Cardiorespiratory Fitness, Smoking Status, and Risk of Incidence and Mortality From Cancer: Findings From the Veterans Exercise Testing Study

Baruch Vainshelboim, Zhongming Chen, Ricardo M. Lima, and Jonathan Myers

Background: To assess the joint and stratified associations between cardiorespiratory fitness (CRF), incidence, and mortality from cancer in never, former, and current male smokers. **Methods:** CRF (treadmill exercise test) was assessed in 4694 men (never smokers [$n = 1715$]; former smokers [$n = 1602$], 32.4 [30.5] pack-years; and current smokers [$n = 1377$], 40.3 [26] pack-years) aged 58.1 (17.3) years, and prospectively followed for 12.7 (7.5) years. Multivariable Cox hazard models were analyzed. **Results:** In joint analyses, where high CRF in never smokers was used as a reference, hazard ratios and 95% (confidence intervals) for cancer incidence and cancer mortality were as follows: moderate CRF 1.41 (1.0–1.9) and 3.0 (1.7–5.5) in never smokers, 1.65 (1.3–2.2) and 3.7 (2.1–6.6) in former smokers, and 1.3 (0.9–1.7) and 3.4 (1.9–6.1) in current smokers, respectively. The corresponding values for low CRF were 1.53 (1.1–2.2) and 5.1 (2.7–9.5), 1.84 (1.3–2.5) and 6.6 (3.7–11.8), and 1.5 (1.1–2.2) and 5 (2.7–9.3), respectively. In stratified analyses by smoking status, compared with low CRF, moderate and high CRF were associated with a 32% to 78% reduction in cancer mortality risk (P trend for all $<.001$). **Conclusion:** Higher CRF is associated with lower risk of incidence and mortality from cancer regardless of smoking status, supporting the potential preventive benefits for public health.

Keywords: public health, epidemiology, population attributable fraction, prevention strategy

Cancer is one of the leading causes of morbidity and mortality worldwide and in the United States.^{1–4} The American Cancer Society estimates that 1 in 3 men and women in the general population will develop some type of cancer during their lifetime, and 1 in 5 will die from cancer.⁴ Smoking is the single most important risk factor for cancer, accounting for approximately 25% of all cancer incidence and 30% of total cancer mortality.^{1–3,5} The prevalence of current smokers is about 20% of the world's adult population (about 800 million men and 200 million women),¹ ranging from approximately 17% of men in the United States to about 31% of men in the European Union.^{5,6} As most people are not currently smokers, including smokers and nonsmokers in a composite analysis of a general population could bias the risk for cancer. Despite the fact that smoking significantly increases the risk of cancer,^{1–5,7,8} most smokers do not develop cancer and, thus, there are factors other than smoking that influence risk.^{4,9–11}

Low cardiorespiratory fitness (CRF) is an established risk factor for the development of many chronic conditions, and it is strongly associated with all-cause, cardiovascular and cancer mortality.^{12–14} Recently, the American Heart Association endorsed the adoption of CRF as a vital sign in clinical practice, making a strong case for including CRF in the risk paradigm.¹³ Although several reports have demonstrated an inverse association between CRF, cancer incidence, and cancer mortality in the general population,^{14–26} only a few studies have reported this association stratified by smoking

status.^{11,27} In this regard, one study has demonstrated that higher CRF was associated with lower cancer mortality in *current* smokers,¹¹ whereas a more recent report found this association to be significant only among *former* smokers.²⁷ This inconsistency with respect to the preventive role of CRF in cancer mortality as well as the association between CRF and cancer incidence across smoking status requires further exploration. Given that smokers and non-smokers have potentially different risks for developing and dying from cancer,^{1–5} investigating the association between CRF, incidence, and mortality from cancer has important public health implications for prevention, screening, and treatment of smoking and nonsmoking individuals. Therefore, this study aimed to assess the association between CRF, total cancer incidence, and cancer mortality among never, former, and current male smokers. An additional aim was to quantify the potential public health impact of eliminating low CRF as a risk factor on cancer outcomes.

