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Curing breast cancer and killing the heart: A novel model to explain elevated cardiovascular disease and mortality risk among women with early stage breast cancer

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ABSTRACT

Due to advances in prevention, early detection and treatment, early breast cancer mortality has decreased by nearly 40% during the last four decades. Yet, the risk of cardiovascular disease (CVD) mortality is significantly elevated following a breast cancer diagnosis, and it is a leading cause of death in this population. This review will discuss the most recent evidence for risks, pathology, mechanisms, and prevention of CVD morbidity and mortality in women with breast cancer. This evidence will be synthesized into a new model '*the compounding risk and protection model*.' This model proposes that the balance between risk factors (i.e., older age, pre-existing traditional CVD risk factors and shared biologic pathways for CVD and cancer such as inflammation, as well as treatment-related and lifestyle toxicity) and potential protection factors (i.e., lifelong non-smoking, regular physical activity, a healthy diet rich in fruits and vegetables, and management of body weight and stress, heart failure therapy) determine the individual risk of CVD morbidity and mortality after diagnosis of early breast cancer.

Contents

Abbreviations and acronyms: AIRR, adjusted incidence rate ratio; CI, confidence interval; CRF, cardiorespiratory fitness; CV, cardiovascular; CVD, cardiovascular disease; HER2, human epidermal growth factor receptor 2; HF, heart failure; HR, hazard ratio; IHD, ischemic heart disease; LV, left ventricular; PA, physical activity; RR, relative risk; SEER, Surveillance, Epidemiology, and End Results; SERM, selective estrogen receptor modulator; VO_2, volume of oxygen consumption; WHI, Women's Health Initiative.

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Breast cancer is the most frequently diagnosed malignancy in women worldwide, and the second leading cause of cancer mortality.[1] Due to advances in prevention, early detection and treatment, early stage breast cancer mortality has decreased by nearly 40% during the last four decades.[1] As a consequence, there is a rapidly expanding population of breast cancer survivors for whom survivorship care, with a particular emphasis on competing risks, is a critical area of clinical and research focus. Indeed, cardiovascular (CV) disease (CVD) is a leading cause of mortality in older breast cancer survivors.[2–4] The 'multiple hit hypothesis'[5] was proposed in 2007 to explain the increased CVD risk in breast cancer survivors by elevated underlying CVD risk factors at the time of diagnosis, the direct adverse effects of cancer therapy on cardiac function, lifestyle perturbations (decreased physical activity (PA)) and a concomitant decline in CV reserve. In 2007, CV toxicity was a recognized consequence of numerous breast cancer therapies, yet limited data were available to support the contention that breast cancer survivors were at increased subclinical and clinical risk of CVD as well as for the proposed components leading to the elevated risk.[5] In the last decade, a wealth of additional evidence confirmed aspects of the multiple hit hypothesis and further characterized the CVD risk, including additional contributing factors, pathogenic mechanisms, as well as potential counter measures. The aim of this review is to update and extend the 'multiple hit hypothesis' using new evidence gained since the publication of the original paper in 2007.

CVD risk in breast cancer

CVD is an important competing risk for death in breast cancer survivors.[2–4] A recent systematic review demonstrates the dramatically strengthened evidence for elevated CVD-related mortality risk in breast cancer, including 14 studies with over 1.2 million women with a history of breast cancer.[6] The absolute risk of dying from CVD following a breast cancer diagnosis was higher (range 1.6% to 10.4%) than among women in the general population without breast cancer.[6] In particular, the elevated risk for cardiomyopathy/heart failure (HF) (adjusted incidence rate ratio (AIRR) = 1.35, 95% confidence interval, (95% CI) =1.19–1.54) appears to be higher than for any CVD (AIRR = 1.13, 95% CI = 1.06 to 1.22) in breast cancer survivors.[2] A population-based study of all female Swedish residents born before 1977 (3.55 million women, breast cancer $n = 122{,}217$, diagnoses 1987–2006) reported an increased risk of dying of CVD in breast cancer survivors, including from HF (hazard ratio (HR) = 1.29, 95% CI = 1.22–1.37), ischemic heart disease (IHD; HR = 1.14, 95% CI = 1.10–1.19), other CVD (including valve disease, conductance abnormalities, pericarditis, myocarditis, HR = 1.24, 95% CI = 1.17–1.32) and diseases of the pulmonary circulation (HR = 1.51, 95% CI = 1.36–1.68) relative to women without breast cancer.[7]

Pre-diagnosis risks

CVD risks exist prior to breast cancer diagnosis, during the active treatment period, and continue into the post-treatment or survivorship period. These risks are categorized as such in the following sections.

Age at diagnosis

The primary risk factor for the development of CVD is advancing age, and likewise, a greater increase in cardiotoxicity and HF risk has been noted in older breast cancer survivors or in longer-term survivorship.[3,8] The risk of CVD-related death increases with age at diagnosis and with length of follow-up, whereby women diagnosed with breast cancer over the age of 75 have nearly a 23-fold higher risk compared to women diagnosed at 50–54 years of age.[9]

Traditional CVD risk factors

Breast cancer and CVD share a number of modifiable risk factors, including obesity, physical inactivity and diabetes.[10] Further, age, hypertension, smoking, and family history of IHD are strong predictors for the development of breast cancer therapy-related CV injury.[11–14] These and other risk factors to be discussed interact to elevate risk for CVD mortality (Fig. 1).

