Current Topics in Breast Cancer Survivorship

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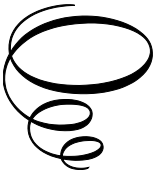
Edited by

Steven S. Coughlin

Cambridge Scholars Publishing



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This book first published 2024

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN (10): 1-5275-7532-2
ISBN (13): 978-1-5275-7532-5

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PREFACE

Current Topics in Breast Cancer Survivorship, which was written by outstanding contributors who are nationally and internationally recognized for their work, provides important information about the health and wellbeing of breast cancer survivors. The audience for the book includes graduate students, health professionals and researchers from many different disciplines such as epidemiology, behavioral science, medicine, oncology, nursing, and health disparities, as well as members of health advocacy organizations. This book will likely be of interest to health professionals and researchers from various disciplines (epidemiology, medicine, nursing, behavioral science, health disparities), and members of non-profit organizations, government agencies, and health advocacy organizations. The book is organized into six key sections. The first section provides information about comorbid conditions such as cardiovascular disease, diabetes, and obesity. The second section provides information about lifestyle factors such as physical activity, diet, nutrition, and social determinants of health. The third section provides information about health disparities by age and race/ethnicity. The fourth section provides information about symptoms, including fatigue, sleep disturbance, pain, depression, anxiety, and cognitive impairment. The fifth section provides information about health services topics, including survivorship care plans and financial toxicity. Finally, the sixth section provides a summary and conclusions.

PART I:

COMORBID CONDITIONS

CHAPTER 1

CARDIOVASCULAR DISEASE AND BREAST CANCER SURVIVORSHIP

STEVEN S. COUGHLIN, PHD
AND AVIRUP GUHA, MD, MPH

Abstract

Cardiovascular disease accounts for 16.3% of deaths in breast cancer patients, exceeding the mortality due to breast cancer in those with pre-existing cardiovascular risk factors. Cardiovascular deaths also exceed cancer mortality in postmenopausal women with hormone receptor positive breast cancer. Several recent studies have examined the risk of cardiovascular disease in breast cancer survivors. The increased risk of cardiovascular disease seen in breast cancer survivors in these cohort studies may be due to the adverse effects of anti-cancer therapy on the cardiovascular system or the results of shared risk factors between cancer and cardiovascular disease such as smoking, physical inactivity, obesity, diabetes, advancing age or inflammation. Racial disparities in cardiovascular disease mortality have also been identified in cohort studies. A broad range of cancer therapies have been shown to cause cardiotoxicity including chemotherapy agents such as anthracyclines, alkylating agents, and antimetabolites, and targeted therapies such as HER2 inhibitors, tyrosine kinase inhibitors, and angiogenesis inhibitors. Patients with pre-existing cardiovascular disease are more prone to cardiac complications from cancer therapies. Several treatment protocols have been developed that limit anthracycline cardiotoxicity, including the use of dexrazoxane and continuous infusion. In addition, several ongoing studies are evaluating the efficacy of prophylactic neurohormonal blockade with angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, or aldosterone antagonists. The detection of cardiotoxicity involves serial echocardiography and blood-based biomarkers such as cardiac troponin. Finally, focusing on optimizing

healthy lifestyle behaviors and reducing cardiac risk factors are important interventions in managing cancer-therapy induced cardiotoxicity.

Introduction

Breast cancer survivors are at increased risk of cardiovascular disease and death from cardiovascular disease (Guha, Fradley, Dent, Weintraub, et al. 2022; Blaes and Konety 2021; Sturgeon, Deng, Bluethmann, Zhou, et al. 2019; Bradshaw, Stevens, Khankari, Teitelbaum, et al. 2016). Although advancements in early detection and breast cancer therapy have resulted in over 90% of women surviving 5 years past their diagnosis of breast cancer, there has been an increase in cardiovascular disease in these women with increased survivorship from breast cancer (Gulati and Mulvagh 2018). Death is more likely to occur from cardiovascular disease than from breast cancer in women with early stage breast cancer (Patnik, Byers, DiGuiseppi, Dabelea et al. 2011). Cardiovascular deaths also exceed cancer mortality in postmenopausal women with hormone receptor positive breast cancer (Barish, Lynce, Unger, Barac 2019). Cardiovascular disease accounts for 16.3% of deaths in breast cancer patients, exceeding the mortality due to breast cancer in those with pre-existing cardiovascular risk factors (Abdel-Qadir, Austin, Lee, Amir 2017).

Cohort Studies of Cardiovascular Disease in Breast Cancer Survivors

Several recent studies have examined the risk of cardiovascular disease in breast cancer survivors (Bradshaw, Stevens, Khankari, Teitelbaum 2016; Patnaik, Byers, DiGuiseppi, Dabelea et al. 2011; Armenian, Xu, Ky, Su, et al. 2016; Koric, Chang, Mark, Rowe 2022; Ramin, Schaeffer, Zheng, Connor 2021). For example, Armenian et al. (Armenian, Xu, Ky, Su, et al. 2016) examined the risk of cardiovascular disease among adult cancer survivors compared to matched controls. Individuals with breast cancer had an increased risk of cardiovascular disease compared with age-matched controls (incident rate ratio = 1.13, $P < 0.01$). Bradshaw et al. (Bradshaw, Stevens, Khankari, Teitelbaum 2016) examined the risk of cardiovascular disease in breast cancer survivors and found an increase in cardiovascular disease comped with age-matched controls 8 years after breast cancer diagnosis. Patnaik et al. (Patnaik, Byers, DiGuiseppi, Dabelea et al. 2011) analyzed data from the Surveillance, Epidemiology, and End Results-Medicare dataset of women older than 66 years diagnosed with breast cancer and found that cardiovascular was the leading cause of death,

