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REVIEW ARTICLE

Cardiovascular Disease in Women With Breast Cancer: A Contemporary Review

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Central Illustration: Cardiovascular Disease in Women With Breast Cancer: An approach, stratification, and cardiotoxicity evaluation model

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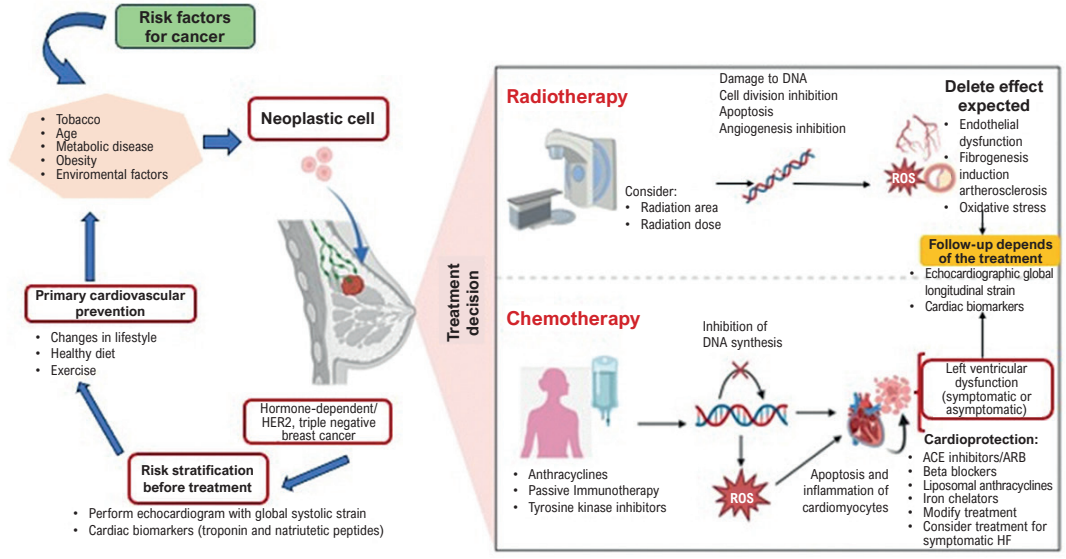

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DNA: Deoxyribonucleic acid; HER2: human epidermal growth factor receptor 2; ACE inhibitors: angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; ROS: Reactive oxygen species.

Abstract

Breast cancer (BC) is the most common malignant neoplasia in women and is responsible for one in six deaths from cancer in the female population. Five years after diagnosis, BC survival rates currently exceed 80%. Cardiovascular disease (CVD) is a frequent cause of morbidity and mortality in BC, mainly in patients receiving cardiotoxic drugs (anthracyclines, immunotherapy) and radiotherapy (RT).

CVD and BC have common risk factors (RF), which are related to aging, traditional and cardiometabolic RFs (obesity, dyslipidemia, consumption of alcoholic beverages), and others associated with sex and reproductive women's age, such as early menarche,

Keywords

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late menopause, nulliparity, use of oral contraceptives, as well as hormone replacement therapy in postmenopause.

Risk stratification and the promotion of an ideal state of cardiovascular (CV) health are fundamental in preventing CVD in survivors. Therapeutic management and follow-up of patients with BC require a multidisciplinary team to reduce complications and mortality of CV origin.

