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Review

Cardiovascular Late Effects and Exercise Treatment in Breast Cancer: Current Evidence and Future Directions

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ABSTRACT

Advances in detection and supportive care strategies have led to improvements in cancer-specific and overall survival after a diagnosis of early-stage breast cancer. These improvements, however, are associated with an increase in competing forms of morbidity and mortality, particularly cardiovascular disease (CVD). Indeed, in certain subpopulations of patients, CVD is the leading cause of mortality after early breast cancer, and these women also have an increased risk of CVD-specific morbidity, including an elevated incidence of coronary artery disease and heart failure compared with their sex- and age-matched counterparts. Exercise treatment is established as the cornerstone of primary and secondary prevention of CVD in multiple clinical populations. The potential benefits of exercise treatment to modulate CVD or CVD risk factors before, immediately after, or in the months/years after adjuvant therapy for early-stage breast cancer have received limited attention. We discuss the risk and extent of CVD in patients with breast cancer, review the pathogenesis of CVD, and highlight existing evidence from select clinical trials investigating the efficacy of structured exercise treatment across the CVD continuum in early breast cancer.

RÉSUMÉ

L'évolution des stratégies de dépistage et de soins de soutien a permis d'améliorer le taux de survie spécifique au cancer et le taux de survie globale après un diagnostic de cancer du sein au stade précoce. Ces améliorations sont toutefois associées à une augmentation de diverses formes de morbidité et de mortalité, plus particulièrement les maladies cardiovasculaires (MCV). En effet, chez certaines sous-populations de patientes, les MCV constituent la principale cause de mortalité suivant un diagnostic de cancer du sein au stade précoce et ces femmes présentent également un risque accru de morbidité liée aux MCV, y compris une incidence accrue de coronaropathie et d'insuffisance cardiaque comparativement aux populations appariées selon l'âge et le sexe. L'instauration d'un programme d'exercice physique est considérée comme une des pierres angulaires de la prévention primaire et secondaire des MCV chez un nombre important de populations cliniques. Cependant, les bienfaits potentiels d'un programme d'exercice physique sur la modulation des MCV et les facteurs de risque de MCV avant, immédiatement après et au cours des mois et des années suivant un traitement adjuvant du cancer du sein au stade précoce ont jusqu'ici été très peu étudiés. Nous traitons donc du risque et de l'étendue des MCV chez les patientes atteintes d'un cancer du sein, passons en revue la pathogenèse des MCV et mettons l'accent sur les données d'études cliniques qui ont examiné l'efficacité d'un programme d'exercice physique structuré pour lutter contre les MCV tout au long de son continuum évolutif chez les patientes atteintes d'un cancer du sein au stade précoce.

Advances in early detection and adjuvant therapy have led to significant improvements in the 5-year survival rate among women diagnosed with early-stage breast cancer, from 80% in 1950 to 98% today.[1,2] However, improvements in overall survival are at risk of being offset by an increased risk of late-occurring cardiovascular toxicities.[1,3] In comparison with age-matched counterparts, patients with breast cancer have a 1.7- to 1.8-fold increased risk of cardiovascular disease (CVD)-specific mortality,[4,5] a 1.2- to 1.3-fold increased risk of CVD (eg, coronary artery disease, cerebrovascular disease, and heart failure [HF]),[6] and a 1.3- to 3.1-fold increased risk of CVD risk factors (eg, hypertension, diabetes, dyslipidemia).[6] The excess CVD risk is likely a consequence of acute direct (ie, direct cytotoxicity/radiation–induced injury) as well as indirect (ie, impacts secondary to therapy, such as deconditioning) effects of breast cancer therapy.[5,7-11] Given the growing clinical importance, a research agenda that systematically addresses

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CVD prevalence, pathogenesis, and treatment in early-stage breast cancer is important and timely.[6,7]

In recent work, our group adapted a classic cardiology paradigm (ie, primordial, primary, secondary, and tertiary prevention) to develop a continuum framework for cancer therapy–associated acute and long-term cardiovascular toxicities in early-stage breast cancer.[8] This framework can be applied to better understand the following: (1) the role of tools and methodologies in identifying individuals with or at high-risk of cardiovascular toxicity and (2) the type and timing of strategies to prevent, mitigate, or treat cardiovascular toxicities.[8] Regarding the latter, several research groups have started to investigate the efficacy of cardiovascular medications (eg, angiotensin-converting enzyme inhibitors, statins) as prophylactic strategies to prevent,[9,10] as well as treat,[11,12] cardiac-related effects (eg, decreases in left ventricular ejection fraction [LVEF]) of known cardiotoxic agents such as anthracyclines and trastuzumab.

