spectively, were 3.5, 13.3, and 44.5 deaths per 10000 person-years of follow-up. Using group 1 as the reference, the hazard ratios for cardiovascular death for groups 2 and 3 were 3.76 (95% CI, 1.57-9.00; $P=.003$) and 12.93 (95% CI, 5.62-29.73; $P<.001$), respectively, and for all-cause death 2.15 (95% CI, 1.49-3.10; $P<.001$) and 5.69 (95% CI, 4.03-8.05; $P<.001$), respectively. While there were few women with intermediate Framingham risk scores, 18 (78%) of the 23 cardiovascular deaths in this group occurred in women with below median values for both exercise capacity and HRR. There were only 28 women and 10 cardiovascular deaths in women with high risk Framingham scores, and all 10 deaths occurred in women with below median values for both exercise test variables.

COMMENT

In our population-based cohort of asymptomatic North American women, exercise testing clearly discriminated mortality risk using exercise variables other than ST-segment responses. Exercise capacity and heart rate responses during exercise and recovery were strong, graded, and independent predictors of cardiovascular and all-cause mortality, while exercise-induced ST-segment depression was not. Failure to achieve target heart rate and ventricular arrhythmia were also predictors of poor prognosis.

Our study has several important new findings. First, exercise-induced ST-segment depression had no predictive value in women, in contrast to its increased risk in men as reported previously[13] and confirmed in our analysis. Even in older women, there was no increased risk associated with ST-segment depression, despite enrichment of the sample with hyperlipidemic women. The hazard ratio for ST-segment depression with cardiovascular mortality was a trivial and nonsignificant 1.02. Thus, a larger sample size or a greater prevalence of ST-segment depression is unlikely to show a substantial effect on risk. The effect of gender on the prognostic value of ST-segment depression is intriguing in light of previous studies showing gender differences in the diagnostic accuracy of ST-segment changes.[25] Mechanisms that may contribute to this remain unclear and may be related to differential effects of estrogens and androgens on the ST-segment and QT interval[26,27] or differences in endothelial dysfunction.[28]

Second, easily obtained exercise testing measures, specifically exercise capacity and HRR, had powerful prognostic value for both cardiovascular and all-cause death. Our study underscores the independent value of exercise capacity in predicting cardiovascular and overall risk in asymptomatic women, as seen earlier in men[8,9] and in other studies with fewer women and shorter follow-up.[12,29-31] Moreover, our results confirm the independent effect of abnormal HRR found in other studies[23,32-35] and suggest that low levels of both HRR and exercise capacity have significantly worse prognosis, even after accounting for age and other risk factors. Research on the role of the autonomic nervous system, inflammation, insulin resistance, genetics, and other novel risk factors may provide insight into the mechanisms by which fitness and autonomic function may influence risk.[36-41]

Third, there is great public health interest in cost-effective and readily available tests that can predict cardiovascular risk in asymptomatic women,[5,6] since nearly two thirds of women who die suddenly have no previous symptoms.[1] Our results support the potential role of exercise treadmill testing for further risk stratification of asymptom-

Table 3. Multivariable-Adjusted Risk of Cardiovascular and All-Cause Death According to Exercise Test Variables*

Variable	Cardiovascular Death		All-Cause Death	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Exercise capacity				
Categorical (≤median)	1.90 (1.18-3.04)	.008	1.60 (1.24-2.05)	<.001
Continuous (per MET decrement)	1.17 (1.07-1.27)	<.001	1.11 (1.06-1.17)	<.001
Heart rate recovery				
Categorical (<22/min)	2.23 (0.81-6.11)	.10	2.07 (1.06-4.05)	.03
Categorical (≤median)	2.16 (1.38-3.36)	.001	1.50 (1.20-1.87)	<.001
Continous (per 10/min-decrement)	1.20 (1.04-1.38)	.01	1.16 (1.07-1.26)	<.001
Target heart rate not attained	1.45 (1.00-2.11)	.05	1.24 (1.01-1.53)	.04
Ventricular arrhythmia	1.69 (1.11-2.58)	.02	1.19 (0.90-1.58)	.20
ST Depression ≥1.0 mm	0.88 (0.48-1.61)	.67	0.69 (0.45-1.04)	.08

