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CARDIO-ONCOLOGY (EH YANG, SECTION EDITOR)

Cardiovascular Disease and Cancer: Is There Increasing Overlap?

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Abstract

Purpose of Review Cancer and cardiovascular disease are the leading causes of mortality in the USA. In this review, we highlight these shared disease pathways and provide a framework for a systems-based approach to reduce overall risk burden.

Recent Findings From traditional risk factors such as age and tobacco use to more recently recognized entities including clonal hematopoiesis, we are gaining insights into shared mechanisms. Because of these overlapping risks, providers on each level of patient care (primary care providers, cardiologists, oncologists) need to recognize and reduce these underlying risk factors.

Summary There is significant overlap in the epidemiology and risk factors for the development of cardiovascular disease and cancer, providing opportunities for joint risk factor modification.

Keywords Cardio-oncology · Cardiotoxicity · Cancer

Introduction

Heart disease and cancer combine to account for 50% of deaths in North America [1]. It is increasingly recognized that there are shared underlying biological mechanisms that contribute to both incident cancer and cardiovascular risk. Today's oncologists and cardiologists must make efforts to understand the interplay between these two leading causes of death in developed countries. Systems strategies are critical for guiding providers in attenuating common risk factors and addressing comorbidities that cause both oncologic and cardiovascular diseases. In an era of health reform and cost containment, targeting common risk factors for these two highly morbid and fatal disease entities needs to be prioritized as it would decrease not only the burden of disease in the population but would be potentially cost-effective.

This article is part of the Topical Collection on *Cardio-oncology*

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Epidemiology

Cardiovascular Disease—Coronary Artery Disease, Peripheral Vascular Disease, and Stroke

Cardiovascular disease (CVD) consists of a group of diseases with the common underlying mechanism of atherosclerosis, with clinical presentations of coronary artery disease (CAD), stroke, and peripheral vascular disease. It is the leading cause of mortality in the USA and developed countries, accounting for more deaths than cancer and chronic lower respiratory disease combined [2]. Based on the original Framingham study cohort with 20 years of surveillance, lifetime risk of developing CAD is nearly one-half of all men and one-third in women [3]. Incidence steeply increases with age, with risk in women trailing men by approximately 10 years. Although the mortality rate has been decreasing, the American Heart Association (AHA) estimates that by 2035, 45.1% of the US population will have some form of CVD [4].

Stroke affects an estimated 7.2 million US adults aged > 20 years with a lifetime risk of approximately 25% [5]. Though the age-adjusted stroke death rate has decreased by 21.7% since 2005, stroke contributes significantly to morbidity and is the leading cause of serious long-term disability in the USA [6].

With the increasing prevalence of both CVD and cancer, there is a growing population either living with or at risk of developing these two disease states concurrently.

Emerging evidence demonstrates a significant increased risk of arterial thromboembolism resulting in myocardial infarction (MI) or ischemic stroke in patients recently diagnosed with common solid or hematologic cancers [7–9]. In a recent large study, Navi and colleagues linked the Surveillance Epidemiology and End Results (SEER) database to Medicare and identified 279,719 pairs of cancer patients with matched controls [7]. They found a 4.7% incidence of arterial thromboembolism (2.0% myocardial infarction and 3.0% ischemic stroke) in cancer patients compared with 2.0% (0.7% myocardial infarction and 1.6% ischemic stroke) in controls at 6 months. The risk was higher in patients with more advanced cancers at the time of diagnosis, and the greatest risk was in lung cancer relative to other site-specific cancers. Many common lifestyle and comorbidity risk factors co-exist in CVD and cancer which may help explain the increasingly recognized convergence.

Heart Failure

In the Framingham study, the lifetime risk of developing heart failure (HF) after the age of 40 was one in five [10]. The burden of HF is expected to increase due to an aging population and advancements in the treatment of hypertension and coronary disease. By 2030, over 8 million people in the USA are expected to have HF [11]. Despite advances in medical therapy, heart failure continues to carry a poor prognosis, with an estimated survival rate of 50% at 5 years [12]. In addition, heart failure is the number one cause of hospitalization among adults > 65 years of age, accounting for an estimated $30.7 billion in direct medical costs in 2012 [11].

Growing evidence has demonstrated an increased risk of cancer among patients with HF. Two studies from Hasin and colleagues, a 2013 case-control study comparing cancer among community subjects newly diagnosed with HF and a 2016 prospective cohort study of patients with myocardial infarction (MI) who went on to develop HF assessing for incidence of cancer [13, 14], found a significantly increased risk of cancer among patients with HF. These results were confirmed in two large cohort studies of Danish and Japanese HF patients [15, 16].

