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Review

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Atherosclerotic Cardiovascular Disease in Cancer Survivors: Current Evidence, Risk Prediction, Prevention, and Management

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ABSTRACT

While advances in cancer treatment have led to improved survival rates, cancer survivors are at a significant risk of developing atherosclerotic cardiovascular disease (ASCVD). This review examines the risk, diagnosis, and prevention of ASCVD in this population. Cancer survivors, especially those diagnosed with certain types, face a significantly higher risk of developing ASCVD than the general population. We introduce the "triad model" to explain this increased risk of ASCVD among cancer patients. This model includes three interconnected components: common catalysts, cancer influence, and treatment impact. The factors contributing to this model are the shared risk factors between cancer and ASCVD, such as smoking, obesity, and systemic inflammation; the direct effects of cancer on cardiovascular health through chronic systemic inflammation and endothelial damage; and the significant effects of anticancer treatments, including chemotherapy and radiation, which can worsen cardiovascular complications and hasten the progression of ASCVD. Furthermore, cancer survivors are at a higher risk of developing and dying from ASCVD, highlighting the necessity for tailored guidelines and strategies for ASCVD prevention and management in this population. The review explores the utility of diagnostic tools, such as coronary artery calcium scoring, in predicting and managing ASCVD risk. It also emphasizes the importance of prevention strategies that include regular cardiovascular monitoring and lifestyle modifications. Finally, the relationship between cancer survival and cardiovascular health highlights the importance of integrated and comprehensive care approaches. Continued research, the development of prediction models, and specific preventative strategies are essential to improve cancer survivors' overall health outcomes.

Keywords: Cancer survivors; Atherosclerosis; Cardiovascular disease; Cardio-oncology

INTRODUCTION

Advancements in medical science have significantly increased the survival rates of cancer patients. Consequently, the paradigm of cancer treatment is shifting from merely improving

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Conflict of Interest

Dr. You reports being the CEO of PHI Digital Healthcare

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Author Contributions

Conceptualization: Choi A, Cho I, Cha MJ; Funding acquisition: Cho I; Supervision: You SC; Writing - original draft: Choi A, Kim S, You SC; Writing - review & editing: Choi A, Kim S, Kim S, Cho I, Cha MJ, You SC.

survival rates to placing greater emphasis on the long-term health impacts and quality of life for cancer survivors.[1,2] Cardiovascular disease (CVD) is a leading cause of death among cancer survivors.[3-5] The implications of cancer survival for cardiovascular health underscores the need for ongoing monitoring of the long-term effects of cancer treatments and the shared risk factors between cancer and CVD. Treatments such as chemotherapy and radiation therapy can significantly impact cardiovascular health.[6,7] Radiation therapy may cause damage to heart tissue and blood vessels, potentially accelerating the progression of atherosclerotic cardiovascular disease (ASCVD).[8] Although cardio-oncology research primarily focuses on the cardiotoxic effects of cancer therapies, the risks associated with and strategies for preventing ASCVD in cancer survivors are still largely unexplored. The purpose of this review is to establish a protocol for the prevention and management of ASCVD in the growing population of cancer survivors.

INCIDENCE OF ASCVD IN CANCER SURVIVORS

In the early stages of cancer treatment, the primary focus was on achieving progression-free survival, often with less consideration for long-term adverse effects, including those related to cardiovascular health. However, as the population ages and cancer treatments advance, the number of cancer survivors has increased. This rise has been accompanied by a higher incidence of new-onset ASCVD within this demographic. Research from Korea's National Health and Nutrition Examination Survey indicates that cancer survivors face a higher risk of developing ASCVD than the general population.[9] An increased risk of ASCVD has been demonstrated for certain cancers, such as bladder/kidney cancer, prostate cancer, colorectal cancer, lung cancer, melanoma, and testicular cancer.[10] Furthermore, individuals aged 60 to 69, especially those with a history of cancer, have been found to be at a heightened risk of developing ASCVD.[11]

CANCER AND ASCVD: THE TRIAD MODEL

We propose the following triad model to explain the increased risk of ASCVD in patients with cancer (**Fig. 1**): 1) common catalysts, 2) cancer influence, and 3) treatment impact. These factors must be considered to develop more effective strategies for CVD prevention and management in cancer survivors.

