Personalizing cardiovascular disease prevention among breast cancer survivors

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Purpose of review
With the advancement of breast cancer therapies, most women diagnosed with breast cancer in the United States are now expected to survive their disease, and management of competing comorbidities, particularly cardiovascular disease (CVD), is crucial.

Recent findings
Recent studies have suggested that CVD is the most common cause of death for women diagnosed with ductal carcinoma in situ or stage I disease and for women aged more than 80 years with stage II disease. Various breast cancer therapies, including targeted therapies, can accentuate CVD risk; referrals for cardiology opinion are not uncommon at the time at which treatment options are under consideration. The use of less cardiotoxic alternatives, such as liposomal doxorubicin, and intensity-modulated radiation therapy should be considered when appropriate. Doppler myocardial imaging and cardiac MRI might allow early recognition of cardiotoxicity.

Summary
It is important to weigh both the risk of CVD and that of breast cancer recurrence in a breast cancer survivor. Certain interventions for the primary prevention of CVD, including diet, physical activity, smoking cessation and aspirin, can reduce breast cancer risk as well. The management of CVD risk factors is of increasing importance in the management of breast cancer survivors.

Keywords
aspirin, breast cancer, cardiovascular risk, personalized medicine, prevention

INTRODUCTION
Breast cancer is the most common malignancy among women, accounting for nearly one in three cancers among women in the United States, and is the second leading cause of cancer death among women [1]. The American Cancer Society estimates 226,870 new cases of invasive breast cancer in 2012 [1].

With an increase in the survival of patients with breast cancers due to improved cancer detection and treatment in an aging population [2], most women diagnosed with breast cancer in the United States are now expected to survive their disease [3]. It is estimated that there are currently more than 2.5 million breast cancer survivors in the United States. The 10-year survival from breast cancer currently approaches 90% for women with hormone receptor-positive disease, including older women (i.e., >65 years), who comprise about 40% of all new breast cancer diagnoses [4]. Several investigators have demonstrated that the long-term survival and prognosis associated with cancer were not necessarily worse and in some instances were better than those of heart failure and stroke [5–7]. Studies have suggested that cardiovascular disease (CVD) is the most common cause of death for women diagnosed with ductal carcinoma in situ or stage I disease and for women aged more than 80 years with stage II disease, and attention to this comorbidity should be prioritized [8–10]. According to the National Center for Health Statistics, if all forms of major CVD were eliminated, life expectancy would rise by almost 7 years, in comparison to an increase of only 3 years if cancer were eliminated as a cause of death [11].
Although living with a diagnosis of breast cancer is cause of fear and concern, it is important that breast cancer survivors be screened for cardiovascular risk factors and be appropriately treated. It is important for primary-care physicians (and cardiologists) when assessing a patient with breast cancer to consider the following:

(1) Weigh competing CVD and breast cancer recurrence risk.

(2) Consider the CVD risk associated with breast cancer therapies.

(3) Recommend strategies for CVD prevention (Fig. 1).

COMPETING CARDIOVASCULAR DISEASE AND BREAST CANCER RECURRENCE RISK

It is important to weigh both the risk of CVD and that of breast cancer recurrence in order to appropriately undertake CVD screening and interventions. Fortunately, various online prognostic calculators are available that can help with this determination. For example, a recent study compared 10-year CVD risk using modified Framingham risk score with 10-year risk of breast cancer recurrence using Adjuvant Online (http://www.adjuvantonline.com) in a cohort of postmenopausal women with stages I–III nonmetastatic breast cancer [12**]. The results showed that 43% of women had a predicted 10-year CVD risk equivalent to the risk of recurrence of breast cancer and 37% had a risk of CVD higher than the risk of breast cancer recurrence. Thus, it is recognized that 80% of postmenopausal women with hormone

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**FIGURE 1.** Flowchart outlining steps for cardiovascular disease (CVD) risk assessment and personalizing CVD prevention among breast cancer survivors.
receptor-positive breast cancer who are considered for adjuvant aromatase inhibitor therapy have a predicted 10-year CVD risk equivalent to, or higher than, their 10-year risk of breast cancer recurrence. Women with stage I breast cancer or heart age more than 65 years were particularly likely to have a higher predicted risk of CVD than risk of breast cancer recurrence at 10 years [12**]. The CVD risk is even higher if one considers the cardiovascular effects of breast cancer therapies. These are outlined in Table 1 and discussed below.

