REVIEW

Risk of death from cardiovascular disease following breast cancer: a systematic review

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Abstract

Purpose Breast cancer incidence and survival is high, which results in high prevalence of breast cancer survivors. The risk of (death from) cardiovascular disease (CVD) is higher in patients exposed to cardiotoxic treatments, in particular if they have pre-existing CVD risk factors. This study systematically summarized the risk of death from CVD following breast cancer.

Methods Databases of Medline, Embase, and the Cochrane Library were systematically searched using the following terms and synonyms: breast cancer, cardiovascular disease, and cause of death. Articles reporting on both risk and risk factors of CVD mortality following breast cancer were eligible for inclusion. The methodological quality of each article was assessed using the Newcastle Ottawa quality assessment scale for cohort studies.

Results Fourteen articles were included assessing the risk of CVD mortality among 1,217,910 women with breast cancer. The methodological quality was high for the

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majority of the studies. Studies were heterogeneous in design, study population, length of follow-up, CVD outcomes, and risk factors. 1.6–10.4% of all women with breast cancer died of CVD. Women with breast cancer had a higher risk of CVD mortality than women from the general population. The risk of CVD mortality was higher among women with breast cancer with older age at diagnosis, left-sided tumor, diagnosis in an earlier calendar period, and black ethnic origin.

Conclusions CVD is an important cause of death following breast cancer. Identification of patients at high risk of CVD is important to optimize CVD prevention and tailor breast cancer treatment.

Keywords Breast cancer · Cardiovascular disease · Absolute risk · Risk factors

Introduction

Breast cancer incidence has increased substantially over the last decades [1, 2], which, in combination with improved survival rates attributable to the availability of screening methods and effective treatments of early and more advance breast cancer [3, 4], leads to an increasing number of breast cancer survivors. Cardiovascular disease (CVD) is an important cause of death among these women as the risk of CVD may be increased by cardiotoxic treatments and CVD risk factors [5–8].

The risk of (death from) CVD following breast cancer is increased in women exposed to cardiotoxic treatments such as mediastinal and left-sided radiotherapy, anthracyclinebased chemotherapy, and trastuzumab, and is even higher in patients with pre-existing CVD risk factors such as diabetes and hypertension [9–12]. With the current high



breast cancer survival rates, especially for women with lower stages, and the large number of women with breast cancer receiving intensive treatment regimens, it is increasingly important to identify patients at high risk of CVD, and to balance the benefits of breast cancer treatment for achieving tumor control with the risks of cardiac toxicity inducing CVD.

As an overview of the available evidence on the risk of dying of CVD in women with breast cancer is currently lacking, we systematically reviewed the literature on the risk and risk factors of death from CVD following breast cancer.

Methods and materials

This systematic review was conducted in accordance with the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13].

A systematic search was performed, and last updated on April 1, 2017, to identify all studies reporting on the risk and risk factors of death from CVD following breast cancer. Databases of Medline (via PubMed), Embase, and the Cochrane Library were systematically searched using the following terms and their synonyms in the search strategy: breast cancer, cardiovascular disease, and cause of death (Table 1). No limits were used.

Articles reporting on both risk and risk factors of CVD mortality in breast cancer patients were eligible for inclusion. Articles with the following criteria were excluded: (1) published before 1990, (2) written in another language than English or Dutch, (3) case reports, reviews, or abstracts. Cross-referencing was performed.

Selection of studies and data extraction

After removal of duplicates, all titles and abstracts of the remained retrieved articles were screened. Abstracts that seemed potentially relevant, based on the in- and exclusion criteria, were screened for full text. The full text of these articles were assessed for eligibility by three investigators independently (S.A.M. Gernaat, P.J. Ho, and N. Rijnberg). Data were extracted using standardized data extraction forms and any disagreements were resolved by discussion. We extracted data on study size, characteristics of breast cancer patients (age, ethnic origin, year of diagnosis, years of follow-up), study design, International Classification of Diseases (ICD) codes for CVD mortality, absolute risk of death from CVD, absolute risk of death from breast cancer. absolute risk of death from any cause, statistical methods used to assess which factors increase the risk of death from CVD, and the risk of CVD mortality per risk factor.

Quality assessment

The methodological quality for each article was assessed by two authors independently (S.A.M. Gernaat and P.J. Ho) using the Newcastle Ottawa Quality Assessment Scale (NOS) for cohort studies [14]. The NOS consists of six multiple-choice questions that address subject selection, comparability, and the assessment of the outcome (i.e. CVD mortality), which sum up to a maximum score of seven. In the present study, a high score on one of these sections indicated that the maximum score (i.e. two for selection and comparability, and three for outcome) was achieved. In all other cases, the study received a low score on that particular section.

Table 1	Search	strategy	performed	in	Medline	(via	Pubmed)
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 Search strategy (Medline via Pubmed)

#1 (Breast Neoplasms[Mesh Terms] OR cancer[Title/Abstract] OR cancers[Title/Abstract] OR carcinoma[Title/Abstract] OR carcinomas[Title/Abstract] OR tumors[Title/Abstract] OR tumors[Title/Abstract] OR tumors[Title/Abstract] OR malignancy[Title/Abstract] OR malignancies[Title/Abstract] OR neoplasms[Title/Abstract] OR mammas[Title/Abstract] OR neoplasms[Title/Abstract] OR mammas[Title/Abstract] OR neoplasms[Mesh Terms]) AND (breast[Title/Abstract] OR breasts[Title/Abstract] OR mammas[Title/Abstract] OR mamm

#2 (Cardiovascular Diseases[Mesh] OR heart[Title/Abstract] OR cardiac[Title/Abstract] OR cardio[Title/Abstract] OR cardiovascular[Title/ Abstract] OR coronary[Title/Abstract] OR ventricular[Title/Abstract] OR valvular[Title/Abstract] OR circulatory[Title/Abstract]) AND (disease[Title/Abstract] OR diseases[Title/Abstract] OR complication[Title/Abstract] OR complications[Title/Abstract] OR failure[Title/ Abstract] OR failures[Title/Abstract] OR dysfunction[Title/Abstract] OR dysfunctions[Title/Abstract] OR mortality[Title/Abstract] OR death[Title/Abstract] OR deaths[Title/Abstract] OR deaths[Title/Abstract] OR arrhythmias[Title/Abstract] OR arrhythmia[Title/ Abstract] OR cardiomyopathy[Title/Abstract] OR cardiomyopathies[Title/Abstract] OR Ischemia[Title/Abstract] OR Ischemia's[Title/ Abstract] OR all[Title/Abstract]) AND (cause[Title/Abstract] or causes[Title/Abstract] OR other[Title/Abstract])

#3 (Cause of death[Mesh Terms] OR mortality[Title/Abstract] OR mortalities[Title/Abstract] OR death[Title/Abstract] OR deaths[Title/Abstract] OR fatality[Title/Abstract] OR fatalities[Title/Abstract] OR dying[Title/Abstract])

#4 #1 AND #2 AND #3

Comparable search strategies have been conducted for Embase and the Cochrane Library

Results

The systematic search yielded 10,170 citations including 5911 unique articles, which were screened for title and abstract using the predefined inclusion and exclusion criteria (Fig. 1). After screening the full text of 39 articles, 27 were excluded for the following reasons: published before the calendar year 1990 (n = 3) or articles that did not report the risk and risk factors of death from CVD (n = 24). Cross-referencing identified two additional papers. In total, 14 articles were included in the current systematic review, including 4,773,576 women of which 1,217,910 were diagnosed with breast cancer [5, 6, 8, 15–25].

Quality assessment

The majority of the studies had the maximum score on the quality assessment for selection, comparability, and outcome [5, 8, 17, 18, 20–22, 26] (Fig. 2). The study by Nichols et al. [15] had a low score on selection as the study population was a selected group of in situ or invasive breast cancer patients and breast cancer ascertainment was by written self-report. The studies by Berkman et al. [6], Darby et al. [23], and Giordano et al. [24] had low scores on comparability as the hazard ratios (HRs) were not adjusted for factors other than age at diagnosis, the CVD mortality rates were unadjusted, and the HRs were only

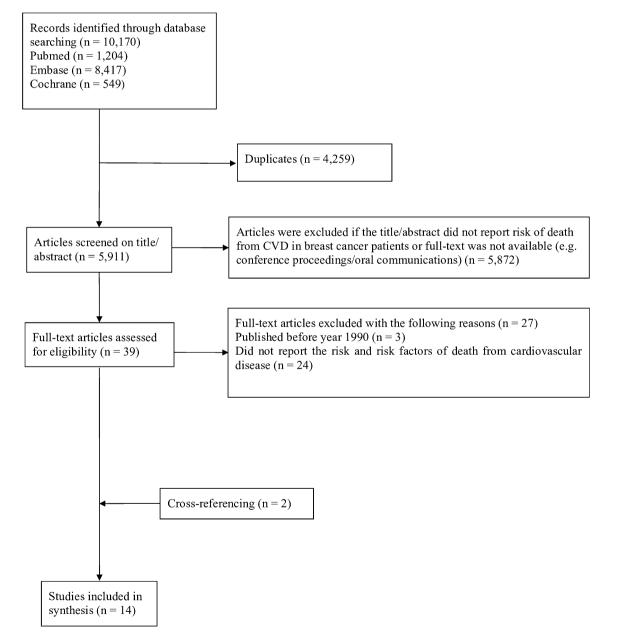


Fig. 1 Flowchart of the systematic review on the risk of death from cardiovascular disease in breast cancer patients

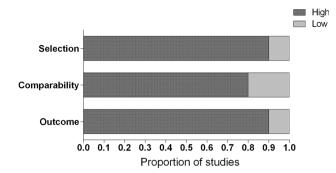


Fig. 2 Quality assessment by the Newcastle Ottawa Quality Assessment Scale Selection was based on the representativeness of the breast cancer cohort and ascertainment of breast cancer. Comparability was based on the comparability of cohorts on the basis of the design or analysis. Outcome was based on the assessment of death from cardiovascular disease, on the length of follow-up (\geq 10 years), and adequacy of follow-up of the cohorts. A high score on one of these sections indicated that the maximum score on that particular section (i.e. two for selection and comparability, and three for outcome) was achieved. In all other cases, the study received a low score on that particular section

adjusted for other factors than age at diagnosis, respectively. The studies by Hooning et al. [25] and McCullough et al. [16] had low scores on the outcome attainment as the assessment of CVD deaths was by hospital records and subjects were lost to follow-up or the follow-up rate was less than 70%, respectively.

Cardiovascular disease mortality in breast cancer patients compared with the general population

Bradshaw et al. [8] included 1413 women with primary in situ or invasive breast cancer diagnosed in the United States (U.S.) between 1996 and 1997, and 1411 age-matched women from the general population (Table 2). Mean age at breast cancer diagnosis and reference date for women from the general population were 59 and 57 years, respectively. During the follow-up time, which ranged between 0.2 and 13.5 years for both groups, 9.4% of women with breast cancer and 7.4% of women from the general population died of CVD. After adjusting for age, menopausal status, and other CVD risk factors, women with breast cancer had a 1.9 (95% confidence interval (CI) = 1.4–2.7) times higher risk to die of CVD after at least 7 years post diagnosis than women from the general population (Table 3).

Riihimäki et al. [5] included all 3,676,472 female Swedish residents born before 1977 (Table 2). Of these, 122,217 were diagnosed with primary invasive breast cancer between 1987 and 2006. During a maximum followup of 19 years, 10.4% and 7.5% of women died of CVD, respectively. Women with breast cancer had a 1.14 (95% CI 1.10–1.19) times higher risk to die of coronary heart disease, a 1.29 (95% CI 1.22–1.37) times higher risk to die of heart failure, and a 1.24 (95% CI 1.17–1.32) times higher risk to die of other heart disease than women from the general population, independent of age, socioeconomic index, and geographical region of residence in Sweden (Table 3).

Cardiovascular disease mortality in breast cancer patients by patient, tumor, and treatment characteristics

Colzani et al. [18] included 12,850 Swedish women younger than 75 years of age at diagnosis with primary invasive stage I to III breast cancer between 1990 and 2006 (Table 2). During a maximum follow-up of ten years, 1.8% of all women died of CVD. After adjusting for clinical, tumor, and treatment characteristics, except the one of interest, women with breast cancer were at increased risk of CVD mortality if they were older at diagnosis (65-74 years vs. 45-54 years: hazard ratio (HR) = 17.9,95% CI 8.0-39.7), if diagnosed in an earlier calendar period (1990-1994 vs. 2000-2006: HR = 2.1, 95% CI 1.2–3.6), and treated with only surgery (HR = 2.1, 95% CI 1.2–3.8) or surgery in combination with hormonal therapy (HR = 2.2, 95% CI 1.5-3.2) compared with surgery in combination with radiotherapy and hormonal therapy (Table 3).

