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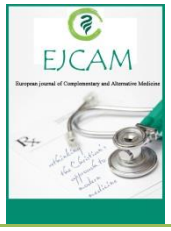

CARDIOVASCULAR COMPLICATIONS IN BREAST CANCER SURVIVORS: A MULTIDIMENSIONAL REVIEW OF RISK, DIAGNOSIS, AND MANAGEMENT

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ABSTRACT

Cardiovascular complications have emerged as a major contributor to long-term morbidity and mortality among breast cancer survivors, reflecting the growing success of modern oncological therapies and the expanding survivorship population. This review provides a comprehensive and multidimensional analysis of cardiovascular risk in breast cancer survivors, integrating epidemiological trends, underlying pathophysiological mechanisms, and clinical implications. The interplay between traditional cardiovascular risk factors and cancer-specific determinants, including treatment-related cardiotoxicity from chemotherapy, targeted therapy, radiotherapy, and endocrine therapy, creates a complex and evolving risk profile. Mechanistic insights highlight the roles of oxidative stress, inflammation, endothelial dysfunction, and hormonal alterations in linking breast cancer and cardiovascular disease. Clinically, survivors may develop a spectrum of complications such as heart failure, ischemic heart disease, arrhythmias, hypertension, and thromboembolic events, often with delayed onset. Advances in diagnostic approaches, including the use of biomarkers and imaging modalities such as echocardiography and cardiac magnetic resonance imaging, have improved early detection of subclinical cardiac injury. Risk assessment tools and stratification models further support personalized surveillance strategies. Preventive measures, including lifestyle modifications, cardioprotective pharmacotherapy, and optimization of cancer treatment protocols, play a critical role in mitigating cardiovascular risk. Management strategies emphasize guideline-directed therapy and the importance of multidisciplinary care through integrated cardio-oncology services. Despite progress, challenges remain in terms of limited long-term data, variability in risk prediction, and disparities in access to care. This review underscores the need for a proactive, patient-centered approach that bridges oncology and cardiology to improve cardiovascular outcomes and overall quality of life in breast cancer survivors.

INTRODUCATION

Breast cancer is the most common cancer diagnosis that is noted in women all over the world, and new technologies in early detection, targeted treatments and multimodal approaches of treatment have greatly enhanced the survival outcome, resulting in a fast growing group of breast cancer survivors. Nonetheless, this achievement has been coupled by the fact that it has brought about long-term treatment related complications, one of which is the cardiovascular disease (CVD) that has become a major cause of morbidity and mortality in this group of people.[1]

This overlapping of the areas of oncology and cardiology has led to the emergence of cardio-oncology that deals with the understanding, prevention, and treatment of cardiovascular complications that are

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related to cancer and cancer therapy. A combination of risk factors such as the combination of shared risk factors, direct cardio toxic effects of cancer treatments, and underlying physiological changes induced by malignancy and treatment put breast cancer survivors at particular risk of cardiovascular risks. The anthracyclines as chemotherapeutic agents are particularly famous in their dose-dependent cardiotoxicity, which causes permanent myocardial damage and heart failure, and the targeted therapy of trastuzumab is known to induce reversible left ventricular dysfunction.[2,3] Also, chest wall radiotherapy has been linked to late vascular injury, which predisposes to coronary artery disease, valvular dysfunction, and pericardial disease. In addition to effects related to treatment, classic cardiovascular risk factors, including hypertension, diabetes mellitus, dyslipidemia, obesity, and sedentary lifestyle, are very common amongst breast cancer survivors and can be enhanced by endocrine therapies, menopause prematurely and metabolic changes caused by the treatment of cancer. Moreover, new data emphasizes the connection of the progression of cancer and cardiovascular pathology with systemic inflammation, oxidative stress, endothelial dysfunction, and genetic predisposition. The combination of these factors is what leads to a complex and multifactorial risk profile that increases with time requiring constant monitoring and risk-specific evaluation. Cardiovascular issues in breast cancer survivors can be clinically observed as heart failure, ischemic heart disease, arrhythmias, hypertension and thromboembolic events and usually some years after the end of cancer treatment. [4]To prevent negative outcomes, it is necessary to detect the disease at its early stage with the help of biomarkers and imaging methods including echocardiography and cardiac magnetic resonance imaging, as well as the validated risk prediction tools. Primarily, in cardiovascular burden reduction, preventive measures are vital, comprising cardio protective pharmacotherapy, changes in lifestyle, and organized follow-up services. In that regard, a multidisciplinary intervention with oncologists, cardiologists, primary care physicians, and other healthcare professionals is necessary in order to maximize the long-term survivorship care. This review attempts to present a multidimensional and systematic overview of cardiovascular complications among breast cancer survivors including epidemiological patterns, pathophysiology, risk factors, clinical expression, diagnostic protocols, prevention measures, and treatment models as well as the issue of current problems and future research in the dynamic area of cardio-oncology.[5]