followed by breast cancer, after a median follow-up of 9.9 years. Koric et al. (Koric, Chang, Mark, Rowe 2022) studied breast cancer survivors who survived at least 10 years identified within the Utah Cancer registry and cancer free controls from the general population. Long-term breast cancer survivors had an increased risk of newly diagnosed cardiovascular disease from 10 to 15 years following cancer diagnosis compared with controls. No increased cardiovascular risks were identified after 15 years. Ramin et al. (Ramin, Schaeffer, Zheng, Connor 2021) examined all-cause and cardiovascular disease mortality in women with breast cancer and age-matched cancer free women in a prospective cohort. Breast cancer survivors had an overall higher risk of dying compared with the controls (HR = 1.79, 95% CI = 1.53 to 2.09) irrespective of time since diagnosis, tumor stage, estrogen receptor status, and older age at diagnosis. Survivors had an increase in cardiovascular disease-related deaths compared with controls beginning at 8 years after diagnosis (HR = 1.65, 95% CI = 1.0 to 2.73).

The increased risk of cardiovascular disease seen in breast cancer survivors in these cohort studies may be due to the adverse effects of anti-cancer therapy on elements of the cardiovascular system or the results of shared risk factors between cancer and cardiovascular disease such as smoking, physical inactivity, obesity, diabetes, advancing age or inflammation (Blaes, van Londen, Sandhu, Lerman, et al. 2018; Murphy, Kakkar, McCarthy, Januzzi 2020). Diabetes is a significant risk factor for cardiovascular disease, and its impact on breast cancer is also established (Gulati and Mulvagh 2018). There is strong evidence supporting inflammation as a mediator of both breast cancer and cardiovascular disease (Gulati and Mulvagh 2018). Clinical studies have found higher rates of hypertension, hypercholesterolemia, and ischemic cardiovascular disease in postmenopausal women receiving aromatase inhibitors (Blaes, van Londen, Sandhu, Lerman, et al. 2018; Haque, Shi, Schottinger, Chung 2016).

Racial Differences in Cardiovascular Disease and Breast Cancer Mortality in Breast Cancer Survivors

Racial disparities in cardiovascular disease mortality have been identified in cohort studies (Troeschel, Liu, Collin, Bradshaw, et al. 2019; Vo, Ramin, Lawrence, Barac, et al. 2023). Vo et al. (Vo, Ramin, Lawrence, Barac, et al. 2023) examined cardiovascular disease mortality among breast cancer survivors in the Surveillance, Epidemiology, and End Results database. SMRs were elevated for Black and Latina women treated with surgery only and chemotherapy with surgery (SMR range = 1.15 to 1.21). SMRs were

particularly high for women with advanced (regional or distant) stage disease among Black women for all treatment and for Asian American, Hawaiian, and other Pacific Islander and Latina women treated with chemotherapy with surgery (SMR range 1.28 to 3.61).

Cardioprotective Strategies to Prevent Breast Cancer Therapy-induced Cardiotoxicity

A broad range of cancer therapies have been shown to cause cardiotoxicity including chemotherapy agents such as anthracyclines, alkylating agents, and antimetabolites, targeted therapies such as HER2 inhibitors, tyrosine kinase inhibitors, and angiogenesis inhibitors (Chen, Kelly, Haw, Lombard, et al. 2021). Anthracyclines cause immediate damage to myocardial cells by free radical generation, although it may take months or years for this damage to become clinically apparent (Healey Bird and Swain 2008). Although physicians have known for over 40 years that anthracyclines cause acute and chronic cardiotoxicity, the cardiotoxic effects of radiation therapy, hormonal therapy, and chemotherapy with taxanes and trastuzumab treatment have been identified more recently (Healey Bird and Swain 2008). Adjuvant systemic therapies may result in late cardiac toxicity decades after completion of treatment (Schmitz, Prosnitz, Schwartz, Carver 2012). Exposure to potentially cardiotoxic therapies such as anthracyclines, trastuzumab, and radiation therapy, together with host factors, places patients at increased risk for cardiovascular disease compared with non-cancer controls (Padegimas, Clasen, Ky 2020). Patients with pre-existing cardiovascular disease are more prone to cardiac complications from cancer therapies. The incidence of cancer therapy-related cardiac dysfunction ranges from 9 to 26% after treatment with doxorubicin, 13-17% with trastuzumab, and 27-34% with combination therapies (Padegimas, Clasen, Ky 2020; Cardinale, Colombo, Bacchiani, Tedeschi, et al. 2015; Drafts, Twomley, D'Agostino, Lawrence et al. 2013; Seidman, Hudis, Pierri, Shak, et al. 2002). In a cohort study of 277 breast cancer patients treated with doxorubicin and/or trastuzumab, the median left ventricular ejection fraction declined to 43%, requiring treatment cessation or interruption in at least 33% of patients (Narayan, Finkelman, French, Plapper, et al. 2017). In order to reduce the risk of cardiovascular disease, there is a growing interest in the use of cardioprotective strategies at the time of cancer therapy initiation (Padegimas, Clasen, Ky 2020).

