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**Title**

Trends in the risk of cardiovascular disease in women with breast cancer in a Dutch nationwide observational cohort

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**Abstract**

**Objectives**

To investigate trends in cardiovascular disease (CVD) risk following breast cancer and to make a comparison with the general female population in the Netherlands.

**Study design**

A nationwide prospective observational cohort study.

**Setting**

The Hospital Discharge Register, the Dutch Population Register, and Cause of Death Registry.

**Participants**

163,881 women with *in situ* (7.6%) or invasive (92.4%) breast cancer, and women from the general population aged over 40 years were identified, ranging from 3,661,141 in 1996 to 4,566,573 in 2010.

**Primary outcome**

Standardized absolute risks of CVD mortality in women with and without breast cancer and for hospitalization for CVD after breast cancer for the years 1996-2010. Relative risk reduction or increase between 1996-2010 was calculated.

**Secondary outcomes**

Age-adjusted relative risk of CVD mortality within five years after breast cancer admission (1997-2010) compared to 1996 calculated with a cox proportional hazard analysis.

**Results**

After median follow-up of 4.3 years, 5.6% patients died of CVD and 19.7% patients were hospitalized for CVD. The absolute ten-year CVD mortality risk following breast cancer decreased from 56 per 1,000 women in 1996 to 41 in 2005 (relative reduction=23.9%). In the general population, the absolute ten-

year risk of CVD mortality decreased from 73 per 1,000 women in 1996 to 55 in 2005 (relative reduction=27.8%). The absolute risk of CVD hospitalization within one year following breast cancer increased from 54 per 1,000 women in 1996 to 67 in 2009 (relative increase=23.6%). The relative risk of CVD mortality was 0.58 (95% confidence interval=0.48-0.70) times lower for women admitted for breast cancer in 2010 compared to 1996.

**Conclusions**

CVD mortality risk decreased in breast cancer patients and in the general population, with patients having the lowest risk. Absolute risk of CVD hospitalization following breast cancer increased over time and is considerable with 19.7%.

**Article summary**

- This nationwide study is the first study that gives insight in trends in the risk of cardiovascular disease (CVD) mortality and hospitalization for CVD following breast cancer between 1996 and 2010 in the Netherlands.
- Trends in CVD mortality following breast cancer were compared to CVD mortality of the general population. Absolute risks were standardized according to the age distribution of women from the general population aged 40 years and older in 1996.
- The validation study showed high accuracy of breast cancer discharge codes notified in the Hospital Discharge Register.
- From 2005 onwards the participation of hospitals in registering patients' discharges decreased from 100% coverage to 89% in 2010, and therefore, not all breast cancer patients in the Netherlands could be identified.
- This study had no information on breast cancer characteristics and CVD risk factors other than type of breast cancer diagnosis (*in situ*/ invasive) and age.

## 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 anthracycline-based chemotherapy[6,7], trastuzumab[8], and radiotherapy[9-11]. 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 death from CVD and hospitalization for 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 a 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.

**Patient and public involvement**

Patients and public were not involved in this study.

**Outcome assessment**

Patients were followed until December 31, 2015 for death from CVD and until December 31, 2010 for 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 invasive breast cancer (ICD-9: 174) or *in situ* breast cancer (ICD-9: 233) 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). Absolute risk of death from CVD (per 1,000 women) was calculated within five, seven, and ten years after year of breast cancer admission and reference year for women from the general population. Absolute risk of CVD hospitalization (per 1,000 women) was calculated within one, three, and five years after year of breast cancer admission. In addition, the underlying causes of hospitalization for CVD were investigated to assess if they were attributable to heart failure and coronary heart disease as cardiotoxic breast cancer treatments including radiation therapy[9,10], chemotherapy[20,21], trastuzumab[22,23], and aromatase inhibitors[24] are associated with these outcomes. 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 used 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**

Most patients were 60 years or older at time of breast cancer admission (Table 1). After a median follow-up of 4.3 years (IQR = 1.7-8.0) following breast cancer, 5.6% of patients died of CVD, 19.7% of patients were hospitalized for CVD, and 22.7% of patients 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 reduction 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 reduction of 27.8%). The absolute risk of death from CVD is lower in women with breast cancer compared to women from the general population.

In breast cancer patients, 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 ten-year CVD mortality rate after a 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 reduction of 48%) for patients aged between 50 and 64 years, and from 5 to 3 (relative reduction of 44.1%) for patients aged younger than 50 years.

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%).

**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 | 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 | 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 | 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 | 6.6 | 15.1 | 9.6 |

Abbreviations: CVD = cardiovascular disease, IQR = Interquartile range

* n = 163,881 (row percentage)

**Table 2.** Relative risk of death from cardiovascular disease and breast cancer among 163,881 breast cancer patients

| Year of breast cancer admission | Death from cardiovascular disease Hazard ratio* (95% confidence interval) | Death from breast cancer Hazard ratio* (95% confidence interval) |
|---|---|---|
| **1996** | 1 | 1 |
| **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 reduction (%) 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 among 163,881 breast cancer patients. Relative reduction (%) 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 cardiovascular disease hospitalizations per 1,000 breast cancer patients. Relative reduction (%) 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)

**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).

**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 (US) and Europe, the absolute risk of death from CVD have 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].

Similar to our study, 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. 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. (2015) 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 that study, breast cancer patients were invited to participate, which may have resulted in a selected study population of patients with good prognosis. Patients with a good prognosis have a higher risk of death from CVD than patients with a 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 show 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 (HER2) 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 29% 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 (VEGF) 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[40]. Similar results have been reported by Cuzick et al. (2007)[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%. 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. 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 type of breast cancer diagnosis (*in situ*/ invasive) and 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.

**Ethics approval and consent to participate**

Not applicable (anonymous data)

**Availability of data and material**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

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**Author's contribution**

Conceptualization: SAMG JB HMV IV

Data curation: JB IV

Formal analysis: JB

Funding acquisition: HMV MLB IV

Investigation: SAMG JB IV HMV

Methodology: SAMG JB IV HMV MLB

Project administration: SAMG HMV.

Supervision: HMV IV MLB DEG DHJB

Visualization: SAMG JB

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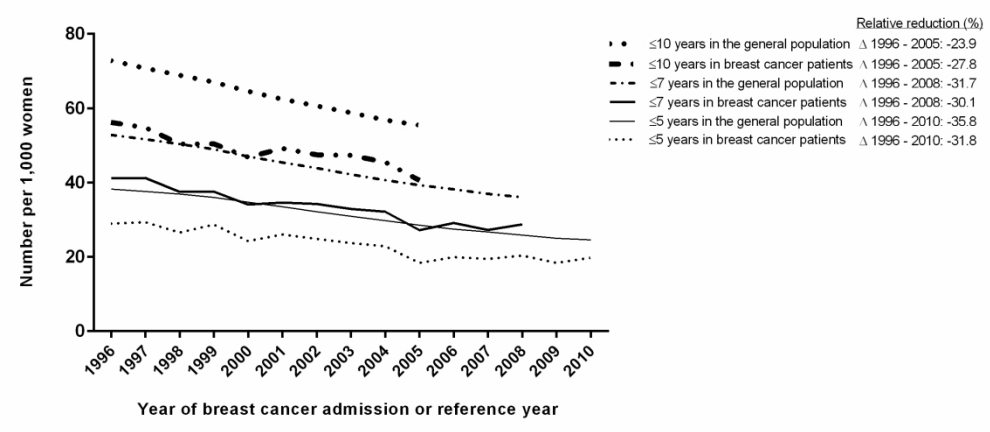
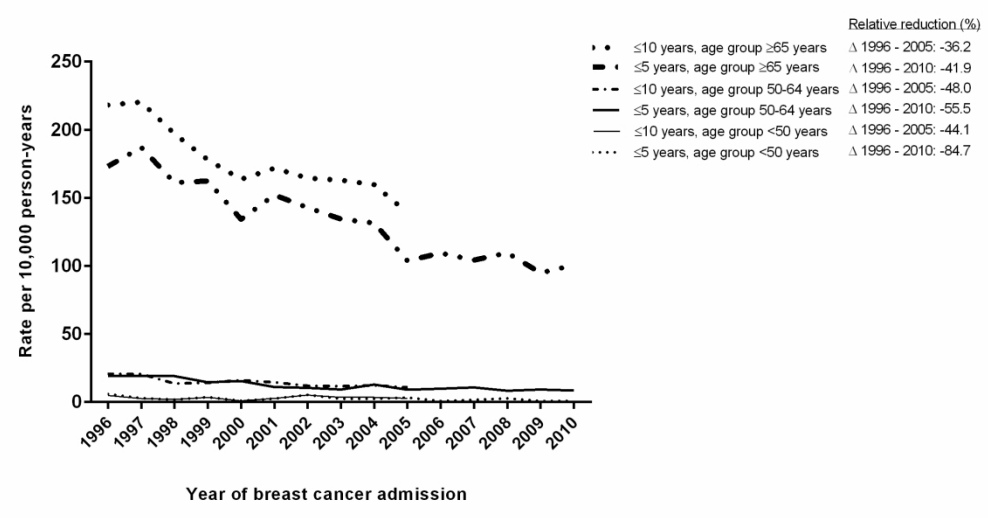


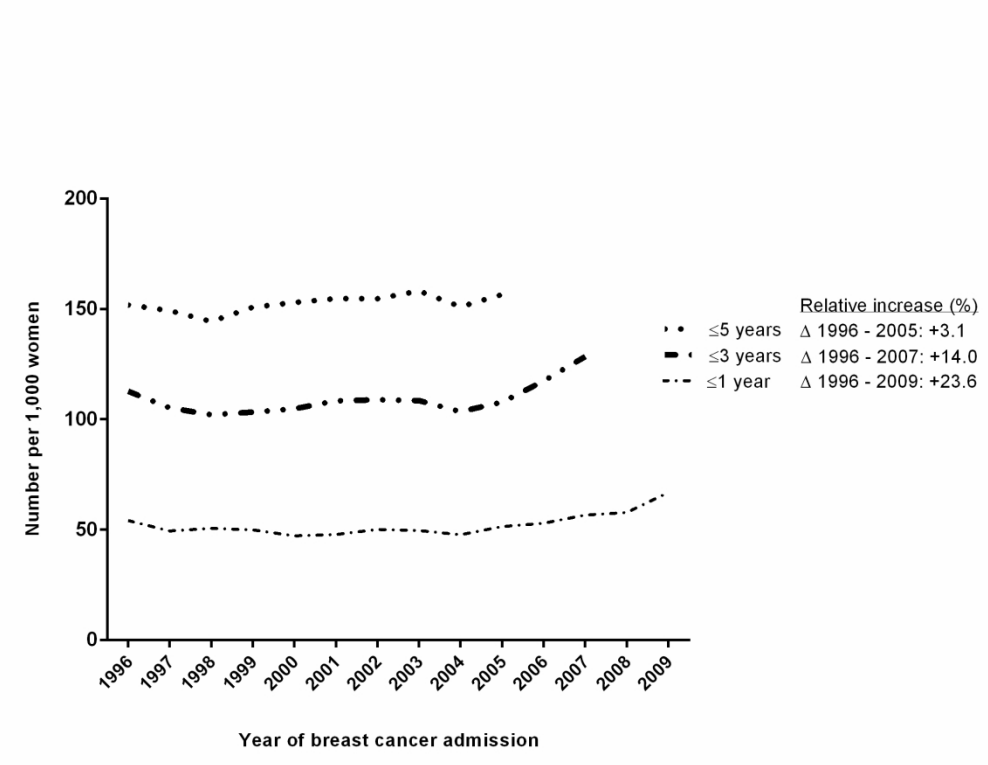

Age-standardized cardiovascular disease mortality in patients with breast cancer patients and in women from the general population. Relative reduction (%) in cardiovascular disease mortality rates within five, seven, and ten years after year of breast cancer admission of reference year between 1996-2010,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

213x93mm (300 x 300 DPI)




Cardiovascular disease mortality rates by age among 163,881 breast cancer patients. Relative reduction (%) 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.

