STATE-OF-THE-ART PAPER

Early Breast Cancer Therapy and Cardiovascular Injury

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Although recent advances in curative-intent therapies are beginning to produce significant survival gains in early breast cancer, these improvements may ultimately be attenuated by increased risk of long-term cardiovascular mortality. This paper reviews emerging evidence on the cardiovascular effects of breast cancer adjuvant therapy and proposes a new entity that we have labeled the "multiple-hit" hypothesis. The evidence that lifestyle modification, especially exercise therapy, may mitigate these adverse effects is also reviewed. These issues are of considerable practical importance for cardiovascular clinicians, as identification and intervention in those at high risk for cardiovascular complications may reduce a major cause of mortality in women with early breast cancer. **(J Am Coll Cardiol 2007;50:1435–41) © 2007 by the American College of Cardiology Foundation**

Breast cancer is the most common malignancy in American women, with approximately 213,000 new cases diagnosed in 2006 (1). Although the incidence of breast cancer has increased by 0.2% per year between 1997 and 2000, improvements in detection and therapy have resulted in significant survival gains with breast cancer-specific mortality decreasing almost 24% between 1990 and 2000. As a result, approximately 2.3 million American women are now living with a previous history of breast cancer, with sufficient survival to be at risk for cardiovascular disease (CVD). The purpose of this paper is to review the cardiovascular effects of current and forthcoming adjuvant therapies for the treatment of early breast cancer so that clinicians will be better able to care for this emerging cohort of new cardiovascular patients. We also review the evidence supporting the potential treatment efficacy of conventional cardiovascular risk factors with both drugs and lifestyle modifications, including exercise therapy, to mitigate and/or prevent therapy-induced CVD in this population.

Early Breast Cancer Patients: A Population at Risk for CVD at Diagnosis

The association between traditional risk factors and CVD has been well studied among women in the general population. For example, an analysis of the Framingham data (2) estimated a 39% lifetime risk of developing CVD in women

at age 50 years. At this age, 40% of women in the population had at least 1 existing risk factor, and 17% had 2 or more risk factors, the latter associated with a 50% lifetime CVD risk. The presence of diabetes at age 50 years in either gender confers the highest lifetime risk for CVD of any single risk factor, with a CVD risk in women to age 75 years of 57% (2). These findings were confirmed by recent data from the Chicago Heart Association Detection Project in Industry, which found that, in comparison with women with favorable CVD risk profile, those with ≥3 risk factors had a substantially greater risk of CVD-related mortality (3). On the basis of this evidence, it is likely that a substantial fraction of breast cancer patients, at the time of diagnosis, will have a significant risk of developing CVD, which is then added to by the direct and indirect effect of breast cancer treatment. Importantly, as reviewed in this paper, the presence of pre-existing CVD risk factors is itself a strong predictor for the development of therapy-induced cardiovascular injury, making the likely lifetime risk for CVD much greater.

Indeed, although many factors have been associated with a primary breast cancer diagnosis, other established but lesser-known risk factors are physical inactivity and obesity. Recent estimates suggest that physical inactivity confers a population-attributable risk of breast cancer among white women of 2% to 15% (4), with overweight and obesity being associated with a 34% and 63% increased breast cancer risk, respectively (5). It could be speculated, therefore, that physical inactivity and obesity rates may be even greater among early breast cancer patients that, in turn, may translate into greater CVD risk independent of the effects of adjuvant therapy. Irwin et al. (6) reported that 62% of breast

cancer patients were either over-weight or obese, whereas Jones et al. (7) reported that 36% are sedentary. Both estimates are similar to those reported for women in the general U.S. population. Clearly, further research is required to estimate the relative proportion of cardiovascular morbidity/mortality attributable to either lifestyle modification and/or adjuvant therapy among women with early breast cancer.

Early Breast Cancer Therapy Selection

Although the broad range of cardiovascular diseases reflects complex interactions between traditional and novel risk factors, the situation is further complicated by the use of adjuvant therapy. Such therapies are selected on the basis of a complex algorithm, including patient factors (age, comorbidities, physiologic status, and patient preference) and tumor factors (tumor size, lymph node involvement, histological grade, and estrogen receptor [ER] and human epidermal growth factor receptor [HER]-2 status) (8). For example, women at low risk of recurrence who have ER-positive tumors may be offered oral hormonal therapy with tamoxifen or aromatase inhibitors. Women at moderate risk of recurrence generally are recommended to undergo 3 to 6 months of anthracycline-based chemotherapy, with or without adjuvant taxanes, and when ER-positive disease is diagnosed, adjuvant hormonal therapy. Women at high or extremely high risk of recurrence are recommended anthracycline-taxane chemotherapy, locoregional radiotherapy, followed by hormone therapy if ER positive. Additionally, for the 25% of women whose tumors possess the HER-2 alteration, 1 year of adjuvant trastuzumab is recommended either with, or after, chemotherapy (8).

