Improved Survival With Higher Pre-diagnosis Cardiorespiratory Fitness in Men Who Developed Digestive System Cancers: A Prospective Pilot Study

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Abstract. *Background/Aim:* Digestive system cancers are the leading cause of cancer mortality and have poor survival particularly in men. The study aimed to assess the association between pre-diagnosis cardiorespiratory fitness (CRF) and cancer mortality in a pilot sample of men who developed digestive system cancers. *Patients and Methods:* Pre-diagnosis CRF (treadmill exercise test) was assessed in 342 men (68.9±21.8 years) who developed digestive system cancers during 6.7±5 years from baseline evaluation. Cox multivariable hazard models were analyzed for total cancer mortality. *Results:* During 7.2±5 years follow-up from baseline, 120 participants died from cancer. Compared to low CRF, moderate and high CRF levels were associated with 57% [0.43, 95%CI=0.24-0.74] and 73% [0.27, 95%CI=0.12-0.59] reduced risks for cancer mortality, respectively (*p* trend=0.002). Survival time from baseline was longer among those with moderate [13.5 (range=12.1-14.9) years] and high [16.1 (range=14.0-18.2) years] compared to low CRF [7.9 (range=5.7-10.1) years]. *Conclusion:* Higher pre-diagnosis CRF is independently associated with lower risk of cancer mortality and longer survival in men who later developed digestive system cancers.

Digestive system cancers as a group are the most common diagnosed cancers and the leading cause of cancer-related deaths worldwide and in US (1, 2). Digestive system cancers include esophagus, stomach, small intestine, colon, rectum, anus, anal canal, anorectum, liver, intrahepatic bile duct, gallbladder, pancreas and other digestive organs (1). Globally,

approximately 5.3 million digestive system cancers were diagnosed and more than 3.5 million died from these in 2018 (2). The American Cancer Society estimates that 328,030 new cases of digestive system cancers will be diagnosed and 165,460 will die from these in the US during 2019. The 5-year survival rates from digestive system cancers are relatively poor, ranging from 65% in colon and rectum to 31% for stomach cancer, 19% for esophageal cancer, 18% for liver cancer and 9% for pancreatic cancer (1).

Efforts to improve survival from digestive system cancers have shown encouraging results particularly using screening and early detection for colorectal cancer, although for other cancers such as esophageal, liver and pancreatic cancer, the survival rates remain poor, and evidence-based screening tools that improve survival are lacking (3). The American Heart Association recently endorsed cardiorespiratory fitness (CRF) as potential screening tool for health outcomes, providing a strong case for using CRF as a vital sign (4). In this regard, low CRF has been established as a risk factor associated with many chronic conditions as well as all-cause, cardiovascular and cancer mortality (4, 5). Although higher CRF has been extensively demonstrated to have protective benefits for health outcomes (4), few studies have assessed the association between CRF and incidence of colorectal and gastro-intestinal cancers (6-8). Only one study has reported on the inverse association between CRF and mortality from digestive system cancers among the general population (9).

To our knowledge, the potential survival benefits of higher pre-diagnosis CRF in men who developed digestive system cancers has yet to be explored. Such data would have potentially important public-health implications for cancer prevention and control of digestive system cancers. Therefore, the aim of the current study was to assess the association between pre-diagnosis CRF and cancer mortality in a pilot sample of men who developed digestive system cancers. Additionally, the study aimed to quantify the potential public health implications of CRF in prevention and control of digestive system cancers.

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Patients and Methods

The present analysis utilized the Veterans Exercise Testing Study (VETS), which has been previously described (10, 11). In brief, the VETS cohort is an ongoing, prospective evaluation of primarily male (96%) Veterans referred for exercise testing for clinical reasons, and has been designed to address the association of exercise test, clinical, and lifestyle factors 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. Clinical information on diagnoses, risk factors and health behaviors (smoking, alcohol and drug abuse) were collected at the time of the exercise test using the Veterans Affairs Computerized Patient Record System (CPRS) and self-reported health history. The current study included male participants who were free from any malignancy at baseline and who developed one or more of digestive system cancers (esophagus, stomach, small intestine, colon, rectum, anus, anal canal, anorectum, liver, intrahepatic bile duct, gallbladder, pancreas and other digestive system organs) during 6.7 ± 5 years from baseline.