Anthracycline chemotherapy is hypothesized to cause cardiomyocyte injury through an increase in oxidative stress (Padegimas, Clasen, Ky 2020). The

quinone moiety of doxorubicin undergoes redox cycling resulting in reactive oxygen species, and anthracycline-iron complexes form which create toxic hydroxyl radicals that are cytotoxic to cardiomyocytes (Padegimas, Clasen, Ky 2020). Several treatment protocols have been developed that limit anthracycline cardiotoxicity, including the use of dexrazoxane and continuous infusion. Dexrazoxane is an iron chelator that reduces reactive oxygen species (Padegimas, Clasen, Ky 2020). Two meta-analyses showed heart failure risk reduction with the use of dexrazoxane (Smith, Cornelius, Plummer, Levitt, et al. 2010). Dexrazoxane prevents doxorubicin-iron complex formation, alleviates mitochondrial oxidative stress, and myocardial apoptosis (Chen, Kelly, Haw, Lombard, et al. 2021).

Anthracycline continuous infusion protocols, rather than bolus dosing, are also a potential cardioprotective strategy (Padegimas, Clasen, Ky 2020). A meta-analysis of four randomized controlled trials that compared bolus to infusion dosing of either epirubicin or doxorubicin showed a higher incidence of cardiotoxicity with bolus dosing (Smith, Cornelius, Plummer, Levitt, et al. 2010). The 2017 American Society of Clinical Oncology Clinical Practice Guidelines recommend consideration of the use of dexrazoxane, continuous infusion, and liposomal formulation for patients receiving high dose anthracycline treatment.

Several ongoing studies are evaluating the efficacy of prophylactic neurohormonal blockade with angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, or aldosterone antagonists. These medications, in addition to beta-blockers, have well-established roles in the treatment of heart failure with reduce left ventricular ejection fraction (Padegimas, Clasen, Ky 2020). The role of aldosterone antagonists has been studied in small trials in breast cancer patients undergoing anthracycline chemotherapy (Akpek, Ozdogru, Sahin, Inanc, et al. 2015). The role of neurohormonal blockade for prophylactic cardioprotection in breast cancer patients treated with anthracyclines remains an area of active investigation (Padegimas, Clasen, Ky 2020).

Beta-blockers have also been studied as a potential cardioprotectant in breast cancer patients treated with anthracyclines. Beta-blockers such as carvedilol have been shown to possess anti-oxidant properties, which may counteract the cardiotoxic reactive species generated by different breast cancer therapies (for example, anthracyclines, trastuzumab, and radiation therapy) (Armenian, Lacchetti, Barac, Carver, et al. 2017). Beta-blockers and ACE inhibitors may slow clinical progression to congestive heart failure by limiting ventricular remodeling (Healey Bird and Swain 2008).

Statins, which are widely used for their lipid-lowering effects, have also been proposed to have anti-inflammatory effects that may prevent chemotherapy-related cardiotoxicity (Padegimas, Clasen, Ky 2020).

Radiation therapy results in cardiotoxic effects, including valvular disease, coronary disease, heart failure, pericardial disease, and arrhythmias (Padegimas, Clasen, Ky 2020). Contemporary treatment strategies have become less cardiotoxic with advancements in cardiac-sparing techniques, and improved localization of treatment (Padegimas, Clasen, Ky 2020).

Early Detection of Heart Failure and Biomarkers

The gold standard for detection of cardiotoxicity involves serial echocardiography together with blood-based biomarkers such as cardiac troponin (Chen, Kelly, Haw, Lombard, et al. 2021; Barish, Lynce, Unger, Barac, et al. 2019). However, not all forms of toxicity are detectable with serial echocardiography and blood-based biomarkers (Chen, Kelly, Haw, Lombard, et al. 2021). Left ventricular ejection fraction is an important predictor of outcome and is widely used to monitor cardiac systolic function during and after chemotherapy (Chen, Kelly, Haw, Lombard, et al. 2021). The precise interval for long-term imaging following breast cancer treatment has not been determined (Gulati and Mulvagh 2018). Clinical practice suggests follow-up at 6 months and 1 year of cancer therapy completion, and then at least at 5-year intervals in asymptomatic patients who have received anthracycline therapies (Gulati and Mulvagh 2018).

There are currently two routinely used cardiac biomarkers: cardiac troponins and brain natriuretic peptide (BNP) (Chen, Kelly, Haw, Lombard, et al. 2021). Cardiac Troponins are cardiomyocyte-specific structural proteins released into the bloodstream when cardiomyocytes are damaged (Sharma, Jackson, Makan 2004). BNP is released in response to hemodynamic stress when ventricles dilate, undergo hypertrophy, or are subject to increased wall tension (Chen, Kelly, Haw, Lombard, et al. 2021). BNP is highly specific for heart failure (Chen, Kelly, Haw, Lombard, et al. 2021).

Summary and Conclusions

Breast cancer patients are at increased risk for the development of cardiovascular disease compared with non-cancer controls. Age, traditional cardiovascular risk factors, and treatment-related exposures contribute to this increased risk (Padegimas, Clasen, Ky 2020). In certain breast cancer

populations, cardiovascular death exceeds cancer death rates. Neurohormonal blockade and beta-blockers have a modest effect on preventing declines in cardiac function (Padegimas, Clasen, Ky 2020). Focusing on optimizing healthy lifestyle behaviors and reducing cardiac risk factors (hypertension, weight gain, smoking, and loss of cardiorespiratory fitness) are important interventions in managing cancer-therapy induced cardiotoxicity (Chen, Kelly, Haw, Lombard, et al. 2021).

References

Abdel-Qadir, Husam, Peter C. Austin, Douglas S. Lee, Eitan Amir, et al. 2017. "A Population-Based Study of Cardiovascular Mortality Following Early-Stage Breast Cancer". JAMA Cardiology, 2: 88-93.

Akpek, Mahmut, Ibrahim Ozdogru, Omer Sahin, Mevlude Inanc, et al. 2015. "Protective Effects of Spironolactone Against Anthracycline-Induced Cardiomyopathy". European Journal of Heart Failure,17: 81-9.

