

Cardiorespiratory Fitness, Lung Cancer Incidence, and Cancer Mortality in Male Smokers



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Introduction: The preventive role of cardiorespiratory fitness in lung cancer among smokers is unknown. This study aims to evaluate the association between cardiorespiratory fitness and lung cancer incidence and cancer mortality in former and current male smokers.

Methods: From 1987 to 2014, cardiorespiratory fitness (quantified from treadmill exercise testing) was assessed in 2,979 men (former smokers, $n=1,602$; current smokers, $n=1,377$) aged 59.1 (SD=17.4) years and prospectively followed up for 11.6 (SD=7) years. Multivariable Cox hazard models and population attributable fraction of low cardiorespiratory fitness (<5 METs) for cancer outcomes were analyzed during 2018.

Results: Of the 99 case patients diagnosed with lung cancer, 79 died of cancer 3.6 (SD=4.6) years after diagnosis. Among former smokers, 1-MET increase and categories of moderate and high cardiorespiratory fitness were associated with 13% ($p=0.016$), 51%, and 77% (p -trend=0.015) reductions in lung cancer incidence, respectively. Among current smokers who were later diagnosed with lung cancer, 1-MET increase and categories of moderate and high cardiorespiratory fitness were associated with 18% ($p=0.008$), 84%, and 85% (p -trend<0.001) reductions in cancer mortality, respectively. The population attributable fraction for lung cancer incidence was 10.8% among former smokers and 22.3% for cancer mortality among current smokers.

Conclusions: Higher cardiorespiratory fitness is associated with lower risk of lung cancer incidence in former smokers and reduced risk of cancer mortality in current smokers who were diagnosed with lung cancer. Screening for low cardiorespiratory fitness and achieving at least moderate cardiorespiratory fitness could potentially reduce lung cancer morbidity and mortality, providing a preventive strategy for smokers.

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INTRODUCTION

Lung cancer remains the most frequent cancer worldwide, with more than 2 million new cases and 1.8 million lung cancer–related deaths.^{1,2} In the U.S., lung cancer is estimated to be the second most common cancer and the leading cause of cancer-related deaths in both men and women.³ Lung cancer is one of the most aggressive cancers in humans, with a mean 5-year survival ranging from 10% to 17%.^{1–4} Tobacco use is the single most important risk factor for developing and dying from lung cancer. Up to 90% of the incidence

and more than 80% of lung cancer mortality are attributable to smoking tobacco. In addition, approximately

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22%–30% of total cancer mortality is linked to smoking cigarettes.^{1–3,5,6} Smoking tobacco is a highly prevalent behavior with nearly 20% of the world's adult population (about 800 million men and 200 million women) currently smoking.¹ Recently, WHO reported that although smoking habits have declined globally, 35% of men in 2015 were current smokers.⁷ In the U.S, approximately 17% of men smoke; in the European Union, about 31% of men are smokers, with a wide variation between countries.^{5,8} Despite the fact that smoking increases the risk for lung cancer about twenty-five-fold, most cigarette smokers do not develop lung cancer, and thus, there may be factors other than smoking that modify risk.^{3,4,9}

These data underscore the importance of effective targeting for risk factors for cancer in primary prevention. Mounting evidence has firmly established that low cardiorespiratory fitness (CRF) is a significant risk factor for the development of many chronic conditions, and it is strongly associated with all-cause, cardiovascular, and cancer mortality.^{10–12} Recently, the American Heart Association endorsed adopting CRF as a vital sign in clinical practice, making a strong case for assessing CRF for primary prevention.¹¹ Several reports have demonstrated the protective benefits of higher CRF against lung cancer^{13–17}; in addition, a few studies have reported inverse associations between CRF and cancer mortality among smokers.^{9,18,19} However, to the authors' knowledge, the associations between CRF and lung cancer incidence among smokers and cancer mortality among smokers who have been diagnosed with lung cancer have yet to be explored. Given that approximately 1 in 5 men are currently smoking^{1,5,7} and thus have a significantly increased risk for developing and dying from lung cancer,^{1,3} investigating the preventive role of CRF in lung cancer has potentially important public health implications for prevention, screening, and treatment.^{1,3,5} Therefore, this study aimed to assess the association between CRF and lung cancer incidence and cancer mortality among former and current male smokers who developed lung cancer. An additional aim was to quantify the potential public health impact of removing low CRF as a risk factor on lung cancer outcomes.