Hooning et al. [25] included 7425 women younger than 71 years of age at diagnosis with primary invasive stage I to IIIA breast cancer in the Netherlands between 1970 and 1986 (Table 2). During a median follow-up of 13.8 years, 5.3% of all women died of CVD. After adjusting for clinical, tumor, and treatment characteristics, women with breast cancer were at increased risk of CVD mortality with each year increase in age at diagnosis (HR = 1.12, 95% CI 1.10–1.14), if diagnosed in an earlier calendar period (1976–1980 vs. 1981–1986: HR = 1.54, 95% CI 1.11–2.14), and treated with a combination of surgery and radiotherapy compared with only surgery (HR = 2.03, 95% CI 1.33–3.10) (Table 3).

Cardiovascular disease mortality in breast cancer patients by laterality of the tumor

Bouchardy et al. [20] included 1245 women with a mean age of 57.4 years at diagnosis with primary lymph nodenegative breast cancer in Switzerland between 1980 and 2004 (Table 2). During a mean follow-up of 7.7 years, 2.2% of all women died of CVD. Among women treated with radiotherapy, an inner quadrant tumor was associated with a 2.46 (95% CI 1.13–5.37) higher risk of dying of CVD, adjusted for clinical, tumor, and treatment characteristics (Table 3).

First author, publication year, country	Type of breast cancer, number of patients	Age at diagnosis or reference date, y	Year of diagnosis, years of follow-up	ICD-9 and/or ICD-10 codes of CVD mortality outcomes		of deaths due to CVD, and BC of total)
CVD mortality in brea	ast cancer patients comp	ared with the general j	oopulation			
Bradshaw, 2016, US ^a	Primary in situ or invasive; 1413	59 or 57 ^d	1996–1997, 13.5 ^e	ICD-9: 394.9, 402.9, 410, 414.0, 427.5 ICD-10: 110, 111.9,	Women with BC Any cause:	Women without BC Any cause:
	Without BC; 1411 ^c			I21.9, I25.1, I25.4, I46.9	29.4 CVD: 9.4	17.2 CVD: 7.4
					BC: 9.6	BC: 0.1
Riihimäki, 2012, Sweden ^a	Primary invasive; 122,217	-	1987–2006, 19 ^e	ICD-9: 410, 411–414, 420–427, 428,	Women with BC	Women without BC
	Women without BC; 3,554,255 ^h			430–438, 440–448	Any cause: 39.3	Any cause: 16.7
				ICD-10: I20, I21–I22, I23–I25, I30–I50, I52, I60–I79	CVD: 10.4	CVD: 7.5
					BC: 18.1	BC: -
CVD mortality in brea	ast cancer patients by pa	tient, tumor, and treatr	ment characteristics			
Colzani, 2011,	Primary invasive	<75	1990–2006, 10 ^e	ICD-9: 390-459	Any cause:	14.4
Sweden ^a	I-III; 12,850			ICD-10: I00–I99	CVD:	1.8
					BC:	9.2
Hooning, 2006, the	Primary invasive	≤ 70	1970–1986, 13.8 ^b	ICD-9: 410–459	Any cause:	56.0
Netherlands ^f	I-IIIA; 7425				CVD:	5.3
					BC:	42.6
CVD mortality in pati	ents with left-sided brea	st cancer compared to	right-sided breast ca	ancer		
Bouchardy, 2009,	Primary invasive	57.4 ^d	1980–2004, 7.7 ^d	ICD-10: I00-I99	Any cause:	12.4
Switzerland ^a	lymph node-				CVD:	2.2
	negative; 1245				BC:	7.3
Darby, 2005, US ^a	Primary in situ or	20–79	1973–2001, 29 ^e	ICD-9: 390-398, 402,	Any cause:	29.5
	invasive; 308,861			404, 410, 411–414, 415–429	CVD:	4.2
				413-429	BC:	16.8
Giordano, 2005, US ^a	Primary in situ or	56.9 ± 13.2^{d}	1973–1988, 9.3 ^b	ICD-9: 410-414	Any cause:	_
	invasive; 24,785			ICD-10: I20–I25	CVD:	_
					BC:	_
Haque, 2017, US ^a	DCIS, 140,914	$\leq 60 \& > 60$	1973–2002, 11.5	-	Any cause:	_
			(IQR: 6.8–15.1) ^b		CVD:	_
					BC:	-
Merzenich, 2016,	Primary in situ or	59 ^d	1998–2008, 6.5	ICD-10: I20–I25, I34–	Any cause:	20.6
Germany ^g	invasive; 11,982	(range: 18-101)	$(0-15)^{b}$	I37, I44–I50	CVD:	2.3
					BC:	10.2
CVD mortality in brea	ast cancer patient with e	thnic differences				
Berkman, 2014, US ^a	Primary DCIS;	≥40	1978–2010, 9.2 ^b	ICD-10: I00–I09, I11,	Any cause:	18.0
	54,518 white women; 6113 black			I13, I20–I51, I60–I69, I70, I72–178	CVD:	6.0
	women			170, 172–178	BC:	1.5
Solanki, 2016, US ^a	Primary in situ or invasive I-III; 462,005 NHW;	NHW: 61.2 ± 13.7^{d}	1991–2011,	ICD-9: 390–459	Non- Hispanic white	Asian and Pacific Islander
	44,531 API	API: 56.3 ± 13.1^{d}	NHW: 6.8 ± 4.9^{d} ,		Any cause: 23.8	Any cause: 15.4
			4 (2–6) ^b		CVD: 5.5	CVD: 2.6
			API: 6.7 ± 5.0^{d} , 3 $(2-5)^{b}$		BC: 10.0	BC: 8.2

First author, publication year, country	Type of breast cancer, number of patients	Age at diagnosis or reference date, y	Year of diagnosis, years of follow-up	ICD-9 and/or ICD-10 codes of CVD mortality outcomes	0	of deaths due to CVD, and BC of total)
CVD mortality in bre	east cancer patients by di	iet, body weight, and h	ealth behaviors			
McCullough, 2016, Switzerland ^g	Primary invasive I-III; 4452 for pre- diagnostic of which 2152 were included in the ≥1-year post- diagnostic analysis	70.7 ± 7.2^{d}	1992–2011, pre- diagnostic diet assessment 9.8 ± 4.9 , post- diagnostic analyses 9.9 ± 3.3^{d}	ICD-9: 390-459 ICD-10: I00-I99	Any cause: CVD: BC:	27.0 5.2 8.9
Nichols, 2009, US ^a	Primary in situ or invasive; 5791	58.4 ± 10.0^{d}	1988–1999, 6.4 ± 1.2^{d}	ICD-10: 100-99	Any cause: CVD: BC:	7.3 1.6 2.1
Veal, 2017, US ^g	Primary DCIS; 1925	20–74	1997–2006, 6.7 ^d	ICD-10: I00-I09, I11, I13, I20-I51, I60-I69, I70, I72-I78	Any cause: CVD: BC:	10.2 1.8 4.5

BC breast cancer, *CVD* cardiovascular disease, *DCIS* ductal carcinoma in situ, *ICD-9* International Classification of Diseases version 9, *ICD-10* International Classification of Diseases version 10, *y* years, *US* United States of America

^a Population-based registry

^b Median with (range if described by the article)

^c Women without breast cancer were matched on age and the expected distribution of survivors in 5-year age groups with women with breast cancer

^d Mean with (±standard deviation if described by the article)

e Maximum

- ^f Hospital-based registry
- ^g Prospective cohort study

^h All women who were born before 1977 who resided in Sweden were included; women without breast cancer were part of the reference group

Darby et al. [23] included 308,861 women between 20 and 79 years of age at diagnosis with primary in situ or invasive breast cancer in the USA between 1973 and 2001 (Table 2). During a maximum follow-up of 29 years, 4.2% of all women died of CVD. In women treated with radiotherapy and diagnosed between 1973 and 1982, left-sided breast cancer led to higher mortality ratios (MR) ten to 14 years post diagnosis (unadjusted MR = 1.42, 95% CI 1.11-1.82) and over 15 years post diagnosis (unadjusted MR = 1.58, 95% CI 1.29–1.95) compared with right-sided breast cancer (Table 3). More than ten years post diagnosis, women with left-sided breast cancer had a higher risk of death from CVD (unadjusted MR = 1.44, 95% CI 1.26-1.65), acute myocardial infarction (unadjusted MR = 1.43, 95% CI 1.10–1.87), and other ischemic CVD (unadjusted MR = 1.60, 95% CI 1.26-2.02) compared with women with right-sided breast cancer.

Giordano et al. [24] included 24,785 women with primary in situ or invasive breast cancer diagnosed in the US between 1973 and 1988 (Table 2). Mean age at diagnosis

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was 56.9 years (standard deviation (SD) = 13.2) at diagnosis. Eight years post diagnosis, women with left-sided breast cancer who were diagnosed in 1979 had a (unadjusted) 1.50 (95% CI 1.15–1.87) times higher risk to die of CVD compared with women with right-sided breast cancer diagnosed in the same year (Table 3).

Haque et al. [26] included 140,914 women of all ages with ductal carcinoma in situ (DCIS) in the US between 1973 and 2002 (Table 2).The median follow-up was 11.5 years (interquartile range = 6.8-15.1). Among women diagnosed between 1973 and 1982, a left-sided tumor was associated with a 1.30 (95% CI 1.18–1.42) higher risk of dying of CVD than a right-sided tumor, independent of clinical, tumor, and treatment characteristics. This association was not found for women diagnosed in a more recent calendar period.

Merzenich et al. [21] included 11,982 women with a mean age of 59 years (range = 18–101) at primary diagnosis of in situ or invasive breast cancer in Germany between 1998 and 2008 (Table 2) [21]. During a median