Armenian, Saro H., Christina Lacchetti, Ana Barac, Joseph Carver, et al. 2017. "Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancer: American Society of Clinical Oncology Clinical Practice Guideline. Journal of Clinical Oncology, 35: 893-911.

Armenian, Saro H., Lanfang Xu, Bonnie Ky, Canlan Sun, et al. 2016. "Cardiovascular Disease among Survivors of Adult-onset Cancer: A Community-Based Retrospective Cohort Study". Journal of Clinical Oncology, 34: 1122-30.

Barish, Rachel, Filipa Lynce, Keith Unger, Ana Barac. 2019. "Management of Cardiovascular Disease in Women with Breast Cancer." Circulation,139: 1110-20.

Blaes, Anne H., Suma H. Konety. 2021. "Cardiovascular Disease in Breast Cancer Survivors: An Important Topic in Breast Cancer Survivorship". Journal of the National Cancer Institute, 113: 105-6.

Blaes, Anne H., G. J. van Londen, Nicole Sandhu, Amir Lerman, et al. 2018. "Cardiovascular Risk in Breast Cancer Patients Receiving Estrogen or Progesterone Antagonists". Current Treatment Options in Cardiovascular Medicine, 20: 48.

Bradshaw, Patrick T., June Stevens, Nikhil Khankari, Susan L. Teitelbum, et al. 2016. “Cardiovascular Disease Mortality among Breast Cancer Survivors”. Epidemiology, 27: 6-13.

Cardinale, Daniela, Alessandro Colombo, Giulia Bacchiani, Ines Tedeschi, et al. 2015. “Early Detection of Anthracycline Cardiotoxicity and Improvement with Heart Failure Therapy”. Circulation, 131: 1981-8.

Chen, Dongqing, Conagh Kelly, Tatt Jhong Haw, Janine M. Lombard, et al. 2021. “Heart Failure in Breast Cancer Survivors: Focus on Early Detection and Novel Biomarkers”. Current Heart Failure Reports, 18: 362-77.

Drafts, Brandon C., Katie M. Twomley, Ralph D’Agostino Jr, Julia Lawrence, et al. 2013. “Low to Moderate Dose Anthracycline-Based Chemotherapy is Associated With Early Noninvasive Imaging Evidence of Subclinical Cardiovascular Disease.” JACC Cardiovascular Imaging, 6: 877-85.

Guha, Avirup, Michael G. Fradley, Susan F. Dent, Neal L. Weintraub, et al. 2022. “Incidence, Risk Factors, and Mortality of Atrial Fibrillation in Breast Cancer: A SEER-Medicare Analysis”. European Heart Journal, 43: 300-12.

Gulati, Martha, Sharon L. Mulvagh. 2018. “The Connection Between the Breast and Heart in a Woman: Breast Cancer and Cardiovascular Disease.” Clinical Cardiology, 41: 253-7.

Haque, Reina, Jiaxiao Shi, Joanne E. Schottinger, Joanie Chung, et al. 2016. “Cardiovascular Disease After Aromatase Inhibitor Use”. JAMA Oncology, 2: 1590-7.

Healey Bird, Brian R.J., Sandra M. Swain. 2008. “Cardiac Toxicity in Breast Cancer Survivors: Review of Potential Cardiac Problems”. Clinical Cancer Research, 14: 14-24.

Koric, Alzina, Chun-Pin Chang, Bayarmaa Mark, Kerry Rowe, et al. 2022. “Cardiovascular Disease Risk in Long-term Breast Cancer Survivors: A Population-Based Cohort Study”. Cancer, 128: 2826-35.

Murphy, Sean P., Rahul Kakkar, Cian P. McCarthy, James L. Januzzi Jr. 2020. “Inflammation in Heart Failure.” Journal of the American College of Cardiology, 75: 1324-40.

Narayan, Hari K., Brian Finkelman, Benjamin French, Theodore Plappert, et al. 2017. “Detailed Echocardiographic Phenotyping in Breast Cancer

Patients: Associations with Ejection Fraction Decline, Recovery, and Heart Failure Symptoms Over 3 Years of Follow-Up. Circulation, 135: 1397-412.

Padegimas, Allison, Suparna Clasen, Bonnie Ky. 2020. “Cardioprotective Strategies to Prevent Breast Cancer Therapy-Induced Cardiotoxicity”. Trends in Cardiovascular Medicine, 30: 22-8.

Patnaik, Jennifer L., Tim Byers, Carolyn DiGuiseppi, Dana Dabelea, et al. 2011. “Cardiovascular Disease Competes with Breast Cancer as the Leading Cause of Death for Older Females Diagnosed with Breast Cancer: A Retrospective Cohort Study”. Breast Cancer Research, 13: R64.

Ramin, Cody, Marcy L. Schaeffer, Zihe Zheng, Avonne E. Connor, et al. 2021. “All-Cause and Cardiovascular Disease Mortality among Breast Cancer Survivors in CLUE II, a Long-standing Community-Based Cohort. J Natl Cancer Inst 2021;113:djaa096.

Schmitz Kathyrn H., Robert G. Prosnitz, Anna L. Schwartz, Joseph R. Carver. 2012. “Prospective Surveillance and Management of Cardiac Toxicity and Health in Breast Cancer Survivors”. Cancer, 118 (8 suppl): 2270-6.

Seidman, Andrew, Clifford Hudis, Mary Kathryn Pierri, Steven Shak, et al. 2002. “Cardiac Dysfunction in the Trastuzumab Clinical Trials Experience”. Journal of Clinical Oncology, 20: 1215-21.