Cardiovascular Complications of Breast Cancer Therapy

In the following sections, we review the available evidence describing the cardiovascular effects of current and forthcoming early breast cancer therapies (i.e., polychemotherapy, radiotherapy, endocrine therapy, HER-2–directed therapies, angiogenesis inhibition) and briefly review the postulated biological mechanisms that may underlie therapy-associated cardiovascular injury.

Polychemotherapy. Unfortunately, each of the many chemotherapeutic agents used in breast cancer management is associated with unique acute and long-term cardiac complications (Table 1). Although the majority of complications are transient effects that do not persist after completing chemotherapy, use of anthracycline-containing regimens (i.e.,

doxorubicin, epirubicin) is well recognized to trigger dose-dependent, cumulative, progressive cardiac dysfunction manifested as decreased left ventricular ejection fraction (LVEF), and ultimately, symptomatic congestive heart failure (HF).

On the basis of the classic data by Von Hoff and associates (9), most treatment protocols limit the cumulative dose of doxorubicin to 450 to 550 mg/m^2. The incidence of HF in modern adjuvant trials is typically between 0% and 1.6% with incidence rates reaching 2.1% in patients receiving doxorubicin with sequential paclitaxel (10). Epidemiologic evidence suggests that, even without an overt decline in ejection fraction at the time of treatment, receiving anthracycline-based adjuvant chemotherapy carries a substantial long-term risk of HF, especially for women older than 65 years of age (11).

Although adjuvant trials typically report only symptomatic cardiac events, recent prospective studies report frequent subclinical left ventricular dysfunction, defined as an absolute decrease in LVEF of >10% U, in 10% to 50% of patients receiving anthracyline-based therapy (12). The long-term consequences of subclinical LV dysfunction are not known, although this permanent damage leaves the patient more susceptible to recurrent progressive dysfunction associated with aging and other disease etiologies. In addition to cumulative dose, the route of drug administration, delivery schedule, co-administered drugs, patient age, presence of CVD risk factors, and cardiac radiation all influence the development of cardiac dysfunction (13). The biological mechanisms underlying chemotherapy-associated cardiac dysfunction remain to be fully elucidated. Generation of reactive oxygen species (ROS) and induction of cardiac myocyte apoptosis are hypothesized to play a central role. Furthermore, ROS may continue to be produced by a drug retained within myocytes contributing to late-occurring cardiovascular injury (14).

Radiotherapy. Recognition of the adverse cardiac effects of older radiotherapy techniques led to the development of alternative approaches such as intensity modulated radiotherapy and 3D-based conformal tomography that deliver more diverse radiation doses and fraction sizes that minimize heart and lung exposure. Hooning et al. (15) examined the long-term CVD risk according to specific radiation fields and interaction with known CVD risk factors among 4,414 10-year survivors of breast cancer treated from 1970 through 1986 in the Netherlands. After 18 years' median follow-up, 62.9 excess cases per 10,000 patient years of CV events were observed compared with the general female population. In addition, radiotherapy to either the left or right side of the internal mammary chain was associated with increased CVD for 1970 to 1979 compared with patients who received no radiotherapy. After 1979, radiation in combination with chemotherapy was associated with a greater risk of HF than patients who received radiotherapy only. Finally, when combined, smoking and radiotherapy were associated with an additive effect on risk of myocardial infarction (15). Giordano et al. (16)

