cohort	9	Deaths due to CVDs and MIs	Did not specify	No for overall CVD mortality (RR=1.03, 95% CI=0.98-1.09) Yes for MI mortality (RR=1.09, 95% CI= 1.02-1.17)
Haybittle (1989)[32]	1376	United Kingdom	1970-1975	RCT	13.2-18	Cardiac deaths (deaths due to heart failure, MI, coronary thrombosis, and other cardiovascular deaths)	Death report forms, copies of death certificates, and correspondence with treating clinicians and examination of the patient's notes	No overall Yes for left-sided RT vs. no left-sided RT (RR=2.26, 95% CI=1.19-4.29) and no for right-sided RT vs. no right-sided RT (RR=1.20, 95% CI=0.64-2.28) Interaction test between left and right is insignificant (p = 0.17)

Cardiovascular Events in Patients with Radiotherapy or without Radiotherapy

Of 22 studies investigating the risk of CVEs for patients that received RT compared with those who did not receive RT, five (23%) found a significant association between RT and CVEs (Table 4).[36,73,75,79,80] An additional three studies found a significant association between RT and CVEs only in subgroup analysis.[74,77,78] These subgroup analyses were based on different treatment types and the presence of pre-existing cardiovascular risk factors.

DISCUSSION

This review summarises the cardiovascular morbidity and mortality risk associated with breast adjuvant RT and the laterality of the RT. When comparing patients who received left-sided RT with those who received right-sided RT, we found that 7 of 35 studies found a significant increase in the risk of CVM and 8 of 28 studies found a significantly increased risk of CVEs. For patients who received RT compared with those who did not receive RT, 7 of 26 studies found a significantly increased risk of CVM and 5 of 22 studies found a significant increased risk of CVEs.

A previous meta-analysis conducted by Cheng et al[4] examined studies of breast cancer patients from 1966 to 2015. The authors[4] found that patients who received RT had an increased risk of coronary heart disease (RR=1.30, 95% CI=1.13-1.49) and cardiac mortality (RR=1.38, 95% CI=1.18-1.62) compared with patients who did not receive RT. They also found that patients who received left-sided RT experienced an increased risk of developing coronary heart disease compared with patients receiving right-sided RT (RR=1.29, 95% CI=1.13-1.48).[4] Patients receiving left-sided RT also experienced an increased risk of cardiac death compared with patients receiving right-sided RT (RR=1.22, 95% CI=1.08-1.37).[4] In contrast to Cheng et al,[4] in the present review, we found newer studies in which there was no significant increased risk of CVEs or CVM in patients who received RT compared with patients who did not receive RT. We also found more studies in which patients who received left-sided RT had no significant increased risk of CVEs or CVM compared with patients who received right-sided RT. These differences likely reflect the fact that the present review includes many new studies since 2015 in which the study populations received modern RT techniques. However, because we did not conduct a meta-analysis in the present review, it remains unclear whether our findings represent a significantly different association between breast cancer RT and cardiovascular risk compared with that reported by Cheng et al.[4]

Table 2. Studies assessing the risk of cardiovascular events in patients who received left-sided RT compared with those who received right-sided RT.

Study (first author)	Study population	Country	Treatment period	Study design	Median or mean follow-up time, y	Endpoint(s)	Endpoint criteria	Significant increased risk of cardiovascular death
Killander (2020)[54]	563	Sweden	1991-1997	RCT	21.3	Cardiac morbidity and mortality	ICD-8, ICD-9, ICD-10	No for PCI (3.8% for right-sided, 2.2% for left-sided, p = 0.33) No for open heart surgery (5.2% for right-sided, 3.4% for left-sided, p = 0.06)
Wennstig (2020)[56]	37,427	Sweden	1992-2012	Population-based cohort	8.1	Risk of IHD	ICD-9, ICD-10	Yes for IHD (HR=1.18, 95% CI=1.06-1.31)
Abouegylah (2019)[51]	202	Unknown	2000-2014	Hospital-based cohort	6.75 for left-sided and 7 for right-sided	Cardiac outcomes (cardiac ischaemia, arrhythmia, heart failure)	Did not specify	Yes for ischaemia (OR=0.08, p = 0.021), and arrhythmias (OR=0.05, p = 0.005)
Chang (2019)[52]	1015	Korea	2002-2013	Population-based cohort	6.1	Acute coronary events (newly diagnosed IHD that requires anticoagulant therapy or coronary revascularisation, as well as cardiac-related death)	ICD and the medical procedure codes from the Electronic Data Interchange	No (HR=1.28, 95% CI=0.71-2.29; p = 0.413)
Kim (2019)[55]	660	Korea	2005-2015	Multicentre cohort	3.9	Cardiovascular events (including CVD mortality, MI, heart failure, and stroke)	Chart review	No (HR=2.38, 95% CI=0.80-7.11; p = 0.12) Yes for left-sided RT + doxorubicin-equivalent dose ≥250 mg/m^2 vs. right-sided RT + cumulative doxorubicin-equivalent dose <250 mg/m^2 (HR=5.22, 95% CI=1.67-21.15; p = 0.006)
Boekel (2018)[47]	14,645	Netherlands	1970-2009	Hospital-based cohort	14	Cardiovascular event (CVD diagnosis or death due to CVD)	ICD-10	Yes for left chest wall RT vs. right breast RT for CVD (HR=1.83, 95% CI=1.39-2.40) and IHD (HR=2.57, 95% CI=1.61-4.11) No for left breast RT vs. right breast RT for IHD (HR=1.38, 95% CI= 0.96-1.99) No for breast RT without IMC (HR=1.11, 95% CI=0.93-1.32)
James (2018)[53]	501	New Zealand	2002-2006	Hospital-based cohort	10.33	Cardiac toxicity (MI, admission for chest pain, coronary angiogram positivity, and ischaemic cardiac death)	ICD-10	No (OR=1.565, 95% CI=0.7-3.6; p = 0.2885)
Wadsten (2018)[44]	2441	Sweden	1992-2012	Population-based cohort	8.8	IHD	ICD-9	No (HR=0.85, 95% CI=0.53-1.37)
Chang (2017)[33]	2577 for 1 institution which was used for acute coronary event (YCCR) and 24,235 for nationwide registry analysis used for cardiac mortality (KBCR)	Korea	1990-2012	Population-based cohort	7 for YCCR and 7.9 for KBCR	Acute coronary event (death resulting from heart disease, or newly diagnosed IHD)	ICD-10	No (HR=1.16, 95% CI=0.59-2.29)

