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Research Paper

Coronary artery calcifications on breast cancer radiotherapy planning CT scans and cardiovascular risk: What do patients want to know?

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ABSTRACT

Background: Coronary artery calcifications (CAC) is a strong predictor of cardiovascular disease (CVD), which can be automatically quantified on routine breast radiotherapy planning computed tomography (CT) scans. Around 8% of patients have (very) high CAC scores and corresponding increased risks of CVD.
Aim: This study explores whether, how, and under what conditions women with breast cancer want to be informed about their CAC-based CVD risk.
Methods: A cross-sectional survey study was conducted in a random sample of UMBRELLA, a prospective breast cancer cohort. Participants (n = 79) filled out a questionnaire about their knowledge on the CVD risk following breast cancer, their interest in being informed about their CVD risk based on CAC score, and preferences on how they would want to receive this information.
Results: Most participants (66%) were not aware that the presence of CAC indicates an increased CVD risk. Participants indicated that they were not or only slightly aware of the risk of treatment-induced cardiotoxicity (48%), and that the risk of cardiotoxicity was higher in patients with pre-existing CVD risk factors (82%). The vast majority (90%) indicated that they want to be informed about in increased CAC-based CVD risk.
Conclusions: The majority of patients with breast cancer wants to be informed about their CAC-based CVD risk. With the majority of patients with breast cancer undergoing radiotherapy, and with low cost and automated options for accurate CAC measurement in planning CT scans, it is important to develop strategies to manage patients with an increased CAC-based risk of CVD.

1. Introduction

Both the increased breast cancer incidence and improved survival rates have resulted in a large group of breast cancer survivors. However, due to shared risk factors and to oncological treatments, some survivors are at increased risk for other medical conditions, including cardiovascular disease (CVD) [1,2]. Cardiotoxic oncological therapies include left-sided radiotherapy and certain systemic therapies (i.e., chemotherapy, endocrine therapy, and targeted therapy) [3–6]. Patients treated for breast cancer and with pre-existing cardiovascular risk factors have the highest risk of treatment-induced cardiotoxicity [7,8].

Most patients with breast cancer are treated with adjuvant whole breast radiotherapy and underwent a low-dose planning CT scan of the chest. As the heart and coronary arteries are visualized in these scans, the amount of calcium in the coronary arteries (CAC) can be quantified into an Agatston score [9,10]. CAC is an independent predictor of CVD

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[9,11,12]. CAC scoring is usually performed manually in dedicated cardiac CT scans, which is a tedious and time-consuming task, especially when the image quality is suboptimal such as in non-gated scans or when many scans need to be scored. Our research group developed a deep-learning algorithm for automated CAC scoring on radiotherapy planning CT scans [10,13]. This can be used as a fast and low-cost tool to identify patients with breast cancer at increased risk of CVD, without any additional exposure of patients to radiation.

In a recent study, we calculated CAC scores on 15,915 planning CT scans of patients with non-metastatic breast cancer using a deep learning algorithm [10,14]. CAC was present in 31% of the patients. After a median follow-up of 51 months, 5% of the patients without CAC were hospitalized or died of CVD compared to 28% of patients with a very high CAC score (score of >400 Agatston units). After adjustment for age and calendar year, patients with breast cancer and CAC scores >400 had a 3.4 (95%CI 2.8–4.2) times higher CVD risk. The association was stronger in patients treated with anthracyclines (i.e., a 5.8 (95%CI 3.0–11.4) times higher risk) [14]. Patients with a high CAC score and associated increased CVD risk may benefit from cardiovascular work-up to identify and treat (unknown) risk CVD risk factors (such as diabetes, hypertension and hypercholesterolemia) and from lifestyle advise (targeting physical activity, smoking cessation and diet).

This study explores whether, how, and under what conditions patients with breast cancer want to be informed about their CAC-based CVD risk. In addition, this study explores knowledge of patients on risk of CVD following breast cancer.

2. Materials and methods

This cross-sectional study was conducted in a random sample of the 'Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaLuAtion' (UMBRELLA) [15]. UMBRELLA includes patients (≥18 years) with histologically proven ductal carcinoma in situ or invasive breast cancer, who were irradiated in the University Medical Center (UMC) Utrecht in the Netherlands. Participants within UMBRELLA provided informed consent for the collection and use of clinical data and patient-reported outcomes for research purposes. UMBRELLA (ClinicalTrials.gov: NCT02839863) was approved by the Medical Ethics Committee of the UMC Utrecht. The current study was exempted from review.