Cardiorespiratory fitness. At baseline, participants underwent maximal symptom-limited exercise testing using an individualized ramp treadmill protocol according to established guidelines (12, 13). 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 (12, 13). A 12-lead electrocardiogram, heart rate, blood pressure and Borg 6-20 perceived exertion rating were continuously recorded throughout the test and standard criteria for test termination were used (12, 13). CRF [in Metabolic Equivalents (METs)] was calculated from peak treadmill speed and grade utilizing established metabolic equations from the American College of Sports Medicine (12). CRF was analyzed as a continuous as well as a categorical variable divided into 3 categories (Low CRF <5METs, Moderate CRF 5 to 10 METs and High CRF >10 METs) (4, 6).

Outcomes ascertainment. The Veterans Affairs CPRS was used for capturing cancer outcomes; total cancer mortality was the primary outcome. Previous reports have demonstrated that the Veterans Affairs death records are relatively complete compared to those from other sources, such as the Social Security Administration (14). The Veterans Affairs records have also good agreement ($\kappa = 0.82$ to 0.91) with state death records (15). Medical records were carefully reviewed by qualified medical personnel who were otherwise blinded to treadmill test results and other study information. Cancer death was verified using International Classification of Diseases, ninth and tenth edition codes and the vital status for each patient was ascertained as of August 2015.

Statistical analysis. Demographic and clinical data of the participants are presented as mean $\pm$ standard deviation. Categorical variables are presented in percentages. Comparisons between participants with low, moderate or high CRF were performed using analysis of variance for continuous variables and chi-square tests for categorical variables. Multivariable Cox proportional hazard models were used to assess the association between CRF and cancer

mortality. The models were adjusted for age, body mass index, hypertension, hypercholesterolemia, diabetes, smoking status (never, former, current), smoking in pack-years and alcohol abuse (16-18). The hazard models also took into account competing events (death resulting from causes other than cancer) (19, 20). In order to address potential reverse causality bias, a secondary analysis was performed after excluding participants who had less than two years follow up. Population attributable fraction (PAF%) for low CRF (<5 METs) compared to ≥ 5 METs as a risk factor was analyzed. PAF% is a metric quantifying the contribution of a risk factor to the burden of disease or death and represents the proportional reduction in population disease or mortality burden that would occur if exposure to a risk factor was eliminated (*e.g.*, no tobacco use). PAF% was calculated using the equation $P[\text{Relative Risk}(\text{RR}) - 1] / [1 + P(\text{RR} - 1)] * 100$ (21) where P = prevalence of the risk factor and RR = a fully adjusted relative risk calculated from the Cox hazard model accounting for competing events (22, 23). 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 confirmed using the scaled Schoenfeld residuals.

Exposure impact number (EIN) was calculated as $\text{EIN} = 1 / [(RR - 1) * PNE] + RR / [(RR - 1) * (1 - PNE)]$ where RR = fully adjusted relative risk from Cox hazard model accounting for competing events and PNE = event rate in non-exposed population (24-27). EIN is the corresponding epidemiological 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 in order to prevent one additional adverse event or outcome. EIN and NNT permit quantification of effort needed to be taken for preventing one 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 (24-27). Data report and presentation followed the “Strengthening the Reporting of Observational Studies in Epidemiology” (STROBE) guidelines (28). SPSS (IBM, Chicago, IL, USA) version 23 was used for statistical analyses. The significance level was set at $p < 0.05$.

