OPPORTUNITIES FOR IMPROVED CARDIOVASCULAR DISEASE PREVENTION IN ONCOLOGY PATIENTS

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ABSTRACT

Purpose of review:

Cancer patients often have cardiovascular risk factors at the time of cancer diagnosis. Current cardiovascular disease prevention guidelines are based on studies that largely excluded these patients. We reviewed and commented on recent data regarding cardiovascular disease prevention in this population.

Recent findings:

Non-pharmacologic therapies aiming to reduce “lifestyle toxicity” produced by cancer treatments have demonstrated potential to decrease the incidence of adverse outcomes. Exercise before, during and after cancer treatment not only promotes higher quality of life and cardio-respiratory fitness but also reduces adverse cardiovascular outcomes. Lipid and cardiometabolic disease management is paramount, but predominantly based on data that excludes these populations of cancer patients and survivors. Lipids and cardiometabolic disease management is paramount, but predominantly based on data that excludes these populations of cancer patients and survivors.

Summary:

A comprehensive approach including medical evaluation, prescriptive exercise, cardiac risk factor modification, education, counseling, pharmacologic and behavioral interventions are needed in these patients. These interventions constitute the core of Cardio-Oncology rehabilitation programs, which if implemented appropriately may help reduce cardiovascular events in this population. Knowledge gaps in these areas are starting to be addressed by ongoing clinical trials.

Keywords: cardio-oncology, cardiovascular disease, prevention, cancer survivor

INTRODUCTION

Cardiovascular disease (CVD) is an important competing cause of death in cancer survivors[1]. Several factors must be considered in order to establish causal relationships between cancer and the development of CVD: 1) shared risk factors for both[2]; 2) potential cardiotoxicity from cancer treatment (acute, subacute or chronic)[3]; 3) molecular pathways in common[4]; and 4) baseline cardiovascular status[5]. Smoking, alcohol use and environmental toxins have been related to both CVD and certain malignancies[2]. Many oncologic treatments have significant cardiovascular adverse effects, such as anthracyclines, human epidermal growth factor receptor tyrosine kinase (HER2) inhibitors, immune checkpoint inhibitors, antimetabolites and radiation therapy (RT) [3,6]. Newer associations linking cancer and CVD include research regarding senescence[7] and hematological phenomenon of clonal hematopoiesis of indeterminate potential[8] that has been associated with CVD. There are no current evidence-based recommendations regarding how to screen survivors for CVD, but there are consensus statement recommendations endorsed by the American Society of Clinical Oncology (ASCO) which defines cancer patients at high risk for cardiac disease[9] and the National Comprehensive Cancer Network which provides clinical guidelines on healthy lifestyle behaviors for cancer patients and survivors and screening for CVD[10]. Gaps in knowledge include whether current preventive measures such as statins work in cancer patients as in the general population as well as the optimal timing and frequency of established screening protocols to prevent cardiotoxicity. It is our belief that recommendations for screening likely will need to be tailored to specific type of cancer and to treatment modality received. In this mini review, we discuss the ASCO definition of high-risk patient and risk factors. Next, we review risk assessment and mitigation strategies in high-risk patients with emphasis on lifestyle measures and hypertension, which are underappreciated but high value targets of prevention. Finally, we focus on three

particularly high-risk patient populations: breast cancer patients, childhood cancer survivors and prostate cancer patients who have received antiandrogenic therapy.

CANCER PATIENTS AT HIGH RISK FOR CARDIAC DISEASE

According to the ASCO Clinical Practice Guidelines[9], cancer patients considered at high risk for cardiac dysfunction include those who:

- Have had treatment with high-dose anthracyclines (e.g. doxorubicin $\geq$ 250 mg/m2, epirubicin $\geq$ 600 mg/m2), high-dose RT (cumulative dose $\geq$ 30 Gy) where the heart is in the treatment field, and combination lower-dose anthracycline (eg, doxorubicin < 250 mg/m2, epirubicin < 600 mg/m2) and lower dose RT (< 30 Gy) where the heart is in the treatment field.
- Have had treatment with lower-dose anthracycline (eg, doxorubicin < 250 mg/m2, epirubicin < 600 mg/m2) or trastuzumab alone with the presence of any of these risk factors: age greater than or equal to 60 years at the time of cancer treatment, compromised cardiac function [e.g. history of myocardial infarction, low-normal left ventricular ejection fraction (50-55%), or greater than or equal to moderate valvular heart disease] before or during treatment.
- Are receiving treatment with lower dose anthracyclines (eg, doxorubicin < 250 mg/m2, epirubicin < 600 mg/m2) followed by trastuzumab.