Epidemiology of Breast Cancer Survivorship and Cardiovascular Disease

Breast cancer survivorship has experienced an extraordinary change in the past decades and much of this has been due to better screening procedures, prompt diagnostic measures, and enhancement of systemic therapy approaches that have significantly increased long-term survival rate. Breast cancer is the most prevalently diagnosed type of cancer in women globally and it constitutes a huge percentage of cancer survivors with many living decades following the first treatment. Along with the increased chances of survival, the focus has moved towards the long term health outcomes, including the burden of cardiovascular disease (CVD) that has become a major cause of morbidity and mortality in breast cancer survivors that is not cancerous[6,7]. According to epidemiological studies, survivors are at a greater risk of developing cardiovascular complications than age-matched persons without history of cancer with the extent of the risk being dependent on age at diagnosis, treatment modalities and pre-existing comorbidities. It is important to note that elderly survivors and women with previous cardiovascular risk factors have a particularly high risk whereas younger women receiving cardio toxic treatments can be subject to premature cardiovascular events. Cohort studies (population-based) have shown that the risk of dying of cardiovascular causes in certain subpopulations is equal or even greater than the risk of breast cancer recurrence particularly more than five to ten years of follow-up after treatment. [8,9]The cumulative exposure to therapies known to have significant cardiotoxic effects, including anthracyclines, trastuzumab, and chest-directed radiotherapy, has an effect on the rate of individual cardiovascular outcomes, including heart failure, ischemic heart disease, stroke, and arrhythmias. Moreover, aromatase inhibitors have been linked to the unfavorable metabolic phenotype, which adds to the cardiovascular risk. Geographic and socioeconomic inequalities can also contribute greatly to the epidemiological trends, where the settings with limited resources tend to exhibit difficulties with survivorship care, the early identification of cardiovascular complications, and the access to the cardio-oncology services. Moreover, increased prevalence of obesity, diabetes and sedentary lifestyles in the world have increased the burden of cardiovascular risk among cancer survivors.[10] The recent epidemiological tendencies point to the essential role of the long-term follow-up and integrated care models that can help to minimize the dual burden of cancer survivorship and cardiovascular disease. Registries and longitudinal studies on a large scale still yield important information about the dynamics of risks over time, and thus it is necessary to adopt more specific surveillance

and preventive actions to enhance the overall survival and quality of life of survivors of breast cancer.[11]

Definition and Conceptual Framework of Cardiovascular Risk in Cancer Survivors

The definition and the conceptual framework of cardiovascular risk among cancer survivors, especially breast cancer survivors, involves a multidimensional interpretation of risk involving the incorporation of classic cardiovascular factors, and cancer-specific and treatment factors. The risk of cardiovascular in this population is determined as the likelihood of having adverse cardiovascular events such as heart failure, coronary artery disease, arrhythmias, high blood pressure, and thromboembolic complications both as a result of pre-existing condition and the combined effect of cancer treatments. In contrast to the general population where risk is mainly influenced by predetermined factors age, smoking, diabetes, dyslipidemia, and hypertension, cancer survivors are at risk of other levels of risks brought about by oncological therapies, tumor biology, and systemic physiological changes posed by malignancy.[12] The existing conceptual framework of cardiovascular risk among cancer survivors can be thus best characterised using an integrative paradigm that incorporates three large domains, namely, patient-related factors, treatment-related exposures, and disease-related mechanisms. Patient variables are cardiovascular health baseline, genetic predisposition, lifestyle behaviors, and comorbidity, which contribute to personal susceptibility to cardiovascular injury. The exposures associated with treatment include the nature, dose, and duration of treatment including anthracyclines, HER2-targeted agents, radiotherapy and endocrine therapy which may have direct or indirect effects on cardiac structure and cardiac functioning including oxidative stress, mitochondrial dysfunction and endothelial injury[13–15]. The mechanisms related to disease cause cancer-related inflammation, immune dysregulation, and metabolic alterations that also further lead to vascular damage and myocardial remodeling. Notably, the cardiovascular risk in cancer survivors is dynamic and changes over time and may present several years or even decades after the therapy is finished, which makes it necessary to assess and manage the risk through a life-course approach. Modern paradigms also focus on the importance of subclinical cardiac injury, which can be detected by the use of biomarkers and high-tech imaging, as a predictor of future cardiovascular events. These multidimensional variables are utilized as risk stratification model in cardio-oncology to identify low risk, intermediate risk, and high-risk patient groups to inform the level of surveillance and preventive measures.[16,17] This theoretical framework concludes by emphasizing the importance of individualized, longitudinal, and interdisciplinary models of cardiovascular risk assessment among cancer survivors, which combine oncology and cardiology knowledge to achieve the best health outcomes and provide better survivorship care.

Diagnostic Approaches and Risk Assessment Tools

Diagnostic approaches and risk assessment tools for cardiovascular disease (CVD) in breast cancer survivors constitute a cornerstone of contemporary cardio-oncology, enabling early identification of subclinical cardiac injury, accurate stratification of risk, and timely implementation of preventive and therapeutic interventions. A comprehensive diagnostic framework begins with a detailed baseline cardiovascular evaluation prior to initiation of cancer therapy, incorporating clinical history, physical examination, assessment of traditional risk factors, and, when appropriate, baseline electrocardiography and imaging. This initial assessment establishes a reference point for longitudinal comparison and helps identify patients at increased risk for treatment-related cardiotoxicity.[18] Circulating biomarkers have emerged as highly sensitive tools for early detection of myocardial injury, with cardiac troponins serving as indicators of cardio myocyte damage and natriuretic peptides such as B-type natriuretic peptide (BNP) or N-terminal pro-BNP reflecting ventricular wall stress and early heart failure. Serial monitoring of these biomarkers during and after cancer therapy enhances the ability to detect evolving cardiac dysfunction even in asymptomatic patients, allowing for early intervention. Imaging modalities remain central to cardiovascular evaluation, with transthoracic echocardiography being the most widely utilized technique due to its non-invasive nature, accessibility, and ability to assess left ventricular ejection fraction (LVEF), diastolic function, and valvular integrity.[19–21] Importantly, advanced echocardiographic parameters such as global longitudinal strain (GLS) provide greater sensitivity in detecting subtle myocardial dysfunction before a decline in LVEF becomes apparent, making it a valuable tool for early surveillance. Cardiac magnetic resonance imaging (MRI) offers superior spatial resolution and tissue characterization, enabling the detection of myocardial fibrosis, edema, and inflammation, and is particularly useful in complex cases or when echocardiographic findings are inconclusive. Additional modalities such as nuclear imaging and computed tomography may be employed for specific indications, including assessment of myocardial perfusion or coronary artery disease. Beyond diagnostic modalities, risk assessment tools play a crucial role in stratifying patients according to their likelihood of developing cardiovascular complications. [22, 23] Established frameworks, such as those proposed by the European Society of Cardiology (ESC) in cardio-