METHODS

Study Population

The Veterans Exercise Testing Study has been described previously.^{20,21} Briefly, the cohort is an ongoing, prospective evaluation of primarily male Veterans (96%) referred for exercise testing for clinical reasons, designed to address exercise test, as well as 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 IRB at Stanford University, CA. 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 and physical activity) were collected at the time of the exercise test using the Veterans Affairs Computerized Patient Record System and self-reported health history. Of 5,540 participants who completed the baseline evaluation, 2,561 participants were excluded because they never smoked ($n=1,941$), were women ($n=352$), had history of any malignancy ($n=76$), and had incomplete or prematurely terminated exercise tests ($n=192$). A total of 2,979 male Veterans (former smokers, $n=1,602$; current smokers, $n=1,377$) were included in the analysis; they were followed up for a mean of 11.6 (SD=7) years. 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 currently smoke cigarettes.²²

Measures

Participants underwent maximal symptom-limited exercise tests using an individualized ramp treadmill protocol according to the established guidelines.^{23,24} The exercise protocol included continuous, individualized increments in treadmill speed and grade adjusted to achieve a targeted duration between 8 and 12 minutes, using predicted CRF considering age and a symptom questionnaire.^{25,26} 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.^{23,24} CRF (in METs) was calculated from peak treadmill speed and grade utilizing well-established metabolic equations from the American College of Sports Medicine.²³ CRF was analyzed as a continuous and categorical variable divided into 3 categories (low CRF, <5 METs; moderate CRF, 5–10 METs; high CRF, >10 METs).^{11,15} Determination of low CRF (<5 METs) as a risk factor was made according to the recent recommendations from the American Heart Association.¹¹

The Veterans Affairs Computerized Patient Record System was used to capture lung cancer 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.²⁷ The Veterans Affairs records also have excellent agreement ($\kappa=0.82–0.91$) with state death records and high sensitivity for incidence of several chronic conditions.^{28–30} Lung cancer diagnosis was verified using pathology reports and International Classification of Diseases, Ninth Revision and ICD-10 codes. Medical records were carefully reviewed by qualified medical personnel who were otherwise blinded to the treadmill test results and other study information. Data collection on cancer diagnosis and vital status for each participant was ascertained as of August 2015.

Statistical Analysis

The authors used SPSS, version 23 for statistical analyses, which were conducted in 2018. The significance level was set at $p<0.05$. Demographic, clinical, and physiologic data of the participants are presented as mean and SD. Categorical variables are presented in absolute numbers or percentages. Comparisons between CRF categories among former and current smokers were performed

using ANOVA for continuous variables and chi-square tests for categorical variables. The continuous and categorical Cox proportional hazard models were adjusted for age, history of alcohol and drug abuse, BMI, smoking pack years, and physical activity status (active or inactive).³¹ 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.^{20,23,32,33}

Population attributable fraction (PAF%) for low CRF (<5 METs) compared with that for moderate and high CRF (≥5 METs) as a risk factor was analyzed.¹¹ PAF% is a well-established metric quantifying the contribution of a risk factor to the burden of disease or death and represents the proportional reduction in disease or mortality burden that would occur if exposure to the risk factor was eliminated. PAF% was calculated according to the following equation:³⁴

$$P(RR-1)/1 + P(RR-1) \times 100,$$

where P refers to the prevalence of the risk factor, and RR is the relative risk calculated from the Cox hazard model.^{35,36} Kaplan–Meier survival analysis and log-rank tests were used for comparing survival time between the CRF categories among those who were diagnosed with lung cancer.

RESULTS

The study sample included 2,979 participants (1,602 former and 1,377 current smokers) with a mean age of 59.1 (SD=17.4) years. Demographic and clinical characteristics of the participants are presented in [Table 1](#). Approximately 33% were obese, 52% had hypertension, 29% had a history of cardiovascular disease, 8.7% had pulmonary disease, and 14.9% had a diagnosis of type 2 diabetes at baseline. Former smokers compared with current smokers were older; had a higher prevalence of obesity, hypertension, dyslipidemia, and diabetes (all $p<0.001$); and had a slightly lower CRF (7.9 [SD=3.2] vs 8.2 [SD=3.4], $p=0.029$) and significantly fewer smoking pack years ($p<0.001$). There was no significant difference in age between CRF categories among former smokers and current smokers. Participants with low CRF compared with those with moderate or high CRF had a higher prevalence of comorbidities both among former and current smokers. During 11.6 (SD=7) years of follow-up, 99 case patients were diagnosed with lung cancer (46 [2.9%] among former smokers and 53 [3.8%] among current smokers), and 79 of these participants died of cancer 3.6 (SD=4.6) years after diagnosis ([Table 1](#)).