**CARDIOVASCULAR DISEASE RISK DUE TO CANCER TREATMENT AND STRATEGIES TO REDUCE CARDIOTOXICITY**

Cardiotoxicity by anthracyclines is well known and is attributed to iron-based oxygen-free radical-induced oxidative stress on cardiac muscle cells. Free radicals induce the peroxidation of myocyte membranes and a subsequent influx of intracellular calcium. Mitochondrial dysfunction has also been noted with, and correlates with, morphologic changes [13,14].

Significant predictors of anthracycline-associated cardiac toxicity include pre-existing cardiovascular disease such as coronary artery disease, hypertension, peripheral vascular disease, emphysema, diabetes, ethnicity, and age [15–18]. Treatment-related risk factors are higher cumulative doses of anthracycline, associated mediastinal radiation therapy and combination chemotherapy (trastuzumab, cyclophosphamide, etoposide, melphalan, paclitaxel, mitoxantrone, idarubicin) [15,18]. Thus, the identification of risk factors, and their appropriate management, in association with careful prescription of chemotherapeutic agents can prevent this potentially irreversible, long-term cardiotoxicity which may appear years or decades following therapy. It is recommended that the cumulative dose of anthracycline should not exceed 600 mg/m² for doxorubicin and 900 mg/m² for epirubicin [19].

Dexrazoxane, an iron-chelating agent, can reduce the cardiotoxic effect of doxorubicin [20]. Whereas routine use of dexrazoxane is not routinely recommended for patients receiving doxorubicin-based chemotherapy, it should be considered for patients with metastases who have received more than 300 mg/m² of doxorubicin who might benefit from continued doxorubicin-containing therapy, with due consideration given to the potential for dexrazoxane to decrease response rates [19]. A recent Cochrane meta-analysis showed that dexrazoxane prevents heart damage but that there was no apparent difference in response rate or survival between the dexrazoxane and control groups [21**]. The evidence regarding other potential cardioprotective options such as carvedilol [22], L-carnitine [23], prenylamine [24], amifostine [25] and acetylcysteine [26] is limited.

**Impact of antihuman epidermal growth factor receptor-2 therapies**

Approximately 20% of breast cancer tumors show overexpression of human epidermal growth factor

| Table 1. Breast cancer interventions that can increase cardiovascular disease risk |
|-----------------|---------------------------------------------------------------|
| **Therapy**     | **Strategies to reduce cardiotoxicity**                       |
| Anthracyclines  | Limit cumulative dose                                         |
|                 | Identification of high risk (coronary artery disease, hypertension, peripheral vascular disease, emphysema, diabetes, age, associated radiation therapy and combination chemotherapy) |
|                 | Using epirubicin or liposomal formulations                    |
|                 | Dexrazoxane (if cardiac damage is expected to be high)        |
| HER-2 inhibitors| Avoid concurrent anthracyclines                               |
|                 | Identification of high risk (hypertension, diabetes, age, combination chemotherapy) |
|                 | Interrupt therapy if drop in LVEF by <10% at any point or absolute value <50% |
| Hormonal therapies| Prevention of thromboembolic events                            |
| Antiangiogenic drugs| Management of hypertension                                    |
|                 | Prevention of thromboembolic events                            |
| Radiotherapy    | Minimizing dose                                              |
|                 | Avoid concurrent cardiotoxic agents                           |
|                 | Use of newer modalities (IMRT)                                |

HER, human epidermal growth factor receptor; IMRT, intensity-modulated radiation therapy; LVEF, left ventricular ejection fraction.
receptor 2 (HER-2) [27,28]. Trastuzumab is a humanized monoclonal antibody, which binds to the extracellular domain of the HER2 and inhibits the growth of HER2-positive tumors. Large clinical trials have shown that trastuzumab can improve survival by greater than 50%; its use has revolutionized the management of otherwise high-risk tumors [29,30,31–33]. Indeed, trastuzumab-based therapy has become the standard of care for HER2-positive breast cancer [34].