Table 1	Potential Short-Term and Long-Term Cardiovascular Risks of Adjuvant Breast Cancer Systemic Therapy		
Adjuvant Therapy Polychemotherapy	**Short-Term Effects**		**Long-Term Effects**
Anthracyclines	Atrial and ventricular arrhythmias Pericarditis/myocarditis Reduced ejection fraction, cardiomyopathy, death		Progressive decrease in left ventricular function, often leading to overt heart failure
Alkylating agents			
Cisplatin	Myocardial ischemia/infarction Hypertension Heart failure Arrhythmias Heart block Endocardial fibrosis		
Cyclophosphamide	Pericarditis/myocarditis Heart failure Atrial ectopy Bradycardia		
Microtubule-targeting drugs			
Taxanes	Bradycardia/atrioventricular block Atrial and ventricular arrhythmias Heart failure Myocardial ischemia		
Antimetabolites			
Fluorouracil	Heart failure Atrial or ventricular ectopy Myocardial ischemia/infarction		
Capecitabine	Heart failure Atrial or ventricular ectopy Myocardial ischemia/infarction		
Methotrexate	Arrhythmias Myocardial ischemia/infarction		
Radiotherapy	Angina Dyspnea Heart failure Diffuse intimal hyperplasia of coronary arteries/left main stenosis Pericardial effusion Sudden death		Coronary artery disease Pericardial constriction Atherosclerosis Mediastinal fibrosis Carotid lesions Thickening of the pericardium Valvular heart disease
Endocrine therapy*			
Tamoxifen	Venous thrombosis		
Aromatase inhibitors	Unknown at this time		
HER-2–directed therapies*			
Trastuzumab	Left ventricular dysfunction Heart failure		
Angiogenesis inhibitors*			
Bevacizumab (not yet evaluated in the adjuvant breast cancer setting)	Hypertension Myocardial infarction Left ventricular dysfunction Venous thrombosis Stroke Heart failure Angina		

*The time-course (early vs. late effects) of cardiovascular risk associated with endocrine therapy, human epidermal growth factor receptor (HER)-2–directed therapies, and angiogenesis inhibitors has not been established given the relatively short period of time that these agents have been used in early breast cancer management.

reported that for women diagnosed and treated between 1973 and 1979, the 15-year CVD mortality rate was significantly greater for left-sided versus right-sided tumors (13% vs. 10.2%). There were no significant differences for women diagnosed and treated after 1984 with newer radiotherapy techniques. Other studies have reported similar findings (17).

Although modern radiation techniques provide lower cardiac mortality risks than older techniques, cardiopulmonary damage does nonetheless occur. Prospective studies report cardiac perfusion defects in 50% to 63% of women and radiologic evidence of irreversible lung fibrosis and associated pulmonary disorders with left-sided breast cancer 6 to 24 months after radiotherapy (18,19).

Risk factors for radiation-induced cardiovascular morbidity and mortality go beyond the myocardial and/or pulmonary volume in the field and the dose delivered to that field (dose-volume histogram), to include the presence of pre-existing CVD risk factors and use of anthracyclines (20). Again, the generation of ROS is thought to play a major role (21).

Endocrine therapy. Traditional endocrine therapy (tamoxifen, oophorectomy) for women with hormone receptor-positive breast cancer has not been clearly associated with cardiovascular injury. Although tamoxifen may have cardioprotective properties, these favorable benefits appear to be offset by a greater incidence of venous thromboembolic events (22). Seminal results have demonstrated the superiority of third-generation aromatase inhibitors (AIs) used instead of or after 2 to 3 years or 5 years of tamoxifen in early breast cancer (23). However, the marked reduction in serum estrogen associated with AI therapy raises concerns about the adverse cardiovascular effects of these agents. In comparison with tamoxifen, AIs have been associated with more CVD events although the incidence of thromboembolic events was significantly lower. Thus, longer-term follow-up is required to fully assess the associated cardiovascular risks.

HER-2–directed therapies. The addition of trastuzumab, (Herceptin), a humanized monoclonal antibody against HER2, to standard adjuvant chemotherapy is associated with improved disease-free and overall survival in HER-2/neu-positive early breast cancer (24,25). However, HER-2–directed therapies are associated with cardiac toxicity, with HF incidence between 2.0% and 4.1%. The corresponding rates of asymptomatic cardiac dysfunction range between 3.0% and 18.0% (24,25). Contributing factors include poor baseline function, reduced post-standard chemotherapy LVEF, age at study entry, and previous or concurrent treatment with doxorubicin (26). Finally, it is important to note that the current follow-up in all adjuvant trials is relatively short (~3 years), and the long-term cardiac effects of these trastuzumab-based strategies remain unknown.

Elegant preclinical studies have demonstrated that erbB2 and its associated ligands, neuregulins, are essential for cardiac structure and function whereas deletion of this gene leads to dilated cardiomyopathy (27). Other in vitro and in vivo work also has suggested that suppression of erbB2 may accelerate the net breakdown of sacromere proteins induced initially by anthracyclines leading to diastolic and systolic dysfunction.

