

Original article

Cardiorespiratory fitness and cancer in women: A prospective pilot study

Baruch Vainshelboim^{a,b,*}, Ricardo M. Lima^{b,c}, Jonathan Myers^b

^a Master of Cancer Care Program, School of Health Sciences, Saint Francis University, Loretto, PA 15940, USA

^b Cardiology Division, Veterans Affairs Palo Alto Health Care System/Stanford University, Palo Alto, CA 94304, USA

^c Faculty of Physical Education, University of Brasilia, Brasilia 70910-900, Brazil

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Abstract

Purpose: To assess the association between cardiorespiratory fitness (CRF) and the incidence and mortality from cancer in women, and to evaluate the potential public health implications for cancer prevention.

Methods: Maximal exercise testing was performed in a pilot cohort of 184 women (59.3 ± 15.2 years) who were followed for 12.0 ± 6.9 years. Cox hazard models adjusted for established cancer risk factors and accounting for competing events were analyzed for all-type cancer incidence and mortality from cancer. Population-attributable risks and exposure impact number were determined for low CRF (<5 metabolic equivalents (METs)) as a risk factor.

Results: During the follow-up, 11.4% of the participants were diagnosed with cancer and 3.2% died from cancer. CRF was inversely and independently associated with cancer outcomes. For every 1-metabolic equivalent increase in CRF, there was a 20% decrease in the risk of cancer incidence (hazard ratio (HR) = 0.80, 95% confidence interval (CI): 0.69–0.92; $p = 0.001$) and a 26% reduction in risk of cancer mortality (HR = 0.74, 95%CI: 0.61–0.90; $p = 0.002$). The population-attributable risks of low CRF were 11.6% and 14% for incidence and mortality of cancer, respectively, and the respective exposure impact numbers were 8 and 20.

Conclusion: Greater CRF was independently associated with a lower risk of incidence and mortality from cancer in women. Screening for low CRF as a cancer risk factor and referring unfit individuals to a supervised exercise program could be a public health strategy for cancer prevention in middle-age women.

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Keywords: Exercise capacity; Exercise testing; Fitness; Public health

1. Introduction

Cancer is one of the leading causes of death in men and women worldwide, with an estimate of >18 million new diagnosed cases and 9.6 million cancer-related deaths occurring in 2018.¹ Data from the United States show that approximately 800,000 women developed cancer and about 200,000 died from cancer in 2018. The American Cancer Society estimates that the lifetime probability for developing any type of cancer is 1 in 3 women, and 1 of 5 will die from cancer.² Cancer incidence is projected to increase by approximately 70% worldwide and 45% in the United States over the next 2 decades,^{3,4} having a substantial economic burden and the largest lost years of life and productivity compared with other causes of death.^{2,5}

Although developing cancer has multifactorial reasons, up to two-thirds of the cancer burden is attributed to lifestyle factors. These include cigarette smoking, poor diet, obesity, and physical inactivity, which are modifiable and potentially preventable.^{6–8} Although the preventive role of physical activity has been well-established both for incidence and mortality of cancer,^{9,10} the role of cardiorespiratory fitness (CRF), in part an objective physiological surrogate of physical activity,^{11,12} is less characterized in cancer, particularly among women.^{12,13} Mounting evidence established that low CRF is an important risk factor for the incidence of many chronic conditions and all-cause, cardiovascular, and cancer mortality.^{12–14} Most of the evidence to date supporting the preventive role of higher CRF in cancer derives from studies in men,^{14–23} and the few existing data among women are limited and inconsistent.^{15,16,24,25} For example, 2 reports observed a decreased cancer mortality risk in women with high CRF compared with those with low CRF,^{24,25} although 2 other studies did not find this association

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* Corresponding author.

E-mail address: baruch.v1981@gmail.com (B. Vainshelboim).

to be significant.^{15,16} In addition, the role of moderate CRF levels and the association between CRF and cancer incidence, among women, to our knowledge have not been explored and warrant further investigation. Given that moderate CRF is achievable for most individuals, there is a high probability for practical implications and a large public health impact. Therefore, in the current pilot analysis, we aimed to assess the association between CRF, all-type cancer incidence, and mortality from cancer in women. We also evaluated the potential public health implications of CRF for cancer prevention. We hypothesized that higher CRF levels would be associated with lower risk of all-type cancer incidence and mortality from cancer among women, and both moderate and high CRF levels would be associated with favorable cancer outcomes.