It has been previously suggested that at the time of breast cancer diagnosis, a substantial fraction of women are already at significant risk for CVD.[5] A recent analysis of the Women's Health Initiative (WHI) that included a large prospective cohort of 4518 post-menopausal women (average age 68 years) with breast cancer and 97,576 women without breast cancer provides valuable insight regarding CVD incidence and risk factor prevalence prior to breast cancer diagnosis.[15] Of those women later diagnosed with breast cancer, 3.9% had a history of CVD at study entry (prior to diagnosis), and another 7.9% were diagnosed with CVD after diagnosis. At study entry, the prevalence of all risk factors were the same between women who were later diagnosed with breast cancer (within 10 years) and those not diagnosed with breast cancer: overweight/obesity (63–65%), current (6%) and past (42–44%) smoking status, hypertension (30–33%), diabetes (4%), and hypercholesterolemia (11%).[15] In all women with CVD during the study, CVD risk factors were higher at study entry; yet, importantly, prevalence of risk factors was not different between women with CVD who did or did not develop breast cancer.[15] This finding suggests that presence of CVD risk factors predict CVD development regardless of breast cancer. Among breast cancer cases specifically, those who also later developed CVD were more likely to be older, a current smoker, have a history of hypertension, diabetes or hypercholesteremia, have a higher waist circumference, and be a non-user of hormone therapy at study entry compared to breast cancer cases without CVD.[15] A recent analysis of the Sister Study cohort also confirmed that a pre or post-menopausal breast cancer diagnosis (mean ages: 52 and 63 years, respectively) and subsequent treatment does not influence the amount of change in individual CVD risk factors and the Framingham 10-year CVD risk score over a 7.8 year follow-up relative to women without breast cancer.[16] Taken together, these prospective cohort studies appear to suggest that CVD risk factors before or at the time of breast cancer diagnosis are not elevated relative to women without breast cancer.

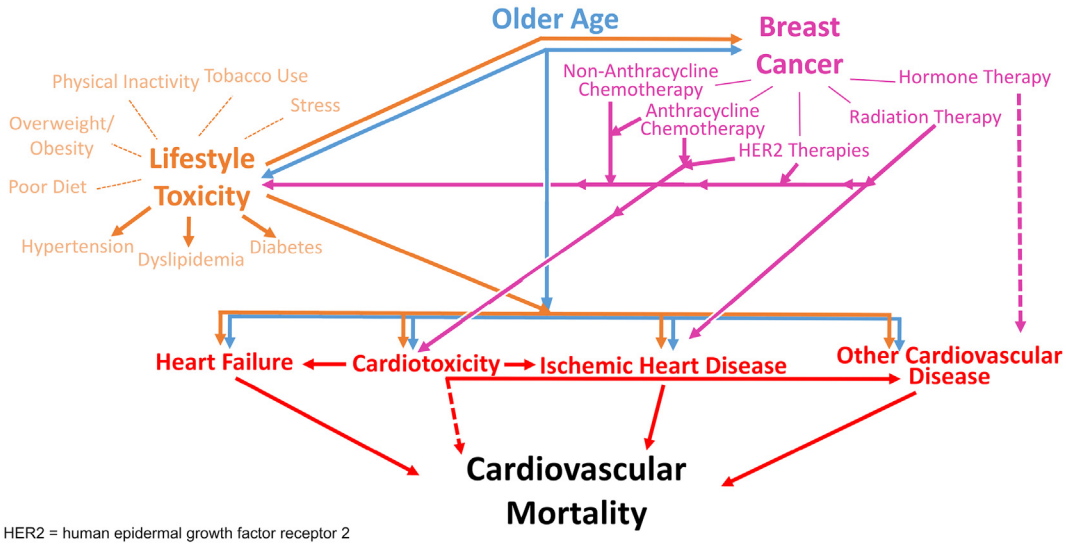

Fig. 1. Interaction of risk factors for elevated cardiovascular mortality in women diagnosed with breast cancer.

Despite the prevalence of CVD risk factors not appearing to be elevated before a breast cancer diagnosis, there are data to suggest that those who have pre-existing CVD risk factors or CVD are more likely to have worse cardiovascular outcomes after a breast cancer diagnosis.[17] In those breast cancer survivors from the WHI with hypertension, diabetes, high waist circumference, hypercholesterolemia, or a greater total number of CVD risk factors at study entry, there was an elevated risk of CVD-related mortality occurring within a median follow-up of 11 years after breast cancer diagnosis.[17] Analysis of the Surveillance, Epidemiology, and End Results (SEER) – Medicare linked database demonstrated that 26% of breast cancer survivors over the age of 66 who died from CVD had underlying CVD at the time of their breast cancer diagnosis.[4] Another SEER analysis demonstrated that the co-occurrence of breast cancer and HF substantially elevates all-cause mortality relative to breast cancer alone, even after adjustment for cancer-related and comorbid disease variables that could also affect survival (HR = 1.62, 95% CI = 1.32–2.00).[18] While the sequence of breast cancer and HF diagnoses was unknown within this dataset, this finding clearly demonstrates that HF significantly worsens prognosis for women with breast cancer.

Presence of shared biologic pathways for cancer and CVD

Beyond shared modifiable risk factors, emerging evidence suggests that there are shared biologic pathways in the development and progression of CVD and cancer.[10,19] Chronic inflammation and oxidative stress are common among many diseases including both cancer and CVD.[10] A number of growth factors or enzymes have been linked to the development or progression of both cancer and CVD, such as growth differentiation factor 15 (GDF-15), neuregulin, and matrix metalloproteinases.[20–24] Individuals with upregulation of these shared biologic pathways could be at increased susceptibility to CVD development prior to the development of breast cancer.

Further, there is preclinical and very preliminary clinical evidence that the presence of cancer, independent of any anti-cancer therapies, is associated with a different cardiac phenotype than non-cancer controls.[25–34] Various tumor-bearing rodent models exhibit differences in LV cardiomyocyte and cardiac structure (e.g., reduced myofibril volume, axon length, LV wall thickness), fibrosis and mitochondrial impairment, altered gene expression of cardiac contractile proteins, and systemic pro-inflammatory changes in TNF-α and IL-6 relative to non-tumor bearing animals.[25–27] A well-controlled recent study in rats demonstrated that implantation of cancer cells caused a significant reduction in endurance exercise capacity (i.e., time to exhaustion) of 15% and 54% at four and eight weeks post-surgery, respectively, which was significantly different from a sham surgery control group.[28] It is challenging to untangle the effect of cancer development from the impact of cancer treatment on exercise capacity, cardiac function, and future development of CVD in clinical research studies. Cross-sectional studies with non-cancer comparison groups report subclinical cardiac dysfunction (as measured by reduced myocardial strain) and suboptimal lipid profiles (i.e., higher total cholesterol, triglyceride and low-density lipoprotein levels, and low high-density lipoprotein levels) in treatment naïve mixed diagnosis cancer patients and breast cancer patients, respectively.[29–34] These two lines of evidence suggest that factors that precede cancer development and/or are associated with the cancer itself could potentially be one of the earliest risk factors contributing to the predisposition of cancer survivors to CVD.[35] However, this evidence is currently preliminary and requires further preclinical and clinical investigation.

