The Association between Cardiorespiratory Fitness and the Risk of Breast Cancer in Women

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ABSTRACT

KATSAROLI, I., L. SIDOSSIS, C. KATSAGONI, X. SUI, C. CADENAS-SANCHEZ, J. MYERS, C. FASELIS, R. MURPHY, I. B. H. SAMUEL, and P. KOKKINOS. The Association between Cardiorespiratory Fitness and the Risk of Breast Cancer in Women. *Med. Sci. Sports Exerc.*, Vol. 56, No. 6, pp. 1134–1139, 2024. **Introduction:** Studies have shown an inverse association between the risk of breast cancer in women and physical activity. However, information on the association between cardiorespiratory fitness (CRF) assessed objectively by a standardized test and the risk of developing breast cancer is limited. **Purpose:** To examine the CRF-breast cancer risk association in healthy females. **Methods:** This retrospective study was derived from the Exercise Testing and Health Outcomes Study cohort (n = 750,302). Female participants (n = 44,463; mean age ± SD; 55.1 ± 8.9 yr) who completed an exercise treadmill test evaluation (Bruce protocol) at the Veterans Affairs Medical Centers nationwide from 1999 to 2020 were studied. The cohort was stratified into four age-specific CRF categories (Least-fit, Low-fit, Moderate-fit, and Fit), based on the peak METs achieved during the exercise treadmill test. **Results:** During 438,613 person-years of observation, 994 women developed breast cancer. After controlling for covariates, the risk of breast cancer was inversely related to exercise capacity. For each 1-MET increase in CRF, the risk of cancer was 7% lower (HR, 0.93; 95% CI, 0.90–0.95; P < 0.001). When risk was assessed across CRF categories with the Least-fit group as the referent, the risk was 18% lower for Low-fit women (HR, 0.82; 95% CI, 0.70–0.96; P = 0.013), 31% for Moderate-fit (HR, 0.69; 95% CI, 0.58–0.82; P < 0.001), and 40% for Fit (HR, 0.60; 95% CI, 0.47–0.75; P < 0.001). **Conclusions:** We observed an inverse and graded association between CRF and breast cancer risk in women. Thus, encouraging women to improve CRF may help attenuate the risk of developing breast cancer. **Key Words:** EXERCISE TREADMILL TEST, FEMALE, BREAST MALIGNANCY, PHYSICAL ACTIVITY

The burden of breast cancer incidence and mortality has significantly increased, with an estimated 2.3 million new cases in 2020 according to the GLOBOCAN data (1). Notably in 2023, breast cancer is estimated to be the most frequently diagnosed malignancy among women in the United States, accounting for 31% of total female cancer cases and the second cause of female cancer mortality, representing the 15% of cancer-related deaths in women (2). Although breast cancer etiology is multifactorial and not fully understood, cumulative data strongly suggest that modifiable and potentially preventable factors, such as excess body weight, sedentary behavior, diet, and alcohol consumption, may increase breast cancer risk and mortality (3–7). Thus, following the 2019 World Cancer Research Fund/American Institute for Cancer Research and American Cancer Society recommendations, maintaining a healthy weight, following a balanced diet including whole grains, vegetables, fruit, and grains, limiting consumption of red meat, sugar, processed foods and alcohol, reducing sitting time, and engaging in regular physical activity are important to prevent breast cancer and decrease risk and mortality (3,4,6–9).

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Evidence suggests that being physically active offers protection against pre- and postmenopausal breast cancer (6,9). Although the mechanisms are not completely understood, it has been speculated that physical activity attenuates at least some of the harmful metabolic and inflammatory effects of excess adiposity, such as insulin resistance, altered adipocytokines, and oxidative stress (10,11), which in turn are related to cancer incidence (10). In addition, physical activity may influence breast cancer risk beyond adiposity modulation, particularly among premenopausal women (9), by reducing circulating estrogen concentrations and increasing sex hormone-binding globulin, which further decreases bioavailability of endogenous sex hormones (12–14).