Methods

Study Population

The Veterans Exercise Testing Study has been previously described.^{28,29} In brief, the Veterans Exercise Testing Study cohort is an ongoing, prospective evaluation of primarily male Veterans (96%) referred for exercise testing for clinical reasons, designed to address exercise test, clinical, and lifestyle factors and their association with health outcomes. The sample generally included participants with cardiometabolic risk factors, signs, or symptoms suggestive of cardiovascular disease, or known cardiometabolic disease. The study was approved by the institutional review board at Stanford University, CA, USA. All participants who underwent a treadmill exercise test at the Veterans Affairs Palo Alto Health Care System between 1987 and 2014 were considered for inclusion.

Vainshelboim is with the Master of Cancer Care Program, School of Health Sciences, Saint Francis University, Loretto, PA, USA. Vainshelboim, Chen, Lima, and Myers are with Cardiology Division, Veterans Affairs Palo Alto Health Care System/Stanford University, Palo Alto, CA, USA. Chen is with the School of Medicine, New York Medical College, Valhalla, NY, USA. Lima is with the Faculty of Physical Education, University of Brasília, Brasília, Brazil. Vainshelboim (baruch.v1981@gmail.com) is corresponding author.

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 the 5540 participants who completed the baseline evaluation, 846 participants were excluded: women ($n=352$), those with a history of any malignancy ($n=76$), incomplete or prematurely terminated exercise tests ($n=192$), and loss to follow-up ($n=226$). A total of 4694 male veterans (never smokers [$n=1715$], former smokers [$n=1602$], and current smokers [$n=1377$]) were included in the analysis and were followed for a mean of 12.7 (7.5) years. Never smokers were defined as those who never smoked or who have smoked less than 100 cigarettes in their lifetime and are currently not smoking. Former smokers were defined as those who smoked at least 100 cigarettes in their lifetime but who had quit smoking at the time of baseline testing, whereas current smokers were defined as those who had smoked at least 100 cigarettes in their lifetime and who are currently smoking.³⁰

Exposure Assessment (CRF)

Participants underwent maximal symptom limited exercise tests using an individualized ramp treadmill protocol according to established guidelines.^{31,32} The exercise protocol included continuous, individualized increments in treadmill speed and grade adjusted to achieve a targeted duration between 8 and 12 minutes, as previously recommended.^{31,32} A 12-lead electrocardiogram, heart rate, blood pressure, and Borg 6 to 20 perceived exertion rating were continuously recorded throughout the tests, and standard criteria for test termination were used.^{31,32} CRF in metabolic equivalents, METs, was calculated from peak treadmill speed and grade utilizing established metabolic equations from the American College of Sports Medicine.³¹ CRF was analyzed as a categorical variable divided into 3 categories (low CRF <5 METs, moderate CRF 5–10 METs, and high CRF >10 METs).^{13,17,33} Determination of low CRF (<5 METs) as a risk factor was made according to recent recommendations from the American Heart Association.¹³

Outcomes Ascertainment (Incidence and Mortality From Cancer)

The Veterans Affairs Computerized Patient Record System was used for capturing cancer outcomes; total cancer incidence and cancer 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.³⁴ The Veterans Affairs records also have good agreement ($\kappa=.82-.91$) with state death records³⁵ and high sensitivity for incidence of several chronic conditions.^{36–38} Medical records were carefully reviewed 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 ninth and tenth edition codes. Cancer diagnosis and vital status for each patient were ascertained as of August 2015.

Statistical Analysis

Demographics and clinical data of the participants are presented as mean (SD) for continuous variables and absolute numbers or percentages for categorical variables. Analysis of variance was performed to compare the participants' ages across CRF categories

and smoking status, as well as for all comparisons between never, former, and current smokers for the continuous variables. Chi-square tests were utilized for all comparisons of categorical data. Multivariable Cox proportional hazard models were used to assess the association between CRF, total cancer incidence, and cancer mortality. Both a stratified analysis by smoking status (never, former, and current smokers) and a joint analysis where high CRF in never smokers used as a reference were utilized. All risk models were adjusted for age, history of alcohol and drug abuse, dyslipidemia, hypertension, body mass index, smoking in pack-years, presence of cardiac and pulmonary disease, diabetes, and physical activity status (active or inactive).^{2,39,40} Physical activity status was evaluated by a participant's response to the question: "Do you engage in some form of physical activity such as brisk walking, jogging, bicycling, or swimming, long enough to work up a sweat, get your heart thumping, or become short of breath at least 3 times per week?" Participants who answered yes were classified as active, whereas participants who answered no were classified as inactive.^{28,31,41,42} The hazard models also took into account competing events (death resulting from causes other than cancer).^{43,44} To address the potential reverse causality bias, a secondary analysis was performed after excluding participants who had less than 2 years follow-up. The proportional hazards assumption was evaluated graphically for CRF categories and was confirmed using the scaled Schoenfeld residuals.