2. Materials and methods

2.1. Participants

The present study used the Veterans Exercise Testing Study (VETS), which has been previously described.^{26,27} In brief, the VETS is an ongoing, prospective evaluation of veterans (aged 21–89 years) who have been referred for exercise testing for clinical reasons. The VETS is designed to address exercise test, clinical, and lifestyle factors and their association with health outcomes. All participants who underwent a maximal treadmill exercise test at the Veterans Affairs Palo Alto Health Care System between 1987 and 2012 were considered for inclusion in the present study. The study was approved by Institutional Review Board at Stanford University, and written informed consent was obtained from all the participants. Clinical information on diagnoses, risk factors, and health behaviors (smoking, alcohol, and drug abuse) was collected at the time of the exercise test using the Veterans Affairs Computerized Patient Record System and self-report health history. Of 204 women who completed the baseline evaluation, 20 were excluded from the present study for the following reasons: history of malignancy ($n = 5$), an incomplete or prematurely terminated exercise test ($n = 8$), and lost to follow-up ($n = 7$). A total of 184 female veterans, who were followed for a mean of 12.0 ± 6.9 years, were included in the present study.

2.2. Measures

Participants underwent maximal sign- or symptom-limited exercise tests using an individualized ramp treadmill protocol according to established guidelines.^{11,28} The exercise protocol included continuous, individualized increments in treadmill speed and grade adjusted to achieve a targeted duration between 8 and 12 min as previously recommended. A 12-lead electrocardiogram, heart rate, blood pressure, and Borg 6–20 perceived exertion rating were continuously recorded throughout the tests, and standard criteria for test termination were used.^{11,28} CRF (in metabolic equivalents (METs)) was calculated from the peak treadmill speed and grade using established metabolic equations from the American College of Sports Medicine.²⁸ CRF was analyzed as a continuous as well as a categorical variable divided into 3 categories (low CRF: <5 METs; moderate CRF: $5–10$ METs; and high CRF: >10 METs).^{12,17}

The Veterans Affairs Computerized Patient Record System was used for capturing cancer outcomes; all-type cancer diagnosis and cancer-related mortality were the primary outcomes. Previous reports have demonstrated that the Veterans Affairs death records are relatively complete compared with those from other sources, such as the Social Security Administration.²⁹ The Veterans Affairs records also have excellent agreement ($\kappa = 0.82–0.91$) with state death records³⁰ and high sensitivity for the incidence of several chronic conditions.^{31–33} Medical records were reviewed carefully by qualified medical personnel who were otherwise blinded to treadmill test results and other study information. Cancer diagnosis was verified using pathology reports and the *International Classification of Diseases* 9th and 10th edition codes. Cancer diagnosis and vital status for each patient were ascertained as of August 2015.

2.3. Statistical analysis

SPSS (Version 23.0; IBM, Armonk, NY, USA) was used for statistical analyses. The significance level was set at $p < 0.05$. Demographic, clinical, and physiological data for the participants are presented as mean \pm SD. Categorical variables are presented in percentages. Continuous and categorical multivariable Cox proportional hazard models were used to assess the association between CRF, cancer incidence, and cancer mortality. The models were adjusted for established cancer risk factors, including age, smoking status (never smokers, previous smokers, and current smokers), history of alcohol and drug abuse, body mass index, and physical activity status (active or inactive).^{6–8} The hazard models also took into account competing events (death resulting from causes other than cancer).³⁴ Comparisons between participants who were diagnosed with cancer and those who were free from cancer were performed using independent samples t tests for continuous variables and χ^2 tests for categorical variables. One-way analysis of variance was performed to compare participants' ages across CRF categories. Population-attributable risk (PAR%) for low CRF as a risk factor was analyzed. PAR% is a metric quantifying the contribution of a risk factor to the burden of disease or death and represents the proportional decrease in population disease or mortality burden that would occur if exposure to a risk factor was eliminated (e.g., no tobacco use). PAR% was calculated as³⁵

