Original Investigation

Midlife Cardiorespiratory Fitness, Incident Cancer, and Survival After Cancer in Men
The Cooper Center Longitudinal Study

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IMPORTANCE Cardiorespiratory fitness (CRF) as assessed by formalized incremental exercise testing is an independent predictor of numerous chronic diseases, but its association with incident cancer or survival following a diagnosis of cancer has received little attention.

OBJECTIVE To assess the association between midlife CRF and incident cancer and survival following a cancer diagnosis.

DESIGN, SETTING, AND PARTICIPANTS This was a prospective, observational cohort study conducted at a preventive medicine clinic. The study included 13 949 community-dwelling men who had a baseline fitness examination. All men completed a comprehensive medical examination, a cardiovascular risk factor assessment, and incremental treadmill exercise test to evaluate CRF. We used age- and sex-specific distribution of treadmill duration from the overall Cooper Center Longitudinal Study population to define fitness groups as those with low (lowest 20%), moderate (middle 40%), and high (upper 40%) CRF groups. The adjusted multivariable model included age, examination year, body mass index, smoking, total cholesterol level, systolic blood pressure, diabetes mellitus, and fasting glucose level. Cardiorespiratory fitness levels were assessed between 1971 and 2009, and incident lung, prostate, and colorectal cancer using Medicare Parts A and B claims data from 1999 to 2009; the analysis was conducted in 2014.

MAIN OUTCOMES AND MEASURES The main outcomes were (1) incident prostate, lung, and colorectal cancer and (2) all-cause mortality and cause-specific mortality among men who developed cancer at Medicare age (≥65 years).

RESULTS Compared with men with low CRF, the adjusted hazard ratios (HRs) for incident lung, colorectal, and prostate cancers among men with high CRF were 0.45 (95% CI, 0.29-0.68), 0.56 (95% CI, 0.36-0.87), and 1.22 (95% CI, 1.02-1.46), respectively. Among those diagnosed as having cancer at Medicare age, high CRF in midlife was associated with an adjusted 32% (HR, 0.68; 95% CI, 0.47-0.98) risk reduction in all cancer-related deaths and a 68% reduction in cardiovascular disease mortality following a cancer diagnosis (HR, 0.32; 95% CI, 0.16-0.64) compared with men with low CRF in midlife.

CONCLUSIONS AND RELEVANCE There is an inverse association between midlife CRF and incident lung and colorectal cancer but not prostate cancer. High midlife CRF is associated with lower risk of cause-specific mortality in those diagnosed as having cancer at Medicare age.

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A well-established, graded, inverse association exists between cardiorespiratory fitness (CRF) and risk of cardiovascular disease (CVD) as well as all-cause mortality in numerous healthy and clinical adult populations.[1-3] Compared with those classified in the lowest CRF category (<7.9 metabolic equivalents [METs]), individuals in the highest CRF category (≥10.9 METs) have a 1.6- to 1.7-fold lower risk of CVD and all-cause mortality, respectively.[4] Accordingly, measurement of CRF via formalized exercise testing provides a wealth of diagnostic and decision-making information in cardiovascular medicine.[5]

In contrast, the value of CRF for prediction of primary cancer risk has received little attention.[1-3,6,7] The reasons for the paucity of interest are not known; however, it is now clear that CVD and cancer account for most deaths in the United States,[8] with these diseases sharing common risk factors (eg, tobacco use, poor diet, insufficient physical activity).[9] The powerful value of CRF in the prediction of CVD indicates that such a measure may also be of importance for the prediction of the primary risk of cancer. Evaluation of this question is important for several reasons.