Results

The analytical sample included 342 male participants who developed digestive system cancers [colorectal ($n = 224$), gallbladder ($n = 59$), liver ($n = 28$), esophageal ($n = 13$), pancreatic ($n = 13$), intrahepatic bile duct ($n = 3$), stomach ($n = 1$) and anus ($n = 1$)] during 6.7 ± 5 years from baseline assessment. Mean age was 68.9 ± 21.8 years, and mean CRF was 8.0 ± 2.9 METs. Demographic and clinical characteristics of the participants are presented in Table I. Approximately 27% were current smokers, 57% had hypertension, 41.5% had hypercholesterolemia, 33.3% were obese, 11.1% had a history of cardiovascular disease and 20.6% had diabetes at baseline. Participants with high CRF compared to participants with moderate and low CRF levels had lower pack-years of smoking, lower prevalence of hypertension and fewer fatalities related to cancer, and a higher prevalence of being physically active (Table I).

Table I. Baseline demographic and clinical characteristics of the cohort.

	Entire Cohort (n=342)	Low CRF (n=53)	Moderate CRF (n=210)	High CRF (n=79)	p-Value
Age (yr)	68.9±21.8	65.7±22.4	68.9±22.1	71.1±20.7	0.371
BMI (kg/m ²)	28.8±5.3	29.5±6.6	29±5	27.8±5.3	0.128
Obesity (BMI>30 kg/m ²)	33.3%	32.1%	35.6%	28.2%	0.487
Smoking status					
Never	20.9%	20%	19.4%	25.7%	0.571
Former	52.3%	46%	54.7%	50%	
Current	26.8%	34%	25.9%	24.3%	
Smoking (pack/years)	35.3±26.5	52.4±34.6	34.1±24	26.1±25.4	<0.001
Hypertension	57%	71.7%	56.2%	49.4%	0.037
Hypercholesterolemia	41.5%	32.1%	41%	49.4%	0.137
Cardiovascular disease	11.1 %	17%	9.5%	11.4%	0.303
Diabetes	20.6%	22%	21.9%	16.3%	0.848
Alcohol abuse	4.1%	3.8%	4.3%	3.8%	0.975
Anti-hypertensive drugs	14.6%	35.8%	11.4%	8.9%	<0.001
Anti-hyperlipidemias	12.6%	9.4%	13.3%	12.7%	0.746
CRF (METs)	8±2.9	4±0.7	7.5±1.4	11.9±1.8	<0.001
Physically active	54.3%	41.5%	50%	74.4%	<0.001

Data presented as means±standard deviation or % of the group for categorical variables. BMI: Body mass index; CRF: cardiorespiratory fitness; METs: metabolic equivalents.

Table II. Hazard models and survival of cardiorespiratory fitness and cancer mortality in men who developed digestive system cancers.

Group/CRF Categories	Low CRF <5 METs	Moderate CRF 5 to 10 METs	High CRF >10 METs	p-trend	1-MET increase	p-Value
Cancer mortality (n/%)	34 (64.2%)	70 (33.3%)	16 (20.3%)	N/A	N/A	<0.001
Hazard ratios (95% confidence interval)	1 (Reference)	0.43 (0.24 to 0.74)	0.27 (0.12 to 0.59)	0.002	0.86 (0.79 to 0.94)	0.001
Mean survival time from baseline (years and 95% confidence interval)	7.9 (5.7 to 10.1)	13.5 (12.1 to 14.9)	16.1 (14.0 to 18.2)	N/A	N/A	<0.001

CRF: Cardiorespiratory fitness; MET: metabolic equivalent; N/A: not applicable. The risk models were adjusted for age, body mass index, hypertension, hypercholesterolemia, diabetes, smoking status (never, former, current) smoking in pack-years, alcohol abuse and accounted for competing events.

