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Review article

Evolving field of cardio-oncology

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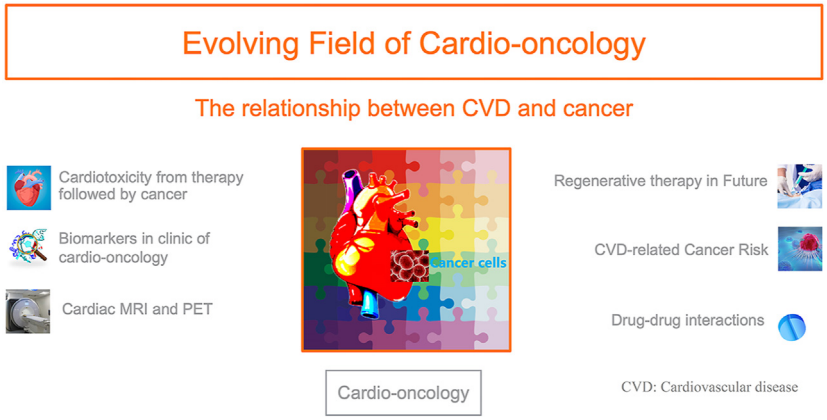
HIGHLIGHTS

- All cancer therapies can be cardiotoxic. Cytochrome P450 and P-glycoprotein mediate the interactions between cardiovascular and cancer drugs.
- Myocardial injury and cardiac insufficiency biomarkers, newly including DNA, and circulating microRNA, indicate cardiotoxicity.
- Cardiac magnetic resonance and positron emission tomography are increasingly used to monitor cardiotoxic therapies, allowing early detection of cardiac damage.
- Cancer and cardiovascular disease (CVD) share risk factors, and CVD prevalence is correlated with increased cancer incidence.

GRAPHICAL ABSTRACT



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ABSTRACT

Therapy development for cancer and cardiovascular disease (CVD) to prolong lifespan makes the relationship between these two conditions more complex. Drug interactions in cardiology and oncology are associated with metabolism and drug transportation. Advances in biomarkers and imaging provide novel methods for detecting cardiotoxicity, including cardiac injury and inflammation. The new concept of CVD-related cancer risk is leading to a new direction of progression termed "reverse cardio-oncology."

Introduction

Cancer and cardiovascular disease (CVD) are leading causes of death globally, making the development of the interdisciplinary field of cardio-oncology almost inevitable. The earliest attention to the correlation between the two conditions arose from the impact of cancer treatment on the heart. Increased CVD risk after a cancer diagnosis may be related to direct (cardiotoxic) or indirect complications, leading to the concept of cardio-oncology. Traditionally, cardio-oncology focuses on the cardiotoxicity of anti-tumor therapy. Advances in cardiology and oncology prolong human life, but the coexistence of CVD and cancer is becoming increasingly common, making the relationship between the two conditions more complex.

Focus areas of cardio-oncology

Cardiotoxicity following cancer therapy

Heart disease and cancer remain the leading causes of death in the

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United States, according to the American Heart Association (AHA). Chemotherapy, molecular-targeted therapy, immunotherapy, and radiation therapy can all damage the cardiovascular system temporarily or permanently, termed cardiotoxicity, which can lead to an increased risk of CVD.

Researchers from the Pennsylvania State Cancer Institute examined data from the Surveillance, Epidemiology, and End Results (SEER) Program from the National Cancer Institute (NCI) and identified 3,234,256 cancer survivors with 28 different cancer types over four decades (1973–2012). A total of 1,228,328 of these patients (38.0%) died from cancer, and 365,689 (11.3%) died from CVD; 76.3% of CVD deaths were due to heart disease.[1] These results show that cancer patients face an increased CVD mortality risk. Peak CVD mortality occurs in the first year of cancer diagnosis, and a flat chronic risk remains after this period for years. The results of this study also show that the longer the tumor survived, the more likely it was that CVD, not the tumor, was the cause of death. Patients with bladder, prostate, bowel, uterine, breast, and throat cancers were most at risk of CVD, and the CVD mortality risk in cancer patients was 2–6 times higher than that of the general population. The persistent risk of CVD is life-long for cancer patients who need continuous care and treatment.