205x107mm (300 x 300 DPI)




Age-standardized number of cardiovascular disease hospitalizations per 1,000 breast cancer patients. Relative reduction (%) 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)

191x147mm (300 x 300 DPI)

**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 |

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# Trends in the risk of cardiovascular disease in women with breast cancer in a Dutch nationwide observational cohort



| | |
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| | |

**Title**

Trends in the risk of cardiovascular disease in women with breast cancer in a Dutch nationwide observational cohort

**Authors**

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**Abstract**

**Objectives**

To investigate trends in cardiovascular disease (CVD) risk following breast cancer.

**Study design**

A nationwide prospective observational cohort study.

**Setting**

The Hospital Discharge Register, the Dutch Population Register, and Cause of Death Registry.

**Participants**

163,881 women with *in situ* (7.6%) or invasive (92.4%) breast cancer, and women from the general population aged over 40 years were identified, ranging from 3,661,141 in 1996 to 4,566,573 in 2010.

**Primary outcome**

Standardized absolute risks of CVD mortality in women with and without breast cancer and for hospitalization for CVD after breast cancer for the years 1996-2010. Relative risk reduction or increase between 1996-2010 was calculated.

**Secondary outcomes**

Age-adjusted relative risks of CVD mortality and breast cancer mortality within five years after breast cancer admission (1997-2010) compared to 1996 calculated with a cox proportional hazard analysis.

**Results**

The absolute ten-year CVD mortality risk following breast cancer decreased from 56 per 1,000 women in 1996 to 41 in 2005 (relative reduction=27.8%). In the general population, the absolute ten-year risk of CVD mortality decreased from 73 per 1,000 women in 1996 to 55 in 2005 (relative reduction=23.9%). The absolute risk of CVD hospitalization within one year following breast cancer increased from 54 per

1,000 women in 1996 to 67 in 2009 (relative increase=23.6%), which was largely explained by an increase in hospitalization for hypertension, pulmonary embolism, rheumatoid heart/valve disease and heart failure. The relative risk of CVD mortality was 0.58 (95% confidence interval=0.48-0.70) times lower for women admitted for breast cancer in 2010 compared to 1996.

**Conclusions**

CVD mortality risk decreased in breast cancer patients and in the general population, with breast cancer patients having a lower risk of CVD mortality than women of the general population. By contrast, there was an increase in hospitalization for CVD in patients with breast cancer.

**Article summary**

- This nationwide study is the first study that gives insight in trends in the risk of cardiovascular disease (CVD) mortality and hospitalization for CVD following breast cancer between 1996 and 2010 in the Netherlands.
- Trends in CVD mortality following breast cancer were compared to CVD mortality of the general population. Absolute risks were standardized according to the age distribution of women from the general population aged 40 years and older in 1996.
- The validation study showed high accuracy of breast cancer discharge codes notified in the Hospital Discharge Register.
- From 2005 onwards the participation of hospitals in registering patients' discharges decreased from 100% coverage to 89% in 2010, and therefore, not all breast cancer patients in the Netherlands could be identified.
- This study had no information on breast cancer characteristics and CVD risk factors other than type of breast cancer diagnosis (*in situ*/ invasive) and age.

## 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]

Previous studies reported associations between some breast cancer treatments and the development of CVD, including anthracycline-based chemotherapy, [6,7] trastuzumab [8] and radiotherapy treatments.[9-10] The highest risks of treatment-induced cardiotoxicity are seen in patients with pre-existing CVD risk factors such as hypertension and high age.[11,12]

In the last decade, efforts have increasingly 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.[13,14] 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.[15,16]

The present study investigated trends in the risk of death from CVD and hospitalization for 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). HDR data was available from 1995 to 2010, and data from PR and Cause of Death Registry were available until 2015.

Details of the registries and linkage procedures used to obtain data for this study have been described previously.[17] Briefly, all registries have a 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. Linkage of data from the different registries was performed in a secured environment of Statistics Netherlands and complies with the privacy legislation in The Netherlands and with the Declaration of Helsinki.[18] For this type of study no approval of the ethics committee is necessary.

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. Surgical removal of breast cancer is standard procedure for breast cancer treatment in the Netherlands. We estimate that less than five percent of the patients with breast cancer were missed due to refusal of surgery.[19]

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.

**Patient and public involvement**

Patients and public were not involved in this study.

**Outcome assessment**

Patients were followed until December 31, 2015 for death from CVD and until December 31, 2010 for 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. Ninety patients with a breast cancer discharge code for invasive breast cancer (ICD-9: 174) or *in situ* breast cancer (ICD-9: 233) 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. Because of this difference in end of study, median follow-up differed for CVD hospitalization and time until death.

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). Absolute risk of death from CVD (per 1,000 women) was calculated within five, seven, and ten years after year of breast cancer admission and reference year for women from the general population. Absolute risk of CVD hospitalization (per 1,000 women) was calculated within one, three, and five years after year of breast cancer admission. Shorter time periods for CVD hospitalization were chosen because it was expected that possible cardiotoxic effects of breast cancer treatments may have a direct effect on CVD hospitalization but less on CVD mortality. The underlying causes of hospitalization for CVD were investigated to assess if they were attributable to heart failure and coronary heart disease as cardiotoxic breast cancer treatments including radiation therapy,[9,10] chemotherapy,[20,21] trastuzuma,[22,23] and aromatase inhibitors[24] are associated with these outcomes. 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 used to estimate the age-adjusted hazard ratio (HR) of death from CVD and death from breast cancer within five years after breast cancer admission for each year (1997-2010) compared to 1996. All analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

**Results**

Most patients (51.3%) were 60 years or older at time of breast cancer admission (Table 1, 2). After a median follow-up of 4.3 years (IQR = 1.7-8.0) following breast cancer, 19.7% of patients were hospitalized for CVD. Seventy percent of the breast cancer patients with a hospital admission for CVD during follow-up were 60 years or older at time of breast cancer treatment (Table 1). Up to 2015, 5.6% of patients died of CVD and 22.7% of patients died of breast cancer (Table 2). 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 reduction of 27.8%, 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 reduction of 23.9%). The absolute risk of death from CVD is lower in women with breast cancer compared to women from the general population.

In breast cancer patients, 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 3). 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 ten-year CVD mortality rate after a 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 reduction of 48%) for patients aged between 50 and 64 years, and from 5 to 3 (relative reduction of 44.1%) for patients aged younger than 50 years.

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 (increase of 13 hospital admissions per 1,000 breast cancer patients, Figure 3). The increase in hospitalization for CVD mainly due to an increase in hospitalizations for high blood pressure (from 6.7 in 1996 to 11.0 hospitalizations in 2009 per 1,000 breast cancer patients), pulmonary embolism (from 4.4 in 1996 to 6.6 hospitalizations in 2009 per 1,000 breast cancer patients), rheumatic heart disease/valve disease (from 1.4 in 1996 to 2.5 hospitalizations in 2009 per 1,000 breast cancer patients) and by admission for heart failure (from 4.7 in 1996 to 5.6 hospitalizations in 2009 per 1,000 breast cancer patients).

**Table 1.** Hospitalizations for cardiovascular disease among 163,881 breast cancer patients

| | **Total breast cancer population** | **Breast cancer patients hospitalized for CVD** |
|---|---|---|
| **Breast cancer patients, n (%)*** | 163,881 (100.0) | 32,276 (19.7) |
| **Type of breast cancer, n (%)** | | |
| *In situ* | 12,378 (7.6) | 2,144 (6.6) |
| Invasive | 151,503 (92.4) | 30,132 (93.4) |
| **Calendar period of breast cancer admission, n (%)†** | | |
| 1996-1999 | 39,485 (24.1) | 11,135 (34.5) |
| 2000-2003 | 44,211 (27.0) | 10.564 (32.7) |
| 2004-2007 | 45,378 (27.7) | 7,687 (23.8) |
| 2008-2010 | 34,807 (21.2) | 2,890 (9.0) |
| **Age at breast cancer admission in years, n (%)** | | |
| <50 | 36,720 (22.4) | 4,155 (12.9) |
| 50-59 | 43,054 (26.3) | 6,507 (20.2) |
| 60-69 | 39,144 (23.9) | 8,582 (26.6) |
| 70-79 | 29,555 (18.0) | 8,713 (27.0) |
| >79 | 15,408 (9.4) | 4,319 (13.4) |
| **Follow-up time in years** | | |
| Median (IQR) | 4.3 (1.7-8.0) | 3.2 (1.1-6.6) |
| **Follow-up time intervals in years, n (%)** | | |
| <1 | 27,276 (16.6) | 7,620 (23.6) |
| 1-4 | 64,138 (39.1) | 13,365 (41.4) |
| 5-9 | 47,665 (29.1) | 8,038 (24.9) |

| | | |
|---|---|---|
| >9 | 24,802 (15.1) | 3,253 (6.6) |
| **Hospitalized for CVD within years after breast cancer admission, n (%)** | | |
| <1 | 8,766 (5.3) | 8,766 (27.2) |
| <3 | 17,485 (10.7) | 17,485 (54.2) |
| <5 | 23,273 (14.2) | 23,273 (72.1) |

Abbreviations: CVD = cardiovascular disease, IQR = Interquartile range

* Percentage of total breast cancer population (n = 163,881)

† Data on hospital admissions was available until 2010. Absolute risks of hospitalization for CVD decrease with more recent calendar period