Cardiorespiratory fitness (CRF) assessed objectively by a standardized exercise treadmill test (ETT) and expressed in METs (1 MET = 3.5 mL·kg^{-1} of body weight per minute) has been generally accepted as a surrogate for habitual physical activity, and high levels of CRF are inversely associated with morbidity and mortality (15). A plethora of evidence confirms that low levels of CRF are related to a high risk of cardiovascular disease (CVD), all-cause mortality, and mortality due to various cancers (15–19). Low CRF is also associated with poor prognosis in breast cancer (20,21). However, there is a lack of studies examining the role of objectively measured CRF on breast cancer prevention (22,23).

Physical activity and CRF are partly distinct components of health, because they describe different parameters (24,25) and the correlation between them is modest (26). Hence, the discrimination between these terms is significant in clinical practice. Physical activity is a behavior, often assessed by self-reported physical activity with relatively low reliability and validity (23,26). CRF is an attribute, reflecting habitual physical activity, genetic influence, and disease status, and depicts a prognostic marker that is measurable, objective, and reproducible (20,27).

Despite evidence that physical activity is associated inversely with the risk of developing breast cancer in females, the association between breast cancer and CRF assessed objectively by a standardized ETT in a large population study has not been examined. There is a paucity of existing data relating CRF and all types of cancer incidence exclusively in women, and to our knowledge, only one has directly studied how CRF interrelates with female overall cancer risk, reporting an inverse association (28). Thus, the main objective of this study is to evaluate the association between CRF and the risk of developing breast cancer in women.

METHODS

Study design and participants. The study included 44,463 female participants with a mean age (SD) of 55.1 (±8.9) yr. Of those, 58.2% were self-identified White, 33.4% self-identified Black, 4.9% self-identified Hispanic, and 3.6% self-identified Indian.

The sample was derived from a larger cohort (*n* = 750,302) in the Exercise Testing and Health Outcomes Study, based at the Veterans Affairs (VA) Medical Center in Washington, DC. All participants completed a symptom-limited ETT evaluation within the US Veterans hospitals across the United States between 1999 and 2020 using the Bruce protocol. All were free from breast cancer and overt heart disease at the time of the ETT. The study was approved by the institutional review board at the VA, Washington, DC (protocol # 0069), and written informed consent was obtained from all the participants.

Procedures. Detailed information on relevant demographic, clinical and medication information, risk factors, and comorbidities as defined by *International Classification of Disease-9* and *International Classification of Disease-10* coding, with at least two recordings at least 6 months apart, were obtained for all participants from the VA Computerized Patient Record System. The VA records have high sensitivity for documenting incidence of chronic conditions (20,21). Data and analyses are presented in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies (29).

Historical information included previous myocardial infarctions, cardiac procedures, congestive heart failure (CHF), hypertension (blood pressure ≥140/90 mm Hg), diabetes mellitus type 2 (DM2), hypercholesterolemia, cancer (all), renal disease, stroke, smoking status (current and past), aspirin, and use of antihypertensive or cardiac medications. Exercise capacity (peak METs) for each participant was calculated by standardized American College of Sports Medicine equations based on treadmill speed and grade (17).

MET extraction. We randomly selected 3000 samples of physician clinical notes on exercise capacity from the dataset and identified METs manually. This annotated dataset was used to train the Natural Language Processing models. In the preprocessing phase, we removed special characters ($, &, etc.) and restricted the note to 30 characters before and after the words METs or MET. These words (METs or MET) were then replaced with a special character to identify their location within the clinical notes. Spacy software was then used to convert the resulting string into word tokens and then to a vector of numbers. The labels created were such that 1 corresponded to a token that contained a MET value and 0 to a token not containing (missing) a MET value. A two-layer convolutional neural network using the TensorFlow software library was used to predict the probable location of METs in the note. The model was trained over 100 epochs. Once METs were extracted, the MET data were randomly and manually checked for errors. The model accuracy on the test dataset was 97% (30).