Inhibition of angiogenesis. Vascular endothelial growth factor and other proteins implicated in tumor angiogenesis and surrounding tumor vasculature have become attractive therapeutic targets because of their critical role in tumor growth and metastases (28). With the demonstrated efficacy of angiogenesis inhibitors (e.g., bevacizumab, sorafenib, sunitinib) and the promising role of newer vascular disrupting agents (ZD6126, TZT-1027, ABT-751), trials are underway in early breast cancer. However, these agents are already known to be associated with cardiovascular complications, with reports of arte-rial thromboembolic events, increase in cardiac troponin, reductions in LVEF and, most commonly, hypertension (29).

Decreased nitric oxide production and bioavailability is postulated to play a major role in angiogenesis inhibition-associated cardiovascular injury (30). Nitric oxide influences a number of biological processes implicated in hypertension including decreased renal sodium excretion, endothelial nitric synthase and circulating endothelial progenitor cells (EPCs) (30).

Unfavorable lifestyle changes. Physical activity and body weight are 2 major independent risk factors for CVD that are often neglected when evaluating cardiovascular consequences of breast cancer adjuvant therapy. Irwin et al. (31) reported that, on average, early breast cancer patients decreased their physical activity by 2 h/week from before to after diagnosis, with greater decreases among women receiving combined treatment as compared with single-modality adjuvant therapy. Furthermore, >70% of breast cancer patients gain between 2.5 to 6.2 kg of body weight during adjuvant therapy (32). Although physical inactivity and weight gain are strong independent predictors of cardiovascular mortality in noncancer adult populations, the clinical value of these factors to predict an elevated CVD-specific morbidity and mortality in breast cancer remains to be determined.

The "Multiple-Hit" Hypothesis

As demonstrated, women diagnosed with early breast cancer are already at risk for CVD, and virtually all adjuvant therapies are associated with unique and varying degrees of cardiovascular injury. Thus, as women progress through the selected treatment regimens, they will be subjected to a series of sequential or concurrent cardiovascular insults coupled with lifestyle perturbations that collectively leave patients with overt or sub clinical CVD. At a minimum, these insults enhance susceptibility to further cardiovascular injury and, ultimately, risk of premature CVD mortality. We have labeled this phenomenon the "multiple-hit" hypothesis (Fig. 1).

Unfortunately, currently few data are available to support the contention of the "multiple hit." The prevalence of CVD risk factors has not been collected either prospectively or retrospectively among early breast cancer patients after modern adjuvant therapy. Hooning et al. (15) reported that 32%, 26%, 10%, and 9% of women treated with radiotherapy were smokers, had hypertension, hypercholesterolemia, and diabetes mellitus, respectively. These data were, however, for women treated between 1970 through 1986 and not likely to reflect current risk factor prevalence. As such, it is not yet possible to estimate the CVD risk among early breast cancer patients simply by adding the potential disease burden of adjuvant therapy to the CVD estimates from the general population. Future, large-scale, prospective studies to comprehensively evaluate CVD risk burden associated with modern adjuvant therapy are urgently required. As an initial step toward this goal, our group recently completed 2 pilot studies evaluating cardiovascular risk profiles using a
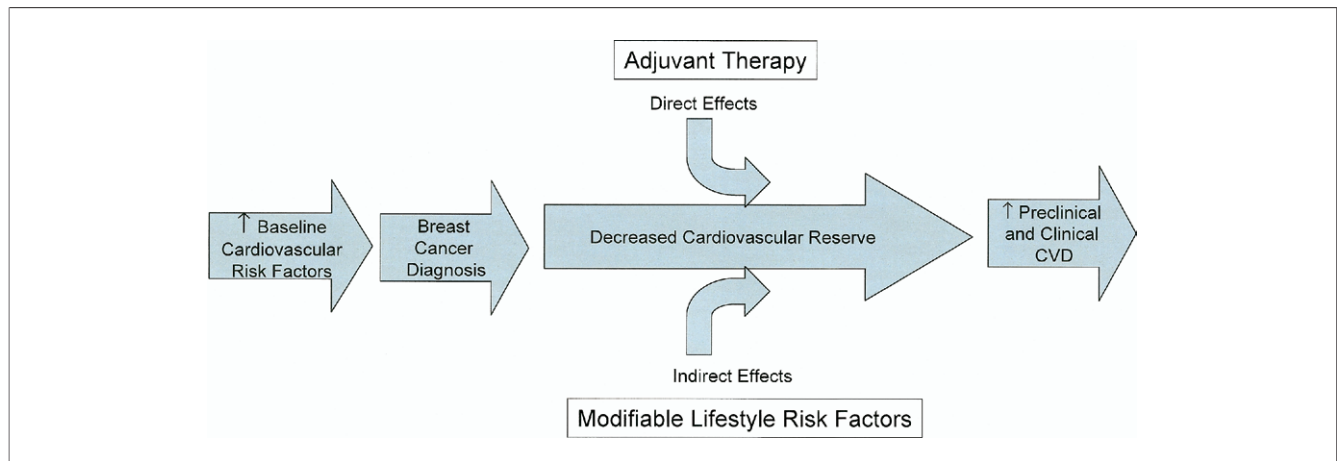
Figure 1   The "Multiple-Hit" Hypothesis

