

# Results of a Population-Based Cohort Study on Heart Disease Risk Following Breast Cancer Treatment

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## Abstract

**Introduction:** Concerns about treatment-related cardiotoxicities in breast cancer patients are growing. The purpose of this study was to ascertain the time- and treatment-specific incidence of ischemic heart disease, heart failure, and arrhythmia in breast cancer patients.

**Methods:** Stockholm-Gotland breast cancer patients diagnosed between 2001 and 2008 were included in a register-based matched cohort study that was followed up until 2017. Flexible parametric models were used to compare breast cancer patients' time-dependent risks of arrhythmia, heart failure, and ischemic heart disease to those of matched controls from the general population. The Cox model was used to estimate treatment-specific effects in breast cancer patients.

**Results:** After being diagnosed with breast cancer, time-dependent analyses revealed an increased risk of heart failure and arrhythmia in the long run. Peril proportions (HRs) inside the principal year of conclusion were 2.14 (95% CI=1.63-2.81) for arrhythmia and 2.71 (95% CI=1.70-4.33) for cardiovascular breakdown. For arrhythmia, the HR was 1.42 (95% CI=1.21-1.67), while for heart failure, it was 1.28 (95% CI=1.03-1.59) after 10 years. Only in the first year following diagnosis did the risk of ischemic heart disease rise significantly (HR=1.45, 95% CI=1.03-2.04). Trastuzumab and anthracyclines were related with expanded hazard of cardiovascular breakdown. Ischemic heart disease was linked to the risk of aromatase inhibitors, but not tamoxifen. Following locoregional radiotherapy, there was no evidence of an increased risk of heart disease.

**Conclusion:** Systemic adjuvant therapies appear to be linked to a higher risk of heart disease. In oncology settings, decision-making regarding adjuvant therapy and patient counselling may be aided by the risk estimates found in this study.

**Keywords:** Heart disease • Breast cancer cohort • Covariates • Hypertension

## Introduction

According to the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2005, the use of adjuvant systemic therapies reduces the risk of death from breast cancer by at least half. Today, eighty percent of breast cancer patients live to at least ten years old, with many becoming long-term survivors. There are, notwithstanding, worries about treatment related late unfavorable wellbeing impacts, including cardiovascular occasions. Common (neo-) adjuvant breast cancer therapies have been linked to an increased risk of heart disease, such as heart failure, arrhythmias, and ischemic heart disease. However, the majority of this evidence comes from studies that focus on particular patient subgroups based on age, cancer stage, or treatment regimen [1].

Despite the fact that the risks of heart disease outweigh the benefits of radiotherapy, some studies have found an increased risk of heart disease in women treated with radiotherapy. The use of bolus injections to lower anthracycline peak concentrations has decreased as a result of increased awareness of the cardiotoxic effects of anthracycline-based chemotherapy regimens, but it is estimated that standard low-dose anthracycline users still face a higher risk of heart failure than non-users. At 11 years of follow-up,

trastuzumab has been shown to lower the risk of breast cancer mortality, there is conflicting evidence regarding its cardiotoxicity. In addition, new research suggests that when compared to tamoxifen, aromatase inhibitors may increase the risk of heart failure in women with hormone receptor positive breast cancer [1].

When planning cardiac surveillance programs and potential prophylactic pharmacotherapy following breast cancer, risk assessment of immediate and subsequent heart disease events is crucial. With long-term follow-up, we present the heart disease risks in a cohort that is representative of the general breast cancer population. We specifically wanted to determine the risk of heart disease based on adjuvant treatments and time since diagnosis. Concerns about treatment-related cardiotoxicities in breast cancer patients are growing. The purpose of this study was to ascertain the time- and treatment-specific incidence of ischemic heart disease, heart failure, and arrhythmia in breast cancer patients [2].