Time during, since of leading Case of leading Easily of leading Constant Easily of leading Constant C	Table 3 Risk factors of deatl	h from cardiovascular d	Table 3 Risk factors of death from cardiovascular disease in women diagnosed with breast cancer			
population CVD $IO (ref)$ A neer patients diagnosed D^7 years ago CVD $IO (ref)$ A population CVD $IO (ref)$ $IO (ref)$ $IO (ref)$ population CV	First author, year of publication	Statistical analysis	Categories	Cause of death (outcome)	Risk of death HR (95% CI)	Covariates
population CVD 10 (ref) A neer patients diagnosed 0-7 years ago CVD 10 (ref) A population CVD 10 (ref) CVD	CVD mortality in breast cancer	patients compared with	the general population			
Breat career patients diagnosed 0-7 years ago 0.59 (0.4-03) Certral population Event career patients diagnosed 57 years ago 0.59 (0.4-03) Retast career patients treated with RT CVD 10 (cf) Breast career patients treated with RT CVD 10 (cf) Breast career patients treated with CT CVD 10 (cf) Breast career patients treated with CT CVD 10 (cf) Central population Breast career patients treated with CT CVD 10 (cf) Breast career patients treated with CT CVD 10 (cf) 10 (cf) Contral population Breast career patients treated with HT CVD 10 (cf) 10 (cf) Breast career patients treated with HT CVD 10 (cf) 10 (cf) 10 (cf) Breast career patients treated with HT CVD 10 (cf) 10 (cf) Breast career patients treated with HT CVD 10 (cf) 10 (cf) Breast career patients treated with HT CVD 10 (cf) 10 (cf) Breast career patients treated with HT CVD 10 (cf) 10 (cf) Breast career patients treated with HT CVD 10 (cf) 10 (cf) Breast career patients treated with HT CVD 10 (cf) 10 (cf) Breast career patients treated with HT	Bradshaw, 2016	Competing risk	General population	CVD	1.0 (ref)	Age, menopausal
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$\label{eq:constraints} \mbox{fields} \mbox$			Breast cancer patients treated without CT		1.1 (0.8–1.5)	
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$ \begin{array}{c c} \mbox{General population} & \mbox{Complications of} & 1.00 (ref) \\ \mbox{Breast cancer patients} & \mbox{CVD} & 1.12 (0.99-1.2) \\ \mbox{Breast cancer patients by patient, tumor, and treatment characteristics} & \mbox{CVD} & 0.3 (0.0-2.5) & \mbox{CVD} & \mbox{Breast cancer patients} & \mbox{A5-54} & \mbox{Breast cancer patients} & Br$			Breast cancer patients		0.95 (0.89–1.02)	
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$\begin{tabular}{cccc} 1095-1990 \\ 2000-2006 \\ 2000-2006 \\ Surgey + RT + HT \\ Surgey + RT + HT \\ Surgey + RT + CT + HT \\ Surgey + RT + CT \\ Surge$			Calendar time at diagnosis	1990–1994	CVD	2.1 (1.2–3.6)	
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$ \begin{array}{cccc} \mbox{Treatment} & \mbox{Surgery} + \mbox{RT} + \mbox{HT} + \mbox{Surgery} + \mbox{RT} + \mbox{CT} & \mbox{Surgery} + \mbox{RT} + \mbox{CT} & \mbox{Surgery} + \mbox{RT} + \mbox{CT} + \mbox{HT} & \mbox{Surgery} + \mbox{RT} + \mbox{CT} & \mbox{Surgery} + \mbox{RT} + \mbox{RT} & \mbox{Surgery} + \mbox{RT} + \mbox{RT} & \mbox{Surgery} + \mbox{RT} + \mbox{RT} & \mbox{CV} & \mbox{Surgery} + \mbox{RT} + \mbox{RT} & \mbox{Surgery} + \mbox{RT} & \mbox{RT} & \mbox{RT} & \mbox{RT} & \mbox{RT} & RT$				2000–2006		1.00 (ref)	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$			Treatment	Surgery	CVD	2.1 (1.2–3.8)	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$				Surgery + RT + HT		1.00 (ref)	
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Surgery + CT Surgery + RT + CT + HT Surgery + RT + CT No. of positive lymph nodes 1 - 3 Surgery + RT + CT Transent 2 in mun 1 - 20 Cox proportional 1 - 20 Cov proportional 2 - 20 Cov proportional 2 - 20 CV propor				Surgery + RT + CT		0.6 (0.1–2.5)	
$ \begin{array}{ccccccc} Surgery + RT + CT + HT \\ Surgery + HT \\ Surgery + TT + HT \\ Surgery + CT + HT \\ Surgery + CT + HT \\ Surgery + CT + HT \\ 1 - 3 \\ 2 - 4 \\ Surgery + RT \\ Surgery + RT \\ Surgery + RT \\ Data diagnosis \\ Cox proportional \\ Total study population \\ Age at diagnosis \\ Continuous) \\ Tradment \\ Age at diagnosis \\ Surgery + RT + CT \\ Surgery + RT + HT \\ Calendar time at diagnosis \\ Surgery + RT + HT $				Surgery + CT		2.0 (0.6–6.8)	
$ \begin{array}{cccc} Surgery + HT \\ Surgery + CT + HT \\ Surgery + CT + HT \\ 1 & 2 \\ Surgery + CT + HT \\ 1 & -2 \\ 2 & -2 \\ Struct & 2 & -2 \\ Struct & Negative \\ Struct & Negative \\ Struct & Negative \\ Struct & Negative \\ Negative & -2 \\ Name & -$				Surgery + RT + CT + HT		0.7 (0.3 - 1.9)	
Surgery + CT + HTNo of positive lymph nodes0 3 L-3 3 3 StatusNo of positiveNegativeCox proportionalTumor size in mm -20 Tumor size in mm -20 CVDStatusPositiveCVDStatus -20 CVDCox proportionalTotal study population -20 hazadAge at diagnosisSurgery + RT + GThazadNegery + RT + GTSurgery + RT + HTCost proportional $10^{-joar sturitors}$ $10^{-joar sturitors}$ TreatmentSurgery + RT + GTSurgery + RT + HTCalendar time at diagnosis $10^{-joar sturitors}$ CVDDownSurgery + RT + GTSurgery + RT + HTCalendar time at diagnosis $10^{-joar sturitors}$ CVD $10^{-joar sturitors}$ Surgery + RT + HTCVDSurgery + RT + GTSurgery + RT + HTCVD $10^{-joar sturitors}$ $10^{-joar sturitors}$ Surgery + RT + HTCalendar time at diagnosis $10^{-joar sturitors}$ Surgery + RT + HTCalendar time at diagnosis $10^{-joar sturitors}$ $10^{-joar sturitors}$ Calendar time at diagnosis $10^{-joar sturitors}$ $10^{-joar sturitors}$ Calendar time at diagnosis $10^{-joar sturitors}$ $10^{-joar sturitors}$ Calendar time at diagnosis $10^{-joar sturitors}$ $10^{-joar sturitors}$ Correstors $10^{-joar sturitors}$ $10^{-joar sturitors}$ Correstors $10^{-joar sturitors}$ $10^{-joar st$				Surgery + HT		2.2 (1.5-3.2)	
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$ \begin{array}{llllllllllllllllllllllllllllllllllll$			No. of positive lymph nodes	0	CVD	1.00 (ref)	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$				1–3		2.0 (1.4–2.9)	
Estrogen receptorNegativeCVDStatusPositiveCVDStatusTunor size in mun1–20CVDStatusTotal study populationTotal study populationCVDCox proportionalTotal study populationTotal study populationCVDCox proportionalTotal study populationSugery + RTCVDCox proportionalTotal study populationSugery + RT + CTCVDContinuous)Sugery + RT + CTSugery + RT + HTCVDCalendar time at diagnosis1970-1975CVDDo-year sturviors1976-1980CVDContinuous)Sugery + RT + HTCVDContinuous)Sugery + RT + HTCVDDo-year sturviorsSugery + RT + HTCVDSugery + RTSugery + RT + HTSugery + RT + HTSugery + RTSugery + RT + HTSugery + RT + HTSugery + RTSugery + RT + HTSugery + RT + HTSugery + RTSugery + RT + HTSugery + RT + HTSugery + RTSugery + RT + HTSugery + RT + HTSugery + RTSugery + RT + HTSugery + RT + HTSugery + RTSugery + RT + HTSugery + RT + HTSugery + RTSugery + RT + HTSugery + RT + HTSugery + RTSugery + RT + HTSugery + RT + HTSugery + RTSugery + RT + HTSugery + RT + HTSugery + RTSugery + RT + HTSugery + RT + HTSugery + RTSugery + RT + HTSugery + RT + HTSugery + RTSugery + RT + SUGSUGF				≥4		(1.0-3.4)	
Status Eatur Tumor size in mun 1–20 CVD Tumor size in mun 1–20 CVD Cox proportional Total study population hazard agnosis Cox proportional Total study population Treatment Surgery + RT + CT Surgery + RT + HT Surgery + RT + HT Calendar time at diagnosis 1970–1975 CVD 1976–1980 1976–1980 CVD 1076–1980 1976–1980 CVD Age at diagnosis 1970–1975 CVD Calendar time at diagnosis 1970–1975 CVD Cuber survivors Surgery + RT + HT Calendar time at diagnosis 1970–1975 CVD CVD 1976 CVD CVD 1976 CVD 1976 CVD 1976–1980 1976 CVD			Estrogen receptor	Negative	CVD	1.00 (ref)	
Tunor size in mm1–20CVD 20 20 20 Cox proportional $Total study population2020Total study populationAge at diagnosis2020Age at diagnosisSurgery + RTCVDCox proportion (or nons))1070-1975CVDTreatment1970-1975CVDCorritonous)1970-1975CVDDotar survivors1970-1975CVDDotar survivors1970-1975CVDTreatmentSurgery + RT + CTSurgery + RT + DTSurgery + DT + DTSurgery + DT + DTSurgery + DT + $			Status	Positive		0.8 (0.5-1.3)	
Cox proportional Total study population hazard Age at diagnosis continuous) Treatment Treatment Surgery + RT Surgery + RT + CT Surgery + RT + HT Surgery			Tumor size in mm	1–20	CVD	1.00 (ref)	
Cox proportional Total study population hazard Age at diagnosis Cominuous) Age at diagnosis Treatment Surgery + RT Regery + RT Surgery + RT Surgery +				>20		1.5 (1.1–2.1)	
Age at diagnosis (continuous) CVD Treatment Surgery + RT Treatment Surgery + RT + CT Surgery + RT + CT Surgery + RT + HT Surgery + RT + CT Surgery + RT + HT Surgery + RT + CT Surgery + RT + CT Surgery + RT + CT Surgery + RT + CT J0-year survivors 1981-86 J0-year survivors CVD Age at diagnosis 1981-86 I0-year survivors CVD Surgery + RT CVD Surgery + RT + CT Surgery + RT + CT Surgery + RT + HT Surgery + RT + HT Calendar time at diagnosis 1970-1975 Calendar time at diagnosis 1970-1975	Hooning, 2006	Cox proportional	Total study population			Clinic	Clinical, tumor,
ent Surgery + RT Surgery + RT + CT Surgery + RT + HT Surgery + RT + HT Surgery + RT + HT Surgery + RT + HT 1976–1980 1976–1980 1981–86 		hazard	Age at diagnosis (continuous)		CVD		treatment, characteristics
Surgery + RT Surgery + RT + CT Surgery + RT + HT Surgery + RT + HT Surgery + RT + HT 1976–1980 1976–1980 1981–86 .attrivers CVD 1981–1975 CVD CVD artime at diagnosis 1970–1975 CVD Surgery + RT + HT Surgery + RT + HT			Treatment	Surgery	CVD	1.00 (ref)	
Surgery + RT + CT Surgery + RT + HT Surgery + RT + HT Surgery + RT + HT 1976–1980 1976–1980 1976–1980 1981–86 sturvivors diagnosis surgery surgery cVD state state cVD state cVD state cVD state st				Surgery + RT		2.03 (1.33–3.10)	
surgery + RT + HT ar time at diagnosis 1970–1975 CVD 1976–1980 1976–1980 CVD 1971–1975 CVD CVD starvivors 1981–86 CVD starvivors Surgery + RT CVD ent Surgery + RT + HT CVD strine at diagnosis 1970–1975 CVD ar time at diagnosis 1970–1975 CVD strine at diagnosis 1970–1986 CVD				Surgery + RT + CT		1.47 (0.81–2.67)	
ar time at diagnosis $1970-1975$ CVD 1976-1980 1976-1980 1981-86 survivors diagnosis unous) curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors curvivors				Surgery + RT + HT		1.70 (0.99–2.93)	
1976–1980 1981–86 <i>survivors</i> diagnosis inuous) ent Surgery Rugery + RT Surgery + RT + HT Surgery + RT + HT Surgery + RT + HT strime at diagnosis 1976–1980 1981–1986			Calendar time at diagnosis	1970–1975	CVD	1.34 (0.93–1.92)	
1981–86 •survivors diagnosis unous) muous) ent Surgery Surgery Surgery Surgery strime at diagnosis 1976–1980 1981–1986				1976–1980		1.54 (1.11–2.14)	
survivors diagnosis inuous) CVD ent Surgery AT Surgery + RT + CT Surgery + RT + HT Surgery + RT + HT Surgery + RT + HT 1970–1975 CVD 1976–1980 1971–1986				1981–86		1.00 (ref)	
diagnosis inuous) CVD ent Surgery RT + CT Surgery + RT + CT Surgery + RT + HT Surgery + RT + HT surgery + RT + HT 1970–1975 CVD 1976–1980 1976–1980			10-year survivors				
Surgery CVD Surgery + RT Surgery + RT + CT Surgery + RT + HT 1970–1975 CVD 1976–1980 1981–1986			Age at diagnosis (continuous)		CVD	1.11 (1.09–1.13)	
Surgery + RT Surgery + RT + CT Surgery + RT + HT 1970–1975 CVD 1976–1980 1981–1986			Treatment	Surgery	CVD	1.00 (ref)	
Surgery + RT + CT Surgery + RT + HT 1970–1975 CVD 1976–1980 1981–1986				Surgery + RT		2.08 (1.25–3.47)	
Surgery + RT + HT 1970–1975 CVD 1976–1980 1981–1986				Surgery + RT + CT		2.38 (1.18-4.77)	
1970–1975 CVD 1976–1980 1981–1986				Surgery + RT + HT		2.42 (1.27-4.61)	
			Calendar time at diagnosis	1970–1975	CVD	1.38 (0.89–2.14)	
				1976–1980		1.62 (1.07–2.46)	
				1981–1986		1.00 (ref)	