Among former smokers, both continuous and categorical models showed independent and inverse relationships between CRF and cancer incidence. Each 1-MET–higher

CRF was associated with a 13% reduction in risk for lung cancer incidence. Expressed categorically, participants with moderate and high CRF had 51% and 77% reductions, respectively, in risk of lung cancer incidence compared with participants with low CRF ([Table 2](#)). Among current smokers who were diagnosed with lung cancer, higher CRF was associated with a lower risk of cancer mortality and longer survival time. In a continuous model, each 1-MET–higher CRF was associated with an 18% reduction in risk for cancer mortality. In a categorical model, moderate and high CRF was associated with 84% and 85% reductions in risk for cancer mortality, respectively. The association between CRF and lung cancer incidence among current smokers was not significant. Among former smokers who were diagnosed with lung cancer, although the continuous model showed a 21% reduction in risk for each higher MET level achieved, the categorical model and survival time showed a trend but were not statistically significant ([Table 2](#)). The PAF% for lung cancer incidence was 10.8% among former smokers; the PAF% for cancer mortality among current smokers who were diagnosed with lung cancer was 22.3%. PAF% was not statistically significant for lung cancer incidence among current smokers, or for cancer mortality among former smokers who were diagnosed with lung cancer ([Table 3](#)).

DISCUSSION

This study aimed to assess the association between CRF and lung cancer incidence and cancer mortality in former and current male smokers. In addition, the authors sought to evaluate the potential public health implications of low CRF as a modifiable risk factor for the prevention of adverse lung cancer outcomes in smokers. The salient and novel findings indicate that higher CRF is independently associated with lower risk of lung cancer incidence among former smokers. Among current smokers who were diagnosed with lung cancer, higher CRF was associated with reduced risk of cancer mortality and longer survival time. In addition, the analyses revealed that by eliminating low CRF as a risk factor, 10.8% of lung cancer incidence in former smokers and 22.3% of cancer mortality in current smokers who were diagnosed with lung cancer could potentially be prevented. Although these observations do not indicate cause and effect, they have important public health implications for several reasons. First, smoking is a highly prevalent behavior that affects nearly 20% of the total adult population who have significantly higher risk for developing and dying from lung cancer. Second, smoking is the single most important risk factor for lung cancer, accounting for approximately 90% of

Table 1. Baseline Demographic and Clinical Characteristics of Former and Current Male Smokers

Characteristic	Entire cohort (N=2,979)	Former smokers				p-value	Current smokers				p-value
		All former smokers (n=1,602)	Low CRF (n=297)	Moderate CRF (n=898)	High CRF (n=407)		All current smokers (n=1,377)	Low CRF (n=229)	Moderate CRF (n=782)	High CRF (n=366)	
Age, years	59.1±17.4	61.8±17.9	60.3±17.3	62.2±18.4	61.9±16.9	0.272	56.1±16.3	57.5±16.8	55.8±16.3	55.9±16	0.373
Smoking (pack/years)	35.3±29	32.4±30.5	43.3±40.7	32.1±27.8	25±24.5	<0.001	40.3±26	50.7±26.3	41.5±27.1	31.3±20.1	<0.001
Obesity (BMI≥30 kg/m ²), %	32.5	37.3	36.4	41.3	29.4	<0.001	27	28.9	29.7	20	0.002
Hypertension, %	52.1	57.3	65.7	59.1	46.7	<0.001	41.3	58.1	50.3	30.3	<0.001
Dyslipidemia, %	37.5	40.1	36.4	40	44.2	0.103	34.1	28.4	34.3	37.2	0.088
Any cardiovascular disease, %	29.2	29.3	45.8	28.1	19.9	<0.001	29	38.4	30.8	19.4	<0.001
Any pulmonary disease, %	8.7	9	15.5	8	6.3	<0.001	8.4	16.6	7.7	4.9	<0.001
Type 2 diabetes, %	14.9	19.4	25.6	21.2	11.8	<0.001	9.5	14.4	10	9.5	0.001
Antihypertensive drugs, %	18.4	18.7	29.6	17	14.3	<0.001	18.1	26.6	19.7	9.3	<0.001
Antihyperlipidemia drug, %	9.3	12.8	12.8	12.8	12.8	0.293	5.2	5.2	5.2	5.2	0.917
Cardiorespiratory fitness (METs)	8±3.4	7.9±3.2	3.7±0.8	7.4±1.4	12.2±1.9	<0.001	8.2±3.4	3.6±0.8	7.4±1.6	12.7±2	<0.001
Prevalence of physical inactivity, %	47.8	47.8	61.9	49.8	28.8	<0.001	47	72.6	50.9	33.1	<0.001
Lung cancer incidence (n/%)	99/3.3	46/2.9	18/6.1	23/2.6	5/1.2	0.001	53/3.8	14/6.1	26/3.3	13/3.6	0.147
Cancer mortality among those who were diagnosed with lung cancer (n/%)	79/2.6	40/2.4	17/94.4	20/87	3/60	0.129	39/2.8	14/100	17/65.4	8/61.5	0.032