CRF categories. Age-specific CRF categories were established based on methods described in our previous work (31). Briefly, we first stratified the cohort into five age categories (30–49, 50–59, 60–69, 70–79, and 80–95 yr). Then, we identified those with a MET level that corresponded to the 25th, 50th, and 75th percentiles within their respective age category and stratified the cohort accordingly. We combined the respective quintiles to form four age-specific CRF quartiles for the entire cohort, defined as Least-fit, Low-fit, Moderate-fit, and Fit.

TABLE 1. Baseline characteristics according to CRF categories.

Characteristics	All (*n* = 44,463)	CRF Categories Least-Fit (*n* = 10,141)	Low-Fit (*n* = 13,798)	Moderate-Fit (*n* = 13,652)	Fit (*n* = 6872)	*P*
Age (yr)	55.1 ± 8.9	56.2 ± 8.6	54.8 ± 9.0	55.6 ± 8.4	53.6 ± 8.4	<0.001
Body weight (kg)	79.5 ± 16.8	84.6 ± 18.7	81.6 ± 16.8	77.5 ± 15.1	71.6 ± 13.0	<0.001
BMI ($kg \cdot m^{-2}$)	29.1 ± 5.5	30.8 ± 6.3	29.8 ± 5.5	28.4 ± 4.9	26.6 ± 4.3	<0.001
Race						<0.001
Self-identified White	25,871 (58.2)	6026 (59.4)	7848 (56.9)	7851 (57.5)	4146 (60.3)	
Self-identified Black	14,846 (33.4)	3416 (33.7)	4808 (34.8)	4594 (33.7)	2028 (29.5)	
Self-identified Hispanic	2167 (4.9)	377 (3.7)	666 (4.8)	701 (5.1)	423 (6.2)	
Self-identified Indian	1579 (3.6)	322 (3.2)	476 (3.4)	506 (3.7)	275 (4.0)	
Smoking (%)	9622 (21.6)	2789 (27.5)	3046 (22.1)	2728 (20.0)	1.059 (15.4)	<0.001
CVD[a] (%)	6918 (15.6)	2296 (22.6)	2078 (15.1)	1797 (13.2)	747 (10.9)	<0.001
Diabetes[b] (%)	6258 (14.1)	2257 (22.3)	2125 (15.4)	1489 (10.9)	387 (5.6)	<0.001
Hypertension[c] (%)	19,485 (43.8)	5699 (56.2)	6340 (45.9)	5488 (40.2)	1958 (28.5)	<0.001
Dyslipidemia[d] (%)	16,298 (36.7)	4509 (44.5)	5193 (37.6)	4773 (35.0)	1823 (26.5)	<0.001
Breast cancer (%)	994 (2.2)	309 (3.0)	312 (2.3)	267 (2.0)	106 (1.5)	<0.001

Data are shown as means ± SD unless specified otherwise.
[a]CVD was defined as history of physician-diagnosed myocardial infarction, CABG, CHF, stroke, and PVD.
[b]Diabetes was defined as glucose ≥126 $mg \cdot dL^{-1}$ or history of physician-diagnosed diabetes.
[c]Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or history of physician-diagnosed hypertension.
[d]Dyslipidemia was defined as total cholesterol ≥200 $mg \cdot dL^{-1}$ or LDL-C ≥130 $mg \cdot dL^{-1}$ or HDL-C <40 $mg \cdot dL^{-1}$ or a combination.

Primary outcome. The primary outcome was the diagnosis of breast cancer. The VA Computerized Patient Record System was used to capture breast cancer outcomes. Previous reports have demonstrated that the VA death records are relatively complete compared with those from other sources, such as the Social Security Administration (32,33). The VA records also have excellent agreement (k = 0.82–0.91) with state death records and high sensitivity for the incidence of several chronic conditions (32). We assessed breast cancer cases only, and vital status was determined as of September 3, 2021.