Abbreviations: 95% CI = 95% confidence interval; AMI = acute myocardial infarction; CAD = coronary artery disease; CHF = congestive heart failure; CVD = cardiovascular diseases; DCIS = ductal carcinoma in situ; EMERSE = Electronic Medical Record Search Engine; HR = hazard ratio; ICD = International Classification of Diseases; ICPC = International Classification of Primary Care; IHD = ischaemic heart disease; IMC = internal mammary chain; IR = incidence ratio; KBCR = Korean Breast Cancer Society; MI = myocardial infarction; MONICA = monitoring or trends and determinants in cardiovascular disease; OR = odds ratio; PCI = percutaneous coronary intervention; RCT = randomised controlled trial; RT = radiotherapy; YCCR = Yonsei Cancer Center.

Table 2. (cont'd)

Study (first author)	Study population	Country	Treatment period	Study design	Median or mean follow-up time, y	Endpoint(s)	Endpoint criteria	Significant increased risk of cardiovascular death
Dess (2017)[43]	2126	United States	1984-2007	Single-centre cohort	9.3	10-year rate of ischaemic cardiac events (AMI, coronary artery bypass grafting, angioplasty or stent placement, diagnosis of CAD)	ICD, EMERSE	No (HR=1.21, 95% CI= 0.79-1.85, p = 0.37)
Rehammar (2017)[46]	19,464	Denmark	1977-2005	Population-based cohort	10.5	Cardiac disease	ICD-10	Yes (HR=1.11, 95% CI=1.03-1.20; p = 0.005)
Wollschläger (2017)[57]	4474	Germany	1998-2008	Multicentre cohort study	8.3	Cardiac event (MI, angina, CHF, arrhythmia, or valvular heart disease)	ICD-10	No (HR=1.07, 95% CI=0.89-1.29)
Boerman (2014)[45]	334	Netherlands	1970-2007	Matched case-control study	9	CHF (acute and chronic), vascular cardiac diseases (unstable and stable angina pectoris, AMI, other chronic IHDs [coronary artery sclerosis], transient ischaemic attack, and cerebrovascular attack), and other cardiac diseases (atrial fibrillation, paroxysmal tachycardia, nonrheumatic valve disease)	ICPC version 1	No for CHF (HR=0.98, 95% CI=0.3-3.6), vascular cardiac diseases (HR=0.7, 95% CI= 0.3-1.4), or other cardiac diseases (HR=0.8, 95% CI=0.4-1.7)
Boekel (2014)[7]	2899 (DCIS patients only)	Netherlands	1989-2004	Population-based cohort	10	MI, other IHDs, other heart disease, pericarditis, valvular dysfunction, cardiomyopathy, arrhythmia, CHF, and/or cerebrovascular disease	ICD-10	No (HR=0.94, 95% CI=0.67-1.32)
Soran (2014)[50]	602	United States	1986-2007	Hospital-based cohort	7.5	Major cardiac events (chest pain, MI, atherosclerosis, angina, stroke)	Self-reported questionnaire	No for chest pain (p = 0.9), MI (p = 0.1), atherosclerosis (p = 0.07), angina (p = 0.3), or stroke (p = 0.1)
Darby (2013)[40]	2168 (963 cases and 1205 controls)	United States	1958-2001 (Sweden), 1977-2000 (Denmark)	Population-based case-control	Did not specify	Major coronary events (MI, coronary revascularisation, or death from IHD)	ICD-10	Yes (p = 0.002)
Bouillon (2011)[10]	3038	France	1954-1984	Single-centre cohort	28	Cardiac diseases (pericarditis, myocarditis, valvular heart diseases, IHD, heart failure)	ICD-8, ICD-9, ICD-10	No (1.28-fold more likely; 95% CI=0.92-1.78)
Haque (2011)[49]	340	United States	1990-1994	Population-based cohort	10	CVD events that were serious enough to require hospitalisation (IHD, AMI, angina, and CVD)	ICD-9, ICD-10	Yes (HR=1.53, 95% CI=1.06-2.21)
Park (2011)[12]	129 (DCIS patients only)	United States	1986-2002	Single-centre cohort	8.2	CAD, MI, CHF, chronic IHD, arrhythmia, valvular disease and/or cardiomyopathy	Did not specify	No, 13.5% of left-sided RT patients developed a cardiovascular event compared with 7% of right-sided patients (p = 0.25)