Active treatment risks

It is likely that the risk factors that have the greatest potential to influence CVD morbidity and mortality in women with breast cancer occur during the active treatment period. CV toxicity is a direct effect of a number of breast cancer therapies. Lifestyle toxicity (i.e., the worsening of lifestyle behaviors) is an indirect sequela of cancer treatment.

CV toxicity of breast cancer therapies

Direct effects of breast cancer therapy include cardiac or vascular structural and functional changes related to receipt of individual or multi-model therapies. For the purposes of this review the primary treatment types that are mostly commonly associated with cardiac or vascular toxicity are discussed. Readers are referred to a more exhaustive review[36] that describes all therapies used to treat breast cancer that may have these effects.

Anthracycline chemotherapy

The anthracycline chemotherapeutic agents, doxorubicin and epirubicin, have been the mainstay of breast cancer therapy since the 1980s, and today remain an important component of third generation regimens.[37] Use of anthracyclines is associated with a dose-dependent, and potentially irreversible left ventricular (LV) dysfunction, termed cardiotoxicity.[38] The modern definition of cardiotoxicity involves a decrease in LV ejection fraction of at least 10 percentage

points to a value <53%.[39] A recent prospective study reported a 10% incidence of anthracycline-related cardiotoxicity among breast cancer patients within a median 5.2 year follow-up.[40] Subclinical cardiotoxicity can be defined as an asymptomatic drop in LV ejection fraction of >10 percentage points, elevated circulating cardiac biomarkers, or deterioration in LV longitudinal strain.[41,42] Incidence of subclinical cardiotoxicity is much higher and likely leaves individuals more susceptible to future challenges to the CV system, including subsequent cancer treatments.[43]

The mechanisms for anthracycline-related CV toxicity are likely multifactorial with summative effects and feedback from diverse processes. The contemporary view is that the primary mechanism is inhibition of topoisomerase 2β, an enzyme regulating DNA unwinding, resulting in activation of cardiomyocyte apoptosis and mitochondrial dysfunction.[44] Readers are referred to recent reviews for more information regarding anthracycline mechanisms.[44,45] The traditional view of the onset of anthracycline-related cardiotoxicity dates back to the 1980s and can include: 1) acute onset, occurring during or within two weeks of treatment completion; 2) early-onset, developing within one year; or 3) late-onset, developing years or decades after treatment.[40] However the understanding of anthracyclines in this respect has shifted in recent years following publication of the largest prospective cohort study to-date ($n = 2625$) of anthracycline-treated adults (51% breast cancer) by Cardinale et al. in 2015.[40] This study reported a median cardiotoxicity onset of 3.5 months, and onset of 98% of all cases within one year after anthracycline completion. However, many of the cases identified within that year were asymptomatic. Therefore, in a real-world setting without close monitoring of cardiac function, many cases could have gone undetected with slow progressive remodeling for months or years before clinical or symptomatic presentation prompting diagnosis.[40] The most consistently reported and robust risk factor for anthracycline-related cardiotoxicity is cumulative dose, while chest radiotherapy, African-American ethnicity, hypertension, diabetes, very young or old age, very low or high body weight, or severe/multiple comorbidities also play a prognostic role.[14]

There is preclinical evidence that anthracyclines accumulate in the tissues and impair function of the smooth muscle of the vasculature as well as the heart.[46] Several clinical studies have reported that anthracycline chemotherapy is associated with increased aortic stiffness concurrent to decreased global systolic function as early as the first month after initiation of low to moderate dose anthracycline chemotherapy.[47,48] However, these effects may not persist long-term; Koelwyn et al. reported that central and peripheral arterial stiffness and peripheral arterial endothelial function of women who were 6.5 years post anthracyclines did not differ from age-, body mass index-, and fitness-matched healthy women.[49] Considering the established role of vascular pathology in traditional heart disease,[50] breast cancer therapy-related vascular toxicity likely plays a role in the increased risk of CVD and exercise intolerance among breast cancer survivors.

Targeted therapies

Human epidermal growth factor receptor 2 (HER2) is a transmembrane tyrosine kinase receptor that is overexpressed in approximately 20% of invasive breast cancers and promotes the malignant phenotype. Trastuzumab and pertuzumab are humanized monoclonal antibodies that bind to the extracellular domain of HER2 to inhibit signaling and control tumor growth, thereby conferring a substantial overall and disease-free survival benefit in HER2 overexpressing breast cancer.[51] The HER2 isoform is also expressed in ventricular cardiac myocytes and by way of neuregulin-1 activation of several downstream signaling cascades, plays a critical role in cardiomyocyte survival and regulation of the myocardium.[22] As a result, trastuzumab inhibition of HER2 can also lead to dilated cardiomyopathy (e.g., LV cavity dilatation, wall thinning, and decreased contractility) and HF.[52,53] In contrast to anthracycline-related cardiotoxicity, trastuzumab-related cardiotoxicity is not dose-dependent and is believed to be relatively reversible following treatment cessation.[53] A recent meta-analysis of randomized controlled trials reported rates of 1.9% and 7.5% for HF and LV ejection fraction declines (>10–15 percentage points) with trastuzumab therapy for breast cancer, but that patients receiving non-anthracycline chemotherapy regimens were not at increased risk for HF.[54] However, observational and real-world clinical practice accounts of trastuzumab-mediated cardiotoxicity have been reported to be approximately twice as prevalent.[55–57] In early trials when trastuzumab was administered concurrently with anthracyclines, 27% of patients developed cardiotoxicity.[58] As a result, trastuzumab and anthracyclines are now infrequently used concurrently, but may be used sequentially. Compared to women with breast cancer who were not treated with trastuzumab, those treated with trastuzumab have a five-fold increased risk (relative risk (RR) = 5.11, 95% CI = 3.00–8.72) of developing HF and two-fold increased risk of an LV ejection fraction decline (RR = 1.83, 95% CI = 1.36–2.47).[51] Hypertension, obesity, postmenopausal status, personal or family history of ischemic heart disease, and current/previous smoking status have been shown to be more common in those developing cardiotoxicity.[12,13]