**Table 2.** Deaths from cardiovascular disease among 163,881 breast cancer patients

| | **Total breast cancer population** | **Breast cancer patients who died from CVD** | **Breast cancer patients who died from breast cancer** |
|---|---|---|---|
| **Breast cancer patients, n (%)*** | 163,881 (100) | 9,115 (5.6) | 37,187 (22.7) |
| **Type of breast cancer, n (%)** | | | |
| *In situ* | 12,378 (7.6) | 483 (5.3) | 607 (1.6) |
| Invasive | 151,503 (92.4) | 8,632 (94.7) | 36,580 (98.4) |
| **Calendar period of breast cancer admission, n (%)†** | | | |
| 1996-1999 | 39,485 (24.1) | 3,540 (38.8) | 12,698 (34.1) |
| 2000-2003 | 44,211 (27.0) | 2,936 (32.2) | 10,946 (29.4) |
| 2004-2007 | 45,378 (27.7) | 1,825 (20.0) | 8,882 (23.9) |
| 2008-2010 | 34,807 (21.2) | 814 (8.9) | 4,661 (12.5) |
| **Age at breast cancer admission in years, n (%)** | | | |
| <50 | 36,720 (22.4) | 121 (1.3) | 8,777 (23.6) |
| 50-59 | 43,054 (26.3) | 481 (5.3) | 8,664 (23.3) |
| 60-69 | 39,144 (23.9) | 1,613 (17.7) | 7,985 (21.5) |
| 70-79 | 29,555 (18.0) | 3,640 (39.9) | 7,111 (19.1) |
| >79 | 15,408 (9.4) | 3,260 (35.8) | 4,650 (12.5) |
| **Follow-up time in years** | | | |
| Median (IQR) | 8.5 (5.3-12.7) | 6.3 (3.3-10.0) | 3.1 (1.2-6.2) |
| **Follow-up time intervals in years, n (%)** | | | |
| <1 | 10,256 (6.3) | 692 (7.6) | 8,044 (21.6) |
| 1-4 | 26,054 (15.9) | 2,921 (32.0) | 16,897 (45.4) |
| 5-9 | 61,602 (37.6) | 3,232 (35.5) | 8,664 (23.3) |
| >9 | 65,969 (40.3) | 2,270 (24.9) | 3,582 (9.6) |

| | | | |
|---|---|---|---|
| **Death within years after breast cancer admission, n (%)** | | | |
| <5 | 36,301 (22.0) | 3,613 (39.6) | 24,941 (67.1) |
| <7 | 45,477 (27.8) | 5,074 (55.7) | 29,544 (79.4) |
| <10 | 55,213 (33.7) | 6,845 (75.1) | 33,605 (90.4) |

Abbreviations: CVD = cardiovascular disease, IQR = Interquartile range

* Percentage of total breast cancer population (n = 163,881)

† Data on cause of death was available until 2015. Absolute risks of death from CVD decrease with more recent calendar period

**Table 3.** Relative risk of death from cardiovascular disease and breast cancer within five years after breast cancer admission among 163,881 breast cancer patients

| Year of breast cancer admission | Five-year CVD mortality Hazard ratio* (95% confidence interval) | Five-year breast cancer mortality Hazard ratio* (95% confidence interval) |
|---|---|---|
| **1996** | 1 | 1 |
| **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) |

Abbreviations: CVD = cardiovascular disease

*Hazard ratios are adjusted for age

***Figure 1.*** Trends in age-standardized 5-, 7- and 10-year cardiovascular disease mortality per 1,000 patients with breast cancer and women from the general population. Relative reduction (%) shows the relative change in cardiovascular mortality compared to reference year 1996.

***Figure 2.*** Trends in 5- and 10-year cardiovascular disease mortality rates in breast cancer patients per 10,000 person-years by age. Relative reduction (%) shows the relative decline in cardiovascular mortality rates compared to reference year 1996.

***Figure 3.*** Trends in 1-, 3- and 5-year age-standardized number of cardiovascular disease hospitalizations per 1,000 breast cancer patients. Relative reduction (%) shows the relative decline in cardiovascular mortality rates compared to reference year 1996.

**Validation of breast cancer discharge codes**

In total, 90 patients were used for validation including five patients with *in situ* breast cancer. Breast cancer diagnosis was confirmed in all patients (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).

**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 (US) and Europe, the absolute risk of death from CVD have decreased.[16,25] 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]

Similar to our study, 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. 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. (2015) 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 that study, breast cancer patients were invited to participate, which may have resulted in a selected study population of patients with good prognosis. Patients with a good prognosis have a higher risk of death from CVD than patients with a 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.[13,14]

The results of our study show that the absolute risk of hospitalization for CVD in the first year after breast cancer increased with 23.6% between 1996 and 2009. Seven percent 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 (HER2) 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 29% 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 (VEGF) 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 and is often caused by venous thromboembolism.[39] This increase may be related to the thrombotic effect of the selective estrogen receptor modulator tamoxifen.[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.[40] Similar results have been reported by Cuzick et al. (2007).[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%. 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 undergone previous (potential cardiotoxic) cancer therapy that resulted in CVD. 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 type of breast cancer diagnosis (*in situ*/ invasive) and 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.

**Ethics approval and consent to participate**

For this type of study no approval of the ethics committee is necessary.

**Availability of data and material**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Additionally, Statistics Netherlands should give their consent.

**Competing interests**

The authors declare that they have no competing interests.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Author's contribution**

Conceptualization: SAMG JB HMV IV

Data curation: JB IV

Formal analysis: JB

Funding acquisition: HMV MLB IV

Investigation: SAMG JB IV HMV

Methodology: SAMG JB IV HMV MLB

Project administration: SAMG HMV.

Supervision: HMV IV MLB DEG DHJB

Visualization: SAMG JB

Writing – original draft: SAMG JB HMV IV MLB DEG DHJB

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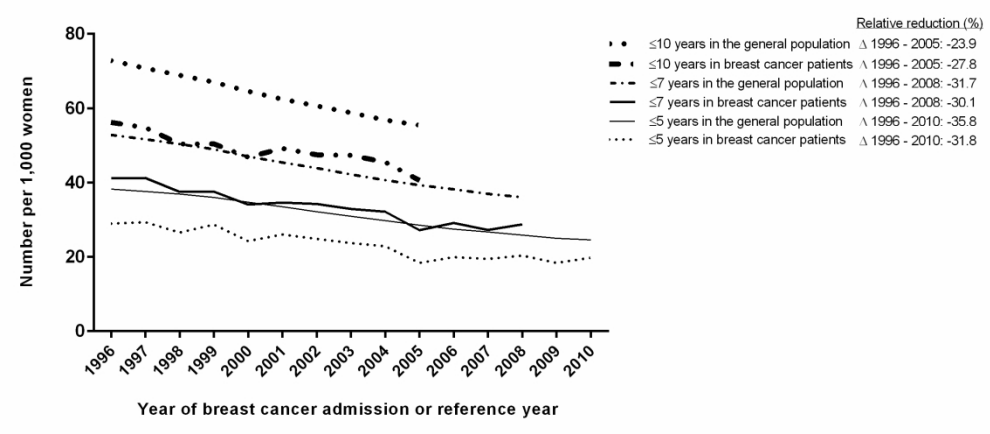


Figure 1. Trends in age-standardized 5-, 7- and 10-year cardiovascular disease mortality per 1,000 patients with breast cancer and women from the general population. Relative reduction (%) shows the relative change in cardiovascular mortality compared to reference year 1996.

213x93mm (300 x 300 DPI)

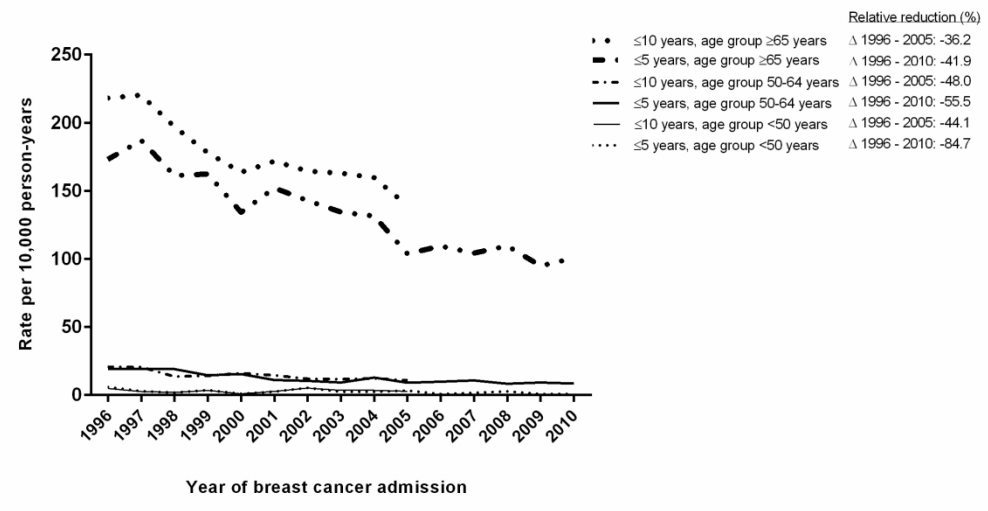


Figure 2. Trends in 5- and 10-year cardiovascular disease mortality rates in breast cancer patients per 10,000 person-years by age. Relative reduction (%) shows the relative decline in cardiovascular mortality rates compared to reference year 1996.

205x107mm (300 x 300 DPI)

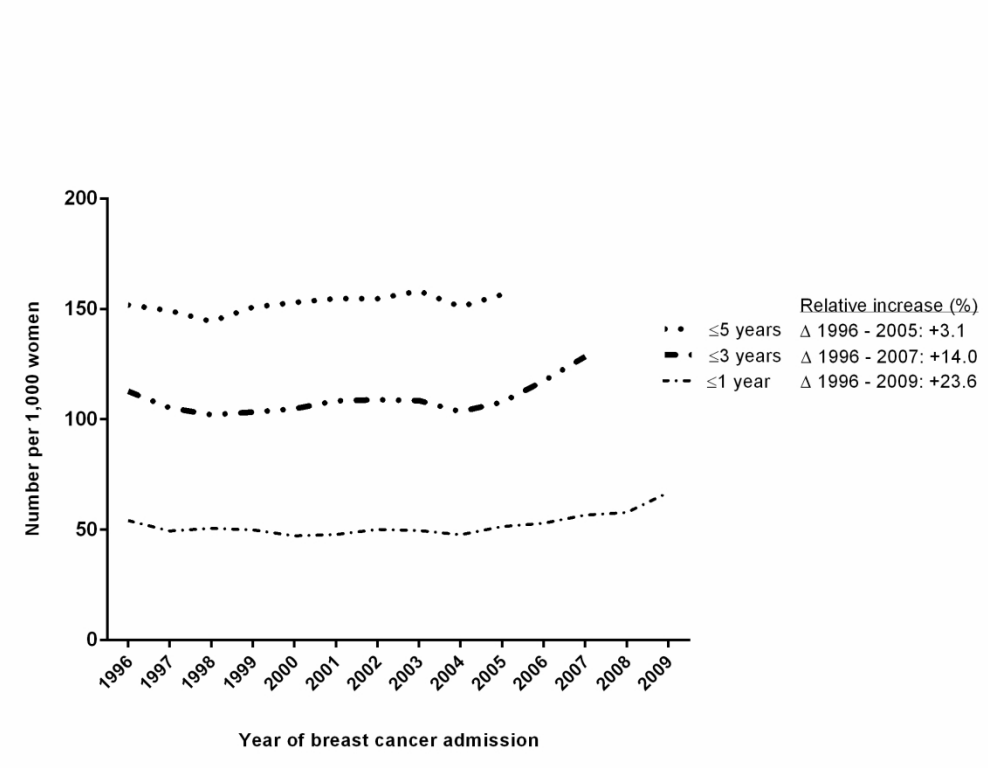


Figure 3. Trends in 1-, 3- and 5-year age-standardized number of cardiovascular disease hospitalizations per 1,000 breast cancer patients. Relative reduction (%) shows the relative decline in cardiovascular mortality rates compared to reference year 1996.