$$\text{PAR}\% = \frac{P(\text{Relative risk (RR)} - 1)}{1 + P(\text{RR} - 1)} \times 100\% \quad \text{Eq. (1)}$$

where P is the prevalence of the risk factor and RR is a fully adjusted relative risk calculated from the Cox hazard model.^{36,37} Kaplan-Meier curves using the log-rank test were constructed for CRF categories, with cancer mortality as the outcome. The proportional hazards assumption was evaluated graphically for CRF categories and was confirmed using the scaled Schoenfeld residuals.

The exposure impact number (EIN) was calculated as

$$\text{EIN} = \frac{1}{(\text{RR} - 1) \times P_{\text{NE}}} + \frac{\text{RR}}{(\text{RR} - 1) \times (1 - P_{\text{NE}})} \quad \text{Eq. (2)}$$

where RR is the fully adjusted relative risk from Cox hazard models accounting for competing events and P_{NE} is the event

rate in the nonexposed population.^{38–41} The EIN is the corresponding epidemiologic measure of a number needed to treat (NNT), an analysis commonly used in randomized, controlled trials. The EIN is the average number of exposed patients to the risk factor who would need to be removed from the exposure to prevent 1 additional adverse event or outcome. The EIN and NNT permit quantification of the effort needed to be taken for preventing 1 event, thus providing an objective comparison of cost effectiveness with other treatments or interventions. In general, the lower EINs and NNTs suggest a more cost-effective intervention for the prevention of an adverse outcome.^{38–41}

3. Results

The study sample included 184 female participants with a mean age of 59.3 ± 15.2 years. Demographic and clinical characteristics of the sample are presented in Table 1. African Americans were 53.8% of the sample, 19.6% Caucasian, 3.8% Hispanic, 16.3% Asian, and 6.5% other races. Pulmonary disease was present in 7.6% of the sample, and 11.9% had a diagnosis of diabetes at baseline. Current smokers were 24.4%, and 21.4% had a history of smoking. About 53% reported that they were physically active, and the CRF was 7.7 ± 3.2 METs (Table 1). There was no significant difference in age between CRF categories (low CRF: 60.3 ± 14.7 years; moderate CRF: 58.3 ± 15.3 years; and high CRF: 60.6 ± 15.5 years; *p* = 0.735). During a mean of 12.0 ± 6.9 years follow-up, 21 women (11.4%) were diagnosed with cancer, 6 (3.2%) died from cancer, and 6 (3.2%) died from other causes (competing events). The most common diagnosed cancers were skin

(3.2%), breast and cervix (2.7%), colorectal (1.6%), lung (1%), brain (1%), and other (2%) cancers.

Women diagnosed with cancer were older (76 ± 20 years vs. 57 ± 13 years; *p* < 0.001) and had lower CRF levels (6.2 ± 3.4 METs vs. 7.9 ± 3.1 METs; *p* = 0.019) compared with women who were free from cancer. After adjustment for potential confounders and accounting for competing events, both the continuous and categorical models of CRF were inversely and independently associated with incidence and mortality from cancer. For every 1-MET increase in CRF, there was a 20% decrease in the risk of cancer incidence (*p* = 0.001) and a 26% decrease in the risk of cancer mortality (*p* = 0.002). In the categorical models, both moderate and high CRF levels were associated with reduced risks of cancer incidence (*p*_{trend} = 0.021) and cancer mortality (*p*_{trend} = 0.014) (Table 2). Kaplan–Meier curves confirmed the association between lower CRF levels and higher cancer mortality. Differences in survival rates were primarily observed between low versus moderate and high CRF categories (Fig. 1). The PARs% for low CRF (<5 METs) were 11.6% and 14.0% for cancer incidence and cancer mortality, respectively (Table 3), and the respective EINs were 8 and 20 (Table 4).

4. Discussion

In the current pilot study, we aimed to assess the association between CRF and all-type cancer incidence and mortality from cancer in women. In addition, we evaluated the potential public health implications of CRF in cancer prevention. The main findings indicate that higher CRF is inversely and independently (from other established cancer risk factors) associated

Table 1
Demographic and clinical characteristics of the study population.

