Radiotherapy and Oncology 123 (2017) 299–305

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Heart disease after breast cancer

Risk of heart disease in relation to radiotherapy and chemotherapy with anthracyclines among 19,464 breast cancer patients in Denmark, 1977–2005

Jens Christian Rehammar [a,b], Maj-Britt Jensen [c], Paul McGale [d], Ebbe Laugaard Lorenzen [a,b], Carolyn Taylor [d], Sarah C. Darby [d], Lars Videbæk [e], Zhe Wang [d,f,1], Marianne Ewertz [a,b,*,1]

[a] Department of Oncology, Odense University Hospital; [b] Institute of Clinical Research, University of Southern Denmark; [c] Danish Breast Cancer Cooperative Group Secretariat, Copenhagen University Hospital, Rigshospitalet, Denmark; [d] Nuffield Department of Population Health, University of Oxford, United Kingdom; [e] Department of Cardiology, Odense University Hospital, Denmark; [f] Medical Research Council Population Health Research Unit, University of Oxford, United Kingdom

ARTICLE INFO

Article history:
Received 7 August 2016
Received in revised form 23 February 2017
Accepted 10 March 2017
Available online 30 March 2017

Keywords:
Breast cancer
Heart disease
Radiotherapy
Anthracyclines

ABSTRACT

Background and purpose: The risk of heart disease subsequent to breast cancer radiotherapy was examined with particular focus on women receiving anthracycline-containing chemotherapy.
Material and methods: Women diagnosed with early-stage breast cancer in Denmark, 1977–2005, were identified from the register of the Danish Breast Cancer Cooperative Group, as was information on cancer-directed treatment. Information on heart disease was sought from the Danish National Patient and Cause of Death Registries. Incidence rate ratios were estimated comparing left-sided with right-sided cancer (IRR, LvR), stratified by calendar year, age, and time since breast cancer radiotherapy.
Results: Among 19,464 women receiving radiotherapy, the IRR, LvR, was 1.11 (95% CI 1.03–1.20, $p = 0.005$) for all heart disease and among those also receiving anthracyclines the IRR, LvR, was 1.32 (95% CI 1.02–1.70, $p = 0.03$). This risk was highest if the treatment was given before the age of 50 years (IRR, LvR, 1.44, (95% CI 1.04–2.01) but there was no significant trend with age or time since treatment.
Conclusions: Radiotherapy for left-sided breast cancer is associated with a higher risk of heart disease than for right-sided with the largest increases seen in women who also received anthracycline-containing chemotherapy.
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The benefits of adjuvant radiotherapy for breast cancer have been demonstrated in randomized trials and include a substantial reduction in disease recurrence and a moderate reduction in breast cancer mortality after either breast conserving surgery or mastectomy with axillary dissection in axillary node-positive patients [1,2]. However, in these trials the overall benefit from radiotherapy was reduced by an increased mortality from heart disease among women randomized to radiotherapy [3].

Women irradiated for left-sided breast cancer receive higher cardiac doses than women irradiated for right-sided breast cancer. In a previous study of almost 35,000 breast cancer patients from Denmark and Sweden for whom adjuvant radiotherapy was indicated, an increased incidence of all heart disease, and also of acute myocardial infarction, angina, pericarditis, and valvular heart disease was reported in women with left-sided breast cancer compared to women with right-sided breast cancer [4]. The Danish women in that study were diagnosed with breast cancer during 1977–2000 and followed to 2006. For these women, the predominant chemotherapy was cyclophosphamide, methotrexate and fluorouracil (CMF).

Anthracyclines, in the form of epirubicin, were first introduced into adjuvant chemotherapy for breast cancer in Denmark in 1990 as part of the DBCG 89D-trial [5]. Anthracyclines have been demonstrated to reduce breast cancer recurrence and mortality [6] but are cardiotoxic, increasing the risk of cardiomyopathy and congestive heart failure [7,8]. Women with pre-existing heart disease, or who are at increased risk of heart disease, have a lower threshold for developing cardiotoxicity and are unlikely to receive adjuvant chemotherapy with anthracyclines. Therefore, the harmful effect of anthracyclines on the heart cannot be assessed by comparing women who did and did not receive it outside a randomized trial. However, it is possible to investigate whether the effect of radiotherapy on the heart is increased, when

* Corresponding author at: Department of Oncology, Odense University Hospital, Sdr. Boulevard 29, DK-5000 Odense, Denmark.
E-mail address: Marianne.ewertz@rsyd.dk (M. Ewertz).
[1] Joint last authors.

http://dx.doi.org/10.1016/j.radonc.2017.03.012
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anthracyclines were also given, by comparing the incidence of heart disease in women with left-sided and right-sided breast cancer who received both radiotherapy and anthracyclines.

Few women diagnosed with breast cancer prior to 2000 received anthracyclines, so the previous cohort study provided little information regarding the effect of anthracyclines in addition to radiotherapy. We have therefore extended this Danish cohort to include breast cancer patients diagnosed up to the end of 2005 and followed for cardiac events until the end of 2013. In addition, we have obtained information on which women were actually given radiotherapy, rather than radiotherapy just being indicated, and also on which women were actually given chemotherapy and on the type of chemotherapy they received. The main aim of this study is to assess the risk of heart disease following breast cancer radiotherapy, especially among women who also received anthracycline-containing chemotherapy.