191x147mm (300 x 300 DPI)

**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 |

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

| Section/Topic | Item # | Recommendation | Reported on page # or Table/Figure |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5-6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 5-6 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | NA |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5-6 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 5-6 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 5-7 |
| Study size | 10 | Explain how the study size was arrived at | 5 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6-7 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6-7 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | NA |
| | | (*c*) Explain how missing data were addressed | NA |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | NA |
| | | (*e*) Describe any sensitivity analyses | 6-7 |
| **Results** | | | NA |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | NA |
| | | (b) Give reasons for non-participation at each stage | NA |
| | | (c) Consider use of a flow diagram | NA: registry study |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Table 1 and 2 |
| | | (b) Indicate number of participants with missing data for each variable of interest | NA: registry study |
| | | (c) Summarise follow-up time (eg, average and total amount) | Table 1 and 2 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | Table 1 and 2 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Table 3 |
| | | (*b*) Report category boundaries when continuous variables were categorized | Table 1-3 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Table 1-3 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | NA |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 13 |
| **Limitations** | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 13-15 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 5,16 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 16 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Trends in the risk of cardiovascular disease in women with breast cancer in a Dutch nationwide cohort study

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| | |

**Title**

Trends in the risk of cardiovascular disease in women with breast cancer in a Dutch nationwide cohort study

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**Abstract**

**Objectives**

To investigate trends in cardiovascular disease (CVD) risk following breast cancer using national registry data

**Methods**

A nationwide cohort study was conducted, comprising 163,881 women with *in situ* (7.6%) or invasive (92.4%) breast cancer and women from the general population, ranging from 3,661,141 in 1996 to 4,566,573 in 2010. CVD mortality rate in women with and without breast cancer and hospitalization rate after breast cancer were calculated for the years 1996-2010. Age-adjusted CVD and breast cancer mortality within five years after breast cancer admission (1997-2010) were compared to 1996 calculated with a cox proportional hazard analysis.

**Results**

The absolute ten-year CVD mortality risk following breast cancer decreased from 56 per 1,000 women in 1996 to 41 in 2005 (relative reduction=27.8%). In the general population, this decreased from 73 per 1,000 women in 1996 to 55 in 2005 (-23.9%). The absolute risk of CVD hospitalization within one year following breast cancer increased from 54 per 1,000 women in 1996 to 67 in 2009 (+23.6%), which was largely explained by an increase in hospitalization for hypertension, pulmonary embolism, rheumatoid heart/valve disease and heart failure. The 5-year CVD mortality risk was 42% lower (hazard ratio 0.58, 95% confidence interval=0.48-0.70) for women admitted for breast cancer in 2010 compared to 1996.

**Conclusions**

CVD mortality risk decreased in breast cancer patients and in the general population, with breast cancer patients having a lower risk of CVD mortality than women of the general population. By contrast, there was an increase in hospitalization for CVD in patients with breast cancer.

**Strengths and limitation of this study**

- This nationwide cohort study is the first study that gives insight in trends in the risk of cardiovascular disease (CVD) mortality and hospitalization for CVD following breast cancer between 1996 and 2010 in the Netherlands.
- Trends in CVD mortality following breast cancer were compared to CVD mortality of the general population. Absolute risks were standardized according to the age distribution of women from the general population.
- The validation study showed high accuracy of breast cancer discharge codes notified in the Hospital Discharge Register.
- From 2005 onwards the participation of hospitals in registering patients' discharges decreased from 100% coverage to 89% in 2010, and therefore, not all breast cancer patients in the Netherlands could be identified.
- This study had no information on breast cancer characteristics and CVD risk factors other than type of breast cancer diagnosis (*in situ*/ invasive) and age.

## 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]

Previous studies reported associations between some breast cancer treatments and the development of CVD, including anthracycline-based chemotherapy, [6,7] trastuzumab [8] and radiotherapy treatments.[9-10] The highest risks of treatment-induced cardiotoxicity are seen in patients with pre-existing CVD risk factors such as hypertension and high age.[11,12]

In the last decade, efforts have increasingly 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.[13,14] Cardiac monitoring before, during, and after treatment with trastuzumab to detect reversible cardiotoxicity is recommended care in the Netherlands.[14,15,16] In parallel, breast cancer patients have also been exposed to improvements in pharmacological prevention of CVD with antihypertensive and statins and non-pharmacological prevention programs such as anti-tobacco programmes, and campaigns focusing on the importance of physical activity.[15,17] However, no recent trend data about CVD mortality and hospitalization after breast cancer is available. The purpose of this study was to investigate trends of risks in CVD mortality and CVD hospitalization following breast cancer diagnosis in 1996-2010 compared with those in women without breast cancer in the Netherlands.

## Methods and Materials

### Study population

Data for the present study were obtained from three Dutch national registries. The Dutch Population Resister was used to obtain demographic characteristics, available from 1995 to 2015. Hospital Discharge Register was used to identify women admitted for breast cancer and CVD hospitalization, available until 2010. The Cause of Death Registry was available until 2015, providing data on causes of death (i.e. CVD, breast cancer or any other cause).

Details of the registries and linkage procedures used to obtain data for this study have been described previously.[18] Briefly, all registries have a 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. Linkage of data from the different registries was performed in a secured environment of Statistics Netherlands and complies with the privacy legislation in The Netherlands and with the Declaration of Helsinki.[19] For this study using national registries, no approval of the ethics committee is required.

For the present study, women from all ages 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. Surgical removal of breast cancer is standard procedure for breast cancer treatment in the Netherlands. We estimate that less than five percent of the patients with breast cancer were missed due to refusal of surgery.[20]

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 the comparison with the general population, women from the general population were identified, ranging from 3,661,141 in 1996 to 4,566,573 in 2010. For this analysis, we focused on women from 40 years or older, because in breast cancer women younger than 40 the prevalence of CVD mortality per year was too low to perform accurate standardization.

**Patient and public involvement**

Patients and public were not involved directly in this study.

**Outcome assessment**

Patients were followed until December 31, 2015 for death from CVD and until December 31, 2010 for 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 Hospital Discharge Register. In total, 90 patients from 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. Breast cancer diagnosis was confirmed in all patients (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).

**Data analysis**

Median (interquartile range (IQR)) was calculated to describe variables with skewed distribution. Time at risk for CVD mortality and hospitalization started at date of breast cancer admission until date of CVD mortality or hospitalization, respectively. Follow-up time was censored at the date of death for patients who died from causes other than CVD or breast cancer or end of study (December 31, 2015 for mortality and December 31, 2010 for CVD hospitalization). 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). Absolute risk of death from CVD (per 1,000 women) was calculated within five, seven, and ten years after year of breast cancer admission and reference year for women from the general population. Absolute risk of CVD hospitalization (per 1,000 women) was calculated within one, three, and five years after year of breast cancer admission. Shorter time periods for CVD hospitalization were chosen because it was expected that possible cardiotoxic effects of breast cancer treatments may have a direct effect on CVD hospitalization but less on CVD mortality. Previous studies showed an association between heart failure and coronary heart disease and prior exposure to chest irradiation,[9,10] chemotherapy, [21,22] trastuzumab, [23,24] and aromatase inhibitors[25]. Therefore, we investigated whether hospitalizations for heart failure and coronary heart disease and other CVD diagnoses changed over the years. To account for competing risks, we also provided cardiovascular mortality expressed per 10,000 person years. CVD mortality rates per 10,000 person-years were calculated within five and ten years after breast cancer admission by age group: 40-50, 50-64, ≥65. Lastly, a cox proportional hazard model was used to estimate the age-adjusted hazard ratio (HR) of death from CVD and death from breast cancer within five years after breast cancer

admission for each year (1997-2010) compared to 1996. Two-sided α with p-value < 0.05 was designated as significant. All analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

**Results**

Most patients (51.3%) were 60 years or older at time of breast cancer admission (Table 1, 2). Up to 2015, 5.6% of patients died of CVD and 22.7% of patients died of breast cancer (Table 1). Death from CVD mainly occurred among patients aged 60 years or older (93.4%). After a median follow-up of 4.3 years (IQR = 1.7-8.0) following breast cancer, 19.7% of patients were hospitalized for CVD (Table 2). Seventy percent of the breast cancer patients with a hospital admission for CVD during follow-up were 60 years or older at time of breast cancer treatment (Table 2). Overall, the absolute risk of death from CVD is lower in women with breast cancer compared to women from the general population. The CVD mortality rate following breast cancer decreased from 56 per 1,000 women in 1996 to 41 per 1,000 women in 2005 (relative reduction of 27.8%, Figure 1). In the general population, this decreased from 73 per 1,000 women in 1996 to 55 per 1,000 women in 2005 (relative reduction of 23.9%). The relative risk for 5-, 7- and 10-year CVD mortality for breast cancer patients compared to the general population remained similar over time (Figure 1).

In breast cancer patients, the age-adjusted risk of death from CVD within five years was 42% (HR 0.58, 95% confidence interval (CI) = 0.48-0.70) lower for patients admitted for breast cancer in 2010 compared to 1996 (Table 3). The risk of death from breast cancer was 51% (HR 0.49, 95% CI = 0.45-0.52) lower for patients admitted for breast cancer in 2010 compared to 1996. The ten-year CVD mortality rate after a 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 reduction of 48%) for patients aged between 50 and 64 years, and from 5 to 3 (relative reduction of 44.1%) for patients aged younger than 50 years.

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 (increase of 13 hospital admissions per 1,000 breast cancer patients, Figure 3). The increase in hospitalization for CVD mainly due to an increase in hospitalizations for high blood pressure (from 6.7 in 1996 to 11.0 hospitalizations in 2009 per 1,000 breast cancer patients), pulmonary embolism (from 4.4 in 1996 to 6.6 hospitalizations in 2009 per 1,000 breast cancer patients), rheumatic heart disease/valve disease (from 1.4 in 1996 to 2.5 hospitalizations in 2009 per 1,000 breast cancer patients) and by admission for heart failure (from 4.7 in 1996 to 5.6 hospitalizations in 2009 per 1,000 breast cancer patients).