Table 2. (cont'd)

Study (first author)	Study population	Country	Treatment period	Study design	Median or mean follow-up time, y	Endpoint(s)	Endpoint criteria	Significant increased risk of cardiovascular death
McGale (2011)[11]	34,825	Sweden and Denmark	1976-2006	Population-based cohort	Not specified.	Heart disease	ICD-8, ICD-9, ICD-10	Yes (IR=1.08, 95% CI=1.02-1.15; p = 0.01)
Gutt (2008)[16]	41	United States	1980-1994	Single-centre cohort	7.9 for left-sided and 11.3 for right-sided	MI, CHF, CAD, arrhythmia, chest pain, and/or valvular disease	Not specified	No for CAD (p = 0.6), MI (p = 0.96), CHF (p = 0.73), arrhythmia (p = 0.31), or valvular disease (p = 0.89)
Borger (2007)[18]	1601	Netherlands	1980-1993	Multicentre cohort	16	CVD (including IHD and other heart diseases)	ICD-9	Yes for CVD (HR=1.38, 95% CI=1.05-1.81) and non-IHD (HR=1.53, 95% CI=1.09-2.15). No for IHD (HR=1.35, 95% CI=0.93-1.98)
Doyle (2007)[48]	25,653	United States	1992-2000	Population-based cohort	13 as max	MI, ischaemia, CHF, and other heart disease (myocarditis, arrhythmia, and valvular disease)	ICD-9	No for MI/ischaemia (HR=1.03, 95% CI=0.93-1.13) or for MI alone (HR=0.99, 95% CI=0.87-1.11)
Jagsi (2007)[41]	828	United States	1984-2000	Single-centre cohort	6.8	Cardiac events (CAD or MI requiring intervention)	ICD-9	Yes for MI (HR=7.92, 95% CI=1.01-62.28; p = 0.05)
Paszat (2007)[20]	619	Canada	1982-1988	Population-based cohort	13.5 minimum	AMI and death due to AMI	Chart review	No (HR=1.42, 95% CI=0.92-2.17)
Harris (2006)[22]	961	United States	1977-1994	Single-centre cohort	12	Chest pain, CAD, MI, CHF and chronic IHD, arrhythmia and palpations and/or valvular disorders	Not specified	Yes for chest pain (IR=2.1, 95% CI=1.5-2.9; p < 0.001), CAD (IR=2.7, 95% CI=1.7-4.5; p < 0.001) and MI (IR=3.1, 95% CI=1.5-6.5; p = 0.002) No for CHF/chronic IHD (IR=1.2, 95% CI=0.8-2.0; p = 0.37), arrhythmia (IR=1.3, 95% CI=0.8-1.9; p = 0.21) and valvular disorders (IR=0.85, 95% CI=0.6-1.3; p = 0.70)
Patt (2005)[42]	16,270	United States	1986-1993	Population-based cohort	9.5	IHD, valvular heart disease, CHF, and/or conduction abnormalities	ICD-9	No for IHD (HR=1.05, 95% CI=0.94-1.16), valvular disease (HR=1.07, 95% CI= 0.89-1.30), CHF (HR=1.05, 95% CI= 0.95-1.17), and conduction abnormalities (HR=1.07, 95% CI= 0.96-1.19)
Vallis (2002)[24]	2128	Canada	1982-1988	Single-centre cohort	10.2	MI and/or other cardiac events	ICD-9 combined with the multinational MONICA criteria	No for MI (p = 0.66) or other cardiac events (p = 0.24)

Table 3. Studies assessing the risk of cardiovascular mortality in patients who received RT compared with those who did not receive RT.