Introduction

Advances in diagnostic and therapeutic methods in breast cancer (BC) patients have increased survival.[1] Cardiovascular (CV) toxicity associated with some cancer therapies — chemotherapy, radiotherapy (RT), or targeted therapy — is a severe complication that increases CV morbidity and mortality. Therefore, it is essential to establish strategies to identify and timely treat patients at risk of presenting this complication, as well as generate multidisciplinary medical teams (cardio-oncology) to provide comprehensive care, which could allow the oncological therapeutic scheme and the cardio-protection measures required.[1–3]

According to the International Agency for Research on Cancer of the World Health Organization (WHO), BC is women's most frequent type of cancer. The incidence is 47.8 per 100,000 women, representing more than 25% of all cancers in 2020, generating the highest mortality (13.6 per 100,000 women per year).[2] Additionally, it is considered that BC survivors are two to seven times more likely to die from cardiovascular disease (CVD) compared to the general population, mainly patients under 40 or over 60.[4,5] The possibility of survival will depend on the stage in which cancer is diagnosed, the therapeutic schemes available, the delay in the start of treatment, and the presence of comorbidities such as systemic arterial hypertension (SAH) and diabetes mellitus (DM). Early detection and timely treatment are associated with better results and survival of 90% of patients five years after diagnosis. The survival rate varies between countries. Lower-income countries generally have limited access to health systems and resources for diagnosis and treatment; hence, they are associated with lower survival.[5]

Cancer treatment can generate signs of cardiotoxicity and develop complications such as left ventricular dysfunction, heart failure (HF), arrhythmias, ischemic heart disease, SAH, thromboembolic events, valvular heart disease, pulmonary arterial hypertension, and pericarditis. The incidence of these complications is reported from 3%, 5%, and up to 48%, depending on the type of treatment, intensity, dose, duration, the combination of different therapeutic regimens, and the presence of cardiovascular risk factors (CVRF).[3,6]

RFs and mechanisms of CVD

CVD and BC share some RFs for the development and presence of cardiotoxic effects secondary to treatment, such as: a) traditional RFs, namely age, obesity, smoking, dyslipidemia (mainly significant elevation of lipoprotein A and apolipoprotein B), lifestyle, and stress; b) sex-specific factors, including early menarche (before age 12), late menopause (after age 55), first pregnancy after 30 years old, nulliparity, preeclampsia, and hormone replacement therapy at menopause for more than five years; and c) pre-existing diseases such as chronic renal failure (CRF) and autoimmune or chronic inflammatory diseases.[7,8] It is considered that the presence or development of some of these RF or their deficient control, together with the effect of the different treatments for BC, stimulate the inflammatory response that favors endothelial dysfunction, atherosclerotic process, autonomic dysfunction, and prothrombotic states with the subsequent increase in CV morbidity and mortality. The existence of these RF also increases the risk of BC. Even though the results of different studies are ambiguous, they reported some association between plasma lipid levels and the increase in body weight generated by an unhealthy diet, with the increase in the risk of BC.[9] It is also important to consider that BC treatment increases the incidence of hypertension and DM in survivors. The combination of these factors and the effects of treatment increases the probability of CV morbidity and mortality in this group of patients. Thus, maintaining a good state of CV health is important for all women, especially those at high risk of developing BC.[9] (Central Illustration)

CV risk stratification

Establishing strategies to identify factors that may contribute to developing CV complications derived from BC treatment in a timely manner is suggested. CV risk stratification in these patients should be carried out before starting treatment and periodically during the different stages of treatment, with long-term follow-up after the end of the therapeutic scheme used. It is important to mention that risk scales currently used to quantify CV risk in women with or without BC do

not include sex-specific RFs. Therefore, it is necessary to systematically investigate the existence of these conditions to re-stratify CV risk. It is also recommended to carry out a comprehensive evaluation by identifying CVRF, pre-existing CVD, and other factors that increase the risk of cardiotoxicity (type of treatment, intensity, duration, previous antineoplastic therapy), for which it is suggested to perform a clinical, electrocardiographic, echocardiographic, metabolic evaluation (renal function, lipid profile, glucose, glycosylated hemoglobin) and quantification of biomarkers (Brain-like Natriuretic Peptide (BNP) or N-terminal proBNP and troponins) (Figure 1).[7,9]