One of the major side effects of trastuzumab is a cardiotoxicity, which is different from that produced by other chemotherapeutic agents and is categorized as type II chemotherapy-related cardiac dysfunction (CRCD) [35]. When compared with type I CRCD produced by anthracyclines, the cardiotoxicity of trastuzumab is reversible, has a broader range of severity, is not dose-related, does not appear to occur in all patients and is not associated with identifiable ultrastructural abnormalities [36,37]. With strict monitoring, symptomatic cardiac failure occurs in fewer than 2% and in the majority of cases is reversible [38,39,40]. The mechanism of trastuzumab-related CRCD probably involves the HER-2 pathway, which is required for the growth, repair and survival of cardiomyocytes, all of which are fundamental to the maintenance of cardiac contractility, function and structure [41]. Animal models have shown that ERβ2 signaling in cardiac muscle cells is essential for the prevention of chamber dilation, wall thickening and decreased contractility [41–43].

Risk factors associated with a higher likelihood of trastuzumab-related cardiotoxicity include previous or concurrent chemotherapy use and age greater than 50 years [38,44–46]. The risk of trastuzumab-related cardiac dysfunction is highest among patients receiving concurrent anthracyclines (especially if the cumulative doxorubicin dose is >300 mg/m²), and concomitant use of trastuzumab and anthracyclines is prohibited. There is minimal, if any, cardiovascular risk when trastuzumab is given with a taxane, or trastuzumab is given with endocrine therapy [29,31,37–39,45,47–50]. Other risk factors include pre-existing cardiac dysfunction (i.e., decreased left ventricular ejection fraction), high BMI, hypertension and diabetes; valvular heart disease and coronary artery disease do not appear to significantly increase risk [44,48,51].

In most cases discontinuation of trastuzumab alone is sufficient to prevent cardiac events in those patients who present with reduced LVEF (<40%) [52]. Other studies report appropriate management of this adverse event with the use of angiotensin-converting enzyme inhibitors (ACEI), β-blockers or diuretics [53]. Determination of LVEF prior to the initiation of trastuzumab treatment and thereafter every 3–6 months is recommended. The use of trastuzumab therapy is not recommended if the LVEF is 55% or less. A drop in LVEF by less than 10% at any point, or an absolute value less than 50%, requires interruption of therapy. Trastuzumab therapy can usually be resumed upon recovery of LVEF [37]. If a patient presents with new evidence of congestive heart failure (CHF) during the reintroduction of treatment, a case-by-case risk–benefit evaluation is required [54].

Lapatinib, a tyrosine kinase inhibitor of HER-2, has fewer cardiac side effects than trastuzumab. An analysis of cardiac function in over 3500 patients treated with lapatinib found that 1.6% of patients experienced a decrease in LVEF, and only 0.2% had symptoms related to cardiac dysfunction, which resolved following symptomatic treatment [36].

Impact of hormonal therapies

An adjuvant treatment strategy incorporating an aromatase inhibitor as primary (initial endocrine therapy), sequential (using both tamoxifen and an aromatase inhibitor in either order) or extended (aromatase inhibitor after 5 years of tamoxifen) therapy has been shown to reduce the risk of breast cancer recurrence compared with 5 years of tamoxifen alone [55].

Despite tamoxifen’s favorable impact on lipid profiles, these benefits do not translate into a cardioprotective effect; in fact, the use of tamoxifen increases the risk of thromboembolic and ischemic cerebrovascular events [56]. In comparison with tamoxifen, aromatase inhibitor therapy is associated with an increased risk of both hypercholesterolemia and hypertension. Tamoxifen is associated with an increased risk of venous thromboembolic events, giving rise to a 1–2% greater risk of deep vein thrombosis compared with women taking aromatase inhibitors [57]. The results of initial studies comparing CVD risk of adjuvant aromatase inhibitor compared with tamoxifen have been unclear [55,58]; however, a recently performed meta-analysis of seven large adjuvant aromatase inhibitor trials involving more than 30,000 patients showed adjuvant aromatase inhibitor use was associated with a slightly increased CVD risk (odds ratio: 1.26, 95% confidence interval: 1.10–1.43, P < 0.001; number needed to harm = 132) [58].

