Breast cancer and cardiovascular disease risk

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Borstkanker en het risico op hart- en vaatziekten
(met een samenvatting in het Nederlands)

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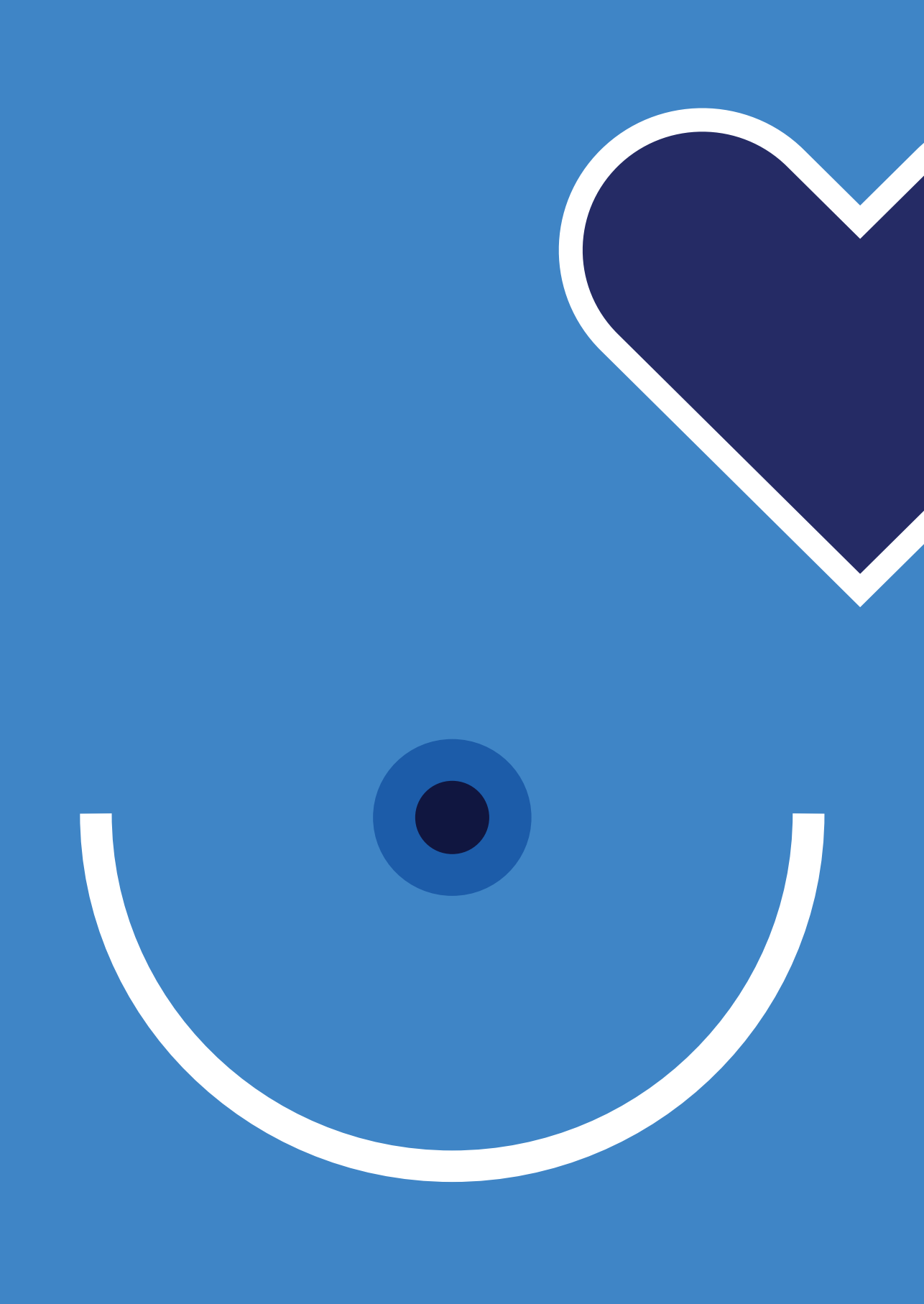


Chapter 1

General introduction and outline

Background

Breast cancer is the most frequently diagnosed cancer in women worldwide, and accounts for 25% of all female cancer cases[1]. In 2012, almost 1.7 million people were diagnosed with breast cancer worldwide[1]. Breast cancer incidence rates are high in more developed areas including North America, Northern and Western Europe, Singapore, and Australia (Figure 1)[1].

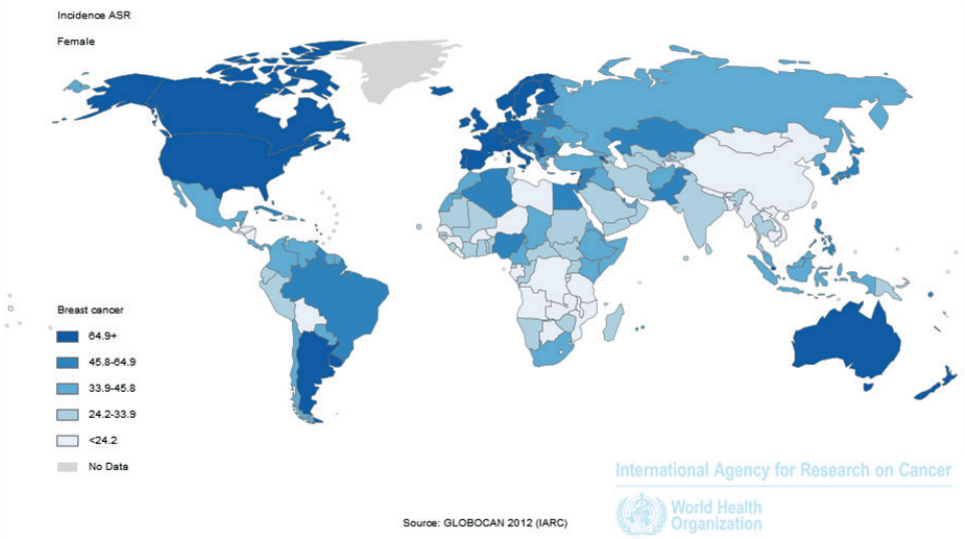


Figure 1. Breast cancer incidence worldwide in 2012. Estimated age-standardized rates per 100,000 (data source: reference[1]).

Global breast cancer incidence rates vary by prevalence of risk factors and access to mammography screening programs[2]. The risk of breast cancer increases with age and is affected by long-term exposure to female hormones and reproductive factors such as early age at menarche, higher age at menopause, nulliparity, higher age at first childbirth, breast feeding, and recent use of hormone replacement therapy (combined estrogen and progestin)[2]. Early age at full-term pregnancy, multiparity, and breastfeeding are associated with a lower risk of breast cancer[2]. Lifestyle related risk factors include adult weight gain and high body mass index (for postmenopausal breast cancer), physical inactivity, and high alcohol intake[2]. Furthermore, around 5% to 10% of breast cancers are caused by genetic factors including mutations in the BReast CAncer (BRCA) genes 1 and 2[3].

Breast cancer death rates have decreased in North America and in Northern and Western Europe since approximately 1990 (Figure 2). This has been mostly attributed to the introduction of breast cancer screening, improved diagnostic breast imaging (digital mammography, magnetic resonance imaging), and improved treatment modalities including more effective and increased use of systemic treatment[4-6]. In contrast to the West, breast cancer death rates have increased in most Asian countries over the last two decades (Figure 2)[7].

The combination of high breast cancer incidence rates and decreased breast cancer mortality rates in more developed countries has resulted in a large group of breast cancer survivors. In 2012, there were over 3 million women who survived breast cancer at least five years worldwide[1]. Many of these women will die of conditions other than breast cancer. Cardiovascular disease (CVD) is one of the most important causes of death in the general population worldwide[8], and is also an important cause of death following breast cancer[9].

Cardiovascular disease in breast cancer patients

The risk of CVD in breast cancer patients is increased by exposure to cardiotoxic cancer therapies including radiation therapy[10,11], chemotherapy[12,13], trastuzumab[14,15], and aromatase inhibitors[16]. Breast cancer patients with pre-existing cardiovascular risk factors have the highest risk of treatment induced cardiotoxicity[17,18].

The majority (>60%) of breast cancer patients undergo radiation therapy after surgery. The goal of radiation therapy is eradication of malignant cancer cells with a minimum amount of damage to surrounding normal tissue. Inevitably, however, radiation therapy involves some radiation exposure to normal tissue within the chest including the heart, particularly in the case of irradiation of left-sided breast cancer and/or internal mammary lymph nodes[19]. Radiation-induced heart damage is characterized by both acute and chronic changes in cardiac tissue, including cardiomyopathy, coronary artery disease, valvular disease, pericardial disease, and arrhythmias[20]. The incidence and onset of coronary artery disease linearly increases with the mean heart radiation dose: 7.4% increase per Gray irradiation without an apparent threshold[21]. Generally, the relative risk of death from circulatory disease is increased with 25% due to radiation therapy[10,11,21]. Radiation-induced CVD can result in symptoms within five years after radiation therapy for breast cancer, however, mostly after more than ten years after irradiation[10,11,21].

Breast cancer patients considered for adjuvant chemotherapy may undergo treatment with anthracycline-based chemotherapy including doxorubicin and epirubicin. Anthracyclines are associated with an increased risk of decreased left ventricular ejection fraction (LVEF) and clinical heart failure, starting during therapy, or early or late after therapy[12,22].

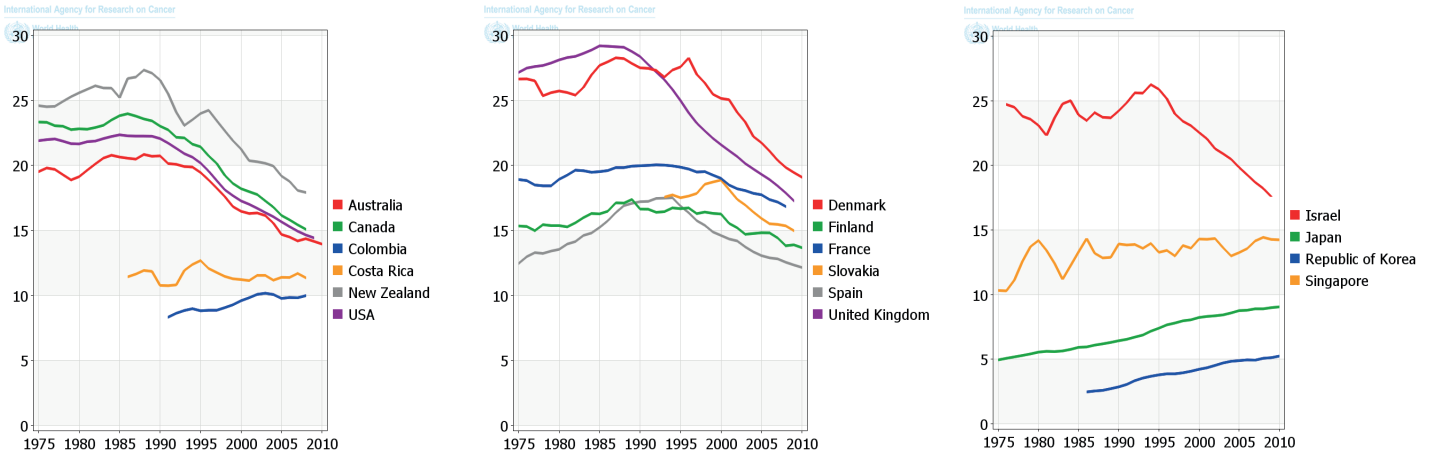


Figure 2. Trends in age-standardized mortality rate per 100,000 persons from breast cancer in selected countries including North America (left), Northern and Western Europe (middle), and Singapore (right) (data source: reference[1]).

Anthracyclines can cause type I irreversible cardiotoxicity characterized by cardiomyocyte loss[23]. The most commonly accepted pathophysiological mechanism of anthracycline-induced cardiotoxicity is the oxidative stress hypothesis: free oxygen radicals are generated and through peroxidation of the cell membrane, cardiomyocytes are damaged[23]. Anthracycline-induced cardiotoxicity is dose-dependent[12]. For example, the percentage of congestive heart failure after doxorubicin was 2% among patients with a cumulative dose of 300 mg/m^2 and 8% among patients with a cumulative dose of 500 mg/m^2 [24]. In a systematic review on cardiotoxicity of anthracycline-based regimens, it was reported that therapy with anthracyclines increase the risk of cardiotoxicity fivefold compared to therapy without anthracyclines[12].

Trastuzumab is a targeted therapy used to treat women with human epidermal growth factor receptor 2 (HER2) positive breast cancer (approximately one in five patients)[25]. Trastuzumab was the first HER2 monoclonal antibody approved by the United States Food and Drug Administration in 1998[26]. Initially, it was used to treat metastatic HER2 positive breast cancer. Since 2004, trastuzumab is also used as adjuvant therapy for early breast cancer and has substantially improved survival for women with HER2 positive breast cancer[26]. Cardiotoxicity, however, is a serious adverse effect[27,28]. Trastuzumab is associated with a decrease in LVEF and heart failure, especially during the course of therapy[27,28]. The risk of heart failure is four times higher in patients treated with trastuzumab alone and seven times higher in patients treated with anthracycline plus trastuzumab[29,30]. The exact mechanisms of trastuzumab-induced cardiotoxicity are unclear. Trastuzumab-induced cardiotoxicity is often reversible with trastuzumab interruption and clinical manifestations of trastuzumab-induced cardiotoxicity can be reduced with heart failure therapies[29,31].

Aromatase inhibitors can be indicated as adjuvant treatment for postmenopausal women with estrogen-receptor and/or progesterone-receptor positive early breast cancer[32]. Aromatase inhibitors reduce estrogen concentrations by inhibiting the conversion of androgens to estradiol by the aromatase enzyme, mainly in fat tissue[16]. Treatment with aromatase inhibitors is associated with 30% higher risk of CVD compared to treatment with tamoxifen[33]. Tamoxifen (a selective estrogen-receptor modulator) is, however, thought to have a cardioprotective effect as it is associated with reduced low-density lipoprotein cholesterol and homocysteine levels[16,34]. Therefore, it is unclear if the increased risk of CVD observed in trials with aromatase inhibitors is due to the cardiotoxic effect of aromatase inhibitors or due to the cardioprotective effect of tamoxifen[16].

Traditional risk factors of CVD, associated with a higher risk of therapy-induced cardiotoxicity, include higher age, present smoking, diabetes, hypercholesterolemia, hypertension, physical inactivity, obesity, family with CVD, and a history of CVD[17,18,35].

Calcification scoring on planning CT scans

Coronary artery calcification (CAC) and thoracic aortic calcification (TAC) are markers of atherosclerosis[36,37]. CAC, measured on cardiac computed tomography (CT) scans, has been shown to be an independent predictor of CVD events and mortality[38]. CAC can be detected in the left main coronary artery, as well as the left descending, the left circumflex, and the right coronary artery[39]. The amount of CAC is most commonly expressed as the Agatston score and categorized scores are clinically used to express the risk of a CVD event[40,41]. Asymptomatic individuals with CAC (Agatston) scores of 100 or higher, and without other CVD risk factors, have a ten-year risk of a CVD event of 20% compared to 1% in asymptomatic individuals without CAC and no other CVD risk factors[38]. TAC, measured on cardiac CT scans, is associated with an increased risk of coronary heart disease, independent of CAC and other CVD risk factors[42,43]. Women with TAC have a nearly threefold higher risk of coronary heart disease compared to women without TAC[42].

Mostly, CAC and TAC are quantified on cardiac CT scans. Electrocardiogram (ECG)-triggering minimizes cardiac motion and enables good visualization. CAC and TAC can also be quantified by the use of chest CT scans that visualize the heart. Previous studies have shown that CAC scores determined on low radiation dose diagnostic CT scans (not ECG-triggered, performed for lung cancer screening) are predictive of future CVD events[44-46]. All breast cancer patients that receive radiation therapy routinely undergo a non-contrast non-ECG-triggered enhanced CT scan of the breasts for radiotherapy planning, on which the heart is visible. As the coronary arteries and aorta are visualized on these scans, calcifications in these areas can be quantified without exposing patients to additional radiation and without additional costs (Figure 3).

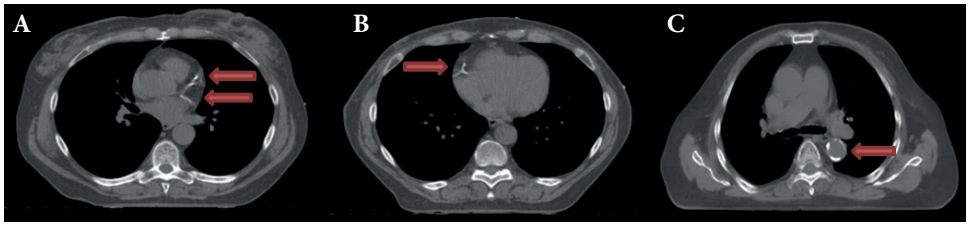


Figure 3. Radiotherapy planning CT scans with calcifications (shown white and highlighted with a red arrow) in the left anterior descending artery (**A**, highest red arrow), left circumflex artery (**A**, lowest red arrow), right coronary artery (**B**), and thoracic aorta (**C**).

In clinical practice, CAC and TAC scoring is performed manually by radiologists using a threshold of 130 Hounsfield Units. Manual calcification annotation is time-consuming and tedious. Also, in the case of non-ECG-triggered planning CT scans, the presence of artifacts caused by cardiac motion, high noise levels caused by lower radiation dose, and partial volume effects caused by decreased image resolution may impede calcification scoring[47,48]. Several algorithms for automatic coronary calcification scoring have been proposed to overcome these issues[49-51]. Before the investigations described in this thesis, it was unknown if planning CT scans of the breasts can reliably be used for automatic calcification scoring. Also, the prevalence of CAC and TAC was unknown among breast cancer patients.

Cardiovascular disease risk in Asian breast cancer patients (Singapore)

The multi-ethnic population of Singapore comprises mainly Chinese, Malay, and Indian people. Like in the West, breast cancer is the most common diagnosed cancer in women, and breast cancer survival rate is high with over 70% of patients, diagnosed between 2008 and 2012, surviving at least five years[1]. Ethnic differences in breast cancer survival have been reported. Malay patients have a higher risk of all-cause mortality compared to Chinese patients, regardless of age at diagnosis, and tumor and treatment characteristics[52]. In addition, ethnic differences in the risk of CVD have been reported. The risk of death from CVD among patients with acute myocardial infarction (without breast cancer) in Singapore is highest among Malay followed by Chinese and Indian[53]. Indians have the highest rate of diabetes[54], while the rate of obesity is highest among Malay[55]. Moreover, Indians have the highest level of lipoprotein A which is a causal genetic risk factor for CVD[56]. Variation in the risk of death from CVD by ethnic origin in Singapore may be due to genetic and/or lifestyle differences[57]. Before the start of the investigation described in this thesis, it was unknown if ethnic differences exist in the risk of CVD in breast cancer patients from Singapore.

Objectives of the thesis

In the light of the above, this thesis has the following main objectives:

1. To examine the absolute risk of hospitalization or death due to CVD in breast cancer patients in different ethnic settings.
2. To investigate determinants of death from CVD following breast cancer in different ethnic settings.
3. To examine the risk of hospitalization or death due to CVD in breast cancer patients compared to women without breast cancer, accounting for the baseline CVD risk, in the Netherlands.
4. To examine the prevalence and reproducibility of automatically detected CAC and TAC on radiotherapy planning CT scans in Western (*i.e.* the Netherlands) and Asian (*i.e.* Singapore) breast cancer patients.

Outline of the thesis

In Chapter 2, the literature on the risk and risk factors of death from CVD following breast cancer is systematically reviewed. In Chapter 3, trends trends in the risk of hospitalization or death due to CVD following breast cancer in the Netherlands are investigated. In Chapter 4, the risk of hospitalization or death due to CVD following breast cancer in the Netherlands is evaluated while accounting for a woman's baseline risk of CVD. In Chapter 5, the risk of death from CVD following breast cancer among women living in Singapore is investigated, and it is studied whether the risk varied by age and ethnic orgin. Chapter 6 included 1) the reproducibility of automatic CAC scoring compared to manual CAC scoring, and 2) the association between automatically detected CAC and traditional CVD risk factors. In Chapter 7, the prevalence and quantity of automatically detected CAC and TAC on radiotherapy planning CT scans are investigated using a new software based on deep learning in Western (*i.e.* the Netherlands) and Asian (*i.e.* Singapore) breast cancer patients. Finally, in Chapter 8, the results are summarized and future perspectives are discussed.

Knowledge obtained in this thesis on the risk of CVD following breast cancer is expected to give insight in the magnitude of the problem and may provide clues to further optimize and personalize breast cancer treatment by systematically taking a breast cancer patient's risk of CVD into account before, during, and after treatment. In addition, knowledge obtained in this thesis may be used to design studies to improve identification of breast cancer patients who are at increased risk of CVD, for whom it is important to weigh the benefits of systemic therapy and radiotherapy in terms of tumor control against the risks of toxicity, including cardiotoxicity.

References

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.1, cancer incidence and mortality worldwide: IARC CancerBase. 2014; 11.
2. Colditz GA, Baer HJ, Tamimi RM. Breast cancer. In: Schottenfeld D, Fraumeni JF Jr, ed. *Cancer epidemiology and prevention*. 3rd ed. New York: Oxford University Press; 2006: 995-1012.
3. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. *Lancet Oncol*. 2001; 2 (3): 133-140.
4. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. 2005; 353 (17): 1784-1792.
5. Bosetti C, Bertuccio P, Levi F, Chatenoud L, Negri E, La Vecchia C. The decline in breast cancer mortality in Europe: An update (to 2009). *Breast*. 2012; 21 (1): 77-82.
6. Althuis MD, Dozier JM, Anderson WF, Devesa SS, Brinton LA. Global trends in breast cancer incidence and mortality 1973-1997. *Int J Epidemiol*. 2005; 34 (2): 405-412.
7. Coughlin SS, Ekwueme DU. Breast cancer as a global health concern. *Cancer Epidemiol*. 2009; 33 (5): 315-318.
8. World Health Organization. Global health observator. http: //www.who.int/gho. Updated 2017. Accessed October/11, 2017.
9. Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD. Cardiovascular disease mortality among breast cancer survivors. *Epidemiology*. 2016; 27 (1): 6-13.
10. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, et al. 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 8,135 women in 22 randomized trials. *Lancet*. 2014; 383 (9935): 2127-2135.
11. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomized trials. *Lancet*. 2005; 366 (9503): 2087-2106.
12. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: Systematic review and meta-analysis of randomized controlled trials. *BMC Cancer*. 2010; 10: 337-2407-10-337.
13. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments. *Nat Rev Cardiol*. 2015; 12 (9): 547-558.
14. Suter TM, Cook-Bruns N, Barton C. Cardiotoxicity associated with trastuzumab (herceptin) therapy in the treatment of metastatic breast cancer. *Breast*. 2004; 13 (3): 173-183.
15. Suter TM, Procter M, van Veldhuisen DJ, et al. Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. *J Clin Oncol*. 2007; 25 (25): 3859-3865.
16. Foglietta J, Inno A, de Iuliis F, et al. Cardiotoxicity of aromatase inhibitors in breast cancer patients. *Clin Breast Cancer*. 2017; 17 (1): 11-17.

17. Zamorano JL, Lancellotti P, Rodriguez Munoz D, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC committee for practice guidelines: The task force for cancer treatments and cardiovascular toxicity of the European society of cardiology (ESC). *Eur Heart J*. 2016; 37 (36): 2768-2801.
18. Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American society of clinical oncology clinical practice guideline. *J Clin Oncol*. 2017; 35 (8): 893-911.
19. Zagar TM, Cardinale DM, Marks LB. Breast cancer therapy-associated cardiovascular disease. *Nat Rev Clin Oncol*. 2015.
20. Taunk NK, Haffty BG, Kostis JB, Goyal S. Radiation-induced heart disease: Pathologic abnormalities and putative mechanisms. *Front Oncol*. 2015; 5: 39.
21. Darby SC, Ewertz M, Hall P. Ischemic heart disease after breast cancer radiotherapy. *N Engl J Med*. 2013; 368 (26): 2527.
22. Stoodley P, Richards D, Meikle S, Clarke J, Thomas L. Acute effects of anthracycline therapy on cardiac function. *Heart Lung Circul*. 2010; 19: S162.
23. Sawyer DB, Peng X, Chen B, Pentassuglia L, Lim CC. Mechanisms of anthracycline cardiac injury: Can we identify strategies for cardioprotection? *Prog Cardiovasc Dis*. 2010; 53 (2): 105-113.
24. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: A retrospective analysis of three trials. *Cancer*. 2003; 97 (11): 2869-2879.
25. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011; 365 (14): 1273-1283.
26. Florido R, Smith KL, Cuomo KK, Russell SD. Cardiotoxicity from human epidermal growth factor receptor-2 (HER2) targeted therapies. *J Am Heart Assoc*. 2017; 6 (9): 10.1161/JAHA.117.006915.
27. Advani PP, Ballman KV, Dockter TJ, Colon-Otero G, Perez EA. Long-term cardiac safety analysis of NCCTG N9831 (alliance) adjuvant trastuzumab trial. *J Clin Oncol*. 2016; 34 (6): 581-587.
28. Chavez-MacGregor M, Zhang N, Buchholz TA, et al. Trastuzumab-related cardiotoxicity among older patients with breast cancer. *J Clin Oncol*. 2013; 31 (33): 4222-4228.
29. Moja L, Brambilla C, Compagnoni A, Pistotti V. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev*. 2006 (4).
30. Bowles EJ, Wellman R, Feigelson HS, et al. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: A retrospective cohort study. *J Natl Cancer Inst*. 2012; 104 (17): 1293-1305.
31. Suter TM, Procter M, van Veldhuisen DJ, et al. Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. *J Clin Oncol*. 2007; 25 (25): 3859-3865.

32. Kwaliteitsinstituut voor de gezondheidszorg CbO VvIK. Landelijke richtlijn mammacarcinoom. 2012.
33. Amir E, Seruga B, Niraula S, Carlsson L, Ocana A. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: A systematic review and meta-analysis. *J Natl Cancer Inst*. 2011; 103 (17): 1299-1309.
34. Love RR. Antiestrogen chemoprevention of breast cancer: Critical issues and research. *Prev Med*. 1991; 20 (1): 64-78.
35. D'Agostino RB S, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham heart study. *Circulation*. 2008; 117 (6): 743-753.
36. Kalsch H, Lehmann N, Mohlenkamp S, et al. Prevalence of thoracic aortic calcification and its relationship to cardiovascular risk factors and coronary calcification in an unselected population-based cohort: The Heinz Nixdorf recall study. *Int J Cardiovasc Imaging*. 2013; 29 (1): 207-216.
37. Budoff MJ, Nasir K, Kinney GL, et al. Coronary artery and thoracic calcium on non-contrast thoracic CT scans: Comparison of ungated and gated examinations in patients from the COPD gene cohort. *J Cardiovasc Comput Tomogr*. 2011; 5 (2): 113-118.
38. Blaha MJ, Budoff MJ, DeFilippis AP, et al. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: Implications for the JUPITER population from MESA, a population-based cohort study. *Lancet*. 2011; 378 (9792): 684-692.
39. Madhavan MV, Tarigopula M, Mintz GS, Maehara A, Stone GW, Genereux P. Coronary artery calcification: Pathogenesis and prognostic implications. *J Am Coll Cardiol*. 2014; 63 (17): 1703-1714.
40. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M,Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990; 15 (4): 827-832.
41. Budoff MJ, Shaw LJ, Liu ST, et al. Long-term prognosis associated with coronary calcification: Observations from a registry of 25,253 patients. *J Am Coll Cardiol*. 2007; 49 (18): 1860-1870.
42. Budoff MJ, Nasir K, Katz R, et al. Thoracic aortic calcification and coronary heart disease events: The multi-ethnic study of atherosclerosis (MESA). *Atherosclerosis*. 2011; 215 (1): 196-202.
43. Iribarren C, Sidney S, Sternfeld B, Browner WS. Calcification of the aortic arch: Risk factors and association with coronary heart disease, stroke, and peripheral vascular disease. *JAMA*. 2000; 283 (21): 2810-2815.
44. Wu MT, Yang P, Huang YL, et al. Coronary arterial calcification on low-dose ungated MDCT for lung cancer screening: Concordance study with dedicated cardiac CT. *AJR Am J Roentgenol*. 2008; 190 (4): 923-928.
45. Jacobs PC, Gondrie MJ, van der Graaf Y, et al. Coronary artery calcium can predict all-cause mortality and cardiovascular events on low-dose CT screening for lung cancer. *AJR Am J Roentgenol*. 2012; 198 (3): 505-511.

46. Chiles C, Duan F, Gladish GW, et al. Association of coronary artery calcification and mortality in the national lung screening trial: A comparison of three scoring methods. *Radiology*. 2015; 276 (1): 82-90.

47. Raggi P. Coronary calcium on electron beam tomography imaging as a surrogate marker of coronary artery disease. *Am J Cardiol*. 2001; 87 (4A): 27A-34A.

48. Takx RA, de Jong PA, Leiner T, et al. Automated coronary artery calcification scoring in non-gated chest CT: Agreement and reliability. *PLoS One*. 2014; 9 (3): e91239.

49. Wolterink JM, Leiner T, Takx RA, Viergever MA, Isgum I. Automatic coronary calcium scoring in non-contrast-enhanced ECG-triggered cardiac CT with ambiguity detection. *IEEE Trans Med Imaging*. 2015; 34 (9): 1867-1878.

50. Brunner G, Chittajallu DR, Kurkure U, Kakadiaris IA. Toward the automatic detection of coronary artery calcification in non-contrast computed tomography data. *Int J Cardiovasc Imaging*. 2010; 26 (7): 829-838.

51. Isgum I, Prokop M, Niemeijer M, Viergever MA, van Ginneken B. Automatic coronary calcium scoring in low-dose chest computed tomography. *IEEE Trans Med Imaging*. 2012; 31 (12): 2322-2334.

52. Bhoo-Pathy N, Hartman M, Yip CH, et al. Ethnic differences in survival after breast cancer in Southeast Asia. *PLoS One*. 2012; 7 (2): e30995.

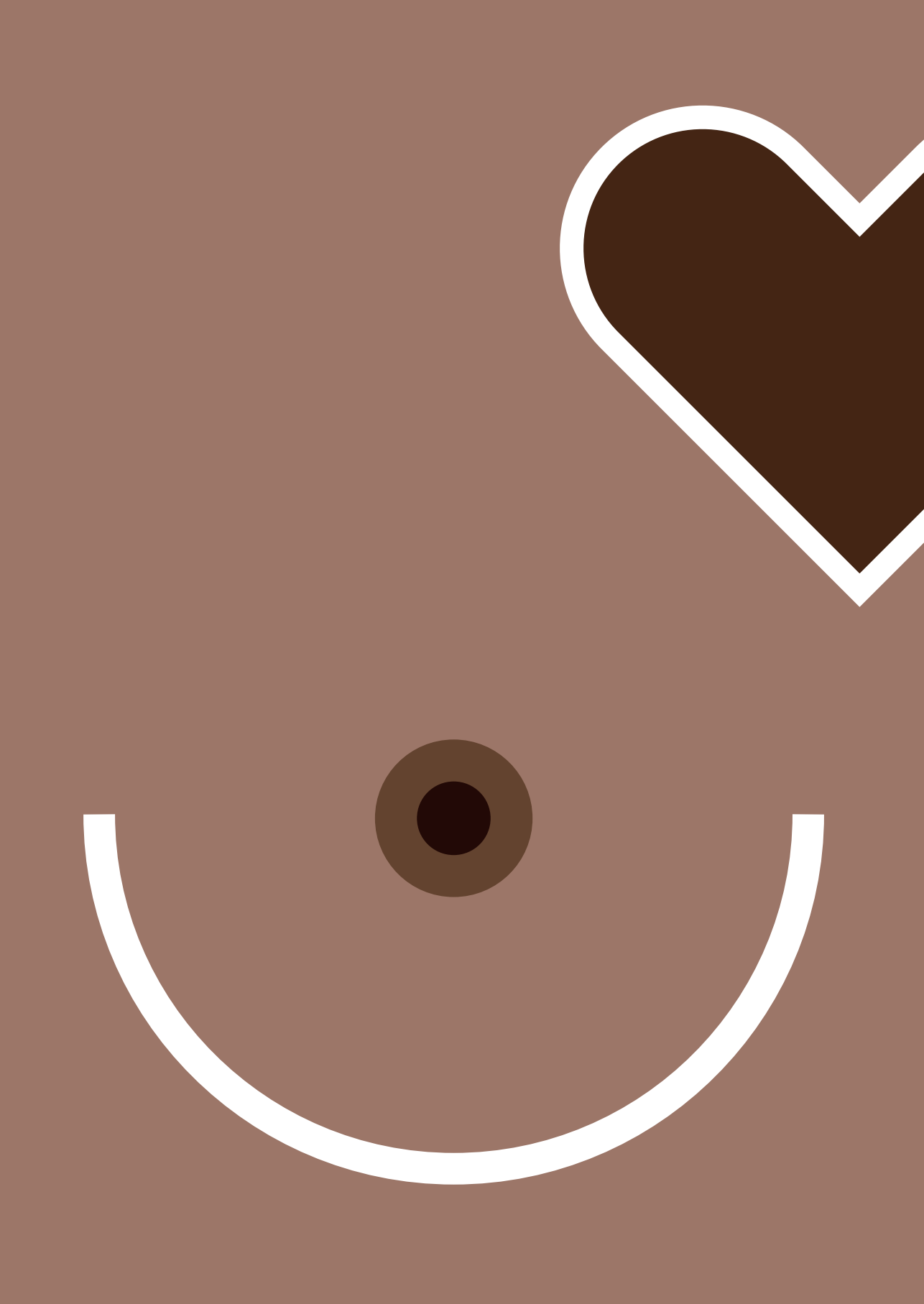
53. de Carvalho LP, Gao F, Chen Q, et al. Differences in late cardiovascular mortality following acute myocardial infarction in three major Asian ethnic groups. *Eur Heart J Acute Cardiovasc Care*. 2014; 3 (4): 354-362.

54. Hughes K, Yeo PP, Lun KC, et al. Cardiovascular diseases in Chinese, Malays, and Indians in Singapore. II. differences in risk factor levels. *J Epidemiol Community Health*. 1990; 44 (1): 29-35.

55. Pan A, Malik VS, Hu FB. Exporting diabetes mellitus to Asia: The impact of western-style fast food. *Circulation*. 2012; 126 (2): 163-165.

56. Hughes K, Aw TC, Kuperan P, Choo M. Central obesity, insulin resistance, syndrome X, lipoprotein (a), and cardiovascular risk in Indians, Malays, and Chinese in Singapore. *J Epidemiol Community Health*. 1997; 51 (4): 394-399.

57. Sasayama S. Heart disease in Asia. *Circulation*. 2008; 118 (25): 2669-2671.



Chapter 2

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

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M. Hartman, D.E. Grobbee, H.M. Verkooijen

Breast Cancer Research and Treatment 2017

Abstract

Purpose

Breast cancer incidence and survival is high, which results in high prevalence of breast cancer survivors. The risk of 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 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 majority of the studies. Studies were heterogeneous in design, study population, length of follow-up, CVD outcomes, and risk factors. 1.6% to 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.

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 CVD following breast cancer is increased in women exposed to cardiotoxic treatments such as (left-sided) radiotherapy, anthracycline-based 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 cardiotoxicity 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. Full text 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 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 (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) [a]

	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 tumor[Title/Abstract] OR tumors[Title/Abstract] OR tumour[Title/Abstract] OR tumours[Title/Abstract] OR malignancy[Title/Abstract] OR malignancies[Title/Abstract] OR neoplasm[Title/Abstract] OR neoplasms[Title/Abstract] OR neoplasms[Mesh Terms]) AND (breast[Title/Abstract] OR breasts[Title/Abstract] OR mamma[Title/Abstract] OR mamma*[Title/Abstract])
#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 mortalities[Title/Abstract] OR death[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

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

Results

The systematic search yielded 10,170 citations including 5,911 unique articles, which were screened for title and abstract using the predefined inclusion and exclusion criteria (Figure 1). After screening the full-text of 39 articles, 27 were excluded for the following reasons: published before the 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 studies had the maximum score on the quality assessment for selection, comparability, and outcome[5,8,17,18,20-22,26] (Figure 2). Nichols et al. (2009)[15] article scored low 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[15]. Berkman et al. (2014)[6], Darby et al. (2005)[23], and Giordano et al. (2005)[24] scored low on comparability as the hazard ratios were not adjusted for factors other than age at diagnosis, the CVD mortality rates were unadjusted, and the hazard ratios were only adjusted for other factors than age at diagnosis, respectively. Hooning et al. (2006)[25] and McCullough et al. (2016)[16] scored low 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. (2016)[8] included 1,413 women with primary *in situ* or invasive breast cancer diagnosed in the United States (US) between 1996 and 1997, and 1,411 age-matched women from the general population (Table 2). Mean age at breast cancer diagnosis and reference date for women from the general population was 59 years and 57 years respectively. During the follow-up time, which ranged between 0.2 to 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 seven years post-diagnosis than women from the general population (Table 3).

Riihimäki et al. (2012)[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 follow-up 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. (2011)[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. (2006)[25] included 7,425 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. (2009)[20] included 1,245 women with a mean age of 57.4 years at diagnosis with primary lymph node-negative 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) times higher risk of dying of CVD, adjusted for clinical, tumor, and treatment characteristic (Table 3).

Darby et al. (2005)[23] included 308,861 women between 20 and 79 years of age at diagnosis with primary *in situ* or invasive breast cancer in the US 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). Over 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. (2005)[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 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. (2017)[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. (2016)[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 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. (2014)[6] included 54,518 white and 6,113 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 to 49, 50 to 59, 60 to 69, and ≥70 years, respectively.

Solanki et al. (2016)[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. (2016)[16] included 4,452 women diagnosed with primary invasive breast cancer in Switzerland between 1992 and 2011 who had scored their diet according to the American Cancer Society (ACS) guidelines before breast cancer diagnosis, and of these, 2,152 women scored their diet also at least one year after breast cancer diagnosis (Table 2). The ACS guidelines recommend following the general food-based guidelines for primary cancer prevention, which includes eating a plant-based 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 ACS 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. (2009)[15] included 5,791 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. (2009) 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/m^2): <18.5) and obesity (BMI: ≥30) respectively, compared with women with a pre-diagnosis normal weight (BMI: 18.5-24.9) (Table 3).

Veal et al. (2017)[22] included 1,925 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).