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First author, vear of publication	n Statistical analysis	Categories	Cause of death	Risk of death HR (95% CI) Covariates	Covariates
			(outcome)		
CVD mortality in breast cancer patients by laterality of the tumor	er patients by laterality of 1	he tumor			
Bouchardy, 2016	Cox proportional	RT and right-sided tumor	CVD	1.00 (ref)	Clinical, tumor, and
	hazard	RT and left-sided tumor		0.52 (0.24–1.12)	treatment
		RT and outer quadrant	CVD	1.00 (ref)	characteristics
		RT and inner quadrant		2.46 (1.13–5.37)	
		RT and right-sided tumor and outer quadrant	CVD	1.00 (ref)	
		RT and right-sided tumor and inner quadrant		2.51 (0.88–7.18)	
		RT and left-sided tumor and outer quadrant	CVD	1.00 (ref)	
		RT and left-sided tumor and inner quadrant		2.17 (0.65–7.25)	
		RT and outer quadrant and right-sided tumor	CVD	1.00 (ref)	
		RT and outer quadrant and left-sided tumor		0.70 (0.21–2.32)	
		RT and inner quadrant and right-sided tumor	CVD	1.00 (ref)	
		RT and inner quadrant and left-sided tumor		$0.52\ (0.18-1.48)$	
Darby, 2005	Poisson regression for	RT on right-sided tumor	CVD	1.00 (ref)	No covariates
	mortality rates	RT on left-sided tumor		1.44 (1.26–1.65)	
		RT on right-sided tumor	AMI	1.00 (ref)	
		RT on left-sided tumor		1.43 (1.10–1.87)	
		RT on right-sided tumor	Other	1.00 (ref)	
			Ischemic		
			CVD		
		RT on left-sided tumor		1.60 (1.26–2.02)	
		RT on right-sided tumor and aged 20-49 years at diagnosis	CVD	1.00 (ref)	
		RT on left-sided tumor and aged 20-49 years at diagnosis		1.54 (1.08–2.19)	
		RT on right-sided tumor and aged 50-59 years at diagnosis	CVD	1.00 (ref)	
		RT on left-sided tumor and aged 50-59 years at diagnosis		1.53 (1.19–1.98)	
		RT on right-sided tumor and aged 60-69 years at diagnosis	CVD	1.00 (ref)	
		RT on left-sided tumor and aged 60-69 years at diagnosis		1.40 (1.15–1.70)	
		RT on right-sided tumor and aged 70-79 years at diagnosis	CVD	1.00 (ref)	
		RT on left-sided tumor and aged 70-79 years at diagnosis		1.28 (0.87–1.90)	
		RT on right-sided tumor and white ethnic origin	CVD	1.00 (ref)	
		RT on left-sided tumor and white ethnic origin		1.39 (1.21–1.61)	
		RT on right-sided tumor and black ethnic origin	CVD	1.00 (ref)	
		RT on left-sided tumor and black ethnic origin		2.25 (1.36–3.72)	
		RT on right-sided tumor and other/ unknown ethnic origin	CVD	1.00 (ref)	
		RT on left-sided tumor and other/ unknown ethnic origin		1.30(0.71 - 2.39)	

First author, year of publication Statistical ran/ysis Cancer of clearly concomponent Risk of the concomponent Glordano, 2005 Cox proportional Right-sided tunner and diagnosed in 1979 CVD 1.00 (ref) Glordano, 2016 Cox proportional Right-sided tunner and diagnosed in 1978 CVD 1.20 (ref) Haque, 2016 Cox proportional Right-sided tunner and diagnosed in 1978 CVD 1.20 (ref) Haque, 2016 Cox proportional Right-sided tunner and diagnosed in 1978 CVD 1.20 (ref) Haque, 2016 Cox proportional Diagnosed 1975-1982 CVD 1.20 (ref) Haque, 2016 Cox proportional Diagnosed 1975-1982 CVD 1.20 (ref) Haque, 2016 Cox proportional Diagnosed 1975-1982 CVD 1.20 (ref) Haque, 2016 Cox proportional Diagnosed 1975-1982 CVD 1.20 (ref) Hadue, 2016 Cox proportional Diagnosed 1975-1982 CVD 1.20 (ref) Hadue, 2016 Cox proportional Diagnosis CVD 1.20 (ref) Hadue Cox proportional Left-sided tunner and Clopensis CVD 1.20 (ref) Hadue Cox proportional Left-sided tunner and Clopensis CVD 1.20 (ref) Hadue Cox proport						
Cov proportional Right-sided tunnor and diagnosed in 1979 CVD Right sided tunnor and diagnosed in 1988 Left-sided tunnor and diagnosed in 1988 CVD Right sided tunnor and diagnosed in 1988 Diagnosed log73-1982 CVD Cox proportional Diagnosed in 1973-1982 CVD Diagnosed log73-1982 Minic CVD Left-sided tunnor Minic CVD Left-sided tunnor Minic CVD Left-sided tunnor Minic CVD Lander Minic CVD Lander Minic CVD Maried Diamon CVD Marinal American CVD CVD	Statistical analysis	Categories		Cause of death (outcome)	Risk of death HR (95% CI) Covariates	Covariates
hand Left-sidel tunor and diagnosed in 1979 Right-sided tunor and diagnosed in 1988 CVD Diagnosed 1973-1923 CS propertional Right-sided tunor Diagnosed 1973-1923 Right-sided tunor Arian diagnosed in 1988 Cox propertional Diagnosed 1973-1923 Right-sided tunor Arian Pacific Right-sided tunor Arian Pacific Right-sided tunor Unspecified Asian Pacific Stata Right-sided tunor and <0.9 years since diagnosis	Cox proportional	Right-sided tumor and diag	gnosed in 1979	CVD	1.00 (ref)	No covariates
Right-sided tumor and diagnosed in 1988 CVD Left-sided tumor Diagnosed 1973-1982 Left-sided tumor Mignosed in 1988 Right-sided tumor Minima Right-sided tumor Minima Right-sided tumor Arifican American Asian/Pacific Arifican American Instand Arifican American Asian/Pacific Unspecified Asian/Pacific Unspecif	hazard	Left-sided tumor and diagr	nosed in 1979		1.50 (1.19–1.87)	
Left-sidel tumor and diagnosed in 1988 Loss proprotional Diagnosed 1973-1982 Rates White Rates White Rates White Rates White Rate Arised tumor Arised tumor Unspecified Arise diagnosis CVD Marial status Maried Unancied Unancied Unancied CVD Bight-sided tumor and CIO years since diagnosis CVD Left-sided tumor and CIO years since diagnosis CVD Left-sided tumor and CIO years since diagnosis CVD Right-sided tumor and CIO years since diagnosis CVD Left-sided tumor and CIO years since diagnosis CVD Region Pacific CVD Region Atlasta CVD Region Pacific CVD Rate Maried CVD Rate Pacific		Right-sided tumor and diag	gnosed in 1988	CVD	1.00 (ref)	
Cox proportional Diagnosed 1973-1982 hazdd Righr-sided tumor Left-sided tumor Minite Left-sided tumor Aimar/ American Left-sided tumor Winite Asian/ Pucific Siand Pucific Island Unspecified Age at diagnosis 500 Marial status Married Unknown CVD Marrial status Married Unknown CVD Core Unknown Core CVD Marrial status CVD Married CVD Married CVD Unknown CVD Core CVD Married CVD <td></td> <td>Left-sided tumor and diagr</td> <td>nosed in 1988</td> <td></td> <td>0.79 (0.52–1.18)</td> <td></td>		Left-sided tumor and diagr	nosed in 1988		0.79 (0.52–1.18)	
Right-sided tumor Left-sided tumor Left-sided tumor Race White American Indian/ American Indian/ Asian/ Pacific	Cox proportional	Diagnosed 1973–1982				Clinical, tumor,
led tumor White African American African American American Indian/ Arisan/Pacific Islander Unspecified Unspecified Unspecified CVD Status Aaian/Pacific Islander Unspecified Unmarried Unmarried Unmarried Unmarried Unmarried Unmarried Unmarried Unmarried CVD Status African Anska East Northern Plains Southwest ed tumor African American Alaska East Northern Plains Southwest ed tumor African American African American Africa	hazard	Right-sided tumor		CVD	1.00 (ref)	treatment
White White CVD African American American Indian/ Asian/ Pacific American Indian/ Asian/ Pacific Islander Asian/ Pacific Islander Unspecified CVD Asian/ Pacific Islander Unspecified CVD Islander Unspecified CVD CVD Astuus Married CVD CVD Astuus Married CVD CVD Ided tumor and <10 years since diagnosis		Left-sided tumor			1.30 (1.18–1.42)	characteristics
African American American Indian' Asian/Pacific Islander Unspecified diagnosis ≤60 CVD status Married Umarried Umarried Umarried Unknown CVD Unknown CVD Unknown CVD Unknown CVD Unknown CVD Unknown CVD Unknown CVD CVD Eed tumor and <10 years since diagnosis cled tumor and <10 years since diagnosis cled tumor and ≥20 years since diagnosis cled tumor Alaska East Northern Plains Southwest sed 1983-1992 cled tumor Alaska Fast Northern Plains Southwest Southwest Southwest Alaska CVD Alaska Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest Southwest		Race	White	CVD	1.00 (ref)	
American Indian/ American Indian/ Asian/ Pacific Islander Islander Unspecified Unspecified CVD 560 CVD 61 Unknown 62 Unknown 64 Umor and <10-19 years since diagnosis			African American		1.14(0.94 - 1.36)	
Asian/ Pacific Islander Islander Unspecified Unspecified Se0 status Unknown Uol-19 years since diagnosis ted tumor and <10-19 years since diagnosis			American Indian/		0.83 (0.66–1.02)	
Islander Unspecified Unspecified 560 ≤ 0 status ≤ 60 ⊂ CVD 560 ≤ 0 tatus Married CVD Unnarried Unknown Unknown Unknown ⊂ CVD ed tumor and <10 years since diagnosis ed tumor and <10 years since diagnosis ced tumor and 10–19 years since diagnosis ced tumor and 10–19 years since diagnosis ced tumor and 220 years for cord Alaska Southwest Southwest Southwest Anterican Anterican Anterican Indian' Asian' Pacific			Asian/ Pacific			
Unspecified Unspecified 60 ≤60 CVD >60 ≤0 CVD status Married CVD Ummarried Ummarried CVD Unknown Unknown CVD ded tumor and <10 years since diagnosis			Islander			
diagnosis ≤ 60 CVD status Married CVD status Married Unmarried Ummarried Unknown died tumor and <10 years since diagnosis died tumor and <10 years since diagnosis died tumor and 10–19 years since diagnosis cVD CVD ded tumor and 10–19 years since diagnosis cVD CVD ded tumor and 220 years since diagnosis cVD CVD ded tumor and ≥ 20 years since diagnosis cVD CVD ded tumor and ≥ 20 years since diagnosis ded tumor and ≥ 20 years since diagnosis cVD CVD ded tumor and ≥ 20 years since diagnosis ded tumor and ≥ 20 years since diagnosis cVD CVD ded tumor and ≥ 20 years since diagnosis ded tumor and ≥ 20 years since diagnosis cVD CVD Alaska Ration Alaska fait d tumor Southwest Southwest Southwest American American Anterican American Anterican American			Unspecified		0.47 (0.03–2.06)	
 >60 status Married CVD Umarried Unmarried Unknown Unknown Unknown CVD Unknown CVD Unknown CVD Unknown CVD Ied tumor and <10 years since diagnosis Ged tumor and 10–19 years since diagnosis Ged tumor and 10–19 years since diagnosis Ged tumor and 10–19 years since diagnosis CVD Ied tumor and ≥20 years since diagnosis CVD Ged tumor and ≥20 years since diagnosis CVD Ged tumor and ≥20 years since diagnosis CVD CVD Alaska East Northern Plains Southwest Southwest Southwest Southwest Southwest American American American American 		Age at diagnosis	≤60	CVD	1.00 (ref)	
status Married CVD Umarried Umarried CVD Umarried Unknown Unknown Unknown Ged tumor and <10 years since diagnosis fied tumor and 10–19 years since diagnosis ted tumor and 10–19 years since diagnosis ted tumor and 10–19 years since diagnosis ted tumor and 220 years since diagnosis ted tumor and ≥ 20 years for the ted tumor White CVD African American Anterican Indian' Asian' Pacific			>60		5.87 (5.30-6.50)	
Unmarried Unknown UnknownUnknown Unknownided tumor and <10 years since diagnosis			Married	CVD	1.00 (ref)	
UnknownUnknownided tumor and <10 years since diagnosis			Unmarried		1.87 (1.70–2.05)	
ided tumor and <10 years since diagnosis led tumor and <10 years since diagnosis ided tumor and 10–19 years since diagnosis ted tumor and 10–19 years since diagnosis ted tumor and ≥ 20 years since diagnosis ted tumor white ted tumor ted tumor White American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American American Am			Unknown		1.77 (1.29–2.37)	
led tumor and <10 years since diagnosis died tumor and 10–19 years since diagnosis ted tumor and 10–19 years since diagnosis died tumor and ≥20 years since diagnosis ted tumor and ≥20 years since diagnosis ted tumor and ≥20 years since diagnosis ted tumor and ≥20 years since diagnosis CVD Alaska East Northern Plains Southwest Southwest Southwest CVD Alaska East Northern Plains Southwest CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska CVD Alaska Alaska CVD Alaska Alaska Alaska CVD Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Alaska Ala		Right-sided tumor and <10) years since diagnosis	CVD	1.00 (ref)	
ided tumor and 10–19 years since diagnosis CVD led tumor and 10–19 years since diagnosis CVD ided tumor and ≥20 years since diagnosis CVD led tumor and ≥20 years since diagnosis CVD Alaska East CVD Alaska East Southwest Southwest CVD sed 1983–1992 CVD ided tumor White CVD African American		Left-sided tumor and <10	years since diagnosis		1.14 (0.99–1.32)	
led tumor and 10–19 years since diagnosis dided tumor and ≥20 years since diagnosis ted tumor and ≥20 years since diagnosis ted tumor and ≥20 years since diagnosis Pacific CVD Alaska East Northern Plains Southwest sed 1983–1992 ted tumor White CVD African American African American Asian/ Pacific		Right-sided tumor and 10-	19 years since diagnosis	CVD	1.00 (ref)	
ided tumor and ≥20 years since diagnosis led tumor and ≥20 years since diagnosis Pacific CVD Alaska East Northern Plains Southwest sed 1983–1992 ted tumor White CVD Alaska CVD CVD CVD CVD CVD CVD CVD CVD		Left-sided tumor and 10-1	9 years since diagnosis		1.32 (1.12–1.57)	
led tumor and ≥20 years since diagnosis Pacific CVD Alaska East Northern Plains Southwest Southwest Southwest CVD CVD CVD Led tumor White CVD African American African American Asian/ Pacific		Right-sided tumor and ≥ 20	0 years since diagnosis	CVD	1.00 (ref)	
Pacific CVD Alaska East Northern Plains Southwest Southwest Southwest CVD Ied tumor Mhite CVD African American American Indian/ Asian/ Pacific		Left-sided tumor and ≥ 20	years since diagnosis		1.30 (1.10–1.54)	
Alaska East Northern Plains Southwest <i>nosed 1983–1992</i> -sided tumor white African American American Indian/ Asian/ Pacific		Region	Pacific	CVD	1.00 (ref)	
East Northern Plains Southwest southwest -sided tumor white CVD CVD CVD CVD African American American American Asian/ Pacific			Alaska		I	
Northern Plains Southwest southwest -sided tumor white African American American Indian/ Asian/ Pacific			East		0.97 (0.86-1.09)	
Southwest tosed 1983–1992 -sided tumor sided tumor White African American American Indian/ Asian/ Pacific			Northern Plains		1.35 (1.21-1.51)	
<i>uosed 1983–1992</i> -sided tumor CVD sided tumor White CVD African American CVD African American American American American American American Asian/ Pacific			Southwest		1.51 (0.98-1.34)	
-sided tumor sided tumor White African American American Indian/ Asian/ Pacific		Diagnosed 1983–1992				
sided tumor White CVD African American American Indian/ Asian/ Pacific		Right-sided tumor		CVD	1.00 (ref)	
White CVD African American American Indian/ Asian/ Pacific		Left-sided tumor			1.02 (0.95–1.10)	
		Race	White	CVD	1.00 (ref)	
			African American		1.14 (0.98–1.32)	
Asian/ Pacific			American Indian/		0.68 (0.56-0.82)	
			Asian/ Pacific			