Abbreviations: CI, confidence interval; MET, metabolic equivalent.
*Hazard ratios and 95% CIs were obtained from multivariable Cox proportional hazards models that included 1 exercise test variable at a time and adjusted for age (years) and the following covariates (categorical variables): current smoking, diabetes, family history of premature coronary heart disease, obesity, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, high triglycerides, and hypertension.

Table 4. Multivariable-Adjusted Risk of Cardiovascular and All-Cause Death According to Exercise Capacity and Heart Rate Recovery Greater Than or Less Than the Median*

	N	Cardiovascular Death		All-Cause Death	
		No. of Deaths	Adjusted Hazard Ratio (95% CI)	No. of Deaths	Adjusted Hazard Ratio (95% CI)
High METs, high HRR	822	7	1.00	39	1.00
Low METs, high HRR	644	19	1.66 (0.69-4.00)	78	1.40 (0.94-2.08)
High METs, low HRR	579	17	1.92 (0.78-4.72)	52	1.30 (0.85-1.98)
Low METs, low HRR	940	103	3.52 (1.57-7.86)	257	2.11 (1.47-3.04)

Abbreviations: CI, confidence interval; HRR, heart rate recovery; METs, metabolic equivalents.
*Hazard ratios and 95% CIs from Cox proportional hazards models that adjusted for age, current smoking, diabetes, family history of premature coronary heart disease, obesity, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, high triglycerides, and hypertension. High and low METs is exercise capacity above or below the study median (7.5 METs). High and low HRR is recovery above or below the study median (55/min).

atic women with low or intermediate Framingham risk scores. In addition, we recommend the promotion of better fitness levels for women regardless of their Framingham risk. Physical inactivity is currently a major public health problem[42] and is more prevalent in women than men.[1] While increased physical activity improves cardiovascular risk profiles,[43] our study suggests that women may benefit from higher fitness levels independent of changes in weight, blood pressure, or lipid levels.

One limitation to our study was that exercise capacity was estimated from near-maximal exercise tests that were not necessarily symptom limited. This may have inappropriately reduced the estimates of peak exercise capacity in some women and possibly underestimated the strength of the association of peak exercise capacity with mortality. In addition, we cannot distinguish effects on incidence from effects on survival since data on incident myocardial infarction or cardiovascular disease were not obtained. However, there are no studies that suggest that fitness is related only to survival after the clinical manifestation of cardiovascular disease. Although changes in classification of causes of death with possible nondifferential misclassification may have occurred during our long study period, this would be expected to underestimate the strength of the association between exercise test variables and mortality. Our study sample included few nonwhites and many with lipid abnormalities, but the prognostic value of exercise capacity and HRR was similar in subgroups with normal and elevated lipid levels. The extent to which these exercise test measures of risk can be modified is also unclear, although exercise capacity may be improved with moderate regular physical activity by about 15% to 30% in a period of several months.[44] Finally, the value of exercise testing to screen asymptomatic populations for the purpose of reducing cardiovascular or overall mortality has not yet been studied in large randomized trials.

In summary, the association of exercise capacity and HRR with cardiovascular and all-cause mortality was strong, consistent, graded, and independent, while exercise-induced ST-segment depression carried no increased risk in this large population-based cohort of women. Our findings support the potential use of exercise testing as a risk-stratification tool for primary prevention in asymptomatic women, incremental to the traditional cardiovascular risk factors.