For the current study, an unselected convenient sample of 290 patients was invited to fill out a questionnaire anonymously. Ninety patients were asked to fill out the questionnaire during a patient day in October 2018 that was organized for UMBRELLA participants. A random sample of 200 participants was sent an email in May 2019, explaining the purpose of the current study and inviting them to participate within the present study. Upon agreement, participants received a comprehensive questionnaire that was developed for this study.

The questionnaire consisted of 13 questions (see supplementary material). Their interest in being informed about their CAC-based CVD risk, as measured on the radiotherapy planning CT scan, was assessed on a 5-point Likert scale ranging from 1 (certainly not) to 5 (certainly yes). Reasons for and against receiving information about the individual CAC-based CVD risk were assessed using multiple response questions, where multiple reasons could be ranked in order of importance. Preferences regarding the way of receiving information about their individual CAC-based CVD risk were assessed. Participants' knowledge on, and concerns about, the risk of treatment-induced cardiotoxicity and the relation between the presence of CAC and CVD risk were assessed on a 5-point Likert scale ranging from 1 (not aware/not concerned) to 5 (completely aware/completely concerned). Participants had the opportunity to add comments, or to elaborate on their answers at the end of the questionnaire. Data were analyzed and summarized using descriptive statistics.

3. Results

In total, 79 (female) participants completed the questionnaire (response rate: 27%). Mean age was 59.0 (SD = 9.1) years. Time since radiotherapy intake was known for 61 (77%) of the participants: About one-third of these participants had their radiotherapy intake within the last year, 23% had their intake between 1 and 2 years ago, and 46% of the participants had their radiotherapy intake more than 2 years ago.

The vast majority (90%; n = 71/79) indicated that they wanted to be informed about their individual CAC score, even in the absence of evidence-based treatment to reduce the risk (Fig. 1A). The main reason for participants for informing about their CAC score was to obtain a comprehensive picture of their health (Fig. 1B). The second most common reason was to have the option to consider adaptations towards less toxic breast cancer therapy. One participant expressed that the knowledge about the CAC score would motivate her to improve her lifestyle. Among the eight patients who did not (or maybe) want to be informed, the main reason against informing was the current insufficient knowledge on the relationship between CAC detected on radiotherapy planning CT scans and the CVD risk (Fig. 1C). One participant pointed that the information can cause stress in case of an increased CVD risk.

Most participants preferred to be informed by their breast cancer physician about their CAC score (n = 59/74) in a face-to-face setting (n = 61/74; Fig. 2). They also indicated that they would prefer to receive additional information in a leaflet (n = 44/74) or website (n = 36/74).

About half of the participants (48%; n = 38/79) were not or were only slightly aware of the risk of treatment-induced cardiotoxicity (Table 1). Almost half of these participants found the fact that breast cancer treatment may be associated with cardiotoxicity (extremely) concerning (42%, n = 15/38). Among the participants who were aware of the risk of treatment-induced cardiotoxicity, 35% (n = 14/41) found this (extremely) concerning. Participants commented that breast cancer treatment took precedence over the potentially higher CVD risk, and that no treatment was no option. In addition, they also commented that information about cardiotoxicity given active breast cancer treatment might have escaped their attention because of so many other things on their mind.

Eighty-two percent of the participants (n = 65/79) were not or were only slightly aware that the risk of treatment-induced cardiotoxicity was higher in patients with pre-existing cardiovascular risk factors, and 42% (n = 27/65) of these patients found this (extremely) concerning (Table 1). Finally, two-thirds (n = 52/79) of the participants did not know or were slightly aware that the presence of CAC is associated with an increased CVD risk (Table 1). Thirty-four percent of these participants (n = 17/52) found this (extremely) concerning.

4. Discussion

CAC scores are strongly associated with the risk of CVD. Identification of patients with breast cancer and a CAC-based increased CVD risk before the start of radiation therapy might allow mitigation of this risk by adoption of targeted cardio-preventive interventions (e.g. lifestyle changes, pharmaco-prevention, close monitoring for early detection of cardiotoxicity). This study shows that most breast cancer survivors were not aware that presence of CAC indicates a higher CVD risk. The vast majority found this information (extremely) concerning. In addition, the majority indicated that, they wanted to be informed about their CVD risk, preferably in person, by their breast cancer physician.