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First author, year of publication Statistical analysis	Categories		Cause of death (outcome)	Risk of death HR (95% CI) Covariates
		Islander		
		Unspecified		0.39 (0.02–1.74)
	Age at diagnosis	≤60	CVD	1.00 (ref)
		>60		10.16 (9.62–11.30)
	Marital status	Married	CVD	1.00 (ref)
		Unmarried		2.25 (2.08–2.42)
		Unknown		1.65 (1.28–2.08)
	Right-sided tumor and	Right-sided tumor and <10 years since diagnosis	CVD	1.00 (ref)
	Left-sided tumor and <	Left-sided tumor and <10 years since diagnosis		1.01 (0.90-1.13)
	Right-sided tumor and	Right-sided tumor and 10-19 years since diagnosis	CVD	1.00 (ref)
	Left-sided tumor and 10	Left-sided tumor and 10-19 years since diagnosis		0.98 (0.88–1.10)
	Right-sided tumor and	Right-sided tumor and ≥ 20 years since diagnosis	CVD	1.00 (ref)
	Left-sided tumor and \geq	Left-sided tumor and ≥ 20 years since diagnosis		0.94 (0.77–1.15)
	Region	Pacific	CVD	1.00 (ref)
		Alaska		0.00 (0.00–14.13)
		East		1.09 (0.99–1.20)
		Northern Plains		1.42 (1.30–1.56)
		Southwest		1.13 (0.97–1.30)
	Diagnosed 1993–1902			
	Right-sided tumor		CVD	1.00 (ref)
	Left-sided tumor			0.99 (0.93–1.05)
	Race	White	CVD	1.00 (ref)
		African American		1.32 (1.20–1.45)
		American Indian/		0.53 (0.46–0.61)
		Asian/ Pacific		
		Islander		
		Unspecified		0.11 (0.01–0.47)
	Age at diagnosis	≤60	CVD	1.00 (ref)
		>60		10.73 (9.86–11.70)
	Marital status	Married	CVD	1.00 (ref)
		Unmarried		2.21 (2.28–2.55)
		Unknown		1.90 (1.60–2.24)
	Right-sided tumor and	Right-sided tumor and <10 years since diagnosis	CVD	1.00 (ref)
	Left-sided tumor and <	Left-sided tumor and <10 years since diagnosis		1.00 (0.98–1.03)
	Right-sided tumor and	Right-sided tumor and ≥ 20 years since diagnosis	CVD	1.00 (ref)
	Left-sided tumor and \geq	Left-sided tumor and ≥ 20 years since diagnosis		1.01 (0.91–1.11)

First author, year of publication	Statistical analysis			• • •		
		Categories		Cause of death (outcome)	Risk of death HR (95% CI)	Covariates
		Region	Pacific	CVD	1.00 (ref)	
		1	Alaska		0.24 (0.01–1.07)	
		Ι	East		1.06 (0.99–1.13)	
		I	Northern Plains		1.25 (1.16–1.35)	
			Southwest		0.87 (0.76–0.99)	
Merzenich, 2016	Cox proportional	RT and right-sided tumor		CVD	1.0 (ref)	Clinical, tumor,
	hazard	RT and left-sided tumor			$0.94 \ (0.64 - 1.38)$	treatment
		No RT and right-sided tumor		CVD	1.0 (ref)	cnaracteristics
		No RT and left-sided tumor			1.07 (0.79–1.46)	
		RT without a history of cardiac disease	c disease	CVD	1.0 (ref)	
		RT with a history of cardiac disease	sease		1.73 (1.11–2.68)	
		RT without chemotherapy		CVD	1.0 (ref)	
		RT with chemotherapy			0.66 (0.37–1.19)	
CVD mortality in breast cancer patients with different ethnic origins	atients with different e	ethnic origins				
Berkman, 2014	Kaplan- Meier	White and diagnosed between 1990 and 2010	1990 and 2010	CVD	1.00 (ref)	No covariates
-	with log-rank	Black and diagnosed between 1990 and 2010	1990 and 2010		6.43 (3.61–11.45)	
	statistics	White and age at diagnosis 40-49 years	-49 years	CVD	1.00 (ref)	
		Black and age at diagnosis 40-49 years	49 years		9.83 (4.56–21.17)	
		White and age at diagnosis 50-59 years	-59 years	CVD	1.00 (ref)	
		Black and age at diagnosis 50-59 years	-59 years		3.35 (2.14–5.24)	
		White and age at diagnosis 60-69 years	-69 years	CVD	1.00 (ref)	
		Black and age at diagnosis 60-69 years	-69 years		2.13 (1.65–2.74)	
		White and age at diagnosis \geq 70 years	0 years	CVD	1.00 (ref)	
		Black and age at diagnosis \geq 70 years	0 years		1.07 (0.93–1.23)	
Solanki, 2016	Cox proportional	Non-Hispanic white		CVD	1.00 (ref)	Age, birthplace,
	hazard	Asian and Pacific islander			0.77 (0.71–0.83)	SEER registry,
		Non-Hispanic white		CVD	1.00 (ref)	AJUC Stage
		Chinese			0.66 (0.56-0.78)	
		Non-Hispanic white		CVD	1.00 (ref)	
		Japanese			0.71 (0.62–0.81)	
		Non-Hispanic white		CVD	1.00 (ref)	
		Filipino			0.90 (0.78–1.03)	
		Non-Hispanic white		CVD	1.00 (ref)	
		Hawaiian			1.43 (1.17–1.75)	
		Non-Hispanic white		CVD	1.00 (ref)	
		Korean			0.68 (0.46–0.99)	

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First author, year of publication Statistical analysis	Categories	Cause of death (outcome)	Risk of death HR (95% CI)	Covariates
	Non-Hispanic white	CVD	1.00 (ref)	
	Vietnamese		0.46 (0.28–0.76)	
	Non-Hispanic white	CVD	1.00 (ref)	
	Asian Indian and Pakistani		0.98 (0.70–1.37)	
	Non-Hispanic white	CVD	1.00 (ref)	
	Pacific Islander		1.33 (0.83–2.15)	
	Non-Hispanic white	CVD	1.00 (ref)	
	Other Asian		0.61 (0.45–0.83)	
	Non-U.S. born Asian and Pacific Islander	CVD	1.00 (ref)	
	U.S. born Asian and Pacific Islander		1.29 (1.08–1.54)	
	Non-U.S. born Chinese	CVD	1.00 (ref)	
	U.S. born Chinese		1.33 (0.81–2.20)	
	Non-U.S. born Japanese	CVD	1.00 (ref)	
	U.S. born Japanese		1.04(0.74 - 1.48)	
	Non-U.S. born Filipino	CVD	1.00 (ref)	
	U.S. born Filipino		0.99 (0.57–1.72)	
	Non-U.S. born Hawaiian	CVD	1.00 (ref)	
	U.S. born Hawaiian		0.97 (0.13–7.38)	
	Non-U.S. born Korean	CVD	1.00 (ref)	
	U.S. born Korean		0.17 (0.02–1.69)	
	Non-U.S. born Asian Indian and Pakistani	CVD	1.00 (ref)	
	U.S. born Asian Indian and Pakistani		0.94 (0.11–8.13)	
	Non-U.S. born Pacific Islander	CVD	1.00 (ref)	
	U.S. born Pacific Islander		4.27 (0.68–26.7)	
	Non-U.S. born Other Asian	CVD	1.00 (ref)	
U.S. born Other Asian	2.06 (0.84-5.10)			
CVD mortality in breast cancer patients by diet, body weight, and health behaviors				
McCullough, 2016 Cox proportional	Pre-diagnostic diet score (continuous)	CVD	0.96 (0.84–1.10)	Clinical, tumor, and
hazard	Pre-diagnostic diet score 0-2	CVD	1.00 (ref)	treatment
	Pre-diagnostic diet score 3-5		0.95 (0.68–1.32)	CVD risk factors
	Pre-diagnostic diet score 6-9		0.94 (0.63–1.39)	
	Post-diagnostic diet score (continuous)	CVD	0.95 (0.79–1.14)	
	Post-diagnostic diet score 0-2	CVD	1.00 (ref)	
	Post-diagnostic diet score 3-5		0.96 (0.60–1.54)	
	Post-diagnostic diet score 6-9		$0.81 \ (0.47 - 1.39)$	