Sharma, S., P.G. Jackson, J. Makan. 2004. “Cardiac Troponins”. Journal of Clinical Pathology, 57: 1025-6.

Smith, Lesley A., Victoria R. Cornelius, Christopher J. Plummer, Gill Levitt, et al. 2010. “Cardiotoxicity of Anthracycline Agents for the Treatment of Cancer: Systematic Review and Meta-Analysis of Randomized Controlled Trials”. BMC Cancer, 10: 337.

Sturgeon, Kathleen M., Lei Deng, Shirley M. Bluethmann, Shouhao Zhou, et al. 2019. “A Population-based Study of Cardiovascular Disease Mortality Risk in US Cancer Patients”. European Heart Journal, 40: 3889-97.

Troeschel, Alyssa N., Yuan Liu, Lindsay J. Collin, Patrick T. Bradshaw, et al. 2019. “Race Differences in Cardiovascular Disease and Breast Cancer Mortality among US Women Diagnosed with Invasive Breast Cancer”. International Journal of Epidemiology, 48: 1897-1905.

Vo, Jacqueline B., Cody Ramin, Wayne R. Lawrence, Ana Barac, et al. 2023. “Racial and Ethnic Disparities in Treatment-Related Heart Disease Mortality among US Breast Cancer Survivors.” JNCI Cancer Spectrum, 7: pkad024.

CHAPTER 2

DIABETES MELLITUS, OBESITY, AND BREAST CANCER SURVIVORSHIP

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Abstract

Breast cancer is a multifactorial disease that affects 13% of women in the United States. Analyzing the complex interplay among breast cancer survivorship, diabetes mellitus, and obesity may change the way medical providers and researchers treat and study breast cancer. Diabetes mellitus and obesity are driven by several genetic and environmental factors that can mediate or attenuate the tumorigenesis of breast cancer. In this chapter, the relationships between breast cancer and these two comorbidities are explored, as well as how the progression of one disease affects the prognosis of another. The mainstay treatment options for diabetes mellitus that could play a role in the progression of breast cancer are also examined. By increasing awareness of the relationships between diabetes, obesity, and breast cancer, interdisciplinary medical teams can better adapt their treatment strategies.

Diabetes

Diabetes has been linked to several cancers including breast cancer and is also associated with obesity and cardiovascular disease. An estimated 11% to 33% of women with a history of breast cancer have comorbid diabetes (Storey, Cohee, Gathirua-Mwangi, Vachon, et al. 2019; Srokowski, Fang, Hortobagyi, Giordano. 2009; Coughlin, Ayyala, Majeed, Cortes, et al. 2020).

The symptoms experienced by women with diabetes overlap with those of women with breast cancer (for example, fatigue, decreased physical function, anxiety, and depression) and diabetes can worsen breast cancer symptoms (Storey, Cohee, Gathirua-Mwangi, Vachon, et al. 2019). The symptoms experienced by women with breast cancer and comorbid diabetes can impair quality of life (Tang, Wang, Zhang, Sun, et al. 2016). Breast cancer survivors who have diabetes experience more problems with their health and preoccupation with being ill than breast cancer survivors who lack a history of diabetes (Coughlin and Ayyaala 2021).

Storey et al. (Storey, Cohee, Gathirua-Mwangi, Vachon, et al. 2019) examined the impact of diabetes on the symptoms of women with breast cancer. The researchers analyzed data from 121 women with breast cancer who self-reported diabetes from 97 sites across the United States. Women with breast cancer and diabetes reported greater fatigue and more sleep disturbances than women with breast cancer without diabetes (Storey, Cohee, Gathirua-Mwangi, Vachon, et al. 2019). Other investigators have also reported greater fatigue among women with breast cancer and diabetes compared to those with breast cancer only (Tang, Wang, Zhang, Sun, et al. 2016; Coughlin and Ayyaala 2021). Diabetes has been associated with poorer sleep quality which may be due to glucose metabolism and suboptimal glycemic control (Reutrakul, Thakkinstian, Anothaisintawee, Chontong, et al. 2016). Alterations in blood glucose can result in hypoglycemia, polydipsia, and polyuria, which can result in sleep disturbances (Storey, Cohee, Gathirua-Mwangi, Vachon, et al. 2019). Sleep disturbances have also been widely reported in women with breast cancer (Otte, Carpenter, Russell, Bigatti, et al. 2010; Ancoli-Israel, Liu, Rissling, Natarajan, et al. 2014).

Diabetes has been associated with poorer breast cancer prognosis and mortality. Mu et al. (Mu, Zhu, Zhang, Xing, et al. 2017) performed a retrospective study among 462 breast cancer patients with type 2 diabetes and 1644 breast cancer patients without diabetes. The 5-year disease-free survival and overall survival rate were significantly lower in the diabetic patients when compared to the non-diabetic patients (Mu, Zhu, Zhang, Xing, et al. 2017). Even when accounting for tumor characteristics and age, the 5-year risks of breast cancer relapse and mortality were significantly higher in the diabetic group of patients when compared to the non-diabetic group (Mu, Zhu, Zhang, Xing, et al. 2017). Their results are further corroborated by a meta-analysis of eight research articles that found that pre-existing diabetes is associated with a 49% increase in all-cause mortality in women with breast cancer (Peairs, Barone, Synder, Yeh, et al. 2011).