	All (n = 184)	Free from cancer (n = 163)	Diagnosed with cancer (n = 21)	<i>p</i>
Age (year)	59.3 ± 15.2	57 ± 13	76 ± 20	<0.001
BMI (kg/m²)	28.2 ± 6.1	28.1 ± 5.8	29.1 ± 8.0	0.484
Race				0.034
Caucasian	19.6	22.1	0	
African-American	53.8	50.3	81	
Hispanic	3.8	4.3	0	
Asian	16.3	16	19	
Other	6.5	7.3	0	
Clinical history				
Family history of coronary artery disease	29.3	27.6	42.9	0.149
Hypertension	37.5	35.6	52.4	0.135
Dyslipidemia	31	34.5	42.9	0.805
Obesity (BMI ≥ 30 kg/m ²)	33.7	34.2	33.2	0.940
Coronary artery disease	15.8	14.7	23.8	0.743
Any pulmonary disease	7.6	8	4.8	0.601
History of alcohol abuse	0.5	0.6	0	0.719
History of drug abuse	1.6	1.8	0	0.531
Diabetes	11.9	5.4	15	0.211
Never smoked	54.2	54.7	50	
Former smokers	21.4	21.6	20	0.386
Current smokers	24.4	23.6	30	
Antihypertensive drugs	17.4	28.8	51.5	0.832
Antihyperlipidemia drug	4.9	4.3	9.5	0.296
CRF (METs)	7.7 ± 3.2	7.9 ± 3.1	6.2 ± 3.4	0.019
Physically active	53.0	51.7	57.1	0.645

Note: Data are presented as mean ± SD or % of the group for categorical variables. Abbreviations: BMI = body mass index; CRF = cardiorespiratory fitness; MET = metabolic equivalent.

Table 2
Risk models of cardiorespiratory fitness, cancer incidence, and cancer mortality in women (Hazard ratios (95%CI)).

	Low CRF	Moderate CRF	High CRF	<i>p</i> _{trend}	1-MET increase	<i>p</i>
Non-accounting for competing events						
Cancer incidence	1	0.34 (0.13–0.92)	0.2 (0.02–0.82)	0.035	0.81 (0.68–0.96)	0.016
Cancer mortality	1	0.1 (0.004–0.570)	0.04 (0.003–0.600)	0.022	0.62 (0.42–0.92)	0.017
Accounting for competing events						
Cancer incidence	1	0.4 (0.17–0.95)	0.2 (0.05–0.70)	0.021	0.8 (0.69–0.92)	0.001
Cancer mortality	1	0.24 (0.07–0.77)	0.12 (0.02–0.72)	0.014	0.74 (0.61–0.90)	0.002

Note: Hazard models were adjusted for age, smoking status, history of drug and alcohol abuse, body mass index, and physical activity status. Abbreviations: CI = confidence interval; CRF = cardiorespiratory fitness; MET = metabolic equivalent.

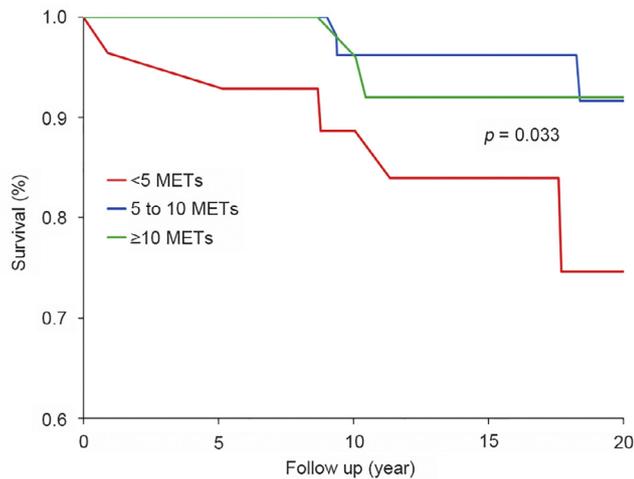


Fig. 1. Kaplan–Meier curves of cardiorespiratory fitness categories and cancer mortality in women. MET = metabolic equivalent.