Chemotherapy and CV damage

The most important factor when choosing the treatment plan is the immunohistochemical test. According to the findings, BC is classified based on hormone receptors (HR): estrogen receptors +/- and progesterone receptors +/-; the expression of the HER2/neu protein (human epidermal growth factor receptor 2) and classified as HER2+ or HER2-. A particular type is triple-negative BC (TNBC), which lacks hormone receptors (estrogen and progesterone) and the HER2 receptor, and does not respond to hormone treatment or anti-HER2 antibodies. The classification according to the subtype is important since it allows selecting the indicated treatment. Hormone-dependent tumors, also known as luminal tumors, are, in turn, classified into luminal type A, sensitive to estrogen and progesterone, which are sensitive to hormone treatment and not very sensitive to chemotherapy, and luminal type B, which have few hormone receptors and may be sensitive to chemotherapy.[10]

Treatment for HER2+ BC consists of therapy directed against HER2+ in combination with classical therapy. The tumor-infiltrating lymphocyte (TIL) score has prognostic value in response to chemotherapy treatment in triple-negative and HER2+ tumors. Patients HER2+ BC in stage I receive a regimen of paclitaxel plus trastuzumab, whereas stage II-III patients receive trastuzumab added to anthracyclines-paclitaxel or

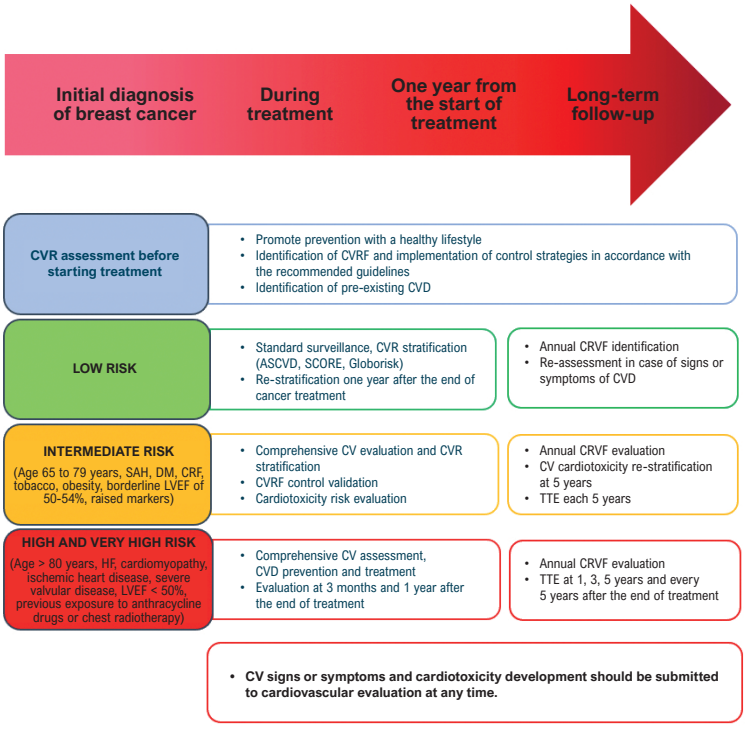

Figure 1 – Cardiovascular risk stratification in women with breast cancer. Adapted from the ESC 2022 Cardio-Oncology Guidelines [12] care scheme and the Heart Failure Study Group [7].
CV: cardiovascular; CVRF: cardiovascular risk factors; CVR: cardiovascular risk; ASCVD: Atherosclerotic Cardiovascular Disease; SCORE: Systematic Coronary Risk Evaluation; CVD: cardiovasvular disease; SAH: systematic arterial hypertension; DM: diabetes mellitus; CRF: chronic renal failure; LVEF: left ventricular ejection fraction; TTE: transthoracic echocardiography; HF: heart failure.