Impact of antiangiogenic therapies

Bevacizumab, a recombinant humanized monoclonal antibody against vascular endothelial growth
factor receptor, was approved for the treatment of metastatic breast cancer, although its use now is controversial [59–61]. Hypertension is an important side effect, with an incidence ranging from 16 to 47% [62]. Other reported cardiac toxicities include CHF in 1.7–4% of patients, particularly in patients previously exposed to anthracyclines or chest wall irradiation [61], as well as a risk of cardiac ischemia and arterial thromboembolic events in 3.3% [63]. Alteration in nitric oxide production, impairment of endothelial cells (thereby blocking angiogenesis), promotion of endothelial cell apoptosis (causing regression of vessels) and alteration in platelet/endothelial cell interactions (causing large-vessel thrombosis) are proposed mechanisms of toxicity for this agent [64,65].

Impact of radiotherapy

Although high-dose radiotherapy can damage virtually any component of the heart, leading to pericardial and coronary artery disease, cardiomyopathy, valvular dysfunction or conduction abnormalities, most manifestations of cardiotoxicity appear as a consequence of damage to blood vessels. In-vitro studies have suggested that radiation induces endothelial activation characterized by activation of the transcription factor nuclear factor κB (NF-κB), resulting in alterations in vascular adhesion molecule expression and chemokine and cytokine production leading to atherosclerosis and a prothrombotic state [66]. Secondary inflammatory changes then result in diffuse myocardial fibrosis and narrowing of capillaries, the histologic hallmarks of radiation-associated cardiotoxicity [67]. Dense collagen and fibrin replace the normal adipose tissue, leading to pericardial fibrosis, effusion, and, in severe cases, tamponade [68].

Recent meta-analyses of trials employing modern radiation techniques found that overall survival was positively associated with radiotherapy [67,69], in contrast to the initial trials, which demonstrated that improved, disease-free survival was countered by excess cardiac mortality [67,70]. Risk factors for the development of radiation therapy-induced cardiac toxicity include total radiation dose, the dose per fraction; the volume of heart irradiated; the concomitant administration of cardiotoxic systemic agents (e.g., anthracyclines); younger age at the time of treatment; and the presence of other risk factors for coronary heart disease (e.g., hypertension, smoking) [71,72].

Multiple reports based upon tumor registry databases have analyzed the long-term effects of radiation therapy in breast cancer survivors [73–77]. Most, but not all, studies show a relative increased incidence of cardiac events in women with left-sided rather than right-sided breast tumors. The latter are presumed to have received lower doses of cardiac irradiation [70]. Even those who received tangential field irradiation after left-sided breast conserving surgery had more coronary artery stenosis, especially in the left anterior descending artery, than patients with right-sided breast cancer [78]. With the advent of conformal and intensity-modulated radiation therapy (IMRT) techniques, which permit the delivery of a high-dose volume that conforms in three dimensions to the shape of the defined target, the dose to normal tissue can be minimized [79]. Further modifications such as intensity-modulated radiotherapy combined with free breathing gating and helical tomotherapy suggested that cardiac toxicity could be decreased, but these concepts still needs to be proven [80–86].