A schematic representation describing the "multiple-hit" hypothesis. At diagnosis, a significant proportion of early breast cancer patients present with pre-existing or heightened cardiovascular disease (CVD) risk factors, which increase the risk of adjuvant therapy-associated cardiovascular injury. Independently, many adjuvant therapies used in breast cancer are associated with unique and varying degrees of direct adverse effects on the cardiovascular system. These direct effects occur in the context of concomitant lifestyle perturbations (indirect effects) that combine to reduce cardiovascular reserve. Collectively, these changes may leave the patient more susceptible to further cardiovascular insults and at higher risk of premature death due to cardiovascular mortality.

wide range of established and novel CVD risk factors among early breast cancer patients following completion of primary therapy. Overall, in comparison to age/gender-matched controls, breast cancer patients had a significantly worse cardiovascular risk profile, thus supporting our contention of the "multiple hit" (33,34).

Although the current and future consequences of the "multiple-hit" hypothesis will be clinically devastating, it is currently not possible to predict which patients are at increased risk of late-occurring CVD. Current monitoring techniques (e.g., echocardiography, radionuclide angiography) have limited ability to detect early cardiac damage (35). In response, the utility of sensitive imaging modalities (i.e., single-photon emission computed tomography, magnetic resonance imaging; exercise or dobutamine stress testing) as well as novel biochemical markers (brain natriuretic peptide, troponin I) that allow more accurate detection and quantification of subclinical cardiac damage have been explored. For example, Cardinale et al. (36) demonstrated that increase in troponin I was a strong predictor of LV dysfunction soon after chemotherapy among cancer patients.

Breast Cancer and Cardiovascular Injury: Prevention and/or Treatment Approaches

Preventive and/or treatment strategies will be required to define and offset the acute and long-term clinical consequences of the "multiple hit." Unfortunately, it is not currently known whether treatment of risk factors modifies CVD incidence among women with breast cancer to the same extent as in general population. However, at least one clinical trial has examined the effects of angiotensin-converting enzyme inhibition (ACEI) on preventing cardiac dysfunction among cancer patients. Based on their prior

work, Cardinale et al. (37) randomized patients who experienced an increase in troponin I shortly after chemotherapy to receive an ACEI (enalapril) or usual care for 12 months. Results indicated a significant reduction in LV function among usual care patients only (37). In a retrospective study, Ewer et al. (38) reported that maximum-tolerated doses of ACEI and beta-blockers allowed therapy to be reinitiated among breast cancer patients who initially had treatment discontinued due to trastuzumab-induced heart failure. On the basis of these findings and our own clinical experience, treatment of risk factors consistent with the American Heart Asssociation guidelines for prevention of CVD in women (39) appears prudent. Effective strategies to preserve LV function are of major importance because therapy is withheld when LVEF decreases <50% and not resumed until LVEF is ≥50%, which has obvious implications for clinical outcome of breast cancer patients.