Cox proportionalOne to 5 year before diagnosis a BMI <18.5 One to 5 year before diagnosis a BMI 18.5 -249 One to 5 year before diagnosis a BMI $\geq 50-299$ One to 5 year before diagnosis a BMI $\geq 50-299$ BMI after diagnosis ($\leq 1.8.5$ BMI after diagnosis ($\leq 1.0.0.5$ Weight (kg) change $-2.010 -0.01$ Weight (kg) change $-10.01 -2.11$ Weight (kg) change $-2.01 -2.00$ Weight (kg) change $-10.01 -2.11$ Weight (kg) change $-10.01 -2.11$ Weight (kg) change $-2.01 -2.00$ Weight (kg) change $-10.01 -2.11$ Weight (kg) change $-10.01 -2.11$ Weight (kg) change $-10.00 -2.01$ MutadiParadiParadiMutadiMutadiMutadiMutadiMutadiMutadiMutadiMu	irst author, year of publication		Categories		Cause of death (outcome)	Risk of death HR (95% CI) Covariates	Covariates
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	ichols, 2009	Cox proportional	One to 5 year before diagnosis a BMI <18.5		CVD	4.15 (1.44–12.0)	Age, menopausal
One to 5 year before diagnosis a BMI 250–299 One to 5 year before diagnosis a BMI 250–299 BMI after diagnosis 18.5–249 BMI after diagnosis 18.5–249 BMI after diagnosis 250–209 BMI after diagnosis 250–200 Weight (kg) change –10.00 –2.11 Weight (kg) change 2.1-6.00 Weight (kg) change		hazard	One to 5 year before diagnosis a BMI $18.5-2^{4}$	4.9		1.00 (ref)	status, and other
One to 5 year before diagnosis a BMI ≥30 BMI after diagnosis <18.5			One to 5 year before diagnosis a BMI $25.0-2$	9.9		1.05 (0.63–1.74)	CVD risk factors
BMI after diagnosis 18.5–24.9 BMI after diagnosis 18.5–24.9 BMI after diagnosis 18.5–24.9 BMI after diagnosis 25.0–29.9 BMI after diagnosis 25.0–20.1 Weight (kg) change –10.0 to –2.1 Weight (kg) change –2.0 to 2.0 Weight (kg) change 2.1–6.0 Weight (kg) change 10.1 Cox proportional Pre-diagnosis behaviors MII Develagnosis behaviors Pre-diagnosis behaviors DMII Pre-diagnosis behaviors Nor-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 Sino-34.9 S			One to 5 year before diagnosis a BMI ≥ 30			2.45 (1.46-4.11)	
BMI after diagnosis $18.5 - 24.9$ BMI after diagnosis $2.50 - 29.9$ BMI after diagnosis $2.50 - 29.9$ BMI after diagnosis 2.00 to -10.1 Weight (kg) change -10.00 to -2.11 Weight (kg) change -10.00 to -2.11 Weight (kg) change 0.10 Weight (kg) change 0.10 Weight (kg) change 0.100 Weight (kg) change 0.11 Pre-diagnosis behaviorsBMIPre-diagnosis behaviorsBMIPre-diagnosis behaviorsBMIPre-diagnosis behaviorsBMIPre-diagnosis behaviorsBMIPre-diagnosis behaviorsBMIPre-diagnosis behaviorsBMIPre-diagnosis behaviorsBMIPre-diagnosis behaviorsBMIPre-diagnosis behaviorsPre-diagnosis behaviorsPre-diagnosis behaviorsPre-diagnosis behaviorsPre-diagnosis behaviorsBMIPre-diagnosis behavio			BMI after diagnosis <18.5		CVD	0.58(0.08-4.34)	
BMI after diagnosis 25.0–29.9 BMI after diagnosis 23.0–29.9 BMI after diagnosis 23.0 to –10.1 Weight (kg) change –50.0 to –2.0 Weight (kg) change –10.00 Weight (kg) change 10.01 Weight (kg) change			BMI after diagnosis 18.5-24.9			1.00 (ref)	
BMI after diagnosis ≥30 Weight (kg) change =50.0 to -10.1 Weight (kg) change =50.0 to -2.1 Weight (kg) change =2.0 to 2.0 Weight (kg) change 2.1-6.0 Weight (kg) change 6.1-10.0 Weight (kg) change 6.1-10.0 Weight (kg) change 6.1-0.0 Weight (kg) change 6.1-0.0 Weight (kg) change 6.1-0.0 Neight (kg) change 6.1-0.0 Weight (kg) change 6.1-0.0 Neight (kg) change 10.1 Pre-diagnosis behaviors Pre-diagnosis behaviors BMI RMI BMI RMI BMI Pre-diagnosis behaviors Sin034.9 Sin0-34.9 25.0-29.9 Sin0-34.9 25.0-29.9 Sin0-34.9 25.0 Physical activity (hours per week) Continuous No activity 0-1.9 Smoking 25.0 Smoking 21.9 Smoking 25.0 Smoking No-stivity Ortight 27.0 Smoking Smoking			BMI after diagnosis 25.0-29.9			0.99(0.59 - 1.66)	
Weight (kg) change -50.0 to -10.1 Weight (kg) change -10.0 to -2.1 Weight (kg) change 2.1-6.0 Weight (kg) change 0.1 Cox proportional Pre-diagnosis behaviors Multi Pre-diagnosis behaviors Multi Pre-diagnosis behaviors Continuous BMI Continuous BMI Continuous BMI Sinch etarity (hours per week) Continuous Continuous No activity (ours per week) Continuous No activity (ours per week) Continuous No activity Outor Smoking Smoking Continuous			BMI after diagnosis ≥ 30			1.65(0.97 - 2.83)	
Weight (kg) change -10.0 to -2.1 Weight (kg) change -2.0 to 2.0 Weight (kg) change 2.1-6.0 Weight (kg) change 6.1-10.0 Weight (kg) change 0.1 Cox proportional Pre-diagnosis behaviors BMI Cox proportional Pre-diagnosis behaviors Continuous BMI Continuous BMI Continuous BMI Continuous BMI BMI BMI Continuous BMI BMI BMI BMI BMI Contuous BMI BMI Contuous BMI BMI Contuous BMI BMI BMI Contuous			Weight (kg) change -50.0 to -10.1		CVD	1.08 (0.42–2.78)	
Weight (kg) change -2.0 to 2.0 Weight (kg) change 5.1-10.0 Weight (kg) change 6.1-10.0 Weight (kg) change 10.1 Cox proportional Pre-diagnosis behaviors Pre-diagnosis behaviors 30.0-34.9 All Prysical activity (hours per week) Continuous Proba Prysical activity (hours per week) Continuous Sind Proba 2.0-4.9 Sind Proba 2.0-4.9 Sind Proba 0.1.9 Sind Stochad 0.1.9 Sind Stochad 0.1.9 Sind Stochad 0.1.9 Sindiff Stochad 0.1.9 Sindiff Stochad 0.1.9 Stochad Stochad Stochad Stochad			Weight (kg) change -10.0 to -2.1			1.02(0.58 - 1.80)	
Weight (kg) change 2.1–6.0 Weight (kg) change 6.1–10.0 Weight (kg) change 10.1 Pre-diagnosis behaviors Cox proportional Pre-diagnosis behaviors MI Continuous Physical activity (hours per week) Continuous Solo-34.9 25.0–29.9 Solo-34.9 25.0–29.9 Physical activity (hours per week) Continuous No activity 0–1.9 Stock 20–4.9 Stock 20–4.9 Stock 20–4.9 Stock 20–4.9 Stock 0–1.9 Stock 0–1.9 Stock 20–4.9 Stock 20–4.9 Stock 20–4.9 Stock 20–4.9 Stock 20–4.9 Stock 20–4.9 Stock 0–1.9 Stock 0–1.9 Stock 20–6.9 Stock 20–6.9 Stock 20–6.9 Stock 20–6.9 Stock 20–6.9 Stock 20–6.9 Stock 20–6.9 <td></td> <td></td> <td>Weight (kg) change -2.0 to 2.0</td> <td></td> <td></td> <td>1.00 (ref)</td> <td></td>			Weight (kg) change -2.0 to 2.0			1.00 (ref)	
Weight (kg) change 6.1–10.0 Weight (kg) change 10.1 Cox proportional <i>Pre-diagnosis behaviors</i> Decominuous BMI Continuous Nazard BMI Continuous Physical activity (hours per week) Continuous Sinobal Alcohol (drinks per week) Continuous Smoking Store 33.0 Store 34.9 Smoking No activity Out-1.9 Struct Smoking Out-1.9 Struct Smoking Out-1.9 Struct Smoking Out-1.9 Struct Smoking Out-1.9 Struct Struct Out-1.9			Weight (kg) change 2.1–6.0			0.79 (0.43–1.44)	
Weight (kg) change 10.1 Cox proportional <i>Pre-diagnosis behaviors</i> BMI Continuous BMI (18, 5–24.9) BMI (25, 0–29.9) BMI (25, 0–24.9) Physical activity (hours per week) Continuous Continuous No activity Alcohol (drinks per week) Continuous Smoking (0–1.9) Smoking No activity Oracity (0–1.9) Smoking (10, 0–1.9) Smoking (10, 0–1.9) Smoking (10, 0–1.9) String Smoking Continuous (10, 0–1.9)			Weight (kg) change 6.1–10.0			0.64 (0.29–1.44)	
Cox proportional <i>Pre-diagnosis behaviors</i> hazard BMI Continuous hazard 18,5–24,9 25,0–29,9 Alcoba Physical activity (hours per week) 26,0–34,9 Physical activity (hours per week) Continuous 0,0–1,9 Alcobal (drinks per week) 0,1–9 2,0–4,9 Smoking Alcobal (drinks per week) 0,1–9 Alcobal (drinks per week) Continuous 0,1–9 Alcobal (drinks per week) 0,1–9 2,0–4,9 Smoking Sino-drinker 0,1–9 Alcobal (drinks per week) Continuous 0,1–9 Alcobal (drinks per week) Continuous 0,1–9 Smoking Sino-drinker 0,1–9 Alcobal (drinks per week) Continuous 0,1–9 Alcobal (drinks per week) Continuous 0,1–9 Alcobal (drinks per week) Sino-drinker 0,1–9 Alcobal (drinker) Sino-drinker 0,1–9 Alcobal (drinker) Sino-drinker 0,1–9 Alcobal (drinker) Sino-drinker 0,1–9			Weight (kg) change 10.1			1.73 (0.83–3.62)	
BMI Continuous 18.5-24.9 25.0-29.9 25.0-24.9 25.0-24.9 25.0-24.9 235.0 235.0 No activity 0-1.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9	eal, 2017	Cox proportional	Pre-diagnosis behaviors				Demographic,
18.5-24.925.0-29.925.0-29.930.0-34.925.0-34.9 ≥ 35.0 ≥ 35.0 ContinuousNo activity0-1.9 ≥ 5.0 drinks per week)Non-drinker0-1.92.0-6.9 ≥ 7.0 Non-smokerFormersmokerCurrentCurrent		hazard	BMI	Continuous	CVD	1.01 (0.95–1.07)	clinical, tumor, and
25.0-29.9 30.0-34.9 ≥ 35.0 ≥ 35.0 ≥ 35.0 ≥ 35.0 Continuous No activity 0-1.9 ≥ 5.0 drinks per week) Non-drinker 0-1.9 $\geq 1.0-6.9$ ≥ 7.0 Non-smoker Former smoker Current				18.5-24.9	CVD	1.0 (ref)	ureaument characteristics
$30.0-34.9$ ≥ 35.0 ≥ 35.0 continuousNo activity $0-1.9$ $2.0-4.9$ ≥ 5.0 drinks per week)Non-drinker $0-1.9$ $2.0-6.9$ ≥ 7.0 Non-smokerFormersmokerCurrentCurrent				25.0-29.9		0.88 (0.37–2.07)	
≥35.0 cctivity (hours per week) Continuous No activity 0-1.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-4.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 2.0-6.9 Non-drinker Non-smoker Former Former Former Former Former				30.0–34.9		1.21(0.45 - 3.24)	
cctivity (hours per week) Continuous No activity 0-1.9 2.0-4.9 ≥ 5.0 drinks per week) Continuous Non-drinker 0-1.9 2.0-6.9 ≥ 7.0 Non-smoker Former smoker				≥35.0		1.85 (0.59–5.85)	
No activity 0-1.9 2.0-4.9 ≥ 5.0 ≥ 5.0 Non-drinker 0-1.9 2.0-6.9 ≥ 7.0 Non-smoker Former smoker			Physical activity (hours per week)	Continuous	CVD	0.83 (0.70–0.98)	
$\begin{array}{llllllllllllllllllllllllllllllllllll$				No activity	CVD	1.0 (ref)	
2.0-4.9 ≥5.0 Continuous Non-drinker 0-1.9 2.0-6.9 ≥7.0 Non-smoker Former smoker				0-1.9		0.52 (0.22–1.23)	
≥5.0 drinks per week) Eontinuous Non-drinker 0-1.9 2.0-6.9 ≥7.0 Non-smoker Former smoker				2.0-4.9		0.38 (0.15–1.00)	
drinks per week) Continuous Non-drinker 0–1.9 2.0–6.9 ≥7.0 Non-smoker Former smoker Current				≥ 5.0		0.29(0.08 - 1.04)	
Non-drinker 0–1.9 2.0–6.9 ≥7.0 Non-smoker Former smoker			Alcohol (drinks per week)	Continuous	CVD	1.01 (0.94–1.08)	
0–1.9 2.0–6.9 ≥7.0 Non-smoker Former smoker Current				Non-drinker	CVD	1.0 (ref)	
2.0–6.9 ≥7.0 Non-smoker Former smoker Current				0-1.9		0.68(0.29 - 1.60)	
≥7.0 Non-smoker Former smoker Current				2.0-6.9		1.22(0.47 - 3.14)	
Non-smoker Former smoker Current				≥7.0		0.49(0.13 - 1.86)	
Former smoker Current			Smoking	Non-smoker	CVD	1.0 (ref)	
Current				Former		0.96 (0.43–2.15)	
				Current			
smoker				smoker		(11.C-+0.U) 1U.Z	