Study (first author)	Study population	Country	Treatment period	Study design	Median or mean follow-up time, y	Endpoint(s)	Endpoint criteria	Significant increased risk of cardiovascular death
Boekel (2020)[58]	408	Netherlands	1976-2009	Population-based case-control	Did not specify	Heart failure	Chart review	No for RT vs. MHD between 0 and 1 Gy (RR=1.4, 95% CI=0.73-2.8; p = 0.51)
Chou (2020)[59]	27,466	Taiwan	2007-2014	Population-based cohort	Did not specify	MACE, identified by emergency visit claims or inpatient data of IHD, CHF, acute ischaemic stroke, and intracranial haemorrhage	ICD-9 Clinical Modification	No, RT + hormone group had a significantly lower risk than the hormone only group (HR=0.609, 95% CI= 0.430-0.862; p = 0.005)
Henson (2020)[5]	1,934,248	Multinational	1987-2002	Population-based cohort	6.7	Cardiac mortality	Did not specify	No, there was a decreased risk (RR=0.94, 95% CI= 0.92-0.95) Yes for RT after mastectomy (RR=1.24, 95% CI= 1.19-1.30)
Killander (2020)[54]	1144	Sweden	1991-1997	RCT	21.3	Cardiac morbidity and mortality	ICD-8, ICD-9, ICD-10	No, 12.4% incidence of cardiac mortality in no RT group vs. 13% in RT group (p = 0.8)
Lee (2020)[60]	91,227	Korea	2007-2013	Population-based cohort	3.1	CHF	ICD-10	No, risk was lower when analysed from BC diagnosis (HR=0.734, 95% CI= 0.652-0.826) and when analysed from 2 years after BC diagnosis (HR=0.688, 95% CI=0.583-0.811)
Lawrenson (2019)[61]	3528	New Zealand	1995-2013	Population-based cohort	10-year follow-up period	Cardiovascular events and cardiovascular mortality	ICD-9	No (HR=0.75, 95% CI= 0.47-1.19)
Obi (2018)[27]	2951	Germany	2001-2005	Population-based case-control	11.9	Cardiac mortality	ICD-10	No (HR=1.57, 95% CI= 0.75-3.29)
Leung (2016)[62]	5132	Taiwan	2000-2010	Population-based case-control study	3.5	Death due to IHD, valvular heart disease, CHF, and/or conduction abnormalities	ICD-9	No (HR=1.40, 95% CI= 0.80-2.47, p = 0.13) No for IHD (HR=1.41, 95% CI=0.56-3.56), valvular heart disease (HR=0.57, 95% CI=0.08-4.26), CHF (HR=1.56, 95% CI= 0.66-3.69), and conduction abnormalities (HR=2.77, 95% CI=0.95-8.06)
Ye (2015)[38]	6515	United States	1990-1997	Population-based cohort	15	Cardiac mortality	Cause of death codes	No (HR=0.57, 95% CI= 0.47-0.69; p < 0.0001)
Boekel (2014)[7]	10,365 (DCIS patients only)	Netherlands	1989-2004	Population-based cohort	10	Death due to MI, other IHDs, other heart disease, pericarditis, valvular dysfunction, cardiomyopathy, arrhythmia, CHF, and/or cerebrovascular disease	ICD-10	No significant difference in cardiovascular death between patients who received left-sided (HR=0.89, 95% CI=0.48-1.66) or right-sided RT (HR=1.29, 95% CI=0.72-2.31) vs. surgery only
Killander (2014)[63]	1110	Sweden	1978-1985	Two RCTs	Not specified	25-year mortality rates due to IHD, CHF, dysrhythmia, and non-rheumatic valvular and/or pericardial disease	ICD-8, ICD-9, ICD-10	Yes, when RT was combined with cyclophosphamide in premenopausal women (p = 0.04) or tamoxifen in postmenopausal women (p = 0.005)

Abbreviations: 95% CI = 95% confidence interval; AMI = acute myocardial infarction; BC = breast cancer; BCS = breast-conserving surgery; Chemo = chemotherapy; CHF = congestive heart failure; CVD = cardiovascular diseases; DCIS = ductal carcinoma in situ; HR = hazard ratio; ICD = International Classification of Diseases; IHD = ischaemic heart disease; MACE = major adverse cardiac events; MHD = mean heart dose; MI = myocardial infarction; RCT = randomised controlled trial; RR = risk ratio; RT = radiotherapy; SMR = standardised mortality ratio.