Population attributable fraction (PAF%) was determined for low CRF (<5 METs) compared with moderate and high (≥ 5 METs) CRF.¹³ PAF% is a well-established metric quantifying the contribution of a risk factor to the burden of disease or death, and it represents the proportional reduction in population disease or mortality burden that would occur if exposure to the risk factor was eliminated (eg, no tobacco use). PAF% was calculated according to the equation: $P(RR-1)/1+P(RR-1) \times 100$,⁴⁵ where P = prevalence of the risk factor and RR = fully adjusted relative risk calculated from the Cox hazard model.^{46,47} Missing data were considered as missing completely at random and analyzed using complete case methods.⁴⁸ Data report and presentation followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.⁴⁹ SPSS (version 23; IBM, Chicago, IL) was used for statistical analyses. The significance level was set at $P < .05$.

Results

The analytical sample included 4694 participants (1715 never, 1602 former, and 1377 current smokers) with a mean age of 58.1 (17.3) years. Demographic and clinical characteristics of the participants are presented in Table 1. Approximately 53% had hypertension, 32% were obese, almost 30% had a history of cardiovascular disease, 6.5% had pulmonary disease, and 14.1% had diabetes at baseline. Former smokers compared with never and current smokers were older and had a higher prevalence of obesity, hypertension, dyslipidemia, and diabetes, and had a slightly lower CRF (Table 1). There was no significant difference in age between CRF categories for each smoking status classification: never smokers (low CRF, 55.3 y [16.3] y; moderate CRF, 55.3 y [17] y; and high CRF, 57.2 y [17.3] y; $P=.12$), former smokers (low CRF, 60.3 y [17.3] y; moderate CRF, 62.2 y [18.4] y; and high CRF, 61.9 y [17.8] y; $P=.27$), and current smokers (low CRF, 57.5 y [16.8] y; moderate CRF, 55.8 y [16.2] y; and high CRF, 55.9 y [16.3] y; $P=.37$).

During a mean follow-up of 12.7 (7.5) years, a total of 1203 cancers were diagnosed, 500 participants died from cancer, and 24 competing events occurred. Former smokers compared with never

Table 1 Baseline Demographic and Clinical Characteristics of the Cohort

	Entire cohort (n = 4694)	Never smokers (n = 1715)	Former smokers (n = 1602)	Current smokers (n = 1377)	P value
Age, y	58.1 (17.3)	55.9 (17)	61.8 (17.9)	56.1 (16.3)	<.001
Smoking, pack-years	35.3 (29)	0	32.4 (30.5)	40.3 (26)	<.001
Obesity, BMI > 30 kg/m ²	32%	31%	37.3%	27%	<.001
History of drugs abuse	1.6%	0.4%	1.9%	3.9%	<.001
History of alcohol abuse	2.4%	0.9%	3.4%	3.4%	<.001
Hypertension	52.9%	54.1%	57.2%	46.3%	<.001
Dyslipidemia	36.3%	34.4%	40.4%	34.1%	<.001
Cardiovascular disease	29.8%	30.8%	29.3%	29%	.50
Pulmonary diseases	6.5%	2.7%	9%	8.4%	<.001
Diabetes	14.1%	12.5%	19.4%	9.5%	<.001
Antihypertensive drugs	21.1%	25.9%	18.7%	18.1%	<.001
Antihyperlipidemia drug	8.8%	7.9%	12.8%	5.2%	<.001
CRF, METs	8.2 (3.5)	8.6 (3.7)	7.9 (3.2)	8.2 (3.5)	<.001
Low CRF <5 METs	16.8%	15.4%	18.5%	16.6%	.02
Moderate CRF 5–10 METs	55.8%	54.8%	56.1%	56.8%	
High CRF >10 METs	27.4%	29.9%	25.4%	26.6%	
Physical inactivity	47.2%	45.3%	47%	50%	.14
Total cancer incidence, n (%)	1203 (25.6)	293 (17.1)	605 (37.8)	304 (22.1)	<.001
Cancer mortality, n (%)	500 (10.7)	105 (6.1)	254 (15.9)	141 (10.2)	<.001
Competing events, n (%)	24 (0.5)	5 (0.3)	13 (0.8)	6 (0.4)	.04

