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Editorial

EDITORIAL

Cardiovascular Disease in Breast Cancer Survivors: An Important Topic in Breast Cancer Survivorship

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With advancements in detection, targeted therapy, and supportive care, there are a growing number of breast cancer survivors—more than 3.8 million. Although more individuals are cured from cancer or living longer with cancer, evidence has been emerging that cancer survivors are at an increased risk for cardiovascular disease and death from cardiovascular disease (1,2). For women with early-stage breast cancer, death is more likely to occur from cardiovascular disease than from breast cancer (3). In this issue of the Journal, Ramin and colleagues (4) describe a cohort of 628 women with breast cancer and 3140 age-matched cancer-free women, aged 45-84 years at the time of enrollment into the CLUE II community-based prospective cohort. After 25 years of follow-up, they demonstrated that breast cancer survivors had an increase in cardiovascular-related deaths compared with cancer-free women beginning 8 years after diagnosis (hazard ratio [HR] = 1.65, 95% confidence interval [CI] = 1.00 to 2.73; n = 20) with the highest risk being in older survivors (HR = 2.24, 95% CI = 1.29 to 3.88; n = 18) and in women with estrogen receptor (ER)-positive breast cancer (HR = 1.85, 95% CI = 1.06 to 3.20; n = 16). For the cohort as a whole, cardiovascular disease (ischemic heart disease) remained the second leading cause of death in breast cancer survivors.

Several recent studies have examined the risk of cardiovascular disease in breast cancer survivors. Armenian and colleagues (5) examined the risk of cardiovascular disease in a cohort of 36 232 adult survivors compared with matched (age, sex, and residential zip code) noncancer controls (n = 73 545). Within this cohort, individuals with breast cancer had an elevated risk of cardiovascular disease as compared with age-matched controls (incident rate ratio = 1.13; $P < .01$). The Long Island Breast Cancer cohort examined the risk of cardiovascular events in breast cancer survivors and demonstrated an increase in cardiovascular disease that surpassed that of age-matched controls 8 years after breast cancer diagnosis (2). In this cohort, unique identifying factors such as chemotherapy use increased cardiovascular disease–related mortality. Use of radiation or endocrine therapy did not appear to demonstrate any difference in cardiovascular risk. In looking at the Surveillance, Epidemiology, and End Results–Medicare data of women older than 66 years diagnosed with breast cancer between 1992 and 2000, cardiovascular disease was the leading cause of death (15.9%) followed closely by breast cancer (15.1%) after a median follow-up of 9.9 years (3). Age and comorbidities at the time of diagnosis had the largest impact on noncancer-related mortality. Tumor characteristics (stage, grade, estrogen receptor status) affected breast cancer–specific mortality. In comparing these studies with the CLUE cohort that was made up primarily of Caucasian women with early-stage breast cancer (mean age = 64 years, 59% stage 1 disease, 73.7% ER-positive), it appears that older women in particular with ER-positive disease have a competing mortality risk from not only breast cancer but also cardiovascular disease.

The excess cardiovascular disease risk seen in breast cancer survivors among the CLUE cohort participants and other related studies is potentially a consequence of the adverse effects of anticancer therapy on components of the cardiovascular system or as a result of shared risk factors between cancer and cardiovascular disease (6). These risk factors include tobacco use, obesity, diabetes, hypertension, hyperlipidemia, advancing age, clonal hematopoiesis, and more recently, inflammation (7,8). It has not been clear within the abovementioned cohort studies whether the elevated risk of cardiovascular disease is related to treatment specifically, comorbidities, shared risk factors, or a common underlying inflammatory pathway. The authors in the CLUE cohort tried to control for this by matching by comorbidities and many shared risk factors such as body mass index (mean = 26.1 kg/m^2) and age. The study by Ramin and colleagues (4) is also unable to account for breast cancer treatments such as anthracyclines and trastuzumab used, which have been known to increase cardiovascular risk. Although difficult to control in large cohort studies, impairment in physical activity, sedentary lifestyle, and development of metabolic syndrome following breast cancer therapy could explain the development of cardiovascular disease and mortality. The cardiovascular disease risk was increased in the women with hormone-positive breast cancer. It is possible this risk is related

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to antiestrogen therapy such as aromatase inhibitors. Large clinical studies have reported higher rates of hypertension, hypercholesterolemia, and ischemic cardiovascular disease in postmenopausal breast cancer survivors receiving aromatase inhibitors (9,10). Other studies have demonstrated that breast cancer survivors develop endothelial dysfunction while on aromatase inhibitors (11); it is not clear if this improves when the antiestrogen therapy is discontinued. Currently, premenopausal breast cancer survivors with hormone sensitive stage I-III breast cancer are recommended to receive 5-10 years of adjuvant endocrine therapy entailing either tamoxifen alone, tamoxifen with ovarian function suppression (OFS), or an aromatase inhibitor (AI) with OFS. Although adjuvant therapy with OFS plus AI maximally reduces disease recurrence and breast cancer-related mortality, the large SOFT and TEXT adjuvant premenopausal endocrine therapy trials assessing this endocrine therapy did not demonstrate an overall survival benefit from use of OFS and AI over OFS and tamoxifen, perhaps in part because of the cardiovascular toxicities of OFS and AI (12). Further work is needed to understand the cardiovascular impact of antiestrogen therapies in premenopausal women, particularly ovarian suppression with the use of aromatase inhibitors.

With the rising number of breast cancer survivors, particularly of aging breast cancer survivors, and individuals living for longer periods of time after a diagnosis (80% survival at 15 years), discussions surrounding chronic disease prevention, particularly cardiovascular disease, with aggressive risk factor modification remain vital, because cardiovascular disease is often the leading cause of mortality, not the breast cancer itself. Further research on the impact of ovarian suppression and the use of aromatase inhibitors will help inform adjuvant endocrine therapy decisions aimed at optimizing the long-term health of premenopausal breast cancer survivors. Future studies evaluating prognostic value and cost effectiveness of cardiac risk stratification and perhaps also preemptive treatment of asymptomatic coronary atherosclerosis in postmenopausal breast cancer patients are necessary given that these studies would have the appeal of improving overall survival in breast cancer survivors.

Notes

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