oncology, integrate clinical variables including age, baseline cardiovascular status, comorbidities, type and cumulative dose of cancer therapy, and exposure to radiation to categorize patients into low, intermediate, or high-risk groups. These models guide the intensity and frequency of surveillance, as well as the initiation of prophylactic cardioprotective strategies. Emerging approaches are further enhancing risk prediction through the incorporation of artificial intelligence and machine learning algorithms, which analyze large datasets to identify patterns and predict individual risk with greater precision[24–26]. Multi-omics technologies, including genomics, proteomics, and metabolomics, are also being explored to uncover novel biomarkers and mechanistic pathways associated with cardiotoxicity, paving the way for personalized medicine in cardio-oncology. Importantly, cardiovascular risk in breast cancer survivors is not static but evolves over time, necessitating continuous and adaptive monitoring throughout the survivorship continuum. Integration of electronic health records, wearable devices, and telemedicine platforms is increasingly facilitating remote monitoring and real-time data collection, improving patient engagement and early detection of adverse events. Overall, the integration of advanced diagnostic tools and robust risk assessment models into routine clinical practice is essential for optimizing cardiovascular care, enabling proactive management, and ultimately improving both cardiac and oncological outcomes in breast cancer survivors.[27–29]

Pathophysiological Link Between Breast Cancer and Cardiovascular Disease

The pathophysiological relationship between breast cancer and cardiovascular disease (CVD) is multi-factorial and multi-layered with an overlapping biological pathway which links tumor biology, host response and effects of treatment. The principle of this relationship is the common basis of chronic inflammation, oxidative stress, and endothelial dysfunction, which would play a role in cancer development and cardiovascular pathology. A pro-inflammatory condition with increased cytokines (interleukins and tumor necrosis factor-alpha) that promote vascular damage, atherosclerosis, and remodelling of the myocardium is related to breast cancer. [30, 31] Also, reactive oxygen species are produced by oxidative stress produced by cancer cells and anticancer therapies causing direct cardiomyocyte injury, mitochondrial dysfunction, and cardiac contractility. Endothelial dysfunction also contributes to vascular complication by decreasing nitric oxide bioavailability, making vascular stiff, and encouraging thrombogenesis. Hormonal factors are also key, since estrogen has cardioprotective properties and its deprivation (either because of natural menopause or ovarian suppression by treatment) may lead to an increased rate of cardiovascular risk factors (dyslipidemia and insulin resistance). In addition, there are cancer-associated metabolic changes, such as lipid metabolism, glucose homeostasis, adipokine signaling, etc., which lead to the emergence of metabolic syndrome, which further predisposes cardiovascular risk. [32] Polymorphisms that influence the drug metabolism and exposure to oxidative damage may be genetic and molecular factors that predispose specific individuals to cancer and cardiovascular complications. Similarities with other mechanisms, which are related to cardiovascular remodeling and ischemic damage, are also associated with the tumor microenvironment, which is affected by hypoxia and angiogenic signaling. Notably, cancer treatments promote these mechanisms; e.g. anthracyclines cause cardiotoxicity by damaging DNA and producing free radicals whereas targeted therapies have the potential to disrupt key signaling pathways that ensure survival of cardiac cells. Moreover, the changes in immune systems, such as immune checkpoints, as well as persistent immune activation, may cause vascular inflammation and myocarditis[33–35]. The interconnectedness of these processes will lead to a compounding and typically progressive effect on cardiovascular health, whereby subclinical changes are present at an early age and clinical changes are seen at a later stage of survivorship. This set of interconnected pathways is the key to creating specific preventive measures, enhancing the early diagnosis, and determining the individualized methods of treatment in the new area of cardio-oncology.[36]

Implications for Clinical Practice and Healthcare Policy

The growing recognition of cardiovascular disease (CVD) as a major determinant of long-term outcomes among breast cancer survivors has profound implications for clinical practice and healthcare policy, necessitating a shift from siloed care toward integrated, longitudinal, and patient-centered survivorship models. In clinical practice, cardiovascular risk assessment should be embedded at every stage of the cancer care continuum, beginning at diagnosis and extending through treatment and long-term follow-up. This requires systematic screening for baseline risk factors, including hypertension, diabetes, dyslipidemia, and prior cardiac disease, alongside careful evaluation of planned cancer therapies with known cardiotoxic potential. Standardized protocols incorporating biomarkers such as troponins and natriuretic peptides, as well as imaging modalities like echocardiography with global longitudinal strain, should be routinely utilized for early detection of subclinical cardiac dysfunction. Risk stratification tools, including those recommended by international cardio-oncology guidelines, enable

clinicians to categorize patients and tailor surveillance intensity and preventive strategies accordingly.[5] Importantly, clinical decision-making must balance oncological efficacy with cardiovascular safety, often necessitating dose adjustments, selection of less cardiotoxic regimens, or the early introduction of cardioprotective medications such as ACE inhibitors, beta-blockers, and statins in high-risk individuals. The emergence of dedicated cardio-oncology services highlights the importance of multidisciplinary collaboration, where oncologists, cardiologists, primary care physicians, pharmacists, nurses, and rehabilitation specialists coordinate care to optimize outcomes and minimize fragmentation. From a healthcare policy perspective, there is an urgent need to institutionalize survivorship care pathways that explicitly incorporate cardiovascular monitoring and management as core components[37]. This includes the development of national and international guidelines that standardize screening intervals, diagnostic criteria, and management protocols for cardiotoxicity. Health systems should invest in the establishment of specialized cardio-oncology clinics and ensure equitable access to diagnostic technologies, including echocardiography and advanced imaging, particularly in resource-limited settings. Workforce training and continuing medical education in cardio-oncology principles are essential to equip healthcare professionals with the necessary skills to manage this complex patient population. Policy initiatives should also promote the inclusion of cardiovascular endpoints in oncology clinical trials to generate robust evidence that informs regulatory decisions and clinical guidelines. Addressing disparities in care is another critical priority, as socioeconomic barriers, geographic limitations, and variations in healthcare infrastructure can lead to delayed diagnosis and suboptimal management of cardiovascular complications. Integration of digital health technologies, such as telemedicine platforms, wearable monitoring devices, and electronic health records, offers opportunities to enhance surveillance, improve patient engagement, and facilitate data-driven decision-making. Furthermore, reimbursement frameworks should be aligned to support preventive care, longitudinal monitoring, and multidisciplinary interventions, rather than focusing solely on acute treatment episodes. Public health strategies should emphasize patient education and awareness regarding cardiovascular risks associated with cancer therapies, empowering survivors to engage in preventive behaviors and adhere to follow-up care. Ultimately, aligning clinical practice with supportive healthcare policies is essential to reduce the burden of cardiovascular disease, improve quality of life, and ensure sustainable, high-quality care for the growing population of breast cancer survivors in the evolving era of precision medicine and integrated healthcare delivery.[38,39]