Radiotherapy

Radiation is a localized therapy that is very commonly used to treat breast tumors, residual breast tissue, and at-risk lymph nodes in the axilla, clavicle or internal mammary chain. Among women with breast cancer, there is a linear relationship between amount of radiation dose delivered to the heart and rates of ischemic heart disease with no apparent threshold.[59] Breast cancer radiotherapy regimens have significantly improved over time due to the development of new techniques, higher radiation beam energy, and contouring modalities for dose delivery, which allow for reduced, but not eliminated (especially in the case of left-sided breast cancer), cardiac doses.[11] A systematic review and meta-analysis of breast cancer regimens published from 2010 to 2015 indicated that more modern regimens still pose a significant CVD mortality risk (HR = 1.30, 95% CI = 1.15–1.46).[60] The mechanism for radiation-related CV toxicity is damage to both the cardiac micro and macro vasculature.[11] Radiation treatment for breast cancer also causes localized arterial stiffening on the treated side.[61] The onset of radiation-related cardiac effects ranges from months for acute conditions (e.g., pericarditis), up to decades for clinical manifestation of IHD.[11] Risk factors for radiation-related CV toxicity include age, hypertension, diabetes, smoking status, and receipt of other cardiotoxic cancer therapies.[11]

Endocrine therapy

Endocrine therapy remains the cornerstone of adjuvant therapy for women with hormone-receptor positive breast cancer. The selective estrogen receptor modulator (SERM), tamoxifen, significantly reduces disease recurrence and breast cancer-related mortality and has lipid lowering and vascular function enhancing effects.[62] However, the potential positive vascular benefits are offset by potential prothrombogenic effects resulting in increased risk of stroke, pulmonary embolism and deep vein thrombosis.[62] Recent meta-analyses comparing randomized trials of SERMs to placebo or tamoxifen to extended (>5 years of therapy) tamoxifen both demonstrated no effect on CVD events, but an elevated risk of venous thromboembolic events.[63,64] Since 2000, the third generation aromatase inhibitors (AI) anastrozole, letrozole, and exemestane, have been increasingly used in lieu of tamoxifen for endocrine therapy for postmenopausal women with early breast cancer due to significant reductions in recurrence. In some but not all of the early large trials comparing tamoxifen to AI's there was a small but significant increased risk of CVD events with AI treatment,[62] in line with the finding from cross-sectional studies that women on AI's have worse arterial stiffness than women on tamoxifen.[65,66] Two recent meta-analyses of randomized controlled trials comparing tamoxifen to AI's show that findings may depend on the type of analysis and outcome. A meta-analysis of individual patient data found no overall difference in number of deaths related to cardiac or vascular origin,[67]

while a meta-analysis of data across trials reported a significant increased risk of CVD events (including primarily disease outcomes but also some deaths, RR = 1.19, 95% CI = 1.07–1.34).[68] A recent meta-analyses of studies comparing AI's to placebo or no treatment, showed prolonged AI use results in a small but significant increase in odds of a CVD event (odds ratio = 1.18, 95% CI = 1.00–1.40).[69]

Lifestyle toxicity related to breast cancer therapy

Relative to treatment toxicity, lifestyle toxicity is a less recognized, but equally as pervasive a consequence of breast cancer diagnosis and therapy.

Physical inactivity and decreased cardiorespiratory fitness (CRF)

Over 15 years ago it was reported that self-reported total and recreational PA decrease and sedentary time increases following a breast cancer diagnosis and subsequent treatment.[70] Unfortunately, despite mounting evidence of the benefits of PA for breast cancer, more recent self-reported and objective accelerometry measures still demonstrate this trend.[71,72] Over the course of cancer treatment, the gold standard measure of CRF, peak VO_2, declines up to 26%.[73] Peak VO_2 is a well-established independent predictor of the development of CVD risk factors, CVD, and CVD-related and all-cause mortality.[74–76] The few studies examining the mechanisms underpinning the reduced peak VO_2 among breast cancer survivors suggest that both cardiac and "non-cardiac" (i.e., skeletal muscle and vasculature) factors result in decreased oxygen transport to and utilization by the exercising muscles.[77–79]

Diet and body weight

Diet and nutritional quality appear to decline with breast cancer therapy. During chemotherapy treatment for early breast cancer, the quality (i.e., consumption of fruits, vegetables, whole grains, poultry and fish versus consumption of refined grains, sweets, high-fat dairy products, and red and processed meats) and quantity of energy and micronutrient intake decrease.[80] Furthermore, fruit and vegetable consumption, a known CVD protective factor, also decrease.[80] Women who gained weight during chemotherapy treatment reported that chemotherapy resulted in decreased enjoyment of food, changes in taste, and selection of 'less healthy foods.'[81]

Body weight gain is closely tied to several aspects of lifestyle, and being overweight/obese is a significant independent prognosticator for CVD.[82] Weight gain, especially with chemotherapy treatment is commonly reported for women with breast cancer.[83] During breast cancer treatment, both reductions in diet quality and PA are associated with weight gain.[80,84] The typical pattern of weight gain reported includes increased fat mass, without associated gains in lean mass, or often with losses in lean mass.[83]

Stress

Cancer diagnosis and treatment are associated with a range of psychological, social, and existential stressors that can continue long after completion of primary treatment into survivorship.[85] Further, nearly 50% of women experience depression, anxiety or both within the first year after diagnosis.[86] Decades of epidemiological evidence support a relationship between psychological stress and CVD.[87] Acute stresses have been shown to induce a drop in LV ejection fraction in some patients with IHD, which was a significant predictor of later CVD events.[88] Large cohort studies have reported that chronic stress at home or work increased the risk of developing a myocardial infarction or IHD by 2.1 times.[87] Depression and anxiety are also consistently linked to CVD via both behavioral (e.g., smoking, physical inactivity, poor diet) and biological (e.g., inflammation, autonomic dysfunction) mechanisms.[89] However, to our knowledge, no study has made a direct link between psychological stress and development of cardiotoxicity.