Identification of therapy-induced cardiomyopathy

Although measurement of ejection fraction by echocardiogram has traditionally been the gold standard to detect therapy-induced cardiomyopathy, new modalities with higher sensitivity and specificity are being developed. Albini et al. [87] have proposed using a flowchart that incorporates blood pressure, both electrocardiogram and dynamic-electrocardiogram findings, and the results of Echo-Doppler before any treatment in order to facilitate the primary prevention of cardiotoxicity. Widely used biomarkers such as brain natriuretic peptide and troponin are also potentially useful screening tools with application in the monitoring of chemotherapy patients [88]. Doppler myocardial imaging (DMI) or Doppler imaging or tissue velocity imaging is increasingly being used to assess parameters closely linked to myocardial function, such as velocity, deformation (strain) and the rate of deformation. It has been shown to predict anthracycline-induced cardiotoxicity before a decline in LVEF is revealed by conventional echocardiography [89]. Another promising technique is cardiac-enhanced MRI, a highly reproducible technique that has also demonstrated an ability to assess subtle changes in myocardial function [90]. Further clinical assessment is required before these newer modalities can be recommended as routine tools in clinical practice.

PRIMARY INTERVENTIONS FOR PREVENTION

Although national CVD guidelines recommend that all adults undergo an office-based assessment to
evaluate their risk of cardiac events using various validated CVD risk prediction algorithms [91], it is estimated that about a third of adults significantly underestimate their risk of CVD and a large number do not undergo screening. It is likely that breast cancer survivors may further underestimate their risk for developing CVD because of an understandable focus on the risk of breast cancer recurrence [92]. Therefore, it is crucial for primary care physicians and cardiologists to screen breast cancer survivors for CVD risk and intervene for primary and secondary CVD prevention as needed. CVD interventions that can reduce breast cancer risk are particularly appropriate in this respect, and are discussed below.

**Diet**

A number of epidemiological studies have evaluated the impact of diet among breast cancer survivors. Statistically significant protective associations of higher intakes of calcium, vitamin C and vegetables and nonsignificant benefits of antioxidants and vitamin E have been reported; but, given the heterogeneity across studies, it is impossible to provide conclusive recommendations of the effectiveness of these supplements [93,94**]. Furthermore, it is suggested that dietary intervention without weight loss or physical activity is not sufficient to improve breast cancer prognosis [93,94**]. Even though definite evidence of improvement in outcomes is lacking, several investigations have shown obesity to be an independent prognostic risk factor for breast cancer recurrence and mortality, and weight loss in obese patients (BMI >30 kg/m²) could have a protective benefit, possibly by reducing the adipose tissue: the major source of endogenous estrogens among postmenopausal women [95,96].

**Physical activity**

Physical activity has been shown to have positive effects on physiology, body composition, physical functions, psychological outcomes and quality of life in patients following treatment for breast cancer [97–100]. Although not consistent, observational data on physical activity appear to be associated with a 30% decreased risk of mortality [101–106]. A meta-analysis of six studies, including over 12,000 patients with breast cancer, showed that prediagnosis physical activity reduced all-cause mortality by 18% but had no effect on breast cancer deaths [107**]. The potential benefit of postdiagnosis physical activity was more convincing, although limited to patients with hormone receptor-positive tumor; in this patient group, it reduced breast cancer deaths by 34%, all-cause mortality by 41% and disease recurrence by 24% [107**].

**Smoking cessation**

The role of smoking cessation in the prevention of CVD is well established and quitting smoking is associated with a substantial reduction in risk of all-cause mortality among patients with CHD [108]. Even though in 2004 the International Agency for Research on Cancer (IARC) and the US Surgeon General Report suggested a lack of association of active smoking in breast cancer [108,109], in 2009 the IARC modified the evidence for active smoking to ‘limited’, based on larger prospective studies [110,111]. According to a recent study, compared with women who had never smoked, breast cancer risk was elevated by 9% among former smokers and by 16% among current smokers and the increased risk of breast cancer persisted for up to 20 years after smoking cessation [112*]. Another study suggested a higher breast cancer incidence with higher quantity and duration of smoking [113*]. A large-scale analysis by the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk concluded that the association between active smoking and breast cancer risk was ‘consistent with causality’ [114**]. However, this causality association is not universally accepted. Evidence linking passive smoking with breast cancer is conflicting and inconclusive [115*].