1. Common catalysts: shared risk factors between cancer and ASCVD

Cancer and ASCVD share several common risk factors, including smoking, obesity, and systemic inflammation, all of which significantly contribute to both conditions.[12,13] Smoking is the most well-known and significant shared risk factor. It is a major cause of various cancers, particularly lung cancer, and the harmful substances in cigarette smoke can damage the arterial lining, leading to atherosclerosis and mutations that result in cancer.[14] Obesity contributes to increased inflammation, hormonal imbalances, and metabolic abnormalities, which in turn elevate the risks of both cancer and ASCVD.[15,16] Inflammation, which is caused by diverse conditions, plays an important role in both tumorigenesis and the progression of atherosclerosis. Chronic inflammation creates a pro-tumorigenic environment. Factors such as prolonged infections, chronic irritation, autoimmune diseases, and certain lifestyle choices can sustain inflammatory responses, thereby increasing the risk of various cancers.[17] Similarly, inflammation is involved in all stages of atherosclerotic development, from the initial lesion formation to plaque progression and eventual rupture, leading to acute ASCVD events.

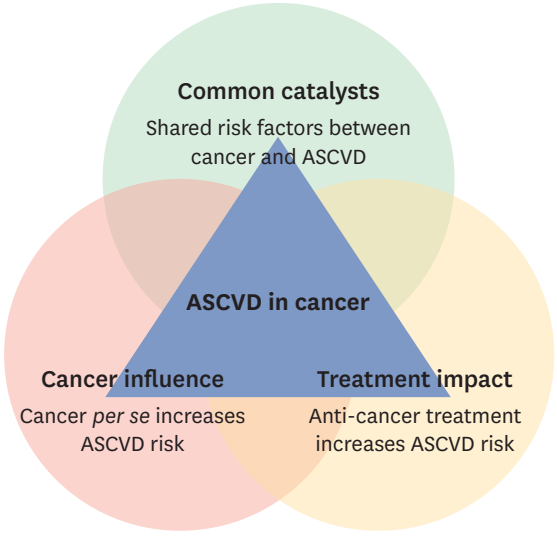

Fig. 1. The interaction between cancer and ASCVD.
ASCVD, atherosclerotic cardiovascular disease.

Inflammatory cells infiltrate the arterial wall, contributing to plaque formation and instability. Exacerbating factors include high cholesterol, hypertension, smoking, and diabetes.[18] Common conditions like obesity, hyperglycemia, hypertension, and hypertriglyceridemia, which cause inflammation, may explain the shared risk factors between ASCVD and cancer.[19,20] Diet and physical inactivity are also shared risk factors for both cancer and ASCVD.[12] Poor dietary habits, such as high consumption of saturated fats and sugars, are linked to increased risks for both cardiovascular health and cancer.[21-24] Inadequate folate intake is also associated with increased risks of ASCVD and colorectal cancer.[25,26] Additionally, physical inactivity is associated with higher risks for both ASCVD and cancer. Prolonged sitting time and low levels of physical activity during leisure time have been found to increase the risk of coronary heart disease and stroke.[27] Moreover, significant adverse effects of sedentary behavior on cancer incidence have been reported.[28] Given that these factors are modifiable, special attention is required in both the treatment and post-treatment care of cancer patients.[29,30]

In addition to physical risk factors, psychological factors like depression and anxiety may also pose a risk for cancer and ASCVD.[31-35] These psychological conditions can promote unhealthy behaviors, including smoking, poor adherence to treatment, and reduced physical activity, potentially increasing the risk of developing cancer and ASCVD.[36]