Note: Data presented as mean±SD or % of the group for categorical variables. Boldface indicates statistical significance ($p<0.05$). p -value represents comparison between cardiorespiratory fitness categories among former and current smokers. (n/); absolute number and percent of the cardiorespiratory fitness category or group. CRF, cardiorespiratory fitness.

Table 2. Categorical and Continuous Multivariable Risk Models of Cardiorespiratory Fitness and Lung Cancer Outcomes in Former and Current Male Smokers

Group/CRF categories	Low CRF (<5 METs),HR (95% CI)	Moderate CRF (5–10 METs),HR (95% CI)	High CRF (>10 METs),HR (95% CI)	p-trend	1-MET increase, HR (95% CI)	p-value
Lung cancer incidence						
Former smokers	1 (ref)	0.49 (0.25, 0.97)	0.23 (0.08, 0.66)	0.015	0.87 (0.78, 0.98)	0.016
Current smokers	1 (ref)	0.59 (0.3, 1.2)	0.58 (0.26, 1.3)	0.288	0.95 (0.87, 1.04)	0.233
Cancer mortality among those who were diagnosed with lung cancer						
Former smokers	1 (ref)	0.56 (0.26, 1.2)	0.18 (0.04, 0.8)	0.057	0.79 (0.68, 0.92)	0.002
Mean survival time from baseline (years)	4.13 (2.5, 5.7)	5.95 (4, 7.9)	9.4 (5.5, 13.2)	0.068	N/A	N/A
Current smokers	1 (ref)	0.16 (0.06, 0.4)	0.15 (0.05, 0.5)	<0.001	0.82 (0.71, 0.95)	0.008
Mean survival time from baseline (years)	3.96 (2.5, 5.4)	10.8 (8.2, 13.4)	12.2 (7.9, 16.5)	<0.001	N/A	N/A

Note: Boldface indicates statistical significance ($p < 0.05$). Risk models were adjusted for age, history of drug and alcohol abuse, BMI, smoking pack-years, and physical activity status.

CRF, cardiorespiratory fitness; HR, hazard ratio; N/A, not applicable.

lung cancer incidence and 80% of lung cancer mortality. Third, lung cancer is one of the most prevalent cancers globally and in the U.S., with a 5-year survival of only 10%–17% underscoring the importance of primary prevention in the high-risk group of smokers.^{1,3-6,8} In particular, along with important efforts directed toward smoking cessation, screening smokers for low CRF and achieving at least moderate CRF levels during middle age could lessen lung cancer morbidity and mortality considerably and serve as a preventive strategy in smokers.

These results are consistent with previous observations showing an inverse association between CRF and adverse lung cancer outcomes.^{9,13,15-18} The findings of this study strengthen these earlier observations and add novel insights with respect to the risk of lung cancer among former smokers as well as reduced cancer mortality and longer survival time among current smokers

who were diagnosed with lung cancer. In addition, this study is the first to demonstrate among male smokers the PAF% of low CRF for development of lung cancer outcomes. This analysis provides an important epidemiologic metric for resource allocation and public health decisions related to cancer prevention programs. It must be noted that although the continuous model demonstrated a significant 21% reduction in risk for cancer mortality and the categorical model showed a trend for reduced risk of cancer mortality and longer survival among former smokers who were diagnosed with lung cancer, neither reached statistical significance. This is likely because of the small number of cancer deaths in each category, for which future larger prospective studies are warranted to further explore these associations. In addition, although CRF showed protective benefits against cancer mortality among current smokers who were diagnosed with lung cancer, the