docetaxel and carboplatin. A pathologic complete response rate has been observed when epratuzumab is added to trastuzumab in the neoadjuvant setting. They can be administered in the adjuvant setting if they do not receive neoadjuvant treatment. The drugs approved as neoadjuvant and adjuvant are trastuzumab, epratuzumab, trastuzumab emtansine, and neratinib. In case of metastasis, trastuzumab, epratuzumab, trastuzumab emtansine, tucatinib, and trastuzumab deruxtecan are used.[11] Interestingly, CV dysfunction has been reported in up to 15-20% of the population, mainly in combination therapy patients.[12,13]

Anthracyclines are considered the main drugs inducing cardiotoxicity, which increases as the cumulative dose administered increases: 3-5% with 400 mg/m^2 and 18-48% with 700 mg/m^2. The risk of toxicity increases with the use of other agents, such as trastuzumab.[14,15] They contribute to DNA damage by generating reactive oxygen species (ROS), which are produced during the intracellular metabolism of the drug.[15,16]

Passive immunotherapy-associated cardiotoxicity with HER2 antagonistic monoclonal antibodies (mAbs), such as trastuzumab and pertuzumab, produces cardiomyopathy by disrupting HER2 protective functions in the cardiomyocyte.[17,18]

Another group of drugs indicated in patients with HER2+ BC are tyrosine kinase inhibitors, demonstrated as extended adjuvant treatment of hormone receptor-positive early-stage BC with HER2+ overexpression.[19]

In all women receiving antineoplastic treatment, risk stratification should be carried out using the HFA-ICOS (HF Association-International Cardio-Oncology Society) scale, a subclinical diagnosis of cardiac dysfunction should be performed, and cardioprotective treatment initiated. The most frequently observed adverse event is cardiac dysfunction, which is currently divided into groups: symptomatic and asymptomatic. The parameters to consider are left ventricular ejection fraction (LVEF), global longitudinal strain (GLS), and elevated cardiac biomarkers.[12]

For patients scheduled to receive anthracyclines, the cumulative dose is of clinical significance, and a dose greater than 250 mg/m^2 of doxorubicin or equivalent increases the cardiotoxicity risk[12] (Table 1).

The baseline evaluation and follow-up during the first 12 months will depend on the type of drug administered (anthracyclines or anti-HER2)[12] (Tables 2 and 3).

Table 1 – Anthracycline equivalence doses using doxorubicin as reference.

	CV toxicity dose ratio	Isoequivalent dose
Daunorubicin	0.6	167 mg/m^2
Epirubicin	0.8	125 mg/m^2
Doxorubicin	1	100 mg/m^2
Idarubicin	5	20 mg/m^2
Mitoxantrone	10.5	9.5 mg/m^2

Adapted from Lyon AR, et al.[12] CV: cardiovascular

Strategies to avoid cardiotoxicity involve adjusting the infusion time and the dose intensity. In patients with high and very high risk of cardiac dysfunction, dexrazoxane and liposomal anthracyclines may be considered.[12,20] The decision to continue or temporarily or permanently suspend treatment in patients receiving anthracyclines and passive immunotherapy depends on cardiac dysfunction, whether it is symptomatic or asymptomatic, and the degree of severity.[14]

Cardioprotection

Cardioprotection consists of initiating:

a) Neurohormonal therapies with beta-blockers (BB) such as carvedilol and nebivolol, renin angiotensin aldosterone system (RAAS) blockers, angiotensin-converting enzyme (ACE) inhibitors, and mineralocorticoid receptor antagonists, whose main objective is to prevent ventricular dysfunction. Compared to placebo, these drugs have shown a lower reduction in LVEF during treatment (1-3% vs. 5%, respectively). Spironolactone administered simultaneously with anthracycline allegedly prevents left ventricular systolic and diastolic dysfunction by decreasing the progression of myocardial fibrosis and remodeling. Statins are also suggested in preventing left ventricular dysfunction due to their antioxidant properties, regulating mitochondrial damage, and anti-apoptotic effect on cardiomyocytes.[13,20]

b) Iron chelators such as dexrazoxane, the only drug approved by the FDA to prevent cardiotoxicity induced by anthracyclines. Their mechanism of action is to bind to iron before entering the cardiomyocytes, preventing the formation of the iron-anthracycline complex, formation of free radicals, and, consequently, myocardial damage.[21]

Table 2 – Follow-up protocol in patients with anthracyclines.