First, given that individual risk (of CVD and cancer) is determined by multiple factors, current guidelines advocate for global or multiple-risk factor assessment, using tools such as the Framingham Risk Score. Currently, CRF is not included as an aspect of general prevention screening guidelines for all average-risk adults. However, CRF improves the discrimination and reclassification of CVD mortality risk prediction,[10] as well as refinement of Framingham Risk Score among adults, even among those at low risk of CVD.[11]

Second, cancer incidence is projected to increase by approximately 45% over the next 2 decades,[12] largely as a result of the rapidly aging population combined with the fact that most cancer diagnoses occur in individuals older than 65 years.[13] Thus, investigation of the predictive value of CRF on primary cancer incidence could have important public health implications because it will provide medical professionals with a quantitative as well as modifiable risk factor (as opposed to a subjective behavioral risk factor) that simultaneously predicts risk of the most common chronic diseases.[14]

Third, there is growing evidence that lifestyle behaviors performed years, even decades, prior to a cancer diagnosis may influence outcomes after diagnosis. Indeed, midlife body mass index (BMI) and physical activity are predictors of cancer-specific as well as all-cause mortality in multiple cancer diagnoses.[15-21] To our knowledge, no study to date has investigated whether objective measures of exercise exposures (ie, CRF) in apparently healthy persons at midlife is predictive of primary risk of cancer as well as cause-specific mortality in those who are subsequently diagnosed as having cancer. Prediction of cause-specific mortality after a cancer diagnosis is becoming increasingly important given that individuals diagnosed as having certain forms of cancer now have sufficient survival to be at risk for noncancer competing causes of mortality, primarily CVD, owing to the chronic and late effects of treatment.[22]

Herein, we report on a prospective investigation of 13 949 men from the Cooper Center Longitudinal Study (CCLS) to examine the association between CRF assessed before age 65 years and (1) incidence of lung, colorectal, or prostate cancer and (2) cause-specific mortality in men diagnosed as having cancer at age 65 years or older (Medicare age). We hypothesized that higher midlife CRF would be associated with reduced incidence of lung, colorectal, and prostate cancer and lower risk of cancer and CVD-related mortality in those subsequently diagnosed as having cancer.

At a Glance

- Does cardiorespiratory fitness (CRF) prevent or improve outcomes in cancer?
- High CRF was associated with reduced incident lung (HR, 0.45 [95% CI, 0.29-0.68]) and colorectal cancer (HR, 0.56 [95% CI, 0.36-0.87]) in white men.
- High CRF is associated with a one-third risk reduction in all cancer-related deaths among men who developed lung, colorectal, or prostate cancer at age 65 years or older compared with low CRF.
- High CRF is associated with a two-thirds reduction in cardiovascular death compared with low CRF among men who developed cancer at age 65 years or older.

Methods

Participants and Procedures

The CCLS is a prospective observational cohort study of participants undergoing a preventive health examination at the Cooper Clinic in Dallas, Texas. Patients enrolled in the CCLS signed an informed consent, and the Cooper Institute's institutional review board approved this study. Patients were not compensated for their participation. A detailed overview of the methods and procedures of the CCLS has been described previously.[3,23,24] The sampling frame for the present study included 25 575 individuals in the CCLS completing an incremental treadmill exercise test between 1971 and 2009 and enrolled in Medicare between 1999 and 2009 (the available years of claims data at the time of this study). The following participants were excluded: (1) women (n = 5871), (2) those lacking traditional fee-for-service Medicare for whom individual claims data were not available (n = 998), (3) individuals without a complete set of baseline variables (n = 2096), (4) participants with myocardial infarction or stroke at their midlife examination visit (n = 413), (5) individuals with a cancer diagnosis or death prior to Medicare age (n = 1640), and (6) participants with a first CCLS visit at age 65 years or older (n = 552) or a chronic illness requiring Medicare coverage prior to age 67 years (n = 56). The final cohort included 13 949 men. Medicare surveillance continued until 2009. The analysis was conducted in 2014.

Midlife Exposures

The preventive health examination consisted of an extensive medical history, laboratory analysis, blood pressure ascertainment, and an incremental exercise treadmill test. Age, sex, and personal medical history were obtained by self-administered questionnaires; all data were physician verified. Blood pressure was measured with standard auscultatory methods, and

Table 1. Association Between Midlife Cardiorespiratory Fitness (CRF) and Later-Life Incident Cancer and Cause-Specific Mortality in the CCLS[a]