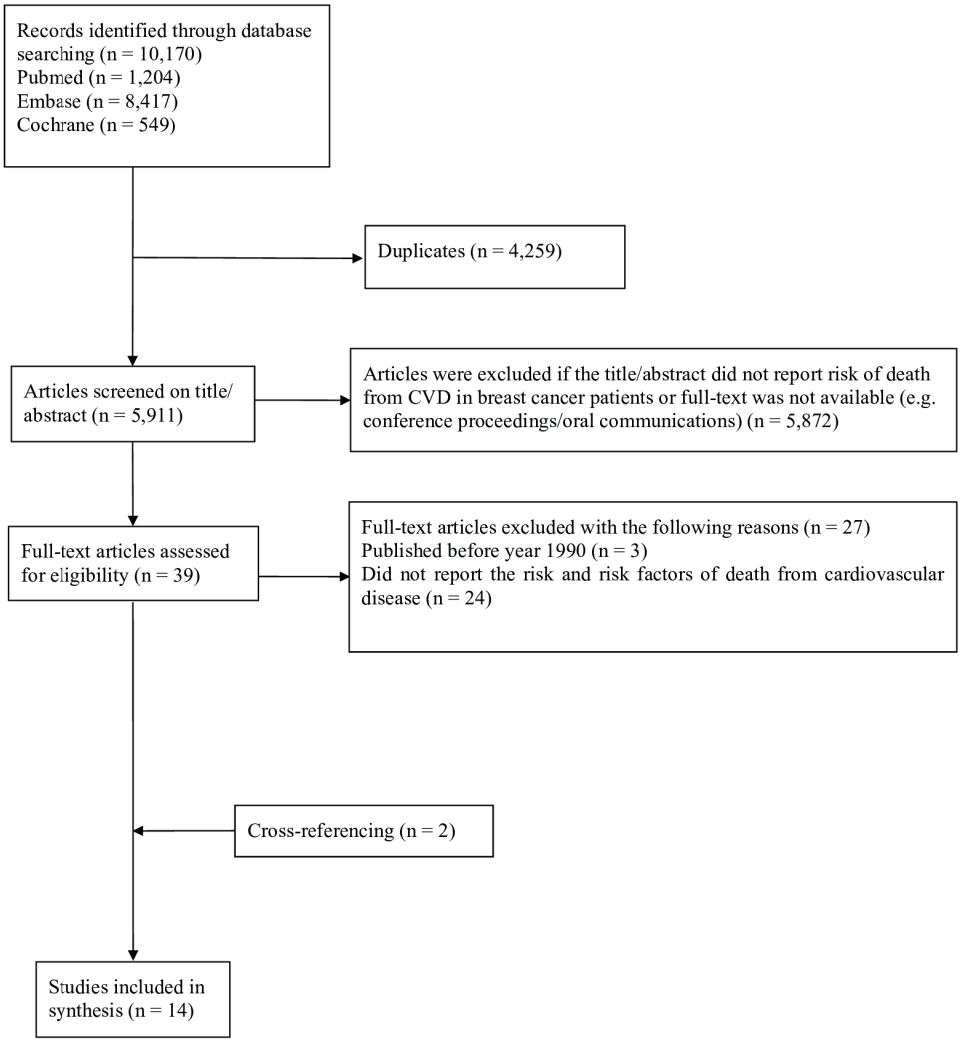


Figure 1. Flowchart of the systematic review on the risk of death from cardiovascular disease in breast cancer patients

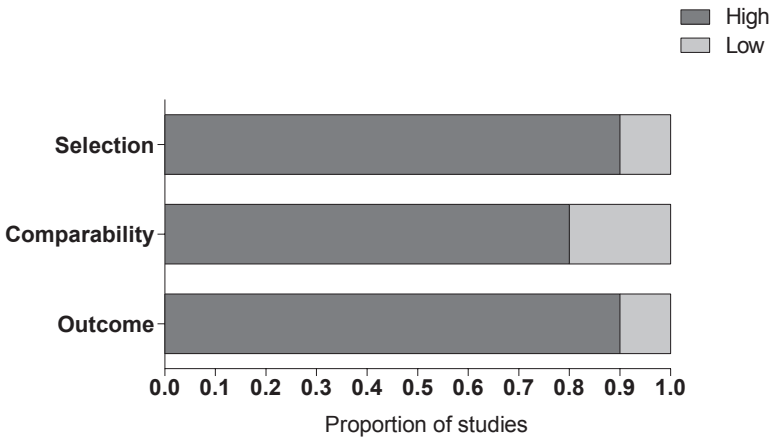


Figure 2. Quality assessment by the Newcastle Ottawa Quality Assessment Scale Selection. Based on the representativeness of the breast cancer cohort and ascertainment of breast cancer. Comparability was based on the comparability of cohorts on the basis of the design or analysis (corrected for age at diagnosis). Outcome was based on the assessment of death from cardiovascular disease, on the length of follow-up (≥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.

Table 2. Characteristics and risk of cardiovascular disease mortality of the fourteen articles included in the systematic review

First author, publication year, country	Type of breast cancer, number of patients	Age at diagnosis or reference date in years	Year of diagnosis, years of follow-up	ICD-9 and/ or ICD-10 codes of CVD mortality outcomes	Percentage of deaths due to any cause, CVD, and BC (percentage of total)	
CVD mortality in breast cancer patients compared with the general population						
Bradshaw, 2016, US[a]	Primary in situ or invasive; 1,413 Without BC; 1,411[c]	59 or 57[d]	1996-1997, 13.5[e]	ICD-9: 394.9, 402.9, 410, 414.0, 427.5 ICD-10: I10, I11.9, I21.9, I25.1, I25.4,I46.9	Women with BC Any cause: 29.4 CVD: 9.4 BC: 9.6	Women without BC Any cause: 17.2 CVD: 7.4 BC: 0.1
Riihimäki, 2012, Sweden[a]	Primary invasive; 122,217 Women without BC; 3,554,255 [h]	-	1987-2006, 19[e]	ICD-9: 410, 411–414, 420–427, 428, 430–438, 440-448 ICD-10: I20, I21–I22, I23–I25, I30–I49, I50, I52, I60–I69, I70–I79	Women with BC Any cause: 39.3 CVD: 10.4 BC: 18.1	Women without BC Any cause: 16.7 CVD: 7.5 BC: -
CVD mortality in breast cancer patients by patient, tumor and treatment characteristics						
Colzani, 2011, Sweden[a]	Primary invasive I- III; 12,850	<75	1990-2006, 10[e]	ICD-9: 390-459 ICD-10: I00-I99	Any cause: CVD: BC:	14.4 1.8 9.2
Hooning, 2006, the Netherlands[f]	Invasive I-IIIA; 7,425	≤70	1970-1986, 13.8[b]	ICD-9: 410–459	Any cause: CVD: BC:	56.0 5.3 42.6
CVD mortality in patients with left-sided breast cancer compared to right-sided breast cancer						
Bouchardy, 2009, Switzerland[a]	Primary invasive lymph node-negative; 1,245	57.4[d]	1980-2004, 7.7[d]	ICD-10: I00-I99	Any cause: CVD: BC:	12.4 2.2 7.3
Darby, 2005, US[a]	Primary in situ or invasive; 308,861	20-79	1973-2001, 29[e]	ICD-9: 390–398, 402, 404, 410, 411–414, 415–429	Any cause: CVD: BC:	29.5 4.2 16.8
Giordano, 2005, US[a]	Primary in situ or invasive; 24,785	56.9 ± 13.2 [d]	1973-1988, 9.3[b]	ICD-9: 410-414 ICD-10: I20–I25	Any cause: CVD: BC:	- - -

Haque; 2017, US[a]	DCIS, 140,914	≤60 and >60	1973-2002, 11.5 (IQR: 6.8-15.1)[b]	-	Any cause: CVD: BC:	- - -
Merzenich, 2016, Germany[g]	Primary in situ or invasive; 11,982	59[d] (range: 18-101)	1998-2008, 6.5 (0-15)[b]	ICD-10: I20-I25, I34-I37, I44-I50	Any cause: CVD: BC:	20.6 2.3 10.2
CVD mortality in breast cancer patient with ethnic differences						
Berkman, 2014, US[a]	Primary DCIS; 54,518 white women; 6,113 black women	≥40	1978-2010, 9.2[b]	ICD-10: I00–I09, I11, I13, I20–I51, I60–I69, I70, I72–178	Any cause: CVD: BC:	18.0 6.0 1.5
Solanki, 2016, US[a]	Primary in situ or invasive I-III; 462,005 NHW; 44,531 API	NHW: 61.2 ± 13.7[d] API: 56.3 ± 13.1[d]	1991-2011, NHW: 6.8 ± 4.9[d], 4 (2-6)[b] API: 6.7 ± 5.0[d], 3 (2-5)[b]	ICD-9: 390-459	Non-Hispanic white Any cause: 23.8 CVD: 5.5 BC: 10.0	Asian and Pacific Islander Any cause: 15.4 CVD: 2.6 BC: 8.2
CVD mortality in breast cancer patients by diet, body weight, and health-behaviors						
McCullough, 2016, Switzerland[g]	Primary invasive I- III; 4,452 for pre-diagnostic of which 2,152 were included in the ≥1 year post-diagnostic analysis	70.7 ± 7.2[d]	1992-2011, pre-diagnostic diet 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; 5,791	58.4 ± 10.0[d]	1988-1999, 6.4 ± 1.2[d]	ICD-10: I00–99	Any cause: CVD: BC:	7.3 1.6 2.1
Veal, 2017, US[g]	Primary DCIS; 1,925	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

Abbreviations: 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, 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

Table 3. Risk factors of death from cardiovascular disease in women diagnosed with breast cancer

First author, year of publication	Statistical analysis	Categories	Cause of death (outcome)	Risk of death HR (95% CI)	Covariates
CVD mortality in breast cancer patients compared with the general population					
Bradshaw, 2016	Competing risk	General population	CVD	1.0 (ref)	Age, menopausal status, CVD risk factors
		Breast cancer patients diagnosed ≤7 years		0.6 (0.4-0.9)	
		General population	CVD	1.0 (ref)	
		Breast cancer patients diagnosed >7 years		1.9 (1.4-2.7)	
		General population	CVD	1.0 (ref)	
		Breast cancer patients with RT		1.1 (0.8-1.6)	
		General population	CVD	1.0 (ref)	
		Breast cancer patients without RT		1.3 (0.9-2.0)	
		General population	CVD	1.0 (ref)	
		Breast cancer patients with CT		1.4 (1.0-2.2)	
		General population	CVD	1.0 (ref)	
		Breast cancer patients without CT		1.1 (0.8-1.5)	
		General population	CVD	1.0 (ref)	
		Breast cancer patients with HT		1.2 (0.9-1.7)	
		General population	CVD	1.0 (ref)	
		Breast cancer patients without HT		1.2 (0.8-1.8)	
Riihimäki, 2012	Cox proportional hazard	General population	CVA	1.00 (ref)	Age, socioeconomic index, geographical region of residence
		Breast cancer patients		1.03 (1.00-1.07)	
		General population	AMI	1.00 (ref)	
		Breast cancer patients		1.01 (0.98-1.00)	
		General population	Other CHD	1.00 (ref)	
		Breast cancer patients		1.14 (1.10-1.19)	
		General population	Heart failure	1.00 (ref)	
		Breast cancer patients		1.29 (1.22-1.37)	
		General population	Other heart disease	1.00 (ref)	
		Breast cancer patients		1.24 (1.17-1.32)	
		General population	Arterial disease	1.00 (ref)	
		Breast cancer patients		0.95 (0.89-1.02)	
		General population	Complications of	1.00 (ref)	
		Breast cancer patients	CVD	1.12 (0.99-1.20)	

CVD mortality in breast cancer patients by patient, tumor and treatment characteristics						
Colzani, 2011	Flexible parametric survival models	Age at diagnosis	<45 45-54 55-64 65-74	CVD	0.3 (0.0-2.5) 1.00 (ref) 6.5 (2.8-14.6) 17.9 (8.0-39.7)	Clinical, tumor, treatment characteristics
		Calendar time at diagnosis	1990-94 1995-99 2000-06	CVD	2.1 (1.2-3.6) 1.6 (0.9-2.9) 1.00 (ref)	
		Treatment	Surgery Surgery + RT + HT Surgery + RT Surgery + RT + CT Surgery + CT Surgery + RT + CT + HT Surgery + HT Surgery + CT + HT	CVD	2.1 (1.2-3.8) 1.0 (ref) 1.4 (0.7-2.5) 0.6 (0.1-2.5) 2.0 (0.6-6.8) 0.7 (0.3-1.9) 2.2 (1.5-3.2) 1.0 (0.2-4.5)	
		Number of positive lymph nodes	0 1-3 ≥4	CVD	1.0 (ref) 2.0 (1.4-2.9) (1.0-3.4)	
		Estrogen-receptor Status	Negative Positive	CVD	1.0 (ref) 0.8 (0.5-1.3)	
		Tumor size (mm)	1-20 >20	CVD	1.0 (ref) 1.5 (1.1-2.1)	
Hooning, 2006	Cox proportional hazard	<u>Total study population</u> Age at diagnosis (continuous)		CVD	1.12 (1.10-1.14)	Clinical, tumor, treatment, characteristics
		Treatment	Surgery Surgery + RT Surgery + RT + CT Surgery + RT + HT	CVD	1.0 (ref) 2.03 (1.33-3.10) 1.47 (0.81-2.67) 1.70 (0.99-2.93)	
		Calendar time at diagnosis	1970-75 1976-80 1981-86	CVD	1.34 (0.93-1.92) 1.54 (1.11-2.14) 1.00 (ref)	

First author, year of publication	Statistical analysis	Categories		Cause of death (outcome)	Risk of death HR (95% CI)	Covariates
		10-year survivors				
		Age at diagnosis (continuous)		CVD	1.11 (1.09-1.13)	
		Treatment	Surgery	CVD	1.00 (ref)	
			Surgery + RT		2.08 (1.25-3.47)	
			Surgery + RT + CT		2.38 (1.18-4.77)	
			Surgery + RT + HT		2.42 (1.27-4.61)	
		Calendar time at diagnosis	1970-75	CVD	1.38 (0.89-2.14)	
			1976-80		1.62 (1.07-2.46)	
			1981-86		1.00 (ref)	
CVD mortality in breast cancer patients by laterality of the tumor						
Bouchardy, 2016	Cox proportional hazard	RT and right-sided tumor		CVD	1.00 (ref)	Clinical, tumor, and treatment characteristics
		RT and left-sided tumor			0.52 (0.24-1.12)	
		RT and outer quadrant		CVD	1.00 (ref)	
		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 mortality rates	RT on right-sided tumor		CVD	1.00 (ref)	No covariates
		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 Ischemic CVD	1.00 (ref)	
		RT on left-sided tumor			1.60 (1.26-2.02)	
		RT on right-sided tumor, aged 20-49 years at diagnosis		CVD	1.00 (ref)	
		RT on left-sided tumor, aged 20-49 years at diagnosis			1.54 (1.08-2.19)	
		RT on right-sided tumor, aged 50-59 years at diagnosis		CVD	1.00 (ref)	

		RT on left-sided tumor, aged 50-59 years at diagnosis			1.53 (1.19-1.98)	
		RT on right-sided tumor, aged 60-69 years at diagnosis		CVD	1.00 (ref)	
		RT on left-sided tumor, aged 60-69 years at diagnosis			1.40 (1.15-1.70)	
		RT on right-sided tumor, aged 70-79 years at diagnosis		CVD	1.00 (ref)	
		RT on left-sided tumor, aged 70-79 years at diagnosis			1.28 (0.87-1.90)	
		RT on right-sided tumor, white ethnic origin		CVD	1.00 (ref)	
		RT on left-sided tumor, white ethnic origin			1.39 (1.21-1.61)	
		RT on right-sided tumor, black ethnic origin		CVD	1.00 (ref)	
		RT on left-sided tumor, black ethnic origin			2.25 (1.36-3.72)	
		RT on right-sided tumor, other/ unknown ethnic origin		CVD	1.00 (ref)	
		RT on left-sided tumor, other/ unknown ethnic origin			1.30 (0.71-2.39)	
Giordano, 2005	Cox proportional hazard	Right-sided tumor, diagnosed in 1979		CVD	1.00 (ref)	No covariates
		Left-sided tumor, diagnosed in 1979			1.50 (1.19-1.87)	
		Right-sided tumor, diagnosed in 1988		CVD	1.00 (ref)	
		Left-sided tumor, diagnosed in 1988			0.79 (0.52-1.18)	
Haque, 2016	Cox proportional hazard	<u>Diagnosed 1973-82</u>				Clinical, tumor, treatment characteristics
		Right-sided tumor		CVD	1.00 (ref)	
		Left-sided tumor			1.30 (1.18-1.42)	
		Race	White	CVD	1.00 (ref)	
			African American		1.14 (0.94-1.36)	
			American Indian/ Asian/ Pacific Islander		0.83 (0.66-1.02)	
			Unspecified		0.47 (0.03-2.06)	
		Age at diagnosis	≤60	CVD	1.00 (ref)	
			>60		5.87 (5.30-6.50)	
		Marital status	Married	CVD	1.00 (ref)	
			Unmarried		1.87 (1.70-2.05)	
			Unknown		1.77 (1.29-2.37)	
		Right-sided tumor, <10 years since diagnosis		CVD	1.00 (ref)	
		Left-sided tumor, <10 years since diagnosis			1.14 (0.99-1.32)	
		Right-sided tumor, 10-19 years since diagnosis		CVD	1.00 (ref)	

First author, year of publication	Statistical analysis	Categories		Cause of death (outcome)	Risk of death HR (95% CI)	Covariates
		Left-sided tumor, 10-19 years since diagnosis			1.32 (1.12-1.57)	
		Right-sided tumor, ≥20 years since diagnosis		CVD	1.00 (ref)	
		Left-sided tumor, ≥20 years since diagnosis			1.30 (1.10-1.54)	
		Region	Pacific	CVD	1.00 (ref)	
			Alaska		-	
			East		0.97 (0.86-1.09)	
			Northern Plains		1.35 (1.21-1.51)	
			Southwest		1.51 (0.98-1.34)	
		Diagnosed 1983-92				
		Right-sided tumor		CVD	1.00 (ref)	
		Left-sided tumor			1.02 (0.95-1.10)	
		Race	White	CVD	1.00 (ref)	
			African American		1.14 (0.98-1.32)	
			American Indian/		0.68 (0.56-0.82)	
			Asian/ Pacific			
			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, <10 years since diagnosis		CVD	1.00 (ref)	
		Left-sided tumor, <10 years since diagnosis			1.01 (0.90-1.13)	
		Right-sided tumor, 10-19 years since diagnosis		CVD	1.00 (ref)	
		Left-sided tumor, 10-19 years since diagnosis			0.98 (0.88-1.10)	
		Right-sided tumor, ≥20 years since diagnosis		CVD	1.00 (ref)	
		Left-sided tumor, ≥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 1993-2002			
		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, <10 years since diagnosis		CVD	1.00 (ref)
		Left-sided tumor, <10 years since diagnosis			1.00 (0.98-1.03)
		Right-sided tumor, ≥20 years since diagnosis		CVD	1.00 (ref)
		Left-sided tumor, ≥20 years since diagnosis			1.01 (0.91-1.11)
		Region	Pacific	CVD	1.00 (ref)
			Alaska		0.24 (0.01-1.07)
			East		1.06 (0.99-1.13)
			Northern Plains		1.25 (1.16-1.35)
			Southwest		0.87 (0.76-0.99)
Merzenich, 2016	Cox proportional hazard	RT and right-sided tumor		CVD	1.00 (ref)
		RT and left-sided tumor			0.94 (0.64-1.38)
		No RT and right-sided tumor		CVD	1.00 (ref)
		No RT and left-sided tumor			1.07 (0.79-1.46)

First author, year of publication	Statistical analysis	Categories	Cause of death (outcome)	Risk of death HR (95% CI)	Covariates
		RT without history of cardiac disease	CVD	1.00 (ref)	
		RT with history of cardiac disease		1.73 (1.11-2.68)	
		RT without chemotherapy	CVD	1.00 (ref)	
		RT with chemotherapy		0.66 (0.37-1.19)	
CVD mortality in breast cancer patient with different ethnic origin					
Berkman, 2014	Kaplan-Meier with log-rank statistics	White, diagnosed between 1990-2010	CVD	1.00 (ref)	No covariates
		Black, diagnosed between 1990-2010		6.43 (3.61-11.45)	
		White, age at diagnosis 40-49 years	CVD	1.00 (ref)	
		Black, age at diagnosis 40-49 years		9.83 (4.56-21.17)	
		White, age at diagnosis 50-59 years	CVD	1.00 (ref)	
		Black, age at diagnosis 50-59 years		3.35 (2.14-5.24)	
		White, age at diagnosis 60-69 years	CVD	1.00 (ref)	
		Black, age at diagnosis 60-69 years		2.13 (1.65-2.74)	
		White, age at diagnosis ≥70 years	CVD	1.00 (ref)	
		Black, age at diagnosis ≥70 years		1.07 (0.93-1.23)	
Solanki, 2016	Cox proportional hazard	Non-Hispanic white	CVD	1.00 (ref)	Age, birthplace, SEER registry, AJCC stage
		Asian and Pacific islander		0.77 (0.71–0.83)	
		Non-Hispanic white	CVD	1.00 (ref)	
		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)	
		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-US born Asian and Pacific Islander	CVD	1.00 (ref)	
		US born Asian and Pacific Islander		1.29 (1.08–1.54)	
		Non-US born Chinese	CVD	1.00 (ref)	
		US born Chinese		1.33 (0.81–2.20)	
		Non-US born Japanese	CVD	1.00 (ref)	
		US born Japanese		1.04 (0.74–1.48)	
		Non-US born Filipino	CVD	1.00 (ref)	
		US born Filipino		0.99 (0.57–1.72)	
		Non-US born Hawaiian	CVD	1.00 (ref)	
		US born Hawaiian		0.97 (0.13–7.38)	
		Non-US born Korean	CVD	1.00 (ref)	
		US born Korean		0.17 (0.02–1.69)	
		Non-US born Asian Indian and Pakistani	CVD	1.00 (ref)	
		US born Asian Indian and Pakistani		0.94 (0.11–8.13)	
		Non-US born Pacific Islander	CVD	1.00 (ref)	
		US born Pacific Islander		4.27 (0.68–26.7)	
		Non-US born Other Asian	CVD	1.00 (ref)	
		US 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 hazard	Pre-diagnostic diet score (continuous)	CVD	0.96 (0.84-1.10)	Clinical, tumor, and treatment characteristics, CVD risk factors
		Pre-diagnostic diet score 0-2	CVD	1.00 (ref)	
		Pre-diagnostic diet score 3-5		0.95 (0.68-1.32)	
		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)	
		Prost-diagnostic diet score 3-5		0.96 (0.60-1.54)	
		Post-diagnostic diet score 6-9		0.81 (0.47-1.39)	

First author, year of publication	Statistical analysis	Categories		Cause of death (outcome)	Risk of death HR (95% CI)	Covariates
Nichols, 2009	Cox proportional hazard	1-5 year before diagnosis, BMI <18.5		CVD	4.15 (1.44-12.00)	Age, menopausal status, CVD risk factors
		1-5 year before diagnosis a BMI 18.5–24.9			1.00 (ref)	
		1-5 year before diagnosis a BMI 25.0–29.9			1.05 (0.63-1.74)	
		1-5 year before diagnosis a BMI ≥30			2.45 (1.46-4.11)	
		BMI after diagnosis <18.5		CVD	0.58 (0.08-4.34)	
		BMI after diagnosis 18.5–24.9			1.00 (ref)	
		BMI after diagnosis 25.0–29.9			0.99 (0.59-1.66)	
		BMI after diagnosis ≥30			1.65 (0.97-2.83)	
		Weight (kg) change -50.0 to -10.1		CVD	1.08 (0.42-2.78)	
		Weight (kg) change -10.0 to -2.1			1.02 (0.58-1.80)	
		Weight (kg) change -2.0 to 2.0			1.00 (ref)	
		Weight (kg) change 2.1 to 6.0			0.79 (0.43-1.44)	
		Weight (kg) change 6.1 to 10.0			0.64 (0.29-1.44)	
		Weight (kg) change 10.1			1.73 (0.83-3.62)	
Veal, 2017	Cox proportional hazard	Pre-diagnosis behaviors				Demographic, clinical, tumor, and treatment characteristics
		BMI	Continuous	CVD	1.01 (0.95-1.07)	
			18.5-24.9	CVD	1.00 (ref)	
			25.0-29.9		0.88 (0.37-2.07)	
			30.0-34.9		1.21 (0.45-3.24)	
			≥35.0		1.85 (0.59-5.85)	
		Physical activity (hours per week)	Continuous	CVD	0.83 (0.70-0.98)	
			No activity	CVD	1.00 (ref)	
			0.0-1.9		0.52 (0.22-1.23)	
			2.0-4.9		0.38 (0.15-1.00)	
			≥5.0		0.29 (0.08-1.04)	
		Alcohol (drinks per week)	Continuous	CVD	1.01 (0.94-1.08)	
			Non-drinker	CVD	1.00 (ref)	
			0.0-1.9		0.68 (0.29-1.60)	
			2.0-6.9		1.22 (0.47-3.14)	
			≥7.0		0.49 (0.13-1.86)	

	Smoking	Non-smoker	CVD	1.00 (ref)	
		Former smoker		0.96 (0.43-2.15)	
		Current smoker		2.07 (0.84-5.11)	
	Post-diagnosis behaviors				Pre-diagnosis health behavior and demographic, clinical, tumor, and treatment characteristics
	BMI	Continuous	CVD	0.96 (0.85-1.08)	
		18.5-24.9	CVD	1.00 (ref)	
		25.0-29.9		0.90 (0.32-2.51)	
		30.0-34.9		0.63 (0.15-2.70)	
		≥35.0		0.36 (0.05-2.74)	
	Physical activity (hours per week)	Continuous	CVD	1.04 (0.91-1.18)	
		No activity	CVD	1.00 (ref)	
		0.0-1.9		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	1.00 (ref)	
		0.0-1.9		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	1.00 (ref)	
		Former smoker		0.92 (0.41-2.08)	
		Current smoker		1.27 (0.22-6.86)	

Abbreviations: AJCC = American Joint Committee on Cancer, AMI = acute myocardial infarction, BMI = body mass index; kg/m², CHD = coronary heart disease, CI = Confidence Interval, CT = chemotherapy, CVA = cerebrovascular accident, CVD = cardiovascular disease, DCIS = ductal carcinoma in situ, HR = hazard ratio, HT = hormonal therapy, MR = mortality ratio, ref = reference category, RT = radiotherapy, SD = standard deviation, US = United States

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 ranged from 1.6%[15] to 10.4%[5], and the risk of CVD mortality was higher in women with breast cancer than women from the general population[5,8]. Higher 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] were 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 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 ten 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. (2011)[37] found that 26% to 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 particular 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[38,39]. 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. (2011)[18] did not found 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[40-43].

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. (2017)[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[44]. 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[45].

References

1. Integraal Kankercentrum Nederland. Cijfers over kanker. http: //cijfersoverkanker.nl/. Accessed July 2017.
2. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, et al. 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*. 2016.
3. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. 2005; 353 (17): 1784-1792.
4. Nakano M, Fujisue M, Tashima R, et al. Survival time according to the year of recurrence and subtype in recurrent breast cancer. *Breast*. 2015; 24 (5): 588-593.
5. Riihimaki M, Thomsen H, Brandt A, Sundquist J, Hemminki K. Death causes in breast cancer patients. *Ann Oncol*. 2012; 23 (3): 604-610.
6. Berkman A, F Cole B, Ades PA, et al. 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*. 2014; 148 (2): 407-413.
7. Taunk NK, Haffty BG, Kostis JB, Goyal S. Radiation-induced heart disease: Pathologic abnormalities and putative mechanisms. *Front Oncol*. 2015; 5: 39.
8. Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD. Cardiovascular disease mortality among breast cancer survivors. *Epidemiology*. 2016; 27 (1): 6-13.
9. Bird BR, Swain SM. Cardiac toxicity in breast cancer survivors: Review of potential cardiac problems. *Clin Cancer Res*. 2008; 14 (1): 14-24.
10. Borger JH, Hooning MJ, Boersma LJ, et al. Cardiac toxic effects of tangential breast irradiation in early breast cancer patients: The role of irradiated heart volume. *Int J Radiat Oncol Biol Phys*. 2007; 69 (4): 1131-1138.
11. McGale P, Darby SC, Hall P, et al. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. *Radiother Oncol*. 2011; 100 (2): 167-175.
12. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol*. 2007; 25 (25): 3808-3815.
13. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. *Ann Intern Med*. 2015; 162 (11): 777-784.
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.

15. Nichols HB, Trentham-Dietz A, Egan KM, et al. Body mass index before and after breast cancer diagnosis: Associations with all-cause, breast cancer, and cardiovascular disease mortality. *Cancer Epidemiol Biomarkers Prev*. 2009; 18 (5): 1403-1409.

16. McCullough ML, Gapstur SM, Shah R, et al. Pre- and post-diagnostic diet in relation to mortality among breast cancer survivors in the CPS-II nutrition cohort. *Cancer Causes Control*. 2016.

17. Solanki PA, Ko NY, Qato DM, Calip GS. Risk of cancer-specific, cardiovascular, and all-cause mortality among Asian and Pacific Islander breast cancer survivors in the united states, 1991-2011. *Springerplus*. 2016; 5: 82-016-1726-3.

18. Colzani E, Liljegren A, Johansson AL, et al. Prognosis of patients with breast cancer: Causes of death and effects of time since diagnosis, age, and tumor characteristics. *J Clin Oncol*. 2011; 29 (30): 4014-4021.

19. Haque R, Yood MU, Geiger AM, et al. Long-term safety of radiotherapy and breast cancer laterality in older survivors. *Cancer Epidemiol Biomarkers Prev*. 2011; 20 (10): 2120-2126.

20. Bouchardy C, Rapiti E, Usel M, et al. Excess of cardiovascular mortality among node-negative breast cancer patients irradiated for inner-quadrant tumors. *Ann Oncol*. 2010; 21 (3): 459-465.

21. Merzenich H, Bartkowiak D, Schmidberger H, et al. 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*. 2017; 161 (1): 143-152.

22. Veal CT, Hart V, Lakoski SG, et al. Health-related behaviors and mortality outcomes in women diagnosed with ductal carcinoma in situ. *J Cancer Surviv*. 2017.

23. Darby SC, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: Prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol*. 2005; 6 (8): 557-565.

24. Giordano SH, Kuo YF, Freeman JL, Buchholz TA, Hortobagyi GN, Goodwin JS. Risk of cardiac death after adjuvant radiotherapy for breast cancer. *J Natl Cancer Inst*. 2005; 97 (6): 419-424.

25. Hooning MJ, Aleman BM, van Rosmalen AJ, Kuenen MA, Klijn JG, van Leeuwen FE. Cause-specific mortality in long-term survivors of breast cancer: A 25-year follow-up study. *Int J Radiat Oncol Biol Phys*. 2006; 64 (4): 1081-1091.

26. Haque W, Verma V, Haque A, Butler EB, Teh BS. Trends in cardiac mortality in women with ductal carcinoma in situ. *Breast Cancer Res Treat*. 2017; 161 (2): 345-351.

27. Kushi LH, Doyle C, McCullough M, et al. 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*. 2012; 62 (1): 30-67.

28. Weaver KE, Foraker RE, Alfano CM, et al. Cardiovascular risk factors among long-term survivors of breast, prostate, colorectal, and gynecologic cancers: A gap in survivorship care? *J Cancer Surviv*. 2013; 7 (2): 253-261.

29. Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American society of clinical oncology clinical practice guideline. *J Clin Oncol*. 2017; 35 (8): 893-911.

30. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, et al. 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 8,135 women in 22 randomized trials. *Lancet*. 2014; 383 (9935): 2127-2135.

31. Guenancia C, Lefebvre A, Cardinale D, et al. Obesity as a risk factor for anthracyclines and trastuzumab cardiac toxicity in breast cancer: A systematic review and meta-analysis. *J Clin Oncol*. 2016; 34 (26): 3157-3165.

32. Vejpongsa P, Yeh ET. Prevention of anthracycline-induced cardiac toxicity: Challenges and opportunities. *J Am Coll Cardiol*. 2014; 64 (9): 938-945.

33. Fan J, Song Y, Chen Y, Hui R, Zhang W. Combined effect of obesity and cardio-metabolic abnormality on the risk of cardiovascular disease: A meta-analysis of prospective cohort studies. *Int J Cardiol*. 2013; 168 (5): 4761-4768.

34. Ringback Weitoft G, Eliasson M, Rosen M. Underweight, overweight and obesity as risk factors for mortality and hospitalization. *Scand J Public Health*. 2008; 36 (2): 169-176.

35. Wu CY, Chou YC, Huang N, Chou YJ, Hu HY, Li CP. Association of body mass index with all-cause and cardiovascular disease mortality in the elderly. *PLoS One*. 2014; 9 (7): e102589.

36. D'Agostino RB S, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham heart study. *Circulation*. 2008; 117 (6): 743-753.

37. Schonberg MA, Marcantonio ER, Ngo L, Li D, Silliman RA, McCarthy EP. Causes of death and relative survival of older women after a breast cancer diagnosis. *J Clin Oncol*. 2011; 29 (12): 1570-1577.

38. Cuzick J, Stewart H, Rutqvist L, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol*. 1994; 12 (3): 447-453.

39. Darby SC, Bronnum D, Correa C, et al. A dose-response relationship for the incidence of radiation-related heart disease. *Int J Radiat Oncol Biol Phys*. 2010; 78 (3): S49-S50.

40. Valina-Toth AL, Zavodnik T, Seicean S, Plana J, Marwick T. African American race is a correlate of heart failure in breast cancer survivors: A study of 26,347 women identified with breast cancer from 1973-2007. *J Am Coll Cardiol*. 2013; 61 (10): E580.

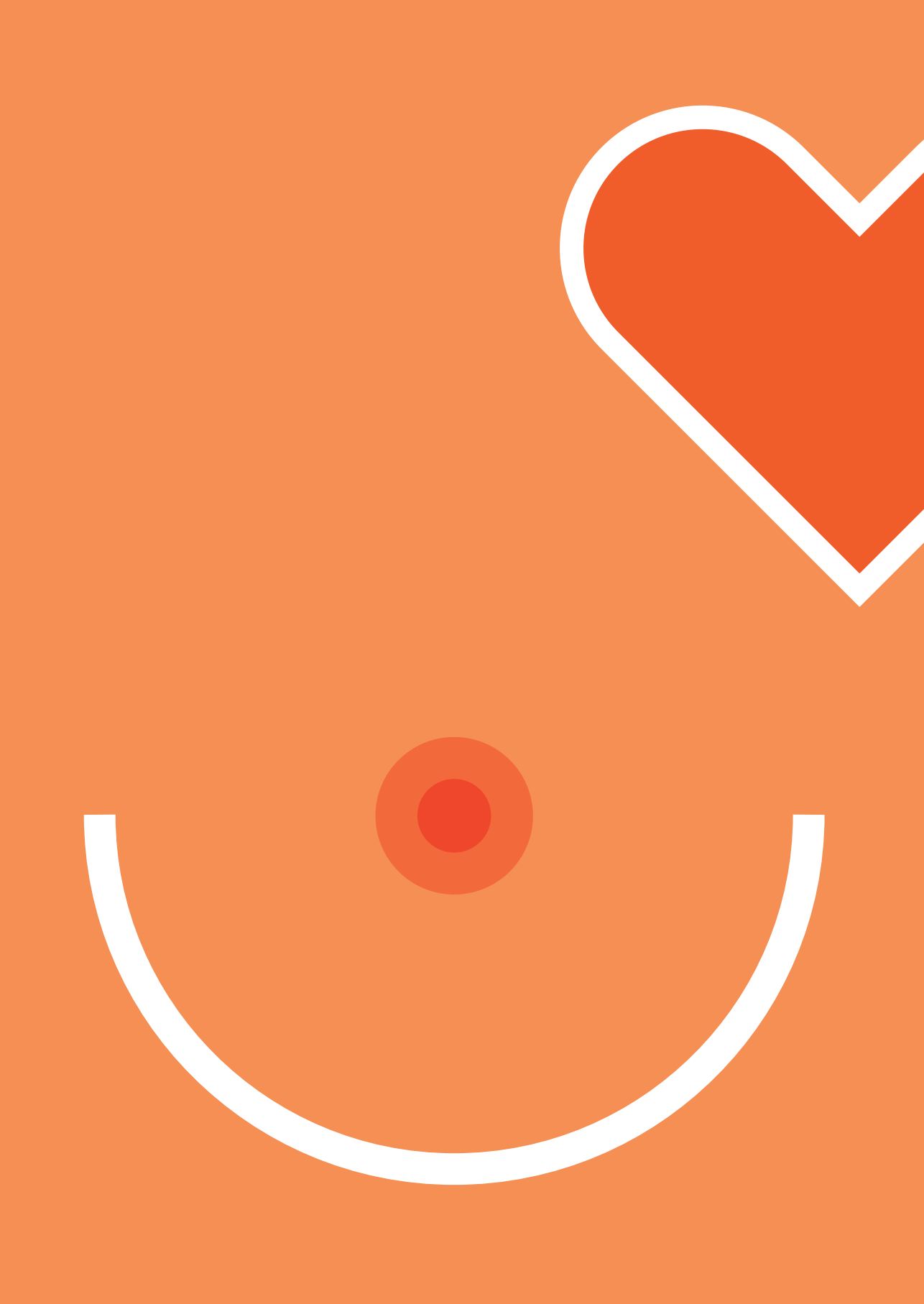
41. Budoff MJ, Nasir K, Mao S, et al. Ethnic differences of the presence and severity of coronary atherosclerosis. *Atherosclerosis*. 2006; 187 (2): 343-350.

42. Sasayama S. Heart disease in Asia. *Circulation*. 2008; 118 (25): 2669-2671.

43. Tammemagi CM, Nerenz D, Neslund-Dudas C, Feldkamp C, Nathanson D. Comorbidity and survival disparities among black and white patients with breast cancer. *JAMA*. 2005; 294 (14): 1765-1772.

44. Gernaat SA, Isgum I, de Vos BD, et al. Automatic coronary artery calcium scoring on radiotherapy planning CT scans of breast cancer patients: Reproducibility and association with traditional cardiovascular risk factors. *PLoS One*. 2016; 11 (12): e0167925.

45. Maas AH, Ottevanger N, Atsma F, Cramer MJ, Leiner T, Poortmans P. Cardiovascular surveillance in breast cancer treatment: A more individualized approach is needed. *Maturitas*. 2016; 89: 58-62.



Chapter 3

Trends in the risk of cardiovascular disease in women with breast cancer in the Netherlands

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Submitted

Abstract

Purpose

Cardiovascular disease (CVD) is an important cause of death in breast cancer patients. The present study investigated trends in the risk of CVD in breast cancer patients in the Netherlands, and a comparison is made with the Dutch general female population.

Methods

163,881 women admitted for *in situ* (7.6%) or invasive (92.4%) breast cancer between 1996 and 2010 in the Netherlands were identified in the Hospital Discharge Register (HDR). Data on death from CVD and hospitalization for CVD were obtained from the Cause of Death Registry and the HDR, respectively. Standardized absolute risks of death from CVD in women with and without breast cancer were calculated for the years 1996-2010. The relative risk decrease or increase in absolute risks of hospitalization or death due to CVD was calculated between 1996 and 2010. CVD mortality rates after breast cancer were calculated by age group (<50, 50-64, ≥65), and a cox proportional hazard analysis was applied to calculate the age-adjusted relative risk of death from CVD within five years after breast cancer admission for each year (1997-2010) compared to 1996.

Results

After median follow-up of 4.3 years following breast cancer admission, 5.6% patients died of CVD and 19.7% patients were hospitalized for CVD. The absolute ten-year risk of death from CVD following breast cancer decreased from 56 per 1,000 women in 1996 to 41 per 1,000 women in 2005 (relative decrease of 23.9%). In the general population, the absolute ten-year risk of death from CVD decreased from 73 per 1,000 women in 1996 to 55 per 1,000 women in 2005 (relative decrease of 27.8%). The absolute risk of hospitalization for CVD within the first year following breast cancer increased from 54 per 1,000 women in 1996 to 67 per 1,000 women in 2009 (relative increase of 23.6%). The majority of deaths from CVD occurred among breast cancer patients over 60 years (93.4%). The relative risk of death from CVD was 0.58 (95% confidence interval (CI) = 0.48-0.70) times lower for patients admitted for breast cancer in 2010 compared to 1996.

Conclusions

Like in the general population, the risk of death from CVD has decreased in breast cancer patients between 1996 and 2010, and mainly occurred among patients aged over 60 years. Breast cancer patients have a lower absolute risk of death from CVD than women from the general population. Over time, the absolute burden of CVD in terms of hospitalization has increased and is considerable with nearly one out of five women having a CVD hospital admission.

Introduction

Breast cancer is the most frequently diagnosed cancer among women worldwide[1]. Breast cancer survival is high in developed countries due to early detection and effective treatments[1-3]. The combination of high breast cancer incidence rates and high survival rates, has resulted in a large group of breast cancer survivors[1]. In 2012, there were over 3 million five-year breast cancer survivors worldwide[1]. Many of these survivors will die of other medical conditions than breast cancer. Cardiovascular disease (CVD) is an important cause of death in the general population[4], and also in breast cancer patients[5].