Cancer Therapy–Related Cardiovascular Toxicity

Cancer therapy-induced cardiovascular toxicity is a significant issue in the survivorship of breast cancer resulting as a direct and indirect impact of the anticancer therapy on the cardiac structure and functioning. One of the best-established agents is anthracycline-based chemotherapy including doxorubicin which leads to dose-related and frequently irreversible cardiotoxicity via oxidative stress, mitochondrial dysfunction, and cardiomyocyte-apoptosis. This may cause progressive left ventricular dysfunction and clinical heart failure which may present years post the treatment. Cardiotoxicity has also been linked to targeted therapy especially those acting on human epidermal growth factor receptor 2 (HER2) such as trastuzumab though can usually be reversed on withdrawal. Such agents disrupt key signaling cascades required by cardiomyocytes to survive and repair, which exposes the myocardium to more damage. Moreover, radiotherapy in the chest area may also lead to long-term cardiovascular dysfunction including fibrosis, endothelial damage and rapid atherosclerosis and in the process raise the risks of coronary artery disease, valvular defects and pericardial disease [40]. Factors that determine the risk of radiation induced cardiotoxicity include the overall dose, fractionation, and the location of cardiac structures to the radiation field. Endocrine treatment, such as aromatase inhibitors, can also lead to cardiovascular risk, through their negative impact on lipid profiles and the encouragement of metabolic disturbances, and selective estrogen receptor modulators have been associated with thromboembolic events. New classes of emerging therapy like the immune checkpoint inhibitors have initiated new aspects of cardiovascular toxicity (i.e. myocarditis, pericarditis, arrhythmias) which are usually immune-mediated. Cumulative and at times synergistic effects of these treatments particularly when combined, increase the total risk to the cardiovascular of breast cancer patients. Notably, the personal predisposition to cardiotoxicity differs depending on underlying cardiovascular conditioning, genetic orientation, age, and comorbidity. The early diagnosis of noninvasive cardiac injury in biomarkers (troponins and natriuretic peptides) and through imaging methods (echocardiography with strain analysis) has become essential in minimizing damage in the long term. Prophylactic measures, such as dose optimization, cardioprotective use, and close follow-up and monitoring, are the key elements in the contemporary oncology care. With the ongoing development of cancer therapies, the issue of finding the balance between therapeutic efficacy and cardiovascular safety has become one of the most pressing problems of

enhancing the long-term survival of breast cancer patients.

Traditional and Non-Traditional Cardiovascular Risk Factors

The combination of traditional and non-traditional cardiovascular risk factors is a complex relationship between patient-based predispositions and cancer-related factors in increasing the burden of cardiovascular disease (CVD) among breast cancer survivors. Risk factors that are rather traditional and well-established in the general population are old age, high blood pressure, diabetes mellitus, dyslipidemia, smoking, obesity, and the lack of physical activity, all of which significantly contribute to the development of cardiovascular complications. These factors tend to be more common among breast cancer survivors and can be further increased by treatment of cancer and changes in lifestyles that are associated with survivorship.[41] An example is that weight gain, lack of exercise and post-chemo or endocrine therapy metabolic changes may exacerbate insulin resistance and lipid disorders, increasing cardiovascular risks. Besides these traditional determinants, non-traditional/cancer specific risk factors are very critical in determining cardiovascular outcomes in this group. They comprise a history of cardiotoxic therapy, including anthracycline therapy, HER2-target therapy, and chest radiotherapy, which can directly cause cardiac tissue and vasculature damage. Premature menopause and estrogen deficiency as a result of treatments also serve as contributors to poor cardiovascular phenotypes by increasing atherosclerosis and metabolic inefficiency. Systemic inflammation, which is another defining feature of cancer and its therapy, is becoming established as a major cause of the connection between oncological and cardiovascular events, which facilitates endothelial dysfunction, plaque development, and thrombogenesis. These effects are further worsened by oxidative stress, immune dysregulation and changes in vascular homeostasis. The new unconventional factors are also genetic susceptibility, epigenetic alterations and psychosocial stressors including anxiety, depression and social isolation which could indirectly impact cardiovascular health via behavioral and neuroendocrine pathways. Furthermore, access to healthcare, health literacy, and survivorship care disparities are also examples of socioeconomic factors that may greatly influence the early detection and management of cardiovascular risk. A synergistic and compounding effect of traditional and non-traditional risk factors on patients with breast cancer predisposes both early and late cardiovascular disease. This multifactorial profile of risk can be recognized to complete risk assessment, and the clinician can apply both traditional cardiovascular risks and cancer-specific factors within the dynamic paradigm of cardio-oncology in order to use personalized prevention and management interventions.