Health Status[b]	Events, No.	Hazard Ratio (95% CI)[c]			
		Low CRF	Moderate CRF	High CRF	1-MET Increase
Healthy to cancer diagnosis	1691	1 [Reference]	0.94 (0.83-1.08)	1.07 (0.93-1.24)	1.01 (0.99-1.04)
Cancer to cancer-related death	219	1 [Reference]	0.76 (0.53-1.08)	0.68 (0.47-0.98)	0.90 (0.84-0.97)
Cancer to CVD-related death	64	1 [Reference]	0.59 (0.33-1.05)	0.32 (0.16-0.64)	0.75 (0.66-0.87)
Healthy to cancer-related death	281	1 [Reference]	0.73 (0.54-0.98)	0.66 (0.48-0.91)	0.96 (0.91-1.02)
Healthy to CVD-related death	495	1 [Reference]	0.48 (0.39-0.59)	0.38 (0.29-0.48)	0.84 (0.80-0.89)

Abbreviations: CCLS, Cooper Center Longitudinal Study; CVD, cardiovascular disease; MET, metabolic equivalent.

[a] In 13 949 men followed for a total of 91 366 person-years.

[b] "Healthy" was defined as having no observed incident cancer or cardiovascular disease at baseline.

[c] Adjusted for age, visit date, body mass index, smoking, systolic blood pressure, cholesterol level, diabetes mellitus, and fasting glucose level.

Table 2. Baseline Characteristics of Cooper Center Longitudinal Study

Characteristic	CRF Group[a]		
	Low CRF (n = 2603)	Moderate CRF (n = 5843)	High CRF (n = 5503)
Age at midlife, mean (SD), y	46 (8)	49 (8)	51 (8)
Median (25th-75th percentile)	45 (40-51)	48 (42-55)	51 (44-57)
Race/ethnicity, No. (%)			
White	2556 (98)	5737 (98)	5426 (99)
CRF (METs), mean (SD)	8.4 (1.2)	10.4 (1.2)	13.0 (1.8)
BMI, mean (SD)	28.6 (4.6)	26.6 (3.1)	25.1 (2.6)
Total cholesterol level, mean (SD), mg/dL	221 (41)	216 (39)	210 (37)
Current smoker, No. (%)	810 (31)	1117 (19)	489 (9)
Glucose level, mean (SD), mg/dL	105 (26)	102 (17)	100 (13)
Blood pressure, mean (SD), mm Hg			
Systolic	124 (15)	122 (14)	122 (14)
Diastolic	83 (10)	82 (10)	81 (9)
Deaths, No. (%)	527 (20)	780 (13)	513 (9)
Cancer related	125 (5)	207 (4)	168 (3)
CVD related	181 (7)	229 (4)	149 (3)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CRF, cardiorespiratory fitness; CVD, cardiovascular disease; MET, metabolic equivalents.

SI conversion factors: To convert total cholesterol and glucose to millimoles per liter, multiply by 0.0259 and 0.0555, respectively.

[a] $P < .001$ for all comparisons except white race ($P = .07$).

BMI was calculated as weight in kilograms divided by height in meters squared. Diabetes mellitus was defined by self-report or blood glucose level of 126 mg/dL or higher. Smoking history was categorized as current, former, or never. A 12-hour fasting antecubital venous blood sample was obtained, and plasma concentrations of glucose and lipids were determined with automated bioassays in the CCLS laboratory. (To convert glucose to millimoles per liter, multiply by 0.0555.)

Cardiorespiratory fitness was assessed by an incremental treadmill test using a modified-Balke protocol as described previously.[23] In brief, treadmill speed was set at 3.3 mph (88 m/min) at a grade of 0% in the first minute, followed by 2% in the second minute with an increase of 1% every minute thereafter. After 25 minutes, the grade was unchanged while the speed was increased by 0.3 mph (5.4 m/min) every additional minute until volitional exhaustion. Using well-characterized regression equations, treadmill time using the Balke protocol permits estimation of peak METs.[25] Time to volitional exhaustion is correlated with direct measurement of maximal oxygen uptake ($r = 0.92$).[26] We defined CRF as both a continuous and categorical variable. We used our previously published age- and sex-specific distribution of treadmill duration from the overall CCLS population[27] to define CRF categories as follows: low (lowest 20%; mean [SD], 8.4 [1.2] METs), moderate (middle 40%; 10.4 [1.2] METs), and high (upper 40%; 13.0 [1.8] METs). All CRF assessments were performed prior to 2009.