This guideline has some caveats to consider such as the unknown long-term outcomes of newer cancer therapeutics, cohorts largely restricted to hematologic and breast cancer survivors, insufficient cardiovascular risk data related to advances in mediastinal RT delivery; as well as the challenge in certain cases to differentiate between primary and secondary cardiac dysfunction[9].

RISK FACTORS

- **Obesity**

  For almost three decades, the American Cancer Society has issued diet and exercise guidelines encouraging cancer survivors to adopt and maintain a healthy lifestyle[11], which includes maintaining a healthy weight, engaging in regular physical activity, and adopting a dietary pattern high in vegetables, fruits and whole grains[12].

  Maintaining a healthy weight and body mass index (BMI) between 18.5 and 25 kg/m2 must be purposeful and not related to cancer recurrence[12,13]. Pre-diagnosis BMI ≥ 30 is associated with higher risk of death from all causes, including cancer-specific causes as well as CVD in patients with colorectal cancer[14]. In breast cancer survivors, post-diagnosis weight loss was not associated with a lower incidence of CVD; however, an increase in waist circumference increased CVD risk[15]. About 60% of cancer survivors do not have a healthy dietary pattern, despite evidence of its proven benefits to prevent cancer recurrence[16].

- **Blood Pressure**

  Hypertension can develop in the acute setting [as seen after administration of high-dose steroids or vascular endothelial growth factor (VEGF) inhibitors] or even years after childhood cancer therapy.

  The risk of developing hypertension in childhood cancer survivors is twice that of their healthy siblings[17] ,and cancer-related risk factors include abdominal or cranial RT[17] and use of steroids[18] or nephrotoxic agents. In children with acute lymphoblastic leukemia treated with high-dose steroids, hypertension is noted in the vast majority, with 16% of them requiring antihypertensive drugs[18] and taking up to 5 years to return to baseline[19]. Additionally, since the prevalence of metabolic syndrome is high in childhood cancer survivors, hypertension is expected to develop three or four decades later[20].

Anti-VEGF monoclonal antibodies and tyrosine kinase inhibitors have been associated with higher incidence of hypertension (36% and 25%, respectively)[21]. The pathogenesis involves reduced nitric oxide production in the arterial wall myocytes, increase in endothelin-1, renal vasoconstriction and impaired natriuresis leading to systemic increase in peripheral resistance[22]. Hypertensive emergencies are noted in about 2% of patients who use bevacizumab, with normalization of blood pressure shortly after treatment in most cases[23,24], however certain reports of cardiovascular events have been published in both the acute[25] as well as long-term settings[26]. Future studies are needed to determine the long-term implications of these medications in the development of cardiovascular events.

- **Cholesterol**

  The current cholesterol guidelines[27] reflect evidence collected on non-cancer patients as cancer would likely constitute part of the exclusion criteria in several studies partly due to a shorter expected survival time[28]. Additionally, the pooled cohort equation used to guide lipid lowering therapy cannot adequately account for specific risks such as mediastinal irradiation or cancer therapies associated with cardiovascular events[29]. Thus, lipid management in cancer patients and survivors remains challenging in the absence of specific clinical studies[30].

- **Smoking**

  The benefits of smoking cessation in cancer survivors has also been reported. In breast cancer survivors, post-diagnosis quitters had 20% lower risk of cardiovascular death and 9% lower risk of all-cause death. The risk of cardiovascular death was also proportionally lower according to the duration of smoking cessation and the amount of smoking[31].