Attributes of Cardiovascular Risk in Breast Cancer Survivors

Cardiovascular risk characteristics of breast cancer survivors are dynamic, multifactorial and time-dependent, and are due to the complexity of interactions between patient-specific factors, cancer biology, and treatment-related exposures. In contrast to the general population, where cardiovascular risk is comparatively constant and foreseeable, risk among survivors of breast cancer changes throughout the cancer care continuum, with a period starting at the moment of diagnosis, peaking during active treatment, and continuing or developing even after the therapy ends. Temporal variability is one of these characteristics, as early-onset cardiotoxicity can be detected during or soon after treatment, whereas late effects can be detected years or even decades later such as heart failure, coronary artery disease, and valvular dysfunction. The other characteristic is heterogeneity, where risk profiles vary and this varies with age, hereditary inclination, underlying cardiovascular condition, and comorbidity, in addition to the type, dosage, and combination of therapies used. The phenomenon of dose dependency is observed especially with the use of such agents as anthracyclines and radiation exposure as cumulative dose is directly associated with the risk of myocardial injury and vascular damage[42]. Moreover, subclinical cardiac dysfunction is a crucial feature, which can be detected with the help of sensitive biomarkers and the latest imaging methods before the development of evident clinical signs, which is why the role of early surveillance cannot be overestimated. This population is further characterized by the notion of cumulative and synergistic risk since the classic risk factors of cardiovascular diseases, including hypertension, diabetes, and obesity tend to compound each other with other factors related to treatment, and those related to the disease, increasing the risk. Moreover, hormonal changes such as estrogen deprivation, caused by therapy, have a cardiovascular effect on breast cancer survivors; hastens metabolic and vascular changes. Long-term cardiovascular susceptibility is also observed in psychosocial and behavioral variables such as stress, lack of physical activity and fatigue caused by treatments. Notably, this risk is dynamic, which is why the presence of specific interventions and preventive measures is possible. Another complication to the characterization of risks is the variability in clinical presentation, which may include asymptomatic ventricular dysfunction, mild, or severe cardiovascular events. In general, these properties indicate that a personalized, longitudinal, and multidisciplinary approach to assessing and managing cardiovascular risks

among breast cancer survivors and combining continuous monitoring, early detection, and specific therapeutic intervention is necessary in the dynamic sphere of cardio-oncology.

Clinical Manifestations and Outcomes

Clinical outcomes and clinical manifestations of cardiovascular disease (CVD) in survivors of breast cancer include a wide range of acute and chronic diseases that can occur during or many years after cancer treatment, which is the cumulative effect of cardiotoxicity in the treatment, as well as of the risk factors. The left ventricular dysfunction is one of the most striking manifestations that may develop into symptomatic heart failure and severely impair the quality of life and survival. This condition can be insidious with fatigue, dyspnea and lack of exercise tolerance or acute with clear evidence of decompensation. Another issue of high concern is the occurrence of ischemic heart disease; especially in patients who have undergone chest radiotherapy, which hastens the occurrence of atherosclerosis and predisposes the patient to myocardial infarction and angina [43]. Structural and electrical myocardial remodeling may result in arrhythmias, such as atrial fibrillation and ventricular arrhythmias, and hypertension is also common as an underlying condition and comorbidity, particularly with some specific target therapies. Deep vein thrombosis and pulmonary embolism, as well, are more common in breast cancer survivors because of a hypercoagulable state caused by malignancy and its treatment. Moreover, pericardial illness, valvular abnormalities, and vascular dysfunction can be developed especially after exposure to radiations. Notably, a significant number of these cardiovascular disorders can be subclinical, being identified only by biomarkers or imaging but eventually develop into a clinically significant disease when not detected and treated early. The consequences of these manifestations are significant, and the cardiovascular disease has become one of the major causes of non-cancer mortality in breast cancer survivors. In other instances, particularly in long-term survivors, cardiovascular death could be as great a risk as cancer relapse. Moreover, cardiovascular complications may restrict the possibility to continue or finish the cancer treatment and, thus, also influence the oncological outcomes. CVD load is also one of the factors that lead to the higher healthcare use, lower functional ability, and lower overall quality of life. The severity of the cardiac involvement, timeliness of diagnosis, and management effectiveness are some of the factors that influence prognosis. These clinical phenomena and outcomes demonstrate the importance of detecting at the earliest, constant monitoring, and combined care strategies to reduce cardiovascular risk and enhance long-term survival results.

Cancer Therapy–Related Cardiovascular Toxicity

Cancer therapy–related cardiovascular toxicity represents a central challenge in the long-term management of breast cancer survivors, arising from the direct and indirect effects of anticancer treatments on cardiac structure, function, and vascular integrity. Among the most extensively studied agents are anthracyclines, such as doxorubicin, which are associated with dose-dependent and often irreversible cardiotoxicity mediated by the generation of reactive oxygen species, mitochondrial dysfunction, and DNA damage leading to cardiomyocyte apoptosis. This injury may initially be subclinical but can progress to left ventricular dysfunction and overt heart failure, sometimes manifesting years or decades after completion of therapy. Targeted therapies, particularly human epidermal growth factor receptor 2 (HER2)-directed agents such as trastuzumab, have also been linked to cardiotoxic effects, though these are typically reversible upon discontinuation or modification of treatment. The mechanism involves disruption of HER2 signaling pathways that are essential for cardiomyocyte survival and repair, thereby rendering the myocardium more susceptible to stress and injury. [40] In addition, chest-directed radiotherapy contributes significantly to long-term cardiovascular risk through mechanisms including endothelial damage, microvascular dysfunction, inflammation, and progressive fibrosis, which collectively accelerate atherosclerosis and increase the risk of coronary artery disease, valvular heart disease, pericardial disease, and conduction abnormalities. The extent of radiation-induced cardiotoxicity depends on factors such as total dose, fractionation, and the volume of cardiac tissue exposed. Endocrine therapies, commonly used in hormone receptor–positive breast cancer, also influence cardiovascular health; aromatase inhibitors are associated with adverse lipid profiles and increased risk of ischemic events, while selective estrogen receptor modulators may increase the risk of venous thromboembolism. Emerging therapeutic modalities, including immune checkpoint inhibitors, have introduced new forms of cardiovascular toxicity such as myocarditis, pericarditis, vasculitis, and arrhythmias, often mediated by immune activation and inflammation, and although relatively rare, these events can be severe and life-threatening [44]. The cumulative and sometimes synergistic effects of multiple treatment modalities further amplify cardiovascular risk, particularly in patients receiving combination therapies. Individual susceptibility to cardiotoxicity varies widely and is influenced by baseline cardiovascular status, age, genetic predisposition, comorbid conditions, and concurrent exposure to other cardio toxic agents. Early detection of cardiotoxicity is therefore critical and relies on the use of sensitive biomarkers such as cardiac troponins and natriuretic peptides, as well as advanced