A more recent study by Selvaraj and colleagues using data from the Physicians' Health Study presented contradictory results to the previously mentioned studies by demonstrating a lack of association between HF and cancer [17]. How to reconciliate the discordant findings may be partially driven by the all-male cohort in the Physicians' Health Study (PHS) analyses. In both the Danish and Japanese cohorts, there was an increased risk of breast cancer in HF patients compared with those without HF. Since the PHS included men, it did not study the associated risk in breast cancer.

Oncology

Exceeded only by heart disease, cancer is the second most common cause of death in the USA. There are an estimated 15.5 million cancer survivors in the USA which is expected to increase to 20.3 million by 2026 [18]. In 2018, 1.7 million new cancer cases are expected to be diagnosed and 600,000 Americans are expected to die of cancer [18]. From 1991 to 2015, the combined cancer death rate dropped by a total of 26%, leading to a growing population who are living with or have survived cancer [19]. The most commonly diagnosed cancers in descending order of incidence are breast, lung, prostate, and colorectal. For all cancer sites combined, the cancer incidence rate is 20% higher in men than in women, while the cancer death rate is 40% higher [20].

Shared Risk Factors

Historically, there has been extensive research on risk factors for cardiovascular disease and cancer as separate entities. Over the last decade, there is increasing recognition of overlap in many of these characteristics (Table 1).

Age

The incidence of both cancer and CVD increases with advancing age. Age alone appears to contribute to the development of CVD even after adjusting for traditional risk factors, with an approximate doubling of the risk for each additional decade of life [21]. Omitting established childhood malignancies, incident cancer rates increase with age as well. Seventy-eight percent of new cancer diagnoses occur in individuals ≥ 55 years in developed countries [22]. The associated timing of CVD and cancer onset is largely influenced by modifiable risk factors as discussed in the later sections.

Physical Inactivity

Less than 25% of adults achieve the recommended amount of daily physical activity. Lack of exercise is attributed to 12.2% of the global burden of myocardial infarction (MI) [23, 24]. The Physical Activity Guidelines for Americans, 2nd Edition, was recently released which included a systematic review reinforcing the cardiovascular benefits in reducing hypertension, diabetes, obesity, and hyperlipidemia [24]. There is accumulating evidence for increased physical activity reducing incident cancer, specifically cancers of the bladder, breast, colon, endometrium, esophagus, kidney, lung, and stomach [24, 25]. The shared biological mechanism in reducing CVD and cancer is likely multifactorial (e.g., hypertension, obesity, diabetes) through reduced adipose tissue, circulating estrogen, modulation of proinflammatory factors, and improved insulin sensitivity [26].

Table 1 Shared modifiable risk factors for cardiovascular disease and cancer

Shared modifiable risk factors for CVD and cancer		
Risk factor	CVD	Cancer
Tobacco	Implicated in 30% of CVD; 50% reduction in CHD risk after 1 year of cessation. Impairs nitric oxide bioavailability, promotes a prothrombotic and inflammatory state, and leads to endothelial damage	Single largest modifiable risk factor. Implicated in 30% of all cancer-related deaths. Strongly associated with lung, esophageal, pancreatic, and bladder cancer.
Alcohol	J-shaped curve with improved CVD outcomes in moderate consumption.	No safe limit. Increase risk of colorectal, oropharynx, esophageal, liver, and breast cancer.
Obesity	Independent risk factor when others controlled. Often associated with other risk factors—dyslipidemia, insulin resistance, sedentary lifestyle, hypertension.	Second largest modifiable risk factor. Implicated in 20% of all cancer. Increased risk with increasing BMI.
Physical inactivity	Less than 30% of adults meet recommended physical activity. Responsible for 12.2% of the global burden of MI.	Increased risk of breast, colorectal, bladder, endometrial, esophagus, kidney, lung, and stomach.
Hypertension	Single largest preventable cause of CVD. Effects one-third of the adult population, two-thirds of adults aged ≥ 60 years.	Weakly linked to increased risk of renal cell carcinoma. Prolonged exposure to ACEIs may have an increased risk of lung cancer.
Hyperlipidemia	Contributes to atherosclerotic plaque formation. Affects over one-third of adults age ≥ 40 years. Only about 50% of patients recommended for treatment are on cholesterol medication.	Mixed results, strongest evidence supports a possible association with breast cancer. Statins may have a role in preventing recurrence in cancer, particularly breast cancer.
Diabetes mellitus	Regarded as a CVD risk equivalent. Contributes to atherosclerosis through hyperglycemia-induced glycosylation, free-radical oxidative damage, and dyslipidemia.	Increased cancer-related death; particularly breast, endometrial, colorectal, and intrahepatic cholangiocarcinoma.
Chronic inflammation	Cornerstone of atherosclerosis and underlying mechanism of many CVD risk factors. Future area of pharmacologic targets.	Underlying mechanism of carcinogenesis. Future area of pharmacologic targets.
CHIP	Associated with CAD, early MI, and ischemic stroke.	Associated with hematologic malignancies.