The risk of CVD is increased in breast cancer patients who have been exposed to cardiotoxic treatments including radiotherapy[9-11], anthracycline-based chemotherapy[6,7], and trastuzumab[8]. The highest risks of treatment-induced cardiotoxicity are seen in patients with pre-existing CVD risk factors such as hypertension and high age[12,13].

Many efforts have been made to reduce the risk of CVD induced by breast cancer treatments. Cancer therapies with a lower risk of cardiotoxicity are increasingly being chosen for patients with a high risk of CVD if this does not impair cancer-specific outcomes[14,15]. Cardiac monitoring before, during, and after treatment with trastuzumab to detect reversible cardiotoxicity is standard of care[14,15]. In parallel, breast cancer patients have also been exposed to improvements in pharmacological prevention of CVD with antihypertensive and statins, to anti-tobacco programmes, and campaigns focusing on the importance of physical activity[16,17].

The present study investigated trends in the risk of hospitalization and death due to CVD in breast cancer patients in the Netherlands, and made a comparison with the Dutch female general population.

Methods and Materials

Study population

Data for the present study were obtained from the Dutch Population Register (PR), Hospital Discharge Register (HDR), and the Cause of Death Registry. These registries were used to obtain data on demographic characteristics (PR), to identify women admitted for breast cancer and subsequently CVD (HDR), and to obtain data on causes of death, *i.e.* CVD, breast cancer, any cause (Cause of Death Registry).

Details of the registries and linkage procedures used to obtain data for this study have been described previously[18]. Briefly, all registries have an unique record identification number, which is assigned to each resident in the Netherlands. This number is a combination of birth date, sex, and postal code, and is unique for 84% of the Dutch population[19]. HDR data was available from 1995 to 2010, and data from PR and Cause of Death Registry were available until 2015. All linkages and analyses were performed in agreement with the privacy legislation in the Netherlands and performed in a secured environment of Statistics Netherlands.

For the present study, women with a first hospital admission for *in situ* (ICD-9: 233, ICD-10: D05) and invasive breast cancer (ICD-9: 174, ICD-10: C50) between 1996 and 2010 were identified. For every identified woman with a breast cancer hospital admission, it was examined if she had a previous hospital admission for breast cancer in the preceding year. In total, the breast cancer study population consisted of 163,881 women, 12,378 (7.6%) were diagnosed with *in situ* and 151,503 (92.4%) with invasive breast cancer. For comparison, women from the general population aged over 40 years were identified, ranging from 3,661,141 in 1996 to 4,566,573 in 2010.

Outcome assessment

Patients were followed for death from CVD and hospitalization due to CVD. Causes of death were coded according to the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10): death from CVD (A18.2, A52.0,D18, G45, I00 – I99, K55, M30 – M31, P29.3, Q20-Q28, R00-R02, R07.1–R07.4, R09.8, R16.1, R23.0, R55, R57.0, R58, R59, R60, R94.3), death from breast cancer (C50, D05), and death from any cause. Causes of death were based on the primary cause of death, *i.e.* the underlying disease that led to death. Hospitalization due to CVD was coded according to ICD-9: 017.2, 093, 228, 289.1-289.3, 390-459, 557, 745-747, 780.2, 782.3, 7825, 7826, 785, 786.50-786.59, 789.2, 794.30-794.39.

Validation of breast cancer hospital discharge codes

A validation study was performed to assess the accuracy of breast cancer discharge codes notified in the HDR. 90 patients with a breast cancer discharge code for *in situ* (ICD-9: 233) or invasive breast cancer (ICD-9: 174) at the University Medical Center Utrecht were randomly selected (five to six patients per year from 1996 to 2010). Medical records of these patients were manually checked for discharge ICD-9 code and discharge date.

Data analysis

Median (interquartile range (IQR)) was calculated to describe variables with skewed distribution. Time at risk started at date of breast cancer admission until date of death, date of CVD hospitalization, or end of study (December 31, 2010 for CVD hospitalization and December 31, 2015 for death), whichever occurred first.

Absolute risks were standardized according to the age distribution of women from the general population aged 40 years and older in 1996, with five year age groups, and presented per year of breast cancer admission (1996-2010). The relative risk decrease or increase in absolute risks of hospitalization or death due to CVD between 1996 and last year of follow-up (depending on the time interval) was calculated. Absolute risks of death from CVD (per 1,000 women) were calculated within five, seven, and ten years after breast cancer admission or reference year for women from the general population. Absolute risks of CVD hospitalization (per 1,000 women) were calculated within one, three, and five years after breast cancer admission. The underlying causes of hospitalization for CVD were investigated to assess if these hospitalizations were caused by heart failure or coronary heart disease as cardiotoxic breast cancer treatments including radiation therapy[9,10], anthracycline-based chemotherapy[20,21], and trastuzumab[22,23] are associated with an increased risk of these diseases. CVD mortality rates (per 10,000 person-years) were calculated within five and ten years after breast cancer admission by age group (<50, 50-64, ≥65), and a cox proportional hazard model was applied to estimate the age-adjusted hazard ratio (HR) of death from CVD and death from breast cancer for each year (1997-2010) compared to 1996. All analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Approximately half of patients (51.3%) were 60 years or older at time of breast cancer admission (Table 1). After median follow-up of 4.3 years (IQR = 1.7-8.0) following breast cancer, 5.6% of patients had died of CVD, 19.7% of patients had been hospitalized for CVD, and 22.7% of patients had died of breast cancer. Death from CVD mainly occurred among patients aged 60 years or older (93.4%).

The absolute ten-year risk of death from CVD following breast cancer decreased from 56 per 1,000 women in 1996 to 41 per 1,000 women in 2005 (relative decrease of 23.9%, Figure 1). In the general population, the absolute ten-year risk of death from CVD decreased from 73 per 1,000 women in 1996 to 55 per 1,000 women in 2005 (relative decrease of 27.8%). The absolute risk of death from CVD is lower in women with breast cancer compared to women from the general population.

The ten-year CVD mortality rate after breast cancer admission in 2005 was 139 per 10,000 person-years for patients aged 65 years or older, 11 per 10,000 person-years for patients aged between 50 and 64 years, and 3 per 10,000 person-years for patients younger than 50 years (Figure 2). Death from CVD after breast cancer admission decreased among all age groups. The ten-year CVD mortality rate decreased from 218 per 10,000 person-years in 1996 to 139 per 10,000 person-years in 2005 (relative decrease of 36.2%) for patients aged 65 years or older, from 21 to 11 (relative decrease of 48%) for patients aged between 50 and 64 years, and from 5 to 3 (relative decrease of 44.1%) for patients aged younger than 50 years. The age-adjusted relative risk of death from CVD within five years was 0.58 (95% confidence interval (CI) = 0.48-0.70) times lower for patients admitted for breast cancer in 2010 compared to 1996 (Table 2). The relative risk of death from breast cancer was 0.49 (95% CI = 0.45-0.52) times lower for patients admitted for breast cancer in 2010 compared to 1996.

The absolute risk of hospitalization for CVD in the first year after breast cancer increased from 54 per 1,000 women in 1996 to 67 per 1,000 women in 2009 (relative increase of 23.6%, Figure 3). The increase in hospitalization for CVD mainly occurred after 2001 and was attributable to high blood pressure (29%), pulmonary embolism (15%), rheumatic heart disease/valve disease (8%), and heart failure (7%).

Validation of breast cancer discharge codes

In total, 90 patients were used for validation including five patients with *in situ* breast cancer. In all patients, breast cancer was confirmed in the respective hospital (Supplementary Table A). Six HDR codes were slightly incorrect as the date of discharge differed with the correct date: one day (n = 1), two weeks (n = 2), two months (n = 2), and five months (n = 1).

Table 1. Cardiovascular disease hospitalizations and causes of death among 163,881 breast cancer patients

	Total breast cancer population (%)	CVD hospitalization (%)	Death from CVD (%)	Death from breast cancer (%)
Percentage of total breast cancer population*	100.0	19.7	5.6	22.7
Type of breast cancer				
In situ	7.6	6.6	5.3	1.6
Invasive	92.4	93.4	94.7	98.4
Calendar period of breast cancer admission				
1996-1999	24.1	34.5	38.8	34.1
2000-2003	27.0	32.7	32.2	29.4
2004-2007	27.7	23.8	20.0	23.9
2008-2010	21.2	9.0	8.9	12.5
Age at breast cancer admission in years				
<50	22.4	12.9	1.3	23.6
50-59	26.3	20.2	5.3	23.3
60-69	23.9	26.6	17.7	21.5
70-79	18.0	27.0	39.9	19.1
>79	9.4	13.4	35.8	12.5
Follow-up time in years				
Median (IQR)	4.3 (1.7-8.0)	4.3 (3.3-10.0)	3.2 (1.1-6.6)	3.1 (1.2-6.2)
Follow-up time intervals in years				
<1	16.6	23.6	16.2	21.6
1-4	39.1	41.4	39.2	45.4
5-9	29.1	24.9	29.5	23.3
>9	15.1	10.1	15.1	9.6

Abbreviations: CVD = cardiovascular disease, IQR = Interquartile range
*n = 163,881 (row percentage)

Table 2. Age-adjusted relative risk of death from cardiovascular disease and breast cancer among 163,881 breast cancer patients

	Death from cardiovascular disease	Death from breast cancer
Year of breast cancer admission	**Hazard ratio* (95% confidence interval)**	**Hazard ratio* (95% confidence interval)**
1996	1.00 (ref)	1.00 (ref)
1997	1.04 (0.88-1.23)	1.02 (0.96-1.09)
1998	0.91 (0.77-1.01)	0.92 (0.86-0.98)
1999	0.97 (0.82-1.14)	0.84 (0.79-0.90)
2000	0.79 (0.66-0.94)	0.75 (0.71-0.80)
2001	0.86 (0.73-1.02)	0.74 (0.70-0.79)
2002	0.81 (0.69-0.96)	0.73 (0.68-0.78)
2003	0.75 (0.63-0.89)	0.66 (0.62-0.71)
2004	0.73 (0.61-0.86)	0.71 (0.66-0.75)
2005	0.58 (0.48-0.70)	0.66 (0.62-0.70)
2006	0.63 (0.52-0.75)	0.63 (0.59-0.68)
2007	0.60 (0.50-0.75)	0.58 (0.54-0.62)
2008	0.62 (0.52-0.74)	0.54 (0.51-0.58)
2009	0.55 (0.46-0.66)	0.54 (0.50-0.58)
2010	0.58 (0.48-0.70)	0.49 (0.45-0.52)

*Hazard ratios are adjusted for age

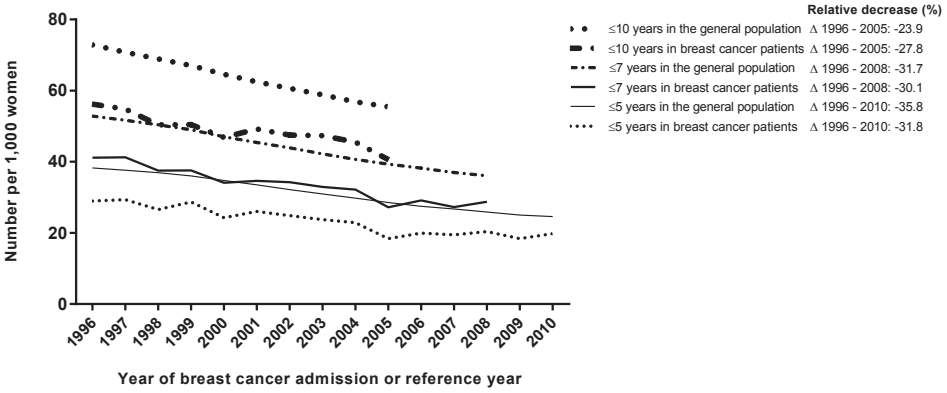

Figure 1. Age-standardized cardiovascular disease mortality in patients with breast cancer patients and in women from the general population. Relative decrease (%) in cardiovascular disease mortality rates within five, seven, and ten years after year of breast cancer admission of reference year between 1996-2010, 1996-2008, and 1996-2005 respectively (Δ), for breast cancer patients and women from the general population.

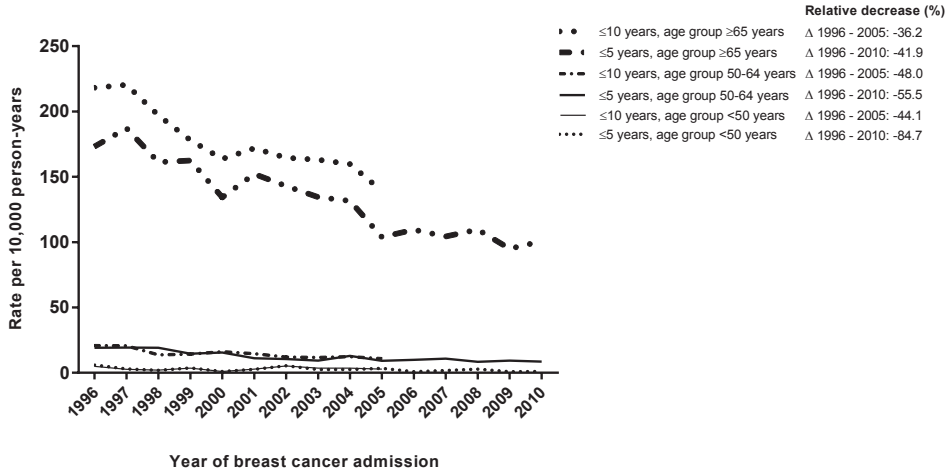

Figure 2. Cardiovascular disease mortality rates by age group among 163,881 breast cancer patients. Relative decrease (%) in cardiovascular disease mortality rates within five and ten years after year of breast cancer admission between 1996-2010 and 1996-2005 respectively (Δ), for patients aged <50, 50-64, and ≥65 years.

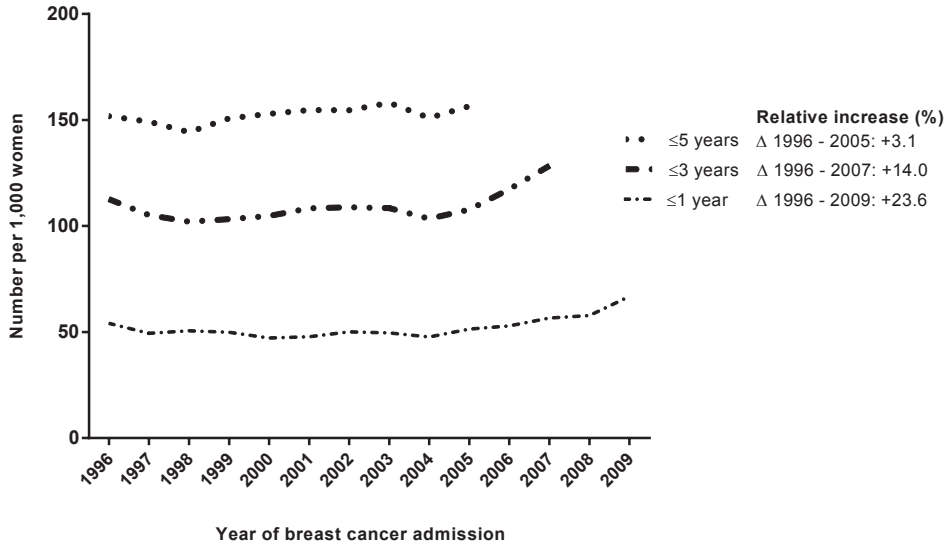

Figure 3. Age-standardized number of hospitalizations for cardiovascular disease per 1,000 breast cancer patients. Relative increase (%) in cardiovascular disease hospitalizations within one, thee, and five years after year of breast cancer admission between 1996-2009, 1996-2007, and 1996-2005 respectively (Δ).

Discussion

Like in the general population, the risk of death from CVD has decreased in breast cancer patients between 1996 and 2010, and mainly occurred among patients aged over 60 years. Breast cancer patients have a lower absolute risk of death from CVD than women from the general population. Over time, the absolute burden of CVD in terms of hospitalization has increased and is considerable with nearly one out of five women having a CVD hospital admission.

In developed parts of the world, including United States and Europe, the absolute risk of death from CVD has decreased[17,25]. The decrease in deaths from coronary artery disease was for around 50% attributable to the increased use of pharmacological treatments such as secondary prevention after heart failure and myocardial infarction[26,27]. The other half was explained by reductions in risk factors like hypertension, hyperlipidaemia, smoking, and physical activity[26,27].

Like us, Riihimäki et al. (2011) showed that the absolute risk of death from CVD is lower in breast cancer patients than in women from the general population[28]. They investigated the risk of death from CVD using nationwide registration data and comparing all women diagnosed with breast cancer with women from the general population without a breast cancer diagnosis[28]. After a maximum follow up of 19 years, 27.1% of breast cancer patients died of CVD and 44.0% of women from the general population died of CVD[28]. This risk of death from CVD in patients and the general population reported by Riihimäki et al. (2011) is higher than in our study, and this can be explained by the longer follow-up (1987-2006 versus 1996-2015) and the higher risks of CVD in the earlier years[28]. Bradshaw et al. (2016) reported a higher absolute risk of death from CVD in women with breast cancer (9.4%) than in women from the general population (7.4%) after a maximum follow-up of 13.5 years (from 1996 to 2010)[29]. They also found a higher relative risk of death from CVD in women with breast cancer after seven years following diagnosis compared to women from the general population (HR = 1.8, 95% CI = 1.3-2.5), adjusted for age and CVD risk factors[29]. In this study, breast cancer patients were invited to participate, which may have resulted in a selected study population of patients with good prognosis. Patients with good prognosis have a higher risk of death from CVD than patients with poor prognosis as breast cancer is a competing risk[30].

In the current study, we found that death from CVD mainly occurred among older women with breast cancer. This is in line with a study from Sweden on the prognosis of breast cancer patients[30]. They showed that 24% of women aged 65 years and above died of CVD

within ten years after breast cancer[30]. High age is one of the most important risk factors of CVD[31], and therefore, older women with breast cancer have a higher risk of dying of CVD than younger women with breast cancer[14,15].

The results of our study showed that the absolute risk of hospitalization for CVD in the first year after breast cancer increased with 23.6% between 1996 and 2009. Seven percentage of this increase was caused by heart failure which is less than expected as heart failure shortly after therapy is a well-known side effect of systemic treatment, including trastuzumab[8] and anthracycline-based chemotherapies[6,7]. Trastuzumab is a targeted therapy used to treat women with human epidermal growth factor receptor 2 positive breast cancer (approximately one in five patients)[32]. Since 2004, trastuzumab is used as adjuvant therapy for early breast cancer[33]. This therapy may have resulted in more hospital admissions for heart failure as cardiotoxicity is its most concerning adverse effect in particular reduced left ventricular ejection fraction and heart failure[34]. The risk of heart failure is four times higher in patients treated with trastuzumab alone and seven times higher in patients treated with anthracycline plus trastuzumab[35,36]. Another 34% of the increase in hospitalization for CVD was caused by high blood pressure. Blood pressure elevation is a common side effect of cancer treatments with vascular endothelial growth factor signaling pathway inhibitors as for example bevacizumab. Bevacizumab is used to treat metastatic breast cancer and was introduced in Europe after 2004[37,38]. However, since an extremely small proportion of patients are treated with bevacizumab, it is unlikely to explain the 34% increase in hospital admissions due to hypertension. Pulmonary embolism explained 15% of the increased number of CVD hospitalizations, is often caused by venous thromboembolism[39]. The selective estrogen-receptor modulator tamoxifen has a thrombotic effect[40,41]. A Danish study reported that women treated with tamoxifen had a higher risk of pulmonary embolism during the first two years after exposure compared to women not receiving tamoxifen (risk ratio = 3.5, 95% CI = 2.1-6.0)[40]. Similar results have been reported by Cuzick et al. (2007): risk ratio of 2.26 (95% CI = 1.36-3.87) comparing women treated with tamoxifen with women receiving placebo[41].

We acknowledge that this study has limitations. For every woman with a breast cancer hospital admission between 1996 and 2010, it was examined if she had a previous hospital admission for breast cancer in the preceding year. This method reduced the percentage of women with a previous hospital admission for breast cancer to 7%. This implies, however, that we have included women with a readmission for breast cancer in the present study. Women who have been readmitted for breast cancer may have a worse breast cancer prognosis and therefore a lower risk of death from CVD. The risk of hospitalization for CVD, however, may be higher among these women with a readmission for breast cancer, as they may have undergo previously (potential cardiotoxic) cancer therapy that resulted

in CVD. Another limitation is that from 2005 onwards, the participation of hospitals in registering patients' discharges decreased from 100% coverage to 89% in 2010. As a result, it not all breast cancer patients in the Netherlands were identified. Furthermore, the present study had no information on breast cancer characteristics and CVD risk factors other than age.

To conclude, the current study shows that the risk of death from CVD in breast cancer patients and in women from the general population decreased in the last decades. Yet, we find an increase in the number of CVD hospitalizations after breast cancer. Future studies should investigate whether the increase in CVD hospitalizations within the first year continues to rise and assess the underlying processes of this increase in more detail.

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References

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.1, cancer incidence and mortality worldwide: IARC CancerBase. 2014; 11.
2. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. 2005; 353 (17): 1784-1792.
3. Bosetti C, Bertuccio P, Levi F, Chatenoud L, Negri E, La Vecchia C. The decline in breast cancer mortality in Europe: An update (to 2009). *Breast*. 2012; 21 (1): 77-82.
4. World Health Organization. Global health observator. http: //www.who.int/gho. Updated 2017. Accessed October/11, 2017.
5. Gernaat SAM, Ho PJ, Rijnberg N, et al. Risk of death from cardiovascular disease following breast cancer: A systematic review. *Breast Cancer Res Treat*. 2017.
6. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol*. 2007; 25 (25): 3808-3815.
7. Rehammar JC, Jensen MB, McGale P, et al. Risk of heart disease in relation to radiotherapy and chemotherapy with anthracyclines among 19,464 breast cancer patients in Denmark, 1977-2005. *Radiother Oncol*. 2017; 123 (2): 299-305.
8. Chavez-MacGregor M, Zhang N, Buchholz TA, et al. Trastuzumab-related cardiotoxicity among older patients with breast cancer. *J Clin Oncol*. 2013; 31 (33): 4222-4228.
9. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, et al. 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 randomized trials. *Lancet*. 2014; 383 (9935): 2127-2135.
10. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomized trials. *Lancet*. 2005; 366 (9503): 2087-2106.
11. Darby SC, Bronnum D, Correa C, et al. A dose-response relationship for the incidence of radiation-related heart disease. *Int J Radiat Oncol Biol Phys*. 2010; 78 (3): S49-S50.
12. Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med*. 1979; 91 (5): 710-717.
13. Serrano C, Cortes J, De Mattos-Arruda L, et al. Trastuzumab-related cardiotoxicity in the elderly: A role for cardiovascular risk factors. *Ann Oncol*. 2012; 23 (4): 897-902.
14. Zamorano JL, Lancellotti P, Rodriguez Munoz D, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC committee for practice guidelines: The task force for cancer treatments and cardiovascular toxicity of the European society of cardiology (ESC). *Eur Heart J*. 2016; 37 (36): 2768-2801.

15. Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American society of clinical oncology clinical practice guideline. *J Clin Oncol*. 2017; 35 (8): 893-911.
16. Kones R. Primary prevention of coronary heart disease: Integration of new data, evolving views, revised goals, and role of rosuvastatin in management. A comprehensive survey. *Drug Des Devel Ther*. 2011; 5: 325-380.
17. Writing Group Members, Mozaffarian D, Benjamin EJ, et al. Heart disease and stroke statistics-2016 update: A report from the American heart association. *Circulation*. 2016; 133 (4): e38-360.
18. Koek HL, de Bruin A, Gast A, et al. Incidence of first acute myocardial infarction in the Netherlands. *Neth J Med*. 2007; 65 (11): 434-441.
19. Reitsma JB, Kardaun JW, Gevers E, de Bruin A, van der Wal J, Bonsel GJ. Possibilities for anonymous follow-up studies of patients in Dutch national medical registrations using the municipal population register: A pilot study. *Ned Tijdschr Geneeskd*. 2003; 147 (46): 2286-2290.
20. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: Systematic review and meta-analysis of randomized controlled trials. *BMC Cancer*. 2010; 10: 337-2407-10-337.
21. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments. *Nat Rev Cardiol*. 2015; 12 (9): 547-558.
22. Suter TM, Cook-Bruns N, Barton C. Cardiotoxicity associated with trastuzumab (Herceptin) therapy in the treatment of metastatic breast cancer. *Breast*. 2004; 13 (3): 173-183.
23. Suter TM, Procter M, van Veldhuisen DJ, et al. Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. *J Clin Oncol*. 2007; 25 (25): 3859-3865.
24. Foglietta J, Inno A, de Iuliis F, et al. Cardiotoxicity of aromatase inhibitors in breast cancer patients. *Clin Breast Cancer*. 2017; 17 (1): 11-17.
25. Wilkins E, Wilson L, Wickramasinghe K, Bhatnagar P, Leal J, Luengo-Fernandez R, Burns R, Rayner M, Townsend N. European cardiovascular disease statistics 2017.
26. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med*. 2007; 356 (23): 2388-2398.
27. Koopman C, Vaartjes I, van Dis I, et al. Explaining the decline in coronary heart disease mortality in the Netherlands between 1997 and 2007. *PLoS One*. 2016; 11 (12): e0166139.
28. Riihimaki M, Thomsen H, Brandt A, Sundquist J, Hemminki K. Death causes in breast cancer patients. *Ann Oncol*. 2012; 23 (3): 604-610.
29. Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD. Cardiovascular disease mortality among breast cancer survivors. *Epidemiology*. 2016; 27 (1): 6-13.
30. Colzani E, Liljegren A, Johansson AL, et al. Prognosis of patients with breast cancer: Causes of death and effects of time since diagnosis, age, and tumor characteristics. *J Clin Oncol*. 2011; 29 (30): 4014-4021.

31. D'Agostino RB S, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham heart study. *Circulation*. 2008; 117 (6): 743-753.

32. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011; 365 (14): 1273-1283.

33. Florido R, Smith KL, Cuomo KK, Russell SD. Cardiotoxicity from human epidermal growth factor receptor-2 (HER2) targeted therapies. *J Am Heart Assoc*. 2017; 6 (9): 10.1161/JAHA.117.006915.

34. Advani PP, Ballman KV, Dockter TJ, Colon-Otero G, Perez EA. Long-term cardiac safety analysis of NCCTG N9831 (alliance) adjuvant trastuzumab trial. *J Clin Oncol*. 2016; 34 (6): 581-587.

35. Moja L, Brambilla C, Compagnoni A, Pistotti V. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev*. 2006 (4).

36. Bowles EJ, Wellman R, Feigelson HS, et al. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: A retrospective cohort study. *J Natl Cancer Inst*. 2012; 104 (17): 1293-1305.

37. Maitland ML, Bakris GL, Black HR, et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. *J Natl Cancer Inst*. 2010; 102 (9): 596-604.

38. Amit L, Ben-Aharon I, Vidal L, Leibovici L, Stemmer S. The impact of bevacizumab (Avastin) on survival in metastatic solid tumors: a meta-analysis and systematic review. *PLoS One*. 2013; 8 (1): e51780.

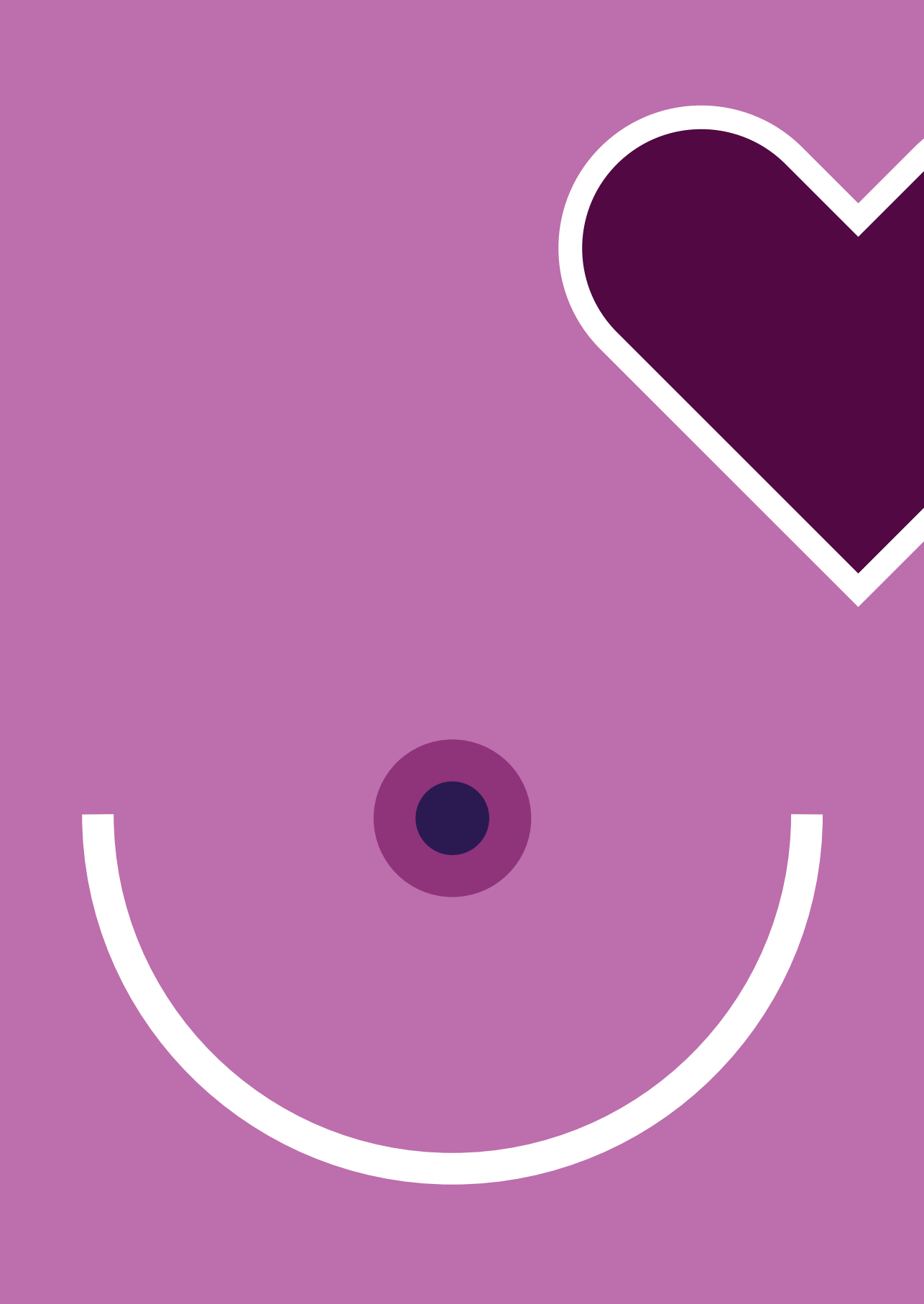
39. Chew HK, Wun T, Harvey DJ, Zhou H, White RH. Incidence of venous thromboembolism and the impact on survival in breast cancer patients. *J Clin Oncol*. 2007; 25 (1): 70-76.

40. Hernandez RK, Sorensen HT, Pedersen L, Jacobsen J, Lash TL. Tamoxifen treatment and risk of deep venous thrombosis and pulmonary embolism: A Danish population-based cohort study. *Cancer*. 2009; 115 (19): 4442-4449.

41. Cuzick J. Aromatase inhibitors in the treatment of breast cancer: Results of the ATAC trial. *Nat Clin Pract Oncol*. 2007; 4: S16-S25.

Supplementary Table A. Validation of breast cancer discharge codes of the Dutch Hospital Discharge Register among 90 patients

	%
Known with breast cancer?	
Yes	100.0
No	0.0
Discharge diagnosis correct?	
Yes	93.7
No	6.6
Reasons for incorrect discharge codes (n = 6)	
Date of discharge differed one day	1.1
Date of discharge differed two weeks	2.2
Date of discharge differed two months	2.2
Date of discharge differed five months	1.1



Chapter 4

The risk of cardiovascular disease following breast cancer by Framingham risk score

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Submitted

Abstract

Purpose

This study evaluates the risk of cardiovascular disease (CVD) following breast cancer, accounting for a woman's baseline risk of CVD.

Methods

Within the EPIC-NL (Dutch contribution of the European Prospective Investigation into Nutrition and Cancer) cohort, 1,103 women were diagnosed with breast cancer. For every breast cancer patient, three to four controls (n = 4,328) were selected matched for age, year, and time since cohort enrollment. Based on CVD risk factors at cohort enrollment, the ten-year risk of CVD was calculated and categorized as low (<10%), intermediate (10%-20%), or high (>20%). Cox proportional hazard models were used to assess the risk of a CVD event (hospitalization or death) or death from CVD of women with versus without breast cancer, adjusted for baseline CVD risk.

Results

After a median follow-up of five and six years, 92 (8.3%) and 325 (7.5%) CVD events occurred in women with and without breast cancer respectively. In the low CVD risk group, women with breast cancer had a 1.44 (95% CI = 1.00-2.06) times higher adjusted risk of a CVD event than women without breast cancer. In the intermediate and high CVD risk categories, the risk of a CVD event was similar in women with and without breast cancer. Overall, women with breast cancer had a 1.77 (95% CI = 1.10-2.86) times higher risk of death from CVD than women without breast cancer.

Conclusions

Among women with a low CVD risk, women with breast cancer have a higher risk of a CVD event than women without breast cancer. Overall, women with breast cancer were at a higher risk of CVD mortality than women without breast cancer.

Introduction

Breast cancer incidence and survival are high in developed countries[1]. Survival has substantially improved due to early detection by screening programs and improved treatments[2-4]. This has resulted in over 3 million 5-year breast cancer survivors worldwide[1]. Many of these women will die of conditions other than breast cancer[5,6]. Cardiovascular disease (CVD) is an important cause of death in the general population, also following breast cancer, with 24% of patients over 65 years dying of this disease[7,8].

Breast cancer patients may have a higher CVD risk compared to the general population. Although cancer treatments such as anthracycline-based regimens, trastuzumab, and radiotherapy reduce the risk of cancer recurrence and death, they have been associated with an increased risk of CVD[9-16]. Anthracycline-based chemotherapy and trastuzumab increase the risk of heart failure by 5-fold compared to regimens without these components[17,18]. Furthermore, radiotherapy increases the risk of death from circulatory disease with 25%[11]. Another reason that breast cancer patients may have a higher CVD risk is because risk factors for both diseases overlap, especially risk factors as obesity and physical inactivity[19]. Breast cancer patients may have a higher prevalence of CVD risk factors than the general population. Pre-existing CVD risk factors have also been associated with a higher risk of cancer treatment-induced cardiotoxicity[20,21].

Traditional CVD risk factors are used to compute the Framingham risk score[22]. Based on age, sex, current smoking, diabetes, and high systolic blood pressure, the ten-year future risk for a CVD event is predicted[22]. Except for a few studies[7,23,24], the majority did not adjust for traditional CVD risk factors when investigating the risk of CVD following breast cancer. None of the studies have taken into account the Framingham risk score[22]. We assessed the risk of CVD for women with a low (<10%), intermediate (10%-20%), and high (>20%) Framingham risk score. Next, we assessed the risk of death from CVD, adjusted for Framingham risk score.

Methods and materials

Study design and population

The current study included women participating in the Dutch contribution to the European Prospective Investigation into Cancer and Nutrition (EPIC-NL), which consists of the MORGEN and Prospect cohorts[25]. Details on the design and rationale of the EPIC-NL study have been described elsewhere[26]. Briefly, Prospect is a prospective cohort study that was set up to investigate the role of nutrition and biomarkers in the etiology of cancer. The MORGEN cohort was set up to monitor risk factors for chronic diseases in the Netherlands. MORGEN includes 22,654 men (45%) and women aged 20 to 64 years residing in three Dutch towns (Amsterdam, Doetinchem, and Maastricht) between 1993 and 1997[27]. Prospect includes 17,357 women aged 49 to 70 living in the city of Utrecht or its vicinity who participated in the nationwide Dutch breast cancer screening program between 1993 and 1997[28]. The ethics committees of the respective institutions approved both studies, and all participants gave their written informed consent.

Women with prevalent cancer at t0 were not eligible for the current study. Furthermore, women were not included if they had not given consent for linkage with vital status or morbidity registries (n = 2,717) or had missing information on hospital admission or cause of death (n = 55). The current study included all women diagnosed with a first (non-) invasive breast cancer during follow-up in the EPIC-NL cohort until December 31, 2010 (referred to as 'exposed' in the current study). Subsequently four women without breast cancer during follow-up were matched to the exposed women on age at breast cancer diagnosis (t1), year of breast cancer diagnosis (t1), and time between EPIC-NL enrolment (t0) and breast cancer diagnosis (t1) (the 'unexposed' group). We would like to stress that this is not a matched case-control study, but rather a prospective follow-up study, matched on the exposure status (breast cancer). The final study population consisted of 1,103 women diagnosed with breast cancer and 4,328 women without breast cancer.

Exposure (breast cancer) assessment

(Non-) invasive breast cancers in the EPIC-NL study were identified through regular linkages to the Dutch Cancer Registry. Details on the registry linkage have been described elsewhere[26]. Briefly, the Dutch Cancer Registry identifies incident cancer cases by hospital records and is 95% complete since 1989.

Framingham risk score

The Framingham risk score was calculated for the total study population based on the following characteristics at t0: age, smoking behavior (current or past/never), diabetes (presence or absence), systolic blood pressure (mmHg), total cholesterol (mmol/L), and high-density lipoprotein (HDL) cholesterol (mmol/L)[22]. The Framingham risk score ranges from -2 to 21, indicating a ten-year risk of a CVD event of lower than 1% to over 30% respectively. The current study categorized the Framingham risk score into three categories: low (score: <13, risk: <10%), intermediate (score: 13-17, risk: 10%-20%), high (score: >17, risk: >20%).

Characteristics

At t0, a general questionnaire was filled out by all participants including questions on demographic characteristics, presence of chronic diseases, and risk factors for chronic diseases. Educational level was categorized into low (primary school and lower vocational education) and other (advanced elementary education, intermediate vocational education, higher general secondary education, higher vocational education, and university). Physical activity was assessed by questions on occupational and recreational physical activity during the past year[29]. The Cambridge Physical Activity Index combined these activities and categorized them into active, moderately active, moderately inactive, and inactive[30,31]. Smoking behavior was categorized into current, former, or never. Alcohol consumption (gram ethanol per day) was assessed with the Food Frequency Questionnaire. The body mass index was calculated as weight divided by height squared, which were measured during physical examination. At this contact, blood pressure was measured twice in supine position on the left arm using a random zero sphygmomanometer (MORGEN) and on the right arm using a Boso Oscillomat (Prospect), from which the mean was taken. The comparability of both measurement procedures is reported in more detail elsewhere[32]. In MORGEN, serum cholesterol levels were assessed from ethylene-diamine-tetra-acetic acid (EDTA) serum samples drawn during physical examination at t0 using an enzymatic method[26]. In Prospect, cholesterol values are measured with EDTA using serum samples and/or with citrate plasma.

History of CVD before t1 was determined by combining data from the general questionnaire at t0 and data from the Dutch Centre for Health Care Information on hospital discharge diagnosis. The Dutch Centre for Health Care Information holds a standardized computerized register of hospital discharge diagnoses coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9).