2. Cancer influence: cancer itself increases ASCVD risk

Cancer itself and its systemic effects can heighten the risk of ASCVD. The disease induces a state of chronic systemic inflammation that hastens the progression of atherosclerosis. Inflammatory cytokines and other mediators can lead to acute cardiovascular disease by damaging the endothelium and encouraging plaque formation.[37] The relationship between cancer and atherosclerosis is complex, involving multiple factors such as the body's immune response to cancer, the production of inflammatory cytokines, and the effects of certain cancer treatments on cardiovascular health.[38]

Several studies have demonstrated a strong link between cancer and an increased incidence of ASCVD. In a large-scale cohort study involving 4,519,243 participants, cancer patients

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exhibited 1.33 and 1.44 times higher risks of cardiovascular mortality and stroke, respectively, than non-cancer controls.[39] Among various cancer subtypes, those with nervous system malignancies faced the highest risk of cardiovascular mortality (hazard ratio [HR], 3.24; 95% confidence interval [CI], 2.22–4.73) and stroke (HR, 11.20; 95% CI, 9.84–12.74). While no significant link was found between cancer and acute myocardial infarction (MI), the risk of acute MI was notably higher in patients with leukemia (HR, 1.21; 95% CI, 1.01–1.46), hematological (HR, 1.23; 95% CI, 1.11–1.37), and thoracic cancers (HR, 1.60; 95% CI, 1.41–1.82). Additionally, a meta-analysis confirmed that cancer survivors have a 1.66-fold increased relative risk of stroke compared to cancer-free controls, with the highest risk observed in those with pancreatic cancer (HR, 2.32; 95% CI, 1.86–2.88).[40] Consistent results were reported in a recent population-based cohort study in China, which indicated elevated risks of ischemic heart disease and stroke in comparison to the standard population, particularly among patients with pancreatic cancer.[41] Notably, the risk of ASCVD incidence was found to be greatest during the first year following the cancer diagnosis.[39,41] This highlights the need for early prevention and aggressive intervention for ASCVD after a cancer diagnosis.

3. Treatment impact: anti-cancer treatment increases ASCVD risk

The long-term adverse effects of cancer treatments, particularly in relation to ASCVD, are significant. The chemotherapy drugs and radiation therapy used to treat cancer can cause cardiovascular complications. This damage significantly accelerates the onset and progression of ASCVD, adding to the health problems faced by cancer patients. The severity of cardiovascular toxicity depends on several factors, including the type of drug, tumor location for radiation therapy, presence of a history of cardiac disease, and dose of a drug or ionizing radiation. Certain drugs damage the cardiovascular system, including direct myocardial damage, hypertension, and accelerated atherosclerosis.[42,43] Anthracyclines, and human epidermal growth factor receptor 2-targeted therapies can lead to cardiotoxicity, primarily heart failure, which may indirectly contribute to ASCVD risk.[44,45] Vascular endothelial growth factor signaling pathway (VSP) inhibitors also elevate the risk of atherosclerosis-related cardiovascular events. A meta-analysis including 77 phase III trials reported that the VSP inhibitors were associated with higher risks of cardiac ischemia (odds ratio [OR], 2.83; 95% CI, 1.72–4.65), and arterial thromboembolism (OR, 1.52; 95% CI, 1.17–1.98), compared to routine care.[46] VSP inhibitors may predispose individuals to accelerated atherosclerosis, vasospasm, and coronary thrombosis.[47] In addition to VSP inhibitors, immune checkpoint inhibitors (ICIs) and fluoropyrimidines are associated with atherosclerotic cardiovascular events. ICIs increase the risk of ASCVD by promoting vascular inflammation and plaque progression.[48] Fluoropyrimidines, such as 5-fluorouracil, can lead to myocardial ischemia induced by coronary vasospasm and endothelial injury.[49] Furthermore, in addition to the increased risk associated with medications, a study reported an increased risk of coronary artery disease following chest radiation, especially in breast cancer patients.[50] This study demonstrated that the rates of major coronary events increased by 7.4% per Gray mean dose in breast cancer patients treated with radiotherapy. Exposure to radiation accelerates the formation of macrophage-rich and inflammatory atherosclerotic lesions, which are prone to rupture and may contribute to ASCVD.[51]

