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Mini Review

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The importance of cardiovascular disease in breast cancer survivors. mini review

Abstract

Objective: Breast cancer (BC) is the most frequent neoplastic disease in women. Recently, cardiovascular disease (CVD) has arisen as a non-cancer related mortality cause between breast cancer survivors. The aim of this paper is to establish the importance of CVD in BC survivors in order to draw attention to this public health problem so new strategies can be implemented in the future.

Methods: A PubMed research of the Mesh terms "Breast Neoplasms" and "Heart Disease Risk Factors" was made. Journals available to the Universidad Nacional Autónoma de México – U.N.A.M. (National Autonomous University of México) were revised. Of 130 articles, 52 were selected and were cited for this review.

Conclusion: Earlier detection rates and advances in breast cancer therapies have improved overall survival in BC patients. CVD is now an important cause of mortality in BC survivors. This might be explained by the conjunction of pre-existing CVD risk factors and cardiovascular injury secondary to cancer therapy.

Keywords: breast cancer, cardiotoxicity, cardiovascular risk, cardiovascular health in women

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Introduction

Breast cancer (BC) is the most frequent neoplastic disease in women. It is the result of an unregulated proliferation of abnormal mammary cells, that culminates in a tumor. Without treatment it is highly mortal, but thanks to the understanding of the main pathophysiological and biomolecular alterations involved in the development of BC new therapeutic strategies have improved the overall survival, even if diagnosis is made in advance stages.[1–3]

As Knisely et al. brightly exposed, cancer and cardiovascular diseases (CVD) have entered into a 'clinical overlap' era.[4] In the last decade, the paradigm of CVD, the principal cause of death worldwide, has arisen between BC survivors.[5] This might be explained by shared CVD and BC risk factors, the prothrombotic state of cancer itself, and treatment-associated cardiotoxic effects.[6–7]

Given the high prevalence and increasing incidence of CV events in BC survivors, it's important to train physicians in this knowledge in order to reduce the risk of CV events and improve quality of life for BC survivors.

Breast cancer and cardiovascular disease

BC has an annual world incidence of 2.26 million new cases. It is the second most frequent cause of death by cancer (just after lung cancer), with a mortality of 13.6 per 100,000 patients annually. However, mortality arises up to 74.4 per 100,000 when we evaluate women of 65 years of age or older.[8]

Earlier detection rates and advances in cancer therapies have improved overall survival in BC patients, which results in a growing survivor population that is at increased risk of other non-cancer related mortality causes, specifically CVD.[9]

Lee et al. proposed back in 2007 the "multiple hit hypothesis" in an attempt to explain the increased CVD risk in BC survivors. They affirm that 1.- CVD risk factors at the time of diagnosis, 2.-lifestyle perturbations and 3.- cardiovascular injury directly associated with cancer therapy collectively leave patients with overt or covert CVD. At a minimum, these insults enhance susceptibility to further cardiovascular injury and, ultimately, risk of premature CVD mortality.[10]

CVD risk factors at the time of diagnosis

Breast cancer and CVD have shared risk factors.[7,11] Risk of death from CVD is even higher in BC survivors with preexisting CVD risk factors at diagnosis, such as diabetes and hypertension, two of the most prevalent comorbidities in the general population.[12,13] The presence of CVD risk factors predicts CVD development regardless of breast cancer.[14]

Other well-known risk factors of CVD mortality in BC survivors are older age at diagnosis[15–17] and black ethnic origin.[18] Women diagnosed with breast cancer over the age of 75 have nearly a 23-fold higher risk compared to women diagnosed before 55 years old.[19] Smoking cessation followed BC diagnosis in up to 50% of the patients[20,21] however, quitting after diagnosis did not appear to reduce CVD risk.[22]

Lifestyle perturbations

Lifestyle toxicity is a less recognized, but equally as pervasive a consequence of breast cancer diagnosis and therapy.[19] BC patients self-report decreased enjoyment of food and selection of "less healthy food".[23] Weight gain is commonly reported by women with breast cancer and only 10% return to their pre-diagnosis weight even after up to six years of follow-up.[24,25] Being overweight or obese is a significant independent risk factor for CVD.[26]

BC diagnosis also generates a wide spectrum of psychoaffective and economic disturbances in the patients affected and their family circle.[27–29] Stress, depression and anxiety are associated with CVD through behavioral and biological mechanisms. Stress induces physical inactivity, poor diet and smoking habits, as well as triggers inflammation pathways.[30]

Cardiovascular injury associated to BC therapy

Different breast cancer therapies are closely associated with cardiotoxicity,[15,19] resulting as a paramount cause of morbidity and mortality in BC survivors.[5,31,32]