Tobacco

Tobacco use is implicated in up to 480,000 deaths per year and 30% of all cancer-related deaths in the USA [27, 28]. It is strongly associated with the incidence of lung, esophageal, pancreatic, and bladder cancer [18]. Though tobacco use has been declining in North America, global use is still rising [29]. The carcinogenetic effect seen in smoking is mediated through direct irritants, resulting in chronic inflammation and oxidative stress, as well as direct carcinogens (nitrosamines) in tobacco [30, 31].

Smoking and the subsequent development of CVD is a major cause of coronary artery disease, stroke, aortic aneurysm, and peripheral arterial disease [32]. Smoking plays a key role in the development of atherosclerosis and the thrombotic state of acute coronary events [33]. Cigarette smoking causes vascular dysfunction by impaired nitric oxide bioavailability, development of a prothrombotic and inflammatory state, and endothelial damage [34].

The atherogenic and carcinogenic effects of smoking have been well demonstrated [35]. Through the production of irritants, carcinogens, and oxidative stress, tobacco smoking stimulates proinflammatory pathways present in the development of CVD and smoking-related cancer. Smoking represents one of the most heavily weighted modifiable risk factors in reducing mortality and constitutes a substantial public health initiative into the prevention of both CVD and cancer [23, 33].

Alcohol

Moderate alcohol consumption is associated with risk reductions in CVD, most notably in CAD [36–38]. Observational studies have shown a J-shaped relationship, with both increased risk of CVD and overall mortality with alcohol use above recommended limits [37, 39]. Alcohol's cardioprotective nature is thought to stem predominately through elevations of high-density lipoprotein (HDL), improved insulin sensitivity, and anti-inflammatory effects through lowered CRP, TNF-alpha, IL-6, and fibrinogen levels [40, 41]. Direct effects of ethanol, its metabolites, and reactive oxygen species produce the deleterious effects seen with increasing use [42].

Compared with non-drinkers, alcohol use increases the risk of colorectal, oropharynx, esophageal, liver, and breast cancers [42, 43]. Even moderate alcohol use has been associated with an increased risk in overall cancer [44]. However, prior studies have been inconsistent in the relationship between

alcohol consumption with CVD and cancer mortality. In a recent pooled analysis of > 300,000 US adults from the National Health Interview Surveys, Xi and colleagues reaffirmed the J-shaped relationship between alcohol consumption and all-cause mortality. Light alcohol use (≤ 3 drinks/week) showed a reduced risk of all-cause and cancer mortality, whereas light to moderate use was associated with a reduced all-cause and CVD mortality. Conversely, binge drinking ≥1 day/week (defined as 5 or more drinks in a day) was deleterious and associated with a higher risk of all-cause, cancer, CVD, or heart disease–related mortality [45].

Shared biologic pathways exist between CVD, cancer, and their association with alcohol. Acetaldehyde, an ethanol metabolite, is considered the carcinogenic toxin of alcohol through aberrant DNA methylation, reactive oxidative stress, and changes in estrogen pathways [46]. Alcohol's immunosuppressive properties have also been implicated to play a role in promoting carcinogenesis [47] Production of reactive oxygen species and immunosuppressive effects may account for the observed risk of cancer and CVD in heavy users.

Obesity

The prevalence of obesity in the USA exceeds 30% in most sex and age groups [48]. Obesity is a known risk factor for the development of CVD as observed in the Framingham cohort [49, 50]. The association of obesity and CVD is likely mediated by other known contributing factors including dyslipidemia, insulin resistance, sedentary lifestyle, a prothrombotic state, and proinflammatory changes associated with obesity [51]. Obesity is also associated with increased metabolic demands of the heart and consequently cardiac output. To compensate, concentric remodeling of the left ventricle ensues irrespective of elevated blood pressure [52, 53].

Obesity represents a significant risk factor for cancer; up to 20% of all cancer may be weight-related [54, 55]. The incidence of cancer is higher in women compared with men with obesity and may be attributable to elevated estrogen levels commonly observed in obesity, a known risk factor for breast and endometrial cancer [56]. In addition, the risk of cancer appears to increase with increasing BMI. This correlation is supported by the dramatic decrease in cancer, approximately 60%, in obese individuals who had a significant weight loss following bariatric surgery [57, 58].

