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Review Article

Cardiac morbidity & mortality in patients with breast cancer: A review

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Cardiovascular disease (CVD) and breast cancer cause substantial morbidity and mortality in women and are major public health concerns. Breast cancer survivors are at a greater risk for CVD-related mortality compared to women without breast cancer. Breast cancer and cardiovascular diseases share a number of common risk factors. Breast cancer treatments like anthracycline based chemotherapy, novel targeted therapy and radiation therapy can cause cardiotoxicity. With improvements in breast cancer prevention and treatment, there is a significant improvement in survival and this shifts focus from disease control to long term effects of treatment and quality of life. Assessing CVD and minimizing complications from cancer therapy are important treatment goals.

Key words Breast cancer - cardio-oncology - cardiotoxicity - cardiovascular diseases

Introduction

Breast cancer is one of the most common cancers among women in India[1-3], and its incidence is increasing[4]. As compared to developed countries, in India, breast cancer occurs at a younger age[3]. Early detection and advances in treatment have decreased mortality in patients with early-stage breast cancer significantly[1], and an increase in the number of breast cancer survivors is also now documented in the developed countries[5]. Cardiovascular disease (CVD), which is a leading cause of mortality in the general population globally, and also in India[6,7] is an important non-cancer risk for death in certain breast cancer survivors[8-11]. There is a paucity of cardiac morbidity and mortality data among breast cancer survivors in India.

Surgery, radiation therapy (RT), chemotherapy, endocrine and targeted therapies are the main modalities of treatment for breast cancer. The cardiotoxic effects of breast cancer treatment modalities are well documented[12]. According to the multiple hit hypotheses, patients with cancer are exposed to multiple serial or concurrent treatment-related risks which may lead to decrease in cardiovascular (CV) reserve, CVD and death[13]. This risk is multiplied further if the patient has underlying CVD risk factors or CVD. Cardiac complications during breast cancer treatment can lead to suboptimal treatment, impact morbidity and overall survival and also limit therapeutic options in case of a relapse. Prevention and management of cardiac complications during and after cancer treatment are a major challenge for clinicians managing breast cancer patients.

In this review, we discuss the CVD risk, cardiotoxicities of the commonly used anti-neoplastic drugs for breast cancer and radiation-induced heart

disease. The early detection and prevention strategies as published in the literature are reviewed and some of the challenges pertaining to the Indian population are also highlighted.

Cardiovascular disease (CVD) in breast cancer

In postmenopausal women with hormone receptor-positive early breast cancer, the predicted 10-year CVD risk was found to be equivalent to or higher than the breast cancer recurrence risk[14]. The risk of CVD in women with breast cancer with low Framingham risk score was reportedly higher as compared to women without breast cancer[15]. The risk of CVD was also high in older women who were survivors of early breast cancer[16]. After adjusting for baseline CVD risk, it was found that women with breast cancer had a higher risk of CVD mortality than those without[14]. Cardiovascular diseases account for nearly 35 per cent of non-breast cancer mortality among breast cancer survivors who were 50 yr of age and older[17]. The increased risk for CVD-related mortality in breast cancer survivors is reportedly around seven years after its diagnosis[17].

Age is a non-modifiable risk factor for CVD. With ageing population and improved survival due to advances in cancer treatment, the overlap of CVD and cancer is likely to increase[18,19]. Ageing cancer survivors may be exposed to potential long-term cardiometabolic side effects of anti-cancer therapy[20].

Breast cancer and CVD share a number of modifiable risk factors such as obesity, physical inactivity and smoking[21]. Hypertension, smoking and family history of ischaemic heart disease (IHD) are strong predictors for the development of breast cancer treatment-related cardiotoxicity[22-24] despite some studies suggesting that CVD risk factors before or at the time of breast cancer diagnosis may not be elevated relative to those without[25]. Patients who have pre-existing CVD risk factors or CVD may, however, be more likely to have worse cardiovascular outcomes after a breast cancer diagnosis[26]. Weight gain, decreased physical activity and decreased exercise tolerance can occur in breast cancer patients and these can further contribute to CVD[27].

A comprehensive clinical evaluation should be done before starting cancer treatment to determine the baseline cardiovascular risk as per standard guidelines. This will help in choosing an optimal treatment strategy for cancer. Treatment of cardiac risk factors including hypertension, diabetes and dyslipidaemia may improve overall outcomes in cancer patients on active therapy and also cancer survivors[28]. In India, we have a small albeit important issue of rheumatic heart disease, and a detailed assessment is required to assess the severity of the disease.

Cardiovascular toxicity due to cancer treatment

Chemotherapy (anthracyclines, taxanes), targeted therapies (trastuzumab, lapatinib), endocrine therapy and radiotherapy are common breast cancer treatments associated with cardiotoxicity (Table). The most frequent cardiotoxicity is asymptomatic or symptomatic left ventricular dysfunction (LVD)[29]. Other cardiovascular toxic effects include hypertension[30], thromboembolic disease[31], pericardial disease[32], arrhythmia[33,34] and myocardial ischaemia[35]. RT to chest can lead to coronary artery disease and fibrotic changes of the valves, pericardium and myocardium when the treatment field involves the heart[36].

Drug-induced cardiotoxicity:

Left ventricular dysfunction (LVD): This is the most common and most feared complication of breast cancer treatment and is largely associated with anthracyclines and trastuzumab.

Anthracyclines: Anthracyclines (doxorubicin, epirubicin) are one among the most commonly used and effective drugs in breast cancer treatment. In the past 30 years, these have become an important component of adjunctive and palliative therapy for breast cancer[37]. Anthracyclines cause irreversible cardiac dysfunction classified as type I cardiotoxicity, and can cause permanent damage at the cellular level, leading to necrosis and apoptosis of myocardial cells followed by fibrosis[38]. The cellular damage was previously considered due to the formation of toxic reactive oxygen species (ROS) causing oxidative stress with lipid peroxidation of cell membranes and vacuolization of myocardial cells and ultimately cell death[39]. Recent studies have shown that anthracyclines also inhibit topoisomerase IIb in myocardial cells, which induces DNA double-strand breaks and activation of the apoptotic programme of the heart via mitochondriopathy and increase in ROS[40].