	Basal	C1	C2	C3	C4	C5	C6	3 mths post-tx	12 mths post-tx
Low risk	ECG, TTE cTn/NP		cTn/NP		TTE cTn/NP		cTn/NP	cTn/NP	TTE
Moderate risk	ECG, TTE cTn/NP		cTn/NP		cTn/NP		cTn/NP	cTn/NP	TTE
High and very high risk	ECG, TTE cTn/NP	cTn/NP	cTn/NP, TTE	cTn/NP	cTn/NP TTE	cTn/NP	cTn/NP TTE	cTn/NP TTE	cTn/NP TTE

Adapted from Lyon AR et al.[12] C: cycle; mths: months; ECG: electrocardiogram; TTE: transthoracic echocardiography; cTn/NP: cardiac troponin/natriuretic peptide; tx: treatment.

Table 3 – Follow-up protocol in patients on anti-HER2 treatment.

	Basal	3 mths	6 mths	9 mths	12 mths	3 mths post-tx.	12 mths post-tx.
Low-moderate risk	ECG, TTE cTn/NP	TTE cTn/NP	TTE cTn/NP	TTE cTn/NP	TTE cTn/NP		TTE cTn/NP
High and very high risk	ECG, TTE cTn/NP	TTE cTn/NP	TTE cTn/NP	TTE cTn/NP	TTE cTn/NP	TTE cTn/NP	TTE cTn/NP

Adapted from Lyon AR et al.[12] Mths: months; ECG: electrocardiogram; TTE: transthoracic echocardiography; cTn/NP: cardiac troponin/natriuretic peptide; tx: treatment

c) Development of new anthracycline derivatives such as liposomal preparations. Liposomes are phospholipid vesicles that serve as a vehicle for drug administration through the encapsulation and stabilization of therapeutic compounds, increasing stability by adding polyethyleneglycol (PEG). Some drugs in this group are pegylated and non-pegylated liposomal doxorubicin. The 2022 ESC cardio-oncology guidelines provide a class 2a recommendation to consider the use of liposomal doxorubicin preparations as primary cardioprotection in patients at high and very high risk of left ventricular dysfunction, and a class 2b indication in patients who have developed cardiac dysfunction with anthracyclines and in whom there is a need to resume treatment with anthracyclines.[22]

Radiation therapy and CVD

The heart is a sensitive organ to toxicity from RT, which increases with the dose received. According to the ALARA concept, radiation exposure to the heart should be kept "as low as reasonably achievable" since there is no safe dose to avoid cardiotoxicity from RT.[12]

The pathophysiological mechanisms of RT-induced cardiotoxicity (RICT) include an acute inflammatory response, release of cytokines, and growth factors (interleukins (IL)1, IL-6, tumor necrosis factor (TNF), and platelet derivatives (PDGF)), resulting in endothelial dysfunction, vasoconstriction, pro-thrombosis, and development of atherosclerosis. Vascular injury due to increased ROS produces oxidative stress, lipid peroxidation, rupture, and decreased DNA synthesis, favoring intima hyperplasia and atherosclerotic plaque formation. Increased extracellular collagen synthesis by fibroblasts induces vascular stiffness and ventricular remodeling.[23]

RT induces damage to cardiac structures, including the pericardium (pericardial effusion, constrictive pericarditis), valves (mitral, aortic, predominantly regurgitation), conduction system, rhythm disturbances

(bradycardia, tachycardia), vascular calcification (porcelain aorta), and arteries, which can lead to macro and microvascular coronary diseases (such as ischemic heart disease). The frequency increases in the years after receiving RT (after 15-20 years), with a prevalence of 10-30% after 5-10 years, being asymptomatic in up to 88% of cases.[24] The incidence of CV events after RT depends on potentiation with other types of treatment (chemotherapy) and the presence of CVRF (Table 4).