Stockholm-Gotland breast cancer patients diagnosed between 2001 and 2008 were included in a register-based matched cohort study that was followed up until 2017. Flexible parametric models were used to compare breast cancer patients' time-dependent risks of arrhythmia, heart failure, and ischemic heart disease to those of matched controls from the general population. The Cox model was used to estimate treatment-specific effects in breast cancer patients. The utilization of adjuvant foundational treatments basically parts the gamble of biting the dust from bosom disease. Today, eighty percent of breast cancer patients live to at least ten years old, with many becoming long-term survivors. However, there are concerns regarding late adverse health effects, such as cardiovascular events, that are associated with therapy. Common (neo-)adjuvant therapies for breast cancer have been linked to an increased risk of heart conditions like arrhythmias, ischemic heart disease, and heart failure. However, the majority of this evidence comes from studies that focus on particular patient subgroups based on age, cancer stage, or treatment regimen [3].

Although the risks of heart diseases outweigh the benefits of radiotherapy,

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some studies have found an increased risk of heart disease in women treated with radiotherapy. As a result of increased awareness of the cardiotoxic effects of anthracycline-based chemotherapy regimens, doses have been reduced and bolus injections have been used less to lower peak concentrations of anthracyclines. However, it is estimated that the standard low-dose group still faces a higher risk of heart failure than non-users. Although trastuzumab has been shown to lower the risk of death from breast cancer after 11 years of follow-up, there is conflicting evidence regarding its cardiotoxicity. In addition, new research suggests that aromatase inhibitors, as opposed to tamoxifen, may increase the risk of heart failure in women with hormone receptor positive breast cancer. When planning cardiac surveillance programs and potential prophylactic pharmacotherapy following breast cancer, risk assessment of immediate and subsequent heart disease events is crucial. With long-term follow-up, we present the heart disease risks in a cohort that is representative of the general breast cancer population. We specifically wanted to determine the risk of heart disease based on adjuvant treatments and time since diagnosis [4].

## Materials and Methods

### Breast cancer cohort

This study made use of the Stockholm-Gotland Breast Cancer Register, which included all women who were diagnosed with primary invasive breast cancer in the Stockholm-Gotland region between the years 2001 and 2008. The Stockholm-Gotland Bosom Malignant growth Register has around close to 100% fulfillment and gives nitty gritty data on cancer and therapy qualities, as well as normal development on locoregional repeats and far off metastases. You can find a more in-depth description of the breast cancer cohort elsewhere. We included all patients between the ages of 25 and 75 with non-metastatic breast cancer (stages I–III) and no prior heart disease diagnosis (N=8015). We randomly selected up to ten women from the Stockholm-Gotland region's general female population, matched by birth year, to compare the risk of heart disease following a breast cancer diagnosis. On the date that the matched patient was diagnosed with breast cancer (the index date), each reference individual was still alive and free of the disease [5].

According to relevant ICD (International Classification of Disease) codes in the Swedish Patient Register and the Cause of Death Register, the following heart diseases were identified by a heart condition (ICD-10:I50, ICD-9:428A, 428B, and 428X), and arrhythmias (I47–I49, ICD-9:427), as well as ischemia (ICD-10:I20–I25, ICD-9:410–414). Except for myocardial infarction, which was solely based on inpatient and cause of death records, our outcome definition included both inpatient and outpatient diagnoses. Only primary diagnoses, not underlying diagnoses, were taken into account for the analyses to guarantee the specificity of the studied outcomes [6].

Particulars of breast cancer treatment we obtained the treatment information from the Stockholm-Gotland Breast Cancer Register. As ~90% of HER-2 positive malignant growths were treated with trastuzumab somewhere in the range of 2005 and 2008 in the Stockholm-Gotland district and the Swedish Endorsed Medication Register doesn't cover information on treatment with trastuzumab, HER-2 energy was utilized as an intermediary when no library information on trastuzumab was accessible during this time span (30% of the HER-2 positive patients had missing data on trastuzumab). The Prescribed Drug Register was used to verify the data on adjuvant endocrine therapy, and tamoxifen and/or aromatase inhibitor use was classified. Radiotherapy was categorized according to tumor laterality (left vs. right) because radiotherapy to the left breast has been linked to heart problems in particular. In this analysis, two tumors were coded separately. Anthracycline-based, anthracycline plus taxane-based, cyclophosphamide-, methotrexate-, and fluorouracil (CMF)-based, and cyclophosphamide-based chemotherapy regimens were all coded [7].