Statistical analysis. Follow-up time is presented as median with interquartile range. We calculated the incidence rate as the ratio of events to person-years of follow-up. Continuous variables are presented as means and SDs and categorical variables as relative frequencies. We tested baseline associations between categorical variables with χ^2 or Z tests. We performed one-way ANOVA to evaluate mean differences of normally distributed variables between individuals who died and those who did not. We tested the assumption of equality of variances between groups by Levene's test, and the assumption of normality with probability–probability plots.

We calculated HRs for breast cancer incidence across the CRF categories (quartiles) for the entire cohort. The least-fit category was used as the reference group. All analyses were adjusted for age, body mass index (BMI), ethnic origin, history of CVD including myocardial infarction, coronary artery bypass graft surgery (CABG), CHF, stroke (all), and peripheral vascular disease (PVD). We also adjusted CVD risk factors (hypertension, DM2, dyslipidemia, and smoking) and current use of cardiac/antihypertensive medications (β-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers, diuretics), insulin, metformin, sulfonylureas, statins, and aspirin in the models.

We tested the assumption of proportionality for all Cox proportional hazards analyses graphically by plotting the logarithm of cumulative hazards with respect to each covariate separately. The proportionality assumption was fulfilled for each model. All hypotheses were two sided, and P < 0.05 was deemed statistically significant. We performed all statistical analyses with SPSS (version 26.0).

RESULTS

Demographics and clinical characteristics of the cohort across CRF categories are presented in Table 1. In general, the prevalence of comorbidities (CVD, hypertension, DM2, dyslipidemia) across the CRF categories was progressively lower with higher CRF. Women in the fit category were also younger than the other CRF categories by approximately 1.0 to 2.5 yr.

During the 438,613 person-years of observation, 994 women developed breast cancer with an average annual event rate of 2.3 per 1000 person-years. An inverse and independent association was observed between CRF and breast cancer. Each 1-MET increase in CRF was associated with a 7% lower risk of developing breast cancer (Table 2). When cancer risk was assessed across CRF categories, the association was inverse and graded. Compared with the Least-fit women, breast cancer risk for Low-fit, Moderate-fit, and Fit women was 18%, 31%, and 40% lower, respectively (P < 0.001) (Table 2 and Fig. 1). The analysis was additionally adjusted for both BMI and commodities (CVD, dyslipidemia, hypertension, and

TABLE 2. Breast cancer risk by CRF categories in 44,463 women.

	HR	95% Confidence Interval Lower	Upper	*P*
CRF				
Least-fit (referent)	1.0			
Low-fit	0.82	0.70	0.96	0.013
Moderate-fit	0.69	0.58	0.82	<0.001
Fit	0.60	0.47	0.75	<0.001
1 MET	0.93	0.90	0.95	<0.001
Overall *P* < 0.001				

Adjusted for age, BMI, CVD including MI, CABG, CHF, stroke, and PVD, smoking, dyslipidemia, hypertension, and diabetes.

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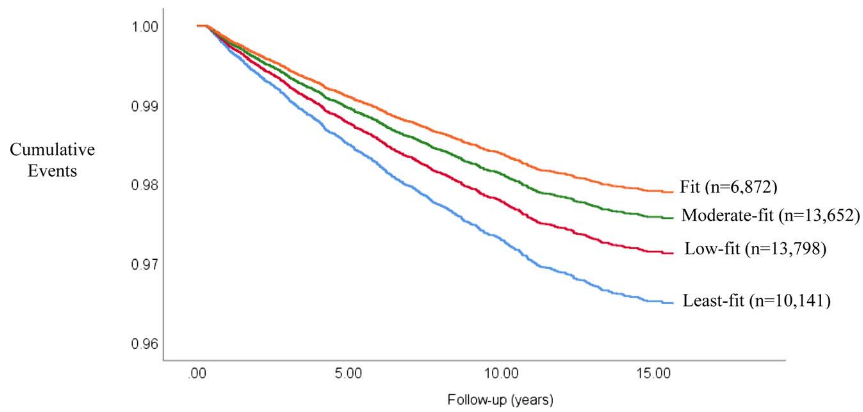

FIGURE 1—Cumulative events for breast cancer in women according to CRF categories.

diabetes), and the results were similar. When the analysis was stratified by self-identified race, the results were similar.

