

Patterns of Chronic Disease Incidence over Time Following Breast Cancer: A Nationwide Cohort Study Based on the Population

Danbee Kang*

Department of Cardiology, Center for Molecular Cardiology, University of Zurich, Zurich, Switzerland

Introduction

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) found in 2005 that adjuvant systemic therapies reduce the risk of breast cancer death by at least half. Eighty percent of breast cancer patients today survive to the age of ten or older, and many of them become long-term survivors. However, concerns exist regarding treatment-related adverse health effects in the future, such as cardiovascular events. Neo-adjuvant breast cancer therapies have been linked to an increased risk of heart disease, including ischemic heart disease, heart failure, and arrhythmias. However, the majority of this evidence comes from studies that concentrate on particular age, cancer stage, or treatment regimen subgroups of patients [1].

Some studies have found an increased risk of heart disease in women treated with radiotherapy, despite the fact that the benefits of radiotherapy outweigh the risks of heart disease. Increased awareness of the cardiotoxic effects of anthracycline-based chemotherapy regimens has decreased the use of bolus injections to lower anthracycline peak concentrations. However, it is estimated that standard low-dose anthracycline users still face a higher risk of heart failure than non-users. Trastuzumab has been shown to lower the risk of breast cancer mortality after 11 years of follow-up, but there is conflicting evidence regarding its cardiotoxicity. Additionally, new research indicates that aromatase inhibitors may increase the risk of heart failure in women with hormone receptor positive breast cancer when compared to tamoxifen [1].

Risk assessment of immediate and subsequent heart disease events is essential when planning cardiac surveillance programs and potential prophylactic pharmacotherapy following breast cancer. We present the heart disease risks in a cohort that is representative of the general breast cancer population through long-term follow-up. Based on adjuvant treatments and time since diagnosis, we wanted to specifically determine the risk of heart disease. Patients with breast cancer are increasingly concerned about cardiotoxic effects of treatment. This study sought to determine the time- and treatment-specific incidence of heart failure, ischemic heart disease, and arrhythmia in breast cancer patients [2].

A register-based, matched cohort study of Stockholm-Gotland breast cancer patients who were diagnosed between 2001 and 2008 was followed up until 2017. The time-dependent risks of arrhythmia, heart failure, and ischemic heart disease in breast cancer patients were compared to those of matched controls from the general population using flexible parametric models. Breast cancer patients' treatment-specific effects were estimated using the Cox model. The risk of succumbing to breast disease is basically reduced through the use of adjuvant foundational treatments. Eighty percent of breast cancer patients today survive to the age of ten or older, and many of them become long-term survivors. However, there are concerns regarding therapy-related late adverse health effects like cardiovascular events. Arrhythmias, ischemic heart disease, and heart failure

***Address for Correspondence:** Danbee Kang, Department of Cardiology, Center for Molecular Cardiology, University of Zurich, Zurich, Switzerland, E-mail: kang_d@gmail.com

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have all been linked to an increased risk from common (neo-)adjuvant breast cancer treatments. However, the majority of this evidence comes from studies that concentrate on particular age, cancer stage, or treatment regimen subgroups of patients [3].

Despite the fact that the benefits of radiotherapy outweigh the risks, some studies have found an increased risk of heart disease in women receiving treatment. Doses have been reduced and bolus injections have been used less to lower anthracycline peak concentrations as a result of increased awareness of the cardiotoxic effects of anthracycline-based chemotherapy regimens. However, the standard low-dose group is still thought to have a greater risk of heart failure than non-users. There is conflicting evidence regarding the cardiotoxicity of trastuzumab, despite the fact that after 11 years of follow-up, it has been demonstrated to lower the risk of breast cancer death. Additionally, new research indicates that aromatase inhibitors, as opposed to tamoxifen, may raise the risk of heart failure in women with hormone receptor positive breast cancer. Risk assessment of immediate and subsequent heart disease events is essential when planning cardiac surveillance programs and potential prophylactic pharmacotherapy following breast cancer. We present the heart disease risks in a cohort that is representative of the general breast cancer population through long-term follow-up. Based on adjuvant treatments and time since diagnosis, we wanted to specifically determine the risk of heart disease [4].

Description

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 Breast Malignant Growth Register has close to 100 percent accuracy and provides detailed information on cancer and treatment characteristics, normal development on locoregional repeats, and distant metastases. The breast cancer cohort is described in greater detail elsewhere. We randomly selected up to ten women from the general female population of the Stockholm-Gotland region, matched by birth year, to compare the risk of heart disease following a breast cancer diagnosis. We included all patients between the ages of 25 and 75 with non-metastatic breast cancer (stages I–III). Each reference was cancer-free and still alive on the index date—the date the matched patient was diagnosed with breast cancer [5].