imaging techniques including echocardiography with global longitudinal strain and cardiac magnetic resonance imaging for tissue characterization. Preventive strategies, including limiting cumulative drug doses, using less cardio toxic formulations such as liposomal anthracyclines, employing cardio protective agents like dexrazoxane in selected cases, and adopting advanced radiotherapy techniques that minimize cardiac exposure, are essential components of modern oncological care. Continuous monitoring during and after therapy allows for timely intervention, including modification of cancer treatment and initiation of cardio protective medications, thereby reducing the risk of long-term cardiovascular complications. As cancer therapies continue to evolve, a deeper understanding of the mechanisms underlying cardiotoxicity and the integration of personalized risk assessment approaches will be crucial in balancing therapeutic efficacy with cardiovascular safety in breast cancer survivors.

Figure 1: Epidemiology of Breast Cancer Survivorship and Cardiovascular Disease

Figure 2: Diagnostic Approaches and Risk Assessment Tools

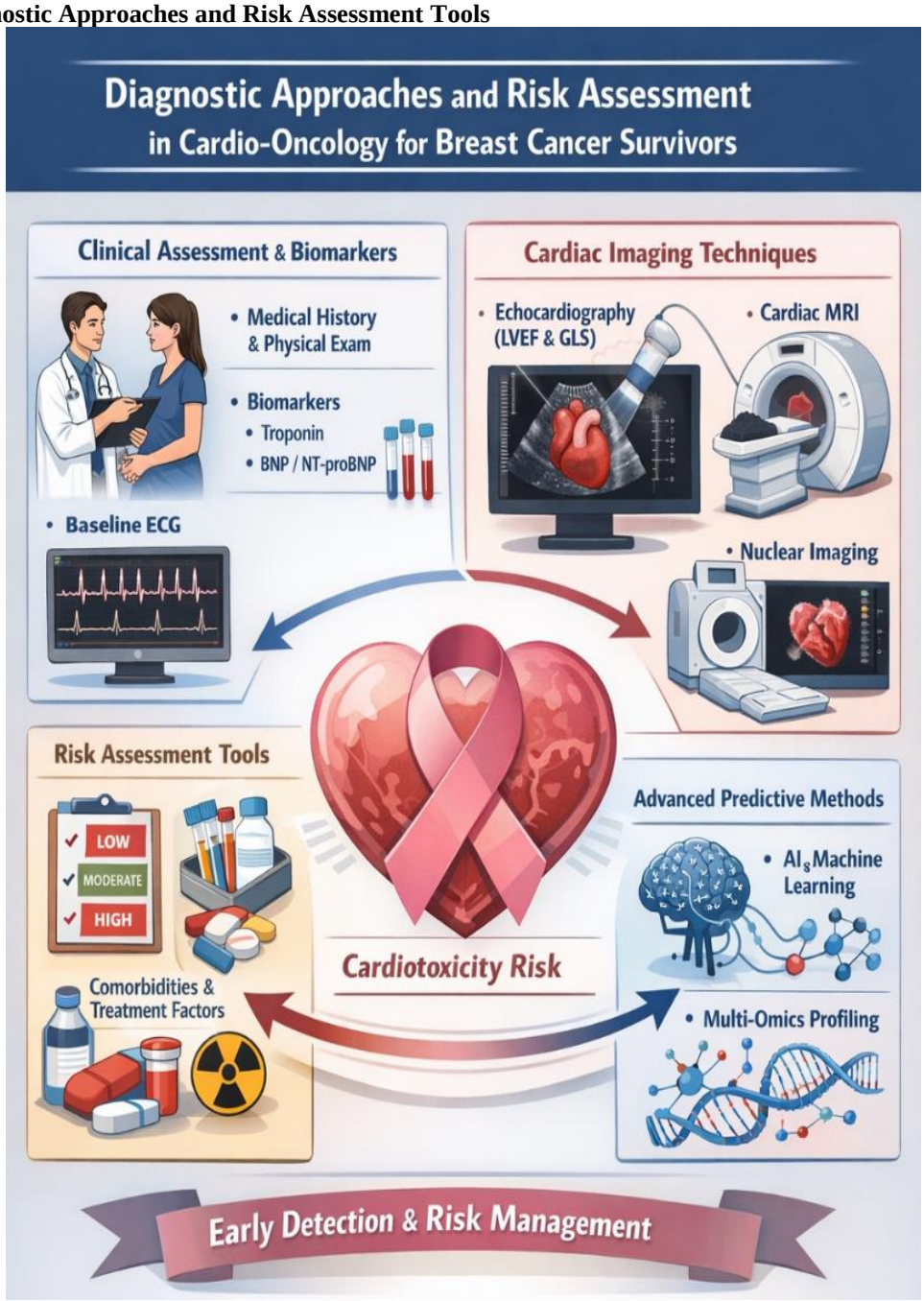

Table 1: Major Cancer Therapies and Associated Cardiovascular Toxicities

Therapy Type	Examples	Mechanism of Cardiotoxicity	Common Cardiovascular Effects	Reversibility
Chemotherapy	Anthracyclines (Doxorubicin)	Oxidative stress, mitochondrial damage, apoptosis	Heart failure, LV dysfunction	Mostly irreversible
Targeted Therapy	Trastuzumab (HER2 inhibitors)	Inhibition of cardiomyocyte survival pathways	LV dysfunction, cardiomyopathy	Often reversible
Radiotherapy	Chest irradiation	Endothelial damage,	CAD, valvular disease,	Irreversible (late

		fibrosis, atherosclerosis	pericarditis	onset)
Endocrine Therapy	Aromatase inhibitors, Tamoxifen	Hormonal imbalance, metabolic changes	Dyslipidemia, thromboembolism	Variable
Immunotherapy	Immune checkpoint inhibitors	Immune-mediated inflammation	Myocarditis, arrhythmias	Potentially reversible if early treated