Biomarkers in cardio-oncology

Many biomarkers have been used to detect cardiotoxicities, such as cardiac injury and inflammation. During early treatment stages, the useful markers for myocardial injury and cardiac insufficiency are cardiac troponin (cTn), natriuretic peptides (NP), interleukin-6 (IL-6), and C-reactive protein (CRP).[2] In addition, microRNAs, along with genome-wide association studies and proteomics, are being examined to identify novel markers for cardiovascular injury or inflammation. So far, the soluble form of suppression of tumorigenicity-2 (sST2) has been used to detect tumor immunotherapy-associated myocarditis induced by immune checkpoint inhibitor (ICI) [Table 1].[3]

Chemotherapy drugs, molecular-targeted therapy, immunotherapy, and radiation therapy can all damage the cardiovascular system. In chemotherapy, anthracyclines are the forerunners of cardio-oncological focus, with the primary goal of ensuring treatment safety for cancer patients. New cancer therapies, including immunotherapy, tyrosine kinase inhibitors, and vascular endothelial growth factor inhibitors (VEGFIs), have also been found to be associated with cardiotoxicity[4] in particular, VEGFIs have been associated with ventricular dysfunction and cardiac arrhythmias [Table 1].[5]

It has been identified that off-target adverse cardiovascular effects from these "targeted" therapies have led to heart failure, myocardial infarction, and other CVDs.[6] Similar to chemotherapy and radiotherapy, these side effects may occur through off-target effects on other receptors in addition to on-target effects on VEGF receptors. The coronary artery is one particular site known to be affected, leading to accelerated atherosclerosis and coronary vasospasm, while interactions with peripheral arteries have been linked to hypertension.[6] With other cardiotoxic anticancer therapies, myocardial injury eventually results in ventricular dysfunction.

Table 1
Biomarkers in clinic of cardio-onology.

References	Biomarkers	Cancer and cardiotoxicity
Ananthan, K.[2]	cTn, NP, IL-6, CRP	Cardiotoxicity
Xu Y.[3]	sST2	Tumor immunotherapy associated myocarditis
Dobbin, S. J. H.[5]	VEGFIs	Cardiotoxicity of ventricular dysfunction and cardiac arrhythmias
Garcia-Pavia, P.[9]	TTNtvs	Cancer therapy-induced cardiomyopathy
Todorova, V. K.[10]	Circulating microRNA	Predict cardiac dysfunction in breast cancer patients
Gupta, S. K.[11]	RNA-binding protein QKI	Doxorubicin-induced cardiotoxicity
Burridge, P. W.[12]	hiPSC-CMs	Doxorubicin-induced cardiotoxicity

cTn: Cardiac troponin; NP: Natriuretic peptides; IL-6: Interleukin-6; CRP: C-reactive protein; sST2: Soluble form of suppression of tumorigenicity-2; VEGFIs: Vascular endothelial growth factor inhibitors; TTNtvs: Titin-truncating variants; hiPSC–CMs: Human induced pluripotent stem cell-derived cardiomyocytes.

In recent years, the knowledge of cardio-oncological interactions has begun to expand, and coexisting risk factors for both CVD and cancer are actively being investigated. Cumulative drug exposures and pre-existing cardiovascular disorders incompletely account for substantial interindividual susceptibility to cardiotoxicity. Genetic factors may partially explain the heterogeneity of cardiotoxicity found in some patients but absent in others that have the same apparent risk factors. The evidence supporting the role of genetic factors is becoming so significant that evidence-based recommendations for the incorporation of available genetic information into clinical therapeutic decisions have been developed for anthracycline-based chemotherapy.[7] Unfortunately, the evidence from retrospective studies has not yet provided enough data to guide clinical decision-making.