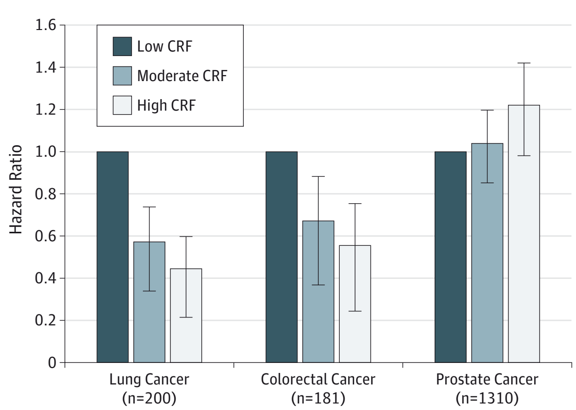
Outcomes

Medicare inpatient claims data were obtained from Centers for Medicare and Medicaid Services (CMS) for participants aged 65 years or older. The CMS data contain 100% of claims paid by Medicare for covered inpatient and outpatient health care services. The earliest date of a cancer diagnosis in a patient of Medicare age was determined through the Chronic Condition Warehouse (CCW) included in the Beneficiary Annual Summary File. Chronic conditions are defined within the CCW from well-established algorithms.[28-31] Three cancer diagnoses (ie, lung, colorectal, and prostate) were evaluated in the present report for men in this sample of the CCLS. The National Death Index was the primary data source for CVD and all-site cancer mortality outcomes. Thus, the outcomes available for analysis were incident lung, colorectal, and prostate cancer, as well as death from CVD and all-site cancer. **Table 1** shows the transitions evaluated in this study and includes (1) healthy men in midlife who had an interim lung, prostate, or colorectal cancer event at Medicare age and died of cancer (n = 219) or CVD (n = 64); (2) healthy men in midlife who subsequently died of cancer but were not diagnosed as having prostate, lung, or colorectal cancer at Medicare age (n = 281) (eg, a man with a history of prostate cancer without a Medicare claim between 2001 and 2009 or a man with cancer other than prostate, lung, or colorectal cancer); and (3) healthy men in midlife without prostate, lung, or colorectal cancer at Medicare age who died of CVD (n = 495).

Statistical Analysis

Differences in means and proportions of baseline characteristics across increasing categories of CRF were tested using the Jonckheere-Terpstra nonparametric method. Proportional hazards regression models were used to estimate hazard ratios (HRs) for site-specific cancer incidence and cause-specific mortality (incident lung, colorectal, and prostate cancer HRs by CRF category, adjusting for age at CCLS examination, BMI, cholesterol level, smoking, systolic blood pressure, blood glucose, diabetes mellitus, and examination year). Differences were considered statistically significant for $P < .05$. Attained age was used as the time scale in the proportional hazards models, which ensures that survival comparisons are among individuals of the same age. Left and right censoring for entry to and exit from Medicare surveillance was implemented using the counting process form of the proportional hazards model, and we assessed the proportional hazards assumption by testing for linear trends in covariate effects across the surveillance period. The analysis of multivariate failures, including incident cancer and CVD or cancer mortality (in those either diagnosed as having cancer or not), was constructed from similarly structured marginal proportional hazards models,[32] using the robust variance estimate[33] to account for the simultaneous presence of the same individual among risk sets of multiple outcomes.

Figure. Cardiorespiratory Fitness (CRF) and Risk of Incident Lung, Colorectal, and Prostate Cancer



The low CRF group is the referent group relative to moderate and high fitness. The error bars for moderate and high fitness represent the 95% confidence limits. Adjusted for age, examination year, body mass index, smoking, total cholesterol level, systolic blood pressure, diabetes mellitus, and fasting glucose level.

Results

Participant Characteristics

Participant characteristics are presented in **Table 2**. The mean (SD) age and CRF levels were 49 (9) years and 11.0 (2.3) METs, respectively. For the overall sample, BMI, total cholesterol level, smoking, glucose levels, and blood pressure decreased across increasing CRF category ($P < .001$ for all comparisons).