Anthracyclines stand out as frequently employed chemotherapy agents, which generate irreversible and dose-dependent myocardial damage by two different mechanisms: excessive production of reactive oxygen species (ROS) and formation of complexes with the TOP2-beta topoisomerase of cardiomyocytes culminating in the formation of fibrotic tissue, DNA mutations and necrosis.[33–35]

Some of the sequelae described following the use of anthracyclines are heart failure, decreased left ventricular ejection fraction (LVEF), and arrhythmias such as atrial fibrillation and ventricular tachycardia.[36–39]

Trastuzumab has been proven to effectively decrease mortality, recurrence and incidence of metastatic disease in HER2-positive BC.[32,40,41]Trastuzumab-induced cardiotoxicity (TIC) is dose-independent and has been described as an asymptomatic reduction of the LVEF and occasionally as a symptomatic heart failure syndrome.[5] There is no international consensus on the mechanisms of trastuzumab-induced cardiotoxicity. In vitro studies have proven that trastuzumab blocks the activity of type 1 Neuregulin, a protein that stimulates the sarcomere contractile function and its structure preservation.[42,43] Previously considered a reversible phenomenon after drug discontinuation, new evidence has demonstrated a long-term impairment of cardiopulmonary function and a permanent decrease in LVEF in up to 40% of BC survivors following trastuzumab administration.[44,45] Nonetheless, benefits still overcome the risks and long-term secondary effects.[46]

Radiotherapy (RT) is widely used in BC. By exposure to x-rays, or γ-rays, RT induces DNA fragmentation and diminishes cell proliferation. Cardiotoxic effects of RT aren't fully understood. However, endothelial injury and increased activity of proinflammatory cytokines, and release of ROS have been described following radiation.[47] Left-sided tumor is associated with more risk of cardiotoxicity secondary to radiotherapy, mainly because of its heart's adjacency.[48–51] RT cardiotoxicity is mainly manifested as pericarditis, cardiomyopathy, valve disease, arrhythmias and coronary disease.[52]

Different cancer treatment options affect in various manners CV structure and function. Alkylating agents may cause LV dysfunction, HF, myocarditis and arrhythmias. Endocrine therapy can cause venous thrombosis, atherosclerosis, dysrhythmias and HF. Cyclin-dependent kinase 4/6 inhibitors have shown QTc prolongation.[31]

Conclusion

At the present day, improved breast cancer survival has resulted in an augmented population of BC survivors at risk of CVD. After a thorough investigation, we couldn't find guidelines that propose how to systematically evaluate cardiovascular risk and a follow-up protocol in BC survivors. Physicians should be able to recognize CVD risk factors in order to provide assertive strategies to prevent and treat CVD. New studies are necessary to establish evidence-based recommendations to prevent and decrease the risk of new cardiovascular events in BC survivors.

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Conflicts of interest

The author declares there is no conflict of interest.