The interplay between obesity, cancer, and CVD is complex and mediated through common changes in hormonal and proinflammatory cytokine pathways observed in obesity. Growing evidence implicates adipokines, cytokines released from adipose tissue, as a key mediator linking obesity to CVD and cancer [59]. Dysregulated inflammatory pathways involving interleukin-6 (IL-6), leptin, adiponectin, insulin-like growth factor-1 (IGF-1), tumor necrosis factor-alpha (TNF-a), and C-reactive protein (CRP) have all been implicated in either tumorigenesis and/or cardiovascular disease [60, 61]. These biologic mechanisms constitute the intermediary between CVD and cancer in obesity.

Hypertension

Hypertension is a major cardiac risk factor. Chronically elevated blood pressure results in vascular and structural cardiac remodeling, ultimately leading to hypertensive heart disease and heart failure [62]. Mechanistically, these changes are mediated through oxidative stress of the arterial wall and left ventricular wall hypertrophy in response to wall stress from elevated blood pressures [62, 63].

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are commonly used in the treatment of hypertension. However, these medications have recently received considerable attention in oncology. Safety concerns regarding an increased risk of cancer, specifically lung cancer, have been the subject of debate. A 2010 meta-analysis of seven randomized controlled trials (RCTs) showed a modest increased risk of new cancer diagnosis (RR 1.08) and lung cancer (RR 1.25) among patients treated with ARBs [64]. However, several subsequent meta-analyses of RCTs, including one by the FDA, refuted these results [65–67]. More recently, Hicks and colleagues presented a 2018 study from the UK Clinical Practice Research Datalink (CPRD) which included 992,061 patients who started on antihypertensive drugs between 1995 and 2015 [68]. They found an increased risk of lung cancer associated with the use of ACEIs compared with ARBs; the highest risk was associated with more than 10 years of ACEI use. These findings need further confirmation in lung cancer, with additional exploration for other cancer types.

Beta-blockers are frequently used as second-line agents for hypertension. Beta-adrenergic receptors are believed to have a role in many cancers through complex downstream pathways including stimulation of norepinephrine and epinephrine, activation of cAMP/PKA signaling, and promotion of vascular endothelial growth factor, matrix metalloproteinases, and interleukins [69, 70]. Studies evaluating the association between beta-blocker use and mortality in oncologic patients have shown lower mortality for patients on beta-blockers [71–75]. Despite these findings, other studies have shown contrasting results with no survival benefit of beta-blockers in cancer patients [76–80]. A recent meta-analysis of 27 clinical studies evaluated the association between beta-blocker (both selective and non-selective) use and cancer recurrence, disease-free survival, and overall survival [81]. There was a signal toward beneficial effect with beta-blockers on disease-free and overall survival, but the effect remained variable and tumor-specific. Due to these inconclusive findings, additional studies are needed to definitively answer whether beta-blocker use confers a survival benefit in cancer patients.

Hypertension has also been directly linked to cancer, particularly renal cell carcinoma [82]. The observed association is potentially linked through angiogenic factors. Vascular endothelial growth factor (VEGF) is known to be elevated in patients with hypertension and plays a key role in angiogenesis seen in malignancy [83, 84]. VEGF signaling normally results in vasodilation by stimulating nitrous oxide production by endothelial cells. However, increased levels of its soluble receptor (also called sFlt-1) bind and sequester VEGF signaling in a mechanism analogous to bevacizumab (VEGF inhibitor). Hypertension is common and presents in up to 80% of patients treated with anti-VEGF or multitargeted kinase inhibitors [85]. Elevated levels of VEGF and disruptions along its signaling pathway may provide the mechanistic overlap between hypertension, malignancy, and targeted chemotherapy agents.

Hyperlipidemia

Atherosclerotic plaque formation is dependent upon low-density lipoprotein (LDL) accumulation within the subendothelial space of blood vessels. A direct correlation exists between elevated cholesterol and risk of cardiovascular disease [86]. The AHA guidelines recommend cholesterol-lowering therapy with statins for primary CVD prevention in at-risk individuals and for secondary prevention [86–88].

Studies relating hyperlipidemia to cancer have been mostly inconclusive. The most consistent studies have shown an increased risk of breast cancer. Observational and basic science studies have shown the cholesterol metabolite, 27-hydroxycholesterol, behaves as an estradiol-like partial agonist on estrogen receptors modulating key pathways in breast cancer pathophysiology [89–91]. 27-Hydroxycholesterol has also been implicated in the development of atherosclerosis [92]. Through downstream effects on estrogen receptors, 27-hydroxycholesterol induces macrophage accumulation in the vascular wall representing the early stages of atherosclerotic plaque [93].