RISK ASSESSMENT

Oncologists rely on the use of various measurement tools that assess functional capacity like the Eastern Cooperative Oncology Group (ECOG) or Karnofsky Performance Status (KPS) scales to determine the suitability of cancer patients to undergo systemic treatment[32]. ECOG uses a 5-point scoring system and KPS uses a linear score from 0 to 100; with lower overall scores corresponding with increased risk for chemotherapy toxicities and poorer outcomes[33]. Both scales have good inter-rater reliability among oncology healthcare professionals[33,34]. A linear and moderate association between KPS and the New York Heart Association Classification (NYHA) classes I-III[35] has been noted, offering the potential to incorporate data from routinely used scales in monitoring the development of cardiovascular events among cancer patients and survivors. For a more objective measurement of cardiopulmonary safety prior to starting lifestyle interventions, a baseline cardiopulmonary stress test is recommended[29]. In the absence of this technology, a six-minute walk or sit-to-stand tests are good alternatives[36].

Coronary artery calcium (CAC) score has a potential role in cardiovascular risk assessment of cancer patients since it has the ability to predict cardiovascular events in asymptomatic individuals[37]. Strengths include the ease in which the score can be calculated and age/sex/race specific percentile calculation associated with the score[37]. In the general population, tailored preventive treatment by using CAC score improves systolic blood pressure control, lowers LDL and waist circumference without increasing downstream medical costs[38]. CAC scoring thus can be useful for risk stratification prior to statin treatment and monitoring for the development of cardiotoxic effects in patients exposed to mediastinal radiation or high-risk chemotherapeutics[39-41].

MITIGATING CVD RISK IN HIGH-RISK CANCER PATIENTS

The following interventions constitute the foundation for Cardio-Oncology Rehabilitation Programs, which using lifestyle and pharmacologic interventions focus on maintenance of cardiorespiratory fitness and CVD prevention in cancer patients undergoing treatment as well as survivors[29] (**Figure 1**).

- **Non-pharmacologic interventions**

  The benefits of physical activity have been mostly studied in cancer survivors who retain the ability to engage in at least moderate exercise. In breast cancer survivors, exercising on average 3.5 hours a week (mostly walking) was protective against metabolic syndrome[42] and also produced a 41% lower risk of all-cause mortality[43]. Similarly, in colon cancer survivors, increasing functional capacity from less than 3 to 3 - 8.9 metabolic equivalents per week was associated with 49% lower risk of all-cause mortality[44]. Furthermore, a meta-analysis of randomized controlled trials including 3632 cancer patients and survivors demonstrated that exercise significantly improved cardio-respiratory fitness with greater benefit achieved when using individualized prescriptive exercise rather than a standard scheduling[45].

  Comparable to the general population, adherence to Mediterranean diet is inversely associated with incident diabetes or CVD in cancer survivors[46]. Other diets such as caloric restriction have also shown protection from anthracycline related toxicity in rodent models through a mechanism of “differential stress resistance”[47]. Further studies in humans are needed to prove the cardiovascular benefits of this latter strategy.

- **Pharmacologic interventions**

  Hypertension management follows current guidelines[48]; with betablockers or renin-angiotensin-aldosterone system inhibitors as first-line treatments due to their potential to prevent cardiomyopathy[49]. Use of non-dihydropyridine calcium channel blockers

concomitantly with VEGF inhibitors is not recommended due to the risk of increasing chemotherapeutic levels secondary to cytochrome P450 3A4 inhibition[50,51].

Despite the limitations of the pooled cohort equation, cholesterol management in cancer patients and survivors follows current guidelines[27]. In addition to initiating moderate-intensity statins in those with a 10-year atherosclerotic cardiovascular disease (ASCVD) risk ≥7.5%, we favor statins use in women who have undergone left-sided RT to the breast[30]. Recommendations for these medications in women who have received anthracyclines with or without trastuzumab is being assessed in current randomized clinical trials (SBSBC study-NCT03971019, NCT02096588).

SPECIFIC POPULATIONS

- **Breast cancer**

  Breast cancer mortality has decreased nearly 40% during the last 4 decades and currently CVD is the leading cause of death in this population[1], with heart failure being the most common form[52]. Traditional CVD risk factors are highly prevalent prior to breast cancer diagnosis and potentiate the development of cardiotoxicity[53,54], which has been largely associated with exposure to anthracyclines[55] and HER2 inhibitors[56]. Furthermore, the decline in cardiorespiratory fitness, high levels of stress and poor dietary patterns constituting “lifestyle toxicity” resulting from cancer therapy are also responsible for an increase in CVD in this population[1,57].