Abbreviations: BMI, body mass index; CRF, cardiorespiratory fitness; MET, metabolic equivalent. Note: Data are presented as mean (SD) or as a percentage of the group for categorical variables.

and current smokers had a higher incidence and mortality from cancer (Table 1). In stratified analyses by smoking status, CRF was associated with cancer incidence only in former smokers. Relative to low CRF, moderate and high CRF were associated with 7% and 29% reduced risks of cancer incidence. The corresponding hazard ratios (HR) and 95% confidence intervals (CIs) were 0.93 (0.75 to 1.2) and 0.71 (0.55 to 0.9), P trend = .03. Both moderate and high CRF were significantly associated with reduced risk of cancer mortality in never, former, and current smokers (Table 2). In joint analyses in which high CRF in never smokers used as a reference, moderate and low CRF levels were associated with increased risk of incidence and mortality from cancer. There were no significant differences in risks of incidence and mortality from cancer between never, former, and current smokers who had high CRF (Figures 1 and 2). The risk of cancer incidence in current smokers was not different between low and moderate CRF (Figure 1). After exclusion of those with less than 2 years follow-up, CRF remained significantly associated with total cancer incidence and cancer mortality (both P trend <.001). In stratified analyses by smoking status, CRF remained a significant predictor of cancer mortality only. Among never smokers (HR = 0.57, 95% CI [0.37 to 0.92], and 0.24, [0.12 to 0.48], P trend <.001), former smokers (HR = 0.63, 95% CI [0.37 to 0.92], and 0.28, [0.17 to 0.45], P trend <.001), and current smokers (HR = 0.78, 95% CI [0.51 to 1.2], and 0.45, [0.26 to 0.81], P = .02), for moderate and high CRF, respectively, association between CRF and total cancer incidence was not significant in stratified analyses after exclusion of those with less than 2 years follow-up. PAFs% for cancer mortality were 8.1%, 95% CI (4.4 to 10.4); 8.7%, 95% CI (6.2 to 11.1); and 6.9%, 95% CI (2.8 to 10) in never, former, and current smokers, respectively, but were not significant for cancer incidence (Table 3).

Discussion

The current study aimed to assess stratified and joint associations between CRF, total cancer incidence, and cancer mortality among never, former, and current male smokers. In addition, we sought to evaluate the potential public health implications of CRF in cancer prevention. The novel findings showed that in a joint analysis where never smokers with high CRF used as a reference, both moderate and low CRF were independently associated with elevated risk of total cancer incidence and cancer mortality among former and current smokers. In addition, regardless of smoking status, high CRF demonstrated comparable protective benefits against cancer incidence and cancer mortality (Figures 1 and 2). In stratified analyses, higher CRF was associated with lower risk of cancer incidence only in former smokers, whereas the risk of cancer mortality was significantly lower across all smoking strata (Table 2). After exclusion of those with less than 2 years follow-up, CRF remained a significant predictor of cancer incidence and cancer mortality in a joint analysis and a predictor of cancer mortality in stratified analyses. In addition, the PAF% analysis revealed that by eliminating low CRF as a risk factor, 6.9% to 8.7% of cancer mortality could potentially be prevented in never, former, and current smokers (Table 3). Although these observations do not indicate causality, they have important public health implications for several reasons. First, smoking is the single most important risk factor for cancer, accounting for approximately 24% of all cancer incidence and 34% of all cancer mortality in men.² Second, although current smokers are a considerable fraction of the entire adult population (approximately 20%),^{1,3–5,8} most people do not smoke, and the assessed risk of cancer in the general population (combined smokers and nonsmokers) could potentially bias the risk

Table 2 Multivariable Cox Hazard Models of CRF and Cancer Outcomes Stratified by Smoking Status