For many decades, cancer therapy-induced cardiomyopathy was almost exclusively associated with the use of cumulative doses of anthracyclines and occurred early (within one year) or late[38]. Rarely, acute cardiotoxicity is also known to occur with anthracyclines which is due to inflammation causing

Table. Common cardiovascular toxicities seen in breast cancer patients

Cardiovascular toxicity	Class of drug	Drug	Incidence per cent
Left ventricular dysfunction	Anthracyclines/analogues	Doxorubicin	3-26
		Epirubicin	0.9-3.3
		Mitoxantrone	5
	Alkylating agents	Cyclophosphamide	7-28
	Anti-microtubule agents	Docetaxel	2.3-8
	Targeted therapy	Trastuzumab	2-28
	HER2 inhibitor		
Myocardial ischaemia	Pyrimidine analogue	Capecitabine	3-9
		Fluorouracil	1-68
		Docetaxel	1.7
		Paclitaxel	5-47
Arrhythmias	Bradycardia		
	Anti-microtubule agents	Paclitaxel	<0.1-31
	QT prolongation		
	Cyclin dependent kinase inhibitors	Ribociclib	
	HER 2 inhibitor	Lapatinib	
	Supraventricular tachyarrhythmias		
	Anthracyclines	Doxorubicin, epirubicin	
	Alkylating agents	Cyclophosphamide	
	Pyrimidine analogue	Capecitabine	
Venous thromboembolism	Endocrine therapy	Tamoxifen	

Source: Refs 27-34,36. HER, human epidermal growth factor receptor 2

myopericarditis[41]. The incidence of cardiotoxicity is three, seven and 18 per cent when patients receive a cumulative dose of doxorubicin at 400, 550 and 700 mg/m^2, respectively[42]. However, recent studies have shown that anthracycline-induced cardiotoxicity can occur at lower cumulative doses as well[43]. Epirubicin, which is a structural analogue of doxorubicin, was suggested to have a lower clinical cardiotoxicity than doxorubicin[38]; however, a recent Cochrane database review comparing doxorubicin and epirubicin did not find a statistically significant difference in heart failure incidence between the two regimens[44]. The other risk factors of anthracycline-induced cardiotoxicity include age, underlying CVD, hypertension, concomitant therapy with cardiotoxic agents (cyclophosphamide, paclitaxel and trastuzumab) and mediastinal RT[45].

Targeted therapies – trastuzumab: Trastuzumab, which is a monoclonal antibody against human epidermal growth factor receptor 2 (HER2), has improved survival in HER2-positive breast cancer by more than 30 per cent and is now a standard treatment for both HER2-positive early as well as metastatic breast cancer[46,47]. However, trastuzumab can cause myocardial dysfunction which is not dose dependent. Myocyte dysfunction caused by trastuzumab is most likely secondary to inhibition of cardiomyocyte human ErbB2 signalling, thereby interfering with their normal growth, repair and survival[48]. Cardiac dysfunction of trastuzumab is typically manifested by an asymptomatic decrease in left ventricular ejection fraction (LVEF) and sometimes by clinical heart failure and is mostly reversible (type 2 cardiotoxicity)[49].

The initial trials of trastuzumab were conducted in metastatic breast cancer. The reported incidence of cardiac toxicity for patients who received trastuzumab alone, trastuzumab and paclitaxel, and trastuzumab plus an anthracycline and cyclophosphamide were 3 to 7, 13, and 27 per cent, respectively[50]. In 2012, Moja *et al*[51] summarized findings from eight major randomized clinical trials of trastuzumab with or without anthracyclines in early breast cancer. The relative risk of developing congestive heart failure and LVEF decline with trastuzumab was 5.11 [90% confidence interval (CI) 3.00 to 8.72] and 1.83

(90% CI 1.36 to 2.47), respectively[51]. Subsequent studies showed that the risk of cardiotoxicity was less with sequential anthracyclines compared to concurrent anthracyclines without compromising cancer outcomes[52-54]. The current trastuzumab-based regimens use sequential anthracycline, and recently, no anthracycline regimens are being used in selected low-risk groups[55].

Pertuzumab is a newer anti-HER2 monoclonal antibody, and addition of pertuzumab to trastuzumab are not associated with increased cardiotoxicity[56,57]. Ado-trastuzumab emtansine which is a conjugate of trastuzumab with a microtubule inhibitor is also not reported to be associated with increased cardiotoxicity[58]. Lapatinib, a dual kinase inhibitor of HER2 and EGFR, is shown to be associated with low incidence of cardiac complications[59,33]. It can cause LVD and can rarely cause QT prolongation[33].

Anthracyclines and trastuzumab have a significant impact on cancer outcomes and are a part of most recommended systemic treatment regimens for breast cancer. The maximum dose of anthracyclines is 200-300 mg/m^2. Sequential therapy is preferred as the risk of cardiotoxicity is high with concurrent anthracycline and trastuzumab[54-56].

Cardiotoxicities other than left ventricular dysfunction (LVD): Myocardial ischaemia, and occasionally myocardial infarction, is caused by 5-fluorouracil[60], capecitabine[61]. Underlying coronary artery disease increases the risk of coronary artery spasm, but patients with normal coronaries may also develop myocardial ischaemia while being treated with these drugs. Pericarditis and pericardial effusion can be caused by anthracyclines and cyclophosphamide[32]. Malignancy is known to be associated with a prothrombotic milieu, which may be exacerbated by chemotherapy. Conventional chemotherapeutics, signalling inhibitors and endocrine cancer therapies can increase the risk of venous or arterial thromboembolism[31]. Arrhythmias either supraventricular or ventricular can frequently occur during chemotherapy. Ribociclib and lapatinib are associated with QT prolongation[60,62] (Table).

Baseline evaluation and risk stratification

Common clinical risk factors for cardiac dysfunction include 'high-dose anthracycline (cumulative dose of doxorubicin >250 mg/m^2), radiotherapy >30 Gy (where heart is in the treatment field), lower-dose anthracycline in combination with lower dose RT, treatment with lower-dose anthracycline or trastuzumab alone and presence of multiple CV risk factors (≥two risk factors, including smoking, hypertension, diabetes, dyslipidaemia, and obesity, during or after completion of therapy), older age (>60 yr) at cancer treatment, compromised cardiac function [*e.g*., borderline low LVEF (50-55%), history of myocardial infarction and moderate valvular heart disease] at any time before or during treatment' as stated in the American Society of Clinical Oncology (ASCO) practice guidelines 2017[63].