**Table 1.** Deaths from cardiovascular disease among 163,881 breast cancer patients

| | **Total breast cancer population** | **Breast cancer patients who died from CVD** | **Breast cancer patients who died from breast cancer** |
|---|---|---|---|
| **Breast cancer patients, n (%)*** | 163,881 (100) | 9,115 (5.6) | 37,187 (22.7) |
| **Type of breast cancer, n (%)** | | | |
| *In situ* | 12,378 (7.6) | 483 (5.3) | 607 (1.6) |
| Invasive | 151,503 (92.4) | 8,632 (94.7) | 36,580 (98.4) |
| **Calendar period of breast cancer admission, n (%)†** | | | |
| 1996-1999 | 39,485 (24.1) | 3,540 (38.8) | 12,698 (34.1) |
| 2000-2003 | 44,211 (27.0) | 2,936 (32.2) | 10,946 (29.4) |
| 2004-2007 | 45,378 (27.7) | 1,825 (20.0) | 8,882 (23.9) |
| 2008-2010 | 34,807 (21.2) | 814 (8.9) | 4,661 (12.5) |
| **Age at breast cancer admission in years, n (%)** | | | |
| <50 | 36,720 (22.4) | 121 (1.3) | 8,777 (23.6) |
| 50-59 | 43,054 (26.3) | 481 (5.3) | 8,664 (23.3) |
| 60-69 | 39,144 (23.9) | 1,613 (17.7) | 7,985 (21.5) |
| 70-79 | 29,555 (18.0) | 3,640 (39.9) | 7,111 (19.1) |
| >79 | 15,408 (9.4) | 3,260 (35.8) | 4,650 (12.5) |

| | | | |
|---|---|---|---|
| **Follow-up time in years** | | | |
| Median (IQR) | 8.5 (5.3-12.7) | 6.3 (3.3-10.0) | 3.1 (1.2-6.2) |
| **Follow-up time intervals in years, n (%)** | | | |
| <1 | 10,256 (6.3) | 692 (7.6) | 8,044 (21.6) |
| 1-4 | 26,054 (15.9) | 2,921 (32.0) | 16,897 (45.4) |
| 5-9 | 61,602 (37.6) | 3,232 (35.5) | 8,664 (23.3) |
| >9 | 65,969 (40.3) | 2,270 (24.9) | 3,582 (9.6) |
| **Interval years between breast cancer admission and death, n (%)** | | | |
| <5 | 36,301 (22.0) | 3,613 (39.6) | 24,941 (67.1) |
| <7 | 45,477 (27.8) | 5,074 (55.7) | 29,544 (79.4) |
| <10 | 55,213 (33.7) | 6,845 (75.1) | 33,605 (90.4) |

Abbreviations: CVD = cardiovascular disease, IQR = Interquartile range

* Percentage of total breast cancer population (n = 163,881)

† Data on cause of death was available until 2015. Absolute risks of death from CVD decrease with more recent calendar period

**Table 2.** Hospitalizations for cardiovascular disease among 163,881 breast cancer patients

| | **Total breast cancer population** | **Breast cancer patients hospitalized for CVD** |
|---|---|---|
| **Breast cancer patients, n (%)*** | 163,881 (100.0) | 32,276 (19.7) |
| **Type of breast cancer, n (%)** | | |
| *In situ* | 12,378 (7.6) | 2,144 (6.6) |
| Invasive | 151,503 (92.4) | 30,132 (93.4) |
| **Calendar period of breast cancer admission, n (%)†** | | |
| 1996-1999 | 39,485 (24.1) | 11,135 (34.5) |
| 2000-2003 | 44,211 (27.0) | 10.564 (32.7) |
| 2004-2007 | 45,378 (27.7) | 7,687 (23.8) |
| 2008-2010 | 34,807 (21.2) | 2,890 (9.0) |
| **Age at breast cancer admission in years, n (%)** | | |
| <50 | 36,720 (22.4) | 4,155 (12.9) |
| 50-59 | 43,054 (26.3) | 6,507 (20.2) |
| 60-69 | 39,144 (23.9) | 8,582 (26.6) |
| 70-79 | 29,555 (18.0) | 8,713 (27.0) |
| >79 | 15,408 (9.4) | 4,319 (13.4) |
| **Follow-up time in years** | | |

| | | |
|---|---|---|
| Median (IQR) | 4.3 (1.7-8.0) | 3.2 (1.1-6.6) |
| **Follow-up time intervals in years, n (%)** | | |
| <1 | 27,276 (16.6) | 7,620 (23.6) |
| 1-4 | 64,138 (39.1) | 13,365 (41.4) |
| 5-9 | 47,665 (29.1) | 8,038 (24.9) |
| >9 | 24,802 (15.1) | 3,253 (6.6) |
| **Interval years between breast cancer admission and CVD hospitalization, n (%)** | | |
| <1 | 8,766 (5.3) | 8,766 (27.2) |
| <3 | 17,485 (10.7) | 17,485 (54.2) |
| <5 | 23,273 (14.2) | 23,273 (72.1) |

Abbreviations: CVD = cardiovascular disease, IQR = Interquartile range

* Percentage of total breast cancer population (n = 163,881)

† Data on hospital admissions was available until 2010. Absolute risks of hospitalization for CVD decrease with more recent calendar period

**Table 3.** Relative risk of death from cardiovascular disease and breast cancer within five years after breast cancer admission among 163,881 breast cancer patients

| Year of breast cancer admission | Five-year CVD mortality Hazard ratio* (95% confidence interval) | Five-year breast cancer mortality Hazard ratio* (95% confidence interval) |
|---|---|---|
| **1996** | 1 | 1 |
| **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) |

Abbreviations: CVD = cardiovascular disease

*Hazard ratios are adjusted for age

***Figure 1.*** Trends in age-standardized 5-, 7- and 10-year cardiovascular disease mortality per 1,000 patients with breast cancer and women from the general population. Relative reduction (%) shows the relative change in cardiovascular mortality compared to reference year 1996.

***Figure 2.*** Trends in 5- and 10-year cardiovascular disease mortality rates in breast cancer patients per 10,000 person-years by age. Relative reduction (%) shows the relative decline in cardiovascular mortality rates compared to reference year 1996.

***Figure 3.*** Trends in 1-, 3- and 5-year age-standardized number of cardiovascular disease hospitalizations per 1,000 breast cancer patients. Relative reduction (%) shows the relative decline in cardiovascular mortality rates compared to reference year 1996.

**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 (US) and Europe, the absolute risk of death from CVD have decreased.[17,26] 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.[27,28] The other half was explained by reductions in risk factors like hypertension, hyperlipidaemia, smoking, and physical activity.[27,28]

Similar to our study, Riihimäki et al. (2011) showed that the absolute risk of death from CVD, after a maximum follow-up of 19 years, is lower in breast cancer patients (27.1%) than in women from the general population (44.0%).[29] 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.[29] This risk of death from CVD in breast cancer patients and the general population reported by Riihimäki et al. 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.[29] Bradshaw et al. (2015) 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).[30] 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.[30] In that study, breast cancer patients were invited to participate,

which may have resulted in a selected study population of patients with good prognosis. Patients with a good prognosis have a higher risk of death from CVD than patients with a poor prognosis as breast cancer is a competing risk.[31]

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.[31] They showed that 24% of women aged 65 years and above died of CVD within ten years after breast cancer.[31] High age is one of the most important risk factors of CVD,[32] and therefore older women with breast cancer have a higher risk of dying of CVD than younger women with breast cancer.[13,14]

The results of our study show that the absolute risk of hospitalization for CVD in the first year after breast cancer increased with 23.6% between 1996 and 2009. Seven percent of this increase was caused by heart failure. This was less than we 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 (HER2) positive breast cancer (approximately one in five patients).[33] Since 2004, trastuzumab is used as adjuvant therapy for early breast cancer.[34] This therapy may have resulted in more hospital admissions for heart failure as the most concerning adverse effect of trastuzumab is in particular reduced left ventricular ejection fraction and heart failure.[35] 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.[36,37] Another 29% 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 (VEGF) signaling pathway inhibitors as for example bevacizumab. Bevacizumab is used to treat metastatic breast cancer and was introduced in Europe after 2004.[38,39] 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 and is often caused by venous thromboembolism.[40] This increase may be related to the thrombotic effect of the selective estrogen receptor modulator tamoxifen.[41,42] 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.[41] Similar results have been reported by Cuzick et al. (2007).[42]

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%. 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 undergone previous (potential cardiotoxic) cancer therapy that resulted in CVD. From 2005 onwards the participation of hospitals in registering patients' discharges decreased from 100% coverage to 89% in 2010. As a result, not all breast cancer patients in the Netherlands were identified. The present study had no information on breast cancer characteristics and CVD risk factors other than type of breast cancer diagnosis (*in situ*/ invasive) and age. Lastly, our validation study showed that in 3 out of 90 patients (3.3%) the date of discharge in the registry was incorrect by two or more months which is some cases may have led to a wrong classification of time between breast cancer admission and CVD mortality and/or hospitalization. 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.

**Ethics approval and consent to participate**

For this type of study no approval of the ethics committee is necessary.

**Availability of data and material**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Additionally, Statistics Netherlands should give their consent.

**Competing interests**

The authors declare that they have no competing interests.

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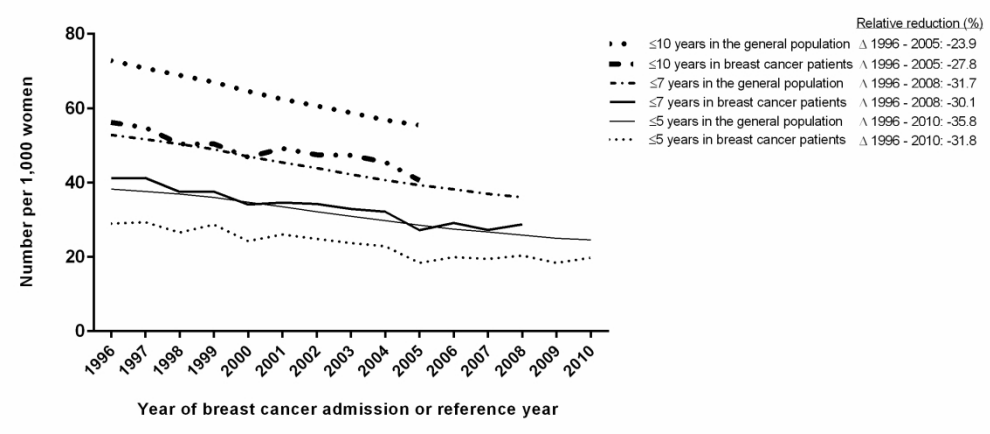


Figure 1. Trends in age-standardized 5-, 7- and 10-year cardiovascular disease mortality per 1,000 patients with breast cancer and women from the general population. Relative reduction (%) shows the relative change in cardiovascular mortality compared to reference year 1996.