	Never smokers	Former smokers	Current smokers
Total cancer incidence	Hazard ratios (95% CI)		
Low CRF <5 METs	1 (reference)	1 (reference)	1 (reference)
Events (n)	50	114	64
Moderate CRF 5–10 METs	0.92 (0.66 to 1.3)	0.93 (0.75 to 1.2)	0.86 (0.63 to 1.2)
Events (n)	166	361	163
High CRF >10 METs	0.7 (0.46 to 0.99)	0.71 (0.55 to 0.94)	0.7 (0.48 to 1)
Events (n)	77	130	77
<i>P</i> trend	.09	.03	.19
Cancer mortality			
Low CRF <5 METs	1 (reference)	1 (reference)	1 (reference)
Events (n)	36	86	43
Moderate CRF 5–10 METs	0.61 (0.4 to 0.9)	0.6 (0.46 to 0.79)	0.68 (0.46 to 0.99)
Events (n)	57	143	75
High CRF >10 METs	0.22 (0.12 to 0.42)	0.26 (0.17 to 0.4)	0.37 (0.21 to 0.62)
Events (n)	12	25	23
<i>P</i> trend	<.001	<.001	.001

Abbreviations: CI, confidence interval; CRF, cardiorespiratory fitness; MET, metabolic equivalent. Note: The risk models were adjusted for age, history of drug and alcohol abuse, body mass index, dyslipidemia, hypertension, diabetes, presence of cardiac or pulmonary disease, pack-years in smoking, physical activity status, and accounting for competing events.

Figure 1 — Joint risk analysis between CRF and cancer incidence in never, former, and current male smokers. The risk model was adjusted for age, history of drug and alcohol abuse, body mass index, dyslipidemia, hypertension, diabetes, presence of cardiac or pulmonary disease, pack-years in smoking, physical activity status, and accounting for competing events. CRF indicates cardiorespiratory fitness; MET, metabolic equivalent.

Figure 2 — Joint risk analysis between CRF and cancer mortality in never, former, and current male smokers. The risk model was adjusted for age, history of drug and alcohol abuse, body mass index, dyslipidemia, hypertension, diabetes, presence of cardiac or pulmonary disease, pack-years in smoking, physical activity status, and accounting for competing events. CRF indicates cardiorespiratory fitness; MET, metabolic equivalent.

and requires a different approach.^{4,5} Third, cancer is one of the leading causes of morbidity and mortality, underscoring the importance of screening and prevention strategies.^{1,3–6,10} From a public health perspective, screening never, former, and current smokers for low CRF and achieving at least moderate CRF levels during

middle age could potentially reduce mortality from cancer and serve as important strategy for cancer prevention and control.

The current results are consistent with previous reports, generally showing a reduced risk of incidence and mortality from cancer with higher CRF among men.^{14–26} These findings also align with the few available reports on the association between CRF and

Table 3 Relative Risk and Population Attributable Fraction of Low CRF for Cancer Incidence and Cancer Mortality in Never, Former, and Current Male Smokers

	Cancer incidence			Cancer mortality		
	Relative risks 95% CI	PAFs% 95% CI	P value	Relative risks 95% CI	PAFs, % 95% CI	P value
Never smokers	1.2 (0.9 to 1.6)	2.6 (−1.7 to 5.8)	.26	2.1 (1.4 to 3.1)	8.1 (4.4 to 10.4)	<.001
Former smokers	1.1 (0.9 to 1.4)	1.7 (−2.1 to 5.5)	.22	1.9 (1.5 to 2.5)	8.7 (6.2 to 11.1)	<.001
Current smokers	1.2 (0.9 to 1.6)	2.8 (−1.8 to 6.2)	.19	1.71 (1.2 to 2.5)	6.9 (2.8 to 10)	.01

Abbreviations: CI, confidence interval; CRF, cardiorespiratory fitness; PAFs, population attributable fractions. Note: Relative risk of CRF was calculated using the Cox proportional hazard model adjusted for age, history of drug and alcohol abuse, body mass index, dyslipidemia, hypertension, diabetes, presence of cardiac or pulmonary disease, pack-years in smoking, physical activity status, and accounting for competing events.