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Acquisition of data: Mora, Cui, Whiteman.
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Disclaimer: Data provided by the National Heart, Lung, and Blood Institute/National Institutes of Health. The views expressed in this article are those of the authors only.
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For we are held by more than the force of gravity to the earth. It is the entity from which we are sprung, and that into which we are dissolved in time. It is the calendar of life as we know it, from the time of origin. Human evolution, like a vagrant moment in geologic time, is there, deep in the comprehensive earth. The blood of the whole human race is invested in it. We are moored there, rooted as surely, as deeply as are the ancient redwoods or bristlecones.
—N. Scott Momaday (1934-)

論文名	Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study.
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対象の内訳		ヒト	動物	地 域	欧米	研究の種類	縦断研究
	対象	一般健常者	空白		( )		コホート研究
	性別	女性	( )		( )		( )
	年齢	30-80歳			( )		前向き研究
	対象数	1000～5000	空白		( )		( )
調査の方法	実測	( )					
アウトカム	予 防	心疾患予防	な し	な し	な し	( )	( )
	維持・改善	な し	な し	な し	な し	( )	( )

図 表	
図表掲載箇所	
概 要 (800字まで)	目的：無症状の女性に対し、コホートにおける運動テストの意義ををを20年間の追求調査を通して決定すること。デザインと設定：1995年までに至る追跡調査。Lipid Research Clinics Prevalence Study (1972-1976)で実施されたほぼ最大限度のBruce protocolを用いたトレッドミルテストから得られたデータ。参加者：心血管疾患を持たない30-80歳で合計2994名の無症状の北米女性。主な測定結果：心血管および全原因による死亡率。結果：20年の追跡調査の間427名(14%)の死亡があり、うち147名が心血管原因によるものであった。低い運動能力、低い心拍回復能(HRR)、および目標心拍数に達成しない者は、全死亡および心血管による死亡率の増加に独立して関連した。運動誘発ST降下による心血管死亡リスクの増加はなかった(年齢補正による危険比、1.02[0.57-1.80]95%信頼区間、P=0.96)。運動能力におけるあらゆる代謝当量(MET)の減少における心血管死の年齢補正による危険比は、1.20[1.18-1.30](95%信頼区間、P<0.001)であった; HRRにおける毎分10拍毎のリスク比は、1.36[1.19-1.55](95%信頼区間、P<0.001)であった。他の多重危険因子による補正後、運動能力およびHRRのいずれもが中央値を下回る女性では、それらの変数が中央値を上回る女性に比べて、心血管死で3.5倍の増加(95%信頼区間、1.57-7.86; P=0.002)があった。
結 論 (200字まで)	ST降下などの心電図異常は死亡リスクと関係なかった。心肺体力が1メッツ減少する毎に1.17倍と1.11倍リスクが増大。心拍数減少が10拍減少する毎に1.20倍と1.16倍リスクが増大
エキスパートによるコメント (200字まで)	負荷心電図で見られる不整脈や虚血の兆候よりも、体力の方が強力な死亡予測因子であることを示した点で価値あり。

担当者　宮地 劉

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EXERCISE CAPACITY AND MORTALITY AMONG MEN REFERRED FOR EXERCISE TESTING

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ABSTRACT

Background Exercise capacity is known to be an important prognostic factor in patients with cardiovascular disease, but it is uncertain whether it predicts mortality equally well among healthy persons. There is also uncertainty regarding the predictive power of exercise capacity relative to other clinical and exercise-test variables.

Methods We studied a total of 6213 consecutive men referred for treadmill exercise testing for clinical reasons during a mean (±SD) of 6.2±3.7 years of follow-up. Subjects were classified into two groups: 3679 had an abnormal exercise-test result or a history of cardiovascular disease, or both, and 2534 had a normal exercise-test result and no history of cardiovascular disease. Overall mortality was the end point.