First author, year of publication Statistical analysis	Categories		Cause of death (outcome)	Risk of death HR (95% CI)	Covariates
	Post-diagnosis behaviors				Pre-diagnosis health
	BMI	Continuous	CVD	0.96 (0.85–1.08)	behavior and
		18.5-24.9	CVD	1.0 (ref)	demographic, clinical mmor and
		25.0-29.9		0.90 (0.32–2.51)	treatment
		30.0 - 34.9		0.63 (0.15–2.70)	characteristics
		≥ 35.0		0.36 (0.05–2.74)	
	Physical activity (hours per week)	Continuous	CVD	1.04 (0.91–1.18)	
		No activity	CVD	1.0 (ref)	
		0-1.9		0.35 (0.04–2.97)	
		2.0-4.9		0.42 (0.05–3.60)	
		≥ 5.0		2.27 (0.40–12.76)	
	Alcohol (drinks per week)	Continuous	CVD	0.90 (0.67–1.22)	
		Non-drinker	CVD	1.0 (ref)	
		0-1.9		1.43 (0.37–5.62)	
		2.0-6.9		1.53 (0.24–9.89)	
		≥7.0		0.57 (0.04–8.52)	
	Smoking	Non-smoker	CVD	1.0 (ref)	
		Former smoker		0.92 (0.41–2.08)	
		Current smoker		1.27 (0.22–6.86)	

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follow-up of 6.5 years (range = 0-15), 2.3% of all women died of CVD. Women with left-sided breast cancer did not have a higher risk of dying of CVD than women with right-sided breast cancer, irrespectively of radiotherapy treatment (Table 3). Among women treated with radiotherapy, women with a history of CVD had a 1.73 times (95% CI 1.11–2.68) higher risk of dying of CVD than women without a history of CVD.

CVD mortality in breast cancer patient by ethnic origin

Berkman et al. [6] included 54,518 white and 6113 black women over 40 years of age at diagnosis with primary DCIS in the US between 1978 and 2010 (Table 2). During a median follow-up of 9.2 years, 6.0% of all women died of CVD. Among women diagnosed with breast cancer between 1990 and 2010, black women had a (unadjusted) 6.43 (95% CI 3.61–11.45) times higher risk of death from CVD compared to white women (Table 3). Unadjusted HRs of CVD death in black compared to white women decreased with increasing age at diagnosis: 9.83 (95% CI 4.56–21.17), 3.35 (95% CI 2.14–5.24), 2.13 (95% CI 1.65–2.74), and 1.07 (95% CI 0.93–1.23) for women of ages 40–49, 50–59, 60–69, and \geq 70 years, respectively.

Solanki et al. [17] included 462,005 non-Hispanic white and 44,531 Asian and Pacific Islander women diagnosed with breast cancer in the US between 1991 and 2001 (Table 2). Median age at breast cancer diagnosis was 61.2 years (SD = 13.7) for non-Hispanic white women and 56.3 years (SD = 13.1) for Asian and Pacific Islander women. The median follow-up for non-Hispanic white women was 4 years (range = 2-6), during which 5.5% of women died of CVD. The median follow-up for Asian and Pacific Islander women was 3 years (range 2-5), during which 2.6% of women died of CVD. After adjusting for patient, tumor, and registry characteristics, Asian and Pacific Islander women with breast cancer had a HR of 0.77 (95% CI 0.71–0.83) for death from CVD compared to non-Hispanic white women with breast cancer (Table 2). Furthermore, US born Asian and Pacific Islander women with breast cancer had a 1.29 (95% CI 1.08-1.54) times higher risk of death from CVD compared to non-US born Asian and Pacific Islander women with breast cancer.

CVD mortality in breast cancer patients by diet, body weight, and health-behaviors

McCullough et al. [16] included 4452 women diagnosed with primary invasive breast cancer in Switzerland between 1992 and 2011 who had scored their diet according to the American Cancer Society (AMC) guidelines before breast cancer diagnosis, and of these, 2152 women scored their diet also at least one year after breast cancer diagnosis (Table 2). The AMC guidelines recommend following the general food-based guidelines for primary cancer prevention, which includes eating a plantbased diet rich in vegetables and fruits, whole grains, and which is limited in red and processed meats [27]. Mean age at diagnosis was 70.7 years (SD = 7.2). During a mean follow-up of 9.8 years (SD = 4.9), 5.2% of all women died of CVD. After adjusting for tumor, treatment, and patient characteristics, both pre-diagnostic and post-diagnostic higher AMC diet scores, indicating an unhealthier diet, were not associated with a higher risk of CVD mortality following breast cancer compared with the lowest diet score category (0-2), indicating a healthier diet (Table 3).

Nichols et al. [15] included 5791 women with primary in situ or invasive breast cancer diagnosed in the US between 1988 and 1999 (Table 2). Mean age at diagnosis was 58.4 years (SD = 10.0). During a mean follow-up of 6.4 years (SD = 1.2), 1.6% of all women died of CVD. After correcting for age, menopausal status, and CVD risk factors, Nichols et al. found a 4.15 (95% CI 1.44–12.0) and 2.45 (95% CI 1.46–4.11) times higher risk of death from CVD in women with a pre-diagnosis underweight (body mass index (BMI; kg/m²): <18.5) and obesity (BMI: \geq 30), respectively, compared with women with a pre-diagnosis normal weight (BMI: 18.5–24.9) (Table 3).

Veal et al. [22] included 1925 women aged between 20 and 74 years at diagnosis of DCIS in the US between 1997 and 2006 (Table 2). During a mean follow-up of 6.7 years, 1.8% of all women died of CVD. More hours per week of physical activity before the breast cancer diagnosis was associated with 0.83 (95% CI 0.70–0.98) lower risk of dying of CVD (Table 3).

Discussion

In this review, we systematically summarized the evidence on the risk and risk factors of death from CVD following breast cancer.

The absolute risk of dying of CVD following breast cancer ranges from 1.6% [15] to 10.4% [5], and the risk of CVD mortality is higher in women with breast cancer than women from the general population [5, 8]. Older age at diagnosis [6, 18, 19, 25], left-sided tumor [23, 24, 26], diagnosis in an earlier calendar period [18, 25], and black ethnic origin [6] are risk factors of CVD mortality following breast cancer.

Several mechanisms are proposed for the increased risk of CVD mortality in women with breast cancer. CVD risk factors, such as obesity and diabetes, may be more present among breast cancer survivors than women from the general population as breast cancer and CVD have shared risk factors [28]. Also, cardiotoxic effects of breast cancer treatments, specifically mediastinal and left-sided radiotherapy, anthracycline-based chemotherapy, and trastuzumab, are well documented to increase the risk of CVD [29–32].

In the current review, studies with longer follow-up, i.e. over 10 years [5, 6, 8], reported higher absolute risks of CVD mortality. The risk of CVD increases with time since diagnosis probably due to increasing age and cardiotoxicity of breast cancer treatments that become apparent after several years [29]. Age is a well-known risk factor for CVD [33–36], and therefore, expected to be found as a risk factor in women with breast cancer [6, 18, 19, 25]. Schonberg et al. [14] found that 26–40% of older women diagnosed with early-stage breast cancer died of CVD, indicating that the risk of CVD is high in specific subgroups and particularly in older women.

The association between left-sided breast cancer and radiotherapy treatment with a higher risk of CVD mortality was found among women diagnosed in the early 1980's [23, 24, 26]. Radiotherapy treatment was more cardiotoxic in these years as it usually involved higher doses with large irradiation fields irradiating parts of the heart [37, 38]. This may also explain the increased risk of CVD mortality among breast cancer patients diagnosed in an earlier calendar period [18, 25]. Colzani et al. [18] did not find an increased risk of CVD mortality among women treated with radiotherapy and/or chemotherapy. Although the baseline risk of CVD was not reported, this result is probably due to patient selection, i.e. women who did not undergo radiotherapy and/or chemotherapy probably had a higher risk of CVD at baseline. The lower risk of CVD in Asian populations [17] and the higher risk of CVD in black populations [6] are reported by several studies and can be explained by the lower and higher presence of CVD risk factors, respectively, such as high blood pressure, obesity, and lipid levels [39-42].

The present systematic review shows that there are only a limited number of studies investigating the risk and risk factors of CVD mortality following breast cancer, and that these studies are heterogeneous in design, study population, and length of follow-up. Also, the determinants and outcomes, in terms of CVD risk factors and death due to CVD, respectively, vary. We acknowledge that, due to the heterogeneous designs of the included studies, we were unable to perform a meta-analysis, which limited the strength of evidence. Besides limitations, the current review has strengths. This is the first study that systematically summarized the literature on the risk and risk factors of death from CVD following breast cancer. Furthermore, the current systematic review includes a large variety of risk factors of death from CVD in women with breast cancer.

To conclude, the combination of high breast cancer incidence, improved breast cancer survival, presence of CVD risk factors, and cardiotoxic breast cancer treatments has resulted into many breast cancer survivors at risk of CVD. Therefore, it is important to understand the incidence and etiology of CVD in these survivors. Furthermore, identification of women with breast cancer at high risk of CVD is important to minimize the number of women suffering and/or dying of CVD after breast cancer treatment and improve quality of life and long-term prognosis. Clinicians should be able to identify breast cancer patients at increased risk of CVD and provide accurate recommendations for CVD risk reduction strategies specifically for breast cancer survivors at high risk of CVD. The current systematic review, in combination with a recent guideline by Armenian et al. [29] on the prevention and monitoring of cardiac dysfunction in survivors of adult cancers, may help clinicians with such a recommendation. In addition, there are studies investigating the identification of women with breast cancer at high risk of CVD using other measurements, for example, by measuring the coronary artery calcification on radiotherapy planning computed tomography scans [43]. This may further help clinicians with identification of breast cancer patients at high risk of CVD. Identification of breast cancer patients at high risk of CVD is important to optimize CVD prevention of (irreversible) cardiac damage, by adjusting breast cancer treatments accordingly and initializing CVD (preventative) treatment. Furthermore, a tailored individual approach with early and late monitoring of cardiac dysfunction in breast cancer survivors should be implemented in routine care [44].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For this type of study format, informed consent is not required. This article does not contain any studies with human participants or animals performed by any of the authors.