Table 2: Cardiovascular Risk Factors in Breast Cancer Survivors

Category	Risk Factors	Impact on Cardiovascular Health
Traditional Risk Factors	Hypertension, diabetes, dyslipidemia, smoking, obesity	Promote atherosclerosis, increase cardiac workload
Treatment-Related Factors	Anthracyclines, trastuzumab, radiotherapy	Direct myocardial injury, vascular damage
Hormonal Factors	Estrogen depletion, premature menopause	Accelerates atherosclerosis, metabolic syndrome
Lifestyle Factors	Physical inactivity, poor diet, stress	Worsens metabolic and cardiovascular profile
Biological Factors	Inflammation, oxidative stress, endothelial dysfunction	Contributes to vascular injury and cardiac remodeling
Psychosocial Factors	Depression, anxiety, social isolation	Indirect cardiovascular risk via behavioral pathways
Socioeconomic Factors	Limited healthcare access, low awareness	Delayed diagnosis and poor management

Table 3: Diagnostic and Preventive Strategies in Cardio-Oncology.

Category	Tools/Interventions	Clinical Purpose
Biomarkers	Troponin, BNP/NT-proBNP	Early detection of myocardial injury
Imaging	Echocardiography (LVEF, GLS), Cardiac MRI	Assess cardiac structure and function
Risk Assessment Tools	ESC risk stratification models	Identify high-risk patients
Pharmacological Prevention	ACE inhibitors, ARBs, beta-blockers, statins	Prevent or reduce cardiotoxicity
Lifestyle Interventions	Exercise, DASH/Mediterranean diet, smoking cessation	Reduce modifiable risk factors
Treatment Modification	Dose adjustment, liposomal formulations	Minimize cardiotoxic exposure
Follow-Up Strategies	Periodic monitoring, multidisciplinary care	Early detection and long-term management

Diagnostic Approaches and Risk Assessment Tools

Risk assessment tools and diagnostic methods of cardiovascular disease (CVD) among breast cancer survivors constitute the critical aspects of modern cardio-oncology allowing to identify subclinical cardiac injury, proper risk classification, and intervene in time to avoid negative outcomes. A diagnostic approach that is well-conceived and developed usually includes a combination of clinical assessment, biomarker assessment, imaging techniques, and proven risk prediction models. The pre-cancer therapy baseline cardiovascular assessment is important in determining the pre-existing risk factors and defining reference parameters to be used in the longitudinal tracking. The circulating biomarkers that include cardiac troponins and natriuretic peptides (BNP or NT-proBNP) are crucial in the early diagnosis of myocardial injury and ventricular stress, and before clinical manifestations occur. Measuring these biomarkers before and after the treatment increases the capacity of identifying the patients who are at a high risk of cardiotoxicity.[5] Cardiac evaluation is based on imaging techniques, the most common of which is transthoracic echocardiography because of its accessibility and the capability to measure left ventricular ejection fraction (LVEF), diastolic functioning, and global longitudinal strain (GLS), which has a high degree of sensitivity to identify early myocardial dysfunction. Improved

imaging technologies like cardiac magnetic resonance imaging (MRI) are able to better characterize the tissue and be able to detect fibrosis, inflammation, and myocardial edema whereas nuclear imaging technologies can be used in certain clinical situations. Risk assessment models have been created together with diagnostic instruments to rank patients according to their risk of getting cardiovascular complications with age, comorbidities, cumulative treatment dose, and type of therapy being one of the factors. Predictive algorithms such as the European Society of Cardiology (ESC) cardio-oncology risk stratification framework and other tools can be used to help monitor strategies individually and inform preventive interventions[45]. New methods such as predictive models driven by artificial intelligence and multi-omics profiling are under consideration to improve the accuracy of the risk prediction. Notably, it is important to monitor the cardiovascular risk over time since survival period may change. These diagnostic and assessment strategies can be easily incorporated into the usual clinical practice, which will enable the early detection of high-risk patients, promote specific surveillance measures and eventually lead to better cardiovascular and overall outcomes among breast cancer survivors.

Preventive Strategies and Risk Reduction

The secondary, tertiary, and primary prevention interventions are best included to enhance the overall outcome of breast cancer survivors and preventive measures to reduce cardiovascular disease (CVD) are one of the preventive approaches to cardiovascular disease in breast cancer survivors. Primary prevention is initiated by extensive baseline cardiovascular risk evaluation before the commencement of cancer treatment, which enables optimization of the risk factors that can be modified, including hypertension, diabetes, dyslipidemia, obesity and smoking.[46] The main approach is lifestyle interventions, among them routine physical exercise, a diet rich in heart-protective foods, such as the Mediterranean diet or the DASH diet, weight control, and stress management, which have all been shown to be effective in lowering the risk of cardiovascular disease. The pharmacological approach is also being extensively used to reduce cardiotoxicity associated with the treatment process, especially in patients at risk; angiotensin-converting enzyme (ACE) and angiotensin receptor blockers (ARB) as well as beta-blockers and statins have demonstrated promise in reducing cardiac dysfunction and adverse remodelling. Optimization and modification of cancer treatments schedules, including the reduction of cumulative anthracycline exposure or the adoption of liposomal delivery systems, is another factor that helps to reduce the risk of cardiotoxicity without sacrificing oncological effectiveness. More sophisticated radiotherapy methods which reduce cardiac exposure, including deep inspiration breath hold (DIBH), further lower the cardiovascular complications in the long term. Secondary prevention refers to the early detection of the subclinical cardiac dysfunction by regularly monitoring biomarkers and imaging and initiating cardioprotective interventions in time before advancing to the symptomatic disease[47]. Tertiary prevention entails prevention of exacerbation of the already established cardiovascular conditions by provision of guideline-based medical treatment of heart failure, ischemic heart disease, arrhythmias. Engagement and education of the patient are important elements since they enable the survivors to identify the symptoms, follow up the treatment, and lead healthier lifestyles. Also, cardio-oncology programs enable the coordination of care, which is ensured by constant monitoring and comprehensive, individualized management throughout the survivorship spectrum. There is a potential of improving prevention and risk reduction by using emerging strategies, such as the application of digital health tools, wearable devices, and personalized medicine approaches. Altogether, an interdisciplinary, multidisciplinary, and proactive strategy is necessary to reduce the risk of cardiovascular conditions and positively influence the survival and quality of life of breast cancer survivors.