References

1. Perou CM, Sørile T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature*. 2000;406(6797):747–52.
2. Tsuji W, Plock JA. Breast Cancer Metastasis. *Introduction to Cancer Metastasis*. 1st edn. El servier. 2017.
3. Waks AG, Winer EP. Breast Cancer Treatment: A Review. *JAMA - Journal of the American Medical Association*. 2019;321(3):288–300.
4. Knisely JPS, Henry SA, Saba SG, et al. Cancer and cardiovascular disease. *The Lancet*. 2020;395(10241):1903–1904.
5. Abdel-Qadir H, Austin PC, Lee DS, et al. A population-based study of cardiovascular mortality following early-stage breast cancer. *JAMA Cardiol*. 2017;2(1):88–93.
6. Gernaat SAM, Boer JMA, van den Bongard DHJ, et al. The risk of cardiovascular disease following breast cancer by Framingham risk score. *Breast Cancer Res Treat*. 2018;170(1):119–127.
7. Koene RJ, Prizment AE, Blaes A, et al. Shared risk factors in cardiovascular disease and cancer. Circulation. 2016;133(11):1104–1114.
8. World Health Organization. Globocan 2020. *Int Agency Res*. 2020. p. 1–2.
9. Padegimas A, Clasen S, Ky B. Cardioprotective strategies to prevent breast cancer therapy-induced cardiotoxicity. *Trends in Cardiovascular Medicine*. 2020;30(1):22–28.
10. Jones LW, Haykowsky MJ, Swartz JJ, et al. Early Breast Cancer Therapy and Cardiovascular Injury. *Journal of the American College of Cardiology*. 2007;50(15):1435–1441.
11. Weaver KE, Foraker RE, Alfano CM, et al. Cardiovascular risk factors among long-term survivors of breast, prostate, colorectal, and gynecologic cancers: A gap in survivorship care? *J Cancer Surviv*. 2013;7(2):253–261.
12. Sharma N, Narayan S, Sharma R, et al. Association of comorbidities with breast cancer: An observational study. *Trop J Med Res*. 2016;19(2):168–171.
13. Gernaat SAM, Ho PJ, Rijnberg N, et al. Risk of death from cardiovascular disease following breast cancer: a systematic review. *Breast Cancer Research and Treatment*. 2017;164(3):537–555.
14. Park NJ, Chang Y, Bender C, et al. Cardiovascular disease and mortality after breast cancer in postmenopausal women: Results from the Women's Health Initiative. *PLoS One*. 2017;12(9):e0184174.
15. Colzani E, Liljegren A, Johansson ALV, et al. Prognosis of patients with breast cancer: Causes of death and effects of time since diagnosis, age, and tumor characteristics. *J Clin Oncol*. 2011;29(30):4014–4021.
16. Haque R, Yood MU, Geiger AM, et al. Long-term safety of radiotherapy and breast cancer laterality in older survivors. *Cancer Epidemiol Biomarkers Prev*. 2011;20(10):2120–2126.
17. Hooning MJ, Aleman BMP, Van Rosmalen AJM, et al. Cause-specific mortality in long-term survivors of breast cancer: A 25-year follow-up study. *Int J Radiat Oncol Biol Phys*. 2006;64(4):1081–1091.
18. Berkman A, Cole B, Ades PA, et al. Racial differences in breast cancer, cardiovascular disease, and all-cause mortality among women with ductal carcinoma in situ of the breast. *Breast Cancer Res Treat*. 2014;148(2):407–413.
19. Kirkham AA, Beaudry RI, Paterson DI, et al. Curing breast cancer and killing the heart: A novel model to explain elevated cardiovascular disease and mortality risk among women with early stage breast cancer.

Progress in Cardiovascular Diseases. 2019;62(2):116–126.