Table 3. (cont'd)

Study (first author)	Study population	Country	Treatment period	Study design	Median or mean follow-up time, y	Endpoint(s)	Endpoint criteria	Significant increased risk of cardiovascular death
Bouillon (2011)[10]	4456	France	1954-1984	Single-centre cohort	28	Death due to vascular diseases (pulmonary heart diseases, hypertensive diseases, cerebrovascular diseases, diseases of arteries, arterioles and capillaries) and cardiac diseases (pericarditis, myocarditis, valvular heart diseases, IHD, heart failure)	ICD-8, ICD-9, ICD-10	Yes for cardiac diseases (1.76-fold more likely, 95% CI=1.34-2.31) No for vascular diseases (1.33-fold more likely, 95% CI=0.99-1.80)
Wang (2011)[14]	1242	Australia	1995	Population-based cohort	Not specified	10-year cardiac mortality	Death certificates codes	No, higher cumulative mortality due to cardiac causes in non-RT group, compared with left-sided and right-sided RT groups (p = 0.001)
Roychoudhuri (2007)[21]	20,871	South East England	1971-1988	Population-based cohort	18.5	IHD and other CVDs	ICD-9, ICD-10	No for IHD mortality (HR=1.28, 95% CI= 0.96-1.70; p = 0.092) and CVD mortality (HR=1.02, 95% CI=0.85-1.23; p = 0.806) when comparing right-sided irradiated patients to right-sided non-irradiated patients Yes for IHD mortality (HR=1.59, 95% CI= 1.21-2.08) and CVD mortality (HR=1.27, 95% CI= 1.07-1.51) when comparing left-sided RT patients to right-sided patients with no RT
Clarke, et al (2005)[64]	42,080	Multinational	1995-2000	RCT	5-, 10-, and 15-year mortality rates	Cardiac mortality	ICD-9	Yes (RR=1.27; 2p = 0.0001)
Ragaz (2005)[65]	318 (164 in Chemo + RT, and 154 in Chemo only)	Canada	1979-1986	RCT	20.75	Cardiac death	Did not specify	No, 1.8% death rate in Chemo + RT and 0.6% in Chemo alone (p = 0.622)
Woodward (2003)[66]	1493	United States	1975-1994	5 separate clinical trials	10	10-year rate of death from MI	Did not specify	No (10-year death rate from MI was 2.4% in RT patients vs. 0.5% in no RT patients [p = 0.057])
Hojris (1999)[67]	3046	Denmark	1982-1990	Two RCTs	9.75	IHD (including AMI)	ICD-8, ICD-10	No (HR=1.12, 95% CI= 0.73-2.95)
Gyenes (1998)[68]	960	Sweden	1971-1976	Multicentre case-control study	20	Death due to IHD and/or CVD	ICD-9	Yes for IHD mortality (HR=2.5, 95% CI=1.1-5.7; p = 0.03) and CVD mortality (HR=2.0, 95% CI=1.0-3.9; p = 0.04) in high dose-volume RT patients compared with surgical controls No for IHD mortality and CVD mortality in low dose-volume RT patients compared with surgical controls Note: High dose-volume was defined as using left-sided tangential 60Co fields. Low dose-volume was defined as using right-sided tangential 60Co fields. Intermediate dose was defined as using electron techniques

Table 3. (cont'd)

Study (first author)	Study population	Country	Treatment period	Study design	Median or mean follow-up time, y	Endpoint(s)	Endpoint criteria	Significant increased risk of cardiovascular death
Rutqvist (1998)[69]	5680	Sweden	1976-1987	Hospital-based case-cohort	9	AMI	Did not specify	No for RT + BCS vs. mastectomy alone (HR=0.4, 95% CI=0.2-1.1)
Cuzick (1994)[29]	7941	Multinational	1949-1974	Multiple RCTs	>10	Cardiac mortality	ICD-9	Yes (SMR=1.62, 95% CI=1.25-2.1; p < 0.001)
Houghton (1994)[30]	2800	United Kingdom	1970-1975	RCT	19	Cardiac death (death due to heart failure, myocardial infarct, or coronary thrombosis)	Did not specify	Yes for mastectomy + RT vs. mastectomy alone (RR=1.52, 95% CI=1.01-2.29; p = 0.04)
Rutqvist (1992)[70]	960	Sweden	1971-1976	RCT	16	Death due to IHD	ICD	Yes for IHD mortality in highest dose-volume RT patients (HR=3.2, p < 0.05). No for lower dose-volume patients Note: High dose-volume was defined as using left-sided tangential 60Co fields. Low dose-volume was defined as using right-sided tangential 60Co fields. Intermediate dose was defined as using electron techniques
Haybittle (1989)[32]	2800	United Kingdom	1970-1975	RCT	13.2-18	Cardiac deaths (deaths due to heart failure, MI, coronary thrombosis, and other cardiovascular deaths)	Death report forms, copies of death certificates, and correspondence with treating clinicians and examination of the patient's notes	Yes (RR=1.65, 95% CI= 1.05-2.58; p = 0.03)
Jones (1989)[71]	1461	United Kingdom	1949-1955	RCT	Did not specify (up to 34 years' follow-up)	Cardiovascular death	Chart review	Yes (p = 0.03), especially after 15+ years of follow-up (p = 0.0045)
Høst (1986)[72]	1115	Norway	1964-1972	RCT	11.0-20.0	Cardiac deaths (AMI)	Death certificates	Yes (p = 0.004)