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References

- Integraal Kankercentrum Nederland Cijfers over kanker. http:// cijfersoverkanker.nl/. Accessed 10 Aug 2016
- 2. Global Burden of Disease Cancer Collaboration. Fitzmaurice C. Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, Dicker DJ, Chimed-Orchir O, Dandona R, Dandona L, Fleming T, Forouzanfar MH, Hancock J, Hay RJ, Hunter-Merrill R, Huynh C, Hosgood HD, Johnson CO, Jonas JB, Khubchandani J, Kumar GA, Kutz M, Lan Q, Larson HJ, Liang X, Lim SS, Lopez AD, MacIntyre MF, Marczak L, Marquez N, Mokdad AH, Pinho C, Pourmalek F, Salomon JA, Sanabria JR, Sandar L, Sartorius B, Schwartz SM, Shackelford KA, Shibuya K, Stanaway J, Steiner C, Sun J, Takahashi K, Vollset SE, Vos T, Wagner JA, Wang H, Westerman R, Zeeb H, Zoeckler L, Abd-Allah F, Ahmed MB, Alabed S, Alam NK, Aldhahri SF, Alem G, Alemayohu MA, Ali R, Al-Raddadi R, Amare A, Amoako Y, Artaman A, Asayesh H, Atnafu N, Awasthi A, Saleem HB, Barac A, Bedi N, Bensenor I, Berhane A, Bernabe E, Betsu B, Binagwaho A, Boneya D, Campos-Nonato I, Castaneda-Orjuela C, Catala-Lopez F, Chiang P, Chibueze C, Chitheer A, Choi JY, Cowie B, Damtew S, das Neves J, Dey S, Dharmaratne S, Dhillon P, Ding E, Driscoll T, Ekwueme D, Endries AY, Farvid M, Farzadfar F, Fernandes J, Fischer F, G/Hiwot TT, Gebru A, Gopalani S, Hailu A, Horino M, Horita N, Husseini A, Huybrechts I, Inoue M, Islami F, Jakovljevic M, James S, Javanbakht M, Jee SH, Kasaeian A, Kedir MS, Khader YS, Khang YH, Kim D, Leigh J, Linn S, Lunevicius R, El Razek HM, Malekzadeh R, Malta DC, Marcenes W, Markos D, Melaku YA, Meles KG, Mendoza W, Mengiste DT, Meretoja TJ, Miller TR, Mohammad KA, Mohammadi A, Mohammed S, Moradi-Lakeh M, Nagel G, Nand D, Le Nguyen Q, Nolte S, Ogbo FA, Oladimeji KE, Oren E, Pa M, Park EK, Pereira DM, Plass D, Qorbani M, Radfar A, Rafay A, Rahman M, Rana SM, Soreide K, Satpathy M, Sawhney M, Sepanlou SG, Shaikh MA, She J, Shiue I, Shore HR, Shrime MG, So S, Soneji S, Stathopoulou V, Stroumpoulis K, Sufiyan MB, Sykes BL, Tabares-Seisdedos R, Tadese F, Tedla BA, Tessema GA, Thakur JS, Tran BX, Ukwaja KN, Uzochukwu BS, Vlassov VV, Weiderpass E, Wubshet Terefe M, Yebyo HG, Yimam HH, Yonemoto N, Younis MZ, Yu C, Zaidi Z, Zaki ME, Zenebe ZM, Murray CJ, Naghavi M (2016) Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. doi: 10.1001/jamaoncol. 2016.5688
- Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, Mandelblatt JS, Yakovlev AY, Habbema JD, Feuer EJ, Cancer Intervention and Surveillance Modeling Network (CIS-NET) Collaborators (2005) Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 353:1784–1792
- Nakano M, Fujisue M, Tashima R, Okumura Y, Nishiyama Y, Ohsako T, Toyozumi Y, Arima N, Nishimura R (2015) Survival time according to the year of recurrence and subtype in recurrent breast cancer. Breast 24:588–593. doi:10.1016/j.breast.2015.06. 003
- Riihimaki M, Thomsen H, Brandt A, Sundquist J, Hemminki K (2012) Death causes in breast cancer patients. Ann Oncol 23:604–610. doi:10.1093/annonc/mdr160
- Berkman A, Cole BF, Ades PA, Dickey S, Higgins ST, Trentham-Dietz A, Sprague BL, Lakoski SG (2014) Racial differences in breast cancer, cardiovascular disease, and all-cause mortality among women with ductal carcinoma in situ of the breast. Breast Cancer Res Treat 148:407–413. doi:10.1007/s10549-014-3168-3

- Taunk NK, Haffty BG, Kostis JB, Goyal S (2015) Radiationinduced heart disease: pathologic abnormalities and putative mechanisms. Front Oncol 5:39. doi:10.3389/fonc.2015.00039
- Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD (2016) Cardiovascular disease mortality among breast cancer survivors. Epidemiology 27:6–13. doi:10.1097/ EDE.000000000000394
- Bird BR, Swain SM (2008) Cardiac toxicity in breast cancer survivors: review of potential cardiac problems. Clin Cancer Res 14:14–24. doi:10.1158/1078-0432.CCR-07-1033
- Borger JH, Hooning MJ, Boersma LJ, Snijders-Keilholz A, Aleman BM, Lintzen E, van Brussel S, van der Toorn PP, Alwhouhayb M, van Leeuwen FE (2007) Cardiotoxic effects of tangential breast irradiation in early breast cancer patients: the role of irradiated heart volume. Int J Radiat Oncol Biol Phys 69:1131–1138
- McGale P, Darby SC, Hall P, Adolfsson J, Bengtsson NO, Bennet AM, Fornander T, Gigante B, Jensen MB, Peto R, Rahimi K, Taylor CW, Ewertz M (2011) Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. Radiother Oncol 100:167–175. doi:10. 1016/j.radonc.2011.06.016
- Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH (2007) Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. J Clin Oncol 25:3808–3815
- Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, Mulrow C, Catala-Lopez F, Gotzsche PC, Dickersin K, Boutron I, Altman DG, Moher D (2015) The PRISMA extension statement for reporting of systematic reviews incorporating network metaanalyses of health care interventions: checklist and explanations. Ann Intern Med 162:777–784. doi:10.7326/M14-2385
- 14. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm
- Nichols HB, Trentham-Dietz A, Egan KM, Titus-Ernstoff L, Holmes MD, Bersch AJ, Holick CN, Hampton JM, Stampfer MJ, Willett WC, Newcomb PA (2009) Body mass index before and after breast cancer diagnosis: associations with all-cause, breast cancer, and cardiovascular disease mortality. Cancer Epidemiol Biomark Prev 18:1403–1409. doi:10.1158/1055-9965.EPI-08-1094
- McCullough ML, Gapstur SM, Shah R, Campbell PT, Wang Y, Doyle C, Gaudet MM (2016) Pre- and postdiagnostic diet in relation to mortality among breast cancer survivors in the CPS-II Nutrition Cohort. Cancer Causes Control. doi:10.1007/s10552-016-0802-x
- Solanki PA, Ko NY, Qato DM, Calip GS (2016) Risk of cancerspecific, cardiovascular, and all-cause mortality among Asian and Pacific Islander breast cancer survivors in the United States, 1991–2011. Springerplus. doi: 10.1186/s40064-016-1726-3
- Colzani E, Liljegren A, Johansson AL, Adolfsson J, Hellborg H, Hall PF, Czene K (2011) Prognosis of patients with breast cancer: causes of death and effects of time since diagnosis, age, and tumor characteristics. J Clin Oncol 29:4014–4021. doi:10.1200/ JCO.2010.32.6462
- Haque R, Yood MU, Geiger AM, Kamineni A, Avila CC, Shi J, Silliman RA, Quinn VP (2011) Long-term safety of radiotherapy and breast cancer laterality in older survivors. Cancer Epidemiol Biomarkers Prev 20:2120–2126. doi:10.1158/1055-9965.EPI-11-0348
- Bouchardy C, Rapiti E, Usel M, Majno SB, Vlastos G, Benhamou S, Miralbell R, Neyroud-Caspar I, Verkooijen HM, Vinh-Hung V (2010) Excess of cardiovascular mortality among node-negative

breast cancer patients irradiated for inner-quadrant tumors. Ann Oncol 21:459–465. doi:10.1093/annonc/mdp341

- 21. Merzenich H, Bartkowiak D, Schmidberger H, Schmidt M, Schwentner L, Wiegel T, Woeckel A, Wollschlager D, Blettner M (2017) 3D conformal radiotherapy is not associated with the long-term cardiac mortality in breast cancer patients: a retrospective cohort study in Germany (PASSOS-Heart Study). Breast Cancer Res Treat 161:143–152. doi:10.1007/s10549-016-4042-2
- 22. Veal CT, Hart V, Lakoski SG, Hampton JM, Gangnon RE, Newcomb PA, Higgins ST, Trentham-Dietz A, Sprague BL (2017) Health-related behaviors and mortality outcomes in women diagnosed with ductal carcinoma in situ. J Cancer Surviv. doi:10.1007/s11764-016-0590-z
- 23. Darby SC, McGale P, Taylor CW, Peto R (2005) 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 6:557–565
- Giordano SH, Kuo YF, Freeman JL, Buchholz TA, Hortobagyi GN, Goodwin JS (2005) Risk of cardiac death after adjuvant radiotherapy for breast cancer. J Natl Cancer Inst 97:419–424.
- Hooning MJ, Aleman BM, van Rosmalen AJ, Kuenen MA, Klijn JG, van Leeuwen FE (2006) Cause-specific mortality in longterm survivors of breast cancer: a 25-year follow-up study. Int J Radiat Oncol Biol Phys 64:1081–1091.
- Haque W, Verma V, Haque A, Butler EB, Teh BS (2017) Trends in cardiac mortality in women with ductal carcinoma in situ. Breast Cancer Res Treat 161:345–351. doi:10.1007/s10549-016-4045-z
- 27. Kushi LH, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV, Gapstur S, Patel AV, Andrews K, Gansler T, American Cancer Society 2010 Nutrition and Physical Activity Guidelines Advisory Committee (2012) American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin 62:30–67. doi:10. 3322/caac.20140
- Weaver KE, Foraker RE, Alfano CM, Rowland JH, Arora NK, Bellizzi KM, Hamilton AS, Oakley-Girvan I, Keel G, Aziz NM (2013) Cardiovascular risk factors among long-term survivors of breast, prostate, colorectal, and gynecologic cancers: a gap in survivorship care? J Cancer Surviv 7:253–261. doi:10.1007/ s11764-013-0267-9
- Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, Dent S, Douglas PS, Durand JB, Ewer M, Fabian C, Hudson M, Jessup M, Jones LW, Ky B, Mayer EL, Moslehi J, Oeffinger K, Ray K, Ruddy K, Lenihan D (2017) Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 35:893–911. doi:10.1200/JCO.2016.70. 5400
- 30. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z, Darby S (2014) 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. Lancet 383:2127–2135. doi:10.1016/S0140-6736(14)60488-8
- Guenancia C, Lefebvre A, Cardinale D, Yu AF, Ladoire S, Ghiringhelli F, Zeller M, Rochette L, Cottin Y, Vergely C (2016)

Obesity as a risk factor for anthracyclines and trastuzumab cardiotoxicity in breast cancer: a systematic review and meta-analysis. J Clin Oncol 34:3157–3165

- Vejpongsa P, Yeh ET (2014) Prevention of anthracycline-induced cardiotoxicity: challenges and opportunities. J Am Coll Cardiol 64:938–945. doi:10.1016/j.jacc.2014.06.1167
- Fan J, Song Y, Chen Y, Hui R, Zhang W (2013) Combined effect of obesity and cardio-metabolic abnormality on the risk of cardiovascular disease: a meta-analysis of prospective cohort studies. Int J Cardiol 168:4761–4768. doi:10.1016/j.ijcard.2013.07. 230
- 34. Ringback Weitoft G, Eliasson M, Rosen M (2008) Underweight, overweight and obesity as risk factors for mortality and hospitalization. Scand J Public Health 36:169–176. doi:10.1177/ 1403494807085080
- Wu CY, Chou YC, Huang N, Chou YJ, Hu HY, Li CP (2014) Association of body mass index with all-cause and cardiovascular disease mortality in the elderly. PLoS ONE 9:e102589. doi:10. 1371/journal.pone.0102589
- 36. D'Agostino RBS, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB (2008) General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 117:743–753. doi:10.1161/CIRCULATIONAHA. 107.699579
- 37. Cuzick J, Stewart H, Rutqvist L, Houghton J, Edwards R, Redmond C, Peto R, Baum M, Fisher B, Host H (1994) Causespecific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. J Clin Oncol 12:447–453. doi:10.1200/JCO.1994.12.3.447
- Darby SC, Bronnum D, Correa C, Ewertz M, Gagliardi G, Gigante B, McGale P, Nisbet A, Taylor C, Hall P (2010) A doseresponse relationship for the incidence of radiation-related heart disease. Int J Radiat Oncol Biol Phys 78:S49–S50
- 39. Valina-Toth AL, Zavodnik T, Seicean S, Plana J, Marwick T (2013) African american race is a correlate of heart failure in breast cancer survivors: a study of 26,347 women identified with breast cancer from 1973 to 2007. J Am Coll Cardiol 61:E580
- Budoff MJ, Nasir K, Mao S, Tseng PH, Chau A, Liu ST, Flores F, Blumenthal RS (2006) Ethnic differences of the presence and severity of coronary atherosclerosis. Atherosclerosis 187:343–350
- Sasayama S (2008) Heart disease in Asia. Circulation 118:2669–2671. doi:10.1161/CIRCULATIONAHA.108.837054
- Tammemagi CM, Nerenz D, Neslund-Dudas C, Feldkamp C, Nathanson D (2005) Comorbidity and survival disparities among black and white patients with breast cancer. JAMA 294:1765–1772
- 43. Gernaat SA, Isgum I, de Vos BD, Takx RA, Young-Afat DA, Rijnberg N, Grobbee DE, van der Graaf Y, de Jong PA, Leiner T, van den Bongard DH, Pignol JP, Verkooijen HM (2016) Automatic coronary artery calcium scoring on radiotherapy planning CT scans of breast cancer patients: reproducibility and association with traditional cardiovascular risk factors. PLoS ONE 11:e0167925. doi:10.1371/journal.pone.0167925
- 44. Maas AH, Ottevanger N, Atsma F, Cramer MJ, Leiner T, Poortmans P (2016) Cardiovascular surveillance in breast cancer treatment: a more individualized approach is needed. Maturitas 89:58–62. doi:10.1016/j.maturitas.2016.04.015