The association of hyperlipidemia, statins, and cancer is complex. While the role of statins in the primary prevention of cancer appears logical due to their pleiotropic effects, studies have been largely inconclusive [94–96]. Statin use following the diagnosis of cancer, however, has been observed to lower the risk of cancer-related mortality irrespective of prior statin use in multiple cohort studies and a recent meta-analysis [97–99]. All statins may not have the same effect, however. A large Danish prospective cohort showed reduced cancer recurrence in limited-stage breast cancer with the use of a more lipophilic statin such as simvastatin post-diagnosis when compared with a hydrophilic statin such as pravastatin or no statin therapy [100]. There are ongoing studies evaluating the potential role of statins as cardioprotection against cardiotoxicity in cancer patients actively receiving chemotherapy [101].

Type 2 Diabetes Mellitus

Diabetes mellitus has deleterious effects on the micro- and macrovasculature and is widely accepted as a CVD risk equivalent [102]. The pathophysiology of atherosclerosis in diabetes involves hyperglycemia-induced glycosylation, free-radical oxidative damage, and dyslipidemia [103]. Elevated levels of IGF-1 during states of hyperglycemia stimulate the migration and proliferation of smooth muscle cells seen in the early stages of atherosclerosis [104].

Several systematic reviews and a 2010 consensus report by the American Diabetic Association have concluded there is convincing evidence of an association between type 2 diabetes mellitus and cancer [105]. Site-specific cancers include breast, colorectal, endometrial, liver, and pancreas [106]. Diabetes and cancer share many risk factors such as obesity, aging, sedentary lifestyle, and diet. However, this association appears to be independent of these risk factors in the epidemiological analysis [107].

Medications used in diabetes may also provide insight into CVD and cancer overlap. Several systematic review and meta-analyses have reported a substantially reduced risk of all cancer mortality and incidence in diabetic patients treated with metformin compared with other traditional regimens [108, 109]. Potential mechanisms for the anti-cancer effect of metformin may include the prevention of weight gain, reduction in hyperinsulinemia, activation of the tumor suppressor protein kinase AMPK (inhibits mTOR, which is frequently activated in cancer including HER-2 expression), and induction of cell cycle arrest and apoptosis resulting in reduction in growth factor signaling [108, 110, 111].

More recently, sodium-dependent glucose transporter 2 (SGLT2) inhibitors received FDA approval for the treatment of diabetes and are recommended for secondary CVD prevention due to their cardioprotective effects. In a recent study by Claudio et al., SGLT2 inhibition in early-stage lung adenocarcinoma reduced tumor progression and prolonged the survival in mice with SGLT2 expression [112].

The association of diabetes with CVD and cancer is multifaceted. Hyperglycemia, hyperinsulinemia, inflammation, IGF-1, and hormonal factors are important elements contributing to the overlap of increased CVD and cancer risk. Hyperinsulinemia has direct tumorigenic effects and increases bioavailable IGF-I, promoting cell proliferation and metastasis [113]. IGF-I also increases bioavailable estrogen by reducing sex hormone–binding globulins, a known risk factor for breast and endometrial cancers [114]. Inflammation, and its ensuing cytokine pathways, is influential in the pathogenesis of diabetes, CVD, and cancer. Dysregulated pathways of TNF-a, IL-6, and IL-1b have been implicated in the development of all three disease states and may represent a common underlying mechanism [115–117].

Chronic Inflammation

Inflammation represents the common underlying mechanism in many of the CVD risk factors (hypertension, hyperlipidemia, diabetes, and smoking) for the development of atherosclerosis. It is now appreciated that inflammation is the cornerstone of atherosclerosis by promoting the expression of adhesion molecules on endothelial cells, allowing leukocyte attachment to blood vessel walls [116]. By assessing biomarkers of inflammation, such as C-reactive protein (CRP), cardiovascular risk can be estimated [118, 119].

The inflammatory role in cancer has long been established since Virchow first observed leukocytes in neoplastic cells, postulating malignancy's inflammatory origin. There is extensive evidence of site-specific inflammation and associated malignancy (human papilloma virus and cervical cancer, inflammatory bowel disease and colorectal cancer, non-healing wounds and squamous cell cancer) [120–122]. This association also holds true in systemic inflammatory conditions such as in systemic rheumatic disorders [123]. Systemic sclerosis, for instance, has a 1.5–5 times increased risk for malignancies of the lung, breast, esophagus, and hematological [124].

Common molecular pathways, by the way of chronic inflammation and oxidative stress, highlight the complex interplay of cancer and cardiovascular disease. This interrelationship is observed in trials of non-steroidal anti-inflammatory drugs (NSAIDs), specifically aspirin, in the reduction of CVD and colorectal cancer. Though recent evidence has placed into question the role in primary CVD prevention, the U.S. Preventive Services Task Force's 2016 update cites sufficient evidence to support the use of aspirin in primary prevention of CVD and colorectal cancer in adults aged 50–59 years. The inflammatory intersection is further reinforced by recent findings in the CANTOS trial (canakinumab anti-inflammatory thrombosis outcomes study) where specific targeting of interleukin 1β (a key mediator of inflammation) conferred cardiovascular benefit and, unexpectedly, a significant decrease in lung cancer incidence [125, 126]. Fueled by the common risk factors, inflammation likely creates the pathologic climate necessary to foster cancer and cardiovascular disease.