Primary Cancer Incidence

Medicare surveillance included a total of 91 366 person-years of follow-up for incident lung, colorectal, and prostate cancer in 13 949 men, for an average 6.5 years of surveillance. During this time, 1310 were diagnosed as having prostate cancer (14.3 per 1000 person-years), 200 men were diagnosed as having lung cancer (incidence 2.2 per 1000 person-years), and 181 were diagnosed as having colorectal cancer (2.0 per 1000 person-years).

There was a significant inverse and graded association across low, moderate, and high CRF and incidence of lung ($P < .001$) and colorectal cancer ($P < .001$) (**Figure**). Compared with men in the low CRF category, the adjusted HRs for lung cancer incidence were 0.57 (95% CI, 0.41-0.81) for moderate CRF and 0.45 (95% CI, 0.29-0.68) for high CRF. The corresponding HRs for colorectal cancer were 0.67 (95% CI, 0.46-0.98) for moderate CRF and 0.56 (95% CI, 0.36-0.87) for high CRF relative to the lowest CRF category, respectively (**Table 3**). A 1-MET increase in CRF was associated with a 17% (95% CI, 0.77-0.90) and 9% (95% CI, 0.84-0.99) relative risk reduction in the risk of lung and colorectal cancer, respectively. There was a significant positive and graded association across low, moderate, and high CRF and incident prostate cancer ($P = .004$). Compared with men in the low CRF category, the adjusted HR for prostate cancer incidence was 1.04 (95% CI, 0.88-1.23) for moderate CRF and 1.22 (95% CI, 1.02-1.46) for high CRF. It is important to note that, considering the mixed association of CRF with incident site-specific lung and colorectal vs prostate cancer, the model demonstrated no association between midlife CRF and incident combined lung, colorectal, and prostate cancer (HR, 0.91 [95% CI, 0.80-1.05]; $P = .19$, moderate vs low CRF; HR, 0.99 [95% CI, 0.86-1.15]; $P = .93$, high vs low CRF) (Table 1).

Table 3. Association Between Midlife Cardiorespiratory Fitness (CRF) and Later-Life Incident Cancer in the Cooper Center Longitudinal Study

		Hazard Ratio (95% CI)[a]			
Cancer	Events, No.	Low CRF	Moderate CRF	High CRF	1-MET Increase
Lung	200	1 [Reference]	0.57 (0.41-0.81)	0.45 (0.29-0.68)	0.83 (0.77-0.90)
Colon	181	1 [Reference]	0.67 (0.46-0.98)	0.56 (0.36-0.87)	0.91 (0.84-0.99)
Prostate	1310	1 [Reference]	1.04 (0.88-1.23)	1.22 (1.02-1.46)	1.03 (1.00-1.06)

Abbreviation: MET, metabolic equivalent.

[a] Adjusted for age, visit date, body mass index, smoking, systolic blood pressure, cholesterol level, diabetes mellitus, fasting glucose level.

Cause-Specific Mortality in Men Diagnosed as Having Lung, Colorectal, or Prostate Cancer

We analyzed the prognostic importance of CRF using a model that allowed for differences in the patterns of mortality following a diagnosis of cancer (Table 1). High midlife CRF was associated with a lower risk of cancer mortality (high vs low CRF HR, 0.68 [95% CI, 0.47-0.98]) and CVD mortality (high vs low CRF HR, 0.32 [95% CI, 0.16-0.64]) following a diagnosis of cancer. It is important to note that midlife CRF remained prognostic of cancer mortality among men diagnosed as having cancer who were not identified during the Medicare surveillance period or among those who died of cancers other than prostate, lung, or colorectal cancer (high vs low CRF HR, 0.66 [95% CI, 0.48-0.91]). Finally, as expected, there was an inverse association between midlife fitness and CVD mortality (high vs low CRF HR, 0.38 [95% CI, 0.29-0.48]) among men without a diagnosis of cancer at Medicare age.