A systematic review conducted by Drost et al[81] found that the mean heart dose steadily decreased from 4.6 Gy in 2014 to 2.6 Gy in 2017 (p = 0.003). Combining this with the dose-dependent relationship between major cardiac events and mean dose to the heart by Darby et al,[40] it is likely that the decrease in mean heart dose owing to improved contemporary RT techniques has led to improved outcomes in breast cancer patients in recent years. Our findings are also in support of this hypothesis since all studies that found a significant association between RT laterality and CVM included treatment groups that started prior to 1985. This is consistent with the systematic review by Cheng et al,[4] which found an increased risk of cardiovascular death and coronary heart disease associated with RT among studies in which the breast cancer patients were diagnosed and irradiated before 1980 (RR=1.45, 95% CI=1.14-1.89) compared with women diagnosed and irradiated after 1980 (RR=1.15, 95% CI=0.92-1.44; p = 0.04). Similarly, Giordano et al[23] found that in 1979, the HR for ischaemic heart disease mortality in left-sided compared with right-sided disease was 1.50 (95% CI=1.19-1.87), but this HR declined by 6% with each succeeding year between 1979 and 1988 (HR=0.94; 95% CI=0.91-0.98).

As such, newer research has started to evaluate whether the use of modern linear accelerator machines instead of ^{60}Co fields and various contemporary radiation techniques reduces the cardiac radiation dose and subsequent cardiac toxicities. One example is intensity-modulated RT, which allows a more conformal target coverage without exposing organs at risk to as much radiation.[82] Other notable advancements in cardiac sparing techniques include the use of deep inspiration

Table 4. Studies assessing the risk of cardiovascular events in patients who received RT compared with those who did not receive RT.

Study	Study population	Country	Treatment period	Study design	Median or mean follow-up time, y	Endpoint(s)	Endpoint criteria	Significant increased risk of cardiovascular events
Chou (2020)[59]	27,466	Taiwan	2007-2014	Population-based cohort	Did not specify	MACE, identified by emergency visit claims or inpatient data of IHD, CHF, acute ischaemic stroke, and intracranial haemorrhage	ICD-9 Clinical Modification	No, RT + hormone group vs. hormone only group (HR=0.831, 95% CI= 0.593-1.164; p = 0.286)
Killander (2020)[54]	1144	Sweden	1991-1997	RCT	21.3	Cardiac morbidity and mortality	ICD-8, ICD-9, ICD-10	No, incidence of admission to hospital with a cardiac diagnosis was 29.7% in no RT group, vs. 31% in RT group (p = 0.7)
Hamood (2019)[73]	338	Israel	2002-2012	Population-based cohort	5.7	CVD events (IHD, CHF, arrhythmias and conduction disorders)	ICD-9	Yes (HR=2.94, 95% CI=1.17-7.38; p = 0.22)
Jacobse (2019)[74]	365 (183 MI cases and 182 controls)	Netherlands	1970-2009	Population-based case-control	13.6 years median time to MI	MI	Did not specify	Yes for RT with IMC (RR=2.45, 95% CI= 1.97-3.05; p = 0.006), No for RT without IMC (RR=1.20, 95% CI= 0.67-2.18)
Lawrenson (2019)[61]	3528	New Zealand	1995-2013	Population-based cohort	10-year follow-up period	Cardiovascular events and cardiovascular mortality	ICD-9	No (HR=0.73, 95% CI= 0.59-0.92)
Lee (2019)[75]	1759	Taiwan	2002-2012	Population-based cohort	5.2	Major heart events (heart failure and CAD)	ICD-9	Yes (HR=1.47, 95% CI=1.24-1.73, p < 0.0001)
Wadsten (2018)[44]	6270	Sweden	1992-2012	Population-based cohort	8.8	IHD	ICD-9, ICD-10	No (HR=0.79, 95% CI= 0.62-1.01)
Wu (2017)[76]	746	United States	1997-1999	RCT	10.5	Cardiac adverse event (IHD, MI, heart failure, relative and absolute decrease of LVEF >20% from baseline, and incidence of arrhythmia)	National Cancer Institute common toxicity criteria for adverse events	No (7.9% for RT vs. 8% for no RT [p = 1.0])
Boekel (2016)[36]	59,388	Netherlands	1989-2005	Population-based cohort	9	Cardiovascular event (a cardiovascular hospital discharge diagnosis, cardiosurgical intervention, or death due to CVD)	ICD-10	Yes for left-sided RT after mastectomy vs. surgery alone (subdistribution HR=1.23, 95% CI= 1.11-1.36)
Leung (2016)[62]	5132	Taiwan	2000-2010	Population-based case-control study	3.5	IHD, valvular heart disease, CHF, and/or conduction abnormalities	ICD-9	No (HR=0.81, 95% CI= 0.57-1.15)
Tan (2016)[77]	5514	Taiwan	2002-2007	Population-based cohort	5.3	CVD (IHD and CHF)	ICD-9	No for RT vs. surgery alone (HR=0.97, 95% CI= 0.62-1.51; p = 0.882) Yes for Chemo + RT vs. surgery alone (HR=1.84, 95% CI=1.34-2.53; p < 0.001)
Boekel (2014)[7]	10,365 (DCIS patients only)	Netherlands	1989-2004	Population-based cohort	10	MI, other IHDs, other heart disease, pericarditis, valvular dysfunction, cardiomyopathy, arrhythmia, CHF, and/or cerebrovascular disease	ICD-10	No for patients from 1997-2005 who received left-sided RT (HR=0.96, 95% CI=0.75-1.23) or right-sided RT (HR=1.02, 95% CI=0.78-1.33) vs. surgery only No for the entire study population who received left-sided RT (HR=1.01, 95% CI=0.79-1.30) or right-sided RT (HR=1.08, 95% CI=0.83-1.41) vs. surgery only