Smoking

Smoking is estimated to be responsible for 10% of all cases of CVD in the general population.[90] The increased risk of CVD events and mortality among former smokers decreases linearly with time since cessation.[91] One potential positive effect of breast cancer diagnosis and subsequent therapy on a lifestyle risk factor is smoking cessation; one-third to one-half of smokers successfully quit following a breast cancer diagnosis, which is a higher rate than in a non-cancer comparison group over a similar time period.[92,93] Smoking history is a risk factor for CVD death and cardiotoxicity among radiation- and trastuzumab-treated breast cancer survivors, respectively.[12,60]

Post-treatment/survivorship risks

Chemotherapy-induced menopause

Prior to menopause, women have a significantly lower risk of CVD than men, but with the onset of menopause, this risk gap is abolished.[82] Approximately one-fifth of breast cancer cases diagnosed in developed countries and up to one-half in less developed countries occur in premenopausal women.[94] The occurrence of ovarian damage with breast cancer treatment depends on age at diagnosis and type of treatment, with women over the age of 40 years at a much higher risk than those younger than 40 years.[95] At least one-third of women of any age and up to 95% of women over the age of 40 years will experience amenorrhea, or loss of their menstrual cycle with various traditional and contemporary chemotherapy protocols used to treat breast cancer.[96] Approximately 40% of cases of chemotherapy-induced amenorrhea will be permanent resulting in onset of menopause much earlier than it would have occurred naturally.[95] Data on early menopause related to another medical intervention, bilateral oophorectomy, demonstrate potential increased risk of CVD and related mortality, which may be attenuated by supplemental estrogen therapy, an option not available to women with hormone-receptor positive breast cancer.[97] The reduced lifelong exposure to estrogen experienced by premenopausal women diagnosed with breast cancer could cause a multitude of negative effects that could increase risk of CVD including an unfavorable redistribution of body fat to the abdomen, and reduced physical activity and resting energy expenditure.[98–100]

Continued poor lifestyle behaviors

Blanchard et al. reported that at 2–10 years post diagnosis, nearly two-thirds of breast cancer survivors do not meet the American Cancer Society physical activity guidelines (defined as accumulation of 150 min of moderate-to-vigorous or 60 min of vigorous physical activity per week).[101] As a late consequence of cancer treatment and a sedentary lifestyle, peak VO_2 remains 27% lower in breast cancer survivors who are 6 months to 3 years post completion of chemotherapy and radiation compared to age-matched healthy sedentary women.[102] Regarding weight gain during breast cancer treatment, even after up to six years of follow-up only 10% of women returned to their pre-diagnosis weight.[103] Psychological stress following a breast cancer diagnosis persists at five years after diagnosis in 15% of women.[86]

Increased susceptibility to future insults

Given that the greatest risk factor for development of LV dysfunction is any prior CV dysfunction or disease, Witteles et al. contend that even transient LV dysfunction would leave individuals more susceptible to future insults including subsequent receipt of another cardiotoxic treatment and IHD.[43] We extend this contention to include all forms of treatment-related CV injury as potential culprits to increase susceptibility to future insults. We also suggest that women with breast cancer who experience subclinical CV injury during active treatment may be

more susceptible to the effects of age-related CV deterioration and development of other chronic diseases in post-treatment/survivorship.

Protection: preventative and treatment strategies

Exercise and PA

While aerobic exercise is considered a promising lifestyle intervention for the prevention of anthracycline-related cardiotoxicity, experimental evidence for this effect is primarily limited to rodent models.[104] This preclinical evidence is overwhelmingly positive, demonstrating protective effects of varying amounts of exercise training before or during receipt of the anthracycline agent, doxorubicin, at the biochemical, histological, and functional level of the heart.[104] However, critical limitations to the translatability of the majority of this work are that the animal models utilized are otherwise healthy (i.e., lacking the cancer, CVD risk factors, and comorbid conditions that clearly interact with anthracycline toxicity in humans) and most utilized exercise prescriptions are not feasible for most humans concurrent with chemotherapy.[104] The few small studies examining the effect of chronic aerobic training during anthracyclines or trastuzumab on cardiac function of women with breast cancer have shown that this intervention does not improve resting LV ejection fraction.[105,106] A recent, small, non-randomized study by Howden et al. reported no effect of exercise training on magnetic resonance imaging-derived resting and exercise cardiac function.[79] This study also reported that declines in peak VO_2 and calculated arterial-venous oxygen difference were attenuated in the exercise group relative to usual care control subjects. This suggests that exercise training-induced peripheral or 'non-cardiac' adaptations may play an important role in preventing a decline in peak VO_2 during adjuvant therapy. In a small RCT, Kirkham et al. reported a potential protective role of acute aerobic exercise (i.e., single, vigorous-intensity, 30-minute session) performed 24 h prior to anthracycline treatments; exercise attenuated circulating markers of anthracycline-related cardiac injury.[107] To our knowledge, no studies have assessed the effect of exercise training on cardiac function of women following completion of breast cancer therapy.

Some observational data demonstrates a role for self-reported exercise performed after diagnosis and primary treatment in the prevention of CVD morbidity and mortality in women with breast cancer. Bao et al. demonstrated that the amount of exercise performed between 6 and 60 months post breast cancer diagnosis was inversely associated with the prevalence of the metabolic syndrome (defined as presence of ≥3 of: waist circumference > 88 cm, fasting blood glucose ≥ 6.1 mmol/L, fasting triglyceride ≥ 1.7 mmol/L, fasting HDL < 1.295 mmol/L, or blood pressure ≥ 130/85 mm Hg) at 60 months post diagnosis.[108] Relative to inactive women, as few as 3.5 h/week of exercise (primarily walking) during this period significantly reduced risk of metabolic syndrome.[108] Post breast cancer diagnosis, physical activity is inversely related to breast cancer specific and all-cause mortality.[109] Women who are inactive prior to diagnosis but increase PA levels after diagnosis have a reduction in risk of all-cause mortality by 45% relative to women who remain inactive.[110] Conversely, women who were active prior to diagnosis and reduce their PA have nearly a four-fold increased risk of overall mortality relative to women who were inactive pre-and post-diagnosis.[110] Therefore, it appears that physical activity behavior after diagnosis is the most important for reducing risk. These results are not differentiated among causes of death, but due to the well-established role between PA and primary and secondary prevention of CVD-related mortality, it is likely that at least part of the positive effect of post diagnosis PA is on CVD-related death in women with breast cancer. In fact, another recent analysis demonstrated that a graded inverse relationship exists between PA self-reported 22 ± 7 months after breast cancer diagnosis and CVD events, which potentially indicates that the greater volume of weekly exercise performed, the better for CVD risk reduction.[111] Furthermore, meeting the recommended amount of weekly PA (150 moderate-to-vigorous minutes) was associated with significant reductions in risk of CVD events irrespective of age, CVD risk factors at diagnosis, menopausal status, and type of cancer therapy.[111] Given this preliminary evidence and the other known benefits of regular exercise, it is recommended that women maintain or improve their aerobic exercise habits after a breast cancer diagnosis.