20. Westmaas JL, Newton CC, Stevens VL, et al. Does a recent cancer diagnosis predict smoking cessation? An analysis from a large prospective US cohort. *J Clin Oncol*. 2015;33(15):1647–1652.
21. Parada H, Bradshaw PT, Steck SE, et al. Postdiagnosis changes in cigarette smoking and survival following breast cancer. *JNCI Cancer Spectr*. 2017;1(1):pkx001.
22. Passarelli MN, Newcomb PA, Hampton JM, et al. Cigarette smoking before and after breast cancer diagnosis: Mortality from breast cancer and smoking-related diseases. *J Clin Oncol*. 2016;32(12):1315–1322.
23. Kwok A, Palermo C, Boltong A. Dietary experiences and support needs of women who gain weight following chemotherapy for breast cancer. *Support Care Cancer*. 2015;23(6):1561–1568.
24. Vance V, Mourtzakis M, Mccargar L, et al. Weight gain in breast cancer survivors: Prevalence, pattern and health consequences. *Obes Rev*. 2011;12(4):282–294.
25. Saquib N, Flatt SW, Natarajan L, et al. Weight gain and recovery of pre-cancer weight after breast cancer treatments: Evidence from the women's healthy eating and living (WHEL) study. *Breast Cancer Res Treat*. 2007;105(2):177–186.
26. Wong ND, Levy D. Legacy of the Framingham Heart Study: Rationale, design, initial findings, and implications. *Global Heart*. 2013;8(1)3–9.
27. Martínez-Basurto AE, Lozano-Arrazola A, Rodríguez-Velázquez AL, et al. Impacto psicológico del cáncer de mama y la mastectomía. *Gac Mex Oncol*. 2014;13(1):53–58.
28. Vivar CG. Impacto psicosocial del cáncer de mama en la etapa de larga supervivencia: propuesta de un plan de cuidados integral para supervivientes. *Aten Primaria*. 2012;44(5):288–292.
29. Ekwueme DU, Trogdon JG. The Economics of Breast Cancer in Younger Women in the U.S.: The Present and Future. *American Journal of Preventive Medicine*. 2016;50(2):249–254.
30. Cohen BE, Edmondson D, Kronish IM. State of the art review: Depression, stress, anxiety, and cardiovascular disease. *American Journal of Hypertension*. 2015;28(11):1295–1302.
31. Mehta LS, Watson KE, Barac A, et al. Cardiovascular Disease and Breast Cancer: Where These Entities Intersect: A Scientific Statement From the American Heart Association. *Circulation.* 2018;137(8):e30–e66.
32. Buzdar AU, Suman VJ, Meric-Bernstam F, et al. Disease-Free and Overall Survival among Patients with Operable HER2-Positive Breast Cancer Treated with Sequential vs Concurrent Chemotherapy: The ACOSOG Z1041 (Alliance) Randomized Clinical Trial. *JAMA Oncol.* 2019;5(1):45–50.
33. Li T, Singal PK. Adriamycin-induced early changes in myocardial antioxidant enzymes and their modulation by probucol. *Circulation*. 2000;102(17):2105–2110.
34. Adderley SR, Fitzgerald DJ. Oxidative damage of cardiomyocytes is limited by extracellular regulated kinases 1/2-mediate induction of cyclooxygenase-2. *J Biol Chem*. 1999;274(8):5038–5046.
35. Yi LL, Kerrigan JE, Lin CP, et al. Topoisomerase IIβ-mediated DNA double-strand breaks: Implications in doxorubicin cardiotoxicity and prevention by dexrazoxane. *Cancer Res*. 2007;67(18):8839–8846.
36. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: A retrospective analysis of three trials. *Cancer*. 2003;97(11):2869–2879.
37. Van Nimwegen FA, Schaapveld M, Janus CPM, et al. Cardiovascular disease after hodgkin lymphoma treatment 40-year disease risk. *JAMA Intern Med*. 2015;175(6):1007–1017.
38. Guglin M, Aljayeh M, Saiyad S, et al. Introducing a new entity: Chemotherapy-induced arrhythmia. *Europace*. 2009;11(12):1579–1586.
39. Mazur M, Wang F, Hodge DO, et al. Burden of Cardiac Arrhythmias in Patients With Anthracycline-Related Cardiomyopathy. *JACC Clin Electrophysiol*. 2017;3(2):139–150.
40. Viani GA, Afonso SL, Stefano EJ, et al. Adjuvant trastuzumab in the treatment of her-2-positive early breast cancer: a meta-analysis of published randomized trials. *BMC Cancer*. 2007;7(1):153.
41. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of Chemotherapy plus a Monoclonal Antibody against HER2 for Metastatic Breast Cancer That Overexpresses HER2. *N Engl J Med*. 2001;344(11):738–792.
42. Kuramochi Y, Guo X, Sawyer DB. Neuregulin activates erbB2-dependent src/FAK signaling and cytoskeletal remodeling in isolated adult rat cardiac myocytes. *J Mol Cell Cardiol*. 2006;41(2):228–235.
43. ElZarrad MK, Mukhopadhyay P, Mohan N, et al. Trastuzumab alters the expression of genes essential for cardiac function and induces ultrastructural changes of cardiomyocytes in mice. *PLoS One*. 2013;8(11):1–14.
44. Yu AF, Flynn JR, Moskowitz CS, et al. Long-term Cardiopulmonary Consequences of Treatment-Induced Cardiotoxicity in Survivors of ERBB2-Positive Breast Cancer. *JAMA Cardiol*. 2020;5(3):309–317.
45. Telli ML, Witteles RM. Trastuzumab-related cardiac dysfunction. *JNCCN J Natl Compr Cancer Netw*. 2011;9(2):243–249.
46. Advani PP, Ballman K V, Dockter TJ, et al. Long-term cardiac safety analysis of NCCTG N9831 (Alliance) adjuvant trastuzumab trial. *J Clin Oncol*. 2016;34(6):581–587.
47. Cuomo JR, Sharma GK, Conger PD, et al. Novel concepts in radiation-induced cardiovascular disease. *World J Cardiol*. 2016;8(9):504–519.
48. Darby SC, McGale P, Taylor CW, et al. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: Prospective cohort study of about 300 000 women in US SEER cancer registries. *Lancet Oncol*. 2005;6(8):557–565.
49. Giordano SH, Kuo YF, Freeman JL, et al. Risk of cardiac death after adjuvant radiotherapy for breast cancer. *J Natl Cancer Inst*. 2005;97(6):419–424.
50. Haque W, Verma V, Haque A, et al. Trends in cardiac mortality in women with ductal carcinoma in situ. *Breast Cancer Res Treat*. 2017;161(2):345–351.
51. Jacob S, Pathak A, Franck D, et al. Early detection and prediction of cardiotoxicity after radiation therapy for breast cancer: The BACCARAT prospective cohort study. *Radiat Oncol*. 2016;11:54.
52. Boerma M. Experimental radiation-induced heart disease: Past, present, and future. *Radiat Res.* 2012;178(1):1–6.