Identification of patients with breast cancer at increased risk of CVD allows mitigation of the individual risk. Currently, there is no strong evidence supporting a strategy to manage or treat an increased CAC score and mitigate the associated CVD risk. Such a strategy may include referral to a dedicated cardio-oncology outpatient clinic for cardiovascular workup and risk evaluation, initiation of cardioprotective pharmacotherapy and/or personalized lifestyle recommendations, and if possible, switching to less cardiotoxic treatment regimen. However, it is

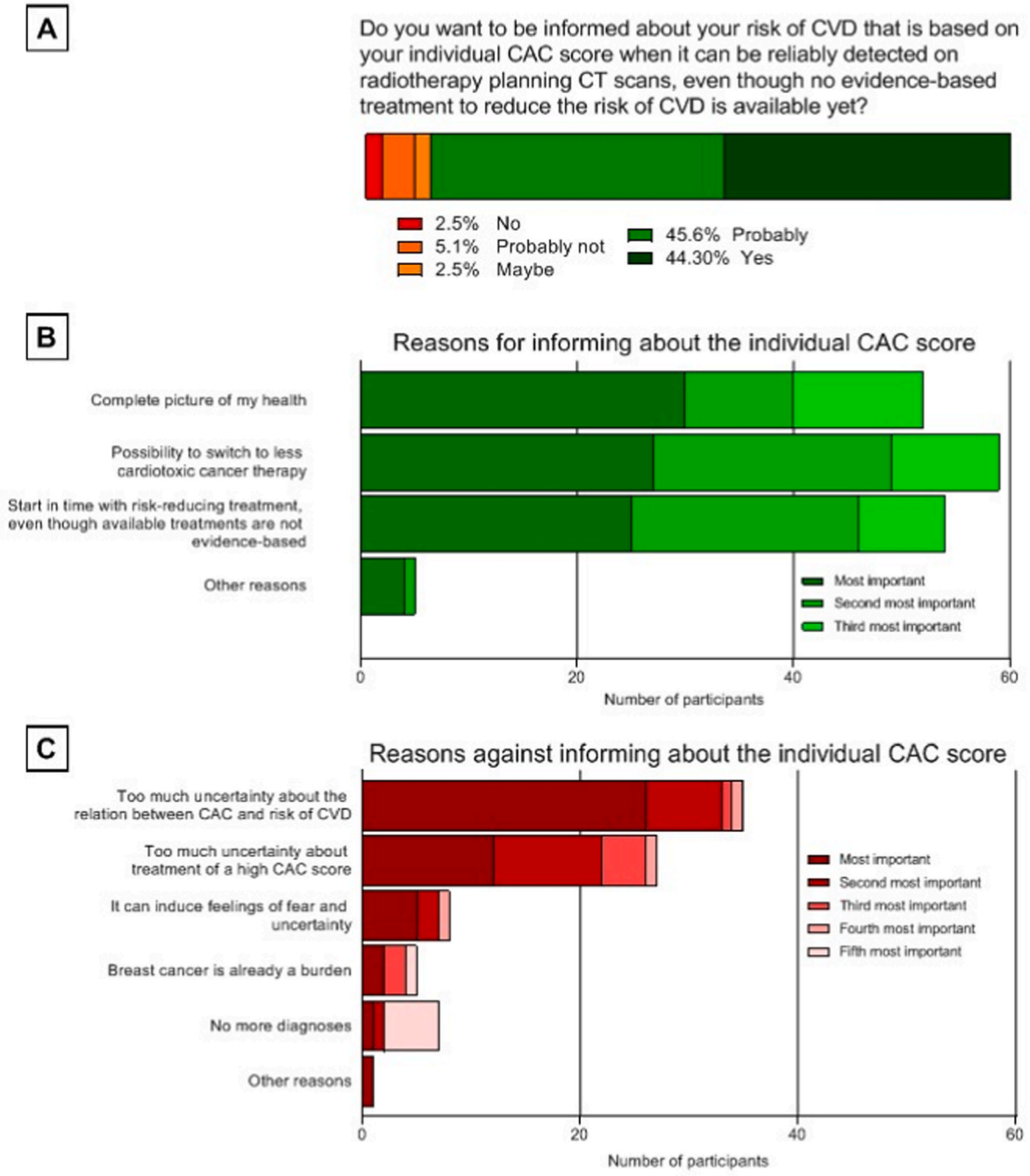

Fig. 1. Interest in, and reasons for and against, being informed about an increased CVD risk that is based on CAC scores as measured on radiotherapy planning CT scans.

unknown if the benefits of de-escalation of treatment in order to reduce the risk of CVD (e.g. changing radiotherapy technique or target volumes, or chemotherapy dose reduction) outweigh the potential risks in terms of tumor control and prevention of breast cancer recurrence. Therefore, more research is needed on strategies to manage and treat patients with an increased CAC-based CVD risk.