Results There were a total of 1256 deaths during the follow-up period, resulting in an average annual mortality of 2.6 percent. Men who died were older than those who survived and had a lower maximal heart rate, lower maximal systolic and diastolic blood pressure, and lower exercise capacity. After adjustment for age, the peak exercise capacity measured in metabolic equivalents (MET) was the strongest predictor of the risk of death among both normal subjects and those with cardiovascular disease. Absolute peak exercise capacity was a stronger predictor of the risk of death than the percentage of the age-predicted value achieved, and there was no interaction between the use or nonuse of beta-blockade and the predictive power of exercise capacity. Each 1-MET increase in exercise capacity conferred a 12 percent improvement in survival.

Conclusions Exercise capacity is a more powerful predictor of mortality among men than other established risk factors for cardiovascular disease. (N Engl J Med 2002;346:793-801.)

DURING the past two decades, exercise capacity and activity status have become well-established predictors of cardiovascular and overall mortality.[1,2] The fact that exercise capacity is a strong and independent predictor of outcomes supports the value of the exercise test as a clinical tool; it is noninvasive, is relatively inexpensive, and provides a wealth of clinically relevant diagnostic and prognostic information.[3,4] However, recent guidelines[4] and commentaries on the topic[5,6] have identified several areas related to the prognostic usefulness of exercise testing that are in need of further study. For example, the majority of previous studies have not clearly assessed the independent prognostic power of exercise capacity relative to other clinical variables and information from exercise testing. In addition, whereas the literature is filled with long-term follow-up studies conducted in relatively healthy populations,[7-11] few studies have focused on more clinically relevant populations — that is, patients referred for exercise testing for clinical reasons. Moreover, although exercise capacity expressed in terms of metabolic equivalents (MET) is the common clinical measure of exercise tolerance, exercise capacity is strongly influenced by age and activity status. It is not known which has greater prognostic value: the absolute peak exercise capacity (measured in MET) or exercise capacity expressed as a percentage of the value predicted on the basis of age. Finally, the use of beta-blocker therapy is common among the patients who are typically referred for exercise testing; although beta-blockade improves survival, it can also reduce exercise capacity. Data related to the influence of beta-blockade on the prognostic value of exercise tolerance are sparse.

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In the present study, we assessed the prognostic value of exercise capacity among patients referred for exercise testing for clinical reasons. We addressed the questions of whether exercise capacity is an independent predictor of the risk of death; whether it is as strong a marker of risk as other established cardiovascular risk factors; whether the percentage of age-predicted exercise capacity achieved is a better marker of risk than the absolute peak exercise capacity; and whether beta-blockade influences the prognostic value of exercise capacity.

METHODS

Exercise Testing

The study population consisted of 6213 consecutive men referred for exercise testing for clinical reasons. Beginning in 1987, a thorough clinical history, current medications, and risk factors in these subjects were recorded prospectively on computerized forms at the time of the exercise tests.[12,13] After providing written informed consent, the subjects underwent symptom-limited treadmill testing according to standardized graded[14] or individualized[15] ramp-treadmill protocols. Before testing, the subjects were given a questionnaire, which we used to estimate their exercise capacity; the use of this estimate allowed most subjects to reach maximal exercise capacity within the recommended range of 8 to 12 minutes.[16] We have previously observed that this protocol results in the closest relation between the measured and estimated exercise capacity.[15] (One MET is defined as the energy expended in sitting quietly, which is equivalent to a body oxygen consumption of approximately 3.5 ml per kilogram of body weight per minute for an average adult.) Subjects were discouraged from using the handrails for support. Target heart rates were not used as predetermined end points. Subjects were placed in a supine position as soon as possible after exercise.[17] Medications were not changed or stopped before testing.