PROGNOSIS OF ASCVD IN CANCER SURVIVORS

The prognosis of ASCVD in cancer survivors is influenced by multiple factors, including the type of cancer, the specific cancer treatments received, the severity of ASCVD, and the

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patient's overall health. The type and intensity of cancer treatment play a crucial role in determining the risk of developing ASCVD. Treatments such as chemotherapy and thoracic radiotherapy, especially those involving anthracyclines, are known for their cardiotoxic effects. While these treatments effectively combat cancer, they can also increase the burden on the cardiovascular system, thereby exacerbating the risk of ASCVD.[52] The risk is further heightened in patients with comorbidities such as hypertension, diabetes, and dyslipidemia, which are commonly observed in cancer survivors. Additionally, lifestyle factors, including physical inactivity and poor dietary habits that may become more prevalent during and after cancer treatment, also contribute to this risk.[14,16]

Suboptimal medical management of ASCVD in cancer survivors may also contribute to their health challenges. A study from a single center revealed that cancer patients were 40% less likely to receive statin or antiplatelet therapies compared to those without a cancer history.[53] Similarly, data from a large-scale Swiss registry of myocardial infarction indicated that cancer patients were less likely to undergo percutaneous coronary intervention, receive P2Y12 blockers, or take statins. Additionally, in-hospital mortality rates were higher among cancer patients in this registry.[54] Understanding these contributing factors is essential for developing strategies to improve the prognosis in this patient population.

EVALUATION OF THE RISK OF ASCVD IN CANCER PATIENTS

Evaluating the risk of ASCVD is essential for determining management strategies to prevent ASCVD in cancer patients. Various risk estimation tools are employed to assess the likelihood of developing ASCVD, with the Pooled Cohort Equation being the most commonly used. This tool calculates the 10-year incidence of ASCVD events in individuals who do not have CVD at the time of assessment.[55] However, there is no established standard for monitoring that is specifically tailored to cancer survivors, which complicates the management of ASCVD risk in this population.

The coronary artery calcium (CAC) score is a well-established marker for predicting the risk of ASCVD. Treatment recommendations for hyperlipidemia in the United States and Europe support its use in patients with moderate risk.[56] Specifically, the cardiovascular risk of asymptomatic patients at moderate risk may be reclassified upward if their CAC score exceeds 100.[56] This recommendation is based on the ability of CAC to stratify risk and guide treatment decisions.

Recognizing the discriminative value of CAC, the Society of Cardiovascular Computed Tomography recommends including a statement about the absence or presence of CAC in reports on non-cardiac chest computed tomography (CT) scans used for cancer imaging.[57] Given the frequent use of chest CT scans in cancer staging and treatment planning, incorporating information on CAC into the baseline assessment can enhance cardiovascular risk stratification in cancer patients without a history of ASCVD.

Additionally, recent studies have highlighted that the CAC score from pretreatment CT is independently associated with future cardiovascular risk in cancer patients.[58-60] A study using radiotherapy planning CT of breast cancer patients showed that the risk of coronary artery disease was 8-fold higher in patients with a CAC score >400 than in those with a CAC score of 0.[58] Similarly, in patients with diffuse large B-cell lymphoma undergoing anthracycline-based chemotherapy, higher CAC scores were linked to an increased risk of

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cardiovascular disease.[59] Although the feasibility of using CAC as an independent risk factor for ASCVD requires further validation, it holds potential for identifying high-risk individuals among cancer patients.

Taken together, quantifying CAC from non-cardiac chest CT scans for cancer imaging can help identify pre-existing subclinical ASCVD and give additional information for a comprehensive baseline evaluation of ASCVD risk in cancer patients and survivors.