Abbreviations: 95% CI = confidence interval; AMI = acute myocardial infarction; BCS = breast-conserving surgery; CAD = coronary artery disease; CHF = congestive heart failure; CVD = cardiovascular diseases; DCIS = ductal carcinoma in situ; HR = hazard ratio; ICD = International Classification of Diseases; ICPC = International Classification of Primary Care; IHD = ischaemic heart disease; IMC = internal mammary chain; LVEF = left ventricular ejection fraction; MACE = major adverse cardiac events; MI = myocardial infarction; OR = odds ratio; RCT = randomised controlled trial; RR = risk ratio; RT = radiotherapy.

Table 4. (cont'd)

Study	Study population	Country	Treatment period	Study design	Median or mean follow-up time, y	Endpoint(s)	Endpoint criteria	Significant increased risk of cardiovascular events
Boerman (2014)[45]	456	Netherlands	1970-2007	Matched case-control study	9	CHF (acute and chronic), vascular cardiac diseases (unstable and stable angina pectoris, AMI, other chronic IHDs [coronary artery sclerosis], transient ischaemic attack, and cerebrovascular attack), and other cardiac diseases (atrial fibrillation, paroxysmal tachycardia, non-rheumatic valve disease)	ICPC version 1	No for CHF (HR=0.4, 95% CI=0.2-1.1), vascular cardiac diseases (HR=0.7, 95% CI=0.4-1.1) and other cardiac diseases (HR=0.9, 95% CI=0.5-1.6)
Killander (2014)[63]	1110	Sweden	1978-1985	Two RCTs	Not specified	Incidence of first admission to hospital due to heart disease	ICD-8, ICD-9, ICD-10	No, when RT + cyclophosphamide was compared with cyclophosphamide alone, in premenopausal women (p = 0.72) or when RT + tamoxifen was compared with tamoxifen alone in postmenopausal women (p = 0.41)
Onwudiwe (2014)[78]	91,612	United States	2000-2005	Population-based case-control	2	Combined risk of cardiovascular event (angina, heart failure, chest pain, ischaemia, valve disorder, heart disease, atherosclerosis, cardiac inflammation, conduction disorder, MI, cardiomyopathy, or elevated blood pressure) or cardiovascular death within 6 months of RT	ICD-9	Yes for high-risk patients (no RT vs. RT, HR=0.723, 95% CI=0.685-0.763) and intermediate-risk patients (no RT vs. RT, HR=0.746, 95% CI=0.650-0.857) No for low-risk patients (no RT vs. RT, HR=1.007, 95% CI=0.838-1.211) Note: High-risk patients were defined as patients with a clinical CVD. Intermediate-risk patients were defined as patients with one or more risk factors and no diagnosis of CVD. Low-risk patients were defined as patients who did not meet the criteria for high or intermediate risk
Haque (2011)[49]	806	United States	1990-1994	Population-based cohort	10	CVD events that were serious enough to require hospitalisation IHD, AMI, angina, and CVD)	ICD-9 and ICD-10	No for left-sided RT vs. no RT (HR=1.00, 95% CI= 0.75-1.35) and for right-sided RT vs. no RT (HR=0.75, 95% CI=0.53-1.06)
Doyle (2007)[48]	48,353	United States	1992-2000	Population-based cohort	13 as max	MI, ischaemia, CHF, and other heart disease (myocarditis, arrhythmia, and valvular disease)	ICD-9	No for MI/ischaemia (HR=1.02, 95% CI= 0.94-1.10) or for MI alone (HR=0.93, 95% CI= 0.84-1.02)
Hooning (2007)[79]	4414	Netherlands	1970-1986	Multicentre case-control study	17.7	IHD (AMI, angina), other heart diseases (pericarditis, valvular dysfunction, cardiomyopathy, dysrhythmia, CHF), and/or other CVDs	ICD-9	Yes for CVDs (HR=1.41, 95% CI=1.14-1.74). 1.49-fold increased risk for RT patients during a period of 1970-1979 and 1.35-fold increased risk during a period of 1980-1986
Geiger (2005)[80]	396 (134 cases and 262 controls)	United States	1980-2000	Case-control	Did not specify	MI	ICD-9, ICD-10	Yes (OR=2.0, 95% CI= 1.1-3.5)
Højris (1999)[67]	3046	Denmark	1982-1990	Two RCTs	9.75	IHD (including AMI)	ICD-8, ICD-10	No (HR=0.95, 95% CI= 0.59-1.54)
Gyenes (1998)[68]	960	Sweden	1971-1976	Multicentre case-control study	20	IHD and/or CVD	ICD-9	No (HR=1.3, 95% CI= 0.7-2.6)
Rutqvist (1998)[69]	5680	Sweden	1976-1987	Hospital-based case-cohort	9	AMI	Did not specify	No for RT + BCS vs. mastectomy alone (HR=0.6, 95% CI=0.4-1.2)