  Strategies to reduce cardiotoxicity in the short term include anthracycline dose reduction, continuous infusion (instead of bolus), liposomal formulation and use of dexrazoxane[56]. Small clinical trials have also examined the role of pharmacologic prevention of anthracyclines and trastuzumab-induced cardiotoxicity, demonstrating the benefits of carvedilol, lisinopril[49] or candesartan use[58]. The use of incremental aerobic exercise

programs have also shown to improve peak VO2 during chemotherapy[59] and when combined with resistance training improve insulin resistance in breast cancer survivors[60]. The use of Cardio-Oncology rehabilitation programs can help individualize exercise prescriptions and other interventions for these patients[29,30].

- **Childhood cancer survivors**

  Approximately 83% of the 12,000 children and adolescents diagnosed with cancer every year in the United States will survive 5 years or longer [61,62]. Childhood cancer survivors are eight times more likely to die of CVD and 15 times more likely to have heart failure than their contemporaries, and this risk remains elevated beyond 50 years of age [63-65]. Exposure to anthracyclines, cyclophosphamide, mitoxantrone and chest RT are some of the most well-documented risk factors for cardiomyopathy, which is the most prevalent type of CVD among this population [66]. Additionally, those with a history of cranial RT are at highest risk for metabolic syndrome due to the damage of the hypothalamic-pituitary axis and thyroid glands, affecting metabolism, growth hormone (GH) production and satiety feedback mechanisms [61].

  Only about 40% of survivors follow lifetime screening according to the Children's Oncology Group[20] and American Heart Association Scientific Statement [61,67], urging the need for better implementation strategies and public health education regarding preventative strategies in Cardio-Oncology. Lifestyle modifications according to the World Cancer Research Fund/American Institute of Cancer Research guidelines are effective in lowering cardiometabolic risk in this population[68]. In young adult survivors of acute lymphoblastic leukemia with GH deficiency, GH replacement decreased the prevalence of metabolic syndrome, improved high-density lipoprotein cholesterol levels and apolipoprotein B/A1 ratios without affecting left ventricular systolic function, quality of life or physical activity[69]. Other pharmacological strategies to prevent cardiotoxicity have not been successful, with two small trials examining the use enalapril for the

treatment of asymptomatic left ventricular systolic dysfunction not showing long-term benefits[70,71]. The effect of statins on long-term cardiovascular outcomes has not been studied in this population, but its use is recommended according to the most recent guidelines[27].

- **Cardiometabolic risk of antiandrogenic therapy in prostate cancer**

  Androgen deprivation therapy (ADT) is achieved surgically via bilateral orchiectomy or medically via gonadotropin-releasing hormone (GnRH) agonists, antagonists, combined androgen blockade or antiandrogens[72-76]. Despite the survival benefits gained, a growing body of research suggests increased risk for adverse metabolic effects and cardiovascular events[72-76]. The development of abdominal obesity[72-74]; increases in total cholesterol, LDL and triglycerides[72-74]; insulin resistance along with higher fasting plasma glucose and glycosylated hemoglobin levels have been noted within few months of ADT initiation[72,73]. Unlike metabolic syndrome in the general population, ADT doesn't seem to change inflammatory markers like C-reactive protein or blood pressure[72]. ADT appears to confer risk for CVD regardless of treatment duration but based on modality. In this way, orchiectomy is associated with only increased risk of diabetes incidence whereas luteinizing hormone releasing hormone and GnRH agonists have 20% increased risk of CVD[73]. Shorter times to fatal myocardial infarction were observed in men aged 65 and older receiving ADT for six months compared to controls; these differences remained when comparing shorter duration of ADT[74]. Older patients on ADT and those with pre-existing CVD are at increased risk for further cardiovascular complications[73,74]. The bulk of evidence of increased risk of major cardiovascular events in cancer patients with ADT, although bio-plausible, is contradictory[73,75]. The RADICAL-PC study suggested that patients undergoing ADT had similar Framingham risk scores than controls after adjustment for confounders[77]. The PRONOUNCE[78] study will investigate long-term CVD

outcomes in patients receiving GnRH receptor agonist (leuprolide) or antagonist (degarelix).