with lower risk of cancer incidence and mortality from cancer (Table 2 and Fig. 1). The PARs% showed that eliminating low CRF as a risk factor would potentially result in considerable decreases in morbidity (11.6%) and mortality (14.0%) from cancer (Table 3). Given the lifetime probability of 1 in 3 women to develop some type of cancer, and approximately 1 of 5 will die from cancer, these findings have important public health implications for cancer prevention programs.² Strategies such as screening and treating middle-aged women with low CRF are potentially cost effective; however, more research using larger, prospective cohorts is warranted with respect to CRF and cancer outcomes in women.

The current results are consistent with 2 previous reports showing an inverse association between CRF and cancer mortality in women.^{24,25} The findings also add a number of novel insights to existing knowledge, with respect to (1) the impact of moderate levels of CRF and their potential protective benefits against cancer mortality, (2) the inverse risk association

Table 3
Prevalence of low cardiorespiratory fitness, relative risk, and population-attributable risks for cancer incidence and cancer mortality in women.

Prevalence of low CRF (<5 METs)	Outcome	Non-accounting for competing events			Accounting for competing events		
		Relative risks (95%CI)	PARs% (95%CI)	<i>p</i>	Relative risks (95%CI)	PARs% (95%CI)	<i>p</i>
(17.4%)	Cancer incidence	3.4 (1.3–8.1)	12.3 (4.0–15.3)	0.013	3.0 (1.3–6.9)	11.6 (4.0–14.8)	0.011
	Cancer mortality	21.2 (2.6–173.8)	16.6 (10.7–17.3)	0.005	5.1 (1.6–15.5)	14.0 (6.5–16.3)	0.005

Note: Relative risk of cancer was calculated using the Cox proportional hazard model adjusted for age, smoking status, history of drug and alcohol abuse, body mass index, and physical activity status.

Abbreviations: CI = confidence interval; CRF = cardiorespiratory fitness; METs = metabolic equivalents; PARs = population-attributable risks.

Table 4
Exposure impact number analysis for cancer incidence and cancer mortality in women.

	Cancer events (<i>n</i>)	Free from cancer (<i>n</i>)	Total (<i>n</i>)	Exposure impact number (<i>n</i>) (95%CI)	<i>p</i>
Cancer incidence (<i>n</i>)					
CRF <5 METs (Exposed)	9	23	32	—	—
CRF ≥5 METs (NonExposed)	12	140	152	8 (3.4–47.0)	0.001
Total	21	163	184	—	—
Cancer mortality (<i>n</i>)					
CRF <5 METs (Exposed)	4	28	32	—	—
CRF ≥5 METs (NonExposed)	2	150	152	20 (6.3–129.0)	0.001
Total	6	178	184	—	—

Note: Exposure Impact Number was calculated using hazard ratio values from a fully adjusted model, accounting for competing events.

Abbreviations: CRF = cardiorespiratory fitness; MET = metabolic equivalent.

between CRF and cancer incidence, (3) the PAR%, and (4) the EIN for low CRF and cancer outcomes in women. This information is important for resource allocation and public health decisions for developing cancer screening and prevention programs. Although the existing data among women are inconsistent with respect to the association between CRF and cancer mortality,^{15,16,24,25} the association between CRF and cancer incidence, to our knowledge, has not been explored. In this regard, Farrell et al.²⁴ and Peel et al.²⁵ demonstrated a decreased risk of cancer mortality only in women with relatively high CRF; however, moderate CRF levels were not significantly associated with cancer mortality in these studies. In contrast, Kampert et al.¹⁶ and Evenson et al.¹⁵ did not observe a significant association between either high or moderate CRF levels and cancer mortality in women. Our study extends these previous findings by demonstrating a significant risk reduction for cancer incidence and cancer mortality in the presence of either moderate or high CRF levels (Table 2 and Fig. 1). Achieving a relatively modest increase in CRF level (e.g., moving from a low to moderate CRF category) was associated with substantial decrease in risk of both cancer incidence and cancer mortality. Based on the PAR% analysis, such a change would potentially result in the prevention of 11.6% to 14.0% of cancer outcomes (Table 2, Table 3, and Fig. 1). The low EINs (8–20) we observed further support the potential cost effectiveness of achieving moderate CRF levels for cancer prevention.¹² This level of CRF has been shown to be attainable by most individuals who participate in a supervised exercise training program.^{12,28} The results suggest that for every 8 women who would be moved from low to moderate CRF, 1 case of cancer incidence would be potentially prevented. Similarly, for every 20 women who would be moved from low to moderate CRF, 1 case of cancer mortality would be potentially prevented (Table 4). Compared with smoking cessation interventions, the NNT ranges from 50 to 120, which requires a much greater investment for 1 smoker to quit.⁴²