Disclosure of the CAC score may induce anxiety and distress. In addition, patient advocates indicated that it might induce guilt in patients who are unable to initiate steps to improve their cardiovascular risk profile and lifestyle. Further research is warranted to study the effect of disclosure of the CAC-based CVD risk in patients that are treated for breast cancer.

Participants preferred to receive face-to-face information from their breast cancer physician about their individual CVD risk that is based on their CAC score. In addition, they indicated that they would prefer to receive additional information in a leaflet. As participants indicated, at that moment (i.e., shortly after breast cancer diagnosis and/or during treatment), they had too much on their mind. At that stage, patients may not be able to process or retain all the information that is provided [16].

The participation rate in this study was 27%. The invitation to participate in this survey study was very informal and participants had to actively express their willingness to participate and upon agreement, they received the questionnaire. Therefore, the response rate might be lower compared with studies that directly send the questionnaire to participants. It may be likely that survey response was associated with individual characteristics such as age, time since diagnosis or degree of

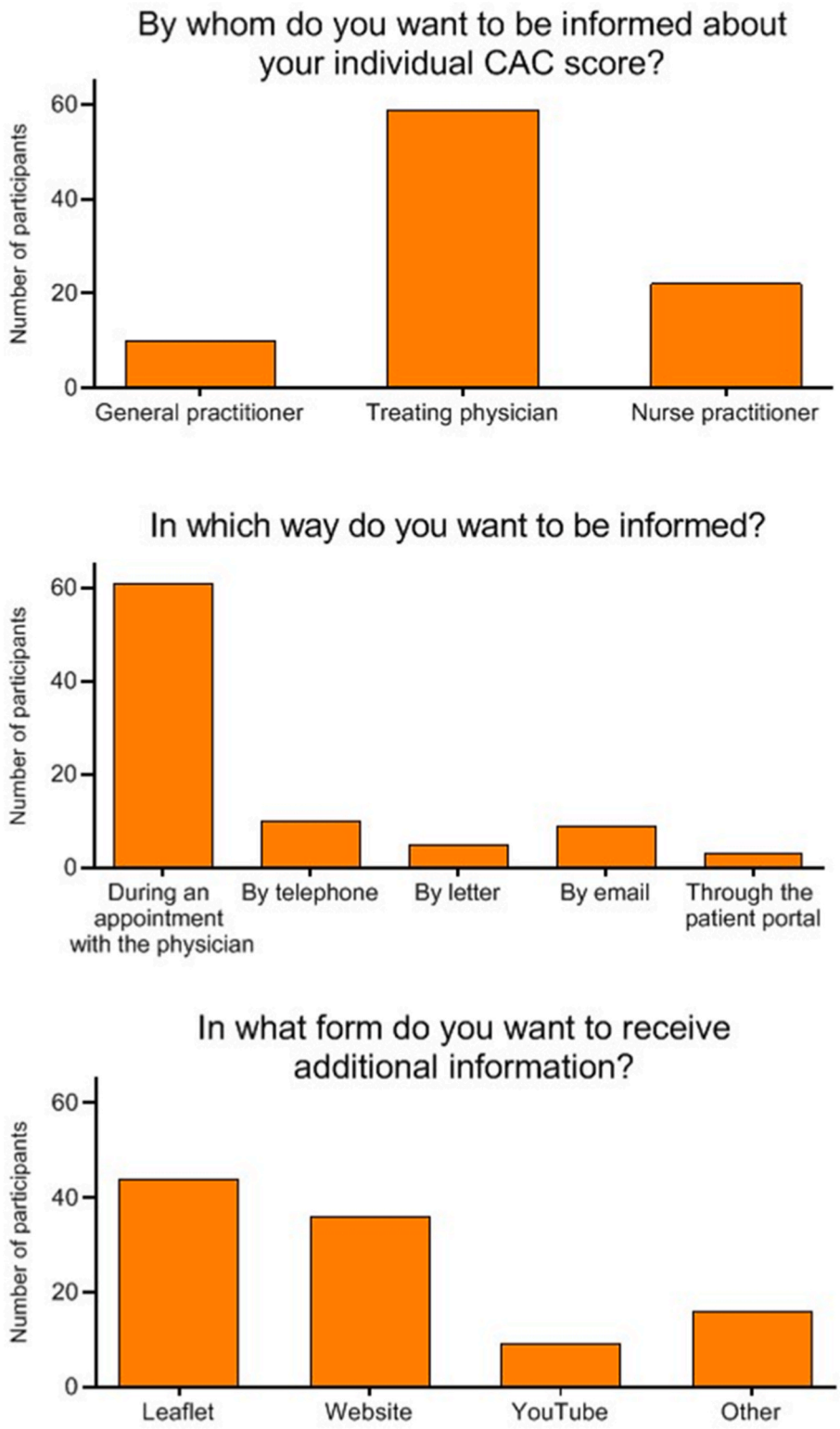

Fig. 2. Preferences for receiving information. Five participants did not answer these questions. Participants could provide more than one answer. Numbers did not add up to the total number of participants (N = 74).