Table 3. Prevalence, Relative Risks, and Population Attributable Fraction of Low Cardiorespiratory Fitness as a Risk Factor for Lung Cancer Outcomes

Variable	Prevalence of low CRF (<5 METs), %	RR (95% CI)	PAF% (95% CI)	p-value
Incidence of lung cancer				
Former smokers	18.5	2.4 (1.2, 4.7)	10.8 (3.1, 14.6)	0.01
Current smokers	16.6	1.7 (0.9, 3.3)	6.8 (–1.8, 11.6)	0.115
Cancer mortality among those who were diagnosed with lung cancer				
Former smokers	39.1	2 (0.9, 4.2)	19.6 (–4.3, 29.8)	0.072
Current smokers	26.4	6.5 (2.6, 16.1)	22.3 (16.3, 24.8)	<0.001

Note: Boldface indicates statistical significance ($p < 0.05$). RR of cardiorespiratory fitness was calculated using the Cox proportional hazard model adjusted for age, history of drug and alcohol abuse, BMI, smoking pack-years, and physical activity status.

CRF, cardiorespiratory fitness; PAF, population attributable fraction.

association with lung cancer incidence was not significant. This finding may suggest that smoking cessation could be more important for primary prevention of lung cancer in current smokers, which should be explored in future studies as well.

Several physiological mechanisms have been proposed in terms of mediating the association between CRF and lung cancer.^{12,37-41} Potential protective pathways of higher CRF might include reduced chronic systemic inflammation (particularly C-reactive protein), which has been suggested to be carcinogenic in a broad spectrum of cancers, including lung tissue.^{4,9,38} Improved immune function through increased natural killer cells; an elevated antioxidant capacity; reduced oxidative stress; and enhanced DNA repair, cell proliferation, and apoptosis are all potential processes that could interact in a complex manner by blocking cancer cell initiation and countering cancer cell replication among healthy individuals.^{4,12,37-43} In addition, healthy individuals may have enhanced pulmonary ventilation, lung perfusion, and cellular gas exchange, which are physiological functions that might decrease the interaction time of potential carcinogens in the airway and thus decrease the development and progression of lung cancer.^{9,44} However, despite growing observational evidence supporting the concept that CRF has a role in lung cancer prevention,^{5,9,13,15-18} prospective controlled studies addressing the protective mechanisms of CRF in the genesis of lung cancer are warranted both in smoking and nonsmoking individuals.

The strengths of this study include its relatively large sample size, extended follow-up time, and prospective assessment of cancer outcomes. In addition, lung cancer diagnosis and cancer mortality were verified through the Veterans Affairs Computerized Patient Record System, which has been demonstrated to be comparatively accurate and complete.²⁷⁻²⁹ CRF was quantified from maximal treadmill exercise testing using established protocols.^{23,24} This method has been widely used in epidemiologic studies and has been shown to be strongly predictive for incidence and mortality from many chronic diseases including lung cancer.^{9-11,15-18}

Limitations

The study also has several limitations. First, although the multivariate hazard models were adjusted for established covariates similar to those in previous studies, data on dietary habits were not collected, which may have some influence on the outcomes; this is also consistent with previous studies.^{9,15-18} 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.^{9,13,15-18} 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, although consistent with previous reports, all-type lung cancer incidence was assessed; information on subtypes of lung cancer was not collected in this study.^{13,15-17} Fifth, although consistent with previous reports on CRF and smoking,^{9,18,19} information on the time since quitting smoking in former smokers was not available. Finally, as is the case with all epidemiologic studies, the findings provide an association between CRF and lung cancer outcomes but preclude establishment of cause and effect.

CONCLUSIONS

Higher CRF is independently associated with lower risk of lung cancer incidence in former male smokers. Among current male smokers who were diagnosed with lung cancer, higher CRF is independently associated with reduced risk of cancer mortality and longer survival time. From a public health perspective, in addition to smoking-cessation programs, reducing the prevalence of low CRF among smokers could considerably lessen lung cancer morbidity and mortality and potentially decrease its associated societal and economic burden. Screening smokers for low CRF as a modifiable risk factor, and achieving at least moderate CRF through supervised exercise programs, may serve as a preventive strategy against lung cancer in smokers. Future prospective studies should address the role of promoting CRF for primary and secondary prevention of lung cancer among smokers.

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