Diet

While not specific to breast cancer, a meta-analysis of 95 studies reported the strong relationship between increased consumption of fruits and vegetables and reduced risk of CVD and all-cause mortality.[112] Given that this single dietary change can also reduce cancer risk, it is strongly recommended for women with breast cancer who are at risk for CVD. Fasting or caloric restriction (reduction in daily caloric intake) are promising dietary interventions with therapeutic potential for prevention of cardiotoxicity during active treatment. Experimental evidence in animals and observational evidence in humans demonstrate that caloric restriction and/or fasting have powerful cardio-protective benefits in non-cancer therapy-related cardiac conditions including myocardial infarction, ischemic heart disease, and aging.[113,114] Currently available efficacy data that is specific to cancer therapy cardioprotection is limited to preclinical studies, ranging from 40 days of 35% caloric restriction providing 100% protection from anthracycline-related cardiotoxicity and related death[115] to 24–60 h of fasting providing protection from treatment toxicity to various organs including the heart in rodents.[116,117] A potential mechanism is a phenomenon labeled 'differential stress resistance,' where nutrient deprivation induces a 1000-fold increase in resistance to oxidative stress in healthy cells but not in cancer cells due to differences in cellular metabolic responses.[116] Kirkham et al. are conducting an ongoing randomized controlled trial (RCT) in early breast cancer investigating the effect of a 48-h 50% caloric restriction intervention prior to receipt of anthracycline chemotherapy on magnetic resonance imaging-derived LV ejection fraction reserve (primary outcome) and aortic distensibility (secondary outcome).[118] In terms of diet in the survivorship period, higher diet quality (as defined earlier) among breast cancer survivors 30 months post-diagnosis reduces the risk of all-cause mortality.[119]

Stress

To our knowledge, no experimental studies have investigated the effect of stress reduction interventions on CVD outcomes in women with breast cancer. However, a meta-analysis of yoga interventions in women with breast cancer reported significantly reduced perceived stress and psychological distress when the intervention was performed during active treatment.[120] Meta-analyses of mindfulness-based stress reduction and yoga interventions performed either during active treatment or post-treatment demonstrate significant reductions in anxiety and depression.[120,121]

Smoking cessation

A meta-analysis of observational data in non-cancer populations indicates that smoking cessation does reduce risk of CVD events and mortality.[91] Due to the well-established risk of smoking for CVD in general and for breast cancer treatment-related cardiac dysfunction and events, smoking cessation in women who are smokers at breast cancer diagnosis would be expected to reduce lifetime risk of development of CVD. To our knowledge, there are no experimental studies testing the impact of smoking cessation on CVD outcomes in breast cancer survivors. A prospective observational study of women with breast cancer did not find that smoking cessation benefited CVD-related mortality.[122] In fact, women who were smoking shortly prior to their diagnosis but then quit afterwards remained at a three-fold elevated risk for CVD mortality relative to women who never smoked.[122] Even women who

Table 1
Comparison of compounding risk and protection model to the multiple hit hypothesis.

Model component	Multiple hit hypothesis	Compounding risk and protection model
Consequences	Hypothesized ↑ risk of CVD and mortality in BC	• Confirmed ↑ risk of CVD and mortality in BC by pooled results from 14 studies • Prevention/treatment strategies can balance risks to determine overall cardiovascular health
Phases of risk and protection approaches	N/A	• Pre-diagnosis • Active treatment • Post-treatment/survivorship
Baseline cardiovascular risk	Hypothesized ↑ prevalence of cardiovascular risk factors	No difference in prevalence of cardiovascular risk factors relative to women without BC, but ↑ CVD risk in those with cardiovascular risk factors
Other pre-diagnosis risks	N/A	• Evidence for age as a major risk factor for treatment toxicity, CVD and mortality in BC • Potential for shared biological pathways between CVD and cancer posing a pre-diagnosis risk
Direct effects of cardiotoxic therapies	Available data as of 2007; CVD-related mortality data for radiation regimens prior to 1990	• Most up-to-date meta-analysis data on risk of LV dysfunction, CVD and CVD-related mortality with contemporary treatment regimens • Evidence for vascular toxicity
Indirect effects	"Unfavorable lifestyle changes": ↓ physical activity and ↑body weight	• "Lifestyle toxicity": continued trend of ↓ physical activity and ↑ body weight, plus ↓ diet quality, ↑ stress; positive effect on smoking status (↑ cessation) • Healthy lifestyle behaviors prior to diagnosis and after treatment completion also contribute to the maintenance of cardiovascular health
Chemotherapy-induced menopause	N/A	Temporary amenorrhea or permanent early menopause ↓ lifetime estrogen exposure which may be an important contributing risk for pre-menopausal BC
Susceptibility to future insults	Suggestion that anthracycline-related subclinical LV dysfunction leaves patients more susceptible to effects of aging and other diseases	Suggestion that all forms of treatment-related cardiovascular injury may ↑ susceptibility to future insults including subsequent treatments, natural progression of CVD or other diseases, infection, and age-related deterioration of cardiovascular function
Prevention and/or treatment approaches	• Potential effects of ACE-inhibitors and β-blockers from two studies • Recommendation to treat risk factors with standard therapies • Exercise training as a promising therapy; minimal supporting evidence available	• Evidence of extensive preclinical data showing exercise intervention efficacy, but clinical data is still limited • Evidence that self-reported exercise after diagnosis ↓ incidence of metabolic syndrome, cardiovascular events and all-cause mortality in BC • Recommendation to maintain or ↑ aerobic exercise habits after BC diagnosis & ↑ consumption of fruits and vegetables • Potential effects of caloric restriction or fasting • Evidence for stress-reducing effects of mindfulness-based stress reduction and yoga interventions • Evidence of greatest benefit with life-long non-smoking • Evidence of ↓ risk of HF or LV ejection fraction decline with β-blockers, statins, angiotensin antagonists and dexrazoxane