concern regarding cardio-toxicity. This selective response may bias the outcomes of the study.

We acknowledge that this study was performed in participants who were already treated for breast cancer. At the moment they filled out the questionnaire, they did not had to deal with a recent breast cancer diagnosis or undergo treatment. Therefore, questions were hypothetical and answers may differ from those given by patients shortly after diagnosis. It might be that reasons for not wanting to be informed about their CAC score and CVD risk weigh more heavily shortly after breast cancer diagnosis, and hence fewer patients might want to be informed at time of breast cancer diagnosis.

Table 1
Participants' knowledge of the risk of treatment-induced cardiotoxicity and the relation between the presence of CAC and risk of CVD.

Breast cancer treatment may increase the risk of damage to the heart and blood vessels.			
Were you aware of this?		**Is this a matter of concern?**	
	n/N (%)		n/N (%)
Not or slightly aware	38/79 (48)	Yes	15/36 (42)[a]
Aware	41/79 (52)	Yes	14/40 (35)[b]
Patients with an increased risk of cardiovascular disease before the start of breast cancer treatment have the highest risk of cardiotoxicity.			
Were you aware of this?		**Is this a matter of concern?**	
	n/N (%)		n/N (%)
Not or slightly aware	65/79 (82)	Yes	27/65 (42)
Aware	14/79 (18)	Yes	5/14 (36)
Coronary artery calcifications are related to the risk of cardiovascular diseases.			
Were you aware of this?		**Is this a matter of concern?**	
	n/N (%)		n/N (%)
Not or slightly aware	52/78 (67)[a]	Yes	17/50 (34)[a]
Aware	26/78 (33)[a]	Yes	11/25 (44)[b]

Answers on the 5-point Likert scales were dichotomized into "Not or slightly aware" (including Not at all aware, Not aware and Slightly aware) and "Aware" (including Aware and Completely aware).
Answers on the 5-point Likert scales were dichotomized into "No" (including Not at all concerned, Not concerned and Slightly concerned) and "Yes" (including Concerned and Extremely concerned).
[a] 2 missing values on this question.
[b] 1 missing value on this question.

4.1. Conclusions

To conclude, patients want to be informed about their CAC score and corresponding risk of CVD. No guidelines or recommendations for the management of patients undergoing cancer treatment with a CAC score that is associated with an increased CVD risk are available yet. Therefore, more research is needed on the feasibility, patients' acceptability, and benefits and harms of automated CAC measurement and its utilization in order to reduce CVD burden in patients treated for breast cancer.

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Author contributions

Roxanne Gal: Data curation, Formal analysis, Investigation, Project administration, Resources, Visualization, Writing – original draft. Madelijn L Gregorowitsch: Data curation, Formal analysis, Investigation, Project administration, Visualization, Writing - review and editing. Marleen J Emaus: Conceptualization, Methodology, Project administration, Writing - review and editing. Erwin LA Blezer: Data curation, Methodology, Writing - review and editing. Femke van der Leij: Methodology, Writing - review and editing. Sanne GM van Velzen: Methodology, Writing - review and editing. Julia J van Tol-Geerdink: Conceptualization, Methodology, Writing - review and editing. Ivana Išgum: Conceptualization, Methodology, Writing - review and editing. Helena M Verkooijen: Conceptualization, Funding acquisition, Methodology, Supervision, Visualization, Writing - review and editing.

Declaration of competing interest

Prof. I Išgum reports grants from the Dutch Cancer Society (KWF), Pie Medical Imaging, the Dutch Technology Foundation, the Netherlands; Netherlands Organisation for Health Research and Development, the Netherlands, and the Dutch Heart Foundation, the Netherlands, and reported being cofounder of, and shareholder in Quantib-U BV. Prof. HM Verkooijen reports research grants from the Dutch Cancer Society (KWF) and Elekta AB. The other authors made no disclosures.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2021.200113.

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