Outcome assessment

The outcomes were a CVD event, defined as a hospitalization for CVD or death from CVD, and death from CVD. Follow-up data on the outcomes was complete until December 31, 2010. Follow-up data on CVD hospitalizations was obtained from the Dutch Centre for Health Care Information. The database was linked to the cohort on the basis of birth date, gender, postal code and general practitioner with a validated probabilistic method[33]. Causes of death were obtained from the Statistics Netherlands and have been coded according to the Ninth Revision of the International Classification of Diseases (ICD-9) until 1996, and after that, according to the Tenth Revision of the International Statistical Classification of Diseases (ICD-10). Death from CVD was based on primary and secondary causes of death. The primary cause of death is defined as the underlying disease that led to death. The secondary cause of death is either a complication of the primary cause, or another disease which might have contributed to the death.

Data analyses

Multiple imputation of missing values was performed using 20 imputed datasets to deal with missing values of demographics and cardiovascular risk factors at t0[34]. In the current study, determinants with missing values were educational level (n = 16, 0.3%), smoking behavior (n = 4, 0.1%), diabetes (n = 6, 0.1%), systolic blood pressure (n = 21, 0.4%), total cholesterol (n = 289, 5.3%), HDL cholesterol (n = 296, 5.5%), alcohol consumption (n = 16, 0.3%), and body mass index (n = 6, 0.1%).

Means (standard deviation (SD)) and medians (interquartile range (IQR)) were used to describe continuous variables with and without normally distributed data, respectively. Time at risk started at t1 and ended at the date of a CVD event (primary outcome) or date of death from CVD (secondary outcome), death from any other cause, end of study (December 31, 2010), or loss to follow-up (n = 29), whichever occurred first. Cox proportional hazard models[35] were used to estimate (adjusted) hazard ratios (HR) and 95% confidence intervals, comparing women with breast cancer to women without breast cancer. In addition, a competing risk analysis[36] was performed to deal with breast cancer as a competing risk: here the HR estimated by the Fine-Gray model account for the fact that women who died of breast cancer are no longer eligible of experiencing the event of interest.

The analyses on the risk of a CVD event (hospitalization or death due to CVD) were performed for the total study population and stratified by low (<10%), intermediate (10%-20%), or high (>20%) Framingham risk category. The analysis including the total study population was adjusted for Framingham risk score and body mass index. The analysis stratified by Framingham risk category was adjusted for age at t1, *i.e.* the stratification by Framingham risk created new groups and therefore women within these groups were

no longer age-matched, and body mass. The analysis on the risk of death from CVD was performed only for the total study population and adjusted for Framingham risk score; the low number of deaths did not allow for stratification by Framingham risk category. In addition, a sensitivity analysis was performed excluding women with a history of CVD to test the hypothesis that women with a known risk of CVD at breast cancer diagnosis receive less cardiac toxic breast cancer treatments.

Statistical analyses were conducted using IBM SPSS statistics version 23, except for the competing risk analyses which were conducted with SAS version 9.4.

Results

At EPIC-NL cohort enrolment (t0), median age of the study population was 54 years (IQR = 50-60) for women with breast cancer and women without breast cancer (Table 1). At t0, median Framingham risk score was not different for women who would develop breast cancer (13, IQR = 9-16) than for women who would not develop breast cancer (12, IQR = 9-16) (Table 1). The majority of women with and without breast cancer were in the low Framingham risk category: 61.3% and 66.0%, respectively. The mean body mass index at t0 was comparable for women with and without breast cancer in the low Framingham risk category: 25.2 (SD = 3.7) and 25.1 (SD = 3.8), respectively (Supplemental material Table A). In the intermediate and high Framingham risk categories, the mean body index was also comparable between women with breast cancer (27.3, SD = 4.2 and 28.5, SD = 3.8, respectively) and without breast cancer (27.2, SD = 4.2 and 28.1, SD = 4.5, respectively).

Breast cancer patients had 5 years (IQR = 2-9) median follow up (since t1) and this was 6 years (IQR = 3-10) for women without breast cancer (Table 1). During this period, 72 women with breast cancer (6.5%) and 290 without breast cancer (6.7%) were hospitalized for CVD (Table 2). Hospitalizations for acute pulmonary heart disease and heart failure were more common in women with breast cancer than in women without breast cancer. There were 24 women with breast cancer (2.2%) and 57 women without breast cancer (1.3%) who died of CVD as primary or secondary cause. Coronary heart disease and cerebrovascular accident were the most common causes of death from CVD in both groups. Death from breast cancer was the most prevalent cause of death among women with breast cancer (n = 115, 10.4%).

The risk of a CVD event (hospitalization or death due to CVD) did not differ between women with breast cancer and women without breast cancer: adjusted HR = 1.16 (95% CI = 0.92-1.47) (Table 3). However, in the low Framingham risk category the risk of a CVD event was higher in women with breast cancer than in women without breast cancer: adjusted HR = 1.44 (95% CI = 1.00-2.06). Excluding women with a history of CVD slightly increased this risk (Supplemental material Table B). Furthermore, in the total study population the risk of death from CVD was higher in women with breast cancer than in women without breast cancer: adjusted HR = 1.77 (95% CI = 1.10-2.86). The competing risk analyses did not change the interpretation of the results described above (Supplemental material Table C).

Table 1. Characteristics of 1,103 women with breast cancer and 4,328 matched* women without breast cancer at time of original cohort (EPIC-NL) enrolment (t0) and at time of breast cancer diagnosis or reference (t1)

	Women with breast cancer	Women without breast cancer
	n = 1,103	**n = 4,328**
At time of original cohort enrolment (t0)		
Original cohort, % (n)		
Prospect	70.4 (776)	68.9 (2,984)
MORGEN	29.6 (327)	31.1 (1,344)
Age at t0, yr, median (IQR)	50-60 (54)	50-60 (54)
Low education, % (n)†	45.2 (499)	43.9 (1,898)
Physical activity, % (n)		
Inactive	8.2 (90)	6.2 (270)
Moderately inactive	26.5 (292)	25.0 (1,080)
Moderately active	25.7 (284)	27.1 (1,174)
Active	39.6 (437)	41.7 (1,804)
Smoking behavior, % (n)		
Current	25.5 (281)	24.7 (1,069)
Former	36.2 (400)	32.6 (1,413)
Never	38.3 (422)	42.7 (1,846)
Alcohol consumption, g/day, mean (sd)	10.3 (13.7)	9.1 (12.4)
Diabetes, % (n)	2.4 (27)	2.0 (86)
Systolic blood pressure, mmHg, mean (sd)	130.8 (20.3)	128.6 (20.0)
Total cholesterol, mmol/L, mean (sd)	5.9 (1.1)	5.9 (1.1)
HDL cholesterol, mmol/L, mean (sd)	1.5 (0.4)	1.5 (0.4)
Body mass index, kg/m², mean (sd)	25.7 (4.1)	25.2 (4.1)
Framingham risk score, median (IQR)‡	13 (9-16)	12 (9-16)
Framingham risk categories, % (n)‡		
<10%	61.3 (676)	66.0 (2,856)
10%-20%	29.1 (321)	26.1 (1,131)
>20%	9.6 (106)	7.9 (341)
At time of breast cancer diagnosis or reference (t1)		
Age at t1, yr, median (IQR)	63 (56-68)	63 (56-68)
Calendar year of t1, n (%)		
1993-1999	26.7 (294)	26.6 (1,153)
2000-2005	38.3 (422)	38.3 (1,658)
2006-2010	35.1 (387)	35.1 (1,517)

	Women with breast cancer	Women without breast cancer
	n = 1,103	**n = 4,328**
History of cardiovascular disease at t1, % (n)	6.2 (68)	5.1 (219)
Time between t0 and t1, yr, median (IQR)	8 (4-11)	8 (4-11)
Follow-up time since t1 (until end of study), yr, median (IQR)	5 (2-9)	6 (3-10)

Abbreviations: IQR = Interquartile Range, sd = standard deviation, yr = years
*Women were matched by 1. age at original cohort enrolment (t0) and 2. time between original cohort enrolment and breast cancer diagnosis (t1-t0)
†Low educational level: lower vocational training or primary school
‡Framingham risk score is based on age at original cohort enrolment, smoking behavior, diabetes, systolic blood pressure, and total and HDL cholesterol

Table 2. Cardiovascular disease hospitalization and/or death and other causes of death in 1,103 women with breast cancer and 4,328 matched* women until December 31, 2010

	ICD-9	ICD-10	Women with breast cancer, % (n)	Women without breast cancer, % (n)
Hospitalization for CVD			**6.5 (72)**	**6.7 (290)**
Coronary heart disease	410-414, 427.5, 798.1, 798.2, 798.9	I20-I25, I46, R96	2.5 (28)	3.2 (137)
Cerebrovascular accident	430-434, 436	I60-I67, I69, G45	1.1 (12)	2.1 (89)
Acute pulmonary heart disease	415	I27	1.3 (14)	0.3 (12)
Heart failure	428	I50	0.8 (9)	0.5 (22)
Arterial embolism and thrombosis	444	I74	0.3 (3)	0.3 (11)
Other	440-443	I70-I73	0.5 (6)	0.4 (19)
Death from CVD†			**2.2 (24)**	**1.3 (57)**
Coronary heart disease	410-414, 427.5, 798.1, 798.2, 798.9	I20-I25, I46, R96	0.4 (4)	0.5 (23)
Cerebrovascular accident	430-438	I60-I67, I69, G45	0.7 (8)	0.4 (16)
Other	401, 415, 417, 424.1, 424.2, 424.9, 425, 427.3, 427.9, 428, 440, 441, 456	I10, I26, I27, I35, I36, I38, I48, I49.9, I50, I70, I71, I85	1.1 (12)	0.4 (18)
Primary cause of death other than CVD			**14.6 (161)**	**3.0 (170)**
Breast cancer	174	C50	10.4 (115)	0.0 (0)
Other type of cancer	140-173, 175-232, 234-239	C00-C49, C51-C97, D00-D49	2.6 (29)	2.3 (98)
Other	All other codes	All other codes	1.5 (17)	1.6 (72)

Abbreviation: CVD = cardiovascular disease, ICD = International Classification of Diseases

*Women were matched by 1) age at original cohort enrolment (t0) and 2) time between original cohort enrolment and breast cancer diagnosis (t1-t0).

†Primary and/ or secondary CVD causes of death.

‡9 women with breast cancer and 8 women without breast cancer died of CVD as secondary cause of death.

Numbers may overlap as women with CVD morbidity may have died of CVD (n = 4 or n =22 for women with or without breast cancer, respectively) or due to another cause.

Table 3. The risk of cardiovascular disease hospitalization and/ or death following breast cancer for the total study population and by low, intermediate or high Framingham risk prior to diagnosis until at most December 31, 2010

	Number of women	Total PY	Number of CVD (%)*	Number of CVD per 100 PY	Unadjusted HR†	Adjusted HR†‡	Adjusted HR†§
CVD event (hospitalization or death)							
Total study population (n = 5,431)							
Women without breast cancer	4,328	28,035	325 (7.5)	1.2	1.00 (ref)	1.00 (ref)	1.00 (ref)
Women with breast cancer	1,103	6,401	92 (8.3)	1.4	1.23 (0.97-1.55)	1.17 (0.92-1.57)	1.16 (0.92-1.47)
Framingham risk <10% (n = 3,532)							
Women without breast cancer	2,856	18,518	129 (4.5)	0.7	1.00 (ref)	1.00 (ref)	1.00 (ref)
Women with breast cancer	676	3,783	39 (5.8)	1	1.45 (1.01-2.07)	1.45 (1.01-2.08)	1.44 (1.00-2.06)
Framingham risk 10%-20% (n = 1,452)							
Women without breast cancer	1,131	7,187	124 (10.9)	1.7	1.00 (ref)	1.00 (ref)	1.00 (ref)
Women with breast cancer	321	2,031	30 (9.3)	1.5	0.86 (0.57-1.29)	0.88 (0.59-1.32)	0.88 (0.59-1.32)
Framingham risk >20% (n = 447)							
Women without breast cancer	341	2,287	68 (19.9)	3	1.00 (ref)	1.00 (ref)	1.00 (ref)
Women with breast cancer	106	584	23 (21.7)	3.9	1.27 (0.78-2.07)	1.27 (0.78-2.07)	1.27 (0.78-2.06)
Death from CVD							
Total study population (n = 5,431)							
Women without breast cancer	4,328	29,207	57 (1.3)	0.2	1.00 (ref)	1.00 (ref)	-
Women with breast cancer	1,103	6,717	24 (2.2)	0.4	1.88 (1.16-3.03)	1.77 (1.10-2.86)	

Abbreviations: CVD = cardiovascular disease, HR = hazard ratio, PY = person-years

*Row percentages of number of women

†Cox proportional hazard models

‡Models on the total study population are adjusted for Framingham risk score (and body mass index). Models stratified by Framingham risk category are adjusted for age at breast cancer diagnosis or reference (age at t1) and body mass index.

Discussion

The results of this study indicated that the risk of a CVD event (hospitalization or death) among women with a low Framingham risk (<10%) was 44% higher in women with breast cancer compared to women without breast cancer. No difference was observed in the total study population. We did find that women with breast cancer have a 77% higher risk of death from CVD than women without breast cancer.

Although breast cancer is the main cause of death in women with breast cancer, CVD is increasingly recognized as an important contributor to mortality in breast cancer survivors[37-39]. CVD may be related to cardiac toxic or metabolic effects of some breast cancer treatments such as trastuzumab, anthracycline-based regimens, and radiotherapy[9,40-42].

Several CVD disorders may contribute to a higher CVD risk following breast cancer. Women with breast cancer in the low Framingham risk category were more often hospitalized with heart failure or acute pulmonary heart disease than low-risk women without breast cancer. Heart failure is a known complication induced by anthracycline-based chemotherapies, trastuzumab, and radiotherapy-induced cardiomyopathy due to coronary artery calcifications caused by high radiotherapy heart dose[43-45]. Acute pulmonary heart disease can be caused by vascular changes as a result of tissue damage due to radiotherapy, as part of the lungs is irradiated[46]. Both heart failure and radiation-induced pulmonary damage may become evident during the first year after treatment or later[46,47]. We also observed that women with breast cancer died more often due to a cerebrovascular accident. Women who received hormonal treatment (tamoxifen) had a 90% higher risk of a cerebrovascular accident[48]. Studies reported conflicting results on the association between cerebrovascular accident and radiotherapy to the supraclavicular lymph nodes: Nilsson et al. (2005) found a 12% higher risk for women with a history of breast cancer, while Hooning et al. (2006) did not found a higher risk in women with breast cancer[48,49].

A study that stratified women by CVD risk at breast cancer diagnosis showed that in the low CVD risk group, women treated with radiotherapy were not at increased risk of CVD[50]. However, CVD risk was increased for women with an intermediate or high CVD risk[50]. These results are, however, difficult to compare with ours as a comparison with women without breast cancer is lacking. Our finding of a higher risk of CVD death in women with breast cancer is in line with many other studies[7,37,51,52]. Riihimaki et al. (2012) showed that women with breast cancer have a 1.29 time higher risk of dying of heart failure[51]. They did, however, not correct for CVD risk factors other than age. Bradshaw et al. (2016) reported a 1.9 times increased risk of CVD death in women with breast cancer, after adjustment for traditional CVD risk factors[7]. This risk manifested approximately seven years after

diagnosis. Furthermore, studies have found increased risk of CVD events up to and beyond 20 years after diagnosis[8,9,53]. Age is a well-known CVD risk factor[54] and cardiac toxicity induced by radiotherapy manifest itself many years following treatment[15,55]. As the current study has a relative short follow-up time (median of five to six years), this may indicate that the risk of death from CVD in breast cancer patients may become larger over time.

There is also a suggestive clarification for the observations in our study. The sensitivity analysis shows that the risk of a CVD event in women with breast cancer with a low Framingham risk score was higher when women with a history of CVD were excluded. This may indicate that in clinical practice women with a higher CVD risk, *i.e.* history of CVD, receive less cardiac toxic cancer treatments than women without a higher CVD risk[56]. As such, women with breast cancer in the low Framingham risk category may have received more often systemic therapy, *i.e.* anthracyclines and trastuzumab, and radiotherapy (including differences in laterality of the irradiated breast and targeted volumes) than women with an intermediate or high Framingham risk. Unfortunately, we were not able to test other hypotheses related to cancer treatment as this information is missing for over one third of patients.

We were not able to account for changes in CVD risk factors after EPIC enrolment. We assume that these factors used for calculating the Framingham risk score remained more or less similar until time of breast cancer diagnosis (t1) and thereafter. However, CVD risk factors may have changed between t0 and t1 (median time of eight years) and after t0. This would result in women shifting to another Framingham risk category. It's unclear how this would affect our results. Another concern is that we likely have missed women with CVD. The use of hospital discharge registry underestimates the true incidence rates, especially for coronary heart disease and heart failure[57]. This underestimation is most likely nondifferential and therefore not creating bias, as it can be expected that the underestimated incidences are not different for women with breast cancer than for women without breast cancer.

To conclude, this study shows that among women with a low Framingham risk, women with breast cancer have a higher risk of a CVD event (hospitalization or death) than women without breast cancer. Overall, women with breast cancer have a higher risk of death from CVD than women without breast cancer adjusted for Framingham risk score. Future research may investigate an individualized approach for breast cancer patients to optimize the balance between high breast cancer tumor control and minimal cancer treatment-induced CVD risk.

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References

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.1, cancer incidence and mortality worldwide: IARC CancerBase. 2014; 11.
2. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, et al. 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*. 2016.
3. Myers ER, Moorman P, Gierisch JM, et al. Benefits and harms of breast cancer screening: A systematic review. *JAMA*. 2015; 314 (15): 1615-1634.
4. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. 2005; 353 (17): 1784-1792.
5. Hanrahan EO, Gonzalez-Angulo AM, Giordano SH, et al. Overall survival and cause-specific mortality of patients with stage T1a,bN0M0 breast carcinoma. *J Clin Oncol*. 2007; 25 (31): 4952-4960.
6. Chapman JA, Meng D, Shepherd L, et al. Competing causes of death from a randomized trial of extended adjuvant endocrine therapy for breast cancer. *J Natl Cancer Inst*. 2008; 100 (4): 252-260.
7. Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD. Cardiovascular disease mortality among breast cancer survivors. *Epidemiology*. 2016; 27 (1): 6-13.
8. Colzani E, Liljegren A, Johansson AL, et al. Prognosis of patients with breast cancer: Causes of death and effects of time since diagnosis, age, and tumor characteristics. *J Clin Oncol*. 2011; 29 (30): 4014-4021.
9. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, et al. 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 8,135 women in 22 randomized trials. *Lancet*. 2014; 383 (9935): 2127-2135.
10. McGale P, Darby SC, Hall P, et al. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. *Radiother Oncol*. 2011; 100 (2): 167-175.
11. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. *Lancet*. 2005; 366 (9503): 2087-2106.
12. Dalfardi B, Kashy-Zonouzy K, Asvadi-Kermani T. Chemotherapy-induced cardiomyopathy in breast cancer patients. *Res Cardiovasc Med*. 2014; 3 (3): e19096.
13. Chavez-MacGregor M, Zhang N, Buchholz TA, et al. Trastuzumab-related cardiotoxicity among older patients with breast cancer. *J Clin Oncol*. 2013; 31 (33): 4222-4228.

14. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol*. 2007; 25 (25): 3808-3815.

15. Darby SC, Bronnum D, Correa C, et al. A dose-response relationship for the incidence of radiation-related heart disease. *Int J Radiat Oncol Biol Phys*. 2010; 78 (3): S49-S50.

16. Rehammar JC, Jensen MB, McGale P, et al. Risk of heart disease in relation to radiotherapy and chemotherapy with anthracyclines among 19,464 breast cancer patients in Denmark, 1977-2005. *Radiother Oncol*. 2017; 123 (2): 299-305.

17. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: Systematic review and meta-analysis of randomized controlled trials. *BMC Cancer*. 2010; 10: 337-2407-10-337.

18. Moja L, Brambilla C, Compagnoni A, Pistotti V. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev*. 2006 (4).

19. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. *Circulation*. 2016; 133 (11): 1104-1114.

20. Jawa Z, Perez RM, Garlie L, et al. Risk factors of trastuzumab-induced cardiotoxicity in breast cancer: A meta-analysis. *Medicine (Baltimore)*. 2016; 95 (44): e5195.

21. Hooning MJ, Botma A, Aleman BM, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst*. 2007; 99 (5): 365-375.

22. D'Agostino RB S, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham heart study. *Circulation*. 2008; 117 (6): 743-753.

23. McCullough ML, Gapstur SM, Shah R, et al. Pre- and postdiagnostic diet in relation to mortality among breast cancer survivors in the CPS-II nutrition cohort. *Cancer Causes Control*. 2016.

24. Nichols HB, Trentham-Dietz A, Egan KM, et al. Body mass index before and after breast cancer diagnosis: Associations with all-cause, breast cancer, and cardiovascular disease mortality. *Cancer Epidemiol Biomarkers Prev*. 2009; 18 (5): 1403-1409.

25. Bingham S, Riboli E. Diet and cancer--the European prospective investigation into cancer and nutrition. *Nat Rev Cancer*. 2004; 4 (3): 206-215.

26. Beulens JW, Monninkhof EM, Verschuren WM, et al. Cohort profile: The EPIC-NL study. *Int J Epidemiol*. 2010; 39 (5): 1170-1178.

27. Smit HA, Verschuren W, Bueno-de-Mesquita HB, Seidell JC. Monitoring van risicofactoren en gezondheid in Nederland (MORGEN-project): Doelstellingen en werkwijze. 1994; 263200001 (Report No.: 263200001).

28. Boker LK, van Noord PA, van der Schouw YT, et al. Prospect-EPIC Utrecht: Study design and characteristics of the cohort population. European prospective investigation into cancer and nutrition. *Eur J Epidemiol*. 2001; 17 (11): 1047-1053.

29. Haftenberger M, Schuit AJ, Tormo MJ, et al. Physical activity of subjects aged 50-64 years involved in the European prospective investigation into cancer and nutrition (EPIC). *Public Health Nutr*. 2002; 5 (6B): 1163-1176.

30. Wareham NJ, Jakes RW, Rennie KL, et al. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European prospective investigation into cancer and nutrition (EPIC) study. *Public Health Nutr*. 2003; 6 (4): 407-413.

31. InterAct Consortium, Peters T, Brage S, et al. Validity of a short questionnaire to assess physical activity in 10 European countries. *Eur J Epidemiol*. 2012; 27 (1): 15-25.

32. Schulze MB, Kroke A, Saracci R, Boeing H. The effect of differences in measurement procedure on the comparability of blood pressure estimates in multi-centre studies. *Blood Press Monit*. 2002; 7 (2): 95-104.

33. Herings RM, Bakker A, Stricker BH, Nap G. Pharmaco-morbidity linkage: A feasibility study comparing morbidity in two pharmacy based exposure cohorts. *J Epidemiol Community Health*. 1992; 46 (2): 136-140.

34. van der Heijden GJ, Donders AR, Stijnen T, Moons KG. Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: A clinical example. *J Clin Epidemiol*. 2006; 59 (10): 1102-1109.

35. Cox DR. Regression models and life-tables. *J R Stat Soc*. 1972; 34: 187-202.

36. Fine JP GR. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association*. 1999; 94: 496-509.

37. Gernaat SAM, Ho PJ, Rijnberg N, et al. Risk of death from cardiovascular disease following breast cancer: A systematic review. *Breast Cancer Res Treat*. 2017.

38. Hooning MJ, Aleman BM, van Rosmalen AJ, Kuenen MA, Klijn JG, van Leeuwen FE. Cause-specific mortality in long-term survivors of breast cancer: A 25-year follow-up study. *Int J Radiat Oncol Biol Phys*. 2006; 64 (4): 1081-1091.

39. Schairer C, Mink PJ, Carroll L, Devesa SS. Probabilities of death from breast cancer and other causes among female breast cancer patients. *J Natl Cancer Inst*. 2004; 96 (17): 1311-1321.

40. Zaorsky NG, Churilla TM, Egleston BL, et al. Causes of death among cancer patients. *Ann Oncol*. 2016.

41. Doyle JJ, Neugut AI, Jacobson JS, Grann VR, Hershman DL. Chemotherapy and cardiotoxicity in older breast cancer patients: A population-based study. *J Clin Oncol*. 2005; 23 (34): 8597-8605.

42. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. *Lancet*. 2005; 365 (9472): 1687-1717.

43. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001; 344 (11): 783-792.

44. Vejpongsa P, Yeh ET. Prevention of anthracycline-induced cardiotoxicity: Challenges and opportunities. *J Am Coll Cardiol*. 2014; 64 (9): 938-945.

45. Vasu S, Hundley WG. Understanding cardiovascular injury after treatment for cancer: An overview of current uses and future directions of cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2013; 15 (1).

46. Omarini C, Thanopoulou E, Johnston SR. Pneumonitis and pulmonary fibrosis associated with breast cancer treatments. *Breast Cancer Res Treat*. 2014; 146 (2): 245-258.

47. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: Incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol*. 2009; 53 (24): 2231-2247.

48. Hooning MJ, Dorresteijn LD, Aleman BM, et al. Decreased risk of stroke among 10-year survivors of breast cancer. *J Clin Oncol*. 2006; 24 (34): 5388-5394.

49. Nilsson G, Holmberg L, Garmo H, Terent A, Blomqvist C. Increased incidence of stroke in women with breast cancer. *Eur J Cancer*. 2005; 41 (3): 423-429.

50. Onwudiwe NC, Kwok Y, Onukwugha E, et al. Cardiovascular event-free survival after adjuvant radiation therapy in breast cancer patients stratified by cardiovascular risk. *Cancer Med*. 2014; 3 (5): 1342-1352.

51. Riihimaki M, Thomsen H, Brandt A, Sundquist J, Hemminki K. Death causes in breast cancer patients. *Ann Oncol*. 2012; 23 (3): 604-610.

52. Roychoudhuri R, Robinson D, Putcha V, Cuzick J, Darby S, Moller H. Increased cardiovascular mortality more than fifteen years after radiotherapy for breast cancer: A population-based study. *BMC Cancer*. 2007; 7: 9.

53. Darby SC, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: Prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol*. 2005; 6 (8): 557-565.

54. Tsao CW, Vasan RS. Cohort profile: The Framingham heart study (FHS): Overview of milestones in cardiovascular epidemiology. *Int J Epidemiol*. 2015; 44 (6): 1800-1813.

55. Cuomo JR, Sharma GK, Conger PD, Weintraub NL. Novel concepts in radiation-induced cardiovascular disease. *World J Cardiol*. 2016; 8 (9): 504-519.

56. Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American society of clinical oncology clinical practice guideline. *J Clin Oncol*. 2017; 35 (8): 893-911.

57. Merry AH, Boer JM, Schouten LJ, et al. Validity of coronary heart diseases and heart failure based on hospital discharge and mortality data in the Netherlands using the cardiovascular registry maastricht cohort study. *Eur J Epidemiol*. 2009; 24 (5): 237-247.

Supplemental material

Table A. Characteristics of 1,103 women with breast cancer and 4,328 matched* women without breast cancer at time of original cohort (EPIC-NL) enrolment (t0) and at time of breast cancer diagnosis or reference (t1) by low, intermediate, and high Framingham risk

	Framingham risk <10%		Framingham risk 10%-20%		Framingham risk >20%	
	Women with breast cancer	Women without breast cancer	Women with breast cancer	Women without breast cancer	Women with breast cancer	Women without breast cancer
	n = 676	n = 2,856	n = 321	n = 1,131	n = 106	n = 341
The following data were collected at time of original cohort enrolment (t0)						
Original cohort, % (n)						
Prospect	59.6 (403)	59.8 (1,707)	84.7 (272)	85.6 (968)	95.3 (101)	90.6 (309)
MORGEN	40.4 (273)	40.2 (1,149)	15.3 (49)	14.4 (163)	4.7 (5)	9.4 (32)
Age at t0, yr, median (IQR)	52 (49-57)	52 (49-57)	58 (54-64)	59 (54-64)	63 (58-67)	63 (58-67)
Low education, % (n)†	39.2 (265)	38.1 (1,088)	57.0 (183)	53.9 (610)	49.1 (52)	59.2 (202)
Physical activity, % (n)						
Inactive	6.7 (45)	5.1 (147)	10.3 (33)	6.8 (77)	11.3 (12)	13.5 (46)
Moderately inactive	23.2 (157)	22.9 (653)	31.8 (102)	28.7 (325)	31.1 (33)	29.9 (102)
Moderately active	26.5 (179)	28.2 (804)	25.5 (82)	24.4 (276)	21.7 (23)	27.6 (94)
Active	43.6 (295)	43.8 (1,252)	32.4 (104)	40.1 (453)	35.8 (38)	29.0 (99)
Smoking behavior, % (n)						
Current	20.7 (140)	21.4 (612)	29.9 (96)	28.8 (326)	41.5 (44)	38.4 (131)
Former	39.5 (267)	35.4 (1,010)	33.0 (106)	28.6 (323)	25.5 (27)	23.2 (79)
Never	39.8 (269)	43.2 (1,234)	37.1 (119)	42.6 (482)	32.1 (34)	38.4 (131)
Alcohol consumption, g/day, mean (sd)	10.5 (13.5)	9.2 (11.7)	9.9 (14.8)	9.2 (13.9)	10.2 (13.0)	8.1 (12.5)
Diabetes, % (n)	0.3 (2)	0.2 (7)	3.7 (12)	2.6 (29)	12.3 (13)	14.7 (50)

Systolic blood pressure, mmHg, mean (sd)	120.9 (13.7)	119.8 (13.7)	142.4 (18.2)	141.5 (17.7)	158.0 (18.8)	158.8 (18.5)
Total cholesterol, mmol/L, mean (sd)	5.6 (1.0)	5.7 (1.0)	6.3 (1.0)	6.4 (1.0)	6.8 (0.9)	6.7 (1.2)
HDL cholesterol, mmol/L, mean (sd)	1.6 (0.4)	1.6 (0.4)	1.4 (0.4)	1.4 (0.4)	1.2 (0.3)	1.2 (0.3)
Body mass index, kg/m², mean (sd)	25.2 (3.7)	25.1 (3.8)	27.3 (4.2)	27.2 (4.2)	28.5 (3.8)	28.1 (4.5)
Framingham risk score, median (IQR)‡	8 (6-11)	8 (5-10)	15 (14-16)	15 (14-16)	19 (18-21)	19 (18-21)
The following data were collected at time of breast cancer diagnosis or reference (t1)						
Age at t1, yr, median (IQR)	60 (53-65)	60 (54-65)	66 (61-71)	66 (62-71)	69 (64-73)	69 (64-73)
Year of t1, n (%)						
1993-1999	25.1 (170)	25.8 (737)	29.0 (93)	27.1 (306)	30.2 (32)	32.0 (109)
2000-2005	35.5 (240)	37.2 (1,062)	42.0 (135)	39.4 (446)	43.4 (46)	44.0 (150)
2006-2010	39.4 (266)	37.0 (1,057)	29.0 (93)	33.5 (379)	26.4 (28)	24.0 (82)
Time between t0 and t1, yr, median (IQR)	8 (4-12)	8 (4-12)	7 (3-11)	8 (4-11)	6 (3-10)	6 (3-10)
Follow-up time since t1 (until end of study), yr, median (IQR)	5 (2-9)	6 (2-10)	6 (3-9)	6 (3-10)	5 (2-8)	7 (3-10)
History of cardiovascular disease at t1, n (%)	3.8 (26)	3.1 (89)	9.3 (30)	8.0 (90)	11.3 (12)	11.7 (40)

Abbreviations: IQR = Interquartile Range, sd = standard deviation, yr = years

*Women were matched by 1) age at EPIC-NL enrollment (age at t0) and 2) time between EPIC-NL enrollment and breast cancer diagnosis (t1-t0)

†Low educational level: lower vocational training or primary school

‡Framingham risk score is based on age at original cohort enrolment (age at t0), smoking behavior, diabetes, systolic blood pressure, and total and HDL cholesterol (all measured at t0)

Table B. The risk of cardiovascular disease hospitalization and/or death following breast cancer for the total study population and by low, intermediate, or high Framingham risk until December 31, 2010. *Sensitivity analysis: women with a history of cardiovascular disease at t1 were excluded.*

	Number of women	Total PY	CVD (%)*	CVD per 100 PY	Unadjusted HRs†	Adjusted HRs†‡	Adjusted HRs†§
CVD event (hospitalization or death)							
Total study population (n = 5,144)							
Women without breast cancer	4,109	28,035	320 (7.8)	1.2	1.00 (ref)	1.00 (ref)	1.00 (ref)
Women with breast cancer	1,035	6,401	89 (8.6)	1.5	1.22 (0.97-1.54)	1.16 (0.92-1.47)	1.16 (0.92-1.47)
Framingham risk <10% (n = 3,417)							
Women without breast cancer	2,767	18,518	129 (4.7)	0.7	1.00 (ref)	1.00 (ref)	1.00 (ref)
Women with breast cancer	650	3783	39 (6.0)	1.1	1.48 (1.03-2.12)	1.47 (1.03-2.11)	1.46 (1.02-2.10)
Framingham risk 10%-20% (n = 1,332)							
Women without breast cancer	1,041	7,187	123 (11.7)	1.8	1.00 (ref)	1.00 (ref)	1.00 (ref)
Women with breast cancer	291	2031	27 (9.3)	1.4	0.80 (0.52-1.22)	0.82 (0.53-1.25)	0.82 (0.54-1.25)
Framingham risk >20% (n = 395)							
Women without breast cancer	301	2287	65 (21.5)	3.1	1.00 (ref)	1.00 (ref)	1.00 (ref)
Women with breast cancer	94	584	23 (24.5)	4.3	1.33 (0.82-2.16)	1.34 (0.82-2.17)	1.33 (0.82-2.17)
Death from CVD							
Total study population (n = 5,144)							
Women without breast cancer	4,109	29,207	51 (1.2)	0.2	1.00 (ref)	1.00 (ref)	-
Women with breast cancer	1,035	6,717	21 (2.0)	0.3	1.83 (1.10-3.05)	1.73 (1.04-2.87)	

Abbreviations: CVD = cardiovascular disease, HRs = hazard ratios, PY = person-years

*Row percentages of number of women

†Cox proportional hazard models

‡Models on the total study population are adjusted for Framingham risk score (and body mass index). Models stratified by Framingham risk category are adjusted for age at breast cancer diagnosis or reference (age at t1) and body mass index.

Table C. The risk of cardiovascular disease hospitalization and/or death following breast cancer in the total study population and by low, intermediate, and high Framingham risk until at most December 31, 2010. *Competing risk analyses: breast cancer as competing risk.*

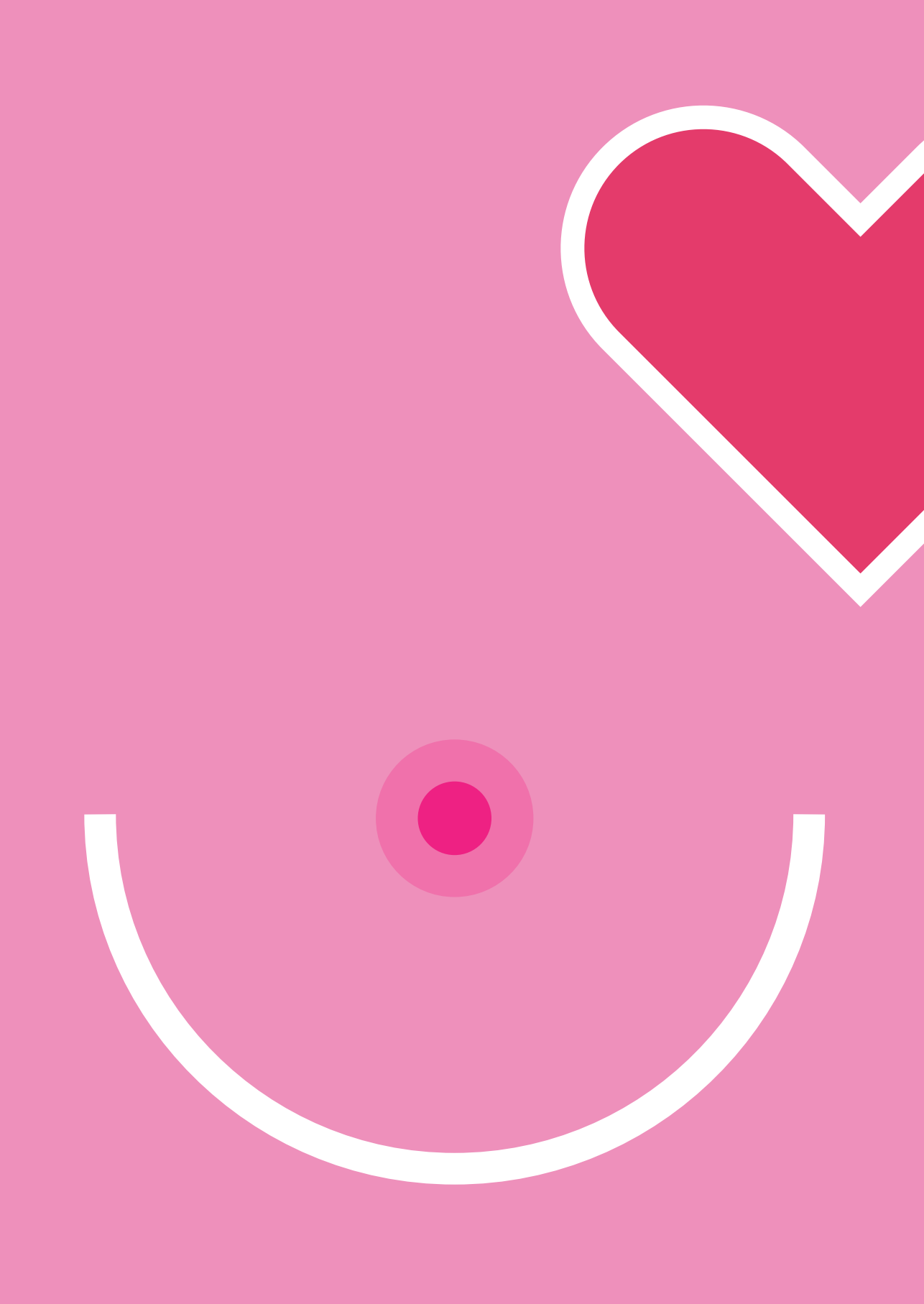
	Number of women	Total PY	CVD (%)*	CVD per 100 PY	Unadjusted HRs†	Adjusted HRs†‡	Adjusted HRs†§
CVD event (hospitalization or death)							
Total study population (n = 5,431)							
Women without breast cancer	4,328	28,035	325 (7.5)	1.2	1.00 (ref)	1.00 (ref)	1.00 (ref)
Women with breast cancer	1,103	6,401	92 (8.3)	1.4	1.14 (0.91-1.44)	1.08 (0.86-1.37)	1.08 (0.86-1.36)
Framingham risk <10% (n = 3,532)							
Women without breast cancer	2,856	18,518	129 (4.5)	0.7	1.00 (ref)	1.00 (ref)	1.00 (ref)
Women with breast cancer	676	3783	39 (5.8)	1	1.35 (0.95-1.93)	1.36 (0.95-1.94)	1.34 (0.94-1.93)
Framingham risk 10%-20% (n = 1,452)							
Women without breast cancer	1,131	7,187	124 (10.9)	1.7	1.00 (ref)	1.00 (ref)	1.00 (ref)
Women with breast cancer	321	2031	30 (9.3)	1.5	0.80 (0.54-1.20)	0.81 (0.54-1.22)	0.81 (0.54-1.22)
Framingham risk >20% (n = 447)							
Women without breast cancer	341	2287	68 (19.9)	3	1.00 (ref)	1.00 (ref)	1.00 (ref)
Women with breast cancer	106	584	23 (21.7)	3.9	1.17 (0.73-1.89)	1.16 (0.72-1.88)	1.16 (0.72-1.87)
Death from CVD							
Total study population (n = 5,431)							
Women without breast cancer	4,328	29,207	57 (1.3)	0.2	1.00 (ref)	1.00 (ref)	-
Women with breast cancer	1,103	6,717	24 (2.2)	0.4	1.72 (1.07-2.77)	1.58 (0.98-2.55)	

Abbreviations: CVD = cardiovascular disease, HRs = hazard ratios, PY = person-years

*Row percentages of number of women

†Models by the Fine and Gray method

‡Models on the total study population are adjusted for Framingham risk score (and body mass index). Models stratified by Framingham risk category are adjusted for age at breast cancer diagnosis or reference (age at t1) and body mass index.