### Covariates

The Stockholm Breast Cancer Register includes information about the date of diagnosis, the patient's menopausal status at the time of diagnosis, and the

type of surgery (breast conserving surgery versus mastectomy). Additionally, tumor characteristics such as tumor size (T), involvement of regional lymph nodes (N), and metastases (M) were retrieved from pathology records and summarized in TNM stage, as defined by the American Joint Committee on Cancer. The Charlson comorbidity index (CCI) score, a widely used method for classifying chronic comorbid conditions. We used ICD codes from the patient register to further identify associated diagnoses prior to cancer to take into account the potential confounding effect of tobacco use, chronic pulmonary disease, and hypertension on the associations.

Statistical analyses we used a flexible parametric model (FPM) with the time since index date as the underlying time scale to compare the risk of heart disease among breast cancer patients and the matched cohort. The hazard ratio (HR) as a measure of association is provided by the FPM, which is similar to the Cox proportional hazards model. The baseline hazard was calculated using a restricted cubic spline with five degrees of freedom (four internal and two boundary knots) at quintiles of the event times in our study. The critical benefit of FPM is that non-relative dangers can undoubtedly be fitted by adding a second spline for the communication with time. The maximum penalized marginal likelihood method was used to estimate the frailty's regression coefficients and variance, taking into account the correlation between the matched clusters. A shared frailty term was used as random effects in the model. The cumulative incidences of heart diseases in breast cancer patients and matched reference individuals were evaluated using Aalen-Johansen estimation, while competing events from other causes of death were taken into consideration [8].

Using Cox proportional hazards models, we next investigated the connection between breast cancer patients' risk of heart disease and adjuvant therapy. These analyses were adjusted for menopausal status at diagnosis, age and year of diagnosis (model 1), cancer stage, and type of surgery, CCI score, hypertension, chronic pulmonary disease, and tobacco use. For adjuvant therapies, all treatment-specific models were mutually adjusted. Taking into account the possibility of radiotherapy administration selection bias, only patients receiving radiotherapy were included in the analysis, which compared left-sided, right-sided, and both-sided breast cancer. The treatment categories with missing data were dealt with using multiple imputation and chained equations. Ten rounds of imputations were used to replace the missing data, and the imputation model included all covariates. Because of the time-dependent effect of treatment, we divided the analysis into two distinct follow-up periods: within the first ten years after the diagnosis of breast cancer and beyond [9].

## Discussion

We demonstrated, in a population-based setting, that breast cancer patients had significantly higher heart disease rates than matched reference individuals from the general population. Even after a decade had passed since diagnosis, there was still an increased risk of heart failure and arrhythmia. Trastuzumab and anthracycline-taxane-based regimens, as well as aromatase inhibitor therapy, were independently linked to an increased risk of heart failure. Ischemic heart disease was also linked to aromatase inhibitor therapy.

as compared to the matched reference individuals from the general population, breast cancer patients had a higher risk of heart failure and arrhythmia, which is comparable to the risk of heart failure that was found in a previous Dutch study. This suggests that our findings can be applied to European nations. However, because the patients in our cohort ranged in age from 25 to 75, these findings should not be generalized to older patients with more comorbidity [9].

## Conclusion

Through this review, we exhibit that contrasted with everyone, ladies with bosom malignant growth have expanded dangers of coronary illness including cardiovascular breakdown and arrhythmia. After one year after diagnosis, the short-term risk of ischemic heart disease decreased. However, it appears that

the increased risk of arrhythmia and heart failure lasts beyond the first ten years after diagnosis. Heart disease risk increases when systemic adjuvant therapies are administered. In oncology practices, the risk estimates found in this study may be used as a reference for decision-making regarding adjuvant therapy and patient counseling.

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## Acknowledgement

None.

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## Conflict of Interest

None.

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