As most patients with breast cancer will be receiving combination of anthracycline, trastuzumab, paclitaxel and RT, they would be at a high risk for cardiotoxicity. Currently, there are no evidence-based risk stratification score for predicting the extent of cardiotoxicity. Genetic studies have identified some single-nucleotide polymorphisms which are associated with anthracycline-induced toxicity and trastuzumab cardiotoxicity[64,65]. Further studies are, however, required before they can be used to predict cardiotoxicity in clinical practice

Baseline evaluation and monitoring for left ventricular dysfunction: All patients should undergo a detailed clinical evaluation. A baseline electrocardiography and assessment of LVEF is recommended by all guidelines [ASCO, American Society of Echocardiography (ASE), European Association of Cardiovascular Imaging (EACVI) and European Society of Medical Oncology (ESMO)][63,66,67] before potentially cardiotoxic treatment. Two-dimensional echocardiography (2D echo) is the most common modality for LVEF assessment. 2D echo has limitations such as inter-observer variability and low sensitivity to detect small changes in LVEF, but it is easily available and can be repeated. Some guidelines also suggest LV multigated acquisition scan as an alternative imaging modality[63,66]; however, exposure to radiation is a concern[68]. LVEF assessment by 3D echo and cardiac magnetic resonance imaging (MRI) is superior to conventional 2D echo LVEF assessment by modified Simpsons method[69,70]. Patients with normal baseline cardiac evaluation are started on the planned breast cancer treatment.

For anthracyclines, routine reassessment of LV function is recommended after a cumulative dose of 250 mg/m^2 doxorubicin or its equivalent anthracycline and after approximately each additional 50 mg/m^2 and at the end of therapy[66]. As regards, trastuzumab LVEF assessment is recommended after every three months during treatment[66].

There has been a variation in the definition of cardiotoxicity over the last decade. As per the most recent ESMO guidelines 2020, 'reduction in LVEF by ≥10 per cent from baseline to LVEF <50 per cent or institution lower limit of normal in asymptomatic patients is considered potential evidence of toxicity'[67].

In case of a significant drop in LVEF, a reassessment is done after 2-3 wk. If confirmed, further anthracyclines are stopped. Patients who are symptomatic with significant decrease in LVEF should be treated with standard heart failure-specific medications as per clinical guidelines[66,67]. In asymptomatic patients with significant decrease in LVEF, guidelines suggest to consider initiation of cardioprotective treatment [angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockade or beta-blocker][66]. In case of trastuzumab, if repeat LVEF done within 3-6 wk is normal (>50%), then trastuzumab can be restarted[67]. The SAFE-HEART Study[71] has shown that, in selected cases with asymptomatic LVD, trastuzumab can be safely continued with appropriate cardioprotective treatment.

Early detection of left ventricular dysfunction: The current universal monitoring guidelines involve change in LVEF as described above[63,65,67]. A drop in LVEF indicates that myocardial dysfunction has already occurred[72]. A better tool is required for early detection of cardiotoxicity before LVEF decreases. The current focus of research in cardio-oncology is on early detection of LVD. Global longitudinal strain (GLS)[73] and some cardiac biomarkers [troponin I, B-type natriuretic peptide (BNP), N-terminal Pro-BNP and myeloperoxidase][74,75] have been studied for identifying patients at risk of cardiotoxicity.

GLS is an index of myocardial deformation and is measured by echo using 2D speckle tracking imaging[76]. Studies have shown that a significant decrease in GLS can predict the development of reduced LVEF in patients treated with anthracyclines and/or trastuzumab[73,77-79]. GLS is performed by a trained sonologist using advanced echo equipment and is preferable to be followed up at the same centre on the same machine. The ASE EACVI 2014 does recommend the estimation of GLS as a part of cardiac monitoring in patients receiving cardiotoxic treatment and a decrease in GLS >15 per cent compared with baseline GLS or an absolute decrease of >8 per cent is considered significant[66]. A meta-analysis of 21 studies, of which 13 were of breast cancer concluded that an absolute or relative decrease in GLS was predictive of chemotherapy-related cardiac dysfunction; however, due to publication bias, the cut-off could not be assessed[80].

Cardinale *et al*[74] first documented that the rise in cardiac troponins during high-dose chemotherapy can predict LVD in the future. A number of later studies, however, confirmed that an increase in plasma concentrations of cardiac troponin, especially persistent elevation, can predict the development of cardiotoxicity in patients treated with anthracyclines and trastuzumab[73,81,82]. A combination of GLS and cardiac troponin estimation during treatment have been found to be better predictor of LVEF decline in the future in some studies[82]. Some authors have also suggested that cardioprotective treatment and frequent cardiac monitoring may be considered in high-risk patients with a decrease in GLS or increase in cardiac troponin levels[67,83]. It is yet to be proven that a decrease in LVEF predicted by these early markers will predict major cardiac events in the future[84].

Prevention of left ventricular dysfunction: Cardiotoxicity, even asymptomatic, can not only negatively impact patients' cancer and cardiac outcome but may also limit their therapeutic options in future in case of a relapse. Other than limiting the cumulative dose of anthracyclines, currently, dexrazoxane is recommended to limit cardiotoxic effects of anthracycline chemotherapy in selected patients[63,85]. Liposomal doxorubicin and infusion instead of boluses is also recommended in some high-risk cases[63,86].

To mitigate cancer therapy-induced cardiotoxicity, a number of primary preventive strategies using standard anti-heart failure medications have been and are being studied. A number of ACE inhibitors (lisinopril[87], perindopril[88], enalapril[87]), angiotensin receptor blocker (candesartan[89]), aldosterone antagonist (spironolactone[87], eplerenone[87]) and beta-blockers (metoprolol[89], carvedilol[90], bisoprolol[88], nebivolol[87]) have been studied. There are also ongoing studies for primary prevention (preventing cardiac damage at the time of cancer therapy) in patients with breast cancer. Only some of these drugs singly or in combination show modest clinical benefits, probably due to patient selection bias and low event rate[87,91]. The routine use of neurohormonal antagonists for cardioprotection is not currently justified, given the marginal benefits and associated adverse events, particularly with long-term use[87]. Role of statins due to their pleotropic effects in the prevention of LVD is also being studied[87].