Sensitivity Analysis Among Nonsmokers

We performed a sensitivity analysis to determine associations between CRF and both colorectal and lung cancer as well as survival after a cancer diagnosis among nonsmokers. Compared with men in the low CRF category, the adjusted HR for lung cancer incidence was 0.74 (95% CI, 0.44-1.24) for moderate CRF and 0.55 (95% CI, 0.31-0.68) for high CRF among nonsmokers. The corresponding HRs for colorectal cancer were 0.63 (95% CI, 0.40-0.99) for moderate CRF and 0.42 (95% CI, 0.25-0.70) for high CRF relative to the lowest CRF category. A similar trend of lower mortality was observed among those in the high CRF group in midlife who developed cancer and were nonsmokers (high vs low CRF HR, 0.77 [95% CI, 0.49-1.21]). Finally, high midlife CRF was associated with a lower risk of CVD mortality (high vs low CRF HR, 0.34 [95% CI, 0.15-0.77]) following a diagnosis of cancer among nonsmoking men.

Discussion

Using a large, prospective cohort study, we found a graded, inverse association between midlife CRF and incident lung and colorectal cancers. This association was not demonstrated for midlife CRF and prostate cancer. Notably, midlife CRF was associated with a lower risk of both cancer and CVD mortality following a diagnosis of lung, colorectal, or prostate cancer in men. Our data suggest that higher levels of midlife CRF provide a mortality benefit into older age even in the setting of a cancer diagnosis.

In the current study, high CRF conferred a 55% and 44% reduction in the risk of lung and colorectal cancer, respectively, compared with low CRF. Every 1-MET increase in CRF was associated with 17% and 9% relative risk reductions in lung and colorectal cancer risk, respectively. These results are similar to those of the Kuopio Ischemic Heart Disease Risk Factor Study,[34] which found that a 1-MET increase in CRF was associated with a 20% and 12% reduction in the relative risk of lung and colorectal cancer, respectively, in 2268 asymptomatic Finnish men. Interestingly, in contrast to lung and colorectal cancer, high CRF was a risk factor for prostate cancer even after adjusting for potential confounding variables. The current results are similar to those of 2 other studies in the literature on CRF and prostate cancer. Laukkanen et al[34] found that a 1-MET increase in CRF was associated with a nonsignificant increase in prostate cancer risk (HR, 1.03; 95% CI, 0.94-1.12), Byun et al,[6] using data from the Aerobics Center Longitudinal Study, found that compared with men in the lowest CRF category, those with moderate or high CRF had adjusted HRs of 1.68 (95% CI, 1.13-2.48) and 1.74 (95% CI, 1.15-2.62) for incident prostate cancer, respectively.

Conflicting data exist in the literature regarding the impact of CRF on prostate cancer risk.[35] The exact reasons for the observed positive association between CRF and incident prostate cancer risk are not known, but differences in related health behaviors, such as screening, may be an important contributing factor. Specifically, men with higher CRF may also be more likely to undergo more frequent preventive health care screening and/or detection visits and, thus, had greater opportunity to be diagnosed as having localized prostate cancer relative to men with lower CRF, possibly with less frequent preventive health care visits. Notably, these findings are also consistent with those of several studies on physical activity and prostate cancer risk, an important predictor of attained CRF.[36] Understanding how screening may affect the association between CRF and prostate cancer, as well as studying the association between CRF and incident advanced-stage prostate cancer, are important areas of future research.

A key, novel finding in the current study was that CRF was an independent predictor of the transition from cancer and ultimately death from either cancer or CVD. High CRF was associated with a 32% risk reduction in cancer death among men who developed lung, colorectal, or prostate cancer at Medicare age compared with those with low CRF. Moreover, CRF was a powerful predictor of CVD death among men. Specifically, high CRF was associated with a 68% reduction in CVD death compared with low CRF among men who developed cancer. It is important to note that the number of individuals living with cancer in the United State is projected to increase from 13.7 million in 2012 to 18 million over the next decade.[37] Simultaneously, owing to important improvements in screening and adjuvant therapy, the 5-year relative survival rate for all cancers has increased from 49% in 1975 to 67% in 2007.[38] Consequently, patients with early-stage cancer now have sufficient survival to be at risk for noncancer competing causes of mortality, particularly CVD. This point is of particular importance given that 70% of cancer-related mortality will occur in individuals 65 years or older.[13] As such, the current findings are of timely importance and shed new light on remaining fit throughout the lifespan in an effort to decrease the morbidity and mortality related to cancer.