Chapter 5

Risk of death from cardiovascular disease following breast cancer in Southeast Asia: a prospective cohort study

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Abstract

Breast cancer incidence and survival is high in Southeast Asia. As such, many women diagnosed with breast cancer are at risk of dying of other causes. Given the increased risk of cardiac toxicity induced by breast cancer treatments, it is important to identify patients at high risk of death from cardiovascular disease (CVD). The aim of this study was to investigate if this risk varies by age and ethnicity. Patient details were obtained from 5,868 Chinese, Malay, and Indian women diagnosed with *in situ* or non-metastasized invasive breast cancer at the National University Hospital of Singapore and KK Women's and Children's Hospital in Singapore. Death causes were obtained from the National Registry of Births and Deaths. Flexible parametric survival models estimated CVD mortality rates and hazard ratios. During a median follow-up of six years, 1,010 deaths occurred of which 6.8% were due to CVD. CVD mortality rates of older women peaked within the first year following diagnosis and increased over time since diagnosis. Indian had more than double the risk of CVD mortality than Chinese, independent of age at diagnosis and stage. Taking ethnicity and age into account may promote CVD risk stratification and management in (Southeast Asian) women with breast cancer.

Introduction

Breast cancer incidence is rising dramatically in Southeast Asia, which, in combination with improved survival rates due to earlier detection and improved treatments, leads to an increasing number of women living with or after breast cancer[1,2]. Many of these women are at risk of dying of other causes than breast cancer[3-5]. Breast cancer patients treated with adjuvant treatments such as radiotherapy or chemotherapy may be at increased absolute risk of treatment-induced cardiac toxicity, and therefore, to develop CVD[6-9]. As such, CVD is now the second most important cause of death among women with breast cancer, with up to 24% of breast cancer patients dying of CVD[4,5].

In the multi-ethnic population of Southeast Asia, comprising mainly of Chinese, Malay, and Indian people, there are ethnic differences in breast cancer survival[10]. Malay breast cancer patients have a higher risk of overall death following breast cancer compared to Chinese, regardless of age at diagnosis, tumor and treatment characteristics[10]. Furthermore, ethnic differences in severity of and death due to CVD is observed in high risk Southeast Asian patients, though not in breast cancer patients, with lowest severity of CVD in Chinese and highest CVD-specific mortality rates in Malay[11,12].

Given the increased risk of cardiac toxicity induced by breast cancer treatments, it is important to identify patients at high risk of CVD mortality. Taking the risk (factors) of CVD into account with breast cancer treatment decision will promote personalized CVD risk stratification and management of (Southeast Asian) breast cancer patients. The objective of the present study was to investigate the risk of CVD mortality following breast cancer in Southeast Asia, and to assess if these risks vary by age at diagnosis and ethnicity.

Methods and materials

Cohort study

This prospective cohort study was conducted within the context of two hospital-based breast cancer registries from the National University Hospital (NUH) and KK Women's and Children's Hospital (KKH) in Singapore. All methods were carried out in accordance with the guidelines and regulations of NUH and KKH. The National University Hospital of Singapore received ethic approval from the National Healthcare Group Domain Specific Review Board and KK Hospital in Singapore received approval from SingHealth Centralized Institutional Review Board. The need for informed consent from all patients was waived by these ethics review boards.

The NUH breast cancer registry contains data of all 4,122 women diagnosed with breast cancer 1990 and 2011. Details of the registry have been described elsewhere[13]. Data were collected retrospectively for 492 patients diagnosed between 1990 and 1995, and prospectively for 3,630 patients diagnosed after 1995. The KKH breast cancer registry contains prospectively collected data of all 2,192 women diagnosed with breast cancer between 2005 and 2015. Both registries from NUH and KKH include data on patient's socio-demographic characteristics, tumor and treatment profile.

For the present study, breast cancer patients with distant metastases at diagnosis (n = 431) were excluded, leaving 5,868 women with *in situ* or non-metastasized invasive breast cancer. Ethnicity was categorized into four groups: Chinese, Malay, Indian, and Other (e.g. Eurasian, Caucasian). Other variables of interest included age at diagnosis, year of diagnosis, tumor stage at diagnosis according to the classification of malignant tumors (TNM)[14], tumor differentiation (good, moderate, poor, unknown), estrogen-receptor status (positive >1% of tumor cells expressing estrogen receptors, negative, unknown), breast cancer treatment including surgery (yes, no, unknown), chemotherapy (yes, no, unknown), radiotherapy (yes, no, unknown) and hormonal therapy (yes, no, unknown).

Outcomes

For the NUH breast cancer registry, information on vital status and cause of death was obtained from the National Registry of Births and Deaths in Singapore on April 30, 2015, and was complete for all 3,841 breast cancer patients from NUH. For the KKH breast cancer registry, vital status of each patient was known until last clinical follow-up visit, and cause of death was verified from the National Registry of Births and Deaths in Singapore for patients who did not show up at the follow-up visit and could not be contacted. The National Registry of Births and Deaths has certificates on causes of death issued by doctors or authorized medical practitioners within 24 hours after death. Causes of death were

classified according to the International Classification of Diseases (ICD) versions 8, 9 or 10 codes, and regrouped into: death as a result of CVD (ICD8: 390 to 459; ICD9: 390 to 459; ICD10: 100 to 199), death as a result of breast cancer (ICD8: 174; ICD9: 174; ICD10: C50), death as a result of all other cause (all ICD codes except those already listed).

Statistical analysis

Demographics, tumor characteristics, treatment details and survival time were described for the total population and for the total number of deaths, deaths from CVD, deaths from breast cancer and deaths from all other cause within ten years of diagnosis. Time at risk for specific causes of death, *i.e.* CVD, breast cancer, and all other causes, was calculated as the minimum of time between date of breast cancer diagnosis and date of death, end of study (April 30, 2015), last clinical follow-up visit, or ten years post diagnosis, whichever occurred first.

Flexible parametric survival models were used to estimate both mortality rates and hazard ratios (HRs) for death from CVD, death from breast cancer, and death from all other cause within 10 years after diagnosis, using restricted cubic spline functions[15]. First, we estimated unadjusted mortality rates for death from CVD, breast cancer and other causes within 10 years after diagnosis for age at diagnosis in three categories (< 50, 50-69, ≥70 years). This model used three internal knots in total: two internal knots for the association between age at diagnosis in categories and follow-up time, and one knot for the time varying effect of age. Mortality rates were reported per 1,000 person-years, using days as underlying time. Second, (crude) HRs with 95% confidence intervals (CI) were estimated as a measure of association between the main determinant ethnicity – Chinese, Malay, and Indian; other ethnicities were excluded due to the small number of 104 patients with heterogeneous origins – and outcomes (death from CVD, breast cancer, or other causes). These HRs are similar to those estimated by the Cox's proportional hazard models. Flexible parametric survival models, however, have the ability to estimate the baseline mortality rates allowing the HRs to change over time. Crude HRs for determinants other than ethnicity and age were estimated in a similar manner. Those that were statistically significant were included in the multivariable model. Due to having only 67 CVD-specific deaths, the maximum degrees of freedom used was limited to six for CVD-specific mortality. The following models were used for the analysis: (1) CVD-specific mortality model which has zero internal knots assuming proportional hazards over 10 years of follow-up and is adjusted for age at diagnosis (per ten year increase) and stage (*in situ* to stage II, stage III or unknown, women with unknown stage showed similar mortality risks as those with stage III), (2) breast cancer-specific mortality model which has two internal knots and is adjusted for age at diagnosis (per 10 year increase), categorized year of diagnosis (1990-2005, 2006-2010, 2011-2015), stage (*in situ* to stage II, stage III or unknown), tumor differentiation grade,

chemotherapy, radiotherapy, and hormonal therapy, and (3) the model for all other cause-specific mortality which has zero internal knots and is adjusted for age at diagnosis (per 10 year increase), categorized TNM stage (*in situ* to stage II, stage III or unknown), and radiotherapy.

Results

Of the 5,868 women with breast cancer in the study, median age at diagnosis was 52 years (interquartile range: 45-60) and median follow-up was six years (interquartile range: 3-10) (Table 1). Of these women, 79.5% (n = 4,663) were Chinese, 11.9% (n = 694) were Malay, 6.0% (n = 351) were Indian, and 2.6% (n = 160) were women with another ethnicity. The majority of women (85.9%, n = 5,024) were diagnosed with breast cancer after 1999. Thirteen percent of women (n = 764) were diagnosed with carcinoma *in situ*, 23.5% (n = 1,381) with stage I, 37.2% (n = 2,181) with stage II, 12.9% (n = 756) with stage III, and stage was unknown for 13.4% (n = 786).

In total, 1,010 deaths occurred within 10 years of follow-up of which 6.8% (n = 67) were due to CVD (Table 1). Of these, 24 deaths were due to acute myocardial infarction, 4 deaths were due to congestive heart failure, 16 deaths were due to acute ischemic heart disease, 3 deaths were due to coronary artery disease, 11 deaths were due to cerebrovascular death (anoxic brain damage), and 9 deaths were due to other heart disease problems (cardiorespiratory failure) (data not presented). The most common cause of death was breast cancer accounting for 76.6% (n = 774) of all deaths, and in 16.7% (n = 169), death was due to other causes than breast cancer or CVD. Of the 740 Chinese women with breast cancer who died, 6.8% (n = 50) died of CVD, 75.0% (n = 555) died of breast cancer, and 18.2% (n = 135) died of other causes. Of the 178 Malay women with breast cancer who died, 4.4% (n = 8) died of CVD, 86.0% (n = 153) died of breast cancer, and 9.6% (n = 47) died of other causes. Furthermore, of the 61 Indian women with breast cancer who died, 13.1% (n = 8) died of CVD, 77.0% (n = 47) died of breast cancer, and 9.9% (n = 6) died of other causes.

Among women over 70 years at breast cancer diagnosis, CVD mortality rates peaked in the first year after diagnosis followed by a decrease until approximately three years after breast cancer diagnosis (Figure 1). Thereafter, CVD mortality rates rose until approximately 12 per 1,000 person-years after 10 years of follow-up. CVD mortality rates among women aged 50 to 69 years at breast cancer diagnosis gradually increased with follow-up until approximately 4 per 1,000 person-years after 10 years of follow-up. In women younger than 50 years, CVD mortality remained almost constant at less than 1 per 1,000 person years during the 10 years of follow-up. Breast cancer-specific mortality rates peaked at one to three years after diagnoses for all breast cancer patients. Women over 70 years had substantially higher breast cancer specific mortality rates within the first five years after diagnosis than younger women. After eight years since diagnosis, similar breast cancer-specific mortality rates (approximately 20 per 1,000 person-years) were seen in all age groups. Mortality rates from other causes were highest among women aged over 70 years, and showed an early peak within the first year after breast cancer diagnosis followed by a steady increase

over time until approximately 25 per 1,000 person-years after ten years of follow-up. In the younger age groups, mortality rates from other causes remained stable over follow-up time at approximately five per 1,000 person-years for women aged between 50-69 years and less than one per 1,000 person-years for women younger than 50 years.

The risk of death from CVD within ten years of diagnosis in Indian women was more than double the risk of Chinese women (HR = 2.5, 95% CI = 1.2-5.2), independent of age at diagnosis and stage (Table 2). Furthermore, the risk of death from breast cancer in Malay women was almost double the risk of Chinese women (HR = 1.9, 95% CI = 1.6-2.3) independent of age at diagnosis, tumor stage, tumor differentiation grade, chemotherapy, radiotherapy, and hormonal therapy.

Table 1. Characteristics of the total study population and by death from cardiovascular disease, breast cancer, and all other cause within ten years of diagnosis in Southeast Asian women with breast cancer

	Total study population	Total deaths	Deaths from cardiovascular disease	Deaths from breast cancer	Deaths from all other cause
	n = 5,868	**n = 1,010**	**n = 67 (6.8%)**	**n = 774 (76.6%)**	**n = 169 (16.7%)**
Ethnicity, n (%)					
Chinese	4,663 (79.5)	740 (73.3)	50 (6.8)	555 (75.0)	135 (18.2)
Malay	694 (11.9)	178 (17.6)	8 (4.4)	153 (86.0)	17 (9.6)
Indian	351 (6.0)	61 (6.0)	8 (13.1)	47 (77.0)	6 (9.9)
Other*	160 (2.6)	31 (3.1)	1 (3.0)	19 (61.0)	11 (35.0)
Median (IQR) age at diagnosis, years	52 (45-60)	56 (47-68)	69 (58-77)	53 (45-63)	65 (54-74)
Age at diagnosis in groups, n (%)					
< 50	2,530 (43.1)	346 (34.3)	9 (2.6)	312 (90.2)	25 (7.2)
50-69	2,781 (47.4)	460 (45.5)	25 (5.4)	347 (75.4)	88 (19.1)
≥70	548 (9.3)	200 (19.8)	33 (16.5)	111 (55.5)	56 (28.0)
Unknown	9 (0.0)	4 (0.0)	0 (0.0)	4 (1.0)	0 (0.0)
Median (IQR) survival time, years	6 (3-10)	3 (2-5)	4 (2-7)	3 (2-5)	3 (2-6)
Calendar time at diagnosis, n (%)					
1990-1994	380 (6.5)	121 (11.9)	9 (7.4)	101 (83.5)	11 (9.1)
1995-1999	445 (7.6)	119 (11.8)	5 (4.2)	97 (81.5)	17 (14.3)
2000-2006	1,913 (32.6)	447 (44.3)	31 (6.9)	350 (78.3)	66 (14.7)
≥2007	3,111 (53.0)	317 (31.4)	22 (6.9)	222 (70.0)	73 (23.0)
Unknown	19 (0.3)	6 (0.6)	0 (0.0)	4 (66.7)	2 (33.3)
TNM stage, n (%)					
In situ	764 (13.0)	17 (1.7)	3 (17.6)	5 (29.4)	9 (52.9)

	Total study population	Total deaths	Deaths from cardiovascular disease	Deaths from breast cancer	Deaths from all other cause
	n = 5,868	**n = 1,010**	**n = 67 (6.8%)**	**n = 774 (76.6%)**	**n = 169 (16.7%)**
I	1,381 (23.5)	91 (9.0)	9 (9.9)	49 (53.8)	33 (36.3)
II	2,181 (37.2)	328 (32.5)	27 (8.2)	253 (77.1)	48 (14.6)
III	756 (12.9)	261 (25.8)	9 (3.4)	226 (86.6)	26 (10.0)
Unknown	786 (13.4)	313 (31.0)	19 (6.1)	241 (77.0)	53 (16.9)
Tumor differentiation grade, n (%)					
Good	713 (12.2)	56 (5.5)	10 (17.8)	23 (41.1)	23 (41.1)
Moderate	1,998 (34.0)	286 (58.0)	26 (9.1)	206 (72.0)	54 (18.9)
Poor	2,158 (36.8)	475 (47.0)	20 (4.2)	394 (82.9)	61 (12.8)
Unknown	999 (17.0)	193 (19.1)	11 (5.7)	151 (78.2)	31 (16.1)
Estrogen-receptor status, n (%)					
Positive	1,772 (30.2)	376 (37.2)	37 (9.8)	269 (71.5)	70 (18.6)
Negative	2,537 (43.2)	382 (37.8)	17 (4.4)	314 (82.2)	51 (13.4)
Unknown	1,559 (26.6)	252 (25.0)	13 (5.2)	191 (75.8)	48 (19.0)
Surgery, n (%)					
Yes	5,262 (89.7)	758 (75.0)	52 (6.9)	579 (76.4)	127 (16.8)
No	345 (5.9)	218 (21.6)	14 (6.4)	166 (76.1)	38 (17.5)
Unknown	261 (4.4)	34 (3.4)	1 (2.9)	29 (85.3)	4 (11.8)
Chemotherapy, n (%)					
Yes	2,797 (47.7)	519 (51.3)	14 (2.7)	450 (86.7)	55 (10.6)
No	2,671 (45.5)	453 (44.9)	52 (11.5)	293 (64.7)	108 (23.8)
Unknown	400 (6.8)	38 (3.8)	1 (2.6)	31 (81.6)	6 (15.8)

Radiotherapy, n (%)					
Yes	2,735 (46.6)	462 (45.7)	20 (4.3)	383 (82.9)	59 (12.8)
No	2,637 (44.9)	506 (50.1)	45 (8.9)	358 (70.8)	103 (20.4)
Unknown	496 (8.5)	42 (4.2)	2 (4.8)	33 (78.6)	7 (16.7)
Hormonal therapy, n (%)					
Yes	3,355 (57.2)	537 (53.2)	44 (8.2)	393 (73.2)	100 (18.6)
No	2,160 (36.8)	433 (42.9)	22 (5.1)	348 (80.4)	63 (14.5)
Unknown	353 (6.0)	40 (4.0)	1 (2.5)	33 (82.5)	6 (15.0)

Abbreviations: IQR = Interquartile range, TNM = Classification of Malignant Tumors
*Includes e.g. Sikh, Eurasian, and Caucasian
Column percentages presented for total study population and total deaths; Row percentages (percentages of total deaths) presented for deaths from cardiovascular disease, deaths from breast cancer, and deaths from all other cause

Table 2. Crude and adjusted hazard ratios of death from cardiovascular disease, breast cancer, and all other cause within ten years of diagnosis in Southeast Asian women with breast cancer

	Cardiovascular disease				Breast cancer				All other cause			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Ethnicity												
Chinese	1.0	(ref)	1.0	(ref)	1.0	(ref)	1.0	(ref)	1.0	(ref)	1.0	(ref)
Malay	1.2	0.6 to 2.6	1.8	0.9 to 3.9	2.1	1.8 to 2.6	1.9	1.6 to 2.3	1.0	0.6 to 1.6	1.2	0.7 to 2.0
Indian	2.2	1.0 to 4.6	2.5	1.2 to 5.2	1.2	0.9 to 1.6	1.2	0.9 to 1.6	0.6	0.3 to 1.4	0.6	0.3 to 1.4
Age at diagnosis*	2.8	2.4 to 3.5	2.7	2.2 to 3.4	1.2	1.2 to 1.3	1.3	1.2 to 1.4	2.3	2.0 to 2.6	2.0	1.8 to 2.3
TNM stage												
In situ	0.4	0.1 to 1.3	0.5	0.2 to 1.6	0.1	0.0 to 0.2	0.1	0.0 to 0.2	0.5	0.2 to 1.0	0.6	0.3 to 1.2
1-2	1.0	(ref)	1.0	(ref)	1.0	(ref)	1.0	(ref)	1.0	(ref)	1.0	(ref)
3	1.3	0.6 to 2.8	1.2	0.6 to 2.7	4.5	3.7 to 5.3	3.6	3.0 to 4.4	1.8	1.1 to 2.8	1.9	1.1 to 3.1
unknown	3.0	1.7 to 5.2	1.7	1.0 to 3.1	4.5	3.8 to 5.4	6.0	4.9 to 7.3	3.3	2.3 to 4.8	2.7	1.8 to 4.0
Year of diagnosis												
2011-2015	1.0	(ref)	-		1.0	(ref)	1.0	(ref)	1.0	(ref)	-	
2006-2010	3.0	0.7 to 12.8			1.7	1.2 to 2.5	1.6	1.1 to 2.3	1.1	0.6 to 1.9		
1990-2005	2.7	0.6 to 11.7			2.1	1.5 to 3.0	2.1	1.5 to 3.1	0.8	0.4 to 1.4		
Tumor differentiation grade												
Good	1.0	(ref)	-		1.0	(ref)	1.0	(ref)	1.0	(ref)	-	
Moderate	1.0	0.5 to 2.0			3.3	2.1 to 5.0	3.2	2.0 to 4.9	0.8	0.5 to 1.4		
Poor	0.8	0.4 to 1.6			6.6	4.3 to 10.0	5.5	3.6 to 8.4	1.0	0.6 to 1.7		
Unknown	1.0	0.4 to 2.3			5.5	3.5 to 8.5	4.8	3.0 to 7.6	1.0	0.6 to 1.8		

Estrogen-receptor status											
Positive	2.1	1.2 to 3.7	-	0.9	0.7 to 1.0	-		1.4	1.0 to 2.1	-	
Negative	1.0	(ref)		1.0	(ref)			1.0	(ref)		
Unknown	1.0	0.5 to 2.1		0.8	0.7 to 1.0			1.2	0.8 to 1.8		
Chemotherapy											
Yes	0.3	0.2 to 0.5	-	1.6	1.4 to 1.8	1.4	1.1 to 1.6	0.5	0.4 to 0.7	-	
No	1.0	(ref)		1.0	(ref)	1.0	(ref)	1.0	(ref)		
Unknown	0.2	0.0 to 1.1		0.8	0.6 to 1.2	0.6	0.2 to 2.0	0.5	0.2 to 1.1		
Radiotherapy											
Yes	0.4	0.2 to 0.7	-	1.0	0.9 to 1.2	0.9	0.7 to 1.0	0.5	0.4 to 0.8	0.8	0.5 to 1.1
No	1.0	(ref)		1.0	(ref)	1.0	(ref)	1.0	(ref)	1.0	(ref)
Unknown	0.3	0.1 to 1.2		0.6	0.4 to 0.9	0.5	0.2 to 1.2	0.5	0.2 to 1.0	0.4	0.2 to 0.8
Hormonal therapy											
Yes	1.2	0.7 to 2.1	-	0.7	0.6 to 0.8	0.7	0.6 to 0.8	1.1	0.8 to 1.5	-	
No	1.0	(ref)		1.0	(ref)	1.0	(ref)	1.0	(ref)		
Unknown	0.3	0.0 to 2.2		0.6	0.4 to 0.8	0.6	0.2 to 1.7	0.7	0.3 to 1.6		

Abbreviations: HR = hazard ratio, CI = confidence interval, TNM = Classification of Malignant Tumors

* Per ten year increase

HRs are estimated with a flexible parametric survival model. Adjusted HRs for death from CVD by ethnicity are adjusted for age at diagnosis and TNM stage. Adjusted HRs for death from breast cancer by ethnicity are adjusted for age at diagnosis, TNM stage, tumor differentiation grade, chemotherapy, radiotherapy, and hormonal therapy. Adjusted HRs for death from all other cause by ethnicity are adjusted for age at diagnosis, TNM stage, and radiotherapy.

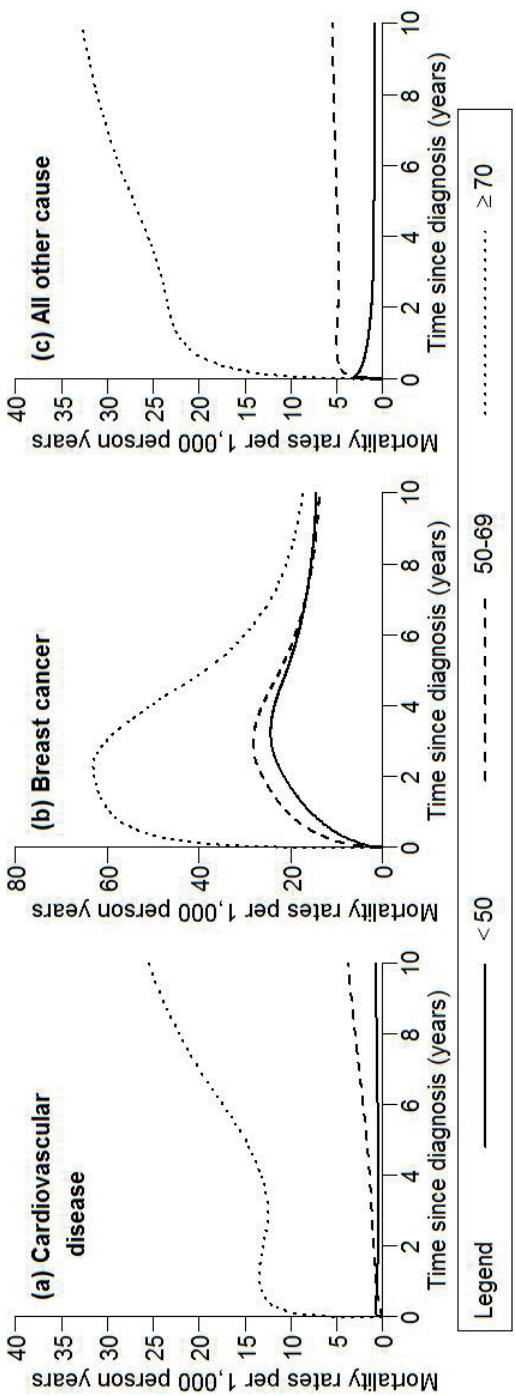

Figure 1. Estimated mortality rates within 10 years of diagnosis in Southeast Asian women with breast cancer diagnosed between 1990 and 2011. Death due to (**a**) cardiovascular disease, (**b**) breast cancer, (**c**) all other cause. Mortality rates estimated from flexible parametric survival models with age as only covariate, allowing age effect to vary by time since diagnosis.

Discussion

Breast cancer survival is improving in Southeast Asia. As such, an increasing amount of women diagnosed with breast cancer are at risk of dying of other causes. Given the increased risk of cardiac toxicity induced by breast cancer treatments, it is important to identify patients at high risk of CVD mortality. The present study showed that the risk of CVD mortality following breast cancer in multi-ethnic Southeast Asia was generally low during the first decade after diagnosis. Breast cancer was the main cause of death. The risk of CVD mortality increased in women with higher age at breast cancer diagnosis and in Indian women.

Among women with a higher age at breast cancer diagnosis, CVD mortality rates peaked within the first year following diagnosis and showed an overall increase during the ten years of follow-up. Similar results have been reported among Caucasian women with breast cancer[4]. Our unadjusted survival analysis showed that women who have been treated with chemotherapy or radiotherapy had a lower risk of dying of CVD than women who did not receive those therapies. Moreover, women with a positive estrogen-receptor status had a higher risk of dying of CVD than women with a negative receptor status. A possible explanation is the phenomenon is that women with breast cancer who received chemotherapy, radiotherapy, and/or had a negative estrogen-receptor status had a higher TNM stage, and therefore died more often due to breast cancer than due to CVD. Also, some selection may have taken place, as women who are at increased risk of CVD were less likely to be treated with cardiac toxic chemotherapy or (left sided) radiotherapy. Furthermore, our study showed that Indian women had an increased risk of CVD mortality following breast cancer compared to Chinese women. Variation in the risk of CVD mortality by ethnicity in our population may be due to genetic differences and/or differences in lifestyle associated comorbidities like obesity and diabetes and dietary habits[16,17]. Differences in the presence of CVD risk factors between Chinese, Malay, and Indian in Southeast Asia have been reported[16,18-21]. Indian women had the highest rate of central obesity and diabetes[20], while the rate of obesity was highest among Malay followed by Indian and Chinese[18,19]. These differences, however, were not fully explained by dietary intake[22] Moreover, Indians had the highest level of lipoprotein a, which is a causal genetic risk factor for cardiovascular disease[21].

In the current study, CVD mortality rates of women with breast cancer aged over 70 years were over 10 per 1,000 person-years shortly after diagnosis until 10 years after diagnosis, however, CVD mortality rates of women from the general population in Singapore aged over 70 years ranged from 19 per 1,000 person-years in 2005 to 17 per 1,000 person-years in 2015 (data not presented)[23]. Furthermore, in this study, CVD mortality rates of women with

breast cancer aged 50 to 69 years were approximately 0.3 per 1,000 person-years throughout the 10 years follow-up while the CVD mortality rates of women from the general population in Singapore aged 50 to 69 years ranged from 1.4 per 1,000 person-years in 2005 to 0.9 per 1,000 person-years in 2015 (data not presented)[23]. These numbers showed that mortality rates of CVD among women with breast cancer patients in Singapore were somewhat lower than that of women from the general population in Singapore.

In the present study, CVD mortality rates increased over time while breast cancer mortality rates decreased after three years since diagnosis. Colzani et al. (2011) found similar results among Caucasian women with breast cancer: CVD-specific mortality rates increased after three years since diagnoses in women aged over 55 years at diagnosis, while breast cancer-specific mortality rates decreased after four years since diagnosis among all ages[4]. These results were not surprising as age is a well-known important risk factor of CVD[24], and the majority of deaths from breast cancer within the first four years following diagnosis in our prospective cohort were women diagnosed with more severe stages *i.e.* II and III.

We acknowledge that the present study has limitations. The follow-up time of our study population was relatively short, which explains (part of) the low absolute risk of CVD mortality. Previous research has shown that the risk of CVD mortality increases up to and beyond 20 years after diagnosis[4,25,26], as age is a well-known CVD risk factor[27] and cardiac toxicity induced by radiotherapy manifest itself many years following treatment[28,29]. Furthermore, misclassification of cause of death due to CVD could have occurred, especially in cases of sudden death from CVD outside a hospital, for example at home, were it is difficult to state the proper cause of death by doctors or authorized medical practitioners that are not familiar with this particular women.

In conclusion, the risk of CVD mortality was generally low in the first decade following breast cancer diagnosis in Southeast Asia. Women with higher age at breast cancer diagnosis and Indian women are at increased risk of CVD mortality following breast cancer. The notion that women who survived breast cancer will subsequently be at risk for CVD is important in their management and in addition, taking ethnic-specific risks and age into account, may promote optimal prevention of CVD in (Southeast Asian) women with breast cancer. Future research may assess factors, dependent or independent of breast cancer, explaining the variation in risk of CVD mortality according to ethnicity. Furthermore, breast cancer patients would benefit from a personalized CVD risk prediction short after breast cancer diagnosis so that treatment can be adjusted accordingly and CVD management can be initialized.

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References

1. Lim GH, Chow KY, Lee HP. Singapore cancer trends in the last decade. *Singapore Med J*. 2012; 53 (1): 3-9; quiz 10.
2. Youlden DR, Cramb SM, Yip CH, Baade PD. Incidence and mortality of female breast cancer in the Asia-pacific region. *Cancer Biol Med*. 2014; 11 (2): 101-115.
3. Riihimaki M, Thomsen H, Brandt A, Sundquist J, Hemminki K. Death causes in breast cancer patients. *Ann Oncol*. 2012; 23 (3): 604-610.
4. Colzani E, Liljegren A, Johansson AL, et al. Prognosis of patients with breast cancer: Causes of death and effects of time since diagnosis, age, and tumor characteristics. *J Clin Oncol*. 2011; 29 (30): 4014-4021.
5. Berkman A, F Cole B, Ades PA, et al. 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*. 2014; 148 (2): 407-413.
6. Bird BR, Swain SM. Cardiac toxicity in breast cancer survivors: Review of potential cardiac problems. *Clin Cancer Res*. 2008; 14 (1): 14-24.
7. Borger JH, Hooning MJ, Boersma LJ, et al. Cardiotoxic effects of tangential breast irradiation in early breast cancer patients: The role of irradiated heart volume. *Int J Radiat Oncol Biol Phys*. 2007; 69 (4): 1131-1138.
8. McGale P, Darby SC, Hall P, et al. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. *Radiother Oncol*. 2011; 100 (2): 167-175.
9. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol*. 2007; 25 (25): 3808-3815.
10. Bhoo-Pathy N, Hartman M, Yip CH, et al. Ethnic differences in survival after breast cancer in south east Asia. *PLoS One*. 2012; 7 (2): e30995.
11. de Carvalho LP, Gao F, Chen Q, et al. Differences in late cardiovascular mortality following acute myocardial infarction in three major Asian ethnic groups. *Eur Heart J Acute Cardiovasc Care*. 2014; 3 (4): 354-362.
12. Gijsberts CM, Seneviratna A, Hoefer IE, et al. Inter-ethnic differences in quantified coronary artery disease severity and all-cause mortality among Dutch and Singaporean percutaneous coronary intervention patients. *PLoS One*. 2015; 10 (7): e0131977.
13. Lim SE, Back M, Quek E, Lau P, Putti T, Wong JE. Clinical observations from a breast cancer registry in Asian women. *World J Surg*. 2007; 31 (7): 1387-1392.
14. Edge SB, Byrd DR, and Compton CC. AJCC cancer staging manual (ed 7) springer. New York, NY, 2010.

15. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med*. 2002; 21 (15): 2175-2197.

16. Jacobson TA. Lipoprotein (a), cardiovascular disease, and contemporary management. *Mayo Clin Proc*. 2013; 88 (11): 1294-1311.

17. Sasayama S. Heart disease in Asia. *Circulation*. 2008; 118 (25): 2669-2671.

18. Pan A, Malik VS, Hu FB. Exporting diabetes mellitus to Asia: The impact of western-style fast food. *Circulation*. 2012; 126 (2): 163-165.

19. Deurenberg-Yap M, Li T, Tan WL, van Staveren WA, Chew SK, Deurenberg P. Can dietary factors explain differences in serum cholesterol profiles among different ethnic groups (Chinese, Malays and Indians) in Singapore? *Asia Pac J Clin Nutr*. 2001; 10 (1): 39-45.

20. Hughes K, Yeo PP, Lun KC, et al. Cardiovascular diseases in Chinese, Malays, and Indians in Singapore. II. differences in risk factor levels. *J Epidemiol Community Health*. 1990; 44 (1): 29-35.

21. Hughes K, Aw TC, Kuperan P, Choo M. Central obesity, insulin resistance, syndrome X, lipoprotein (a), and cardiovascular risk in Indians, Malays, and Chinese in Singapore. *J Epidemiol Community Health*. 1997; 51 (4): 394-399.

22. Mak KH, Chia KS, Kark JD, et al. Ethnic differences in acute myocardial infarction in Singapore. *Eur Heart J*. 2003; 24 (2): 151-160.

23. http: //www.healthdata.org/gbd/data-visualizations.

24. D'Agostino RB S, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham heart study. *Circulation*. 2008; 117 (6): 743-753.

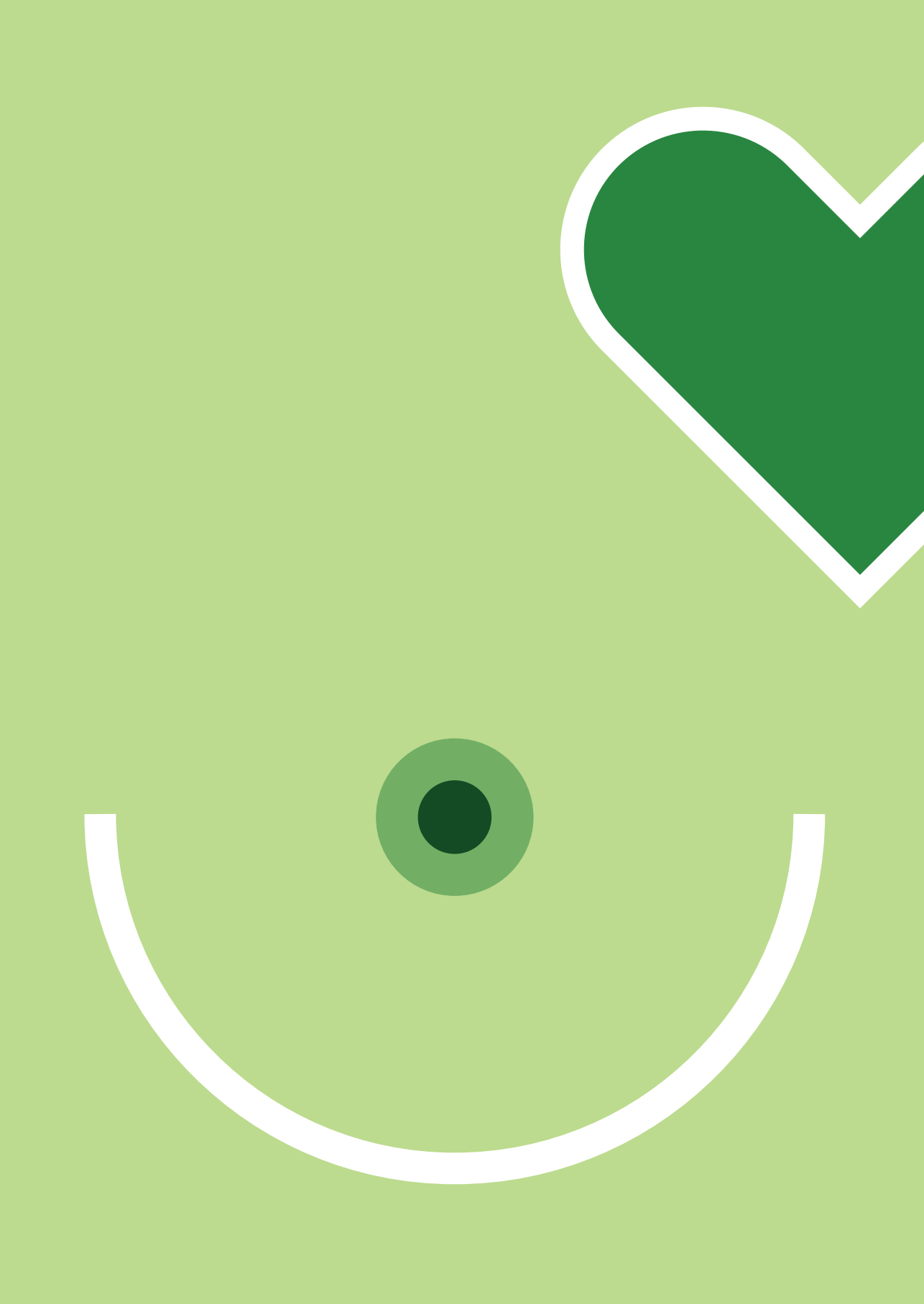
25. Darby SC, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: Prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol*. 2005; 6 (8): 557-565.

26. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, et al. 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*. 2014; 383 (9935): 2127-2135.

27. Tsao CW, Vasan RS. Cohort profile: The Framingham heart study (FHS): Overview of milestones in cardiovascular epidemiology. *Int J Epidemiol*. 2015; 44 (6): 1800-1813.

28. Darby SC, Bronnum D, Correa C, et al. A dose-response relationship for the incidence of radiation-related heart disease. *Int J Radiat Oncol Biol Phys*. 2010; 78 (3): S49-S50.

29. Cuomo JR, Sharma GK, Conger PD, Weintraub NL. Novel concepts in radiation-induced cardiovascular disease. *World J Cardiol*. 2016; 8 (9): 504-519.



Chapter 6

Automatic coronary artery calcium scoring on radiotherapy planning CT scans of breast cancer patients: reproducibility and association with traditional cardiovascular risk factors

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Abstract

Purpose

Coronary artery calcium (CAC) is a strong and independent predictor of cardiovascular disease (CVD) risk. This study assessed reproducibility of automatic CAC scoring on radiotherapy planning computed tomography (CT) scans of breast cancer patients, and examined its association with traditional cardiovascular risk factors.

Methods

This study included 561 breast cancer patients undergoing radiotherapy between 2013 and 2015. CAC was automatically scored with an algorithm using supervised pattern recognition, expressed as Agatston scores and categorized into five categories (0, 1-10, 11-100, 101-400, >400). Reproducibility between automatic and manual expert scoring was assessed in 79 patients with automatically determined CAC above zero and 84 randomly selected patients without automatically determined CAC. Interscan reproducibility of automatic scoring was assessed in 294 patients having received two scans (82% on the same day). Association between CAC and CVD risk factors was assessed in 36 patients with CAC scores >100, 72 randomly selected patients with scores 1-100, and 72 randomly selected patients without CAC. Reliability was assessed with linearly weighted kappa and agreement with proportional agreement.

Results

134 out of 561 (24%) patients had a CAC score above zero. Reliability of CVD risk categorization between automatic and manual scoring was 0.80 (95% Confidence Interval (CI) = 0.74-0.87), and slightly higher for scans with breath-hold. Agreement was 0.79 (95% CI = 0.72-0.85). Interscan reliability was 0.61 (95% CI = 0.50-0.72) with an agreement of 0.84 (95% CI = 0.80-0.89). Ten out of 36 (27.8%) patients with CAC scores above 100 did not have other cardiovascular risk factors.