However, therapy-induced toxicity not only is limited to the heart but also can have deleterious effects across the cardiac/pulmonary/vascular/muscular axis.[7,8,13] For example, both localized (eg, radiotherapy) and systemic (eg, chemotherapy or hormone therapy) treatment modalities can cause pulmonary dysfunction, anemia, arterial stiffness, and skeletal muscle dysfunction (eg, reduced oxidative phosphorylation).[7,14,15] The pleiotropic nature of these therapy-induced deficits creates a strong rationale for the design and testing of intervention strategies that can simultaneously improve function across these multiple organ systems and, consequently, the overall reserve capacity of the cardiovascular network.[16] Exercise treatment has the unique capacity to improve the reserve function of multiple organs, culminating in marked augmentation of global cardiovascular reserve capacity in numerous clinical settings.[17]

Against this background, we outline here the extent of CVD in patients with breast cancer, briefly overview the pathogenesis of CVD, and adopt our cancer-CVD continuum framework (Fig. 1) to review existing evidence from investigations of structured exercise treatments.

Prevalence of CVD

The prevalence of CVD has been comprehensively reviewed previously and is summarized in Table 1.[12,18] Importantly, evidence indicates that there is considerable long-term risk of CVD, particularly for women older than 65 years of age.[27] For instance, data from the Surveillance, Epidemiology, and End Results indicated that after 12 years of follow-up, CVD was the leading cause of death (15.9%), closely followed by breast cancer (15.1%).[28] Furthermore, Hooning et al.[6] reported that compared with women from the general population, patients with early breast cancer had a 30% increased standardized incidence ratio of CVD events. These findings demonstrate an increased CVD prevalence and incidence in patients with breast cancer and highlight the prematurity of its development compared with women matched in age and without a history of cancer. Unfortunately, in the absence of effective CVD screening and prevention strategies, there is no reason to expect that these rates will improve over time, especially against the backdrop of increasing breast cancer incidence, high survival rates, and rapidly evolving treatment regimens.[13]

Pathogenesis of CVD

As patients progress through treatment regimens, they sustain subclinical and overt therapy-induced cardiovascular injuries, which when coupled with adverse lifestyle perturbations, may result in a significantly elevated incidence of CVD risk factors, overt CVD, and CVD-related mortality.[4,6,29] We labeled this phenomenon the "multiple hit" hypothesis.[7] A brief overview is provided here.

Therapy-related direct cardiovascular injury

For a comprehensive overview of the mechanisms of therapy-induced cardiovascular toxicity, the reader is referred to previous excellent reviews.[30,31] In the following sections, we briefly outline the biological mechanisms that may underlie therapy-associated (ie, anthracyclines, radiotherapy, trastuzumab, or endocrine therapy) cardiovascular toxicity.

The adverse cardiovascular effects of anthracycline therapy (eg, doxorubicin) are well recognized.[11,32] In brief, anthracycline-induced generation of reactive oxygen species influences multiple pathways of cardiotoxicity risk, including the tumor suppressor protein and p53,[33] and suppresses sarcomere protein synthesis through depletion of GATA-4–dependent gene expression and cardiac progenitor cells.[34,35]

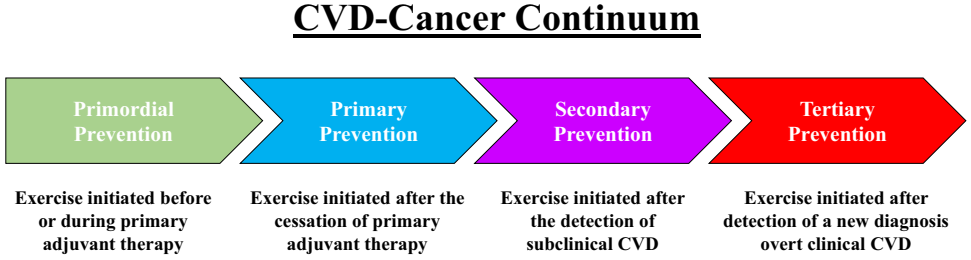

Figure 1. Exercise-cardiovascular disease (CVD) continuum in oncology. Primordial prevention: exercise initiated before or during primary adjuvant therapy (ie, definitive surgery followed by radiotherapy, chemotherapy, or trastuzumab) to mitigate or attenuate (or both) potential therapy-induced toxicity. Primary prevention: exercise initiated after the cessation of primary adjuvant therapy to reverse/attenuate subclinical cardiovascular impairments. Secondary prevention: exercise initiated after the detection of left ventricular ejection fraction decline of $\geq$ 10% from baseline (before treatment) or beyond the lower limit of normal ($<$ 53%), poor peak oxygen consumption ($<$ 15 mL/kg/min), angina, or transient ischemic attack. Tertiary prevention: exercise initiated after detection of a new diagnosis of overt symptomatic heart failure, coronary artery disease, stroke, valve replacement, or serious arrhythmia after initiation of anticancer therapy.