DISCUSSION

The main finding of the current study was that CRF was inversely and independently associated with the risk of developing breast cancer. Breast cancer risk was 7% lower for each 1-MET increase in CRF. When the risk was assessed across CRF categories, compared with the Least-fit category, women in the Low-fit category had an 18% lower risk of breast cancer and declined progressively to 40% for women in the highest fitness category. As far as we know, the current study is the largest to examine the relationship between CRF assessed objectively by a standardized ETT and the risk of developing breast cancer risk in women. There is relatively sparse data on CRF and female cancer. To the best of our knowledge, only one study has examined how CRF impacts on cancer risk solely in women, because most of the cancer studies have focused mainly on men or both sexes (19,22,28,34–37). Accordingly, reports from the UK Biobank cohort study reported that higher fitness levels were related to lower lung, digestive, and breast cancer risk for both males and females (38), whereas the Henry Ford Exercise Testing Cohort demonstrated that women with high fitness were not found to be at a lower risk of colorectal cancer compared with women with low fitness, when the analysis was stratified by sex (39).

The only study to date that has directly examined the association of cancer risk and CRF in women has demonstrated that higher CRF was related to lower cancer risk (28). More specifically, in the Veterans Exercise Testing Study, 184 female veterans underwent maximal sign- or symptom-limited exercise tests using an individualized ramp treadmill protocol adjusted to achieve a targeted duration between 8 and 12 min. During a mean of 12.0 ± 6.9 yr of follow-up, 11.4% of women were diagnosed with cancer and 3.2% died from cancer. The Veterans Exercise Testing Study demonstrated that achieving a relatively modest CRF level could lead to a substantial decrease in both cancer incidence and mortality; for every eight women who would move from low to moderate CRF, one case of cancer could be potentially prevented. Moreover, for every 1-MET increase in CRF, there was a 20% decrease in the risk of cancer incidence and a 26% decrease in the risk of cancer mortality. Therefore, our study not only confirms the inverse association between CRF and breast cancer risk but also provides novel insights by demonstrating a progressive reduction in breast cancer risk across different CRF categories. Moreover, the current results are the largest to examine the relationship between CRF objectively assessed by a standardized ETT and the risk of developing breast cancer and contribute to the limited existing data that predominantly focuses on men or both sexes. By adding to the growing body of evidence in this area, our findings further support the importance of CRF assessment as a potential risk stratification tool and highlight the potential benefits of enhancing CRF through moderate-intensity physical activity for breast cancer prevention in women.

Although the mechanisms underlying the association between CRF and reduced breast cancer risk are not well understood, several hypotheses can be suggested: (i) physical activity has been shown to decrease circulating levels of estrogen (12–14), a hormone that plays a critical role in breast cancer development and progression; (ii) physical activity may enhance insulin sensitivity and reduce insulin-like growth factors, which have been implicated in breast cancer pathogenesis (40); (iii) physical activity has been regarded as an effective approach to mitigate the adverse side effects of breast cancer treatment by improving muscular strength, lean mass, and aerobic capacity (41); (iv) regular physical activity has immunomodulatory effects and stimulates short-term increases in immunoglobulins, neutrophils, natural killer cells, cytotoxic T cells, and immature B cells, which, over time, enhance immunity (42,43); and (v) regular physical activity has been associated with favorable changes in adiposity, reducing overall body fat and decreasing the production of adipokines and inflammatory markers that may promote tumorigenesis (44). Taken together, it appears that regular physical activity and higher CRF levels have been associated with improvements in various physiological factors, including hormonal profiles, immune function, and metabolic regulation, which may contribute to the observed risk reduction.