PREVENTION AND MANAGEMENT: ASCVD IN CANCER PATIENTS

Cancer survivors face a higher ASCVD risk than the general population, a risk that escalates as cancer survival rates improve, subsequently raising the mortality and morbidity burden. However, the prevention of ASCVD is frequently neglected in standard cancer care, and there is a deficiency of evidence-based guidelines for the long-term surveillance of ASCVD in cancer survivors.

For the prevention and management of ASCVD, risk stratification is crucial and involves using traditional cardiovascular risk factors and/or imaging modalities such as CAC scans. This approach significantly aids in shaping treatment strategies. Additionally, post-treatment screening can facilitate the early detection of ASCVD. The Society for Cardiovascular Angiography and Interventions recommends that cancer survivors who have undergone at-risk chemotherapy treatments (e.g., nilotinib, ponatinib, and cisplatin) and/or thoracic radiation therapy should undergo screening with coronary computed tomography angiography (CCTA) or noninvasive stress testing every 5 years.[61] For patients at high risk—those with pre-existing ASCVD or multiple ASCVD risk factors—who have received thoracic radiation, it is advised to perform CCTA and stress testing every 2 years.[61]

In addition to baseline cardiovascular risk evaluation and screening examinations, pharmacological therapies may help reduce the risk of incident ASCVD. A study involving cancer survivors with acute myocardial infarction indicated that treatment with aspirin and beta-blockers improves survival.[54] By modifying ASCVD risk factors through medication, it may be possible to decrease the likelihood of ASCVD events in cancer survivors. However, the efficacy of cardioprotective medications in this patient group is not fully established and requires further validation through additional studies. Clinicians must also be aware of potential drug-drug interactions between cardiovascular and anticancer medications. The concurrent use of statins and pazopanib, for example, may increase the hepatotoxicity associated with pazopanib.[62] Imatinib, an inhibitor of the CYP3A4 enzyme, can increase the exposure to simvastatin and lovastatin, which are primarily metabolized by CYP3A4.[47] Additionally, the combination of P2Y12 receptor inhibitors such as clopidogrel, ticagrelor, and prasugrel with dasatinib, ibrutinib, nintedanib, and olaparib may increase the risk of bleeding due to their additive effects.[47] Therefore, a careful evaluation of the benefits and risks is crucial before initiating cardioprotective medications in cancer patients.

For managing acute coronary diseases in cancer patients undergoing anticancer treatment, both invasive and non-invasive approaches may be utilized. According to the 2022 European Society of Cardiology guidelines on cardio-oncology, an invasive strategy is advised for cancer patients with a life expectancy of more than 6 months who present with ST-segment

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elevation myocardial infarction (STEMI) or high-risk non-ST-segment elevation acute coronary syndromes (NSTE-ACS).[47] Conversely, for those with a life expectancy of less than 6 months and/or a very high bleeding risk, presenting with STEMI or NSTE-ACS, a conservative non-invasive strategy should be considered.

CONCLUSION

In conclusion, the intersection of cancer and ASCVD underscores the necessity for comprehensive and integrative care for ASCVD in cancer survivors. With advancements in cancer treatment, the population of cancer survivors is growing. Consequently, the risk of ASCVD in this group is also on the rise. Therefore, a comprehensive strategy is essential, encompassing regular cardiovascular monitoring, lifestyle modifications, and control of established risk factors. The prognosis of ASCVD in cancer survivors is influenced by various factors, such as the type and intensity of cancer treatment, comorbidities, and lifestyle choices. Managing ASCVD in this group requires early detection and intervention. Assessing ASCVD risk in cancer patients is particularly challenging because current risk assessment tools are not designed for this specific population. Therefore, prevention and management strategies for ASCVD in cancer survivors need to account for the unique risk factors associated with cancer treatment. Given the interplay between cancer and cardiovascular health, it is necessary to develop customized screening strategies and guidelines specifically for cancer survivors.

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