ST-segment depression was measured visually. Ventricular tachycardia was defined as a run of three or more consecutive premature ventricular contractions, and if 10 percent or more of all ventricular contractions were premature, the subject was considered to have frequent premature ventricular contractions.[18] Exercise capacity (in MET) was estimated on the basis of the speed and grade of the treadmill.[19] Subjects with either a decrease of 10 mm Hg in systolic blood pressure after an initial increase with exercise or a decrease to 10 mm Hg below the value measured while standing before testing were considered to have exertional hypotension.[20]

No test results were classified as indeterminate.[21] The exercise tests were performed, analyzed, and reported according to a standardized protocol and with the use of a computerized data base.[22] Normal standards for age-predicted exercise capacity were derived from regression equations developed on the basis of results in veterans who were referred for exercise testing[23] and the predicted peak exercise capacity was calculated as $18.0-(0.15\times\text{age})$. The percentage of normal exercise capacity achieved was defined as follows: (achieved exercise capacity ÷ the predicted energy expenditure) × 100.

We defined subjects with cardiovascular disease as those with a history of angiographically documented coronary artery disease, myocardial infarction, coronary bypass surgery, coronary angioplasty, congestive heart failure, peripheral vascular disease, or an abnormal result on an exercise test that was suggestive of coronary artery disease (ST-segment depression of ≥1.0 mm, exercise-induced angina, or both). Seven percent of the population (435 subjects) had a history of mild pulmonary disease and were included in the group with an abnormal exercise-test result, a history of cardiovascular disease, or both, which included a total of 3679 subjects. The other 2534 subjects, who had no evidence of cardiovascular disease, were classified as normal.

Follow-up

The Social Security death index was used to match all subjects to their records according to name and Social Security number. Vital status was determined as of July 2000.

Statistical Analysis

NCSS software (Salt Lake City) was used for all statistical analyses. Overall mortality was used as the end point for survival analysis. Censoring was not performed, since data on interventions were not available for all subjects. Survival analysis was performed with the use of Kaplan–Meier curves for the comparison of variables and cutoff points, and a Cox proportional-hazards model was used to determine which variables were independently and significantly associated with the time to death. Analyses were adjusted for age in single years as a continuous variable.

In order to compare our results with those of previous studies, the relative risk of death was calculated for each quintile of exercise capacity; subjects with an exercise capacity of less than 5 MET were considered to have a high risk of death, and those with an energy expenditure of more than 8 MET were considered to have a low risk. Receiver-operating-characteristic curves were constructed in order to compare the absolute exercise capacity achieved and exercise capacity expressed as a percentage of the age-predicted value in terms of their discriminatory accuracy in predicting survival. The receiver-operating-characteristic curves were compared with the use of the z statistic.

RESULTS

The mean (±SD) follow-up period was 6.2±3.7 years, and the average annual mortality was 2.6 percent. No major complications occurred, although nonsustained ventricular tachycardia (three or more consecutive beats) occurred during 1.1 percent of the exercise tests. A total of 83 percent of the subjects who were classified as normal achieved a maximal heart rate that was at least 85 percent of the age-predicted value.

Demographic Characteristics

As compared with the normal subjects, subjects with cardiovascular disease were older, had a slightly lower body-mass index (defined as the weight in kilograms divided by the square of the height in meters), and had more extensive use of medicines in addition to more cardiovascular interventions (Table 1).

Exercise-Test Results

Age-adjusted demographic characteristics and the results of exercise testing in the subjects who survived and those who died in both groups are presented in Table 2. The regression equation that predicted the peak exercise capacity on the basis of age was $18.4-(0.16\times\text{age})$; with this equation, $r(\pm SE)=-0.50\pm0.31$, $P<0.001$. The regression equation used to predict the maximal heart rate on the basis of age was $187-(0.85\times\text{age})$; with this equation, $r(\pm SE)=-0.39\pm0.23$, $P<0.001$.