Abbreviations: ACE = angiotensin-converting inhibitors; BC = breast cancer; CVD = cardiovascular disease; HF = heart failure; LV = left ventricular; N/A = not available;

quit smoking up to 10 years prior to a breast cancer diagnosis are still at a 47–69% elevated risk for CVD mortality.[122] Further, smoking shortly prior to diagnosis and quitting after diagnosis did not appear to reduce risk (RR = 0.84, 95% CI =0.51–1.38).[122]

Risk-based treatment planning

In current practice, treatment plans include risk analysis and risk aversion techniques. One method is dose minimization, whereby cumulative lifetime anthracycline dose limits of 240–300 mg/m^2 are used for early breast cancer to minimize risk of cardiotoxicity. Additionally, cardiotoxic therapies are contraindicated in patients with underlying structural heart disease or persistent arrhythmias.[123,124] Some treatment centers also restrict anthracycline use to certain ages (e.g., <65–75 years) and to high-risk cancers (e.g., node positive or neoadjuvant patients) to further mitigate risk.

Alternative administration routes

Manipulation of anthracycline administration routes, such as slower infusion in lieu of a bolus injection, liposomal encapsulation of doxorubicin, and use of an equiactive, but less cardiotoxic analog have been studied as possible methods to reduce cardiotoxicity.[125] However, these methods are not widely used. The only widely used analog of doxorubicin, epirubicin, has reduced antitumor activity when used at equal dosing to reduce cardiotoxicity, so it is administered in much higher doses, which negates the lower expected level of cardiotoxicity.[125]

Pharmacology

Commonly used HF medications have been studied in the context of prevention and treatment of anthracycline and trastuzumab-related cardiotoxicity during the active treatment period. The most commonly studied drug classes are beta-blockers, angiotensin-converting enzyme inhibitors, statins, and diuretics. The only pharmacological therapy developed specifically for cardiotoxicity is dexrazoxane, an iron chelator, that is thought to prevent DNA damage and cardiomyocyte death when infused prior to anthracyclines.[125] A meta-analysis of prophylactic pharmacological interventions consisting of 12 RCTs confirmed significant risk reduction of HF or LV ejection fraction drop by beta-blockers (RR = 0.31, 95% CI = 0.16–0.63), statins (RR = 0.31, 95% CI = 0.13–0.77), angiotensin antagonists (RR = 0.11, 95% CI = 0.04–0.29) and

dexrazoxane (RR = 0.35, 95% CI = 0.27–0.45).[126] However, the majority of studies to-date have had limited sample sizes and lacked long-term follow-up, so the extension of benefit to long-term CVD risk is unknown.[125] As a result, their use in clinical practice varies widely between centers and is not widely endorsed by clinical guidelines. Dexrazoxane is currently only Federal Drug Administration-approved as a cardio-protectant for women with metastatic breast cancer who have received a cumulative dose of 300 mg/m^2 of anthracyclines and is used infrequently.

The compounding risk and protection model

The 'multiple hit hypothesis' was introduced over 10 years ago as an early recognition of the emerging concern regarding elevated CVD risk among women with early stage breast cancer and provided a framework for the cardio-oncology community's research efforts. New evidence warrants revisiting the multiple hit hypothesis. Here we propose the 'compounding risk and protection model' as an updated framework that incorporates understanding gained over the past decade and introduces emerging risk and protective factors modulating CVD morbidity and mortality among women with breast cancer (Table 1). The 'compounding risk and protection model' describes the potential risks that may accumulate and intensify the negative aspects of one another on the CV health of women with breast cancer, as well as protective factors (including treatments) that may attenuate the risk intensity (Fig. 2). Pre-existing CVD and CVD risk factors (i.e., hypertension, obesity, diabetes, hypercholesterolemia, smoking) prior to diagnosis do not appear to be elevated relative to women who do not develop breast cancer, but when present, increase future risk of CVD mortality. Inflammation, oxidative stress, and other growth factors may contribute to cancer and/or CVD development and may introduce subclinical CV changes prior to receipt of treatments. Receipt of anthracycline chemotherapy, trastuzumab, radiation, and aromatase inhibitor therapies can cause independent and additive toxic effects on the cardiovascular system. Concurrent with (and sometimes preceding) active treatment, lifestyle toxicity (including reduced PA/decreased peak VO_2, reduced diet quality (especially reduced fruit and vegetable intake) smoking, and increased stress and body weight) is common and may enhance treatment toxicity and persist into post-treatment survivorship. In pre-menopausal women, chemotherapy commonly induces temporary amenorrhea or permanent menopause, resulting in reduced lifetime exposure to the cardio-protective benefits of estrogen. After cardiotoxic therapy-induced subclinical injury, the heart and vasculature may be more susceptible to future insults including future treatments and aging. While there is no evidence to indicate that exercise prior to cancer diagnosis reduces post-treatment cardiovascular risk, it is, along with a healthy diet rich in fruits and vegetables, body weight and stress management, and never smoking, known to be