CONCLUSION

Cancer patients are an underrepresented population in current cardiovascular disease prevention studies. Non-pharmacologic interventions, mainly focusing on exercise and healthy nutrition, not only improve quality of life and reduce cancer recurrence risk but may also improve overall cardiovascular outcomes. Hypertension is managed per current guidelines for the general population, although betablockers and renin-angiotensin-aldosterone system inhibitors are preferred initial therapies. Further studies focusing on pharmacologic strategies for dyslipidemia are needed to evaluate if current lipid targets are appropriate and sufficient in these patients

KEY POINTS

- Cardiovascular disease is a competing cause of death in cancer survivors.
- Healthy nutrition and exercise prescriptions during and after cancer treatment contribute to maintenance of cardio-respiratory fitness and may help reduce the incidence of adverse cardiovascular outcomes.
- Hypertension is managed according to current guidelines, with betablockers and renin-angiotensin-aldosterone system inhibitors as first-line options.
- Evidence-based treatments for dyslipidemia in this specific population are yet to be defined.

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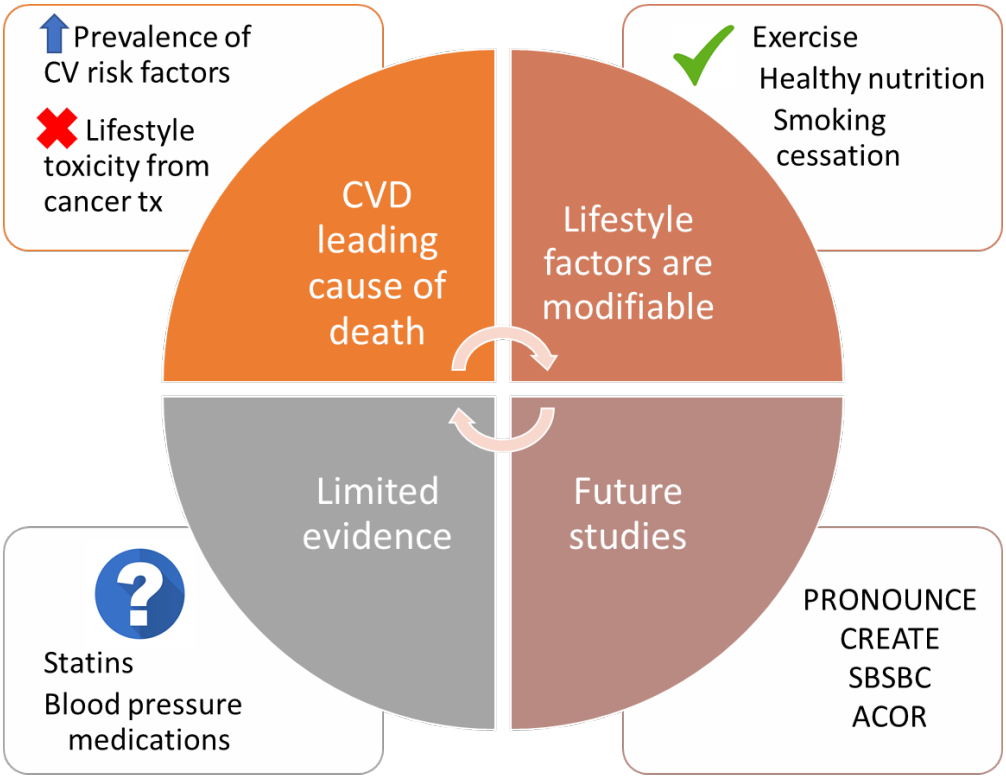
FIGURES

Figure 1. Representation of current evidence in cardiovascular disease prevention in patients with cancer.



CV: cardiovascular; CVD: cardiovascular disease; tx: therapy; PRONOUNCE: Cardiovascular Safety of Degarelix Versus Leuprolide for Advanced Prostate Cancer; CREATE: Caloric Restriction and Exercise protection from Anthracycline Toxic Effects; SBSBC: Survival Benefits of Statin in Breast Cancer Patients; ACOR: Australia and New Zealand Cardio-Oncology Registry.