213x93mm (300 x 300 DPI)

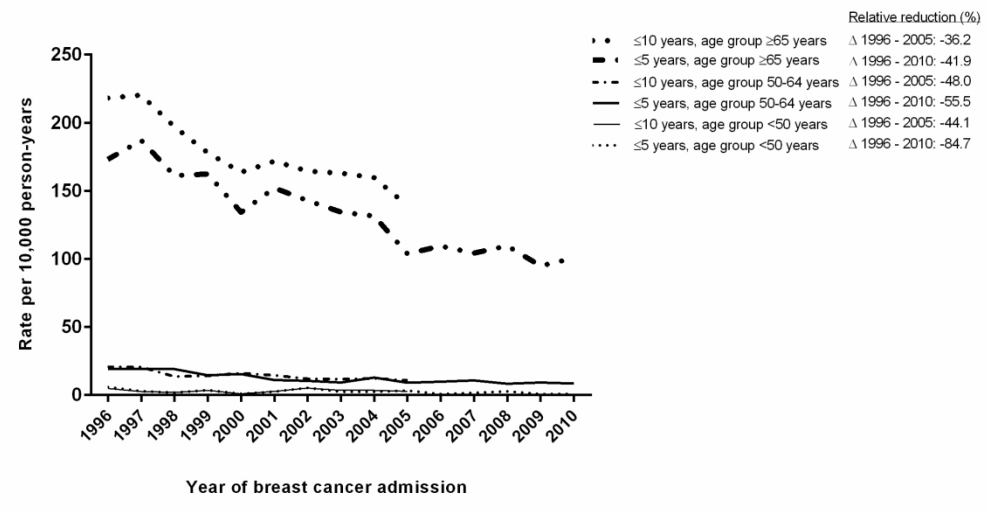


Figure 2. Trends in 5- and 10-year cardiovascular disease mortality rates in breast cancer patients per 10,000 person-years by age. Relative reduction (%) shows the relative decline in cardiovascular mortality rates compared to reference year 1996.

205x107mm (300 x 300 DPI)

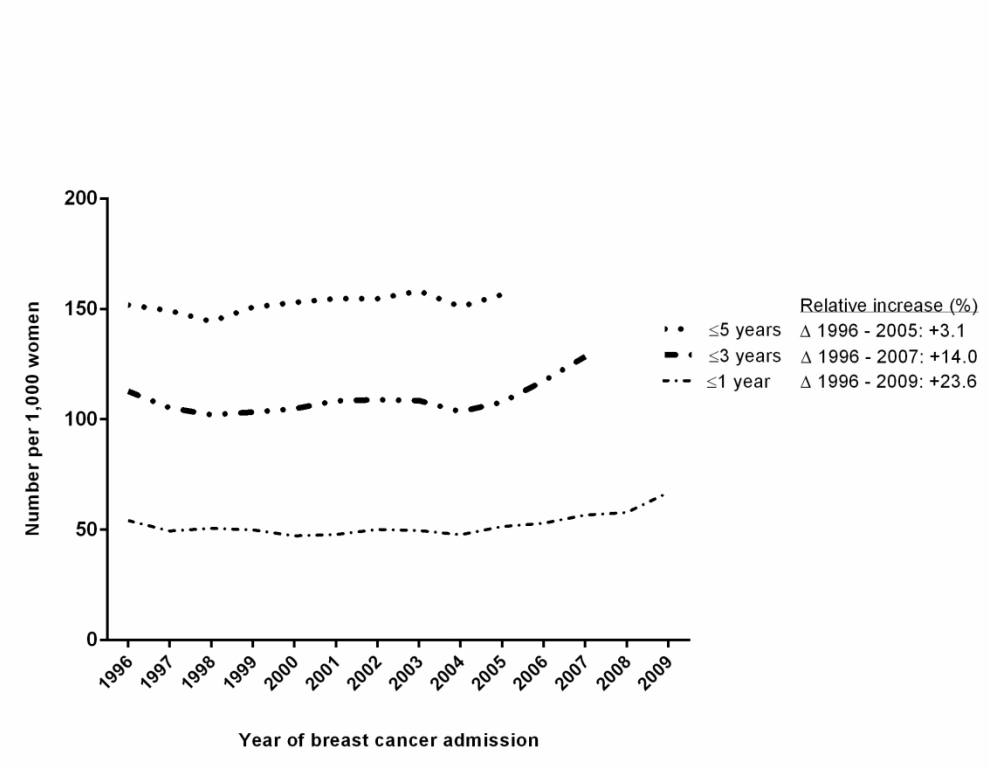


Figure 3. Trends in 1-, 3- and 5-year age-standardized number of cardiovascular disease hospitalizations per 1,000 breast cancer patients. Relative reduction (%) shows the relative decline in cardiovascular mortality rates compared to reference year 1996.

191x147mm (300 x 300 DPI)

**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 |

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

| Section/Topic | Item # | Recommendation | Reported on page # or Table/Figure |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5-6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 5-6 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | NA |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5-6 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 5-6 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 5-7 |
| Study size | 10 | Explain how the study size was arrived at | 5 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6-7 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6-7 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | NA |
| | | (*c*) Explain how missing data were addressed | NA |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | NA |
| | | (*e*) Describe any sensitivity analyses | 6-7 |
| **Results** | | | NA |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | NA |
| | | (b) Give reasons for non-participation at each stage | NA |
| | | (c) Consider use of a flow diagram | NA: registry study |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Table 1 and 2 |
| | | (b) Indicate number of participants with missing data for each variable of interest | NA: registry study |
| | | (c) Summarise follow-up time (eg, average and total amount) | Table 1 and 2 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | Table 1 and 2 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Table 3 |
| | | (*b*) Report category boundaries when continuous variables were categorized | Table 1-3 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Table 1-3 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | NA |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 13 |
| **Limitations** | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 13-15 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 5,16 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 16 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Trends in the risk of cardiovascular disease in women with breast cancer in a Dutch nationwide cohort study

| | |
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| | |

**Title**

Trends in the risk of cardiovascular disease in women with breast cancer in a Dutch nationwide cohort study

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**Abstract**

**Objectives**

To investigate trends in cardiovascular disease (CVD) risk following breast cancer using national registry data

**Methods**

A nationwide cohort study was conducted, comprising 163,881 women with *in situ* (7.6%) or invasive (92.4%) breast cancer and women of the general population, ranging from 3,661,141 in 1996 to 4,566,573 in 2010. CVD mortality rate in women with and without breast cancer and hospitalization rate after breast cancer were calculated for the years 1996-2010. Age-adjusted CVD and breast cancer mortality within five years after breast cancer admission (1997-2010) were compared to 1996 calculated with a cox proportional hazard analysis.

**Results**

The absolute ten-year CVD mortality risk following breast cancer decreased from 56 per 1,000 women in 1996 to 41 in 2005 (relative reduction=27.8%). In the general population, this decreased from 73 per 1,000 women in 1996 to 55 in 2005 (-23.9%). The absolute risk of CVD hospitalization within one year following breast cancer increased from 54 per 1,000 women in 1996 to 67 in 2009 (+23.6%), which was largely explained by an increase in hospitalization for hypertension, pulmonary embolism, rheumatoid heart/valve disease and heart failure. The 5-year CVD mortality risk was 42% lower (hazard ratio 0.58, 95% confidence interval=0.48-0.70) for women admitted for breast cancer in 2010 compared to 1996.

**Conclusions**

CVD mortality risk decreased in women with breast cancer and in women of the general population, with women with breast cancer having a lower risk of CVD mortality. By contrast, there was an increase in hospitalization for CVD in women with breast cancer.

**Strengths and limitation of this study**

- This nationwide cohort study is the first study that gives insight in trends in the risk of cardiovascular disease (CVD) mortality and hospitalization for CVD following breast cancer between 1996 and 2010 in the Netherlands.
- Trends in CVD mortality following breast cancer were compared to CVD mortality of the general population. Absolute risks were standardized according to the age distribution of women of the general population.
- The validation study showed high accuracy of breast cancer discharge codes notified in the Hospital Discharge Register.
- From 2005 onwards the participation of hospitals in registering patients' discharges decreased from 100% coverage to 89% in 2010, and therefore, not all women with breast cancer in the Netherlands could be identified.
- This study had no information on breast cancer characteristics and CVD risk factors other than type of breast cancer diagnosis (*in situ*/ invasive) and age.

## 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 2018, the estimated number of women who have survived breast cancer after being diagnosed within the preceding five years is 6.87 million worldwide (GLOBOCAN 2018).[1] Many of these survivors will die of other medical conditions than breast cancer. Cardiovascular disease (CVD) is an important cause of death in women of the general popualtion,[4] and also in women with breast cancer.[5]

Previous studies reported associations between some breast cancer treatments and the development of CVD, including anthracycline-based chemotherapy, [6,7] trastuzumab [8] and radiotherapy treatments.[9-10] The highest risks of treatment-induced cardiotoxicity are seen in patients with pre-existing CVD risk factors such as hypertension and high age.[11,12]

In the last decade, efforts have increasingly 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.[13,14] Cardiac monitoring before, during, and after treatment with trastuzumab to detect reversible cardiotoxicity is recommended care in the Netherlands.[14,15,16] In parallel, women with breast cancer have also been exposed to improvements in pharmacological prevention of CVD with antihypertensive and statins and non-pharmacological prevention programs such as anti-tobacco programmes, and campaigns focusing on the importance of physical activity.[15,17] However, no recent trend data about CVD mortality and hospitalization after breast cancer is available. The purpose of this study was to investigate trends of risks in CVD mortality and CVD hospitalization following breast cancer diagnosis in 1996-2010 compared with those in women without breast cancer in the Netherlands.

## Methods and Materials

### Study population

Data for the present study were obtained from three Dutch national registries. The Dutch Population Resister was used to obtain demographic characteristics, available from 1995 to 2015. Hospital Discharge Register was used to identify women admitted for breast cancer and CVD hospitalization, available until 2010. The Cause of Death Registry was available until 2015, providing data on causes of death (i.e. CVD, breast cancer or any other cause).

Details of the registries and linkage procedures used to obtain data for this study have been described previously.[18] Briefly, all registries have a 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. Linkage of data from the different registries was performed in a secured environment of Statistics Netherlands and complies with the privacy legislation in The Netherlands and with the Declaration of Helsinki.[19] For this study using national registries, no approval of the ethics committee is required.

For the present study, women from all ages 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. Surgical removal of breast cancer is standard procedure for breast cancer treatment in the Netherlands. We estimate that less than five percent of the patients with breast cancer were missed due to refusal of surgery.[20]

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 the comparison with the general population, women of the general population without breast cancer were identified, ranging from 3,661,141 in 1996 to 4,566,573 in 2010. For this analysis, we focused on women from 40 years or older, because in breast cancer women younger than 40 the prevalence of CVD mortality per year was too low to perform accurate standardization.

**Patient and public involvement**

Patients and public were not involved directly in this study.

**Outcome assessment**

Patients were followed until December 31, 2015 for death from CVD and until December 31, 2010 for 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 Hospital Discharge Register. In total, 90 patients from 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. Breast cancer diagnosis was confirmed in all patients (Supplementary Table A). Six Hospital Discharge Register 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).

