

EDITORIAL COMMENT

# Exercise and Cardiovascular Outcomes in Older Women With Breast Cancer



## The Heart of the Matter\*

Lindsay L. Peterson, MD, MSCR,<sup>a</sup> Jennifer A. Ligibel, MD<sup>b</sup>

Every year, more than 100,000 women over the age of 65 years are diagnosed with breast cancer, making this the fastest-growing group of breast cancer patients (1). Breast cancer in older women differs in a number of ways from cancers in younger women. Histologically, older women are more likely to develop cancers that are hormone receptor positive, HER2/neu negative, and of lower tumor grade than younger women (2). Breast cancer is also often diagnosed at a later stage in older women, with tumors being more likely to be larger in size and more likely to involve lymph nodes, possibly related to less frequent screening (2). This may contribute to the worse breast cancer outcomes seen in older women, because the risk of breast cancer mortality increases with increasing age (3).

Recurrence and mortality outcomes in older women vary significantly by stage, histological characteristics, and the presence of pre-existing comorbidities, with non-breast cancer deaths accounting for an increasingly larger proportion of overall mortality with increasing age and number of comorbidities. For example, a Surveillance, Epidemiology, and End Results (SEER) Program Medicare analysis of 63,566 women over the age of 66 years diagnosed with breast cancer between 1992 and 2000 found that cardiovascular disease was the primary cause of mortality in study participants, accounting for 15.9%

of all deaths (95% confidence interval [CI]: 15.6% to 16.2%) (4). Breast cancer was the second most common cause of mortality, accounting for 15.1% of deaths (95% CI: 14.8% to 15.4%). Cardiovascular disease was the most common cause of mortality for all patients with stage I breast cancer, whereas women with higher stage and grade cancers, as well as women with hormone receptor-negative tumors, were more likely to die of breast cancer. With increasing age, women of all stages were more likely to die of causes other than breast cancer. Age and the presence of comorbidities were associated with higher risk of both breast cancer-related and all-cause mortality, underscoring the potential importance of treatment tolerance and functional status on outcomes in older women with breast cancer.

Cardiorespiratory fitness (CRF) is an important moderator of functional status in older adults (5); declines in CRF have been associated with an increase in coronary heart disease and cardiovascular events (6). CRF has also been shown to be a prognostic factor in breast cancer, with individuals with higher CRF being at lower risk of breast cancer-related mortality (7,8). CRF declines with age at about 5% per decade, with a more rapid decline in women over the age of 60 (9). Additionally, studies have shown that breast cancer patients have lower CRF than healthy women and that CRF declines further in cancer patients after adjuvant therapy (10).

Several studies have demonstrated that exercise interventions can help to prevent decreases in CRF during breast cancer treatment and can lead to improvements in CRF in post-treatment breast cancer survivors, although data in older women are limited (11-14). Higher levels of physical activity have also been linked to a lower risk of developing and dying of breast cancer, with a recent review of 16 studies of breast cancer survivors demonstrating that women

\*Editorials published in *JACC: CardioOncology* reflect the views of the authors and do not necessarily represent the views of *JACC: CardioOncology* or the American College of Cardiology.

From the <sup>a</sup>Washington University School of Medicine, Department of Medicine, St. Louis, Missouri, USA; and the <sup>b</sup>Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA. Dr. Peterson is supported by the American Cancer Society. Dr. Ligibel is supported by the Susan G. Komen Foundation under grant support; and receives in kind product donations from Fitbit and Nestle Health Sciences to support the BWEL study.

who engaged in the highest levels of physical activity after diagnosis had a lower risk of breast cancer mortality (hazard ratio [HR]: 0.72; 95% CI: 0.60 to 0.85) compared with inactive women (15,16).

In addition to the strong association between physical activity and breast cancer outcomes, a recent study demonstrated that recreational physical activity patterns after breast cancer diagnosis are also related to lower risk of cardiovascular events in breast cancer patients (17). In this analysis of 2,973 breast cancer survivors (mean age of 57 years), individuals who engaged in >9 metabolic equivalent (MET)-h/week of recreational physical activity had a 23% lower risk of cardiovascular events (95% CI: 0.67 to 0.88;  $p = 0.002$ ) compared with less active individuals. In women over the age of 70, this benefit was even more pronounced, with an approximately 36% lower risk of cardiovascular events for those engaging in >9 MET-h/week compared with less (17).

SEE PAGE 41

In this issue of *JACC: CardioOncology*, Okwuosa et al. (18) provide additional evidence that higher levels of physical activity before diagnosis are associated with lower risk of cardiovascular events in women with breast cancer. The study evaluated the relationship between physical activity patterns before breast cancer diagnosis and cardiovascular outcomes (including heart failure, myocardial infarction, angina, coronary revascularization, peripheral and coronary artery disease, transient ischemic attack, stroke and cardiovascular death). Notably, almost two-thirds of the study population were over the age of 65 at the time of breast cancer diagnosis, and 40% were over age 70. The authors found that individuals in the top quartile of pre-diagnosis physical activity levels (reporting a median activity level of 18 MET-h/week of recreational physical activity) had a significantly lower risk of cardiovascular events (HR: 0.63; 95% CI: 0.45 to 0.88;  $p$  for trend = 0.016) and coronary heart disease death (HR: 0.41; 95% CI: 0.21 to 0.78;  $p$  for trend = 0.006) than inactive individuals. Additionally, individuals meeting current physical activity recommendations (9 MET-h/week) before a diagnosis of breast cancer had a 46% lower risk of coronary heart

disease death (95% CI: 0.35 to 0.89) compared with those not meeting recommendations (<9 MET-h/week).