Clonal Hematopoiesis of Indeterminate Potential

Clonal hematopoiesis of indeterminate potential (CHIP) is defined as the presence of expanded somatic blood-cell clone in individuals without other established hematologic abnormalities. Jaiswal and colleagues showed that detectable somatic mutations were uncommon in those younger than 40 years of age and increased significantly with older age, affecting approximately 10% of individuals older than 70 years [127]. The majority of mutations occurred in DNMT3A, TET2, and ASXL1. Even though the majority of affected individuals did not have the criteria for myelodysplastic syndrome or other hematologic abnormalities, the presence of CHIP was associated with increased risk of hematologic cancer, incident coronary artery disease, ischemic stroke, and all-cause mortality.

Due to the preliminary findings that CHIP may be associated with increased risk for CAD, Jaiswal and colleagues further evaluated whether CHIP causally contributes to atherosclerotic cardiovascular disease [128]. They demonstrated that somatic mutations leading to CHIP were significantly associated with increased risk for CAD and early myocardial infarction. Dorsheimer and colleagues expanded on these prior studies by demonstrating CHIP mutations were significantly associated with both disease progression and mortality in 200 ischemic HF patients [129]. These findings raise the question regarding whether DNA sequencing could enable early detection of blood cancers, prediction of HF progression and mortality, and identification of persons at high risk for CAD to target with more intensive risk factor reduction.

Congenital Heart Disease

Survival in adult congenital heart disease (ACHD) has significantly improved over recent decades [130]. Cancer prevalence among ACHD patients is 1.6 to 2 times higher than the general population [131]. Hepatocellular carcinoma (HCC) is a known long-term complication following the Fontan procedure [132]. During childhood, many congenital patients are exposed to low-dose ionizing radiation (LDIR) from cardiac procedures. Cohen et al. recently presented a large population-based study demonstrating an association between increased LDIR-related cardiac procedures and incident cancer risk [133]. These findings, if substantiated, would have significant clinical implications regarding the role of increased cancer surveillance and careful patient selection prior to performing cardiac procedures.

Implications for Primary Care Providers

Primary care providers (PCPs) have a key role in risk factor modification (Fig. 1). When these providers are working to promote the health of their patients, screening for and management of certain chronic conditions can reduce the downstream risk of both cardiovascular disease and incident cancer. Conveying this information may yield stronger "teachable moments" as there may be implicit variability in fear of cancer compared with cardiac disease in different demographics.

Following the completion of cancer treatment, PCPs have the responsibility of longitudinal surveillance for potential cardiac complications and cancer recurrence. They should continue efforts to reduce modifiable risk factors, as these often contribute to heightened risk for secondary malignancies or cardiovascular disease. Because of their ability to see