**Aspirin**

Evidence-based guidelines for the use of aspirin to decrease CVD events in women are well established. Despite this, aspirin is underused in women, and according to a survey only 41% of women who meet the criteria for primary prevention and 48% of women who meet the criteria for secondary prevention report that they take aspirin on a daily basis [116].

The use of aspirin, but not other NSAIDs, has been reported to lower the risk of breast cancer, particularly at higher frequency [117*]. A recent meta-analysis of 33 studies (19 cohort studies, 13 case–control studies, and one randomized controlled trial) that included 1,916,488 individuals showed aspirin use to be associated with reduced risk for breast cancer (odds ratio = 0.86) [118**]. The protective effect of aspirin does not appear to differ appreciably by stage, menopausal status, BMI or estrogen receptor status [117*,118**,119].

**Statins**

The role of statins in breast cancer prevention is controversial. Earlier observational studies reported modest to large statistically significant reductions in the risk of breast cancer associated with overall use
of statins [119–121]. The possibility of within-class differences with lower incidence of breast cancer patients limited to the use of hydrophobic statins was also suggested [122]. However, results from secondary analyses of randomized trials have been inconsistent and four overlapping meta-analyses found no protective effect [123–126].

**Other drugs**

Although some studies have suggested that β-blockers can reduce breast cancer progression and mortality [127–129], this effect has been inconsistent and not shown by other studies [130,131]. ACEI/angiotensin ii receptor blocker (ARB) might have a potential benefit in anthracycline-induced cardiotoxicity, and clinical trials combining ACEI with doxorubicin in breast cancer are ongoing. There was a recent concern that ARBs might be associated with a modestly increased risk of new cancer, particularly lung cancer; however, recent investigations have shown that there is no such relationship with breast cancer [132,133*,134,135*].

**CONCLUSION**

With increasing survival among women with breast cancer, most women with breast cancer die from cardiovascular disease rather than cancer itself. Most treatment options for breast cancer, including emerging therapies such as angiogenesis inhibitors and newer radiotherapeutic approaches, are not free from cardiotoxic side effects. With advances in treatment, many women receive more than one form of therapy, and the potential cumulative cardiotoxicity can be a challenge for cardiologists as well as oncologists. Attempts to reduce individual toxicities by defining maximum doses, the development of lesser cardiotoxic analogs, and IMRT as well as better monitoring and early recognition of cardiotoxicity by use of biomarkers, DMI and cardiac MRI are in various stages of development. Simultaneously, the growing evidence suggests protective effects of conventional cardioprotective interventions such as diet, physical activity, smoking cessation and aspirin on breast cancer recurrence as well, and these should be preferentially considered among breast cancer survivors (Table 2) [93,94**,107**,111,114**,117*,118**,124,127,128,131,133*,135*,136].

**Acknowledgements**

None.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

2. Latest cancer statistics by American Cancer Society.

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**Table 2. Association of the various cardiovascular disease primary and secondary interventions on breast cancer risk**

<table>
<thead>
<tr>
<th>CVD intervention</th>
<th>Breast cancer risk</th>
<th>Key references</th>
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<tbody>
<tr>
<td>Diet</td>
<td>Unclear</td>
<td>[93,94**]</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Protective</td>
<td>[107**]</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>Protective</td>
<td>[112*,114**]</td>
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<tr>
<td>Aspirin</td>
<td>Protective</td>
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</tr>
<tr>
<td>Statins</td>
<td>Unclear</td>
<td>[124]</td>
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<tr>
<td>β-blockers</td>
<td>Unclear</td>
<td>[127,128,131]</td>
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<tr>
<td>ACE inhibitors</td>
<td>Protective</td>
<td>[134,135*]</td>
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ACE, angiotensin converting enzyme; CVD, cardiovascular disease.
Prevention


Review assessed the efficacy of different cardioprotective agents in preventing heart damage in cancer patients treated with anthracyclines.


Evaluate the efficacy and safety of a new nonanthracycline regimen with trastuzumab.


Review on trastuzumab-induced cardiac toxicity.


Meta-analysis on role of diet and physical activity in breast cancer.


Meta-analysis on role of diet and physical activity in cancer.
Prevention