This study thus continues to demonstrate an important role of exercise in supporting favorable outcomes in older women with breast cancer. However, studies show that only one-third of breast cancer patients meet guideline recommendations of 150 min of moderate or vigorous physical activity per week, and very few engage in 18 MET-h of exercise per week (19). In the general population, older females are the least likely demographic to meet the recommended amounts of physical activity (20). Although many studies have demonstrated that it is feasible to increase physical activity in breast cancer patients during and after cancer treatment, many of these studies have focused on supervised exercise programs, which makes it difficult to scale this work to clinical populations. Additionally, few trials have focused on older breast cancer patients, who may have additional barriers to the implementation of exercise programs. Thus, work is needed to develop scalable interventions to increase physical activity in large groups of individuals, especially in older breast cancer survivors.

In conclusion, this study adds to the growing body of observational data that physical activity and exercise may impact morbidity and mortality in cancer patients. As more and more patients survive their breast cancer, cardiovascular disease is and will continue to become a major risk of morbidity and mortality for survivors. Finding strategies to help patients engage in recommended amounts of physical activity before and after a breast cancer diagnosis will be critical to improving outcomes in women with early breast cancer, in particular in the rising number of older adults with breast cancer.

**ADDRESS FOR CORRESPONDENCE:** Dr. Jennifer A. Ligibel, Director, Leonard P. Zakim Center for Integrative Therapies and Healthy Living, Associate Professor of Medicine, Harvard Medical School, Dana Farber Cancer Institute, 450 Brookline Avenue, Boston, Massachusetts 02215, USA. E-mail: [Jennifer.Ligibel@dfci.harvard.edu](mailto:Jennifer.Ligibel@dfci.harvard.edu). Twitter: [@DanaFarber](https://twitter.com/DanaFarber).

## REFERENCES

- Howlander N, Noone AM, Krapcho M, et al., editors. SEER Cancer Statistics Review, 1975-2016 April 2019. National Cancer Institute, April 2019, [https://seer.cancer.gov/csr/1975\\_2016/](https://seer.cancer.gov/csr/1975_2016/). Accessed August 2019.
- Wildiers H, Kunkler I, Biganzoli L, et al. Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. *Lancet Oncol* 2007;8:1101-15.
- VanderWalde A, Hurria A. Early breast cancer in the older woman. *Clin Geriatr Med* 2012;28:73-91.
- Patnaik JL, Byers T, DiGiuseppi C, Dabelea D, Denberg TD. 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 Res* 2011;13:R64.
- Bouchard D, McGuire K, Davidson L, Ross R. Cardiorespiratory fitness, obesity, and functional limitation in older adults. *J Aging Phys Act* 2011; 19:336-46.

6. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA* 2009;301:2024-35.
7. Schmid D, Leitzmann MF. Cardiorespiratory fitness as predictor of cancer mortality: a systematic review and meta-analysis. *Ann Oncol* 2015;26:272-8.
8. Peel JB, Sui X, Adams SA, Hebert JR, Hardin JW, Blair SN. A prospective study of cardiorespiratory fitness and breast cancer mortality. *Med Sci Sports Exerc* 2009;41:742-8.
9. Fleg JL, Morrell CH, Bos AG, et al. Accelerated longitudinal decline of aerobic capacity in healthy older adults. *Circulation* 2005;112:674-82.
10. Peel AB, Thomas SM, Dittus K, Jones LW, Lakoski SG. Cardiorespiratory fitness in breast cancer patients: a call for normative values. *J Am Heart Assoc* 2014;3:e000432.
11. Haykowsky MJ, Scott JM, Hudson K, Denduluri N. Lifestyle interventions to improve cardiorespiratory fitness and reduce breast cancer recurrence. *Am Soc Clin Oncol Educ Book* 2017;37:57-64.
12. Dias Reis A, Silva Garcia JB, Rodrigues Diniz R, et al. Effect of exercise training and detraining in autonomic modulation and cardiorespiratory fitness in breast cancer survivors. *J Sports Med Phys Fitness* 2017;57:1062-8.
13. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis [published correction appears in *J Cancer Surviv* 2011;5:112]. *J Cancer Surviv* 2010;4:87-100.
14. Pekmezi DW, Demark-Wahnefried W. Updated evidence in support of diet and exercise interventions in cancer survivors. *Acta Oncol* 2011;50:167-78.
15. Schmid D, Leitzmann MF. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. *Ann Oncol* 2014;25:1293-311.
16. Kraschnewski JL, Schmitz KH. Exercise in the prevention and treatment of breast cancer: what clinicians need to tell their patients. *Curr Sports Med Rep* 2017;16:263-7.
17. Jones LW, Habel LA, Weltzien E, et al. Exercise and risk of cardiovascular events in women with nonmetastatic breast cancer. *J Clin Oncol* 2016;34:2743-9.
18. Okwuosa TM, Ray RM, Palomo A, et al. Pre-diagnosis exercise and cardiovascular events in primary breast cancer: women's health initiative. *J Am Coll Cardiol CardioOnc* 2019;1:41-50.
19. Mason C, Alfano CM, Smith AW, et al. Long-term physical activity trends in breast cancer survivors. *Cancer Epidemiol Biomarkers Prev* 2013;22:1153-61.
20. Centers for Disease Control and Prevention. Participation in leisure-time aerobic and muscle-strengthening activities that meet the federal 2008 Physical Activity Guidelines for Americans among adults aged 18 and over, by selected characteristics: United States, selected years 1998-2016. In: Health, United States, 2017. Hyattsville, MD: National Center for Health Statistics, 2018.

---

**KEY WORDS** breast cancer, cardiovascular disease, exercise, geriatric oncology