Conclusions

Automatic CAC scoring on radiotherapy planning CT scans is a reliable method to assess CVD risk based on Agatston scores. One in four breast cancer patients planned for radiotherapy had elevated CAC score. One in three patients with high CAC scores didn't had other CVD risk factors and wouldn't have been identified as high risk.

Introduction

Breast cancer patients treated with adjuvant treatments such as radiotherapy or chemotherapy may be at increased absolute risk of treatment-induced cardiotoxicity[1-4]. This risk is higher in patients with pre-existing cardiovascular disease (CVD) risk factors[5,6]. One of the strongest individual predictive factors of CVD risk is the presence and amount of coronary artery calcium (CAC), representing the extent of coronary atherosclerosis, independent of traditional CVD risk factors like hypercholesterolemia, hypertension or diabetes[7]. The amount of CAC is most commonly expressed as Agatston score, and categorized Agatston scores are clinically used to express the risk of CVD events[8]. Asymptomatic individuals with Agatston scores of 100 and higher, and without other CVD risk factors, have a 20% ten-year risk of a CVD event, compared to 1% in asymptomatic individuals without CAC[8,9].

CAC is quantified in the main coronary arteries, namely left main (LM), left anterior descending (LAD), left circumflex (LCX) and right coronary artery (RCA). Standardly, CAC is quantified on cardiac computed tomography (CT) scans that are made using electrocardiography (ECG)-triggering, which minimizes cardiac motion and thus enabling good visualization of the CAC. Nevertheless, CAC can also be quantified using any CT scans visualizing the heart, and previous studies have shown that CAC scores determined using non-dedicated acquisition protocols, *i.e.* without ECG-synchronization and using low radiation dose, are predictive of future CVD events[10-15]. In clinic, CAC scoring is performed by manual expert annotation, which is time-consuming and tedious when performed using non-dedicated CT scans due to presence of artefacts caused by cardiac motion, high noise levels caused by lower radiation dose, and partial volume effect caused by decreased image resolution[16,17]. To overcome this and enable large scale studies, several algorithms for automatic CAC scoring in both dedicated cardiac, and non-dedicated chest CT scans have been proposed[18-23].

All breast cancer patients treated with radiotherapy routinely undergo low-dose planning CT scans of the chest. As the coronary arteries are visualized on these scans, CAC can be quantified without exposing patients to additional radiation and without additional costs. It is, however, unknown whether radiotherapy planning CT scans of breast cancer patients can reliably be used for (automatic) CAC scoring.

The objective of this study was to evaluate reproducibility of automatic CAC scoring on breast radiotherapy planning CT scans and to examine the association between CAC scores and traditional CVD risk factors.

Methods and materials

Study design and patients

This study was conducted within the prospective Utrecht cohort for Multiple BReast cancer intErvention studies and Long-term evaLuAtion (UMBRELLA). The UMBRELLA cohort was approved by the Medical Ethics Review Committee of the University Medical Center Utrecht (UMBRELLA protocol number = 15-165). Recruitment in the cohort started in October 2013 and all breast cancer patients planned for radiotherapy were eligible for participation. Until March 2015, 628 consecutive breast cancer patients signed informed consent of the UMBRELLA study and were enrolled. Six patients withdrew informed consent, 60 patients did not undergo a planning CT scan, and one patient was excluded due to CT image artifacts caused by metal implants, leaving 561 patients for inclusion.

Patient and treatment characteristics, *i.e.* age at time of CT scan, tumor stage at diagnosis according to the International Union against Cancer (UICC) classification of malignant tumors (TNM)[24] and type of treatments, were systematically collected within the context of the UMBRELLA cohort and based on clinical records and national cancer registry data. Traditional CVD risk factors, including diabetes, hypertension, hypercholesterolemia, smoking status, and history of CVD, were extracted from electronic medical files at the radiotherapy department. As for diabetes, hypertension, hypercholesterolemia, smoking status, and history of CVD, patients were scored as positive when medication had been prescribed or when it had been explicitly noted in the electronic files. Smoking status was categorized as never or not reported, former, or current. History of CVD was scored as positive in case patients had experienced ischemic heart disease, heart failure, stroke, atrial fibrillation, or angina pectoris before start of the radiotherapy.

Procedures

Radiotherapy planning CT scans were performed with a Brilliance CT (Philips Medical Systems) scanner with 16 x 0.75mm collimation, 120 kVp, 3mm section thickness, without contrast enhancement, without ECG-synchronization. All patients underwent a planning CT scan without breath-hold, and patients with left-sided breast cancer underwent an additional planning CT scan with breath-hold.

Automatic CAC scoring was performed in all patients to assess presence and the amount of CAC. CAC was automatically scored in the LM, LAD, LCX and RCA with the algorithm described by Isgum et al[23]. Briefly, CAC was identified using a supervised machine learning approach. Following clinical procedure, three-dimensional connected components above the standard threshold of 130 Hounsfield Units (HU) were considered candidate calcifications. Based on their volume, spatial, and texture characteristics, CAC was

identified using supervised classification and expressed as Agatston scores, volume (mm^3) and number of CAC[8]. The scan with the highest Agatston score was selected for patients with multiple CT scans. Scans with automatically determined CAC scores of 1000 and above (n = 6) were manually inspected and corrected if needed. Each patient was assigned to one of five CVD risk categories based on Agatston score: low (0), fair (1-10), moderate (11-100), intermediate (101-400), high (> 400)[17,25,26].

In the current study, we assessed (1) reproducibility between automatic and manual expert scoring, (2) interscan reproducibility of automatic CAC scoring, and (3) associations between CAC scores and other traditional CVD risk factors.

Automatic and manual CAC scores were compared in 163 patients. Manual scoring was performed in the first 79 consecutive patients with automatically determined CAC scores above 0 and in 84 randomly selected patients without CAC. CAC was manually annotated by a radiologist in training with experience in over 1,000 scans, who was blinded to the automatically determined CAC scores and patient's characteristics, except for date of birth. Interscan reproducibility of automatic CAC scoring was assessed in all 294 patients having received (at least) two CT scans, either on the same day (82%) or within a maximum of five months (18%)[27]. Associations between CAC scores and traditional CVD risk factors were assessed in all 36 patients with automatic CAC scores above 100, 72 randomly selected patients with scores 1-100, and 72 randomly selected patients without CAC.

Statistical analysis

Demographics, tumor characteristics, treatment details and CAC scores were described for all patients. Reproducibility between automatic and manual CAC scoring as well as the interscan reproducibility of automatic CAC scoring was assessed with reliability and agreement analyses[28]. Reliability – agreement beyond chance - of CAC score categories was assessed with Cohen's linearly weighted kappa (κ)[29]. Reliability of continuous CAC score was measured with Intraclass Correlation Coefficient (ICC). The two-way random effects and absolute agreement ICC was used to assess reliability between automatic and manual CAC scoring, taking into account the variance between patients and structural differences between automatic and manual CAC scoring. The two-way random consistency ICC was used to assess reliability between two automatically scored scans. Agreement - degree to which CAC scores are identical between methods (*i.e.* automatic versus manual CAC scoring and automatic versus automatic CAC scoring) - of CAC score categories was assessed with proportional agreement. Agreement of continuous CAC score was assessed with Bland-Altman plots and its back log transformed 95% limits of agreement due to inconsistent variances, which increase with higher CAC scores.

Overall associations between CAC scores and traditional CVD risk factors were assessed with Chi-Square and Kruskal-Walles tests for categorical and continuous variables respectively. Analyses were performed with IMB SPSS statistics version 20 and an online statistical tool[30].

Results

Median age at time of CT scan of all 561 breast cancer patients in the present study was 61 years (interquartile range: 54-68), and 355 (63%) patients were diagnosed with stage 1 disease (Table 1). Almost all patients were treated with surgery and radiotherapy (n = 556, 99%), and 427 (76%) patients had a CAC score of zero. Of the 134 (24%) patients with a CAC score above zero, 36 (27%) patients had a score above 100. Six CT scans had an automatically determined CAC score of 1,000 and above, and these high CAC scores were caused by large CAC depositions in the mitral annulus. Three of those were corrected to a CAC score of zero, and two were corrected to a score between 50 and 100. One scan was corrected to a CAC score above 2,000.

Automatic versus manual CAC scoring

Reproducibility between automatic and manual CAC scoring was assessed in 163 patients, including 58 scans performed with breath-hold and 105 without breath-hold. The reliability of CAC score categories was 0.80 (95% Confidence Interval (CI) = 0.74-0.87), and slightly higher for scans performed with breath-hold (0.86, 95% CI = 0.77-0.96) than for those without breath-hold (0.77, 95% CI = 0.68-0.85, Tables 2 and 3). The proportion of agreement for CVD risk categories was also high at 0.79 (95% CI = 0.72-0.85), and higher for scans performed with breath-hold (0.88, 95% CI = 0.76-0.95) than for those without breath-hold (0.74, 95% CI = 0.65-0.82). The reliability of continuous CAC score (ICC) was 0.86 (95% CI = 0.81-0.89), and higher for scans performed with breath-hold (0.95, 95% CI = 0.91-0.97) than for those without breath-hold (0.66, 95% CI = 0.54-0.76, Table 3). For continuous CAC scores a Bland-Altman plot showed a mean difference between the automatic and manual scored scans of -29.3 with back log transformed 95% limits of agreement as a function of the average (X) of -1.5X and 1.5X (Figs 1A and 1B).

Interscan reproducibility of automatic CAC scoring

Interscan reproducibility of automatic CAC scoring was assessed in all 294 patients who underwent two CT scans: 237 (81%) patients underwent one CT scan performed with breath-hold and one without, 50 (17%) underwent two scans performed without breath-hold, and 7 (2%) underwent two scans performed with breath-hold. Reliability of CVD risk categories was 0.61 (95% CI = 0.50-0.72), and the proportion of agreement for CVD risk categories was 0.84 (95% CI = 0.80-0.89, Tables 4 and 3). Reliability of continuous CAC score (ICC) was 0.34 (95% CI = 0.23-0.44, Table 3). For continuous CAC scores a Bland-Altman plot showed a mean difference between the two automatically scored scans of 8.6 with back log transformed 95% limits of agreement as a function of the average (X) of -1.4X and 1.4X (Figs 2A and 2B).

Associations between categorized CAC scores and traditional CVD risk factors

Diabetes was significantly more prevalent among patients with CAC scores above 100 than in those with CAC scores of zero: 27.8% versus 5.6% (p = 0.001) (Table 5). Patients with CAC scores above 100 had more often three to five CVD risk factors compared to patients with scores between 1-100 or with CAC scores of zero: 33.3%, 16.7%, and 9.7% respectively (p = 0.023). Interestingly, ten of the 36 patients (27.8%) with CAC scores above 100 did not have any other traditional CVD risk factor and would have been missed evaluating the risk clinically.

Table 1. Demographics, tumor and treatment characteristics, and CAC (Agatston) scores of 561 breast cancer patients

	n (%)
Median age at time of scan in years (interquartile range)	61 (54-68)
Tumor stage at diagnosis	
In situ	65 (11)
1	354 (63)
2	118 (21)
3	21 (4)
4	3 (1)
Combination of treatments	
Surgery + RT	216 (39)
Surgery + RT + CT	69 (12)
Surgery + RT + HT	101 (18)
Surgery + RT + CT + HT	170 (30)
Other[a]	5 (1)
Median CAC in Agatston score (interquartile range)	3 (0-55)
CAC in Agatston score categories	
0	427 (76)
1-10	46 (8)
11-100	52 (9)
101-400	28 (5)
>400	8 (2)
Median volume of CAC in mm^3 (interquartile range)	7 (0-86)
Median number of CAC (interquartile range)	1 (0-2)

Abbreviations: CAC = coronary artery calcification; RT= radiotherapy; CT = chemotherapy; HT = hormonal treatment; mm^3 = cubic millimeter

[a]No surgery + CT + HT and/ or RT, only surgery, or surgery with CT or HT

Table 2. Agreement between automatically and manually determined Agatston scores on 163 breast planning CT scans

Manual coronary artery calcium in Agatston score categories	Automatic coronary artery calcium in Agatston score categories					
	0	**1-10**	**11-100**	**101-400**	**> 400**	**Total**
0	75	1	5	0	0	81
1-10	4	2	1	1	0	8
11-100	4	2	31	2	0	39
101-400	1	0	7	14	0	22
>400	0	0	0	6	7	13
Total	84	5	44	23	7	163

Table 3. Reproducibility of automatic coronary artery calcium scoring versus manual, and interscan reproducibility of automatic scoring, on breast planning CT

	Categorical[a]		**Continuous**
	Linearly weighted kappa (95% CI)	**Proportion of agreement (95% CI)**	**Intraclass correlation coefficient of CAC (Agatston) scores (95% CI)**
Automatic vs. manual (n = 163)	0.80 (0.74-0.87)	0.79 (0.72-0.85)	0.86 (0.81-0.89)
Breath-hold (n = 58)	0.86 (0.77-0.96)	0.88 (0.76-0.95)	0.95 (0.91-0.97)
Without breath-hold (n = 105)	0.77 (0.68-0.85)	0.74 (0.65-0.82)	0.66 (0.54-0.76)
Automatic vs. automatic(n = 294)	0.61 (0.50-0.72)	0.84 (0.80-0.89)	0.34 (0.23-0.44)

Abbreviations: CAC = coronary artery calcium; CI = Confidence Interval
[a]Cardiovascular disease risk categories of coronary artery calcium based on Agatston score: 0, 1-10, 11-100, 101-400, >400

Table 4. Agreement of automatically determined Agatston scores on radiotherapy planning CT of 294 breast cancer patients

Automatic coronary artery calcium in Agatston score categories	Automatic coronary artery calcium in Agatston score categories					
	0	**1-10**	**11-100**	**101-400**	**> 400**	**Total**
0	228	10	6	1	0	245
1-10	8	9	4	0	0	21
11-100	4	2	6	3	0	15
101-400	1	2	1	6	1	11
> 400	1[a]	0	0	1	0	2
Total	242	23	17	11	1	294

[a]Patient underwent one CT scan with breath-hold and one without breath-hold. The scan with breath-hold had an automatic coronary artery calcium score of 423, which was in agreement with the manual coronary artery calcium score after inspection. The scan without breath-hold had an automatic coronary artery calcium score of zero, which was manually inspected and corrected to a score of 885. The disagreement is caused by missed coronary artery calcium in the left anterior descending artery.

Table 5. Cardiovascular risk factors in relation to coronary artery calcium (Agatston) scores of 108 breast cancer patients.

	CAC score: 0 n = 72 (%)	**CAC score: 1-100 n = 72 (%)**	**CAC score: >100 n = 36 (%)**	**P value**
Median CAC (Agatston) score (IQR)	0 (0-0)	12 (3-30)	257 (134-389)	*<0.001*
Median age at time of scan in years (IQR)	57 (50-64)	62 (55-67)	70 (63-74)	<0.001
Diabetes				0.001
Yes	4 (5.6)	5 (6.9)	10 (27.8)	
No	68 (94.4)	67 (93.1)	26 (72.2)	
Hypertension				0.007
Yes	15 (20.8)	31 (43.1)	16 (44.4)	
No	57 (79.2)	41 (56.9)	20 (55.6)	
Hypercholesterolemia				0.492
Yes	9 (12.5)	14 (19.4)	5 (13.9)	
No	63 (87.5)	58 (80.6)	31 (86.1)	
Smoking status				*0.437*
Current	8 (11.1)	12 (16.7)	3 (8.3)	
Former	11 (15.3)	15 (20.8)	10 (27.8)	
Never/ not reported	53 (73.6)	45 (62.5)	23 (63.9)	
History of CVD				*0.019*
Yes	15 (20.8)	13 (18.1)	15 (41.7)	
No	57 (79.2)	59 (81.9)	21 (58.3)	
Number of CVD risk factors				0.023
0	34 (47.3)	20 (27.7)	10 (27.8)	
1	16 (22.2)	19 (26.4)	8 22.2)	
2	15 (20.8)	21 (29.2)	6 (16.7)	
3-5	7 (9.7)	12 (16.7)	12 (33.3)	

Abbreviations: CAC = coronary artery calcium, CVD = cardiovascular disease, IQR = interquartile range

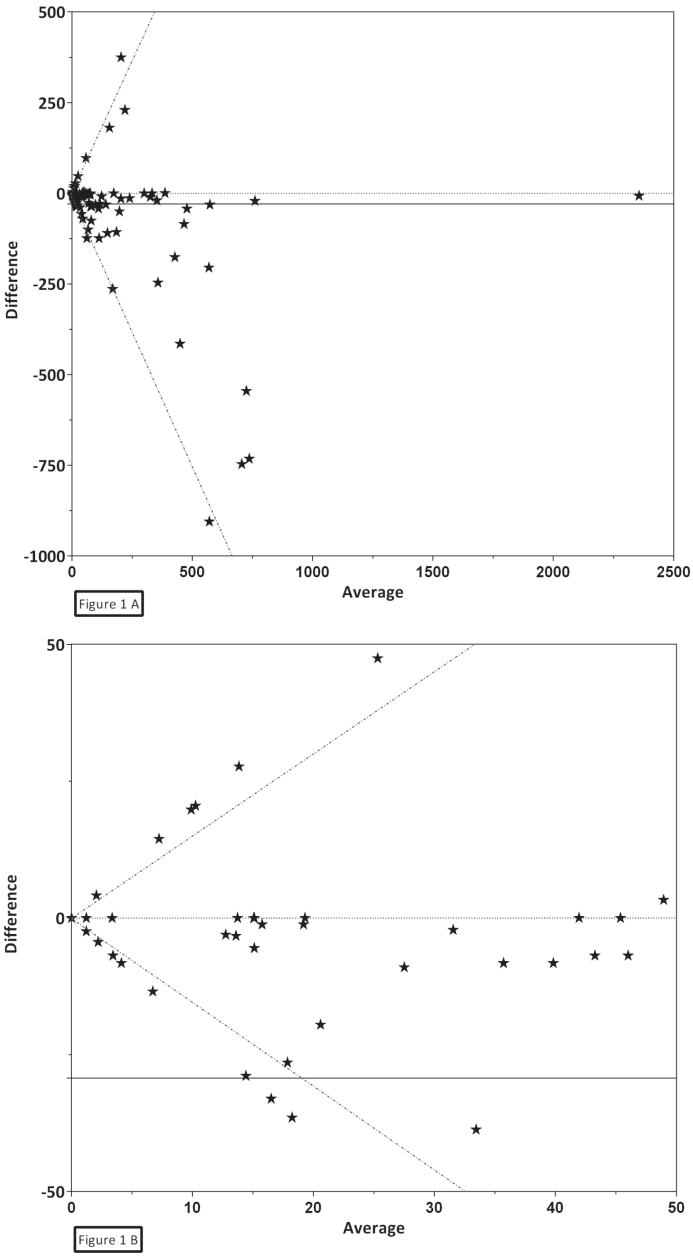


Figure 1A and 1B. Bland-Altman plot for the agreement between automatically and manually determined CAC on planning breast CT. CAC (Agatston) scores were assessed automatically and manually of 163 breast cancer patients using radiotherapy planning CT scans. Mean (X) = -29.3, standard deviation = 131.2, back log transformed upper limit of agreement = 1.5*X, back log transformed lower limit of agreement = -1.5*X. 1A is full plot and 1B is zoomed plot.

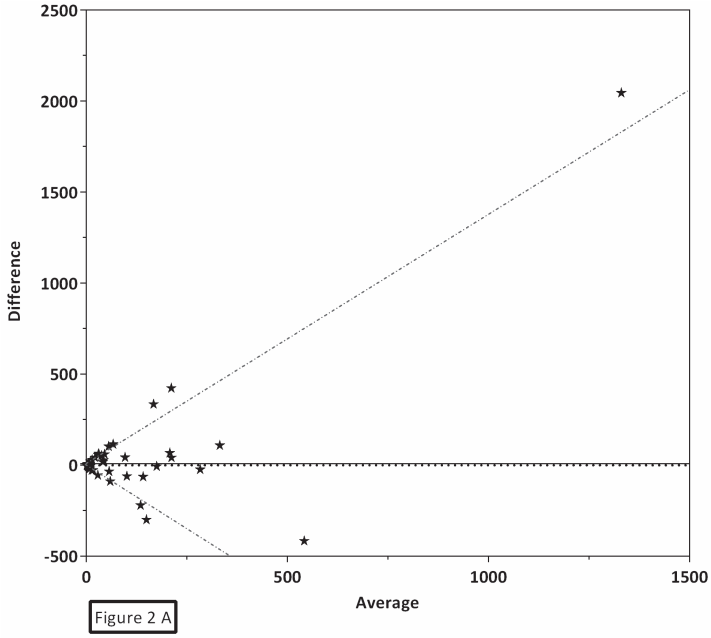


Figure 2 A

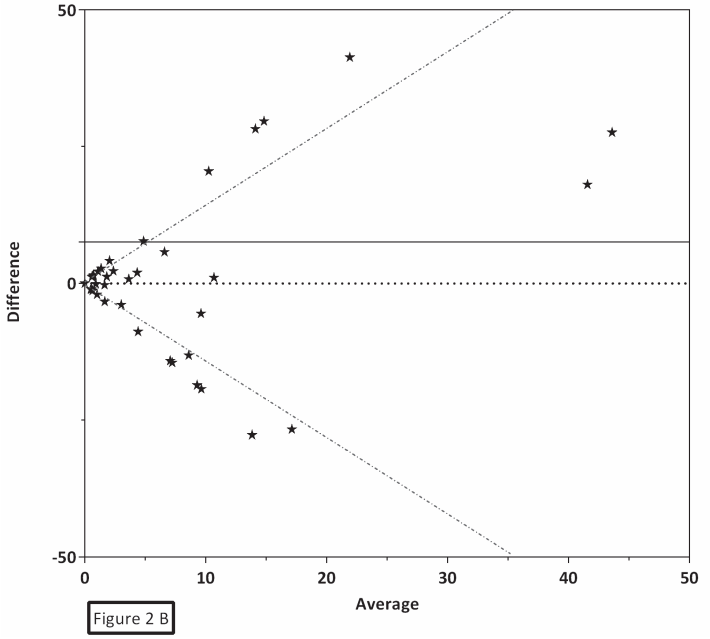


Figure 2 B

Figure 2A and 2B. Bland-Altman plot for the agreement of automatically determined CAC on planning breast CT**.** CAC (Agatston) scores were assessed in two scans of the same patient in a set of 294 breast cancer patients using radiotherapy planning CT scans. Mean (X) = 7.6, standard deviation = 128.7, back log transformed upper limit of agreement = 1.4*X, back log transformed lower limit of agreement = -1.4*X. 2A is full plot and 2B is zoomed plot.

Discussion

This study showed that automatic CAC scoring on radiotherapy planning CT scans is a reliable method to assess CVD risk categories based on CAC scores. One in four breast cancer patients planned for radiotherapy had elevated CAC score. In a small study of breast cancer patients, one in three patients with high CAC did not have any other CVD risk factor and may hence be missed in the cardiac morbidity risk evaluation.

The algorithm to automatically score CAC was developed for low-dose, non-dedicated CT scans acquired in a lung cancer screening trial[23]. In this context, Takx et al. evaluated reproducibility of the algorithm in 1749 participants by comparing it to manual scoring by a radiologist[17]. This study showed a very good reliability between automatic and manual CAC scoring, with a κ of 0.85 for CVD risk categorization and ICC of 0.90 for continuous CAC score. Our study showed comparable, albeit slightly lower, reliability results for automatic versus manual CAC scoring, with a linearly weighted kappa of 0.80 for CVD risk categorizaties and ICC of 0.86 for continuous CAC score. This was not surprising since the algorithm was trained with non-representative training data, namely low-dose chest CT scans[23]. Retraining the algorithm with representative radiotherapy planning CT scans of breast cancer patients will most likely increase its performance.

In this study, CT scans with an automatically determined CAC score of 1,000 and higher were inspected. Five scans contained large false positives representing CAC in the mitral annulus that were strongly affected by cardiac motion and difficult to differentiate from CAC in LCX in non-dedicated CT scans[31]. Please note that such calcifications are also predictive of future CVD events[32]. Reproducibility between automatic and manual CAC scoring was much higher in CT scans performed with breath-hold than in those without. Breath-holding technique is often used for patients who receive left-sided radiotherapy in order to minimize heart radiation exposure[33]. CT scans with breath-hold show reduced respiration motion artifacts allowed for more accurate automatic CAC scoring, and enhanced reproducibility between automatic and manual CAC scoring. The interscan reliability of CVD risk categories based on CAC scores between two automatically scored scans was much lower than the reliability between automatic and manual CAC scoring (0.61 versus 0.80, respectively). Difference in respiratory motion artifacts between CT scans performed with and without breath-hold has very likely contributed to this lower reliability of automatic CAC scoring, since 237 out of 294 (81%) patients had one CT scan performed with breath-hold and one scan without. Around 50% of all breast cancer patients were treated with radiotherapy and therefore routinely undergo planning CT scans[33,34].

Previous studies have shown that CAC is a stronger risk factor than traditional CVD risk factors, such as diabetes, hypertension and smoking status[35-37]. CAC scores of 100 and above are related to an increased risk of multivessel disease, coronary heart disease and overall CVD events[9,36,38]. In our study, 10 out of 36 patients (27.8%) with CAC scores above 100 did not have any other CVD risk factor. Though these patients are at increased CVD risk, they would not have been detected as high risk based on traditional CVD risk factors only.

We acknowledge that this study has limitations. Information on traditional CVD risk factors of breast cancer patients were retrieved from medical files at the radiotherapy department. These files are filled out by radiation oncologists or oncology nurses and may have resulted in underreporting of smoking and other traditional CVD risk factors. Moreover, we were not able to provide a cardiovascular risk score as blood pressure and cholesterol levels, which were necessary for, were not routinely measured in clinic. Another limitation is that we cannot assume an association between the presence and amount of CAC measured on non-dedicated radiotherapy planning CT scans and increased CVD risk. The Multi-Ethnic Study of Atherosclerosis (MESA) showed a strong association between the presence and amount of CAC and increased CVD risk. However, MESA measured CAC on dedicated cardiac CT scans and included a different study population as our study with different ethnicities (white, black, Hispanic, Asian), males and females, and without active cancer treatment[9,35,37]. Moreover, presence and amount of CAC have shown to be predictive in distinguishing patients with increased CVD risk based on CAC scores using non-dedicated chest CT scans of subjects in lung cancer screening trials[12,39,40]. Furthermore, so far there are no treatments to slow down or arrest the progression of CAC, and trial results have to be waited for. A randomized placebo-controlled trial is investigating the effect of 24-month treatment with menaquinon-7 supplementation (vitamin K antagonist) on the progression of CAC[41]. Moreover, a Dutch randomized-controlled trial is investigating whether early detection of CVD risk based on CAC score with subsequent lifestyle and/ or treatment intervention will reduce CVD morbidity and mortality in a high-risk population.

To conclude, automatic CAC scoring on radiotherapy planning CT scans is a reliable method to assess CVD risk categories based on CAC scores, preferably at breath-hold examinations, without additional radiation exposure or costs involved. In this prospective cohort study of 561 patients, we demonstrated that one in four patients has elevated CAC, and that one in three patients with high CAC scores didn't have other CVD risk factors and would therefore not have been identified as high risk. Knowing a patient's baseline CVD risk is essential when evaluating a left-sided radiotherapy planning CT scan, given the dose received by the heart during radiotherapy is associated with an increased risk of major CVD events[43]. The clinical relevance of automatic CAC scoring on planning CT scans in relation to increased absolute risk of a major CVD event still needs to be evaluated. The future clinical

application of the presence and amount of CAC measured on planning CT scans, and the patient's corresponding CVD risk, may be twofold. Radiation and medical oncologists may use it to identify patients who are candidates for less cardiotoxic treatments, and may refer patients with high cardiac morbidity to cardiologists for further diagnostic evaluation and treatment. General practitioners may use the information to start lifestyle interventions and/or treatments such as antihypertensive, to reduce the patient's CVD risk.

In a follow-up study, the automatic CAC scoring software will be adapted and optimized for radiotherapy planning CT scans of breast cancer patients. Moreover, associations between CAC assessed on radiotherapy planning CT scans and CVD risk (factors) of breast cancer patients will be investigated including patient's preferences and needs regarding disclosure of their CAC scores.

References

1. Bird BR, Swain SM. Cardiac toxicity in breast cancer survivors: Review of potential cardiac problems. *Clin Cancer Res*. 2008; 14 (1): 14-24.
2. Borger JH, Hooning MJ, Boersma LJ, et al. Cardiotoxic effects of tangential breast irradiation in early breast cancer patients: The role of irradiated heart volume. *Int J Radiat Oncol Biol Phys*. 2007; 69 (4): 1131-1138.
3. McGale P, Darby SC, Hall P, et al. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. *Radiother Oncol*. 2011; 100 (2): 167-175.
4. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol*. 2007; 25 (25): 3808-3815.
5. Taunk NK, Haffty BG, Kostis JB, Goyal S. Radiation-induced heart disease: Pathologic abnormalities and putative mechanisms. *Front Oncol*. 2015; 5: 39.
6. Lee YC, Chuang JP, Hsieh PC, Chiou MJ, Li CY. A higher incidence rate of acute coronary syndrome following radiation therapy in patients with breast cancer and a history of coronary artery diseases. *Breast Cancer Res Treat*. 2015.
7. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. *Circulation*. 1995; 92 (8): 2157-2162.
8. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M,Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990; 15 (4): 827-832.
9. Blaha MJ, Budoff MJ, DeFilippis AP, et al. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: Implications for the JUPITER population from MESA, a population-based cohort study. *Lancet*. 2011; 378 (9792): 684-692.
10. Wu MT, Yang P, Huang YL, et al. Coronary arterial calcification on low-dose ungated MDCT for lung cancer screening: Concordance study with dedicated cardiac CT. *AJR Am J Roentgenol*. 2008; 190 (4): 923-928.
11. Jacobs PC, Gondrie MJ, van der Graaf Y, et al. Coronary artery calcium can predict all-cause mortality and cardiovascular events on low-dose CT screening for lung cancer. *AJR Am J Roentgenol*. 2012; 198 (3): 505-511.
12. Chiles C, Duan F, Gladish GW, et al. Association of coronary artery calcification and mortality in the national lung screening trial: A comparison of three scoring methods. *Radiology*. 2015; 276 (1): 82-90.
13. Budoff MJ, Malpeso JM. Is coronary artery calcium the key to assessment of cardiovascular risk in asymptomatic adults? *J Cardiovasc Comput Tomogr*. 2011; 5 (1): 12-15.

14. Budoff MJ, Nasir K, Kinney GL, et al. Coronary artery and thoracic calcium on non-contrast thoracic CT scans: Comparison of ungated and gated examinations in patients from the COPD gene cohort. *J Cardiovasc Comput Tomogr*. 2011; 5 (2): 113-118.

15. Kim SM, Chung MJ, Lee KS, Choe YH, Yi CA, Choe BK. Coronary calcium screening using low-dose lung cancer screening: Effectiveness of MDCT with retrospective reconstruction. *AJR Am J Roentgenol*. 2008; 190 (4): 917-922.

16. Raggi P. Coronary calcium on electron beam tomography imaging as a surrogate marker of coronary artery disease. *Am J Cardiol*. 2001; 87 (4A): 27A-34A.

17. Takx RA, de Jong PA, Leiner T, et al. Automated coronary artery calcification scoring in non-gated chest CT: Agreement and reliability. *PLoS One*. 2014; 9 (3): e91239.

18. Shahzad R, van Walsum T, Schaap M, et al. Vessel specific coronary artery calcium scoring: An automatic system. *Acad Radiol*. 2013; 20 (1): 1-9.

19. Wolterink JM, Leiner T, Takx RA, Viergever MA, Isgum I. Automatic coronary calcium scoring in non-contrast-enhanced ECG-triggered cardiac CT with ambiguity detection. *IEEE Trans Med Imaging*. 2015; 34 (9): 1867-1878.

20. Brunner G, Chittajallu DR, Kurkure U, Kakadiaris IA. Toward the automatic detection of coronary artery calcification in non-contrast computed tomography data. *Int J Cardiovasc Imaging*. 2010; 26 (7): 829-838.

21. Kurkure U, Chittajallu DR, Brunner G, Le YH, Kakadiaris IA. A supervised classification-based method for coronary calcium detection in non-contrast CT. *Int J Cardiovasc Imaging*. 2010; 26 (7): 817-828.

22. Xie Y, Cham MD, Henschke C, Yankelevitz DF, Reeves AP. Automated coronary artery calcification detection on low-dose chest CT images. *SPIE International Symposium on Medical Imaging 2014*. Feb 2014; 9035 (90350F).

23. Isgum I, Prokop M, Niemeijer M, Viergever MA, van Ginneken B. Automatic coronary calcium scoring in low-dose chest computed tomography. *IEEE Trans Med Imaging*. 2012; 31 (12): 2322-2334.

24. Sobin LH, Gospodarowicz MK, Wittekind C. *TNM classification of malignant tumours, 7th edition*. 7th ed. Wiley-Blackwell; 2009.

25. Budoff MJ, Shaw LJ, Liu ST, et al. Long-term prognosis associated with coronary calcification: Observations from a registry of 25,253 patients. *J Am Coll Cardiol*. 2007; 49 (18): 1860-1870.

26. Shaw LJ, Raggi P, Callister TQ, Berman DS. Prognostic value of coronary artery calcium screening in asymptomatic smokers and non-smokers. *Eur Heart J*. 2006; 27 (8): 968-975.

27. Maher JE, Bielak LF, Raz JA, Sheedy PF, Schwartz RS, Peyser PA. Progression of coronary artery calcification: A pilot study. *Mayo Clin Proc*. 1999; 74 (4): 347-355.

28. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977; 33 (1): 159-174.

29. Brenner H, Kliebsch U. Dependence of weighted kappa coefficients on the number of categories. *Epidemiology*. 1996; 7 (2): 199-202.

30. Lowry R. Kappa as a measure of concordance in categorical sorting. http: //vassarstats.net/kappa.html. Updated 2017. Accessed September, 2017.

31. van Hamersvelt RW, Willemink MJ, Takx RA, et al. Cardiac valve calcifications on low-dose unenhanced ungated chest computed tomography: Inter-observer and inter-examination reliability, agreement and variability. *Eur Radiol*. 2014; 24 (7): 1557-1564.

32. Willemink MJ, Takx RA, Isgum I, et al. Prognostic value of heart valve calcifications for cardiovascular events in a lung cancer screening population. *Int J Cardiovasc Imaging*. 2015; 31 (6): 1243-1249.

33. Taylor CW, Kirby AM. Cardiac side-effects from breast cancer radiotherapy. *Clin Oncol (R Coll Radiol)*. 2015.

34. Cutter D, Ferreira V, Basagiannis C, et al. Cardiovascular magentic resonance imaging and radiation-induced heart disease following radiotherapy for breast cancer. *Cancer Res*. 2011; 71 (24).

35. Kronmal RA, McClelland RL, Detrano R, et al. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: Results from the multi-ethnic study of atherosclerosis (MESA). *Circulation*. 2007; 115 (21): 2722-2730.

36. Lehmann N, Mohlenkamp S, Mahabadi AA, et al. Effect of smoking and other traditional risk factors on the onset of coronary artery calcification: Results of the Heinz Nixdorf recall study. *Atherosclerosis*. 2014; 232 (2): 339-345.

37. Gepner AD, Young R, Delaney JA, et al. Comparison of coronary artery calcium presence, carotid plaque presence, and carotid intima-media thickness for cardiovascular disease prediction in the multi-ethnic study of atherosclerosis. *Circ Cardiovasc Imaging*. 2015; 8 (1): 10.1161/CIRCIMAGING.114.002262.

38. Nasir K, Rubin J, Blaha MJ, et al. Interplay of coronary artery calcification and traditional risk factors for the prediction of all-cause mortality in asymptomatic individuals. *Circ Cardiovasc Imaging*. 2012; 5 (4): 467-473.

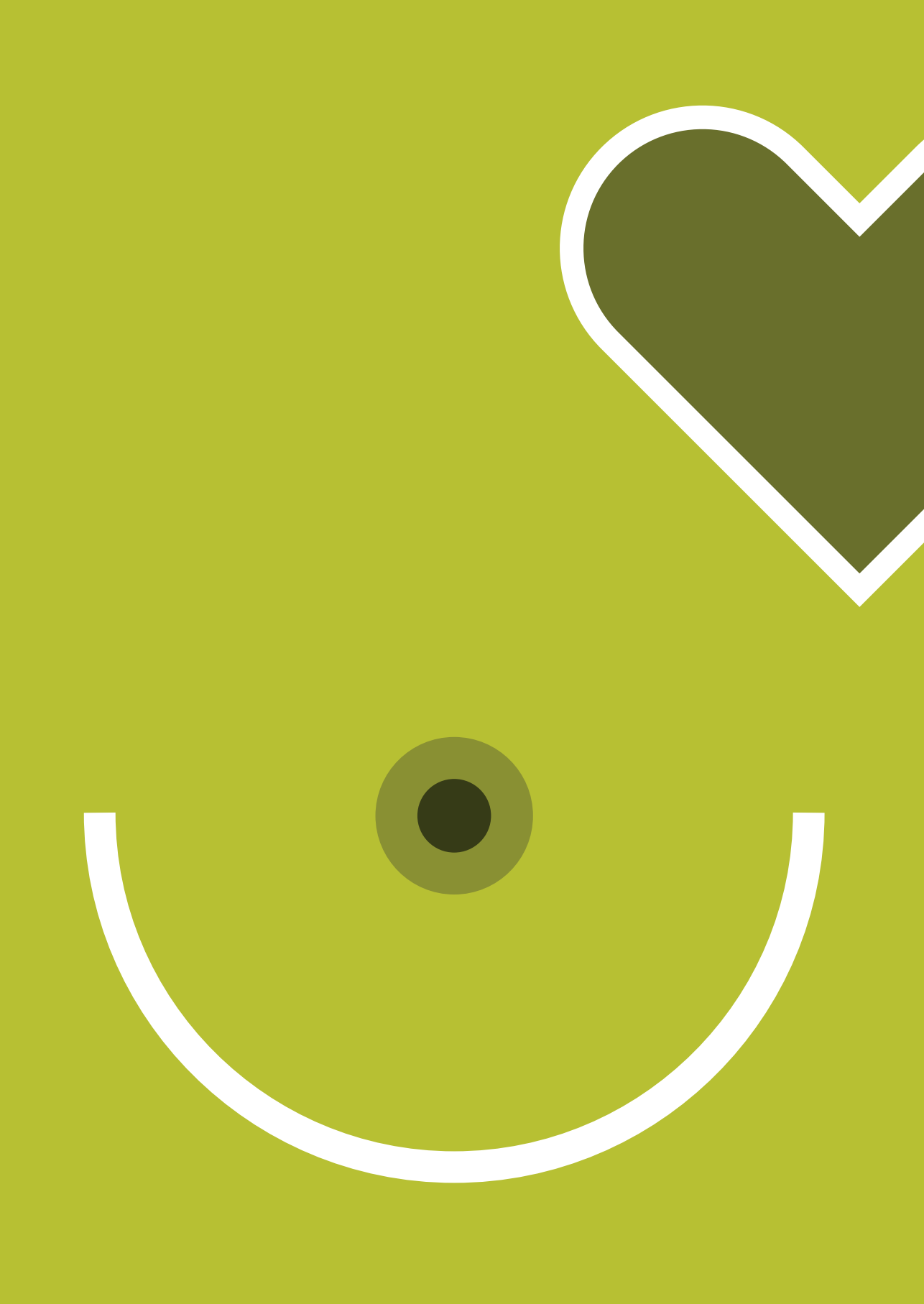
39. Jairam PM, Gondrie MJ, Grobbee DE, et al. Incidental imaging findings from routine chest CT used to identify subjects at high risk of future cardiovascular events. *Radiology*. 2014; 272 (3): 700-708.