Various physiological mechanisms have been proposed to mediate the association between CRF and cancer-related outcomes.^{42–45} Cancer is a broad and varied group of diseases; therefore, the biological pathways by which CRF influences cancer are likely to differ based on cancer type and site. Potential protective mechanisms might include improved insulin sensitivity, decreased chronic inflammation, enhanced regulation of sex steroid hormones and growth-related hormones, decreased adipose tissue, optimized immune function, elevated antioxidant capacity, enhanced DNA repair, cell proliferation, and apoptosis.^{42–45} These mechanisms likely interact in a complex manner by blocking cancer cell initiation and countering cancer cell replication among fit women. However, despite increasing observational evidence supporting the hypothesis that CRF has a role in cancer prevention, prospective, controlled studies addressing for the mechanistic effect of fitness on cancer genesis are needed.

The strengths of this study include the focus on female participants, extended follow-up time (mean 12 years), and prospective assessment of cancer outcomes. In addition, cancer outcomes were verified through the Veterans Affairs computerized medical records system, which has been demonstrated to be comparatively

accurate and complete.^{29–33} CRF was assessed objectively from maximal treadmill exercise test using an established technique.²⁸ This method has been widely used in clinical and epidemiologic studies and has been shown to be strongly predictive for incidence and mortality of many chronic diseases, including cancer in women.^{13,24,25,28} The hazard models were adjusted for established cancer risk factors and accounted for competing events, demonstrating the independent association between CRF and cancer outcomes.^{6–8} The study also has several limitations. First, this was a pilot study in which the sample size and number of cancer events were relatively small, limiting the ability to assess the association with specific types of cancer. In this regard, the analysis of cancer incidence included a group of all skin cancers, whereas subdivision of melanoma and nonmelanoma was not available. Given the limited sample size, the findings require confirmation from large, prospective cohorts. Second, women veterans are a unique population with a rich mixture of comorbidities, and the current sample included predominance of African Americans. These factors may have influenced the results by selection bias, although the findings are consistent with previous reports among women, providing some support for generalization.^{24,25} Third, the multivariable hazard models, although adjusted for established cancer risk factors that are similar to those in previous studies of CRF and cancer,^{15,16,24,25} the models did not include dietary habits, menopausal status, or other lifestyle factors that may have influenced the results. Finally, similar to previous studies, the findings provide an association between CRF and cancer outcomes, but they do not demonstrate a cause-and-effect relationship.

5. Conclusion

Higher CRF is associated with lower risk of incidence and mortality from cancer in women, independently from other cancer-related risk factors. Eliminating low CRF as a risk factor would potentially decrease cancer morbidity and mortality and lessen the societal and economic burden related to cancer. Screening for low CRF and referring unfit individuals to a supervised exercise program, may serve as an effective public health strategy for achieving moderate CRF and contributing for cancer prevention in middle-age women. Future prospective studies should address the role of promoting CRF for cancer prevention.

Authors' contributions

BV was responsible for the study design and conception; interpretation of the results, statistical analysis, and drafting, writing, and submitting the manuscript; RML was responsible for the interpretation of the results, statistical analysis, drafting the article, and revising the manuscript for critically important intellectual content; JM was the principal investigator and was responsible for the study design and conception, data collection, interpretation of the results, statistical analysis, drafting the article, and revising the manuscript for critically important intellectual content. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

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