Even though the evidence for an inverse correlation between physical activity and breast cancer is well established

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(3,4,9,45), there is no consensus regarding the optimal type, intensity, and volume of physical activity needed for establishing an "anticancer" exercise regimen. There is also a lack of understanding how these different exercise features interrelate with an individual's characteristics (46). In clinical practice, evaluating an individual's level of physical activity to determine the ideal exercise dose is as important as defining the dose of a drug, and self-reported physical activity, although practical, low cost, and a useful tool for population studies, provides only a snapshot of the person's health-related behaviors (27). On the contrary, CRF reflects the intergraded function of multiple body systems and overall health status. Hence, CRF assessment might be a more representative marker to personalize exercise prescription, especially among individuals at high risk. CRF is an objective and reproducible measure of health that, according to the American Heart Association, can be used as an index as strong a risk marker as other established risk factors such as smoking, hypercholesterolemia, hypertension, family history of coronary heart disease, BMI, and elevated serum glucose (27). Nevertheless, CRF is not routinely assessed in clinical practice, despite the fact that CRF assessment in health care settings is feasible through direct measures as well as with nonexercise algorithms that are applicable in routine practice (27,47).

However, considering our finding that the risk of breast cancer was 7% lower for each 1-MET increase and that structured exercise programs of moderate intensity can increase CRF in 12 to 14 wk (16), we can conservatively assume that the American College of Sport Medicine recommendation of engaging in moderate-intensity physical activities ≥150 min·wk^{-1} should be adequate to improve CRF and lower the risk of developing breast cancer in women. Thus, health care professionals should advocate that women engage in moderate-intensity physical activity to improve and maintain adequate CRF (16,20).

The present study has several strengths, including the large sample size, consisting exclusively of female participants, and long-term monitoring of outcomes. CRF was objectively assessed using a widely accepted technique that has been shown to strongly predict the incidence and mortality of many chronic diseases, including cancer (23,28,48,49).

There are also limitations, including the lack of self-reported physical activity data and other established cancer risk factors, such as dietary habits, menopausal status, or family history of cancer. The lack of information regarding the incidence of major subtypes of breast cancer (ER+/, PR+/−, HER2+/−, or triple negative breast cancer) in our sample is also another limitation to consider. Furthermore, given that there is a different breast cancer risk burden according to weight status and/or fat mass, comorbidities such as insulin resistance and/or diabetes and self-identified race/ethnicity, a close examination of how CRF interrelates with all the above parameters, could potentially contribute to form personalized exercise prescription for those women at higher risk, and there lies another limitation. Finally, the retrospective nature of the study does not demonstrate causation. Accordingly, we cannot discern whether increased cancer risk was the outcome of poor CRF or subclinical disease that underlies low CRF (reverse causality).

CONCLUSIONS

Our findings support an inverse and graded association between CRF and breast cancer risk in women independent of other established risk factors. Given the lifetime probability of a woman developing breast cancer is approximately 12% (23), and a risk reduction of 7% for each 1-MET increase in CRF supported by our findings, advocating such an improvement in CRF for women, especially among those with relatively poor CRF, is an important public health message. Besides, CRF improvement is feasible by the standard recommendation of engaging in moderate-intensity physical activities of ≥150 min·wk^{-1}. Even though CRF assessment is easy in clinical practice and could provide health care professionals a deeper understanding of how different health parameters interrelate to optimize individualized exercise prescription, the objective for an anticancer regimen should be focused on incorporating a behavioral change to a more physically active lifestyle. Therefore, promoting regular physical activity as part of a holistic lifestyle approach integrating weight control, a well-balanced nutrition, smoking cessation, and moderate alcohol consumption, among others, should become part of the routine health care counseling in women for primary breast cancer prevention.

Conflicts of interest: The authors declare that there is no conflict of interest. The authors declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

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