During a mean of 7.2±5 years follow-up from baseline, 120 participants died from cancer and 3 participants died from causes other than cancer. In a continuous model, each 1-MET higher CRF was associated with a 14% reduced risk [0.86, 95%CI=0.79-0.94, $p=0.001$] for cancer mortality. In a categorical model where low CRF was used as the reference, moderate and high CRF levels were associated with 57% [0.43, 95%CI=0.24-0.74] and 73% [0.27, 95%CI=0.12-0.59] reduced risks for cancer mortality (p trend=0.002), respectively. Survival time from baseline was significantly longer among those with moderate [13.5 (range=12.1-14.9) years] and high [16.1 (range=14.0-18.2) years] compared to low CRF [7.9 (range=5.7-10.1) years], respectively (Table II and Figure 1). After exclusion of those with less than two years follow up, CRF remained a significant predictor of cancer mortality. The

hazard ratios and 95% confidence intervals were 0.89, 95%CI=0.81-0.97, $p=0.012$ in the continuous model and 0.51, 95%CI=0.27-0.99 and 0.33, 95%CI=0.14-0.8, p trend=0.041 in the categorical model for moderate and high CRF, respectively. PAF was 9.4%, 95%CI=5.2-12.0 and EIM was 4.5, 95%CI=2.8-11.0, $p=0.001$ (Table III).

Discussion

The current pilot study aimed to assess the association between pre-diagnosis CRF and cancer mortality in male participants who later developed digestive system cancers. The study also sought to quantify the potential public health implications of CRF in prevention and control of digestive system cancers. The findings demonstrated that

Figure 1. Kaplan-Meier survival curves of cardiorespiratory fitness categories and cancer mortality in men who developed digestive system cancers. MET: Metabolic equivalent.

higher pre-diagnosis CRF is independently associated with lower risk of cancer mortality and longer survival. For each one higher MET level, there was a 14% reduced risk for cancer mortality (Table II). Eliminating low CRF as risk factor is potentially cost-effective which could potentially prevent 9.4% of cancer mortality in men who develop digestive system cancers later in life. While these observations do not indicate causality and require confirmation in larger prospective studies, they provide important information for cancer prevention and control. Since digestive system cancers are prevalent in the general population and are associated with poor survival particularly in men (1, 2), these findings have important public health implications for developing effective strategies for reducing mortality and improving survival in people who develop digestive system cancers. The data suggest that screening middle-age men for CRF and achieving higher fitness levels through regular exercise are potentially cost-effective strategies that could reduce mortality from cancer and improve survival time in men who later develop digestive system cancers.

The current results are consistent with previous studies on the relationship between CRF and incidence of colorectal and gastro-intestinal track cancers (6-8). The study also parallels a previous study on the inverse association between CRF and mortality from digestive system cancers in men from the general population (9). The present study extends this earlier report by providing novel data with respect to pre-diagnosis CRF and survival benefits in men who developed digestive system cancers. Particularly, the current study is the first to demonstrate a reduced risk of

cancer mortality and longer survival time with higher pre-diagnosis CRF in men who develop digestive system cancers later in life. CRF remained a significant predictor of cancer mortality even after adjusting for potential confounders, accounting for competing events and excluding individuals with less than two years follow-up. In addition, the study provides novel data quantifying the potential public health implications of CRF in prevention and control of digestive system cancers. The PAF% analysis showed that by eliminating low CRF as risk factor in the pre-diagnosis phase of digestive system cancers, 9.4% of cancer mortality could potentially be prevented in men who later develop digestive system cancers. The low EIN (approximately 5) supports that this strategy is potentially cost-effective. For every 5 men with low CRF (<5 METs) that could be moved to ≥ 5 METs, one cancer-related death could be avoided in men who develop digestive system cancers later in life (Table III). Given the extensive body of literature demonstrating that most people can improve ≥ 1 MET with a regular exercise program (4), screening for impaired CRF and achieving higher levels can potentially improve survival from cancer in men who develop digestive system cancers. However, larger prospective studies are needed to confirm this observation.