40. Mets OM, Vliegenthart R, Gondrie MJ, et al. Lung cancer screening CT-based prediction of cardiovascular events. *JACC Cardiovasc Imaging*. 2013; 6 (8): 899-907.

41. Vossen LM, Schurgers LJ, van Varik BJ, et al. Menaquinone-7 supplementation to reduce vascular calcification in patients with coronary artery disease: Rationale and study protocol (VitaK-CAC trial). *Nutrients*. 2015; 7 (11): 8905-8915.

42. de Koning HJ, Oudkerk M. Risk or benefit in screening for cardiovascular disease (ROBINSCA). http: //www.robinsca.nl. Accessed 11/03, 2015.

43. Darby SC, Ewertz M, Hall P. Ischemic heart disease after breast cancer radiotherapy. *N Engl J Med*. 2013; 368 (26): 2527.



Chapter 7

Automated measurement of calcifications in the coronary arteries and thoracic aorta on radiotherapy planning CT scans of Western and Asian breast cancer patients

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Submitted

Abstract

Purpose

Coronary artery calcification (CAC) and thoracic aortic calcification (TAC) are predictors of cardiovascular disease (CVD) events. This study quantified the prevalence of CAC and TAC based CVD risk on radiotherapy planning computed tomography (CT) scans of Dutch and Singaporean breast cancer patients. In addition, reproducibility and generalizability of software based on deep learning for automatic calcification scoring in these populations was assessed.

Methods

Women with *in situ* or invasive breast cancer from the Netherlands (n = 1,199) and Singapore (n = 1,090) with a radiotherapy planning CT scan were included. CAC and TAC were automatically scored using software based on deep learning. CAC was categorized into 0, 1-10, 11-100, 101-400 and >400 Agatston scores. Differences in CAC and TAC score between both populations were assessed using Chi-Square Test (categorical variables) or Mann-Whitney U Test (continuous variables with skewed distributions). Reliability between automatic and manual scoring was assessed in 240 randomly CT scans from both populations (120 each), and assessed with linearly weighted kappa for CAC categories and intraclass correlation coefficient for TAC.

Results

The median age at time of CT scan was higher in patients from the Netherlands than Singapore: 57 (interquartile range (IQR)= 50-66) versus 52 years (IQR = 45-60), p<0.01. The automatic software detected CAC in more patients from the Netherlands than Singapore: 24.2% versus 17.3%, p<0.01. TAC was more present in patients from the Netherlands than Singapore: 73.0% versus 62.2%, p<0.01. In both populations, CAC and TAC increased with age. Reliability of CAC categories was excellent in the Netherlands and Singapore: 0.85 (95% confidence interval (CI) = 0.77-0.93) and 0.90 (95% CI = 0.84-0.96) respectively. Also, reliability of TAC was very high in the Netherlands and Singapore: 0.98 (95% CI = 0.96-0.98) and 0.99 (95% CI = 0.98-0.99) respectively.

Conclusions

The prevalence of CAC and TAC in breast cancer patients from the Netherlands and Singapore was considerable and increased with age. Automatic scoring using deep learning software is a reliable method to measure CAC and TAC on breast planning CT scans, and generalizable to other populations.

Introduction

Cardiovascular disease (CVD) is an important cause of death in women with breast cancer with 24% of patients over 65 years dying of this disease[1,2]. The risk of CVD following breast cancer is increased by exposure of cardiotoxic breast cancer therapies such as radiation therapy[3-5], anthracycline-based chemotherapy[6], and trastuzumab[7,8]. Breast cancer patients with pre-existing CVD risk factors have the highest risk of treatment induced cardiotoxicity[9].

Coronary artery calcification (CAC) and thoracic aorta calcification (TAC) are markers of atherosclerosis[10-13]. In clinical practice, these calcifications are measured on chest or cardiac computed tomography (CT) scans[14,15]. CAC, measured on cardiac CT scans, is an independent predictor of CVD events and mortality[16,17]. Similarly, TAC, measured on cardiac CT scans, is associated with an increased risk of coronary heart disease, independent of CAC and other CVD risk factors[18,19]. The majority (>60%) of breast cancer patients undergoes radiation therapy after surgery and receives a non-contrast enhanced CT scan of the breasts including the heart for individual radiation treatment planning. CAC and TAC can be visualized and quantified on these scans[20]. Information on CAC and TAC can be used to estimate the risk of CVD in the individual breast cancer patient.

In the present study, we applied a new deep learning software for automated quantification of CAC and TAC on planning CT scans[21]. We aim to investigate the prevalence and quantity of CAC and TAC based CVD risk in Western (*i.e.* the Netherlands) and Asian (*i.e.* Singapore) breast cancer patients. In addition, we assessed reproducibility and generalizability of the software in these populations.

Methods

Design and study population

This cross-sectional study included women diagnosed with *in situ* or invasive breast cancer who underwent a radiotherapy planning CT scan at the Radiation Oncology Departments of the University Medical Center Utrecht (UMCU) in the Netherlands or the National University Hospital of Singapore (NUHS) in Singapore. At the UMCU, breast cancer patients were included in the context of the Utrecht cohort for Multiple BReast cancer intErvention studies and Long-term evaLuAtion (UMBRELLA) study, which includes all breast cancer patients referred to the Radiation Oncology Department of the UMCU since 2013[22]. Here, patients gave informed consent for use of their routine clinical, imaging, pathology, and follow up data. 1,199 patients were enrolled in UMBRELLA between 2013 and 2016. At NUHS, 1,090 breast cancer patients with a radiotherapy planning CT scan were included from January 2005 (date of introduction of digital planning CT scan) to September 2015. We excluded one patient's CT scan as severe anatomical deformities of the chest limited the calcification detection. Information on date of birth was extracted from the patient's CT scan. The Medical Ethical Review Board waived the need of informed consent of patients in Singapore.

Imaging data

At the UMCU, planning CT scans were conducted with a Philips Brilliance Big Bore CT scanner using 16 x 0.75mm collimation, 120 kVp, 3mm slice thickness. At NUHS, all planning CT scans were conducted with a Philips Brilliance Big Bore CT scanner using 16 x 1.5 collimation, 120 kVp, 5mm slice thickness. All breast cancer patients received a CT scan during free breathing, without contrast enhancement or ECG-synchronization. At the UMCU, the majority of patients planned for left-sided and/or parasternal irradiation underwent an additional deep inspiration breath-hold scan. For patients with multiple CT scans (49.5% at UMCU and 2.1% at NUHS), the first CT scan if possible with application of the deep inspiration breath-hold technique, was used.

Automatic calcification quantification

All CT scans were automatically scored for atherosclerotic calcifications in the thoracic aorta and coronary arteries, *i.e.* left coronary artery (LAD) including the left main coronary artery, left circumflex (LCX), and right coronary artery (RCA), using a method based on deep learning described by Lessmann et al (2017)[21]. Briefly, the algorithm consists of two consecutive convolutional neural networks (CNN) labeling calcified voxels. To enable learning from contextual spatial information, the first CNN exploits a large field of view and is hence able to identify potential calcifications and determine their anatomical label. To

analyze detailed local texture, the second CNN exploits a smaller field of view. This network identifies true calcifications among the previously detected potential calcifications. The algorithm was developed to analyze low-dose chest CT scans. First, all scans were cropped to a standardized field of view prior similar to the field of view of chest CT scans, using CNN based localization to enable analysis of radiotherapy planning CT scan images[23]. The algorithm was trained with data originally used to develop the algorithm (1,181 low-dose chest CT scans from the National Lung Screening Trial)[24] and with 563 radiotherapy planning CT scans of breast cancer patients within UMBRELLA. Calcifications were identified as voxels above 130 Hounsfield Unit (HU). Therefore, 3D region growing with a threshold of 130 HU was performed on all automatically identified calcification voxels.

CAC was expressed in the Agatston score and each patient was assigned to one of five CVD risk categories: 0, 1-10, 11-100, 101-400, >400[25-28]. TAC was expressed in volume scores (mm^3). Scans with extremely high automatically detected CAC score (>1,000) (n = 10) and TAC volume (>10,000) (n = 4) were manually inspected and corrected if needed.

Manual calcification quantification

To quantitatively evaluate reproducibility of the automatic and manual calcification scoring method, CT scans were randomly selected from UMCU and NUHS (120 each). Manual annotation of CAC and TAC on these scans by using a threshold of 130 HU defined the reference. Calcifications in the coronary arteries were labeled as LAD, LCX, RCA. The reference annotation was conducted by trained medical students (AJ and SM) and PhD students (SGMvV and SAMG), each with experience in over 500 CT scans.

Statistical analysis

Median (interquartile range (IQR)) was used to describe continuous variables with skewed distributions. The number of breast cancer patients with CAC Agatston scores above zero and above 100 were calculated per age category for Dutch and Singaporean patients separately. In addition, median (IQR) volume (in mm^3) of TAC was calculated per age category. Differences between breast cancer patients from the Netherlands and Singapore were tested with Chi-Square Test (or Fisher's exact test when the cell count was less than five) in case of categorical variables, and with Mann-Whitney U Test in case of continuous variables with skewed distributions.

The performance of the software, *i.e.* reproducibility, was evaluated with reliability and agreement measures. Reliability (agreement beyond chance) of CAC categories was assessed with Cohen's linearly weighted kappa[29]. Reliability of continuous CAC Agatston score and TAC volume were assessed with intraclass correlation coefficient (ICC). The two-way random effects and absolute agreement ICC was used to assess reliability between

automatic and manual calcification scoring, taking into account the variance between patients and structural differences between automatic and manual calcification scoring. Agreement (degree to which CAC categories are identical between automatic versus manual CAC scoring method) was assessed with proportional agreement. Analyses were performed with IBM SPSS statistics version 23 and an online statistical tool[30].

Results

Median age at time of planning CT scan was higher in breast cancer patients from the Netherlands than from Singapore: 57 (IQR = 50-66) versus 52 (IQR = 45-60), p<0.01 (Table 1). The prevalence of CAC was higher in patients from the Netherlands than Singapore: 24.2% versus 17.3% (p<0.01). Among these, 6.5% and 6.2% of patients from the Netherlands and Singapore had a CAC score above 100. Similarly, the prevalence of TAC was higher among patients from the Netherlands than Singapore (73.0% versus 62.2%, p<0.01). Three CT scans had an automatically determined CAC score of 1,000 and above. Two were corrected to a higher CAC score (from 4,761 to 5,473 and from 1,243 to 1,310) and one CT scan was corrected to a lower CAC score (from 1,191 to 721).

The prevalence of CAC increased with higher age from 3% for patients younger than 41 years to 38% for patients between 41 and 70 years (Figure 1). The prevalence of CAC was higher in breast cancer patients of 70 years or older from Singapore than the Netherlands (70% versus 55%, p<0.05). CAC scores over 100 were present in 10% to 15% for patients between 61 and 70 years, and in 18% to 29% for patients of 70 years and older (Figure 2). Median TAC volumes (mm^3) increased with age from 41 mm^3 for patients between 51 to 60 years to almost 2,000 mm^3 for patients of 70 years or older (Figure 3).

Performance of automatic analysis

For the Dutch population, reliability of CAC categories assessed with linearly weighted kappa was 0.85 (95% confidence interval (CI) = 0.77-0.93) and slightly higher for scans with deep inspiration breath-hold (Table 2). Proportion of agreement for CAC categories was 0.87 (95% CI = 0.79-0.92) and slightly higher for scans with deep inspiration breath-hold. For continuous CAC score, the ICC was 0.95 (95% CI = 0.93-0.97) and slightly higher for scans with deep inspiration breath-hold. For TAC score, the ICC was 0.98 (95% CI = 0.96-0.98) and slightly higher for scans with deep inspiration breath-hold. For the Singaporean population, linearly weighted kappa was 0.90 (95% CI = 0.84-0.96) and proportion of agreement was 0.90 (95% CI = 0.84-0.95) for CAC categories (Table 2). The ICC was 0.99 (95%CI = 0.98-.99) for TAC score.

Table 1. Distribution of age and cardiac calcification in 2,288 breast cancer patients by country of residence

	The Netherlands (Western population) n = 1,199	**Singapore (Asian population) n = 1,089**	**P value***
Age at time of CT scan, years, median (IQR)	57 (50-66)	52 (45-60)	<0.01
Age at time of CT scan in categories, years, % (n)			<0.01†
<41	5.7 (68)	12.6 (137)	
41-50	20.9 (250)	32.2 (351)	
51-60	32.8 (393)	32.4 (353)	
61-70	28.9 (346)	16.1 (174)	
>70	11.8 (142)	6.7 (73)	
Coronary artery calcification into Agatston score categories, % (n)			<0.01‡
0	75.8 (909)	82.7 (901)	
1-10	8.8 (106)	3.9 (43)	
11-100	8.8 (106)	7.1 (77)	
101-400	4.4 (53)	3.9 (43)	
>400	2.1 (25)	2.3 (25)	
Thoracic aortic calcification			
Median (IQR) in volume (mm^3)	91 (0-692)	41 (0-495)	<0.01
Patients with calcifications, % (n)	73.0 (875)	62.2 (677)	<0.01

Abbreviations: CT = computed tomography, IQR = interquartile range
*Statistically significant differences between countries were tested with the Chi-Square Test in case of a categorical variable (or Fisher's exact test when the cell count was less than five) and with the Mann-Whitney U Test in case of a continuous variable.
†All categories except for 51-60
‡Categories 0 and 1-10

Table 2. Reproducibility of calcifications in coronary arteries and thoracic aorta comparing automatic versus manual scoring on radiotherapy planning CT scans of breast cancer patients stratified by country of residence

	Coronary artery calcification (Agatston) scores			Thoracic aorta calcification in volume (mm^3)
	Categorical		Continuous	Continuous
	Linearly weighted kappa (95% CI)	Proportion of agreement (95% CI)	Intraclass correlation coefficient (95% CI)	Intraclass correlation coefficient (95% CI)
The Netherlands				
Automatic vs. manual (n = 120)	0.85 (0.77-0.93)	0.87 (0.79-0.92)	0.95 (0.93-0.97)	0.98 (0.96-0.98)
Breath-hold (n = 40)	0.88 (0.76-1.00)	0.90 (0.75-0.97)	1.00 (0.99-1.00)	0.97 (0.96-0.98)
Without breath-hold (n = 80)	0.84 (0.75-0.94)	0.85 (0.75-0.92)	0.94 (0.90-0.96)	1.00 (0.99-1.00)
Singapore				
Automatic vs. manual				
Without breath-hold (n = 120)	0.90 (0.84-0.96)	0.90 (0.84-0.95)	0.99 (0.99-1.00)	0.99 (0.98-0.99)

Abbreviation: CI = confidence interval

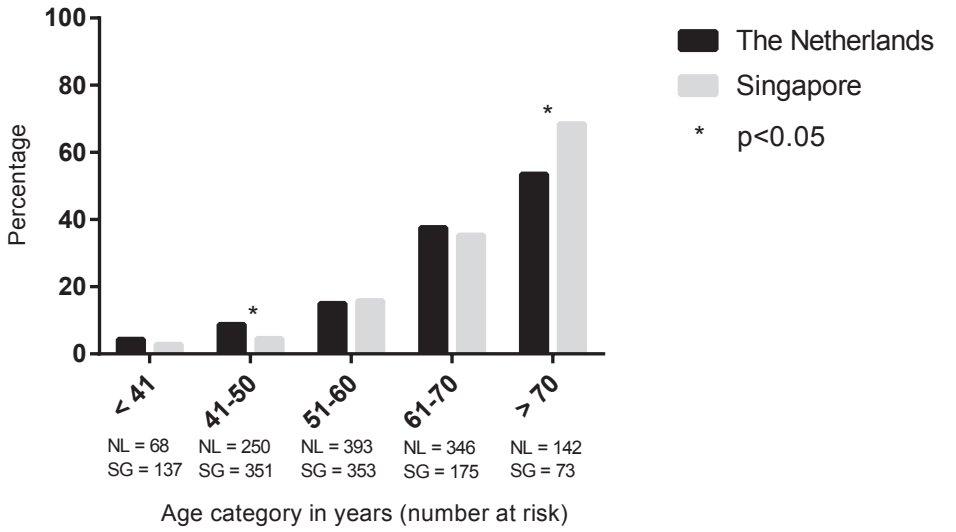

Figure 1. Distribution of breast cancer patients with a coronary artery calcification (Agatston) score above zero by age category and country of residence.

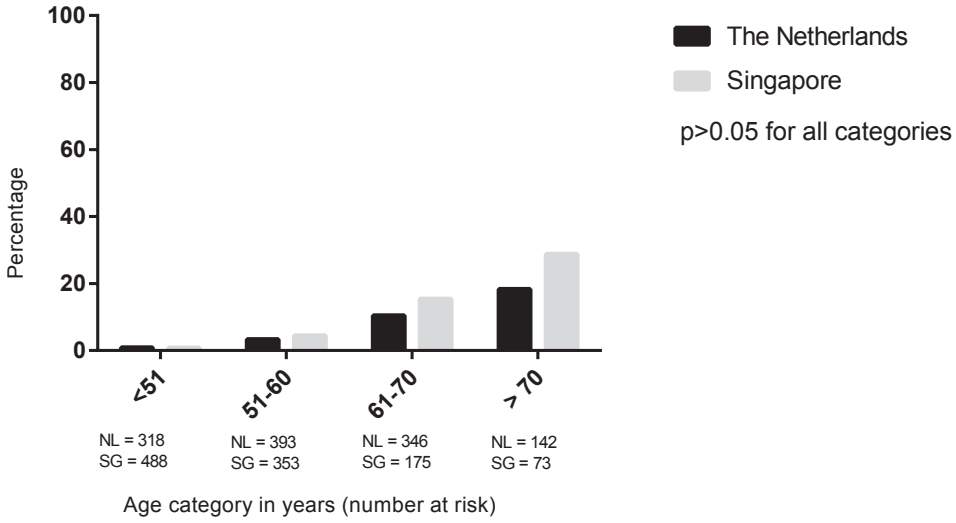

Figure 2. Distribution of breast cancer patients with a coronary artery calcification (Agatston) score above 100 by age category and country of residence.

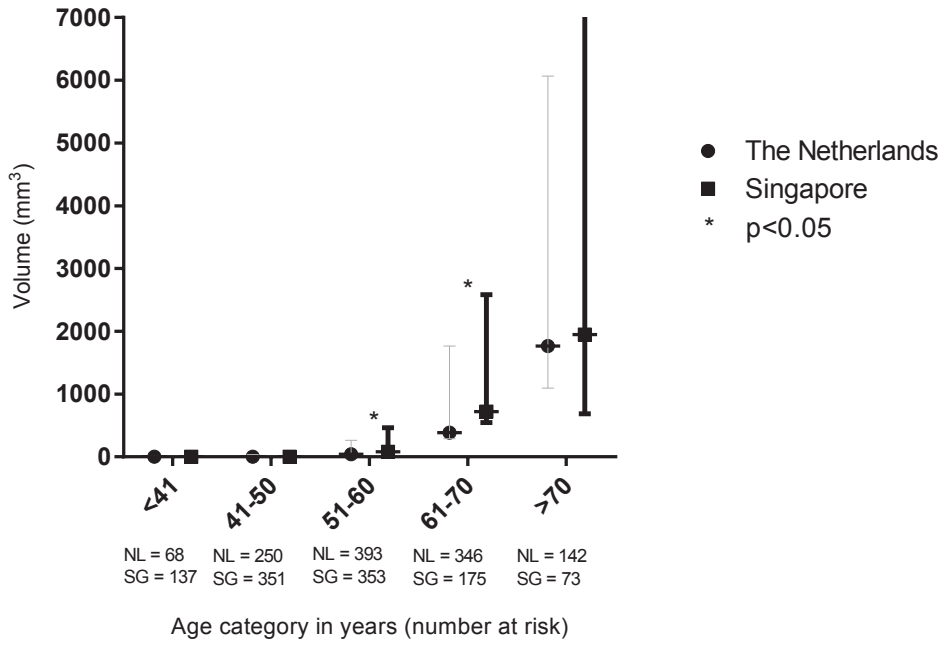

Figure 3. Median thoracic aortic calcification (interquartile range) in breast cancer patients by age category and country of residence.

Discussion

The prevalence of CAC and TAC in breast cancer patients from the Netherlands and Singapore is considerable and increases with age. Up to one third of breast cancer patients aged under 70 years has CAC. More than half of patients aged over 70 years has CAC with higher prevalence in patients from Singapore than the Netherlands (70% versus 55%). TAC is present in two third of patients from the Netherlands and Singapore. This study also showed that the new deep learning automatic scoring is a reliable method to measure CAC and TAC on radiotherapy planning CT scans and generalizable to other populations.

Knowing a breast cancer patient's CVD risk is important, especially when treatment with cardiotoxic chemotherapy is considered which is mainly among patients aged under 70 years. In these cases, together with the patient, physicians may decide to timely start with cardioprotective medication or opt for cancer therapy with reduced cardiotoxicity[31-33]. Patients with a high risk of CVD can be monitored before, during, and after treatment, and may reduce their risk of CVD by treatment with antihypertensive or statins or adapting a healthier lifestyle[31,32].

The present study found a higher prevalence of CAC in Singaporean patients compared to Dutch patients which was mainly originating from differences in CAC categories 0 and 1-10. This may be explained by the difference in slice thickness which was larger in scans from Singapore (5mm) than the Netherlands (3mm). Therefore, the partial volume effect might have been more severe in scans from Singapore resulting in a lower detection rate of low CAC scores (*i.e.* <10) in these scans. Furthermore, the present study shows high reproducibility of automatic compared to manual CAC and TAC scoring on breast planning CT scans of both populations. As such, the deep learning method can be used to measure CAC and TAC in different populations with different disease characteristics and scan protocols. With a reliability between 0.94 and 1.00 for CAC continuous score, the software based on deep learning performed similar or better compared to previously reported inter-observer agreement for CAC scoring in chest CT using a software based on supervised pattern recognition (ICC = 0.95)[27]. Planning CT scans performed with deep inspiration breath-hold have a higher reproducibility of automatic calcification detection, probably due to the fact that these scans have less motion artifacts compared with scans performed during free breathing. The use of deep-inspiration breath-hold is a technique that significantly reduces the irradiated volume and dose to the heart compared to free breathing, especially for patients with left-sided local or internal mammary lymph node radiotherapy[34].

Our results are in contrast with those of another Dutch study looking at CAC in patients with noninvasive or invasive breast cancer treated with breast-conserving surgery between 2008 and 2010[35]. This study reported a CAC prevalence of 47% (unadjusted for age), which is almost double the prevalence reported in the current study. Both study populations were of comparable age. Unlike the present study, Mast et al. (2012) used cardiac CT scans to detect CAC manually[35]. It is however unlikely that the difference in scan type and CAC scoring (automatic versus manual) explains the difference in CAC prevalence between the current study and those reported by Mast et al. (2012)[35], as we showed high reproducibility of automatic versus manual CAC scoring on radiotherapy planning CT scans. As the breast cancer population of Mast et al. (2012) consisted only of 80 patients, their reported CAC estimates are less precise than those CAC estimates reported in the current study[35].

The Multi-Ethnic Study of Atherosclerosis (MESA) investigated CAC and TAC in women free from clinically apparent CVD with different ethnic origins living in the United States[14]. MESA used electrocardiogram (ECG)-triggered cardiac CT scans to detect calcifications[14]. CAC was more present in white women (44.6%) than in Chinese women (36.6%) (unadjusted for age)[36]. Compared to our study, this study population was older which may (partly) explain the higher CAC prevalence[36]. Kanaya et al. (2014) compared prevalence of CAC in white MESA women and in South Asian women using data from a community-based cohort of asymptomatic women in the United States[37]. For the latter population, non-ECG-triggered and non-contrast enhanced cardiac CT scans were used to assess the CAC[37]. Similarly to our study, South Asian women aged over 70 years had higher CAC scores than white women aged over 70 years. Furthermore, the prevalence of TAC has been evaluated in women aged between 42 and 50 years participating in the Health Women Study in the United States[38]. This study reported a prevalence of TAC (volume not specified) of 78% which is comparable to the prevalence of TAC reported in the current study (73%)[38].

We acknowledge that the association between CAC and TAC (automatically) detected on radiotherapy planning CT scans and the risk of cardiovascular events has not been established. This knowledge gap will be filled by the BRAGATSTON study, a study on Automated Quantification of Coronary Artery Calcifications on Radiotherapy Planning CTs for Cardiovascular Risk Prediction in Breast Cancer Patients (NCT03206333). BRAGATSTON, is an ongoing multicenter study led by the University Medical Center Utrecht[39], with the aim to quantify the association between TAC and CAC and risk of CVD, and to optimize and validate the newly UMCU developed automated software based on deep learning[17].

To conclude, the prevalence of CAC and TAC is considerable in breast cancer patients both from the Netherlands and Singapore, and increases with age. Up to one third of breast cancer patients aged under 70 years has CAC and these patients often receive cardiotoxic breast cancer treatments. Early identification of breast cancer patients at high risk of CVD may help physicians find a good balance between optimal tumor control and minimal treatment-induced CVD.

References

1. Colzani E, Liljegren A, Johansson AL, et al. Prognosis of patients with breast cancer: Causes of death and effects of time since diagnosis, age, and tumor characteristics. *J Clin Oncol*. 2011; 29 (30): 4014-4021.
2. Gernaat SAM, Ho PJ, Rijnberg N, et al. Risk of death from cardiovascular disease following breast cancer: A systematic review. *Breast Cancer Res Treat*. 2017.
3. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, et al. 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 8,135 women in 22 randomized trials. *Lancet*. 2014; 383 (9935): 2127-2135.
4. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomized trials. *Lancet*. 2005; 366 (9503): 2087-2106.
5. Taylor CW, Kirby AM. Cardiac side-effects from breast cancer radiotherapy. *Clin Oncol (R Coll Radiol)*. 2015.
6. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: Systematic review and meta-analysis of randomized controlled trials. *BMC Cancer*. 2010; 10: 337-2407-10-337.
7. Suter TM, Cook-Bruns N, Barton C. Cardiotoxicity associated with trastuzumab (Herceptin) therapy in the treatment of metastatic breast cancer. *Breast*. 2004; 13 (3): 173-183.
8. Suter TM, Procter M, van Veldhuisen DJ, et al. Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. *J Clin Oncol*. 2007; 25 (25): 3859-3865.
9. D'Agostino RB S, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham heart study. *Circulation*. 2008; 117 (6): 743-753.
10. Kalsch H, Lehmann N, Mohlenkamp S, et al. Prevalence of thoracic aortic calcification and its relationship to cardiovascular risk factors and coronary calcification in an unselected population-based cohort: The Heinz Nixdorf recall study. *Int J Cardiovasc Imaging*. 2013; 29 (1): 207-216.
11. Budoff MJ, Nasir K, Kinney GL, et al. Coronary artery and thoracic calcium on non-contrast thoracic CT scans: Comparison of ungated and gated examinations in patients from the COPD gene cohort. *J Cardiovasc Comput Tomogr*. 2011; 5 (2): 113-118.
12. Nasir K, Katz R, Al-Mallah M, et al. Relationship of aortic valve calcification with coronary artery calcium severity: The multi-ethnic study of atherosclerosis (MESA). *J Cardiovasc Comput Tomogr*. 2010; 4 (1): 41-46.
13. Kohsaka S, Jin Z, Rundek T, et al. Impact of mitral annular calcification on cardiovascular events in a multiethnic community: The Northern Manhattan study. *JACC Cardiovasc Imaging*. 2008; 1 (5): 617-623.

14. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: Objectives and design. *Am J Epidemiol*. 2002; 156 (9): 871-881.

15. Hughes-Austin JM, Dominguez A,3rd, Allison MA, et al. Relationship of coronary calcium on standard chest CT scans with mortality. *JACC Cardiovasc Imaging*. 2016; 9 (2): 152-159.

16. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med*. 2008; 358 (13): 1336-1345.

17. Blaha MJ, Budoff MJ, DeFilippis AP, et al. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: Implications for the JUPITER population from MESA, a population-based cohort study. *Lancet*. 2011; 378 (9792): 684-692.

18. Budoff MJ, Nasir K, Katz R, et al. Thoracic aortic calcification and coronary heart disease events: The multi-ethnic study of atherosclerosis (MESA). *Atherosclerosis*. 2011; 215 (1): 196-202.

19. Iribarren C, Sidney S, Sternfeld B, Browner WS. Calcification of the aortic arch: Risk factors and association with coronary heart disease, stroke, and peripheral vascular disease. *JAMA*. 2000; 283 (21): 2810-2815.

20. Gernaat SA, Isgum I, de Vos BD, et al. Automatic coronary artery calcium scoring on radiotherapy planning CT scans of breast cancer patients: Reproducibility and association with traditional cardiovascular risk factors. *PLoS One*. 2016; 11 (12): e0167925.

21. Lessmann N, van Ginneken B, Zreik M, de Jong PA, de Vos BD, Viergever MA, Išgum I. Automatic calcium scoring in low-dose chest CT using deep neural networks with dilated convolutions. *IEEE Transactions on Medical Imaging, in press*. 2017.

22. Young-Afat DA, van Gils CH, van den Bongard HJGD, Verkooijen HM, UMBRELLA Study Group. The Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaLuAtion (UMBRELLA): Objectives, design, and baseline results. *Breast Cancer Res Treat*. 2017; 164 (2): 445-450.

23. de Vos BD, Wolterink JM, de Jong PA, Leiner T, Viergever MA, Isgum I. ConvNet-based localization of anatomical structures in 3-D medical images. *IEEE Trans Med Imaging.* 2017; 36 (7): 1470-1481.

24. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011; 365 (5): 395-409.

25. Budoff MJ, Shaw LJ, Liu ST, et al. Long-term prognosis associated with coronary calcification: Observations from a registry of 25,253 patients. *J Am Coll Cardiol*. 2007; 49 (18): 1860-1870.

26. Shaw LJ, Raggi P, Callister TQ, Berman DS. Prognostic value of coronary artery calcium screening in asymptomatic smokers and non-smokers. *Eur Heart J*. 2006; 27 (8): 968-975.

27. Takx RA, de Jong PA, Leiner T, et al. Automated coronary artery calcification scoring in non-gated chest CT: Agreement and reliability. *PLoS One*. 2014; 9 (3): e91239.

28. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M,Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990; 15 (4): 827-832.

29. Brenner H, Kliebsch U. Dependence of weighted kappa coefficients on the number of categories. *Epidemiology*. 1996; 7 (2): 199-202.

30. Lowry R. Kappa as a measure of concordance in categorical sorting. http: //vassarstats.net/kappa.html. Updated 2017. Accessed September, 2017.

31. Zamorano JL, Lancellotti P, Rodriguez Munoz D, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC committee for practice guidelines: The task force for cancer treatments and cardiovascular toxicity of the European society of cardiology (ESC). *Eur Heart J*. 2016; 37 (36): 2768-2801.

32. Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American society of clinical oncology clinical practice guideline. *J Clin Oncol*. 2017; 35 (8): 893-911.

33. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med*. 2016; 375 (8): 717-729.

34. Bartlett FR, Donovan EM, McNair HA, et al. The UK HeartSpare study (stage II): Multicenter evaluation of a voluntary breath-hold technique in patients receiving breast radiotherapy. *Clin Oncol (R Coll Radiol)*. 2017; 29 (3): e51-e56.

35. Mast ME, Heijenbrok MW, Petoukhova AL, Scholten AN, Schreur JH, Struikmans H. Preradiotherapy calcium scores of the coronary arteries in a cohort of women with early-stage breast cancer: A comparison with a cohort of healthy women. *Int J Radiat Oncol Biol Phys*. 2012; 83 (3): 853-858.

36. Bild DE, Detrano R, Peterson D, et al. Ethnic differences in coronary calcification: The multi-ethnic study of atherosclerosis (MESA). *Circulation*. 2005; 111 (10): 1313-1320.

37. Kanaya AM, Kandula NR, Ewing SK, et al. Comparing coronary artery calcium among U.S. south asians with four racial/ethnic groups: The MASALA and MESA studies. *Atherosclerosis*. 2014; 234 (1): 102-107.

38. Sutton-Tyrrell K, Kuller LH, Edmundowicz D, et al. Usefulness of electron beam tomography to detect progression of coronary and aortic calcium in middle-aged women. *Am J Cardiol*. 2001; 87 (5): 560-564.

39. MJ Emaus, I Išgum, JP Pignol, H Meijer, HM Verkooijen. Automated quantification of coronary artery calcifications on radiotherapy planning CTs for cardiovascular risk prediction in breast cancer patients: The BRAGATSTON study. https: //clinicaltrials.gov/ct2/show/NCT03206333. Accessed November, 2017.

Chapter 8

Summary and future perspectives

Preamble

There were over three million five-year breast cancer survivors worldwide in 2012[1]. Many of these women will die of conditions other than breast cancer. Cardiovascular disease (CVD) is an important cause of death in breast cancer patients. Breast cancer therapies such as radiation therapy[2,3], chemotherapy[4], trastuzumab[5,6], and aromatase inhibitors[7] are associated with an increased risk of CVD (Chapter 1). CVD can be accelerated by these cardiotoxic therapies, especially in patients with pre-existing CVD risk factors[8,9]. The risk of CVD in breast cancer patients is examined in this thesis. The main study results and methodological issues have been discussed in the preceding chapters. Therefore, in the present chapter, results will be summarized and future perspectives will be discussed.

Summary

In Chapter 2, the literature on the risk and risk factors of death from CVD in breast cancer patients is systematically reviewed. Fourteen articles were included assessing the risk of death from CVD among 1,217,910 breast cancer patients. The absolute risk of death from CVD ranged from 1.6% to 10.4%, with higher absolute risks with longer follow-up time. Breast cancer patients had a higher risk of death from CVD compared to women from the general population. Within the population of breast cancer patients, the risk of CVD was higher among patients with higher age at diagnosis and among those patients with left-sided irradiation.

In Chapter 3, the risk of hospitalization and death due to CVD is investigated among 163,881 women admitted for breast cancer in the Netherlands between 1996 and 2015. In addition, a comparison with women from the general population was made. Information on CVD was obtained from the Hospital Discharge Register and information on death from CVD was obtained from the Cause of Death Registry. After median follow-up of 4.3 years following breast cancer admission, 5.6% of patients had died of CVD and 19.7% of patients had been hospitalized for CVD. The majority (93.4%) of deaths from CVD occurred among patients of 60 years and over. The standardized absolute ten-year risk of death from CVD after breast cancer decreased from 56 per 1,000 women in 1996 to 41 per 1,000 women in 2005 (relative decrease of 23.9%). Similarly, the absolute ten-year risk of death from CVD for women from the general population decreased from 73 per 1,000 women in 1996 to 55 per 1,000 women in 2005 (relative decrease of 27.8%). The relative risk of death from CVD within five years after breast cancer decreased since 1996: the age-adjusted hazard ratio (HR) for women treated in 2010 was 0.58 (95% confidence interval (CI) = 0.48-0.70) compared to those treated in 1996. This effect can be explained by an increased use of CVD

treatments including secondary prevention after heart failure and myocardial infarction, and by reductions in CVD risk factors such as total cholesterol, smoking prevalence, and physical activity[10]. The absolute risk of CVD hospitalization within the first year after breast cancer increased from 54 per 1,000 women in 1996 to 67 per 1,000 women in 2009 (relative increase of 23.6%). This increase may be due to the introduction of trastuzumab[11].

In Chapter 4, the risk of hospitalization and death due to CVD after breast cancer is investigated using data from the Dutch contribution to the European Prospective Investigation into Nutrition and Cancer (EPIC-NL) cohort, including 1,103 women diagnosed with breast cancer and 4,328 age-matched controls without breast cancer. Based on CVD risk factors at EPIC-NL cohort enrolment (age, smoking status, diabetes mellitus, systolic blood pressure, total cholesterol, high-density-lipoprotein cholesterol) women were categorized into low, intermediate, or high CVD risk. Information on CVD hospitalization was obtained from the Hospital Discharge Register and information on death from CVD was obtained from the Cause of Death Registry. Women with breast cancer had a 1.77 (95% CI = 1.10-2.86) times higher risk of death from CVD than women without breast cancer, after accounting for baseline CVD risk. In the low CVD risk group, breast cancer patients had an increased risk of hospitalization for CVD or death from CVD compared to women without breast cancer (adjusted hazard ratio = 1.44, 95% CI = 1.00-2.06).

In Chapter 5, the risk of death from CVD after breast cancer is investigated using the multi-ethnic Asian Singapore breast cancer cohort, which consisted of 5,868 women from Chinese (79.5%), Malay (11.9%), Indian (6.0%), and other (2.6%) ethnic origin. Information on cause of death was obtained from the Singapore National Registry of Births and Deaths. After a median follow-up of six years, 1,101 deaths occurred of which 67 (6.8%) were due to CVD. Indian patients had a 2.5 (95% CI = 1.2-5.2) times higher adjusted risk of death from CVD than Chinese patients. Variation in the risk of death from CVD by ethnicity in this population may be due to genetic differences and/or differences in lifestyle. For example, Indian ethnicity is associated with the highest risk of diabetes mellitus[13]. Also, Indians have the highest level of lipoprotein A, a genetic risk factor for CVD[14].

In Chapters 6 and 7, the prevalence and amount of automatically measured calcification is investigated on planning computed tomography (CT) scans of the breasts used for radiotherapy planning. In addition, the performance of automatic calcification scoring methods was examined: software based on supervised pattern recognition[15] was examined in Chapter 6 and more recently developed software based on the state-of-the-art deep learning technique[16] was investigated in Chapter 7.

In Chapter 6, the reproducibility of automatic coronary artery calcification (CAC) scoring was evaluated on planning CT scans of the breasts used for radiotherapy planning, and the association between CAC scores and presence of traditional CVD risk factors (diabetes mellitus, hypertension, hypercholesterolemia, current smoking, history of CVD) was examined. We used data from the ongoing prospective Utrecht cohort for Multiple BReast cancer intErvention studies and Long-term evaLuAtion (UMBRELLA) study, in which breast cancer patients are included, who are referred to the Department of Radiation Oncology of the University Medical Center Utrecht (UMCU) in the Netherlands[17]. CAC was automatically measured on planning CT scans of 561 breast cancer patients, using software based on supervised pattern recognition[15]. CAC was expressed as Agatston score and categorized into five CVD risk groups: low (0), mild (1-10), moderate (11-100), intermediate (101-400), high (>400)[18,19]. The prevalence of CAC was 24%. Ten of 36 patients (27.8%) with severe CAC (Agatston score over 100) did not have any other CVD risk factor. The performance of automatic CAC scoring compared to manual CAC scoring for Agatston categories was good: the reliability assessed by linearly weighted kappa was 0.80 (95% CI = 0.74-0.87) and was slightly higher for scans conducted with deep inspiration breath-hold (0.86, 95% CI = 0.77-0.96).

In Chapter 7, the prevalence and amount of CAC and thoracic aortic calcification (TAC) was compared between a Western (the Netherlands) and an Asian (Singapore) population of breast cancer patients, using new software based on deep learning[16]. 1,199 breast cancer patients from the UMBRELLA study[17] and 1,089 breast cancer patients from the Radiation Oncology Department of the National University of Singapore were included. CAC was expressed as Agatston score and categorized into five CVD risk groups: low (0), mild (1-10), moderate (11-100), intermediate (101-400), high (>400)[18,19]. Overall, the prevalence of CAC was 24.2% in patients from the Netherlands and 17.3% in patients from Singapore. The prevalence of CAC increased with age from 3% for patients aged under 41 to 38% for patients aged between 41 and 70. Among patients aged over 70 years, CAC was more prevalent in patients from Singapore (70%) than in patients from the Netherlands (55%). The prevalence of TAC was 73.0% in patients from the Netherlands and 62.2% in patients from Singapore. The performance of automatic CAC and TAC scoring was good compared to manual scoring. The reliability assessed by linearly weighted kappa of CAC in CVD risk categories assessed in scans from the Netherlands was 0.85 (95% CI = 0.77-0.93) and was slightly higher for scans with deep inspiration breath-hold. For scans from Singapore, the linearly weighted kappa was 0.90 (95% CI = 0.84-0.96). The reliability assessed with intraclass correlation coefficient for TAC was 0.98 (95% CI = 0.96-0.98) for scans from the Netherlands, and 0.99 (95% CI = 0.98-0.99) for scans from Singapore.