**Data analysis**

Median (interquartile range (IQR)) was calculated to describe variables with skewed distribution. Time at risk for CVD mortality and hospitalization started at date of breast cancer admission until date of CVD mortality or hospitalization, respectively. Follow-up time was censored at the date of death for patients who died from causes other than CVD or breast cancer or end of study (December 31, 2015 for mortality and December 31, 2010 for CVD hospitalization). Absolute risks were standardized according to the age distribution of women of 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). Absolute risk of death from CVD (per 1,000 women) was calculated within five, seven, and ten years after year of breast cancer admission and reference year for women of the general population. Absolute risk of CVD hospitalization (per 1,000 women) was calculated within one, three, and five years after year of breast cancer admission. Shorter time periods for CVD hospitalization were chosen because it was expected that possible cardiotoxic effects of breast cancer treatments may have a direct effect on CVD hospitalization but less on CVD mortality. Previous studies showed an association between heart failure and coronary heart disease and prior exposure to chest irradiation,[9,10] chemotherapy, [21,22] trastuzumab, [23,24] and aromatase inhibitors[25]. Therefore, we investigated whether hospitalizations for heart failure and coronary heart disease and other cardiovascular diagnoses changed over the years. To account for competing risks, we also provided cardiovascular mortality expressed per 10,000 person years. CVD mortality rates per 10,000 person-years were calculated within five and ten years after breast cancer admission by age group: 40-50, 50-64, ≥65. Lastly, a cox proportional hazard model was used to estimate the age-adjusted hazard ratio (HR) of death from CVD and death from breast cancer within five years after breast cancer admission for each year (1997-2010) compared to 1996. Two-sided α with p-

value < 0.05 was designated as significant. All analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

**Results**

Most patients (51.3%) were 60 years or older at time of breast cancer admission (Table 1, 2). Up to 2015, 5.6% of patients died of CVD and 22.7% of patients died of breast cancer (Table 1). Death from CVD mainly occurred among patients aged 60 years or older (93.4%). After a median follow-up of 4.3 years (IQR = 1.7-8.0) following breast cancer, 19.7% of patients were hospitalized for CVD (Table 2). Seventy percent of women with breast cancer with a hospital admission for CVD during follow-up were 60 years or older at time of breast cancer treatment (Table 2). Overall, the absolute risk of death from CVD is lower in women with breast cancer compared to women of the general population. The CVD mortality rate following breast cancer decreased from 56 per 1,000 women in 1996 to 41 per 1,000 women in 2005 (relative reduction of 27.8%, Figure 1). In the general population, this decreased from 73 per 1,000 women in 1996 to 55 per 1,000 women in 2005 (relative reduction of 23.9%). The relative risk for 5-, 7- and 10-year CVD mortality for women with breast cancer compared to women of general population remained similar over time (Figure 1).

Women admitted to the hospital with breast cancer in 2010 had 42% lower (HR 0.58, 95% confidence interval (CI) = 0.48-0.70) age-adjusted 5-year risk of death from CVD compared to those in 1996 (Table 3). Furthermore, women admitted in 2010 had 51% lower (HR 0.49, 95% CI = 0.45-0.52) age-adjusted 5-year risk of death from breast cancer compared to those in 1996 (Table 3). The ten-year CVD mortality rate after a 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 reduction of 48%) for patients aged between 50 and 64 years, and from 5 to 3 (relative reduction of 44.1%) for patients aged younger than 50 years.

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 (increase of 13 hospital admissions per 1,000 women with breast cancer, Figure 3). The increase in hospitalizations for CVD in the first year after breast cancer was mainly due to an increase in hospitalizations for high blood pressure. Hospitalization for high blood pressure increased from 6.7 in 1966 to 11.0 hospitalization in 2009 per 1,000 women with breast cancer, accounting for 29% of the total increase in CVD hospitalizations in the first year after breast cancer. Pulmonary embolism rose from 4.4 in 1996 to 6.6 hospitalizations in 2009 per 1,000 women with breast cancer, similar to 15% of the total CVD hospitalizations increase. Rheumatic heart disease/valve disease and heart failure rose from 1.4 to 2.5 and 4.7 and 5.6 per 1,000 women with breast cancer during the same time period, accounting for 8% and 7% of the increase in CVD hospitalizations, respectively.

**Table 1.** Deaths from cardiovascular disease among 163,881 women with breast cancer

| | **Total breast cancer population** | **Breast cancer patients who died from CVD** | **Breast cancer patients who died from breast cancer** |
|---|---|---|---|
| **Breast cancer patients, n (%)*** | 163,881 (100) | 9,115 (5.6) | 37,187 (22.7) |
| **Type of breast cancer, n (%)** | | | |
| *In situ* | 12,378 (7.6) | 483 (5.3) | 607 (1.6) |
| Invasive | 151,503 (92.4) | 8,632 (94.7) | 36,580 (98.4) |
| **Calendar period of breast cancer admission, n (%)†** | | | |
| 1996-1999 | 39,485 (24.1) | 3,540 (38.8) | 12,698 (34.1) |
| 2000-2003 | 44,211 (27.0) | 2,936 (32.2) | 10,946 (29.4) |
| 2004-2007 | 45,378 (27.7) | 1,825 (20.0) | 8,882 (23.9) |
| 2008-2010 | 34,807 (21.2) | 814 (8.9) | 4,661 (12.5) |
| **Age at breast cancer admission in years, n (%)** | | | |
| <50 | 36,720 (22.4) | 121 (1.3) | 8,777 (23.6) |
| 50-59 | 43,054 (26.3) | 481 (5.3) | 8,664 (23.3) |

| | | | |
|---|---|---|---|
| 60-69 | 39,144 (23.9) | 1,613 (17.7) | 7,985 (21.5) |
| 70-79 | 29,555 (18.0) | 3,640 (39.9) | 7,111 (19.1) |
| >79 | 15,408 (9.4) | 3,260 (35.8) | 4,650 (12.5) |
| **Follow-up time in years** | | | |
| Median (IQR) | 8.5 (5.3-12.7) | 6.3 (3.3-10.0) | 3.1 (1.2-6.2) |
| **Follow-up time intervals in years, n (%)** | | | |
| <1 | 10,256 (6.3) | 692 (7.6) | 8,044 (21.6) |
| 1-4 | 26,054 (15.9) | 2,921 (32.0) | 16,897 (45.4) |
| 5-9 | 61,602 (37.6) | 3,232 (35.5) | 8,664 (23.3) |
| >9 | 65,969 (40.3) | 2,270 (24.9) | 3,582 (9.6) |
| **Interval years between breast cancer admission and death, n (%)** | | | |
| <5 | 36,301 (54.4) | 5,052 (55.4) | 24,941 (67.0) |
| 5-9 | 18,912 (28.4) | 2,686 (29.5) | 8,664 (23.3) |
| >9 | 11,403 (17.1) | 1,377 (15.1) | 3,582 (9.6) |

Abbreviations: CVD = cardiovascular disease, IQR = Interquartile range

* Percentage of total breast cancer population (n = 163,881)

† Data on cause of death was available until 2015. Absolute risks of death from CVD decrease with more recent calendar period

**Table 2.** Hospitalizations for cardiovascular disease among 163,881 women with breast cancer

| | **Total breast cancer population** | **Breast cancer patients hospitalized for CVD** |
|---|---|---|
| **Breast cancer patients, n (%)*** | 163,881 (100.0) | 32,276 (19.7) |
| **Type of breast cancer, n (%)** | | |
| *In situ* | 12,378 (7.6) | 2,144 (6.6) |
| Invasive | 151,503 (92.4) | 30,132 (93.4) |
| **Calendar period of breast cancer admission, n (%)†** | | |
| 1996-1999 | 39,485 (24.1) | 11,135 (34.5) |
| 2000-2003 | 44,211 (27.0) | 10.564 (32.7) |
| 2004-2007 | 45,378 (27.7) | 7,687 (23.8) |
| 2008-2010 | 34,807 (21.2) | 2,890 (9.0) |
| **Age at breast cancer admission in years, n (%)** | | |
| <50 | 36,720 (22.4) | 4,155 (12.9) |
| 50-59 | 43,054 (26.3) | 6,507 (20.2) |
| 60-69 | 39,144 (23.9) | 8,582 (26.6) |
| 70-79 | 29,555 (18.0) | 8,713 (27.0) |
| >79 | 15,408 (9.4) | 4,319 (13.4) |

| | | |
|---|---|---|
| **Follow-up time in years** | | |
| Median (IQR) | 4.3 (1.7-8.0) | 3.2 (1.1-6.6) |
| **Follow-up time intervals in years, n (%)** | | |
| <1 | 27,276 (16.6) | 7,620 (23.6) |
| 1-4 | 64,138 (39.1) | 13,365 (41.4) |
| 5-9 | 47,665 (29.1) | 8,038 (24.9) |
| >9 | 24,802 (15.1) | 3,253 (6.6) |
| **Interval years between breast cancer admission and CVD hospitalization, n (%)** | | |
| <1 | 8,766 (5.3) | 8,766 (27.2) |
| <3 | 17,485 (10.7) | 17,485 (54.2) |
| <5 | 23,273 (14.2) | 23,273 (72.1) |

Abbreviations: CVD = cardiovascular disease, IQR = Interquartile range

* Percentage of total breast cancer population (n = 163,881)

† Data on hospital admissions was available until 2010. Absolute risks of hospitalization for CVD decrease with more recent calendar period

**Table 3.** Relative risk of death from cardiovascular disease and breast cancer within five years after breast cancer admission among 163,881 women with breast cancer

| Year of breast cancer admission | Five-year CVD mortality Hazard ratio* (95% confidence interval) | Five-year breast cancer mortality Hazard ratio* (95% confidence interval) |
|---|---|---|
| **1996** | 1 | 1 |
| **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) |

Abbreviations: CVD = cardiovascular disease

*Hazard ratios are adjusted for age

***Figure 1.*** Trends in age-standardized 5-, 7- and 10-year cardiovascular disease mortality per 1,000 patients with breast cancer and women of the general population. Relative reduction (%) shows the relative change in cardiovascular mortality compared to reference year 1996.

***Figure 2.*** Trends in 5- and 10-year cardiovascular disease mortality rates in women with breast cancer per 10,000 person-years by age. Relative reduction (%) shows the relative decline in cardiovascular mortality rates compared to reference year 1996.

***Figure 3.*** Trends in 1-, 3- and 5-year age-standardized number of cardiovascular disease hospitalizations per 1,000 women with breast cancer. Relative reduction (%) shows the relative decline in cardiovascular mortality rates compared to reference year 1996.