However, there have been conflicting results about the association between diabetes and breast cancer-specific mortality. A prospective cohort study of 8,108 women with invasive breast cancer found that while pre-existing diabetes had an increased adjusted risk of overall mortality, it did not have an increased risk of breast cancer-specific mortality (Luo, Virnig, Hendryx, Wen, et al. 2014). Peairs et al. (Peairs, Barone, Synder, Yeh, et al. 2011) also found no increase in breast cancer-specific mortality associated with diabetes. On the other hand, type 2 diabetes was associated with a two-fold increase in breast cancer-specific mortality in a retrospective study (Lee, Torres, Troeshel, He, et al. 2020). Thus, while diabetes has been associated with overall worse outcomes in breast cancer patients, its relation to breast cancer-specific mortality is still being investigated.

Coughlin et al. (Coughlin and Ayyala 2021) found that 53.9% of African American breast cancer survivors had comorbid diabetes compared with 22.4% of white breast cancer survivors ($p < 0.001$). African American women are 2.14 times more likely to develop diabetes than white women (Carnethon, Pu, Howard, Albert, et al. 2017). The combined prevalence of diagnosed and undiagnosed type 2 diabetes mellitus is 21.8% in African Americans and 11.3% in non-Hispanic whites (Menke, Casagrande, Geiss, Cowie 2015). African Americans are twice as likely to die from diabetes than non-Hispanic whites (Rosenstock, Whitman, West, Balkin, et al. 2014). Compared to white women, African American breast cancer survivors are more likely to be obese and less likely to engage in physical activity (Coughlin, Yoo, Whitehead, Smith 2015), which likely increases their risk of cancer recurrence and comorbid conditions such as diabetes.

The strong association between diabetes and breast cancer highlights the need to investigate how diabetic treatments can affect breast cancer. Some studies show that certain drugs like metformin could mediate certain biochemical pathways in order to attenuate tumorigenesis (Cejuela, Martin-Castillo, Menendez, Pernas 2022). Metformin is an oral biguanide that increases insulin sensitivity and decreases hepatic production of glucose. It is the first-line treatment for polycystic ovarian syndrome, which is characterized by an insulin-resistant state which often presents in women of child-bearing age as irregular menstrual cycles, androgen excess, and infertility (LaMoia and Shulman 2021). Metformin activates adenosine monophosphate-activated protein kinase (AMPK) and inhibits mTOR signaling. The mTOR signaling pathway is overactive in many cancer types, including breast cancer. By downregulating mTOR, metformin could have anti-neoplastic effects by increasing apoptosis and promoting cell cycle arrest (Cejuela, Martin-Castillo, Menendez, Pernas 2022). Furthermore,

metformin has been shown to target aromatase-positive, CD68-positive M2-like macrophages that are found in breast tumor microenvironments. This effect of metformin is especially important due to the poor prognosis associated with CD68 positive macrophages in breast cancer (Goff and Danforth 2021).

Insulin is another first-line treatment for diabetes. However, unlike metformin, insulin has been associated with a worse prognosis for breast cancer. Insulin contributes to a pro-tumorigenic microenvironment by increasing inflammation, epithelial-to-mesenchymal transition, and angiogenesis (Yee, Mortimer, Natarajan, Dietze, et al. 2020). In addition, insulin activates the AKT signaling pathway, which has been associated with a worse prognosis in breast cancer patients (Yee, Mortimer, Natarajan, Dietze, et al. 2020). Diabetic breast cancer patients being treated with insulin had a 1.61 times higher risk of 5-year breast cancer relapse and a 1.68 times higher mortality compared to diabetic patients who were not treated with insulin (Mu, Zhu, Zhang, Xing, et al. 2017). Since insulin treatments are associated with a poorer breast cancer prognosis, the interdisciplinary medical team should consider modifications to diabetic treatment plans by using other supportive medications, such as metformin or statins (Tseng 2015).

Of note, it is imperative that patients diagnosed with breast cancer who also have a comorbid disorder are managed by an interdisciplinary team that takes a holistic approach to treatment and care. Furthermore, there are several social determinants of health that must be considered when evaluating breast cancer survivorship in conjunction with diabetes mellitus and obesity. Access to care and compliance with medications and therapeutic modalities are associated with better survivorship in breast cancer (Coughlin 2019).

Obesity

Obesity has been associated with diabetes mellitus, cardiovascular disease, and other chronic diseases and is also a major risk factor for the development of cancer and mortality related to cancer (Pati, Irfan, Jameel, Ahmed, et al. 2023). About 50% of breast cancer patients are overweight/obese at diagnosis (Demark-Wahnefried, Rimer, Winer 1997). In addition, breast cancer patients tend to gain weight during and after treatment (Vance, Mourtzakis, McCargar, Hanning, et al. 2011). Obesity is an independent risk factor for postmenopausal breast cancer (particularly for estrogen receptor-positive/progesterone receptor-positive breast cancer,

as well as a prognostic factor for breast cancer (Chan and Norat 2015). A systematic review and meta-analysis of 82 observational studies and randomized controlled trials found that higher body mass index (BMI) before or after cancer diagnosis was associated with higher all-cause mortality in breast cancer survivors (Chan, Vieira, Aune, Bandera, et al. 2014). Compared with normal weight patients, women who were obese before breast cancer diagnosis experienced a 41% increased risk of all-cause mortality (95% CI 29 to 53%). Another meta-analysis of 13 studies involving women with triple negative breast cancer showed that women who were overweight had shorter disease-free survival (HR = 1.26, 95% CI 1.09 to 1.46 and overall survival (HR = 1.29, 95% CI 1.11 to 1.51) compared with women who were normal weight (Harborg, Zachariae, Olsen, Johannsen, et al. 2021). Obesity is inversely related to pre-menopausal breast cancer (World Cancer Research Fund/American Institute for Cancer Research 2007). Studies indicate that obesity, measured by BMI, is associated with adverse breast cancer outcomes, including increased risk of recurrence, mortality, and second primary cancers, and increased risk of developing lymphedema, diabetes, and cardiovascular disease (Chan and Norat 2015). Abdominal obesity has a negative impact on breast cancer survival highlighting the need for using waist circumference and waist-to-hip ratio as well as BMI to evaluate prognosis in the clinical setting (Chan and Norat 2015). In addition, the efficacy of cancer treatments is significantly lower in obese breast cancer patients, resulting in greater challenges in patient care and disease management in this patient population (Lee, Kruper, Dieli-Conwright, Mortimer 2019).