The following heart conditions (ICD-10) were identified by relevant ICD (International Classification of Disease) codes in the Swedish Patient Register and the Cause of Death Register: Arrhythmias (I47–I49, ICD-9:427), as well as ischemia (ICD-10: 428A, 428B, and 428X) Our outcome definition included both inpatient and outpatient diagnoses (except for myocardial infarction, which was solely based on inpatient and cause of death records). To guarantee the specificity of the studied outcomes, the analyses only considered primary diagnoses and not underlying diagnoses [4].

The Stockholm-Gotland Breast Cancer Register provided us with details regarding the treatment for breast cancer. The Swedish Endorsed Medication Register does not cover information on treatment with trastuzumab, so HER-2 energy was used as an intermediary when no library information on trastuzumab was available during this time period (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 the use of tamoxifen and/or aromatase inhibitors was classified because radiotherapy to the left breast has been linked specifically to heart problems, it was categorized according to tumor laterality (left vs. right). Two distinct tumors were coded in this analysis. Chemotherapy

regimens based on anthracycline, anthracycline plus taxane, cyclophosphamide, methotrexate, and fluorouracil (CMF), and cyclophosphamide were all coded [3].

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. This information is included in the Stockholm Breast Cancer Register. Other details include the date of diagnosis, the patient's menopausal status at the time of diagnosis, and the type of surgery (breast conserving surgery versus mastectomy). A widely used method for classifying chronic comorbid conditions is the Charlson comorbidity index (CCI) score. To account for the potential confounding effect of tobacco use, chronic pulmonary disease, and hypertension on the associations, we further identified associated diagnoses prior to cancer using ICD codes from the patient register. In order to compare the risk of heart disease between breast cancer patients and the matched cohort, we conducted statistical analyses with a flexible parametric model (FPM) that used the time since the index date as the underlying time scale. The FPM, which is comparable to the Cox proportional hazards model, provides a measure of association in the form of the hazard ratio (HR). At quintiles of the event times in our study, a restricted cubic spline with five degrees of freedom (four internal and two boundary knots) was used to calculate the baseline hazard. The main advantage of FPM is that it is possible to fit non-relative risks by adding a second spline that communicates with time. The frailty's regression coefficients and variance were estimated using the maximum penalized marginal likelihood approach, taking into account the correlation between the matched clusters. The model used random effects caused by a term for shared weakness. Aalen-Johansen estimation was used to calculate the cumulative incidence of heart disease in breast cancer patients and matched reference individuals, taking into account competing events from other causes of death [1].

We then looked into the relationship between adjuvant therapy and breast cancer patients' risk of heart disease using Cox proportional hazards models. Menopausal status at diagnosis, age and year of diagnosis (model 1), stage of cancer, type of surgery, CCI score, hypertension, chronic pulmonary disease, and tobacco use were all adjusted in these analyses. All treatment-specific models were mutually adjusted for adjuvant therapies. The analysis, which compared left-sided, right-sided, and both-sided breast cancer, only included patients receiving radiotherapy due to the possibility of radiotherapy administration selection bias. Multiple imputation and chained equations were used to deal with the treatment categories for which there was no data. The missing data were replaced by ten rounds of imputations, and the imputation model included all covariates. We divided the analysis into two distinct follow-up periods because of the treatment's time-dependent effect: within the first ten years following a breast cancer diagnosis and beyond [2].

In a population-based setting, we demonstrated that compared to matched reference individuals from the general population, breast cancer patients had significantly higher rates of heart disease. Even after a decade had passed since diagnosis, the risk of heart failure and arrhythmia remained elevated. Heart failure was independently linked to treatment with aromatase inhibitors, trastuzumab, and anthracycline-taxane-based regimens. Aromatase inhibitor therapy was also linked to ischemic heart disease. Breast cancer patients had a higher risk of heart failure and arrhythmia when compared to the matched reference individuals

from the general population. This risk is comparable to the risk of heart failure found in a previous Dutch study. This suggests that Europe can benefit from our findings. However, these findings should not be applied to older patients with more comorbidity because the patients in our cohort ranged in age from 25 to 75 [5].

Conclusion

This review demonstrates that, in contrast to everyone else, women with benign growth in the scrotum face increased risks of cardiovascular disease, such as arrhythmia and cardiovascular breakdown. The short-term risk of ischemic heart disease decreased after one year of diagnosis. However, it appears that the increased risk of heart failure and arrhythmia persists after ten years have passed since diagnosis. When systemic adjuvant therapies are used, the risk of heart disease rises. The risk estimates found in this study can be used in oncology practices to make decisions about adjuvant therapy and patient counseling.

Acknowledgement

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Conflict of Interest

None.

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