Future perspectives

This thesis confirms previous studies, showing that the relative risk of death from CVD is higher in breast cancer patients compared to women without breast cancer, when pre-existing CVD risk factors are taken into account. Below, the relevance of assessing the risk of CVD before breast cancer therapy and the potential role of automatic calcification detection on radiotherapy planning CT scans will be discussed. Finally, potential clinical approaches to reduce cardiotoxicity and the risk of CVD in breast cancer patients will be considered.

Assessing the risk of cardiovascular disease before breast cancer therapy

The risk of CVD in breast cancer patients is increased by exposure to cardiotoxic treatments including radiation therapy[2,3], anthracycline-based chemotherapy[4], trastuzumab[5,6], and aromatase inhibitors[20] (Chapter 1). Radiation therapy inevitably involves some radiation exposure to surrounding normal tissue including the heart, particularly in case of irradiation of left-sided breast cancer and/or internal mammary lymph nodes[21]. The incidence and onset of coronary artery disease linearly increases with the mean heart radiation dose: 7.4% increase per Gray irradiation, without an apparent threshold[22,23]. Radiation-induced CVD can results in symptoms within five years after radiation therapy, however, mostly after more than ten years following irradiation[23,24]. Anthracyclines increase the risk of decreased left ventricular ejection fraction (LVEF) and clinical heart failure, during therapy, early or late after therapy[4,25]. Anthracycline-induced cardiotoxicity is dose-dependent[4]. Trastuzumab is associated with a decrease in LVEF and heart failure, mainly occurring during therapy[26,27]. The risk of heart failure is four times higher in patients treated with trastuzumab alone and seven times higher in patients treated with anthracycline plus trastuzumab[28,29]. Trastuzumab-induced cardiotoxicity is often reversible with trastuzumab interruption and clinical manifestations of trastuzumab-induced cardiotoxicity can be reduced with heart failure medications[8]. Treatment with aromatase inhibitor is associated with 30% higher risk of CVD compared to treatment with tamoxifen[30].

Patients with pre-existing CVD risk factors have a higher risk of cancer therapy-induced cardiotoxicity compared with patients without pre-existing CVD risk factors[26,32-36]. Risk factors of cancer therapy induced cardiotoxicity are: 1) history of CVD, 2) lifestyle related risk factors including smoking, high alcohol intake, and obesity, and 3) other CVD risk factors including high age, family history of CVD, and hypertension[8,9]. Estimating a patient's CVD risk prior to initiation of breast cancer therapy is important to identify patients who could benefit from cancer therapy with reduced cardiotoxicity, cardiac monitoring, and/or cardioprotective medication[8,9]. For example, LVEF is monitored before, during, and after cancer therapy with trastuzumab, and if indicated with doxorubicin

for patients with a known high risk of CVD (*i.e.* history of CVD). LVEF is measured by echocardiography[8,9]. A 10% or greater reduction of LVEF below the lower limit (usually ≥50%) suggests cardiotoxicity, and cardioprotective medication is started and/or treatment with trastuzumab is discontinued if necessary[8].

In Chapter 4, it was reported that breast cancer patients with a low baseline risk of CVD had a 44% higher risk of a CVD event (hospitalization or death) compared to low CVD risk women without breast cancer. In the group of women (with or without breast cancer) with intermediate and high baseline risk of CVD, breast cancer patients did not have a higher risk of a CVD event. One possible explanation is that patients in the low baseline CVD risk group received more often cardiotoxic cancer therapy than patients in the intermediate and high baseline CVD risk groups, as physicians would be more careful with cardiotoxic cancer therapy among patients with pre-existing CVD risk factors. Also, it is very likely that there were patients in the low baseline CVD risk group with an unidentified increased risk of CVD. These patients could have been identified by coronary artery calcification (CAC) score automatically measured on radiotherapy planning CT scans. In Chapter 6, it was reported that almost 30% of breast cancer patients with severe CAC (Agatston score over 100) did not have any other CVD risk factor[37]**.** Asymptomatic individuals with severe CAC, and without other CVD risk factors, have a ten-year risk of a CVD event of 20% compared to 1% in asymptomatic individuals without CAC and no other CVD risk factors[38].

In current practice, breast cancer patients at increased risk of CVD are not identified as such and many are exposed to cardiotoxic cancer therapies without cardiac monitoring. The CVD events in breast cancer patients assessed in this thesis by prevalence of hospitalizations and deaths due to CVD, are probably the tip of the proverbial iceberg as many patients with CVD will not be hospitalized for CVD or die of CVD. Also without a hospitalization for CVD, CVD may significantly affect patients as CVD is associated with lower levels of overall quality of life, and higher levels of fatigue and depression[39,40]. Tools to estimate an individual patient's CVD risk may be helpful to distinguish patients with a high CVD risk from those patients with a low CVD risk. In this respect, we believe that automated measurement of CAC and thoracic aortic calcification (TAC) on computed tomography (CT) scans of breast cancer patients planned for radiation therapy may be of value.

Automatic calcification detection on planning CT scans

The newly developed software based on deep learning that automatically detects CAC and TAC on planning CT scans is promising[16]. Automatic calcification scoring performs well compared to manual calcification scoring, is fast (less than one minute per scan), and can be performed without additional radiation exposure or costs. The prevalence of CAC and TAC is considerable in breast cancer patients from the Netherlands and Singapore, and

increases with age. CAC occurred in up to one third of patients aged under 70 years and TAC was prevalent in two third of patients. According to current breast cancer guidelines, a substantial proportion of patients under 70 years are eligible for systemic treatment including anthracycline-based regimens and trastuzumab. In the future, calcification status may be used to screen patients for CVD risk, and thus to indicate who could benefit from cardiac monitoring, cancer therapy with reduced cardiotoxicity and/or cardioprotective medication[8,9].

Although the automatic detection of CAC and TAC on planning CT scans is promising, it's association with CVD in breast cancer patients has not yet been confirmed. The Multi-Ethnic Study of Atherosclerosis (MESA) reported associations between CAC as well as TAC and risk of CVD. MESA used electrocardiogram (ECG)-gated cardiac CT scans to manually detect calcifications. MESA included males (60%) and females (40%) between 2000 and 2002 (n = 6,814) from six communities in the United States who identified themselves as white, African-American, Hispanic, or Chinese[38,41]. They were between 45 and 84 years and had no clinical manifestations of CVD. The CVD risk profile of MESA participants is likely to be higher than breast cancer patients. Almost half of MESA participants had hypertension, their mean body mass index was 28 kg/m^2, and more than 10% of MESA participants had diabetes mellitus and used lipid lowering medications[41]. Breast cancer patients are more likely to have a higher socioeconomic status which is associated with a low CVD risk profile[42,43]. In chapter 4, it was reported that two third of breast cancer patients had a low ten-year risk of CVD. Also, the type of CT scans that are used to automatically measure calcifications in breast cancer patients are different from those scans used in MESA: non-ECG gated CT scans of the breasts including the heart versus ECG-gated cardiac CT scans. In a lung cancer screening setting, however, CAC has shown to be predictive for CVD risk using non-ECG gated chest CT scans[44].

The evidence for the association between automatically measured CAC and TAC on radiotherapy planning CT scans and CVD risk is aimed to be provided by BRAGATSTON, a study on 'Automated Quantification of Coronary Artery Calcifications on Radiotherapy Planning CTs for Cardiovascular Risk Prediction in Breast Cancer Patients'[45]. BRAGATSTON is a multicenter historic study led by the UMC Utrecht. The aims of BRAGATSTON are threefold: 1) to optimize and validate the newly UMC Utrecht developed automated software based on deep learning[16], 2) to assess the association between CAC on radiotherapy planning CT scans and the risk of CVD event (hospitalization or death) in breast cancer patients, and 3) to assess the added value of CAC measured automatically on radiotherapy planning CT scans over traditional CVD risk factors to predict CVD events in breast cancer patients[45].

So far, the patient's preferences on timing and way of disclosure of CVD risk have not been investigated, and neither their attitude towards cardio-prevention and lifestyle changes should calcifications be detected during their breast cancer treatment. Involving the breast cancer patient in research on these topics would be important, such as by means of patient reported outcomes including quality of life. In this way, further clues may be gathered to optimize and personalize breast cancer treatment, reduce the risk of cancer therapy-induced cardiotoxicity, and improve breast cancer survivorship.

Potential approaches to reduce cardiotoxicity and the risk of CVD in breast cancer patients

The main aim of breast cancer therapy is to optimize tumor control and breast cancer survival, while minimizing the risk of side effects including therapy-induced cardiotoxicity. One way to minimize the risk of therapy-induced cardiotoxicity in breast cancer patients is radiation dose reduction to the heart. The introduction of 3D planning in the 90's has resulted in optimization of the target coverage and minimization of the dose to the normal tissues including the heart. Deep inspiration breath-hold has increasingly been used, since approximately ten years, for patients planned for left-sided and/or internal mammary node irradiation to reduce radiation dose to the heart[46]. Also, the introduction of modern radiotherapy techniques, including intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) especially for internal mammary lymph nodes irradiation, have resulted in significant radiation dose reduction to the heart[46]. There is still room for improvement in this field. For example, deep inspiration breath-hold technique in combination with VMAT may further reduce the radiation dose to the heart[47]. In addition, accelerated partial breast irradiation (APBI) is an even newer technique for low-risk breast cancer patients. With use of APBI it is often possible to significantly reduce radiation dose to the heart as compared with whole breast irradiation[48]. With the use of APBI, only the volume of breast tissue at highest risk of recurrence, *i.e.* the tumor bed, is irradiated[46]. External beam APBI can also be combined with VMAT and deep inspiration breath-hold[49]. In addition, magnetic resonance imaging (MRI) guidance for radiotherapy (MRI-Linac) is a future radiation treatment that can potentially reduce the risk of radiation-induced cardiotoxicty[50,51]. MRI-Linac combines MRI guidance with radiotherapy and has the potential of fast, high soft-tissue contrast visualization of tumors and organs at risk during radiation therapy[51]. In the future, MRI-Linac will be used for partial breast irradiation and could possibly further reduce irradiated heart volume. Although the use of MRI-Linac sound promising, evidence of potential benefits of this technique remain to be generated.

Approaches to reduce the risk of cardiotoxicity induced by systematic treatments include switching to less cardiotoxic therapies or using a validated gene-expressing profile to identify patients in whom chemotherapy can be safely withheld[8,9,52]. The Dutch guidelines recommend the use of a validated gene expression profile in patients with an invasive ductal

carcinoma with estrogen-receptor and/or progesterone-receptor positive disease, HER2 negative disease, and an indication for adjuvant chemotherapy based on conventional prognostic factors[53]. In addition, the use of cardioprotective drugs such as angiotensin-converting enzyme (ACE) inhibitor and beta-blockers during cardiotoxic breast cancer therapy is recommended, if continuation with breast cancer therapy is necessary despite generated cardiotoxicity[8,9].

Increasingly more breast cancer patients at risk of CVD are referred to the cardiologist before, during, and/or after cancer treatment. Increasing awareness of cancer therapy-induced cardiotoxicity and its symptoms among oncologists, cardiologists, and general practitioners is important to timely notice CVD and start with (preventive) treatment. The field of cardio-oncology has received increasing attention in recent years[8,9,54-56]. The complex issue of CVD as a consequence of cancer therapy requires teams of specialists in cardiology and oncology to improve cardiac health of cancer survivors. It has been suggested that cardio-oncology teams should develop guidelines to minimize occurrence and severity of cardiotoxicity of breast cancer patients[8,9]. Oncology and cardiology teams can work together to evaluate the patient's risk of CVD as an integral part of the choice of cancer therapy[8,9,56]. Before, during, and after cancer therapy, the breast cancer patient should be monitored to detect CVD side effects timely and enable treatment by CVD medication, modulation of cancer therapy, or both[8,9,56,57]. In addition, adaptation of a healthy lifestyle including exercise and diet should be discussed with all patients[8,9].

In the era of personalized medicine, looking beyond the tumor to the whole patient is important to find the optimal treatment for breast cancer. For each individual breast cancer patient, the benefits of cancer treatment in terms of tumor control and disease-free survival should be carefully weighed against the risks of toxicity, including cardiotoxicity, to optimize the possibility of a healthy life after breast cancer.

References

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.1, cancer incidence and mortality worldwide: IARC CancerBase. 2014; 11.
2. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, et al. 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 8,135 women in 22 randomised trials. *Lancet*. 2014; 383 (9935): 2127-2135.
3. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomized trials. *Lancet*. 2005; 366 (9503): 2087-2106.
4. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: Systematic review and meta-analysis of randomized controlled trials. *BMC Cancer*. 2010; 10: 337-2407-10-337.
5. Suter TM, Cook-Bruns N, Barton C. Cardiotoxicity associated with trastuzumab (Herceptin) therapy in the treatment of metastatic breast cancer. *Breast*. 2004; 13 (3): 173-183.
6. Suter TM, Procter M, van Veldhuisen DJ, et al. Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. *J Clin Oncol*. 2007; 25 (25): 3859-3865.
7. Foglietta J, Inno A, de Iuliis F, et al. Cardiotoxicity of aromatase inhibitors in breast cancer patients. *Clin Breast Cancer*. 2017; 17 (1): 11-17.
8. Zamorano JL, Lancellotti P, Rodriguez Munoz D, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC committee for practice guidelines: The task force for cancer treatments and cardiovascular toxicity of the European society of cardiology (ESC). *Eur Heart J*. 2016; 37 (36): 2768-2801.
9. Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American society of clinical oncology clinical practice guideline. *J Clin Oncol*. 2017; 35 (8): 893-911.
10. Koopman C, Vaartjes I, van Dis I, et al. Explaining the decline in coronary heart disease mortality in the Netherlands between 1997 and 2007. *PLoS One*. 2016; 11 (12): e0166139.
11. Chavez-MacGregor M, Zhang N, Buchholz TA, et al. Trastuzumab-related cardiotoxicity among older patients with breast cancer. *J Clin Oncol*. 2013; 31 (33): 4222-4228.
12. Maitland ML, Bakris GL, Black HR, et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. *J Natl Cancer Inst*. 2010; 102 (9): 596-604.
13. Hughes K, Yeo PP, Lun KC, et al. Cardiovascular diseases in Chinese, Malays, and Indians in Singapore. II. differences in risk factor levels. *J Epidemiol Community Health*. 1990; 44 (1): 29-35.

14. Hughes K, Aw TC, Kuperan P, Choo M. Central obesity, insulin resistance, syndrome X, lipoprotein (a), and cardiovascular risk in Indians, Malays, and Chinese in Singapore. *J Epidemiol Community Health*. 1997; 51 (4): 394-399.

15. Isgum I, Prokop M, Niemeijer M, Viergever MA, van Ginneken B. Automatic coronary calcium scoring in low-dose chest computed tomography. *IEEE Trans Med Imaging*. 2012; 31 (12): 2322-2334.

16. Lessmann N, van Ginneken B, Zreik M, de Jong PA, de Vos BD, Viergever MA, Išgum I. Automatic calcium scoring in low-dose chest CT using deep neural networks with dilated convolutions. *IEEE Transactions on Medical Imaging, in press*. 2017.

17. Young-Afat DA, van Gils CH, van den Bongard HJGD, Verkooijen HM, UMBRELLA Study Group. The Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaLuAtion (UMBRELLA): Objectives, design, and baseline results. *Breast Cancer Res Treat*. 2017; 164 (2): 445-450.

18. Budoff MJ, Shaw LJ, Liu ST, et al. Long-term prognosis associated with coronary calcification: Observations from a registry of 25,253 patients. *J Am Coll Cardiol*. 2007; 49 (18): 1860-1870.

19. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M,Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990; 15 (4): 827-832.

20. Foglietta J, Inno A, de Iuliis F, et al. Cardiotoxicity of aromatase inhibitors in breast cancer patients. *Clin Breast Cancer*. 2017; 17 (1): 11-17.

21. Zagar TM, Cardinale DM, Marks LB. Breast cancer therapy-associated cardiovascular disease. *Nat Rev Clin Oncol*. 2015.

22. Darby SC, Ewertz M, Hall P. Ischemic heart disease after breast cancer radiotherapy. *N Engl J Med*. 2013; 368 (26): 2527.

23. Darby SC, Bronnum D, Correa C, et al. A dose-response relationship for the incidence of radiation-related heart disease. *Int J Radiat Oncol Biol Phys*. 2010; 78 (3): S49-S50.

24. Darby S. Epidemiology of radiotherapy induced cardiac damage. *Radiother Oncol*. 2011; 98: S11-S12.

25. Serrano JM, Cristobal C, Graupner C, et al. Anthracycline cardiotoxicity: Incidence at present time. *Eur Heart J*. 2012; 33: 796.

26. Chavez-MacGregor M, Zhang N, Buchholz TA, et al. Trastuzumab-related cardiotoxicity among older patients with breast cancer. *J Clin Oncol*. 2013; 31 (33): 4222-4228.

27. Advani PP, Ballman KV, Dockter TJ, Colon-Otero G, Perez EA. Long-term cardiac safety analysis of NCCTG N9831 (alliance) adjuvant trastuzumab trial. *J Clin Oncol*. 2016; 34 (6): 581-587.

28. Moja L, Brambilla C, Compagnoni A, Pistotti V. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev*. 2006 (4).

29. Bowles EJ, Wellman R, Feigelson HS, et al. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: A retrospective cohort study. *J Natl Cancer Inst*. 2012; 104 (17): 1293-1305.

30. Amir E, Seruga B, Niraula S, Carlsson L, Ocana A. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: A systematic review and meta-analysis. *J Natl Cancer Inst*. 2011; 103 (17): 1299-1309.

31. Love RR. Antiestrogen chemoprevention of breast cancer: Critical issues and research. *Prev Med*. 1991; 20 (1): 64-78.

32. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med*. 1979; 91 (5): 710-717.

33. Serrano C, Cortes J, De Mattos-Arruda L, et al. Trastuzumab-related cardiotoxicity in the elderly: A role for cardiovascular risk factors. *Ann Oncol*. 2012; 23 (4): 897-902.

34. Dranitsaris G, Rayson D, Vincent M, et al. The development of a predictive model to estimate cardiotoxic risk for patients with metastatic breast cancer receiving anthracyclines. *Breast Cancer Res Treat*. 2008; 107 (3): 443-450.

35. Tarantini L, Gori S, Faggiano P, et al. Adjuvant trastuzumab cardiotoxicity in patients over 60 years of age with early breast cancer: A multicenter cohort analysis. *Ann Oncol*. 2012; 23 (12): 3058-3063.

36. Hooning MJ, Botma A, Aleman BM, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst*. 2007; 99 (5): 365-375.

37. Gernaat SA, Isgum I, de Vos BD, et al. Automatic coronary artery calcium scoring on radiotherapy planning CT scans of breast cancer patients: Reproducibility and association with traditional cardiovascular risk factors. *PLoS One*. 2016; 11 (12): e0167925.

38. Blaha MJ, Budoff MJ, DeFilippis AP, et al. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: Implications for the JUPITER population from MESA, a population-based cohort study. *Lancet*. 2011; 378 (9792): 684-692.

39. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: A clinical review. *Eur Heart J*. 2014; 35 (21): 1365-1372.

40. Djarv T, Wikman A, Lagergren P. Number and burden of cardiovascular diseases in relation to health-related quality of life in a cross-sectional population-based cohort study. *BMJ Open*. 2012; 2 (5): 10.1136.

41. Budoff MJ, Nasir K, Katz R, et al. Thoracic aortic calcification and coronary heart disease events: The multi-ethnic study of atherosclerosis (MESA). *Atherosclerosis*. 2011; 215 (1): 196-202.

42. Akinyemiju TF, Pisu M, Waterbor JW, Altekruse SF. Socioeconomic status and incidence of breast cancer by hormone receptor subtype. *Springerplus*. 2015; 4: 508-015-1282-2.

43. Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: A review of the literature. *Circulation*. 1993; 88 (4 Pt 1): 1973-1998.

44. Chiles C, Duan F, Gladish GW, et al. Association of coronary artery calcification and mortality in the national lung screening trial: A comparison of three scoring methods. *Radiology*. 2015; 276 (1): 82-90.

45. MJ Emaus, I Išgum, JP Pignol, H Meijer, HM Verkooijen. Automated quantification of coronary artery calcifications on radiotherapy planning CTs for cardiovascular risk prediction in breast cancer patients: The BRAGATSTON study. https: //clinicaltrials.gov/ct2/show/NCT03206333. Accessed November, 2017.

46. Taylor CW, Kirby AM. Cardiac side-effects from breast cancer radiotherapy. *Clin Oncol (R Coll Radiol)*. 2015.

47. Sakka M, Kunzelmann L, Metzger M, Grabenbauer GG. Cardiac dose-sparing effects of deep-inspiration breath-hold in left breast irradiation: Is IMRT more beneficial than VMAT? *Strahlenther Onkol*. 2017.

48. Gale AA, Jain AK, Vallow LA, Serago CF, Buskirk SJ, Heckman MG. Cardiac dose evaluation for 3-dimensional conformal partial breast irradiation compared with whole breast irradiation. *J Appl Clin Med Phys*. 2009; 10 (1): 2868.

49. Essers M, Osman SO, Hol S, Donkers T, Poortmans PM. Accelerated partial breast irradiation (APBI): Are breath-hold and volumetric radiation therapy techniques useful? *Acta Oncol*. 2014; 53 (6): 788-794.

50. van Heijst TC, den Hartogh MD, Lagendijk JJ, van den Bongard HJ, van Asselen B. MR-guided breast radiotherapy: Feasibility and magnetic-field impact on skin dose. *Phys Med Biol*. 2013; 58 (17): 5917-5930.

51. Lagendijk JJ, Raaymakers BW, Raaijmakers AJ, et al. MRI/linac integration. *Radiother Oncol*. 2008; 86 (1): 25-29.

52. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med*. 2016; 375 (8): 717-729.

53. Kwaliteitsinstituut voor de gezondheidszorg CbO VvIK. Landelijke richtlijn mammacarcinoom. 2012.

54. Herrmann J, Lerman A, Sandhu NP, Villarraga HR, Mulvagh SL, Kohli M. Evaluation and management of patients with heart disease and cancer: Cardio-oncology. *Mayo Clin Proc*. 2014; 89 (9): 1287-1306.

55. Wickramasinghe CD, Nguyen KL, Watson KE, Vorobiof G, Yang EH. Concepts in cardio-oncology: Definitions, mechanisms, diagnosis and treatment strategies of cancer therapy-induced cardiotoxicity. *Future Oncol*. 2016; 12 (6): 855-870.

56. Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: The need for cardio-oncology and cardio-oncological prevention. *J Natl Cancer Inst*. 2010; 102 (1): 14-25.

57. Kalam K, Marwick TH. Role of cardioprotective therapy for prevention of cardiotoxicity with chemotherapy: A systematic review and meta-analysis. *Eur J Cancer*. 2013; 49 (13): 2900-2909.

Appendices

Summary in Dutch – Nederlandse samenvatting

Borstkanker is wereldwijd de meest voorkomende vorm van kanker onder vrouwen[1]. De wereldwijde incidentie van borstkanker varieert door de aanwezigheid van risicofactoren, zoals hogere leeftijd en langdurige blootstelling aan vrouwelijke hormonen, en door toegang tot borstkankerscreening[2]. Sinds 1990 is sterfte aan borstkanker in de westerse wereld afgenomen[1]. Dit wordt voornamelijk geweten aan de introductie van borstkankerscreening, verbeterde diagnostische beeldvorming van de borsten en verbeterde borstkankerbehandelingen[3-5]. De combinatie van hoge incidentie en afgenomen sterfte heeft geresulteerd in een grote groep vrouwen die na de borstkankerdiagnose een geruime tijd leven[1]. In 2012 waren er wereldwijd meer dan drie miljoen vrouwen die borstkanker ten minste vijf jaar hadden overleefd[1]. Een groot deel van deze vrouwen zal komen te overlijden aan andere ziektes dan borstkanker. Hart- en vaatziekten (HVZ) zijn een belangrijke doodsoorzaak onder vrouwen met borstkanker. Borstkankerbehandelingen zoals radiotherapie[6,7], chemotherapie[8], trastuzumab[9,10] en aromatase remmers[11], worden geassocieerd met een verhoogd risico op HVZ (Hoofdstuk 1). De ontwikkeling van HVZ kan door deze cardiotoxische therapieën worden versneld, met name bij borstkankerpatiënten met reeds bestaande HVZ risicofactoren[12,13]. Het risico op HVZ bij borstkankerpatiënten is onderzocht in dit proefschrift.

In hoofdstuk 2 wordt de literatuur over het risico op en risicofactoren van sterfte aan HVZ bij vrouwen met borstkanker systematisch weergegeven. Veertien artikelen werden geïncludeerd met in totaal 1.217.910 borstkankerpatiënten. Het absolute risico op sterfte aan HVZ reikte van 1,6% tot 10,4%, waarbij studies met een langere studieduur een hoger absoluut risico rapporteerden. Borstkankerpatiënten hadden een hoger risico om te sterven aan HVZ in vergelijking tot vrouwen in de algemene populatie. Het risico op HVZ was hoger bij oudere borstkankerpatiënten en bij borstkankerpatiënten met linkszijdige bestraling.

Hoofdstuk 3 bevat het onderzoek naar het risico op opnames wegens en sterfte aan HVZ onder 163.881 vrouwen met borstkanker tussen 1996 en 2010 in Nederland. Ook werd een vergelijking gemaakt met vrouwen van de algemene bevolking. Informatie over ziekenhuisopnames voor HVZ was afkomstig van het Landelijke Medisch Register en informatie over sterfte aan HVZ was afkomstig van het Doodsoorzaken Register. Na een mediane duur van 4,3 jaar sinds opname voor borstkanker, waren 5,6% van de borstkankerpatiënten gestorven aan HVZ en waren 19,7% van de borstkankerpatiënten opgenomen voor HVZ. De meerderheid (93,4%) van de borstkankerpatiënten die waren gestorven aan HVZ, waren 60 jaar of ouder. Het gestandaardiseerde absolute 10-jaars risico op sterfte aan HVZ na borstkanker, was gedaald van 56 per 1.000 vrouwen in 1996 naar 41 per 1.000 vrouwen in 2005 (relatieve afname van 23,9%). In dezelfde periode is het absolute

10-jaars risico op sterfte aan HVZ onder vrouwen van de algemene bevolking afgenomen van 73 per 1.000 vrouwen naar 55 per 1.000 vrouwen (relatieve afname van 27,8%). Het relatieve risico om te sterven aan HVZ binnen vijf jaar na borstkankeropname, gecorrigeerd voor leeftijd, is sinds 1996 afgenomen: vrouwen die in 2010 waren opgenomen hadden een 42% (95% betrouwbaarheidsinterval (BI) = 0,48-0,70) lager risico om te sterven aan HVZ in vergelijking tot vrouwen die in 1996 waren opgenomen. Dit verminderde risico kan worden verklaard door een toegenomen gebruik van HVZ behandelingen (inclusief secundaire preventie na hartfalen en myocardinfarct) en door een afname van risicofactoren voor HVZ zoals de waarde van totaal cholesterol, roken en weinig fysieke activiteit[14]. Het absolute risico op een opname voor HVZ binnen het eerste jaar na borstkanker is toegenomen van 54 per 1.000 vrouwen in 1996 naar 67 per 1.000 vrouwen in 2009 (relatieve toename van 23,6%). Deze toename zou kunnen komen door de introductie van trastuzumab[15].

In hoofdstuk 4 is het risico op opnames voor en sterfte aan HVZ na borstkanker onderzocht. Hierbij wordt gebruik gemaakt van een grootschalig prospectief onderzoek naar kanker en voeding: *the Dutch contribution to the European Prospective Investigation into Nutrition and Cancer study* (EPIC-NL). 1.103 vrouwen met borstkanker en 4.328 vrouwen zonder borstkanker werden geïncludeerd. Op basis van HVZ risicofactoren (leeftijd, roken, diabetes mellitus, systolische bloeddruk, totaal cholesterol en hoge-densiteit-lipoproteïne cholesterol) werden vrouwen in een lage, midden of hoge HVZ risicocategorie ingedeeld. Informatie over ziekenhuisopnames voor HVZ was afkomstig van het Landelijke Medisch Register en informatie over sterfte aan HVZ was afkomstig van het Doodsoorzaken Register. Vrouwen met borstkanker hadden een 1,77 (95% BI = 1,10-2,86) keer hoger risico om te overlijden aan HVZ in vergelijking met vrouwen zonder borstkanker, gecorrigeerd voor HVZ risicofactoren. In de laag HVZ risicogroep, hadden vrouwen met borstkanker een 1,44 (95% BI = 1,00-2,06) keer hoger risico om opgenomen te worden voor HVZ in vergelijking met vrouwen zonder borstkanker.

In hoofdstuk 5 wordt het risico op sterfte aan HVZ na borstkanker binnen een multi-etnisch borstkankercohort in Singapore onderzocht. Dit cohort bestond in totaal uit 5.868 vrouwen, waarvan 79,5% van Chinese afkomst, 11,9% van Maleise afkomst, 6,0% van Indiase afkomst en 2,6% van een andere etnische afkomst. Informatie over sterfte aan HVZ was afkomstig van de Nationale Registratie voor Geboorte en Sterfte in Singapore. Na een mediane duur van 6 jaar na borstkankerdiagnose, waren 1.101 borstkankerpatiënten gestorven waaronder 67 (6,8%) door HVZ. Indiase borstkankerpatiënten hadden een 2,5 (95% BI = 1,2-5,2) keer hoger gecorrigeerd risico om te overlijden aan HVZ. Etnische variatie in het risico op sterfte aan HVZ, zou kunnen komen door genetische verschillen en/of verschillen in

levenswijze. De Indiase etniciteit wordt bijvoorbeeld geassocieerd met een hoog risico op diabetes mellitus[16] en met een hoge lipoproteïne A waarde, een genetische risicofactor voor HVZ[17].

In hoofdstuk 6 en 7 is de prevalentie en ernst van automatisch gemeten calcificaties op basis van radiotherapie planning computertomografie (CT) scans van de borsten onderzocht. Deze CT scans worden gebruikt voor het plannen van de bestraling. Tevens is de prestatie van automatische scoringmethoden onderzocht in hoofdstuk 6 en 7. Hoofdstuk 6 omvat de software gebaseerd op patroonherkenning[18] en hoofdstuk 7 omvat een recent ontwikkelde software gebaseerd op een nieuwe techniek genaamd 'deep learning'.

In hoofdstuk 6 is de reproduceerbaarheid van automatisch gemeten calcificaties in de kransslagaders op basis van radiotherapie planning CT scans van de borsten geëvalueerd. Ook werd de associatie tussen calcificaties in de kransslagaders en de aanwezigheid van traditionele risicofactoren voor HVZ (diabetes mellitus, hypertensie, hypercholesterolemie, roken en HVZ voorgeschiedenis) onderzocht. Er werd gebruik gemaakt van data afkomstig van een lopend prospectief onderzoek naar de uitkomst van behandeling en kwaliteit van leven van borstkankerpatiënten (UMBRELLA). In UMBRELLA worden vrouwen met borstkanker geïncludeerd die worden verwezen naar de radiotherapie afdeling van het Universitair Medisch Centrum Utrecht (UMCU) in Nederland[19]. De mate van calcificatie in de kransslagaders werd automatisch gemeten op planning CT scans van 561 borstkankerpatiënten met een software gebaseerd op patroonherkenning[18]. Dit werd uitgedrukt in een Agatston score en gecategoriseerd in vijf HVZ risicogroepen: laag (0), mild (1-10), matig (11-100), aanzienlijk (101-400) en hoog (>400)[20,21]. De prevalentie van calcificaties in de kransslagaders was 24%. Tien van de 36 borstkankerpatiënten met een hoge Agatston score (boven de 100) hadden geen andere risicofactoren voor HVZ. De prestatie van de automatische calcificatie scoringmethode, in vergelijking met de manuele methode, was goed voor de HVZ risicogroepen. De betrouwbaarheid geanalyseerd door een lineair gewogen kappa was 0,80 (95% BH = 0,74-0,87). Die voor CT scans uitgevoerd met ingehouden adem was iets hoger, namelijk 0,86 (95% BH = 0,77-0,96).

In hoofdstuk 7 zijn de prevalentie en ernst van calcificaties in de kransslagaders en in de thoracale aorta in een westerse populatie (Nederland) en een Aziatische populatie (Singapore) van borstkankerpatiënten vergeleken. Hierbij werd gebruik gemaakt van een recent ontwikkelde software gebaseerd op 'deep learning'[22]. 1.199 Borstkankerpatiënten van de UMBRELLA studie[19] en 1.089 borstkankerpatiënten van de afdeling radiotherapie van het Nationale Universitair Ziekenhuis in Singapore werden geïncludeerd. De ernst van calcificatie in de kransslagaders werd uitgedrukt in een Agatston score en gecategoriseerd in vijf HVZ risicogroepen: laag (0), mild (1-10), matig (11-100), aanzienlijk (101-400)

en hoog (>400)[20,21]. De prevalentie van calcificaties in de kransslagaders was 24,2% bij Nederlandse patiënten en 17,3% bij Singaporese patiënten. De prevalentie van calcificaties in de kransslagaders nam toe met de leeftijd, van 3% voor patiënten onder de 41 jaar tot aan 38% voor patiënten met een leeftijd tussen de 41 en 70 jaar. Onder patiënten boven de 70 jaar waren calcificaties in de kransslagaders vaker aanwezig bij Singaporese patiënten (70%) dan bij Nederlandse patiënten (55%). De prevalentie van calcificatie in de thoracale aorta was 73,0% bij Nederlandse patiënten en 62,2% bij Singaporese patiënten. De prestatie van de automatische methode om calcificaties in de kransslagaders en de thoracale aorta te meten was goed in vergelijking met de manuele methode. De betrouwbaarheid, geanalyseerd met een lineair gewogen kappa, van HVZ risicogroepen voor calcificaties in de kransslagers gemeten op scans uit Nederland was 0,85 (95% BI = 0,77-0,93) en iets hoger voor scans uitgevoerd met ingehouden adem. Voor scans uit Singapore was de lineair gewogen kappa 0,90 (95% BI = 0,84-0,96). De betrouwbaarheid, geanalyseerd met een intra-klasse correlatiecoëfficiënt, voor calcificaties in de thoracale aorta was 0,98 (95% BI = 0,96-0,98) gemeten op scans uit Nederland. Voor scans uit Singapore was de intra-klasse correlatiecoëfficiënt 0,99 (95% BI = 0,98-0,99).

Hoofdstuk 8 bevat de Engelstalige samenvatting en de discussie. De discussie spitst zich toe op de relevantie van het bepalen van het HVZ risico voorafgaand aan de borstkankerbehandeling, de potentiële toekomstige rol van de automatische methode om calcificaties te meten op radiotherapie planning CT scans en mogelijke manieren om het risico op HVZ te reduceren in de klinische praktijk.

Concluderend, bevestigen de onderzoeken beschreven in dit proefschrift voorgaande studies die lieten zien dat het relatieve risico om te sterven aan HVZ (rekening houdend met reeds bestaande risicofactoren voor HVZ) hoger is voor vrouwen met borstkanker in vergelijking met vrouwen zonder borstkanker. Het bepalen van het HVZ risico voorafgaand aan de borstkankerbehandeling is belangrijk, omdat borstkankerpatiënten met reeds bestaande HVZ risicofactoren een hoger risico hebben op borstkankerbehandeling geïnduceerde cardiotoxiciteit in vergelijking met borstkankerpatiënten zonder reeds bestaande HVZ risicofactoren. Het automatisch meten van calcificaties in de kransslagaders en thoracale aorta, op radiotherapie planning CT scans, kan mogelijk in de toekomst worden gebruikt om het risico op HVZ te bepalen. De methode is snel en kan worden uitgevoerd zonder extra kosten of bestraling. Op deze manier kan worden ingeschat welke borstkankerpatiënten mogelijk voordeel kunnen hebben van aanvullende hartbewaking, een borstkankerbehandeling die minder cardiotoxisch is en/of het geven van medicatie voor het hart.

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List of publications

Publications of this thesis

Chapter 2
S.A.M. Gernaat, P.J. Ho, N. Rijnberg, M.J. Emaus, L.M. Baak, M. Hartman, D.E. Grobbee, H.M. Verkooijen. Risk of death from cardiovascular disease following breast cancer: a systematic review.
Breast Cancer Research and Treatment 2017; 164 (3): 537-555.

Chapter 3
S.A.M. Gernaat*, J. Buddeke*, M.L. Bots, D.H.J.G. van den Bongard, D.E. Grobbee, I. Vaartjes, H.M. Verkooijen. Trends in the risk of cardiovascular disease in women with breast cancer.
*Both authors contributed equally
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Chapter 4
S.A.M. Gernaat, J.M.A. Boer, D.H.J.G. van den Bongard, A.H.E.M. Maas, C.C. van der Pol, R.M. Bijlsma, D.E. Grobbee, H.M. Verkooijen, P.H. Peeters. The risk of cardiovascular disease following breast cancer by Framingham risk score.
Submitted.

Chapter 5
S.A.M. Gernaat*, P.J. Ho*, N. Rijnberg, S.C. Lee, S.H. Lim, Y.S. Yap, D.E. Grobbee, M. Hartman, H.M. Verkooijen. Risk of death from cardiovascular disease following breast cancer in Southeast Asia: a prospective cohort study.
*Both authors contributed equally
Scientific Reports 2017; 7 (1): 1365.

Chapter 6
S.A.M. Gernaat, I. Išgum, B.D. de Vos, R.A. Takx, D.A. Young-Afat, N. Rijnberg, D.E. Grobbee, Y. van der Graaf, P.A. de Jong, T. Leiner, D.H. van den Bongard, J.P. Pignol, H.M. Verkooijen. Automatic coronary artery calcium scoring on radiotherapy planning computed tomography scans of breast cancer patients: reproducibility and association with traditional cardiovascular risk factors.
PLoS One 2016; 11 (12): e0167925.

Chapter 7
S.A.M. Gernaat, S.G.M. van Velzen, V. Koh, M.J. Emaus, I. Išgum, N. Lessmann, S. Moes, A. Jacobson, P.W. Tan, D.E. Grobbee, D.H.J. van den Bongard, J. Tang I-Hsiung, H.M .Verkooijen. Coronary artery calcification and thoracic aortic calcification automatically measured on planning CT scans using deep learning in a Western and an Asian population of breast cancer patients.
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Other publications

L.B.M. Weerink, B.L. van Leeuwen, S.A.M. Gernaat, A.R. Absalom, M.G. Huisman, H. van der Wal-Huisman, G.J. Izaks, G.H de Bock. Vitamin status and the development of postoperative cognitive decline in elderly surgical oncologic patients.
Annals of Surgical Oncology 2017.

D.A. Young-Afat, C.H. van Gils, H.J.G.D. van den Bongard, H.M. Verkooijen, UMBRELLA Study Group. The Utrecht cohort for multiple BREast cancer intervention studies and long-term evaLuAtion (UMBRELLA): Objectives, design, and baseline results.
Breast Cancer Research and Treatment. 2017; 164 (2): 445-450.

P.J. Ho, S.A.M. Gernaat, M. Hartman, H.M. Verkooijen. Health-related quality of life in Asian breast cancer patients: a systematic review.
Submitted.

P.J. Ho, M. Hartman, S.A.M. Gernaat, S.C. Lee, L. Hupkens, H.M. Verkooijen. Associations between workability and patient-reported physical, psychological, and social outcomes in breast cancer survivors: a cross-sectional study.
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