Notably, we chose to focus on CRF as the exposure of interest rather than physical activity for several reasons. It is well established that level of physical activity significantly influences level of CRF,[24] and structured exercise training is associated with 10% to 25% improvements in measures of CRF.[39] Moreover, regular physical activity is associated with significant reductions in the risk of certain forms of cancer, with the evidence classified as convincing for breast and colon cancer.[40,41] Several epidemiological studies[42,43] suggest that, in general, self-reported regular exercise (eg, brisk walking for 30 minutes, 5 days a week) is associated with substantial reductions in the risk of cancer-specific death following a diagnosis of cancer. Notably, physical activity and CRF are correlated but provide distinct information.[44] Cardiorespiratory fitness is also highly reproducible and objectively assessed via incremental exercise tolerance testing compared with physical activity, which is largely determined by self-report questionnaires. A prior study[45] demonstrated that CRF is be a more potent marker of mortality than physical activity. As such, given the current study findings and prior evidence, we contend that measurement of CRF should be used more frequently in the cancer prevention setting.

Our findings do not address whether improvements in CRF via exercise training interventions are an effective strategy to lower cancer incidence or reduce the risk of death following a cancer diagnosis in men. However, there is considerable evidence that aerobic training interventions following standard exercise prescription guidelines are associated with a 15% to 30% CRF improvement in men with chronic conditions but without cancer,[46,47] as well as in those with cancer.[48] In addition, exercise training also has been shown to modulate circulating host pathways postulated to mediate the association of CRF with cancer incidence and/or prognosis.[42] Nevertheless, the predictive value of CRF on cancer incidence and mortality does not necessarily indicate that CRF augmentation will lower cancer and /or CVD events.[49] Adequately powered randomized clinical trials are required to definitively address these questions.

Important limitations need to be considered when interpreting the present findings. First, we were unable to determine the length and intensity of smoking in the CCLS. To overcome this limitation, we performed a sensitivity analysis among nonsmokers, finding similar associations between fitness and both cancer risk and survival after cancer. Second, we were not able to identify outcomes that occurred between study entry and the onset of Medicare eligibility, as the cancer outcome was derived from administrative data from the CMS. However, Medicare data have been shown to be a reliable source of information across multiple clinical cancer outcomes.[50,51] Furthermore, Medicare data represent a cost-effective resource, providing the ability to assess associations between CRF and both cancer incidence and long-term mortality outcomes that would be prohibitively expensive to replicate in a prospective cohort study of comparable size and duration. Third, CRF was assessed years prior to a diagnosis of lung, colorectal, or prostate cancer or death in men diagnosed as having cancer. Thus, it is not known how changes in CRF and related behaviors, such as physical activity from the initial preventive health care to cancer diagnosis as well as changes in CRF and physical activity after diagnosis, may have had an impact on these current findings. Fourth, it is not known how CRF may differentially have an impact on cancer prognosis among those who are diagnosed at different stages of cancer, because cancer stage was not captured in the current study. Finally, the specific nature of cancer treatments provided to each patient on an individual level was not characterized, and so the impact of chemotherapy, radiation, and or surgical interventions in the sample could not be quantified.

Conclusions

To our knowledge, this is the first study to demonstrate that CRF is predictive of site-specific cancer incidence, as well as risk of death from cancer or CVD following a cancer diagnosis. These findings provide further support for the effectiveness of CRF assessment in preventive health care settings. Future studies are required to determine the absolute level of CRF necessary to prevent site-specific cancer as well as evaluating the long-term effect of cancer diagnosis and mortality in women.

ARTICLE INFORMATION

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Acquisition, analysis, or interpretation of data: Lakoski, Willis, Leonard, Gao, Radford, Farrell, Douglas, DeFina, Jones.
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