The relative risk (RR) of CV events is higher when RT is directed to the left breast (RR 1.10): myocardial infarction 1.22, angina 1.25, pericarditis 1.65, valve disease 1.54, as well as the presence of LV dysfunction, alterations in myocardial mobility and perfusion detected by imaging methods. The RR of an acute ischemic event is 7% for each 1 Gy increase in the mean cardiac dose (MCD) administered; there is no specific safety threshold. The cumulative incidence of coronary events in patients managed with targeted three-dimensional RT (3D-RT) after 9-10 years is 16.5% per Gy of MCD.[25] The recently published Danish BC Group Study reports a cumulative risk for developing coronary events of 1.7% (95% CI 1.4–2.0) at 11 years. The incidence of events related to RT directed to the left breast compared to the right was greater at ten years after treatment (1.44 vs 1.07).[25]

The risk of RICT is multifactorial and dynamic, as it depends on adjuvant oncological therapies, comorbidities, a history of previous CV disease, administration technique, and exposure dose. The patient must undergo an initial risk assessment before receiving RT, primarily directed at the left breast. The calculation of the initial and ten-year cardiovascular risk (CVR) is recommended (recommendation I-B), and the performance of an echocardiogram in patients with a history of previous CVD (recommendation IIa-C).[12]

RICT prevention is relevant. The WHO suggests levels of prevention and applicable strategies, according to the level of prevention: damage prevention through specific administration techniques, close monitoring during treatment, and control of CVRF (primary prevention), early detection (imaging techniques) that allows measures to modify its evolution (secondary prevention), and, in the presence of damage (tertiary prevention), strategies to reduce sequelae (modification of schemes).[26,27] Several techniques can help in the primary prevention of vascular toxicity secondary to RT, reducing radiation exposure to the heart, namely improving the direction of the RT beam, controlling breathing (activating or holding it), modifying the distribution of the administered doses (intensity modulation), and administrating protons. However, there are no techniques or treatments that achieve total protection. Regarding secondary prevention, in patients who already had a previous CV event, the most important action is the control of CVRF.[12]

The development of RICT is multifactorial and chronic, resulting from an acute inflammatory process and endothelial dysfunction. The condition and action of CV events are relevant and frequently subclinical, so it is advisable to carry out good CV prevention and continuous monitoring of patients undergoing RT through the collaboration of an interdisciplinary team.[26,27]

Primary prevention of CVD in surviving patients with BC

Female BC survivors are a growing population with specific health needs, a situation that is due to advances in early detection and therapies that lead to significant improvements in prognosis and long-term survival. Due to associated comorbidities, they often present a risk of death not related to cancer. CVD has a high prevalence and is the leading cause of death among cancer survivors. Both conditions share common RFs and pathophysiological mechanisms.[28] Up to 11.3% of cancer survivors die from CVD (ischemic heart disease, hypertension, cerebrovascular disease, atherosclerosis, aneurysm, and aortic dissection), with ischemic heart disease being the first cause of death, even in women with BC.[29]

Table 4 – Risk of cardiotoxicity induced by radiotherapy.

Risk level	Mean cardiac dose of radiotherapy + chemotherapy dose
Low	• <5 Gy
Moderate	• 5 to 15 Gy • <5 Gy + cumulative dose of doxorubicin ≥100 mg/m²
High	• >15 to 25 Gy • 5 to 15 Gy + cumulative dose of doxorubicin ≥100 mg/m²
Very high	• >25 Gy • >15 Gy + cumulative dose of doxorubicin ≥100 mg/m²

Adapted from Lyon AR, et al.[12] Gy: Gray.