breath hold, enhanced patient positioning, and heart blocking.[83] Deep inspiration breath hold and respiratory gating rely on the principle that during inspiration, the diaphragm flattens, and the lungs expand, causing the heart to be pulled away from the chest wall and thus decrease the radiation dose to the heart and the left anterior descending artery.[84] A 2019 study conducted by Simonetto et al[85] found that the use of deep inspiration breath hold reduced the risk of estimated mean heart dose by 35%, compared with free breathing. Furthermore, to reduce the heart dose in breast cancer patients, prone positioning can be used to increase the planning target volume to heart distance by displacing cardiac structures and substructures out of irradiated volumes.[86-88] Other common methods include multileaf collimator modification during RT planning.[89,90] However, an important pitfall is that it may shield part of the breast tissue, which needs to be irradiated; thus, a balance must be achieved in order to maximise the heart shielding while minimising the target volume missed.[89] In addition to these RT techniques, the omission of internal mammary chain lymph node irradiation and rib inclusion for chest wall RT has been utilised in early-stage breast cancer patients to reduce the dose to the normal tissue. However, long-term studies are needed to investigate the effect of contemporary RT planning techniques in minimising radiation exposure to nearby normal tissue and the heart.

In addition to the use of modern RT techniques, considerations must be made in terms of whether RT is being combined with chemotherapeutic agents as common chemotherapeutic agents have known cardiotoxic effects.[91-94] A 10-year cohort study of breast cancer patients receiving concomitant RT and chemotherapy found that there was no significant association between CVEs and RT laterality (HR=2.38, 95% CI=0.80-7.11; p = 0.12).[55] However, there was a significant increase in CVEs for patients receiving left-sided RT with a doxorubicin-equivalent dose ≥250 mg/m^2 compared with patients receiving right-sided RT with a cumulative doxorubicin-equivalent dose <250 mg/m^2 (HR=5.22, 95% CI=1.67-21.15; p = 0.006).[55] Similarly, a 2016 study found that there was no significant increase in the risk of CVEs for patients who received RT compared with those who received surgery alone (HR=0.97, 95% CI=0.62-1.51; p = 0.882).[77] However, there was a significant increase in CVEs in patients who received RT and chemotherapy compared with those who received surgery only (HR=1.84; 95% CI=1.34-2.53; p < 0.001).[77]

There are several limitations to this systematic review. First, the heterogeneity of the data made it difficult to make direct comparisons among studies. Many of the studies did not report data on the individual types of CVEs or the specific cause of CVM, and so we used a composite outcome of CVE and CVM, which included myocardial infarction, coronary artery disease, conduction abnormalities, congestive heart failure, and other cardiovascular diseases. Heterogeneity also exists because of the lack of detail on RT techniques, RT volume, dose, and fractionation. In addition, variability in morbidity and mortality assessment, as well as in the follow-up time of the studies, is another source of heterogeneity. Second, the dose-dependent relationship of cardiovascular risk cannot be evaluated since radiation doses were not available for all studies. Lastly, because this was a systematic review, and a meta-analysis was not conducted, studies were not weighted based on the number of patients. In the future, a meta-analysis would aid in determining whether there is a significant increase in the risk of CVEs and CVM associated with the use of RT and/or RT laterality. Other confounding variables may also be investigated and stratified, such as menopausal status, types of adjuvant chemotherapy and hormonal agents, which may impact cardiotoxicity.

CONCLUSION

Although modern RT techniques seem to have minimised the cardiac exposure in breast cancer patients receiving RT, more comprehensive studies with longer follow-up periods must be conducted to investigate any associated cardiovascular risk.

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