Methods

Material

Since 1977, the Danish Breast Cancer Cooperative Group (DBCG) has maintained a register of all women diagnosed with early-stage breast cancer in Denmark [9]. All Danish hospitals involved in the diagnosis and treatment of breast cancer patients report to the DBCG and its register is more than 95% complete. Women diagnosed with early-stage breast cancer from June 1977 to December 2005 were identified from the DBCG register. Women were excluded if they had bilateral cancer or cancer of unknown laterality, had a previous diagnosis of invasive cancer (apart from non-melanoma skin cancer), did not undergo surgery (e.g. had biopsy only), were diagnosed with breast cancer after emigration from Denmark or were aged less than 20 years or more than 80 years at diagnosis. Information on tumour characteristics and details of therapies actually received was also obtained from the DBCG register. Using the unique personal identification numbers issued to all Danish citizens, the DBCG register was linked with the Danish Register of Causes of Death (RCD) [10] for deaths since 1977, and the Danish National Patient Register (NPR) [11] for in-patient diagnoses since 1977 and outpatient diagnoses since 1995. Information was complete up to 31 December 2013. Information on prior cardiac disease, defined as ICD10-codes I00-I52 (or the corresponding ICD8-codes) at least 30 days before breast cancer diagnosis, was identified from the NPR.

The study was approved by the Danish Data Protection Agency and by the Danish Health and Medicines Authority.

Statistical analysis

Descriptive analyses were conducted by tabulating the total number of women, and the number who received radiotherapy, according to breast cancer laterality and each of a number of other characteristics. For every value of each characteristic, a Mantel–Haenszel X^2-test of whether the percentage given radiotherapy was the same for women with left-sided and right-sided cancer was conducted [12]. For further analyses, each woman's contribution to the person-years at risk was calculated from six months after the date of breast cancer diagnosis and until the earliest of: diagnosis of any heart disease, 90th birthday, death, emigration, or 31 December 2013. For each endpoint of interest (all heart disease, ischemic heart disease, etc.) the total number of observed events and the person-years at risk were tabulated by calendar year of radiotherapy (starting from 1977–1980, then in 5-year groups), age at radiotherapy (starting from 20–24, then in 5-year groups) and time since radiotherapy (in 5-year groups). Tabulations were made for all women combined and for women in various different treatment categories. For women given radiotherapy, separate tabulations were made according to age at radiotherapy and years since radiotherapy. Incidence rate ratios comparing women in different categories, stratified by year, age, and time since breast cancer radiotherapy (all in 5-year groups), were estimated by logistic regression. To account for the differing numbers of women with left-sided and right-sided breast cancer, a variable taking the value of the ratio, left versus right, of the number of years at risk was included in the model, with the coefficient constrained to one. Tests of whether an individual rate ratio differed from one, of the homogeneity of the rate ratio across several different groups of women (for example those receiving different adjuvant medical treatments), and also tests for a trend in the rate ratio across several groups of women were based on the logarithms of the estimated rate ratios and their estimated variances. Calculations were performed using Stata version 13 [13]

Results

Between 1977 and 2005, 71,423 women were registered with a diagnosis of breast cancer by the DBCG. A total of 11,267 patients were excluded, leaving 60,156 women (Fig. 1). These women accrued 817,212 person-years, with a median follow up of 10.5 years (interquartile range 4.5–16.3 years).

When all 60,156 women were considered, the incidence rate ratio comparing women with left-sided breast cancer to women with right-sided breast cancer (IRR, LvR) for all heart disease was 1.05 (95% confidence interval (CI) 1.01–1.09, $p = 0.01$, Table 1). When the women were subdivided according to radiotherapy status, the IRR, LvR for the 19,464 for who received radiotherapy, was higher, at 1.11 (95% CI 1.03–1.20) and the significance level was more extreme ($p = 0.005$). In contrast, among women whose status was recorded in the DBCG as radiotherapy not indicated, radiotherapy indicated but not recorded, or radiotherapy unknown, the IRRs, LvR, were closer to unity and none were significantly increased.

Among the 19,464 women (32.4%) who received radiotherapy (Table 2) slightly fewer had left-sided than right-sided breast cancer (32.0% vs 32.7%) and, with such large numbers, this 0.7% difference was statistically significant ($p = 0.05$). When the analysis was repeated separately for women with different characteristics, differences of at least 1% in the proportion given radiotherapy for left-sided versus right-sided disease were seen for women who were: aged <50 years (1.0%), aged 70–79 years (1.1%), node positive (1.2%), given anthracyclines (1.9%), and for women given other types of chemotherapy (2.3%). However, as the numbers of women in the individual categories of these characteristics were smaller, the differences were, in most cases, not statistically significant. Among 4770 women who had prior heart disease recorded in the NPR, the percentage of women given radiotherapy was identical for women with left-sided and right-sided breast cancer. Among 3564 women receiving both radiotherapy and anthracyclines, chemotherapy dose was available for 94%, all receiving epirubicin. The median number of cycles was 7 (range 1–10), with a mean cumulative dose of 721 mg, corresponding to 410 mg/m^2 of epirubicin. Anthracycline dose was unavailable for the remaining 6%, who received either epirubicin or doxorubicin.

When the 19,464 women who received radiotherapy were subdivided according to patient and tumour characteristics, there was no significant heterogeneity in the IRR, LvR according to year of breast cancer radiotherapy, age at breast cancer radiotherapy, nodal status, surgery, prior heart disease or adjuvant medical treatment given ($p = 0.33$) (Table 3). There were, however, some notable differences. For women given breast radiotherapy during 2001–2005 (i.e., the period in which anthracyclines were given) the IRR, LvR was significantly increased (IRR, LvR: 1.15, 95% CI

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