**Discussion**

Like in the general population, the risk of death from CVD has decreased in women with breast cancer between 1996 and 2010, and mainly occurred among patients aged over 60 years. Women with breast cancer have a lower absolute risk of death from CVD than women of 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 (US) and Europe, the absolute risk of death from CVD have decreased.[17,26] The decrease in deaths from coronary artery disease was for around 50% attributable to the increased use of pharmacological treatments after heart failure and myocardial infarction.[27,28] The other half was explained by reductions in risk factors like hypertension, hyperlipidaemia, smoking, and physical activity.[27,28]

Similar to our study, Riihimäki et al. (2011) showed that the absolute risk of death from CVD, after a maximum follow-up of 19 years, is lower in women with breast cancer (27.1%) than in women of the general population (44.0%).[29] They investigated the risk of death from CVD using nationwide registration data and comparing all women diagnosed with breast cancer with women of the general population without a breast cancer diagnosis.[29] This risk of death from CVD in women with breast cancer and the general population reported by Riihimäki et al. 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.[29] Bradshaw et al. (2015) reported a higher absolute risk of death from CVD in women with breast cancer (9.4%) than in women of the general population (7.4%) after a maximum follow-up of 13.5 years (from 1996 to 2010).[30] They also found a higher relative risk of death from CVD in women with breast cancer after seven years following diagnosis compared to women of from the general population (HR = 1.8, 95% CI = 1.3-2.5), adjusted for age and CVD risk factors.[30] In that study, women with breast cancer were invited

to participate, which may have resulted in a selected study population of patients with good prognosis. Patients with early-stage breast cancer have a higher risk of death from CVD than patients with a poor prognosis as breast cancer is a competing risk.[31]

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 women with breast cancer.[31] They showed that 24% of women aged 65 years and above died of CVD within ten years after breast cancer.[31] High age is one of the most important risk factors of CVD,[32] and therefore older women with breast cancer have a higher risk of dying of CVD than younger women with breast cancer.[13,14] Moreover, in the current study we showed that older women with breast cancer had the least improvement in CVD mortality over time compared to younger women with breast cancer. It seems that older women with breast cancer do not benefit as much younger women from the worldwide improvements in CVD risk management and CVD treatments.

The results of our study show that the absolute risk of hospitalization for CVD in the first year after breast cancer increased with 23.6% between 1996 and 2009. Seven percent of this increase was caused by heart failure. This was less than we 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 (HER2) positive breast cancer (approximately one in five patients).[33] Since 2004, trastuzumab is used as adjuvant therapy for early breast cancer.[34] This therapy may have resulted in more hospital admissions for heart failure as the most concerning adverse effect of trastuzumab is in particular reduced left ventricular ejection fraction and heart failure.[35] 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.[36,37] Another 29% 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 (VEGF) signaling pathway inhibitors as for example bevacizumab. Bevacizumab is used to treat metastatic breast cancer and was introduced in Europe after 2004.[38,39] 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 and is often caused by venous thromboembolism.[40] This increase may be related to the thrombotic effect of the selective estrogen receptor modulator tamoxifen.[41,42] 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.[41] Similar results have been reported by Cuzick et al. (2007).[42]

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%. 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 undergone previous (potential cardiotoxic) cancer therapy that resulted in CVD. From 2005 onwards the participation of hospitals in registering patients' discharges decreased from 100% coverage to 89% in 2010. As a result, not all women with breast cancer in the Netherlands were identified. The present study had no information on breast cancer characteristics and CVD risk factors other than type of breast cancer diagnosis (*in situ*/ invasive) and age. Lastly, our validation study showed that in 3 out of 90 patients (3.3%) the date of discharge in the registry was incorrect by two or more months which is some cases may have led to a wrong classification of time between breast cancer admission and CVD mortality and/or hospitalization. To conclude, the current study shows that the risk of death from CVD in women with

breast cancer and in women of 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.

**Ethics approval and consent to participate**

For this type of study no approval of the ethics committee is necessary.

**Availability of data and material**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Additionally, Statistics Netherlands should give their consent.

**Competing interests**

The authors declare that they have no competing interests.

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**Author's contribution**

Conceptualization: SAMG JB HMV IV

Data curation: JB IV

Formal analysis: JB

Funding acquisition: HMV MLB IV

Investigation: SAMG JB IV HMV

Methodology: SAMG JB IV HMV MLB

Project administration: SAMG HMV.

Supervision: HMV IV MLB DEG DHJB

Visualization: SAMG JB

Writing – original draft: SAMG JB HMV IV MLB DEG DHJB

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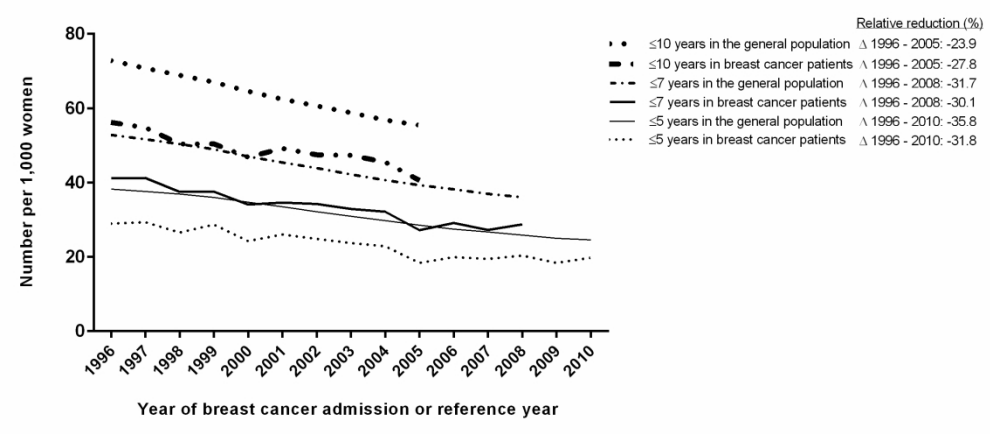


Figure 1. Trends in age-standardized 5-, 7- and 10-year cardiovascular disease mortality per 1,000 patients with breast cancer and women from the general population. Relative reduction (%) shows the relative change in cardiovascular mortality compared to reference year 1996.

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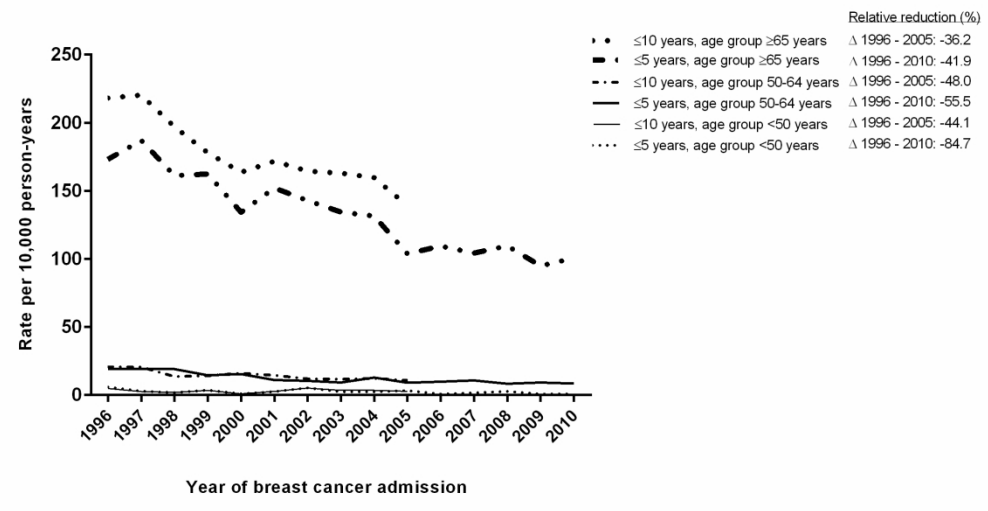


Figure 2. Trends in 5- and 10-year cardiovascular disease mortality rates in breast cancer patients per 10,000 person-years by age. Relative reduction (%) shows the relative decline in cardiovascular mortality rates compared to reference year 1996.

205x107mm (300 x 300 DPI)

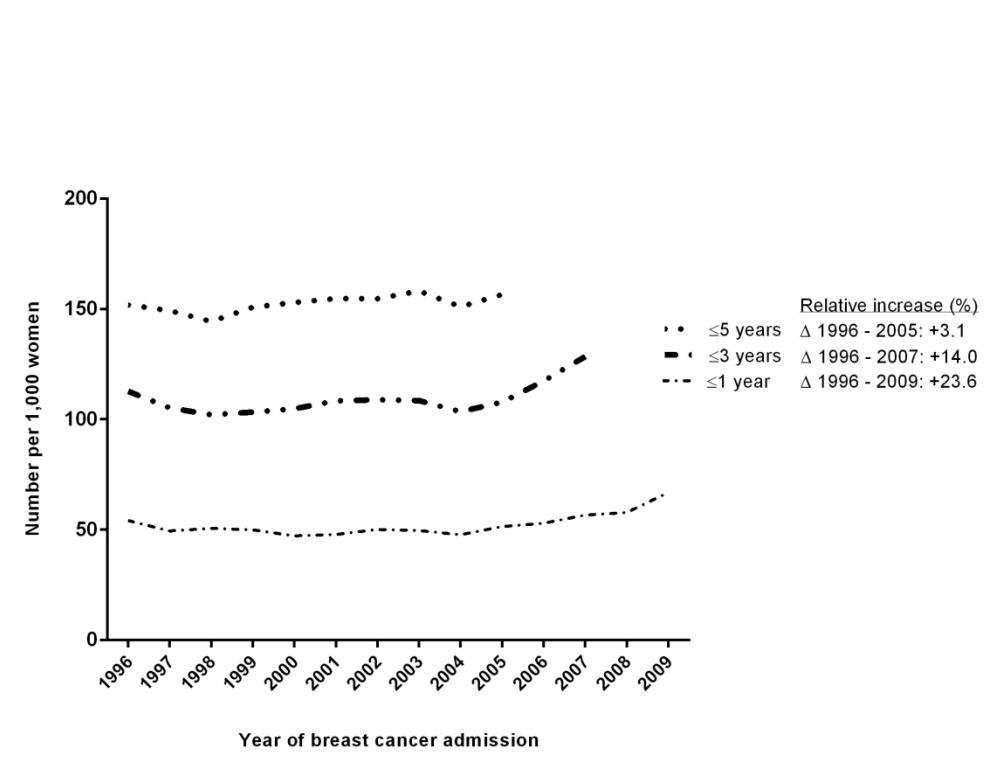


Figure 3. Trends in 1-, 3- and 5-year age-standardized number of cardiovascular disease hospitalizations per 1,000 breast cancer patients. Relative reduction (%) shows the relative decline in cardiovascular mortality rates compared to reference year 1996.

191x147mm (300 x 300 DPI)

**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 |

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

| Section/Topic | Item # | Recommendation | Reported on page # or Table/Figure |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5-6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 5-6 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | NA |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5-6 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 5-6 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 5-7 |
| Study size | 10 | Explain how the study size was arrived at | 5 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6-7 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6-7 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | NA |
| | | (*c*) Explain how missing data were addressed | NA |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | NA |
| | | (*e*) Describe any sensitivity analyses | 6-7 |
| **Results** | | | NA |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | NA |
| | | (b) Give reasons for non-participation at each stage | NA |
| | | (c) Consider use of a flow diagram | NA: registry study |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Table 1 and 2 |
| | | (b) Indicate number of participants with missing data for each variable of interest | NA: registry study |
| | | (c) Summarise follow-up time (eg, average and total amount) | Table 1 and 2 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | Table 1 and 2 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Table 3 |
| | | (*b*) Report category boundaries when continuous variables were categorized | Table 1-3 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Table 1-3 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | NA |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 13 |
| **Limitations** | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 13-15 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 5,16 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 16 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.