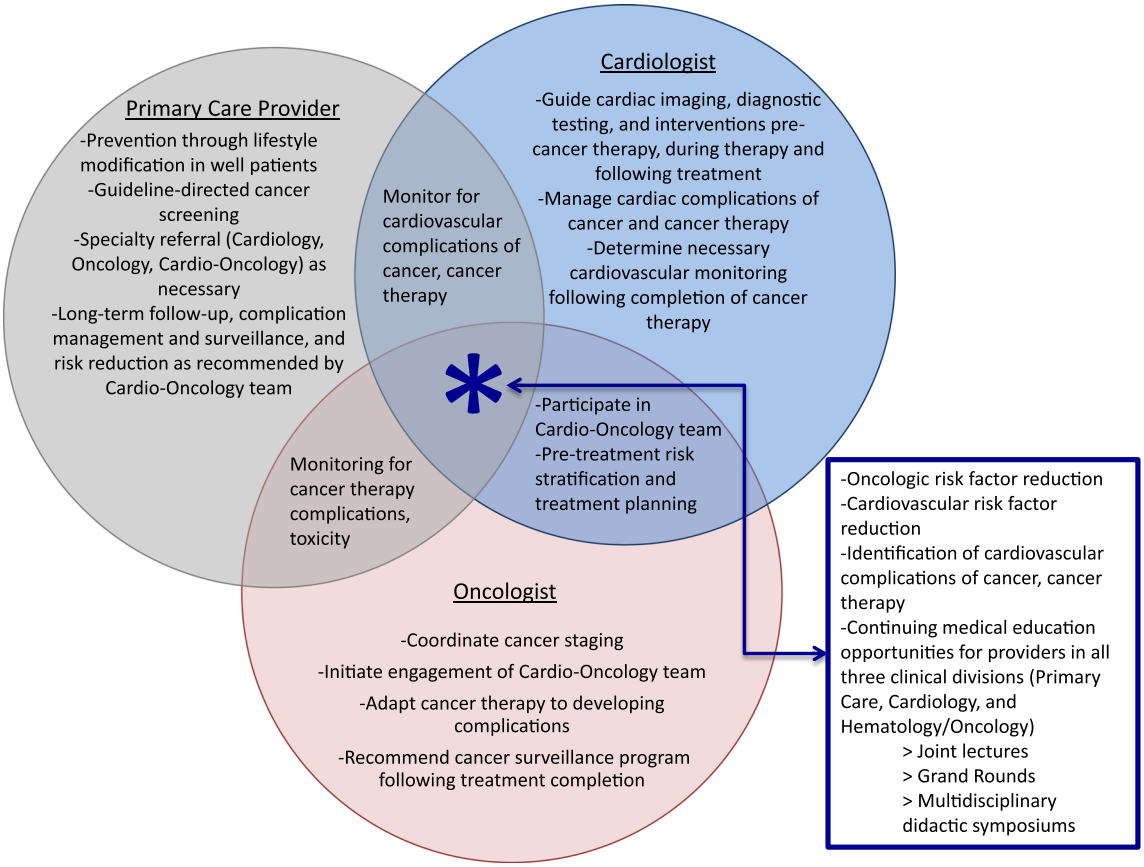

Fig. 1 Collaborative roles between primary care providers, cardiologists, and oncologists in patient management of shared risk factors for cardiovascular disease and cancer

patients on a more frequent basis than subspecialty providers, PCPs should serve as the nexus between reducing the risk for development of cardiovascular and oncologic disease, for interval monitoring, and reinforcing any recommendations made by subspecialty providers [134••,135].

Implications for Cardiologists

Prior to a Cancer Diagnosis

The majority of responsibility for age-appropriate oncologic screening is held by PCPs. However, there may be opportunities for cardiologists to overlap cardiovascular and oncologic screening. Specific examples of these opportunities include (a) the combination of coronary artery calcium computed tomography (CT) scans and low-dose lung CT for lung cancer screening in age and risk factor appropriate patients and (b) the interpretation of breast arterial calcium score as a corollary for cardiovascular disease [136••]. Rather than practicing cardiology in a silo of cardiovascular-specific health, non-cardiac aspects of population health should be considered.

Given that smoking is a risk factor for both lung cancer and cardiovascular disease, it may be valuable to include evaluation of coronary artery calcium in a patient's initial lung cancer screening CT (generally ordered by PCPs). Similarly, when cardiologists order coronary CTs in patients that meet age and tobacco use criteria for lung cancer screening, including an assessment of the lung parenchyma provides a valuable screening opportunity [136••,137].

Breast arterial calcification is present in nearly 13% of screening mammography studies, and it correlates with age, diabetes, and increased parity (all cardiovascular risk factors). Because breast arterial calcification is not associated with smoking history, it is thought to represent a different pathophysiological pathway to coronary disease as compared with smoking, which contributes to coronary disease through intimal atherosclerosis. Multiple cohort studies have shown elevated hazard ratios and odds ratios for the association of breast arterial calcification with cardiovascular disease, specifically including cardiovascular death, coronary artery disease, and heart failure [138–141]. A practical approach may be to recommend that providers screen more aggressively for cardiovascular risk factors when breast arterial calcification is seen on mammography to avoid missing an opportunity to institute risk reduction measures [136••,142].

After Cancer Diagnosis: Pre-treatment

Therapeutic choices for cancer treatment should involve a multidisciplinary team to optimally balance the risks and benefits of targeted cancer therapies while being cognizant of their potential cardiotoxicities. Members of this team should provide insight regarding (a) pre-therapy cardiovascular disease optimization and risk modification and (b) which complications a patient is more likely to have based on their underlying pre-treatment comorbidities and health history [143, 144]. Underlying cardiovascular disease increases the risk of treatment-related cardiotoxicity, and cardiotoxicity is more common in patients with previously undetected cardiovascular risk factors.