Recommendations for the treatment of major risk factors include optimal lifestyle behaviors in conjunction with pharmacotherapy, as required. Specifically, beta-blockers and/or ACEI, with the addition of other agents (e.g., thiazides), are recommended for the initial therapy of hypertension. Regarding hypercholesterolemia, the use of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (statins) is recommended to achieve low-density lipoprotein cholesterol <100 mg/dl. The use of sulfonylurea or biguanide (metformin) is recommended for women with type II diabetes mellitus to achieve a glycosylated hemoglobin (HbA$_{1c}$) <7% (39). Of note, exercise training may be effective in this setting because of its demonstrated effects on cardiovascular reserve, individual risk factors, and overall reductions in CVD mortality (40,41). Moreover, a recent meta-analysis (42) reported that exercise training resulted in

a significant improvement in exercise capacity among women with early breast cancer while epidemiologic data suggested that greater physical activity after therapy was associated with decreased breast cancer-specific and all-cause mortality (43). Only one study to date has examined the effects of exercise training on CVD risk factors among early breast cancer patients (44).

There is also a paucity of data examining any adverse or beneficial effects of recommended risk factor-modification strategies on cancer outcomes. However, several preclinical studies have demonstrated that lipophilic statins (e.g., simvastatin, fluvastatin), ACEI, and metformin have antineoplastic activity in several experimental models of breast carcinogenesis (45–47). On the basis of these promising data, several clinical trials are underway to investigate the potential antitumor efficacy of these agents in breast cancer patients. As a cautionary note, all preclinical studies have examined the potential efficacy of CVD medications without concurrent cancer therapy. Thus, little is known about the potential interaction between these agents.

Pharmacologic CVD medications as well as lifestyle approaches (e.g., exercise training) influence a wide spectrum of biological processes that may be particularly relevant for the antineoplastic effects of cancer therapies. For example, in addition to their vasodilatory effects, ACEI and exercise training are also potent antioxidants and actively scavenge ROS and lower oxidative stress (48). Because radiotherapy and certain cancer chemotherapeutics rely on ROS-mediated deoxyribonucleic acid damage to induce apoptosis, one could speculate that these interventions might inhibit the efficacy of these therapies. On the other hand, reduction in ROS oxidative damage may confer protection against doxorubicin-induced cardiac toxicity (48).

Similarly, statins and exercise therapy increase the production, number, and function of circulating EPCs via vascular endothelial growth factor-dependent mechanisms (49,50). Several reports have demonstrated that EPCs significantly contribute to tumor angiogenesis (51); thus, one might speculate that interventions that induce EPC activity would augment tumor growth. Paradoxically, however, preclinical studies have reported that statins and exercise (without concurrent antitumor therapy) inhibit established breast tumor growth and metastatic progression (52). Although strategies that improve overall global tumor blood flow may improve the delivery and efficacy of anticancer drugs in established breast tumors (53), in the adjuvant setting where treatment is directed at micrometastases, the clinical relevance of these observations is unknown. Clearly, the use of any risk factor modification strategy during early breast cancer therapy needs to be rigorously evaluated using appropriate end points (e.g., cardiac and cardiovascular function, adverse events, cancer drug pharmacokinetics, and relapse-free survival).

Clinical Implications

In middle-aged and elderly women who already are at risk for CVD, the direct and indirect effects of adjuvant therapy coupled with an unhealthy lifestyle and presence of modifiable risk factors all contribute to either overt CVD or an elevated risk of future CVD in women with early breast cancer. Cardiovascular clinicians need to understand this risk and diagnostic, preventive, and/or therapeutic strategies that effectively address this need are urgently required. On the basis of our current understanding, we recommend that a formal baseline CVD risk assessment, using either Framingham (54) or Reynolds (55) risk scores, be performed before adjuvant therapy. All women should be counseled about the value of a healthy lifestyle, and a program of individualized primary prevention should be undertaken as described in the American Heart Association guidelines (39). Unfavorable risk factors should to be managed, ideally before the initiation of adjuvant therapy. Consideration should be given to more aggressive management of risk factors than might otherwise be indicated, in view of the "multiple-hit" hypothesis presented here, although further research would be required before making such a recommendation universal.

Conclusions

Recent advancements in curative-intent therapies have led to dramatic improvements in breast cancer-specific mortality but at the direct expense of increased risk of cardiovascular-related mortality. Evidence reviewed in this paper suggests that established and forthcoming breast cancer adjuvant therapies are associated with varying degrees of direct cardiovascular injury in conjunction with significant indirect lifestyle changes that concomitantly reduce cardiovascular reserve, which we term the "multiple hit." We speculate that the consequences of the "multiple hit" will become an increasingly important issue in the management of women with early breast cancer. Overall, this information is of critical importance to cardiovascular physicians who will increasingly be called upon to evaluate and treat these women.

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