The Atherosclerosis Risk in Communities (ARIC) study showed significant associations between adult survivors of cancer and CVD. A cancer diagnosis was associated with 6.4 more CVD cases per 1,000 person-years than the general population. Compared with people without previous cancer, cancer survivors had a higher risk of CVD (37%) and HF 52%.[28]

In female BC survivors, hyperglycemia, dyslipidemia, SAH, and abdominal obesity are the main RFs for type 2 diabetes mellitus (DM2) and CVD. Chronic inflammation and oxidative stress are also associated with the risk of BC. Therefore, primary prevention strategies can modify the CVR of patients.[29,30]

Control of RFs

The prognosis of surviving women with BC can be modified by effectively treating pre-existing comorbidities, such as DM2 and SAH. CVD can be prevented by adequately controlling CVRF and promoting improved CV health (healthy diet, physical activity, ideal weight, and tobacco abstinence). Subjects in middle adulthood (45 years old) with optimal RF profiles have a significantly lower CV risk throughout life than those with even one relevant RF (4.1% vs. 20.2% among women).[5]

Adherence to ideal CV health behaviors or factors, such as the American Heart Association (AHA) Life's Essential 8 campaign, is associated with a lower incidence of BC.[31]

Importance of lifestyle

Cardiopulmonary function and quality of life in patients with BC improve with exercise. Such patients should follow the physical activity recommendations of the AHA, with moderate-intensity aerobic exercise, equivalent to a physical activity of ≥ 30 minutes at least five days a week.[31]

Weight loss interventions, particularly multimodal (diet, exercise, and psychosocial support) in overweight or obese BC survivors, can reduce weight, body mass index, and abdominal circumference, improving quality of life.[32,33]

Routine physical activity represents a CV risk reduction strategy in female BC survivors. Increased exercise capacity and a higher cardiac recovery rate were associated with reduced abdominal circumference, systolic blood pressure, triglyceride levels, fasting blood glucose, and risk of metabolic syndrome ($p < 0.02$) and with increased HDL ($p = 0.03$).[34]

Primary and secondary prevention strategies in BC

The creation of primary and secondary prevention of CVD programs in the cardio-oncology setting provides the opportunity to individualize cardioprotective treatment for cancer patients based on detecting and controlling underlying CVRF and promoting a healthy lifestyle.[31,33]

Women with BC should be screened for lipid disorders and insulinemia to avoid CV complications. In patients with BC aged 40 to 75 years, with LDL > 70 mg/dl and DM2 or risk score according to the ASCVD (Atherosclerotic CVD) scale at ten years > 7.5%, statin therapy is recommended in addition to changes to the lifestyle. Use should be individualized for those with a score of < 5% (low risk). With an ASCVD of 5% to < 7.5%, statin initiation is favored in those women who undergo radiation treatment of the left hemithorax.[35] In women at risk of HF, it is recommended to maintain blood pressure (BP) values < 130/80 mm Hg. Recommendations for primary and secondary prevention in surviving women with BC are based on changes in lifestyle with diet and exercise, in addition to the pharmacological approach.[31-34]

Conclusion

CVD is the leading cause of mortality in women with BC. Both share RFs in common, so identification and control are essential in preventing the disease.

Primary CV prevention is essential in all women, particularly in those with CVRFs common to BC, especially those related to sex-specific factors that are not included in the currently available risk scales.

CV toxicity development depends on the type and intensity of the treatment (chemotherapy, RT). Given the interaction of conditioning RFs and the interrelation of the pathophysiological mechanisms of BC and CVD, comprehensive care through a multidisciplinary cardio-oncology team is required.

Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data, writing of the manuscript, critical revision of the manuscript for intellectual content: Puente Barragán A, Nuriulú Escobar P, Madrid Miller A, Moreno Ruiz LA; figure design and elaboration: Nuriulú Escobar P, Madrid Miller A; elaboration: Nuriulú Escobar P; collect bibliography: Moreno Ruiz LA.

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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