Management of Cardiovascular Complications in Survivors

Cardiovascular complication management in breast cancer survivors is an individualized and multidisciplinary management approach that requires consideration of both the acute outcomes and the long-term outcomes of cardiotoxicity and optimal oncological outcomes. The focus of management is ensuring that a guideline based medical therapy is identified and initiated at an early age in accordance with the particular cardiovascular condition. In patients with left ventricular dysfunction or heart failure, the standard treatments such as angiotensin-converting enzyme or angiotensin receptor blockers, beta-blockers, mineralocorticoid receptor blockers, and, in some cases, sodium-glucose cotransporter-2 blockers are used to enhance the cardiac activity, decrease the symptoms, and avoid the disease progression. The treatment plans of ischemic heart disease encompass antiplatelet drugs, statins, revascularization, and vigorous management of risk factors that are modifiable.[48] Atrial fibrillation and other arrhythmias are treated using rate or rhythm control measures and anticoagulation on the basis of thromboembolic risk measures. Notably, the choices made on either continuation, modification or discontinuation of cancer treatment must be weighed against the risks of cardiovascular complications and may necessitate close interaction between oncologists

and cardiologists. Temporary suspension or dosage reduction of cardiotoxic drugs may need to occur in a few cases, and cardioprotective drugs are administered to permit the administration of life-saving cancer treatment to continue. The management also involves the treatment of hypertension associated with treatment, thromboembolic, pericardial disease and valvular dysfunction, all necessitating certain treatment interventions according to the existing clinical guidelines. Serial imaging and biomarker monitoring should be followed up regularly to measure the treatment response and define the progression or recurrence of cardiac dysfunction. Supervised exercise and lifestyle counseling programs are also part of rehabilitation programs that can help in enhancing functional capacity and general cardiovascular health. Patient education is crucial in determining compliance to treatment, early symptom awareness, and preventive measures. Moreover, psychosocial support is pertinent since anxiety and depression may have adverse effects on cardiovascular and cancer-related outcomes. The collaboration of cardio-oncology services provides organized care, which allows linking specialties with each other and tailor individual treatment plans. New treatment methods and precision medicine modalities are also supplementing management techniques by focusing on risk profiles and the underlying mechanisms of individuals. In general, the cardiovascular complications of breast cancer survivors can be managed efficiently only with the help of constant monitoring, evidence-based interventions, and a patient-centered approach that will maximize cardiac and oncological outcomes.

CONCLUSION

Cardiovascular complications have emerged as a critical determinant of long-term health outcomes among breast cancer survivors, reflecting the evolving landscape of cancer care where improved survival has shifted focus toward survivorship quality and chronic disease management. The intersection of breast cancer and cardiovascular disease is characterized by a complex interplay of traditional risk factors, cancer biology, and treatment-related toxicities, resulting in a multifactorial and dynamic risk profile that extends across the lifespan. Advances in cancer therapeutics, while life-saving, have introduced significant cardiovascular challenges, including cardiomyopathy, ischemic heart disease, arrhythmias, and vascular dysfunction, often manifesting years after treatment completion. This underscores the importance of recognizing cardiovascular disease not merely as a comorbidity but as a central component of survivorship care. The integration of epidemiological insights, pathophysiological understanding, and clinical evidence has highlighted the necessity for early risk identification, continuous monitoring, and proactive intervention. Diagnostic innovations, including sensitive biomarkers and advanced imaging modalities, have enhanced the ability to detect subclinical cardiac injury, enabling timely preventive and therapeutic strategies. Equally important are comprehensive risk reduction approaches that combine lifestyle modification, pharmacological interventions, and optimization of cancer treatment protocols to minimize cardiotoxicity without compromising oncological efficacy. The management of cardiovascular complications requires adherence to evidence-based guidelines and a personalized approach that accounts for individual risk factors, treatment exposures, and patient preferences. Central to this effort is the role of multidisciplinary care, particularly through the development of cardio-oncology services that facilitate collaboration between oncologists, cardiologists, and allied healthcare professionals, ensuring coordinated and holistic care delivery. Despite these advancements, significant challenges remain, including gaps in long-term data, variability in risk prediction models, and disparities in access to care, which limit the effectiveness of current strategies. Addressing these issues will require robust prospective research, incorporation of emerging technologies such as artificial intelligence and multi-omics, and the development of standardized, globally applicable guidelines. From a healthcare policy perspective, there is an urgent need to integrate cardiovascular care into cancer survivorship programs, enhance provider education, and improve infrastructure for long-term follow-up and monitoring. Ultimately, optimizing cardiovascular health in breast cancer survivors is essential not only for reducing morbidity and mortality but also for improving overall quality of life and functional outcomes. A proactive, multidisciplinary, and patient-centered approach that bridges oncology and cardiology will be key to advancing survivorship care and meeting the growing needs of this expanding patient population.

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