Although the precise mechanisms by which higher pre-diagnosis CRF might provide protective benefits are not fully understood, there are several potential explanations. Digestive system cancers such as colorectal, stomach and pancreatic are associated with obesity, physical inactivity, smoking and heavy alcohol consumption (1, 16). These are related to increased systemic inflammation, abnormal metabolic and hormonal states, compromised immune function and oxidative stress (29-33). In contrast, higher CRF is associated with lower chronic inflammation, enhanced immune system function, reduced oxidative stress and elevated antioxidant capacity, as well as enhanced hormonal and metabolic regulation (4, 34). Additionally, higher CRF is a well-established health marker associated with reduced risk of all-cause, cardiovascular and cancer-related mortality in the general population as well as those with chronic conditions (4, 5). It is possible that higher pre-diagnosis CRF conferred some protection with respect to cancer progression, metastasis and ultimately cancer death (31-33). However, despite growing observational evidence supporting the concept that CRF has a role in reduced risk of cancer mortality (4, 5, 9), prospective and mechanistic studies are warranted.

The strengths of the current study include a prospective assessment of cancer mortality outcomes and extended follow-up time (mean of approximately 7 years). In addition, outcomes were verified through the Veterans Affairs computerized medical records system, which has been demonstrated to be comparatively accurate and complete (14,

Table III. Population attributable fraction and exposure impact number of low cardiorespiratory fitness in men who developed digestive system cancers.

Prevalence of low CRF (<5 METs)	Relative risks (95%CI)	PAFs% (95%CI)	EIN (95%CI)	p-Value
15.5%	2.5 (1.5-4.4)	9.4 (6.4-12.2)	4.5 (2.8-11.0)	<0.001

CI: Confidence interval; CRF: cardiorespiratory fitness; EIN: exposure impact number; MET: metabolic equivalent; PAF: population attributable fraction. The risk models were adjusted for age, body mass index, hypertension, hypercholesterolemia, diabetes, smoking status (never, former, current) smoking in pack-years, alcohol abuse and accounted for competing events.

35, 36). CRF was quantified from treadmill exercise testing utilizing established protocols (12, 13). This method has been widely used in epidemiological studies and has been shown to be strongly predictive for total cancer mortality and mortality from digestive system cancers (4-6, 8, 9). The study also has several limitations. First, although the sample size was relatively small and individuals with different digestive system cancers were included, the number of deaths enabled fully adjusted multivariable analyses, providing an independent association between CRF and cancer death. Second, although the multivariable hazard models were adjusted for established confounders similar to those in previous studies (6, 9), data on dietary habits were not available, which may have an influence on risk. Third, Veteran participants are a unique population with a rich mixture of co-morbidities that may have influenced the results by selection bias, although the findings are consistent with previous reports of CRF and digestive system cancer outcomes (6, 8, 9). Fourth, the study was limited to men, and the extent to which the findings apply to women requires further investigation. Finally, as is the case in all epidemiological studies, the findings provide an association between exposure (CRF) and adverse outcome (cancer mortality), but preclude the establishment of cause and effect.

In summary, higher pre-diagnosis CRF is independently associated with a lower risk of cancer mortality and longer survival time in men who later developed digestive system cancers. Eliminating low CRF as risk factor could reduce mortality from cancer and extends survival. In addition to established screening tools for colorectal cancer, assessing and encouraging improvements in CRF may serve as a cost-effective public-health strategy for the prevention and control of digestive system cancers. Future large prospective studies should be conducted to ascertain these findings and further explore the impact of promoting CRF in primary and secondary prevention in this population.

Conflicts of Interest

The Authors declare there are no conflicts of interest regarding this study.

Authors' Contributions

BV was responsible for study design and conception, statistical analysis, results interpretation, drafting, writing and submitting the manuscript. ZC contributed to the conception and design of the study, was responsible for data collection, contributed to results interpretation, drafting the article and revising it critically for important intellectual content. JM contributed to the conception and design of the study, served as principle investigator of the study, data collection and results interpretation, contributed to drafting the article and revising it critically for important intellectual content. All Authors read and approved the final version.

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