A study by Jaiswal et al.[8] supported the hypothesis that somatic mutations in hematopoietic cells contribute to the development of human atherosclerosis; they proposed that clonal hematopoiesis, a common condition associated with an increased risk of malignancy, also acts as a modifiable risk factor for CVD. Garcia-Pavia et al.[9] studied dilated cardiomyopathy using DNA sequencing; patients with cancer therapy-induced cardiomyopathy had more rare protein-altering variants, particularly Titin-truncating variants (TTNtvs), among nine prioritized genes. They also built a mouse model of TTN cardiomyopathy, where wild-type mice and TTN-variant mice were administered doxorubicin (DOX) (adriamycin). DOX is an anthracycline chemotherapy agent effective in treating a wide range of malignancies with a well-established dose–response cardiotoxic profile and can lead to heart failure. TTN-variant mice administered DOX had cardiac dysfunction, while the cardiac function of TTN-variant mice without DOX exposure and that of the wild-type mice administered DOX was normal[Table 1].

Besides DNA markers, other biomarkers have been explored for the prediction of presymptomatic cardiotoxicity. Another study aimed to obtain information about circulating microRNAs in cancer patients in the early phases of DOX chemotherapy using quantitative RT-PCR.[10] Thirty-two microRNAs were significantly dysregulated in the patients with abnormal cardiac function compared to those in patients without DOX-induced cardiotoxicity (DIC); functional analysis of these miRNAs suggested associations with cell death, cell cycle, and inflammation. This indicated that a miRNA signature in the early stages of DOX-based chemotherapy may potentially predict cardiac dysfunction in breast cancer patients. Gupta et al.[11] studied transcriptomes from rodent cardiomyocytes using transcriptome profiling; here, the RNA-binding protein Qki (Quaking) was associated with DIC. Overexpression of Qki5 strongly attenuated the toxic effect of DOX by regulating a set of circular RNAs, indicating this may be an interesting potential therapeutic target molecule to combat DIC. At present, it is not possible to predict which patients will be affected by DIC. Burridge et al.[12] found that human induced pluripotent stem cell–derived cardiomyocytes (hiPSC–CMs) derived from breast cancer patients who suffered from clinical DIC were consistently more sensitive to DIC, demonstrating that hiPSC–CMs can demonstrate individual patients' predispositions to DIC at the cellular level. Selective targeting of topoisomerase enzymes for cancer treatment also continues to be a highly active area of both basic and clinical research; topoisomerase II beta expressed in the heart has been found to be associated with anthracycline-related cardiotoxicity. Further studies must fully examine the relationship between topoisomerase II beta gene expression levels and cardiotoxicity [Table 1].

About the application of cardiac magnetic resonance imaging and positron emission tomography

Cardiac magnetic resonance imaging (CMR) has a higher resolution compared to echocardiograms, especially in patients with poor acoustic

windows.[13] CMR is used to assess left ventricle (LV) function, tissue characterization, myocardial injury, and myocardial fibrosis; LV function is accurately evaluated through measurement of left ventricle ejection fraction (LVEF), volumes at end-diastole (LVEDV), and end-systole (LVESV), strain, mass, and heart wall motion. This imaging method is non-ionizing, non-invasive, and accurate, and can be especially useful in monitoring cardiac function during treatment with potentially cardiotoxic chemotherapy.[14] Despite this, there are still challenges associated with its application during cancer therapy, such as high cost, efficiency, and accessibility. Several applications of nuclear cardiology imaging modalities in immunotherapy-related cardiotoxicity patients have found their way into clinical diagnostics.[15] Some special modalities of positron emission tomography (PET) imaging can allow for simultaneous oncologic staging and cardiac assessment with the benefit of possible early detection of cardiac damage, which is important as it could enable the identification of patients at risk who require timely therapy.