There is limited evidence for use of neurohormonal drugs for prevention of cardiotoxicity in cancer patients with subclinical cardiotoxicity (decreased GLS, increased troponin I) but is recommended by some guidelines[67] and should be considered on a case-to-case basis. Results of the SUCCOUR (study of role of GLS guidance of cardioprotective therapy (CPT) in improvement of cardiac function of at-risk patients undergoing potentially cardiotoxic chemotherapy) trial[92] may provide some guidance regarding use of GLS in clinical practice. This study included cancer patients receiving anthracycline-based chemotherapy with at least one additional risk factor for cardiotoxicity. It compared LVEF *vs.* GLS-guided approach to start cardioprotective therapy during chemotherapy; the primary end point was change in 3D LVEF[92]. The study did not achieve the primary end point. In subgroup analysis GLS-guided CPT significantly reduced a meaningful fall of LVEF to the abnormal range. The authors concluded that the results support the use of GLS in monitoring for cancer therapy related cardiac dysfunction[92].

Endocrine therapy

Endocrine therapy contributes to cardiotoxicity indirectly by influencing some risk factors for CVD. Endocrine therapy is given in ER/PR-positive patients for long duration of five years and in some cases up to 10 years, so it is important to select appropriately as per patients' risk profile[93]. In comparison with tamoxifen, longer duration of aromatase inhibitors (anastrozole, letrozole) use is associated with increased risk for CVD[94,95]. The increased risk of cardiovascular events with aromatase inhibitors relative to tamoxifen is likely the result of cardioprotective effects of the latter[96]. Tamoxifen use is associated with increased risk of venous thromboembolism[31].

Radiotherapy-induced heart disease (RIHD)

Radiotherapy has an important role in the treatment of breast cancer in the adjuvant setting; however, there is potential for cardiac and pulmonary toxicity[97]. In view of proximity to the heart, those with left-sided breast cancers may be at a higher risk of developing cardiac effects[98]; however, some studies did not observe a significant difference in cardiac events between women receiving RT for left- *vs*. right-sided cancers[97,99,100]. This may probably be due to modern radiotherapy techniques that are more targeted and less cardiotoxic than older techniques[101].

Various mechanisms of damage due to radiation include endothelial injury, oxidative stress and inflammation, endoplasmic reticulum and mitochondrial damage. These cause diffuse myocardial interstitial fibrosis, microcirculatory damage, leading to ischemia and fibrosis, pericardial fibrosis, valvular fibrosis and atherosclerosis[102,103]. Clinical manifestations include coronary artery disease, cardiomyopathy, pericarditis, valvular heart disease, perfusion defects and conduction abnormalities. The time for the development of the above manifestations after radiotherapy varies from a few weeks in case of pericarditis to more than 10 yr for cardiomyopathy[103].

Risk factors: The risk of developing cardiac morbidity mainly IHD in breast cancer patients treated with adjuvant radiotherapy was evaluated by Darby *et al*[103]. An important observation in this study was that there was no threshold for the development of cardiac toxicities. The authors suggested that it is important to reduce the cardiac dose during irradiation as much as possible and complete shielding of the heart should be considered wherever feasible. The risk of radiation-induced heart disease increases with higher radiotherapy dose, younger age at irradiation and the presence of conventional cardiovascular risk factors (smoking and hypertension)[103,104] and adjuvant treatment (anthracylines, taxanes, trastuzumab)[105].

Diagnosis: There are no specific tests to diagnose radiotherapy-induced heart disease (RIHD). LVEF monitoring and structural evaluation of the heart is done by 2D echo[106]. In patients with suspected coronary artery disease, stress myocardial perfusion scan, and in selected cases, coronary angiogram can be done[106]. Cardiac MRI or computerized tomography (CT) scan can help in better cardiac structural evaluation[106]. The role of cardiac biomarkers and myocardial strain imaging in the early detection of radiation-induced myocardial dysfunction is still under evaluation[107].

Prevention and treatment: Deep inspiration breath holding, respiratory gating, lateral decubitus position, use of modern 3D conformal radiotherapy and now proton beam therapy limit the total radiation dose, the dose per fraction and the volume of heart exposed to radiation[108-110]. Role of statins, colchicine and ACE inhibitors in the prevention of RIHD is also being studied[111,112]. The treatment for RIHD is symptom based, as per standard guidelines and is not specific for it. The results of the ongoing pragmatic Randomized Trial of Proton *versus* Photon Therapy for Patients

with Non-Metastatic Breast Cancer: A Radiotherapy Comparative Effectiveness Consortium Trial which is aimed at studying the cardiovascular morbidity and mortality will add to the current knowledge in this field[113].

Cardiac monitoring in breast cancer survivors

Clinicians should focus on optimal management of CVD risks, management of known or treatment-induced CVD and risk and symptom-based cardiac monitoring. There is a variation in recommendations for monitoring of cardiac function in high-risk asymptomatic cancer survivors by different organizations. For instance, ASCO (2017) recommends cardiac imaging between 6 and 12 months, with no recommendations after this period if LVEF is normal[63], and recent ESMO 2020[67] guidelines suggest additional screening at two-year post-treatment and possibly periodically later.

Conclusion

Overall, assessing for CVD risk pre-treatment, minimizing complications from cancer therapy and appropriate cardiac monitoring plans for early detection of potential treatment-induced cardiovascular toxicity are important for better outcomes in patients with breast cancer. Early detection of cardiac injury will facilitate early therapeutic measures, avoiding treatment delays and allows for completion of planned treatment. Cardiac morbidity is an important quality of life issue among breast cancer survivors, and it is important for clinicians to focus on the long-term cardiovascular effects of cancer treatment.

Cardio-oncology is a growing field which involves collaboration between the oncologist, cardiologist, internist and other healthcare professionals in multidisciplinary cardiovascular care of cancer patients. Involvement of cardio-oncologists is advisable from the initial assessment, monitoring, and management of cardiovascular complications of cancer therapy to survivorship, termed as cardio-oncology[114]. There is a need for developing the cardio-oncology programme which will allow for development of strategies for pre-treatment risk stratification, monitoring on active treatment, cardiac surveillance in cancer survivors which will be specific for Indian population, taking into consideration the cost and benefit ratio.