After Cancer Diagnosis: During Treatment

In addition to high-risk patient features (age greater than 60 years, underlying cardiovascular risk, and baseline impaired cardiac function), high-risk therapies include (a) high-dose anthracycline treatment, (b) high-dose radiotherapy with heart in field of radiation, and (c) low-dose anthracycline therapy combined with low-dose radiotherapy (with the heart in the radiation field) [145•]. The American Society of Clinical Oncology defines high-dose anthracycline therapy as doxorubicin at ≥ 250 mg/m^2 or epirubicin at ≥ 600 mg/m^2. High-dose radiotherapy ≥ 30 Gy [146]. Additionally, the development of oncologic risk score calculators for non-oncologists, or combined oncologic and cardiovascular risk calculators, would facilitate the use of these potential combined screening tools [136••,147•]. This is an opportunity for advancement in a cohort where cardiovascular risk scores developed in other populations may not directly apply due to unique aspects of the average cancer patient receiving chemotherapy, since they do not consider cancer-specific risk.

After Cancer Diagnosis: Post-treatment

Following the completion of therapy, ongoing cardiology involvement is needed. Cancer-related cardiac complications can be delayed until decades later [144, 148]. High-risk patients require longitudinal cardiac monitoring [143, 149]. Aggressive management of shared risk factors prevents cancer recurrence, secondary malignancy, or cardiovascular disease. Survivors of childhood cancer have shown that they have more heart disease by age 40 in comparison with cancer-free siblings [150]. Rates of hypertension, diabetes, dyslipidemia, and tobacco use are higher among survivors, and they have a seven times higher likelihood of dying from cardiovascular disease compared with the general population [149, 151•]. Common risk calculators, such as the Framingham risk calculator for cardiovascular disease, do not take into account oncologic history when estimating risk [149]. Tailored calculators for this population do exist although many cardiologists are not aware of them, such as the Childhood Cancer Survivor Study calculator that was designed to provide more accurate estimates of cardiac risk to cancer survivors [150].

Implications for Oncologists

Patients are typically referred to oncologists after a diagnosis of malignancy is suspected or confirmed. Due to focus on oncologic prognosis, baseline cardiac conditions and potential cardiotoxic risks of cancer treatment are sometimes under-emphasized [136••]. The American Cancer Society, American Diabetes Association, and American Heart Association have together emphasized the importance of combined preventative measures for cancer, diabetes, and heart disease, focusing on the impressionable period after oncologic diagnoses are made during which care providers can counsel on and emphasize the importance of behavioral and lifestyle changes. Given the increased mortality in cancer patients with cardiovascular comorbidities, oncologists are uniquely positioned to have meaningful conversations about risk factor reduction in the context of a new cancer diagnosis or upon follow-up [152].

Baseline and Follow-up Cardiovascular Testing

With the established overlap in the epidemiology of cancer and cardiovascular disease, a new cancer diagnosis should prompt at least a limited cardiovascular risk assessment prior to the initiation of cancer therapy [145•]. Certain malignancies have a greater risk of concurrent cardiovascular disease (i.e., lung, breast, and colon cancers). Using available risk calculators and clinical history can be useful upfront as this may guide type or dosing of chemotherapy if there is a significant cardiovascular risk [136••, 153]. "Cardiovascular testing" should begin with risk calculators such as the Atherosclerotic Cardiovascular Disease (ASCVD) score that can be rapidly employed to get a general sense of cardiovascular risk. However, in patients with active or past malignancy, interpretation of these risk scores is unclear [4]. Understanding cardiovascular risk is more critical with patients that have low-grade cancer and long-life expectancy. For example, in CML patients chronically on tyrosine kinase inhibitors, recognition of baseline risk is critical to follow-up due to the possibility of amplifying cardiovascular complications while on therapy and a prolonged time horizon of anticipated exposure.

Conclusion

There is significant overlap in the epidemiology and risk factors for the development of cardiovascular disease and cancer. Clinically, it offers tremendous opportunities for joint risk factor modification. It reinforces the necessity of cardio-oncology specialists for support prior to cancer therapy initiation in high-risk cohorts, during therapy in patients at risk or with evident disease, and following the conclusion of therapy for longitudinal follow-up and risk reduction. There is a potential for the use of cardioprotective medications with high-risk cancer therapies, and an input from cardiologists to guide this process is necessary. Certain cancer therapies are well established to place patients at risk for cardiovascular complications, and with the rapid emergence and uptake of newer oncologic therapies (such as immune checkpoint inhibitors and tyrosine kinase inhibitors), less common cardiovascular complications are becoming evident. Moving forward, it will be essential for primary care providers, cardiologists, and oncologists to work together to optimize the care of and reduce the risk in their shared patients with a collaborative approach.

Compliance with Ethical Standards

Conflict of Interest Logan Vincent declares that she has no conflict of interest.

Douglas Leedy declares that he has no conflict of interest.

Sofia Carolina Masri declares that she has no conflict of interest.

Richard K. Cheng has served as a consultant and participated on advisory boards for Alnylam Pharmaceuticals (modest) and Ionis/Akcea Pharmaceuticals (modest).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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