Future applications of regenerative therapy

Any chemotherapy drug can cause heart damage, and the combination of multiple drugs may increase cardiotoxicity. Therapies most commonly associated with the direct cytotoxic cardiac injury include anthracyclines, anthraquinones, tyrosine kinase inhibitors, and alkylating agents. The cardiotoxic effects of anthracyclines are thought to be related to myocardial cell damage caused by oxygen free radicals and lipid peroxidation.[16]

Regenerative therapy is a promising treatment for cardiomyopathy caused by anthracyclines. A study on anthracycline cardiotoxicity in animal models showed that transendocardial injection of allogeneic mesenchymal stem cells (MSC) reduced fibrosis and ventricular remodeling.[17] In addition to this trial, a study of patients with anthracycline cardiotoxicity treated with allogeneic MSCs delivered using direct cardiac injection is currently wrapping up, with results hopefully available soon; this trial is known as the SENECA trial and was conducted by the USA National Heart, Lung, and Blood Institute.

Studies on CVD-related cancer risk and drug–drug interactions

Increased CVD risk is associated with complications of cancer treatments, and the field of cardio-oncology keeps expanding with the increasing use of novel cancer treatments. These novel treatments lead to another direction in the field, as one of the central unanswered questions is whether or not prevalent CVD can initiate new tumorigenesis. Some studies have focused on the new concept of cancer risk associated with CVD; the study of this direction of progression has been termed “reverse cardio-oncology” [Table 2].

Reverse cardio-oncology has been studied recently, which considers CVD to be a risk factor for oncology. It has been identified that patients with CVD have a higher risk of oncology than the general population.[18] Moreover, cardiokines, extracellular vesicles, inflammatory mediators, and miRNA are involved in the mechanism of reverse cardio-oncology.

Table 2
Studies about cardiovascular disease-related cancer risk.

References	Cardiovascular Disease-related Cancer Risk factors
Golemis, E. A.[25]	Smoking risk
Quail, D. F.[26]	Obesity
Stocks, T.[28]	Elevated blood pressure
Bahl, M.[29]	Dyslipidaemia, high plasma total cholesterol, and low-density lipoprotein cholesterol levels
Jaiswal, S.[30]	Genetics
Hasin, T.[31]	Heart failure, myocardial infarction
Berton, G.[32]	Acute coronary syndromes
Qureshi, A. I.[33]	Ischemic stroke

Furthermore, the drug–drug interactions of CVD and cancer play an important role in cardio-oncology. Immunotherapies for cancer would lead to cardiovascular toxicities.[19] The potential mechanism involved the cytochrome P450 (CYP450) family of enzymes and the P-glycoprotein (P-g) transporter. CYP450 and P-g play an important role in drug metabolism and drug resistance, which mediate the interactions between oncology and cardiology drugs.[20] For the drugs are substrates, antagonists, or inhibitors of the same enzymes, receptors, or transporters, the combination use treatment in cardiology and oncology may induce drug-related toxicities. The evaluation of the role that CYP450 and P-g play in drug interactions leads to precision medicine from collaborative multidisciplinary teams.

During studies[21–23] on the cardiotoxicity of cancer treatments, observational and preclinical studies have both suggested a positive correlation between CVD and pan-cancer incidence, although the core cause of the relationship is still unknown. As the two leading causes of death in most countries, cancer and CVD share numerous modifiable and non-modifiable risk factors. In addition, the systemic disorder induced by CVD has recently been shown to drive cancer progression.[22] Further, evidence suggests incident CVD after a primary cancer diagnosis may also drive cancer progression.[23]