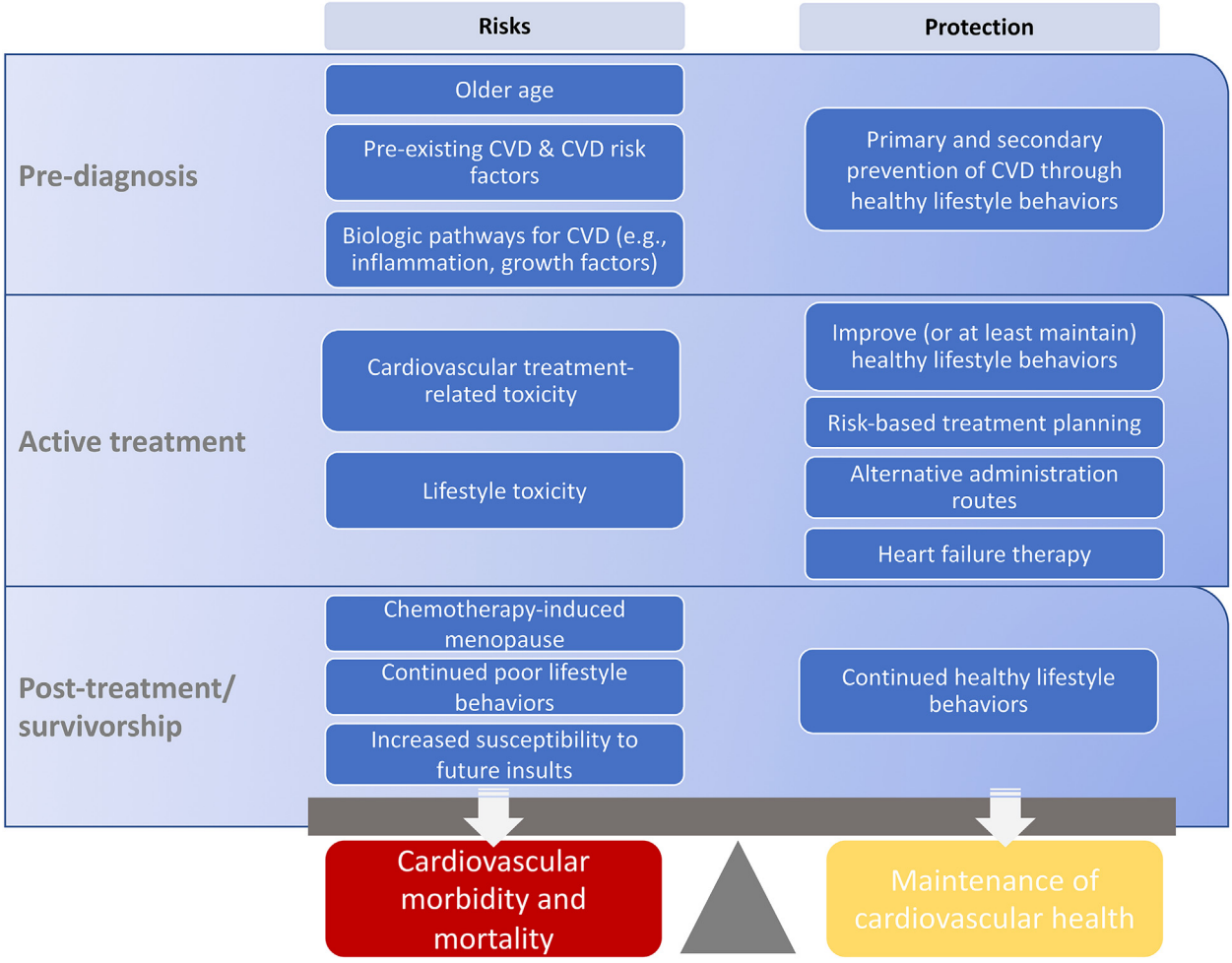

Fig. 2. The compounding risk and protection model. A diagram demonstrating the potential risks that may accumulate and intensify negative aspects of one another on cardiovascular health, and protective factors (including treatments) that may attenuate risk intensity. Together, the balance of risk and protection factors determines the individual risk of cardiovascular morbidity and mortality after diagnosis of early breast cancer. Cardiovascular risk factors include hypertension, obesity, diabetes, hypercholesterolemia, and smoking. Lifestyle toxicity includes reduced physical activity, decline in diet quality, increased body weight and psychological stress; whereas healthy lifestyle behaviors consist of regular physical activity, healthy diet, management of body weight and stress, and not smoking.

effective in the primary and secondary prevention of CVD in non-cancer populations. Life-long non-smoking may provide a substantial cardiovascular risk reduction. Selection of therapy regimens based on presenting risk factor profiles of patients, dose minimization, and use of alternative administration routes for cardiotoxic therapies are preventative strategies that may be employed in treatment planning. Increasing or maintaining typical healthy lifestyle behaviors during active treatment is likely to provide some protective benefit. Continuing these health behaviors into the survivorship period is likely to provide ongoing benefits. Lastly, there is some evidence that readily available and inexpensive HF drugs may mitigate or treat anthracycline and trastuzumab-related cardiotoxicity. Together, the balance of the risk and protective factors will determine a woman's cardiovascular health after the diagnosis of early breast cancer. This information can be used by clinicians, researchers, and even survivors to understand the risks and approaches for risk reduction for CVD morbidity and mortality after the diagnosis of early breast cancer. Future research is recommended to assess the impact of multiple risk factors and multi-disciplinary interventions on cardiovascular health of women with breast cancer in order to quantify the compounding of risk and protection factors.

Summary

The past decade has produced a substantial amount of new data that contributes to our understanding of the extent and mechanisms of, risk factors for, and preventative strategies for CVD morbidity and mortality among women diagnosed with breast cancer. Not only is it now well established that women with a history of breast cancer are at greater risk of dying from CVD than women without breast cancer, but CVD is a leading cause of death for older women with breast cancer. Prior to diagnosis, risks include older age, presence of traditional CVD risk factors, and presence of shared biologic pathways for CVD and cancer such as inflammation, while potential protective factors include healthy lifestyle behaviors such as lifelong non-smoking, regular PA, a healthy diet rich in fruits and vegetables, and management of body weight and stress. The greatest risks likely occur during active breast cancer treatment and include CV and lifestyle toxicity (i.e., the worsening of lifestyle behaviors). Anthracyclines, trastuzumab, and radiation therapy can cause cardiac and potentially vascular dysfunction that can progress to HF or IHD. In turn, maintenance or improvement of healthy lifestyle behaviors and prophylactic HF medications are potential protective therapies that require further investigation. During the post-treatment period, the balance of lifestyle behaviors remains important, as is the potential for chemotherapy-induced early menopause for women with pre-menopausal breast cancer, and the potential for increased susceptibility to future CV insults. The ‘competing risk and protection model’ proposes these risks accumulate and intensify CVD risk but that the balance of potential protective factors determines the individual risk of CVD morbidity and mortality after diagnosis of early breast cancer.

Conflict of interest

None of the authors have any conflicts of interests with regard to this publication.

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