Several hormonal and metabolic pathways have been proposed to explain the adverse effect of obesity on breast cancer risk and prognosis in postmenopausal women (Rose, Komninou, Stephenson 2004). Postmenopausal obese women have elevated estrogen levels because of an in increased aromatization of androgens to estrogens in peripheral adipose tissues (Chan and Norat 2015). The increased level of estrogen promotes cell proliferation and has been implicated in hormone sensitive breast cancer development and progression (Cleary and Grossmann 2009). Obesity, particularly abdominal obesity, is associated with an increased level of circulating insulin that is mitogenic, anti-apoptotic, and pro-angiogenic, leading to worse breast cancer prognosis (Goodwin, Ennis, Pritchard, Trudeau, et al. 2002). Several adipokines produced by adipose tissue are related to hyperinsulinemia and angiogenesis promotion, which contributes to the aggressive behavior of breast cancer (Rose, Komninou, Stephenson 2004). Finally, obesity is associated with chronic, low-grade inflammation (Chan and Norat 2015). Large amounts of pro-inflammatory cytokines such as

tumor necrosis factor-alpha and interleukin-6 produced in adipose tissue have been associated with tumor progression (Van Kruijsdijk, van der Wall, Visseren 2009).

Because obesity increases the risk of breast cancer and worsens prognosis, weight loss interventions post-diagnosis may be worth pursuing. Rock et al. (Rock, Pande, Flatt, Ying, et al. 2013) studied overweight and obese women who attended group sessions that encouraged the implementation of health-promoting behaviors. Participants who lost ≥5% of their body weight throughout the course of the study experienced beneficial changes in several biomarkers associated with disease progression, including leptin, insulin, and sex-hormone binding protein, compared to participants who did not lose ≥5% of their body weight, regardless of menopause status.

In order to properly evaluate the relationship between weight loss and breast cancer prognosis, it is important to identify the cause of the weight loss. Shang et al. (Shang, Hattori, Fleming, Jaskowiak, et al. 2021) found that among 2,888 women diagnosed with nonmetastatic breast cancer, participants who experienced BMI losses of at least 0.5 kg/m^2/year had poorer all-cause mortality, breast-cancer specific mortality, and disease-free survival compared to participants who maintained a stable BMI. The proposed reasons for the unfavorable outcomes include the side effects of chemotherapies, a progression of comorbid conditions, and advanced stage disease (Shang, Hattori, Fleming, Jaskowiak, et al. 2021). Thus, the effect of weight loss on breast cancer prognosis is dependent on the nature of the weight loss. Intentional weight loss due to healthy lifestyle modifications is beneficial while unintentional weight loss can be detrimental as it signals deteriorating health.

Lifestyle changes that include diet, exercise, and behavior therapy are the cornerstone of interventions for obesity in cancer patients (Pati, Irfan, Jameel, Ahmed, et al. 2023). Although each of these interventions on their own may lead to weight loss, employing all three as a combined approach seems to lead to the greatest changes in anthropometric outcomes, as well as improved mental health status and health-related quality of life (Lake, Damery, Jolly 2022). In addition to healthy lifestyle modifications, potential therapies for obesity in breast cancer patients include drug therapy and weight reduction surgery (Pati, Irfan, Jameel, Ahmed, et al. 2023).

References

Ancoli-Israel, Sonia, Liangi Liu, Michelle Rissling, Loki Natarajan, et al. 2014. “Sleep, Fatigue, Depression, and Circadian Activity Rhythms in Women with Breast Cancer Before and After Treatment: A 1-Year Longitudinal Study”. Supportive Care in Cancer, 22: 2535-45.

Carnethon, Mercedes R., Jia Pu, George Howard, Michelle A. Albert, et al. 2017. “Cardiovascular Health in African Americans: A Scientific Statement from the American Heart Association”. Circulation, 136: e393-423.

Cejuela, Monica, Begona Martin-Castillo, Javier A. Menendez, Sonia Pernas. 2022. “Metformin and Breast Cancer: Where Are We Now?” International Journal of Molecular Sciences, 23: 2705.

Chan, D.S.M., A.R. Vieira, D. Aune, E.V. Bandera, et al. 2014. “Body Mass Index and Survival in Women with Breast Cancer—Systematic Literature Review and Meta-Analysis of 82 Follow-Up Studies”. Annals of Oncology, 25: 1901-14.

Chan, Doris S.M., Teresa Norat. 2015. “Obesity and Breast Cancer: Not Only A Risk Factor of the Disease”. Current Treatment Options in Oncology, 16: 22.

Cleary, Margot P., Michael E. Grossmann. 2009. “Obesity and Breast Cancer: The Estrogen Connection”. Endocrinology, 150: 2537-42.

Coughlin, Steven S. 2019. “Social Determinants of Breast Cancer Risk, Stage, and Survival”. Breast Cancer Research and Treatment, 177: 537-548.

Coughlin, Steven S., Deepak Ayyala. 2021. “Symptoms Associated With Comorbid Diabetes among Breast Cancer Survivors”. Breast Cancer Research and Treatment, 189: 781-6.