There is a need for development of a simple to use risk stratification tool so that the primary prevention, monitoring and surveillance are restricted to the highest risk patients, leading to optimal use of available resources. Given that there is no long-term cardiac monitoring protocol for breast cancer patients in India, a collaboration of multiple centres to document the cardiac morbidity and mortality in Indian breast cancer population receiving curative treatment will be useful. This will help in developing cost-effective monitoring protocols for Indian patients with breast cancer.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018; *68* : 7-30.
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, *et al*. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; *136* : E359-86.
3. Malvia S, Bagadi SA, Dubey US, Saxena S. Epidemiology of breast cancer in Indian women. *Asia Pac J Clin Oncol* 2017; *13* : 289-95.
4. Asthana S, Chauhan S, Labani S. Breast cancer and cervical cancer risk in India: An update. *Indian J Public Health* 2014; *58* : 5-10.
5. Miller KD, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, *et al.* Cancer treatment and survivorship statistics, 2019. *CA Cancer J Clin* 2019; *69* : 363-385.
6. Mensah GA, Roth GA, Fuster V. The global burden of cardiovascular diseases and risk factors: 2020 and beyond. *J Am Coll Cardiol* 2019; *74* : 2529-32.
7. India State-Level Disease Burden Initiative CVD Collaborators. The changing patterns of cardiovascular diseases and their risk factors in the states of India: the Global Burden of Disease Study 1990–2016. *Lancet Glob Health* 2018; *6* : e1339–51.
8. Armenian SH, Xu L, Ky B, Sun C, Farol LT, Pal SK, *et al.* Cardiovascular disease among survivors of adult-onset cancer: A community-based retrospective cohort study. *J Clin Oncol* 2016; *34* : 1122-30.
9. Patnaik JL, Byers T, Di Guiseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: A retrospective cohort study. *Breast Cancer Res* 2011; *13* : R64.
10. Gernaat SAM, Ho PJ, Rijnberg N, Emaus MJ, Baak LM, Hartman M, *et al.* Risk of death from cardiovascular disease following breast cancer: A systematic review. *Breast Cancer Res Treat* 2017; *164* : 537-55.
11. Riihimäki M, Thomsen H, Brandt A, Sundquist J, Hemminki K. Death causes in breast cancer patients. *Ann Oncol* 2012; *23* : 604-10.

12. Carver JR, Shapiro CL, Ng A, Jacobs L, Schwartz C, Virgo KS, *et al.* American society of clinical oncology clinical evidence review on the ongoing care of adult cancer survivors: Cardiac and pulmonary late effects. *J Clin Oncol* 2007; *25* : 3991-4008.

13. Jones LW, Haykowsky MJ, Swartz JJ, Douglas PS, Mackey JR. Early breast cancer therapy and cardiovascular injury. *J Am Coll Cardiol* 2007; *50* : 1435-41.

14. Bardia A, Arieas ET, Zhang Z, Defilippis A, Tarpinian K, Jeter S, *et al.* Comparison of breast cancer recurrence risk and cardiovascular disease incidence risk among postmenopausal women with breast cancer. *Breast Cancer Res Treat* 2012; *131* : 907-14.

15. Gernaat SAM, Boer JMA, van den Bongard DHJ, Maas AHEM, van der Pol CC, Bijlsma RM, *et al.* The risk of cardiovascular disease following breast cancer by Framingham risk score. *Breast Cancer Res Treat* 2018; *170* : 119-27.

16. Schairer C, Mink PJ, Carroll L, Devesa SS. Probabilities of death from breast cancer and other causes among female breast cancer patients. *J Natl Cancer Inst* 2004; *96* : 1311-21.

17. Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD. Cardiovascular disease mortality among breast cancer survivors. *Epidemiology* 2016; *27* : 6-13.

18 Campisi J. Aging, cellular senescence, and cancer. *Annu Rev Physiol* 2013; *75* : 685-705.

19. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, *et al.* Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation* 2006; *113* : 791-8.

20. Fredslund SO, Gravholt CH, Laursen BE, Jensen AB. Key metabolic parameters change significantly in early breast cancer survivors: an explorative PILOT study. *J Transl Med* 2019; *17* : 105 .

21. Mehta LS, Watson KE, Barac A, Beckie TM, Bittner V, Cruz-Flores S, *et al*. Cardiovascular disease and breast cancer: Where these entities intersect: A scientific statement from the American Heart Association. *Circulation* 2018; *137* : e30-66.

22. Sardaro A, Petruzzelli MF, D'Errico MP, Grimaldi L, Pili G, Portaluri M. Radiation-induced cardiac damage in early left breast cancer patients: Risk factors, biological mechanisms, radiobiology, and dosimetric constraints. *Radiother Oncol* 2012; *103* : 133-42.

23. Gunaldi M, Duman BB, Afsar CU, Paydas S, Erkisi M, Kara IO, *et al.* Risk factors for developing cardiotoxicity of trastuzumab in breast cancer patients: An observational single-centre study. *J Oncol Pharm Pract* 2016; *22* : 242-7.

24. Lotrionte M, Biondi-Zoccai G, Abbate A, Lanzetta G, D'Ascenzo F, Malavasi V, *et al.* Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity. *Am J Cardiol* 2013; *112* : 1980-4.

25. Park NJ, Chang Y, Bender C, Conley Y, Chlebowski RT, van Londen GJ, *et al.* Cardiovascular disease and mortality after breast cancer in postmenopausal women: Results from the Women's Health Initiative. *PLoS One* 2017; *12* : e0184174.

26. Anderson C, Nichols HB, Deal AM, Park YM, Sandler DP. Changes in cardiovascular disease risk and risk factors among women with and without breast cancer. *Cancer* 2018; *13* : R64-8.

27. Simon MS, Beebe-Dimmer JL, Hastert TA, Manson JE, Cespedes Feliciano EM, Neuhouser ML, *et al.* Cardiometabolic risk factors and survival after breast cancer in the Women's Health Initiative. *Cancer* 2018; *124* : 1798-807.

28. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, *et al.* 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Thorac Cardiovasc Surg* 2015; *149* : e5-23.

29. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments: What the cardiologist needs to know. *Nat Rev Cardiol* 2010; *7* : 564-75.

30. Jain M, Townsend RR. Chemotherapy agents and hypertension: A focus on angiogenesis blockade. *Curr Hypertens Rep* 2007; *9*: 320-8.

31. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost* 2007; *5* : 632-4.

32. Lestuzzi C. Neoplastic pericardial disease: Old and current strategies for diagnosis and management. *World J Cardiol* 2010; *2* : 270-9.

33. Perez EA, Koehler M, Byrne J, Preston AJ, Rappold E, Ewer MS. Cardiac safety of lapatinib: Pooled analysis of 3689 patients enrolled in clinical trials. *Mayo Clin Proc* 2008; *83* : 679-86.

34. Buza V, Rajagopalan B, Curtis AB. Cancer treatment-induced arrhythmias: Focus on chemotherapy and targeted therapies. *Circ Arrhythm Electrophysiol* 2017; *10* : e005443.

35. Alter P, Herzum M, Soufi M, Schaefer JR, Maisch B. Cardiotoxicity of 5-fluorouracil. *Cardiovasc Hematol Agents Med Chem* 2006; *4* : 1-5.

36. Alahari-Dhir A, Sawant SP, editors. Evidence-based management of cancers in India: guidelines for cardio oncology (Part C). Mumbai: Tata Memorial Hospital; 2015.

37. Blum JL, Flynn PJ, Yothers G, Asmar L, Geyer CE Jr., Jacobs SA, *et al.* Anthracyclines in early breast cancer: The ABC trials – USOR 06–090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology). *J Clin Oncol* 2017; *35* : 2647-55.

38. Smith LA, Cornelius VR, Plummer CJ, Levitt G, Verrill M, Canney P, *et al.* Cardiotoxicity of anthracycline agents for the treatment of cancer: Systematic review and meta-analysis of randomised controlled trials. *BMC Cancer* 2010; *10* : 337.

39. Childs AC, Phaneuf SL, Dirks AJ, Phillips T, Leeuwenburgh C. Doxorubicin treatment *in vivo* causes cytochrome C release and cardiomyocyte apoptosis, as well as increased mitochondrial efficiency, superoxide dismutase activity, and Bcl-2:Bax ratio. *Cancer Res* 2002; *62* : 4592-8.
40. Yeh ET, Chang HM. Oncocardiology-past, present, and future: A review. *JAMA Cardiol* 2016; *1* : 1066-72.
41. Dazzi H, Kaufmann K, Follath F. Anthracycline-induced acute cardiotoxicity in adults treated for leukaemia. Analysis of the clinico-pathological aspects of documented acute anthracycline-induced cardiotoxicity in patients treated for acute leukaemia at the University Hospital of Zürich, Switzerland, between 1990 and 1996. *Ann Oncol* 2001; *12* : 963-6.
42. Von Hoff DD, Layard MW, Basa P, Davis HL Jr., Von Hoff AL, Rozencweig M, *et al.* Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med* 1979; *91* : 710-7.
43. Hequet O, Le QH, Moullet I, Pauli E, Salles G, Espinouse D, *et al.* Subclinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults. *J Clin Oncol* 2004; *22* : 1864-71.
44. Van Dalen EC, Michiels EM, Caron HN, Kremer LC. Different anthracycline derivates for reducing cardiotoxicity in cancer patients. *Cochrane Database Syst Rev* 2010; *2010* : CD005006.
45. Volkova M, Russell R 3rd. Anthracycline cardiotoxicity: Prevalence, pathogenesis and treatment. *Curr Cardiol Rev* 2011; *7* : 214-20.
46. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, *et al.* Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011; *365* : 1273-83.
47. Dawood S, Broglio K, Buzdar AU, Hortobagyi GN, Giordano SH. Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: An institutional-based review. *J Clin Oncol* 2010; *28* : 92-8.
48. Mohan N, Jiang J, Dokmanovic M, Wu WJ. Trastuzumab-mediated cardiotoxicity: Current understanding, challenges, and frontiers. *Antib Ther* 2018; *1* : 13-7.
49. Ewer MS, Vooletich MT, Durand JB, Woods ML, Davis JR, Valero V, *et al.* Reversibility of trastuzumab-related cardiotoxicity: New insights based on clinical course and response to medical treatment. *J Clin Oncol* 2005; *23* : 7820-6.
50. Seidman A, Hudis C, Pierri MK, Shak S, Paton V, Ashby M, *et al.* Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol* 2002; *20* : 1215-21.
51. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, *et al.* Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev* 2012; *4* : CD006243.
52. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, *et al*. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; *344* : 783-92.
53. Sparano JA, Wang M, Martino S, Jones V, Perez EA, Saphner T, *et al.* Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med* 2008; *358* : 1663-71.
54. Tolaney SM, Barry WT, Dang CT, Yardley DA, Moy B, Marcom PK, *et al.* Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med* 2015; *372* : 134-41.
55. Kern P, Kalisch A, von Minckwitz G, Pütter C, Kolberg HC, Pott D, *et al.* Neoadjuvant, anthracycline-free chemotherapy with carboplatin and docetaxel in triple-negative, early-stage breast cancer: A multicentric analysis of rates of pathologic complete response and survival. *J Chemother* 2016; *28* : 210-7.
56. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, *et al.* Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): A randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012; *13* : 25-32.
57. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, *et al.* Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* 2015; *372* : 724-34.
58. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, *et al.* Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012; *367* : 1783-91.
59. Dogan E, Yorgun H, Petekkaya I, Ozer N, Altundag K, Ozisik Y. Evaluation of cardiac safety of lapatinib therapy for ErbB2-positive metastatic breast cancer: A single center experience. *Med Oncol* 2012; *29* : 3232-9.
60. Kanduri J, More LA, Godishala A, Asnani A. Fluoropyrimidine-associated cardiotoxicity. *Cardiol Clin* 2019; *37* : 399-405.
61. Stewart T, Pavlakis N, Ward M. Cardiotoxicity with 5-fluorouracil and capecitabine: More than just vasospastic angina. *Intern Med J* 2010; *40* : 303-7.
62. Thill M, Schmidt M. Management of adverse events during cyclin-dependent kinase 4/6 (CDK4/6) inhibitor-based treatment in breast cancer. *Ther Adv Med Oncol* 2018; *10* : 1758835918793326.
63. Saro HA, Christina L, Ana B, Carver J, Constine LS, Denduluri N, *et al.* Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2017; *35* : 893-911.
64. Leong SL, Chaiyakunapruk N, Lee SW. Candidate gene association studies of anthracycline-induced cardiotoxicity: A systematic review and meta-analysis. *Sci Rep* 2017; *7* : 39.
65. Gomez Pena C, Davila-Fajardo CL, Martinez-Gonzalez LJ, Carmona-Sáez P, Soto Pino MJ, Sánchez Ramos J, *et al*. Influence of the HER2 Ile655Val polymorphism on trastuzumab-induced cardiotoxicity in HER2-positive breast cancer patients: A meta-analysis. *Pharmacogenet Genomics* 2015; *25* : 388-93.
66. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, *et al.* Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: A report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2014; *27* : 911-39.

67. Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, *et al*. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Ann Oncol* 2020; *31* : 171-90.

68. Fazel R, Krumholz HM, Wang Y, Ross JS, Chen J, Ting HH, *et al.* Exposure to low-dose ionizing radiation from medical imaging procedures. *N Engl J Med* 2009; *361* : 849-57.

69. Lang RM, Mor-Avi V, Sugeng L, Nieman PS, Sahn DJ. Three-dimensional echocardiography: The benefits of the additional dimension. *JACC* 2006; *48* : 2053-69.

70. Thavendiranathan P, Wintersperger BJ, Flamm SD, Marwick TH. Cardiac MRI in the assessment of cardiac injury and toxicity from cancer chemotherapy: A systematic review. *Circ Cardiovasc Imaging* 2013; *6* : 1080-91.

71. Lynce F, Barac A, Geng X, Dang C, Yu AF, Smith KL, *et al.* SAFE-HEaRt: a pilot study assessing the cardiac safety of HER2 targeted therapy in patients with HER2 positive breast cancer and reduced left ventricular function. *J Clin Oncol* 2018; *36* (Suppl 15) : 1038.

72. Witteles RM, Fowler MB, Telli ML. Chemotherapy-associated cardiotoxicity: How often does it really occur and how can it be prevented? *Heart Fail Clin* 2011; *7* : 333-44.

73. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Tan TC, *et al*. Assessment of echocardiography and bio- markers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. *Circ Cardiovasc Imaging* 2012; *5* : 596-603.

74. Cardinale D, Sandri MT, Martinoni A, Tricca A, Civelli M, Lamantia G, *et al.* Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. *J Am Coll Cardiol* 2000; *36* : 517-22.

75. Ky B, Putt M, Sawaya H, French B, Januzzi JL Jr., Sebag IA, *et al.* Early increases in multiple biomarkers predict subsequent cardiotoxicity in patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab. *J Am Coll Cardiol* 2014; *63* : 809-16.

76. Patel J, Rikhi R, Hussain M, Ayoub C, Klein A, Collier P, *et al.* Global longitudinal strain is a better metric than left ventricular ejection fraction: Lessons learned from cancer therapeutic-related cardiac dysfunction. *Curr Opin Cardiol* 2020; *35* : 170-7.

77. Fei HW, Ali MT, Tan TC, Cheng KH, Salama L, Hua L, *et al.* Left ventricular global longitudinal strain in HER2 + breast cancer patients treated with anthracyclines and trastuzumab who develop cardiotoxicity is associated with subsequent recovery of left ventricular ejection fraction. *Echocardiography* 2016; *33* : 519-26.

78. Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: A systematic review. *J Am Coll Cardiol* 2014; *63* : 2751-68.

79. Negishi K, Negishi T, Hare JL, Haluska BA, Plana JC, Marwick TH. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. *J Am Soc Echocardiogr* 2013; *26* : 493-8.

80. Oikonomou EK, Kokkinidis DG, Kampaktsis PN, Amir EA, Marwick TH, Gupta D, *et al.* Assessment of prognostic value of left ventricular global longitudinal strain for early prediction of chemotherapy-induced cardiotoxicity: A systematic review and meta-analysis. *JAMA Cardiol* 2019; *4* : 1007-18.

81. Cardinale D, Colombo A, Torrisi R, Sandri MT, Civelli M, Salvatici M, *et al.* Trastuzumab-induced cardiotoxicity: Clinical and prognostic implications of troponin I evaluation. *J Clin Oncol* 2010; *28* : 3910-6.

82. Todorova VK, Makhoul I, Siegel ER, Wei J, Stone A, Carter W, *et al.* Biomarkers for presymptomatic doxorubicin-induced cardiotoxicity in breast cancer patients. *PLoS One* 2016; *11* : e0160224.

83. Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, *et al.* Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation* 2006; *114* : 2474-81.

84. Nicol M, Baudet M, Cohen-Solal A. Subclinical left ventricular dysfunction during chemotherapy. *Card Fail Rev* 2019; *5* : 31-6.

85. Reichardt P, Tabone MD, Mora J, Morland B, Jones RL. Risk-benefit of dexrazoxane for preventing anthracycline-related cardiotoxicity: Reevaluating the European labeling. *Future Oncol* 2018; *14* : 2663-76.

86. Smith LA, Cornelius VR, Plummer CJ, Levitt G, Verrill M, Canney P, *et al.* Cardiotoxicity of anthracycline agents for the treatment of cancer: Systematic review and meta-24 analysis of randomised controlled trials. *BMC Cancer* 2010; *10* : 337.

87. Padegimas A, Clasen S, Ky B. Cardioprotective strategies to prevent breast cancer therapy-induced cardiotoxicity. *Trends Cardiovasc Med* 2020; *30* : 22-8.

88. Pituskin E, Mackey JR, Koshman S, Jassal D, Pitz M, Haykowsky MJ, *et al.* Multidisciplinary approach to novel therapies in cardio-oncology research (MANTICORE 101-Breast): A randomized trial for the prevention of trastuzumab-associated cardiotoxicity. *J Clin Oncol* 2017; *35* : 870-7.

89. Gulati G, Heck SL, Røsjø H, Ree AH, Hoffmann P, Hagve TA, *et al.* Neurohormonal blockade and circulating cardiovascular biomarkers during anthracycline therapy in breast cancer patients: results from the PRADA (prevention of cardiac dysfunction during adjuvant breast cancer therapy) study. *J Am Heart Assoc* 2017; *6* : e006513.

