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Original Research

Long-term outcome of cardiac function in a population-based cohort of breast cancer survivors: A cross-sectional study

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Abstract ***Background:*** Chemotherapy and radiotherapy for breast cancer may lead to cardiac dysfunction, but the prevalence of long-term echocardiographic evidence of cardiac dysfunction is unknown among survivors.
Methods: In a cross-sectional study in primary care, we included 350 women who survived breast cancer for at least 5 years after diagnosis (treated with chemotherapy and/or radiotherapy) and 350 matched women (age and primary care physician). The primary outcome was cardiac dysfunction, defined as a left ventricular ejection fraction (LVEF) < 54% and an age-corrected decreased left ventricular (LV) diastolic function. Secondary outcomes included serum N-terminal pro B-type natriuretic peptide (NT-proBNP) levels, newly diagnosed cardiovascular diseases and cardiovascular medication.
Results: The median age at diagnosis was 63 (interquartile range (IQR) 57–68) years for the breast cancer survivors. Median follow-up after diagnosis was 10 (IQR 7–14) years. LVEF < 54% was present in 52 (15.3%) survivors and 24 (7%) controls (OR 2.4, 95%CI 1.4–4.0), but there was no significant increased prevalence of either LVEF < 50% or LV

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diastolic dysfunction. Serum NT-proBNP levels were increased, cardiovascular disease was more frequently diagnosed and cardiovascular medication use was more frequent among survivors compared with controls. These associations remained after adjustment for relevant covariates at diagnosis and at follow-up.

Conclusions: In the long term, breast cancer survivors are at increased risk of mild LV systolic dysfunction, increased NT-proBNP levels, and cardiovascular disease compared with matched controls, even after adjustment for cardiovascular risk factors. Previous breast cancer treatment with chemotherapy, radiotherapy or both should be considered when assessing a patient's cardiovascular risk profile.

1. Introduction

Breast cancer is the most common cancer among women, with approximately 0.5 million women affected annually in Europe [1,2]. Courtesy of screening programs and advances in cancer treatment, the 5-year overall survival rates have increased to 82% [3]. Although adjuvant therapies like anthracycline-based chemotherapy, trastuzumab, and radiotherapy are very effective, they may cause cardiac dysfunction decades after treatment [4]. This late cardiac dysfunction can remain subclinical because of its gradual onset and presentation with vague symptoms. Since the prevalence of subclinical cardiac dysfunction is unknown among long-term survivors of breast cancer, and no interventions have been established to manage it, there are no specific follow-up recommendations. Timely diagnosis of cardiac dysfunction is important because early treatment of associated risk factors may prevent further deterioration and improve prognosis [5].

Previous long-term studies among adult female breast cancer survivors have focussed on the frequency of only diagnosed cardiac dysfunction, which may have underestimated the prevalence of cardiac dysfunction [4,6–10]. By contrast, studies in selected hospital populations may have overestimated the prevalence of cardiac dysfunction in these women [11–14]. This is exacerbated by the lack of controlled long-term studies assessing the incidence of undiagnosed cardiac dysfunction in adult female breast cancer survivors with echocardiographic data in non-hospital settings [15]. Therefore, we assessed the prevalence of long-term echocardiographic-based cardiac dysfunction among breast cancer survivors treated with chemotherapy (with or without radiotherapy) or radiotherapy only, and compared that with the prevalence of cardiac dysfunction among matched controls in a primary care setting.

2. Participants and methods

2.1. Study design

We performed a cross-sectional, population-based study to assess the frequency of cardiac dysfunction in a primary care setting. All inhabitants of the Netherlands are enlisted in an electronic record of a primary care physician (PCP), who registers everything according to International Classification of Primary Care (ICPC) [16] and Anatomical Therapeutic Chemical (ATC) classification codes [17].

Relevant data were retrieved from patients' medical records at primary care practices and were entered into a separate, anonymous, password-protected database. In practices contributing to data registries, we were able to retrieve information from non-respondents. The medical ethics committee of the University Medical Center Groningen (UMCG) approved this study, and all participants gave written informed consent. The study was also registered at clinicaltrials.gov [ID:NCT01904331].

2.2. Participants

Women were considered breast cancer survivors if they were diagnosed with breast cancer stage I–III, had been free of disease for at least 5 years, and were included from the electronic patient records of 80 PCPs in the north of the Netherlands. When women had been diagnosed with a local/locoregional recurrence of breast cancer, they were included if they had been free of disease for at least 5 years. The inclusion criteria were treatment for breast cancer with chemotherapy, radiotherapy or both. The exclusion criteria were metastatic disease at time of breast cancer diagnosis, breast cancer treatment after 80 years of age, and treatment for other types of cancer. For each included survivor, a randomly selected control was invited from the same PCP, from the same age (±1 year), but without a history of cancer or cancer treatment (chemotherapy or radiotherapy). We excluded women with severe mental or physical illness from both groups when they were not able to come to the university hospital according to their PCP. Compliance with the inclusion and exclusion criteria was checked using the electronic patient records and checked with the PCP.

2.3. Assessments and procedures

For all women, we collected data based on the ICPC codes for cardiovascular (CV) risk factors and