Coughlin, Steven S., Deepak Ayyala, Ban Majeed, Letisia Cortes, et al. 2020. “Cardiovascular Disease among Breast Cancer Survivors”. Cardiovascular Disease Medicine, 2: 10.31487.

Coughlin, Steven S., Wonsuk Yoo, Mary S. Whitehead, Selina A. Smith. 2015. “Advancing Breast Cancer Survivorship among African American Women”. Breast Cancer Research and Treatment, 153: 253-61.

Demark-Wahnefried, Wendy, Barbara K. Rimer, Eric P. Winer. 1997. "Weight Gain in Women Diagnosed With Breast Cancer". Journal of the American Dietetic Association, 97: 519-26.

Goff, Stephanie L., David N. Danforth. 2021. "The Role of Immune Cells in Breast Tissue and Immunotherapy for the Treatment of Breast Cancer". Clinical Breast Cancer, 21: e63-e73.

Goodwin, Pamela J., Marguerite Ennis, Kathleen I. Pritchard, Maureen E. Trudeau, et al. 2002. "Fasting Insulin and Outcome in Early-Stage Breast Cancer: Results of a Prospective Cohort Study". Journal of Clinical Oncology, 20: 42-51.

Harborg, Sixten, Robert Zachariae, Julia Olsen, Maja Johannsen, et al. 2021. "Overweight and Prognosis in Triple-Negative Breast Cancer Patients: A Systematic Review and Meta-Analysis". NPJ Breast Cancer, 7: 119.

Lake, Blossom, Sarah Damery, Kate Jolly. 2022. "Effectiveness of Weight Loss Interventions in Breast Cancer Survivors: A Systematic Review of Reviews. BMJ Open, 12: e062288.

LaMoia, Traci E., Gerald I. Shulman. 2021. "Cellular and Molecular Mechanisms of Metformin Action". Endocrine Reviews, 42: 77-96.

Lee, Kyung N., Mylin A. Torres, Alyssa N. Troeschel, Jiabei He, et al. 2020. "Type 2 Diabetes, Breast Cancer-Specific and Overall Mortality: Associations by Metformin Use and Modification by Race, Body Mass, and Estrogen Receptor Status". PLoS ONE, 15: e0232581.

Lee, Kyuwan, Laura Kruper, Christin M. Dieli-Conwright, Joanne E. Mortimer. 2019. "The Impact of Obesity on Breast Cancer Diagnosis and Treatment". Current Oncology Reports, 21: 41.

Luo, Juhua, Beth Virnig, Michael Hendryx, Sijin Wen, et al. 2014. "Diabetes, Diabetes Treatment and Breast Cancer Prognosis". Breast Cancer Research and Treatment, 148: 153–62.

Menke, Andy, Sarah Casagrande, Linda Geiss, Catherine C. Cowie. 2015. "Prevalence of and Trends in Diabetes among Adults in the United States, 1988-2012". JAMA, 314: 1021-9.

Mu, Lan, Nannan Zhu, Jiao Zhang, Fang Xing, et al. 2017. “Type 2 Diabetes, Insulin Treatment and Prognosis of Breast Cancer”. Diabetes/Metabolism Research Reviews, 33: 10.1002/dmrr.2823.

Otte, Julie L., Janet S. Carpenter, Kathleen M. Russell, Silvia Bigatti, et al. 2010. “Prevalence, Severity, and Correlates of Sleep-Wake Disturbances in Long-Term Breast Cancer Survivors”. Journal of Pain and Symptom Management, 39: 535-47.

Pati, Sukanya, Wadeed Irfan, Ahmad Jameel, Shahid Ahmed, et al. 2023. “Obesity and Cancer: A Current Overview of Epidemiology, Pathogenesis, Outcomes, and Management”. Cancers, 15: 485.

Peairs, Kimberly S., Bethany B. Barone, Claire F. Snyder, Hsin-Chieh Yeh, et al. 2011. “Diabetes Mellitus and Breast Cancer Outcomes: A Systematic Review and Meta-Analysis. Journal of Clinical Oncology, 29: 40–6.

Reutrakul, Sirimon, Ammarin Thakkinstian, Thunyarat Anothaisintawee, Sasipas Chontong, et al. 2016. “Sleep Characteristics in Type 1 Diabetes and Associations With Glycemic Control: Systematic Review and Meta-Analysis”. Sleep Medicine, 23: 26-45.

Rock, Cheryl L., Chetna Pande, Shirley W. Flatt, Carl Ying, et al. 2013. “Favorable Changes in Serum Estrogens and Other Biologic Factors After Weight Loss in Breast Cancer Survivors Who Are Overweight or Obese. Clinical Breast Cancer, 13: 188-95.

Rose, D.P., D. Komninou, G.D. Stephenson. 2004. “Obesity, Adipocytokines, and Insulin Resistance in Breast Cancer”. Obesity Reviews, 5: 153-65.

Rosenstock, Summer, Steve Whitman, Joseph F. West, Michael Balkin, et al. 2014. “Racial Disparities in Diabetes Mortality in the 50 Most Populous US Cities”. Journal of Urban Health, 91: 873-85.

Shang, Lihua, Masaya Hattori, Gini Fleming, Nora Jaskowiak, et al. 2021. “Impact of Post-Diagnosis Weight Change on Survival Outcomes in Black and White Breast Cancer Patients”. Breast Cancer Research, 23: 18.

Srokowski, Tomasz P., Shenying Fang, Gabriel N. Hortobagyi, Sharon H. Giordano, et al. 2009. “Impact of Diabetes Mellitus on Complications and Outcomes of Adjuvant Chemotherapy in Older Patients with Breast Cancer”. Journal of Clinical Oncology, 27: 2170-6.