90. Avila MS, Ayub-Ferreira SM, de Barros Wanderley MR Jr., das Dores Cruz F, Gonçalves Brandão SM, Rigaud VO, *et al.* Carvedilol for prevention of chemotherapy-related cardiotoxicity: The CECCY trial. *J Am Coll Cardiol* 2018; *71* : 2281-90.

91. Bansal N, Adams MJ, Ganatra S, Colan SD, Aggarwal S, Steiner R, *et al.* Strategies to prevent anthracycline-induced cardiotoxicity in cancer survivors. *Cardiooncology* 2019; *5* : 18.

92. Thavendiranathan P, Negishi T, Somerset E, Negishi K, Penicka M, Lemieux J, *et al*. Strain-guided management of potentially cardiotoxic cancer therapy. *J Am Coll Cardiol* 2021; *77* : 392-401.

93. Matthews A, Stanway S, Farmer RE, Strongman H, Thomas S, Lyon AR, *et al.* Long term adjuvant endocrine therapy and risk of cardiovascular disease in female breast cancer survivors: Systematic review. *BMJ* 2018; *363* : k3845.

94. Amir E, Seruga B, Niraula S, Carlsson L, Ocaña A. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: A systematic review and meta-analysis. *J Natl Cancer Inst* 2011; *103* : 1299-309.

95. Khosrow-Khavar F, Filion KB, Al-Qurashi S, Torabi N, Bouganim N, Suissa S, *et al.* Cardiotoxicity of aromatase inhibitors and tamoxifen in postmenopausal women with breast cancer: A systematic review and meta-analysis of randomized controlled trials. *Ann Oncol* 2017; *28* : 487-96.

96. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, *et al.* Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. *Lancet* 2005; *366* : 2087-106.

97. Patt DA, Goodwin JS, Kuo YF, Freeman JL, Zhang DD, Buchholz TA, *et al.* Cardiac morbidity of adjuvant radiotherapy for breast cancer. *J Clin Oncol* 2005; *23* : 7475-82.

98. Doyle JJ, Neugut AI, Jacobson JS, Wang J, McBride R, Grann A, *et al.* Radiation therapy, cardiac risk factors, and cardiac toxicity in early-stage breast cancer patients. *Int J Radiat Oncol Biol Phys* 2007; *68* : 82-93.

99. Giordano SH, Kuo YF, Freeman JL, Buchholz TA, Hortobagyi GN, Goodwin JS. Risk of cardiac death after adjuvant radiotherapy for breast cancer. *J Natl Cancer Inst* 2005; *97* : 419-24.

100. Nixon AJ, Manola J, Gelman R, Bornstein B, Abner A, Hetelekidis S, *et al.* No long-term increase in cardiac-related mortality after breast-conserving surgery and radiation therapy using modern techniques. *J Clin Oncol* 1998; *16* : 1374-9.

101. Harris EE. Cardiac mortality and morbidity after breast cancer treatment. *Cancer Control* 2008; *15* : 120-9.

102. Slezak J, Kura B, Babal P, Barancik M, Ferko M, Frimmel K, *et al.* Potential markers and metabolic processes involved in the mechanism of radiation-induced heart injury. *Can J Physiol Pharmacol* 2017; *95* : 1190-203.

103. Darby SC, Cutter DJ, Boerma M, Constine LS, Fajardo LF, Kodama K, *et al.* Radiation-related heart disease: Current knowledge and future prospects. *Int J Radiat Oncol Biol Phys* 2010; *76* : 656-65.

104. Hooning MJ, Botma A, Aleman BM, Baaijens MH, Bartelink H, Klijn JG, *et al.* Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst* 2007; *99* : 365-75.

105. Magné N, Castadot P, Chargari C, Di Leo A, Philippson C, Van Houtte P. Special focus on cardiac toxicity of different sequences of adjuvant doxorubicin/docetaxel/CMF regimens combined with radiotherapy in breast cancer patients. *Radiother Oncol* 2009; *90* : 116-21.

106. Lancellotti P, Nkomo VT, Badano LP, Bergler-Klein J, Bogaert J, Davin L, *et al.* Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: A report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr* 2013; *26* : 1013-32.

107. Gkantaifi A, Papadopoulos C, Spyropoulou D, Toumpourleka M, Iliadis G, Kardamakis D, *et al.* Breast radiotherapy and early adverse cardiac effects. The role of serum biomarkers and strain echocardiography. *Anticancer Res* 2019; *39* : 1667-73.

108. Zagar TM, Kaidar-Person O, Tang X, Jones EE, Matney J, Das SK, *et al.* Utility of deep inspiration breath hold for left-sided breast radiation therapy in preventing early cardiac perfusion defects: A prospective study. *Int J Radiat Oncol Biol Phys* 2017; *97* : 903-9.

109. Chang JS, Chen J, Weinberg VK, Fowble B, Sethi RA. Evaluation of heart dose for left-sided breast cancer patients over an 11-year period spanning the transition from 2-dimensional to 3-dimensional planning. *Clin Breast Cancer* 2016; *16* : 396-401.

110. Mulliez T, Veldeman L, Speleers B, Mahjoubi K, Remouchamps V, Van Greveling A, *et al.* Heart dose reduction by prone deep inspiration breath hold in left-sided breast irradiation. *Radiother Oncol* 2015; *114* : 79-84.

111. van der Veen SJ, Ghobadi G, de Boer RA, Faber H, Cannon MV, Nagle PW, *et al.* ACE inhibition attenuates radiation-induced cardiopulmonary damage. *Radiother Oncol* 2015; *114* : 96-103.

112. O'Herron T, Lafferty J. Prophylactic use of colchicine in preventing radiation induced coronary artery disease. *Med Hypotheses* 2018; *111* : 58-60.

113. Bekelman JE, Lu H, Pugh S, Baker K, Berg CD, Berrington de González A, *et al*. Pragmatic randomised clinical trial of proton versus photon therapy for patients with non-metastatic breast cancer: The Radiotherapy Comparative Effectiveness (RadComp) Consortium trial protocol. *BMJ Open* 2019; *9* : e025556.

114. Wickramasinghe CD, Nguyen KL, Watson KE, Vorobiof G, Yang EH. Concepts in cardio-oncology: Definitions, mechanisms, diagnosis and treatment strategies of cancer therapy-induced cardiotoxicity. *Future Oncol* 2016; *12* : 855-70.

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