The majority of cardiac primary tumors are benign, with an incidence of 0.0017%–0.1900%.[24] Among modifiable CVD risks, smoking has known tumorigenic effects, as it causes inflammation, mutagenesis, and epigenetic modifications.[25] Obesity is associated with increased plasma leptin, glucose, insulin, and insulin-like growth factor 1 level, and activates growth factor signaling pathways that result in tissue microenvironments primed for cell growth and proliferation.[22] Obesity also increases the production of chronic inflammatory cytokines and induces immune suppression.[26] Steven et al.[27] pooled data from 12 prospective cohort studies and demonstrated that high levels of leisure-time physical activity were associated with lower risks of 13 cancers. A prospective study in Nordic people (577,799 adults) showed a small increased risk of cancer incidence in patients with elevated blood pressure across several cancer types in men, though this same risk was not present in women; there was, however, increased risk for cancer-specific mortality in both men and women.[28] The role of hypertension in the relationship between CVD and cancer remains unclear. As an important CVD risk factor, dyslipidemia has been found to be associated with cancer, especially with hormone-sensitive tumors such as prostate and breast cancer, although the evidence is still conflicting. A prospective study on the contribution of lipids toward breast cancer outcome showed that high plasma total cholesterol and low-density lipoprotein cholesterol levels were linked to recurrence risk.[29]

Genetic predisposition is one of the non-modifiable risk factors for both cancer and CVD. A common condition that occurs due to mutations in hematopoietic stem cells, age-related clonal hematopoiesis of indeterminate potential (CHIP), is associated with increased risk of both hematologic cancer and CVD due to increased coronary artery calcification and atherosclerosis.[30]

Increasing clinical evidence suggests that CVD prevalence is correlated with increased cancer incidence. It is still unknown whether prevalent CVD leads to new tumor formation, or if the systemic disorder it causes accelerates the growth of pre-existing, possibly unknown, tumors. Among coronary artery disease patients with a first myocardial infarction (MI), Hasin et al.[31] found incidence density rates for cancer diagnosis (per 1000 person-years) were 33.7 for patients with heart failure (HF) and 15.6 for patients without ($p = 0.002$); this suggested that HF after MI leads to an increased risk of cancer. A long-term prospective study showed that patients with acute coronary syndromes (ACS) have a higher incidence of malignancy than the general population, leading to a worse prognosis.[32] In the Vitamin Intervention for Stroke Prevention study, the annual rate of age-adjusted cancer incidence appeared to be higher among ischemic stroke patients than in the general population, and incident cancer increased the risk of mortality in stroke survivors by three times.[33] Avraham et al.[34] showed that the crude incidence rate and

deaths from non-hematological cancer were higher in patients between 40 and 60 years of age with moderate to severe aortic stenosis.

In a retrospective analysis of the Life After Cancer Epidemiology (LACE) Study and Pathways studies, two prospective case-cohort studies on early-stage breast cancer, patients with a post-diagnosis CVD event (MI, CAD, stroke, HF, or arrhythmia) had an adjusted 59% increased risk of cancer recurrence (95% confidence interval [CI]: 1.23–2.06) and 60% increased risk cancer-specific mortality (95% CI: 1.16–2.22) compared to patients without a CVD event.[20]

Prospects in cardio-oncology

As discussed previously, the systemic dysregulation associated with CVD can have pro-tumorigenic effects. In addition to cardiotoxicity during cancer treatment, the CVD-cancer relationship has been found to be more complicated in an increasing number of epidemiological and preclinical studies. As human life expectancy continues to increase, CVD and cancer will likely keep dominating the fatal diseases, leading to more common co-occurrence with worse outcomes. Cooperative study and care from cardiologists and oncologists are needed, as this will make the interrelationships between treatments, pathogenesis, and other aspects of CVD and cancer clearer.

Limitations

This article reviewed the remarkable development of the field of cardio-oncology in recent years. Because this field is so recent, there is little to no detailed description of traditional, historical cardio-oncology. Additionally, the data collection was not comprehensive, as it was solely based on the knowledge of the authors. There will be evolving advancement of the knowledge in this field after the publication of the 2022 European Society of Cardiology guidelines on cardio-oncology.

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Author contributions

Meiyan Liu designed the study and revised the manuscript. Lijun Zhang performed the figure and tables. Guo Li wrote the manuscript.

Ethics statement

None.

Data availability statement

The datasets used in the current study are available from the corresponding author on reasonable request.

Conflict of interest

None.

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