cancer mortality among smokers.^{11,27} The current study strengthens these earlier observations and adds several novel insights that have potentially important public health implications. To our knowledge, the results of the current study are the first to demonstrate the risk association between higher CRF and total cancer incidence in former smokers. Second, to our knowledge, these findings are the first to show that high CRF is associated with a comparable risk of incidence and mortality from cancer regardless of smoking status. Third, current smokers with either moderate or high CRF have a reduced risk of developing cancer. Finally, the PAF% of low CRF for cancer mortality is also new and valuable information with respect to resource allocation and public health decisions for cancer prevention programs in never, former, and current smokers. Interestingly, in a stratified analysis, although, among former smokers, higher CRF was associated with lower risk of cancer incidence, among never and current smokers, this association was not significant (Table 2). This is likely due to the small number of cancer cases in each CRF category in never smokers, and may suggest that smoking cessation may have more of an impact than higher CRF for primary prevention of cancer incidence among current smokers. Future larger prospective studies are warranted to further explore these observations. Given that higher CRF is beneficial for reducing the risk of cancer outcomes regardless of smoking status, achieving at least moderate CRF could potentially reduce 6.9% to 8.7% of cancer mortality.^{1–6}

Several physiological mechanisms have been proposed that may mediate the association between CRF and cancer.^{14,50–54} Potential protective pathways related to higher CRF might include reduced chronic-systemic inflammation (particularly C-reactive protein), which has been suggested as being carcinogenic in a broad spectrum of cancers.^{9,10,51} Improved immune function through an increased number of natural killer cells, an elevated antioxidant capacity, reduced oxidative stress and enhanced DNA repair, cell proliferation, and apoptosis are all potential mechanisms that could interact in a complex manner by blocking cancer cell initiation and countering cancer cell replication among fit individuals.^{10,14,50–56} However, despite growing observational evidence supporting the concept that CRF has a role in cancer prevention,^{9,11,15,17,18,21} prospective controlled studies addressing these mechanisms are warranted.

The strengths of the current study include its relatively large sample size ($n = 4694$), extended follow-up period (mean of approximately 13 y), 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.^{34,37,38} CRF was quantified from treadmill exercise testing utilizing established protocols.^{31,32} This method has been widely used in

epidemiologic studies and has been shown to strongly predict incidence and mortality from many chronic diseases, including cancer.^{9,11–13,17,18,26} Classification of CRF categories and determination of a low CRF threshold (<5 METs) as a risk factor were set according to previous studies and recent recommendations from the American Heart Association, providing additional support for the association with cancer outcomes.^{13,17,33} The study also has several limitations. First, although our multivariable hazard models were adjusted for established covariates similar to those in previous studies, data on dietary habits were not collected, which may have an influence on cancer risk.^{9,11,17,18,21} Second, veteran participants are a unique population with a rich mixture of comorbidities that may have influenced the results by selection bias, although the findings are consistent with previous reports.^{9,11,15,17,18,21,27} Third, the study was limited to men, and the extent to which the findings apply to women needs to be examined in future studies. Fourth, due to a small number of cancer cases in each smoking strata, the analyses utilized a composite outcomes of total cancer incidence and cancer mortality. Fifth, exposure variables (smoking status and CRF) were assessed at baseline; the potential change during the follow-up is unknown. Finally, as is the case of all epidemiological studies, the findings provide an association between CRF and cancer outcomes, but preclude the establishment of cause and effect.

Conclusion

In a joint analysis, higher CRF was independently associated with a lower risk of total cancer incidence and cancer mortality among never, former, and current male smokers. High CRF shows a comparable risk of cancer outcomes, regardless of smoking status. In a stratified analysis, higher CRF was independently associated with a lower risk of cancer incidence only in former smokers, although a reduced risk of cancer mortality was significant across all smoking strata. Therefore, reducing the prevalence of low CRF among never, former, and current smokers could potentially lessen mortality from cancer and serve as a preventive strategy for public health. In addition to efforts directed toward smoking cessation, screening smokers and nonsmokers for low CRF and encouraging low-fit individuals to achieve at least moderate CRF through supervised exercise programs may play an important role in cancer prevention and control. Future prospective studies should address the role of promoting CRF for primary and secondary prevention of cancer among smokers and nonsmokers.

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