Predictors of Death from Any Cause

Clinical and exercise-test predictors of mortality from the Cox proportional hazards model are present-

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF NORMAL SUBJECTS AND SUBJECTS WITH CARDIOVASCULAR DISEASE.*

VARIABLE	ALL SUBJECTS (N=6213)	NORMAL SUBJECTS (N=2534)	SUBJECTS WITH CARDIOVASCULAR DISEASE (N=3679)	P VALUE
Demographic characteristics				
Age (yr)	59±11.2	55.5±11.8	61.5±10.1	<0.001
Height (in.)	69.2±4.1	69.4±3.4	69.2±3.6	0.02
Weight (lb)	191.2±39	193.7±37	188.8±36	<0.001
Body-mass index	28.0±5.2	28.4±5.1	27.3±5.0	<0.001
Medications (%)				
Digoxin	5.4	0	9.1	
Calcium antagonist	27.3	17.2	34.3	<0.001
Beta-blocker	18.9	12.0	23.7	<0.001
Nitrate	23.3	9.5	32.9	<0.001
Antihypertensive agent	24.0	19.3	27.3	<0.001
Medical history (%)				
Atrial fibrillation	3.1	0.8	2.7	<0.001
Pulmonary disease	6.9	0	11.7	
Stroke	3.6	0	6.1	
Claudication	5.3	0	8.9	
Typical angina	31.3	7	31.2	<0.001
Myocardial infarction	29.3	0	49.4	
Congestive heart failure	8.4	0	14.2	
Interventions (%)				
Coronary bypass surgery	9.3	0	14.1	
Percutaneous transluminal coronary angioplasty, stenting, or both	5.2	0	8.7	

*Plus–minus values are means ±SD. To convert values for height to centimeters, multiply by 2.54; to convert values for weight to kilograms, multiply by 0.45. For comparisons where no P value is given, the differences are due to the classification criteria specified in the study design.

TABLE 2. AGE-ADJUSTED CHARACTERISTICS AND EXERCISE-TEST RESPONSES AMONG SUBJECTS WHO DIED AND SUBJECTS WHO SURVIVED.*

VARIABLE	NORMAL SUBJECTS				SUBJECTS WITH CARDIOVASCULAR DISEASE			
	TOTAL (N=2534)	SURVIVED (N=2246)	DIED (N=288)	P VALUE	TOTAL (N=3679)	SURVIVED (N=2711)	DIED (N=968)	P VALUE
Age (yr)	55±12	55±12	62±10	<0.001	61±10	60±10	65±9	<0.001
Height (in.)	69.4±3.4	69.4±3.1	69.7±4.9	0.08	69.2±3.7	69.2±3.5	69.3±4.2	0.34
Weight (lb)	193.7±37.5	194.1±37.1	191.0±40.1	0.19	188.8±36.1	190.7±36.3	183.7±34.4	<0.001
Body-mass index	28.3±5.1	28.4±5.1	27.5±5.0	0.005	27.8±5.0	28.1±5.0	26.9±4.7	<0.001
Resting values								
Heart rate (beats/min)	78±16	78±16	83±16	<0.001	78±26	77±29	79±16	0.24
Blood pressure (mm Hg)								
Diastolic	84±12	84±12	83±13	0.16	82±18	82±19	80±12	<0.001
Systolic	132±20	133±20	131±21	0.13	134±23	135±23	132±24	<0.001
Maximal values								
Heart rate (beats/min)	145±24	145±23	140±25	<0.001	132±29	133±28	127±32	<0.001
Blood pressure (mm Hg)								
Diastolic	86±16	86±15	85±16	0.37	86±23	86±20	85±30	0.53
Systolic	184±28	184±27	178±32	<0.001	174±31	176±31	168±32	<0.001
Exercise capacity (MET)	9.5±3.8	9.7±3.7	8.4±3.5	<0.001	7.2±3.3	7.4±3.3	6.5±2.8	<0.001

*Plus–minus values are means ±SD. P values are for comparisons between the subjects who survived and those who died in each group. To convert values for height to centimeters, multiply by 2.54; to convert values for weight to kilograms, multiply by 0.45. MET denotes metabolic equivalents.

ed in Table 3. After adjustment for age, the best predictor of an increased risk of death among normal subjects was peak exercise capacity, followed by pack-years of smoking. Among subjects with cardiovascular disease, the best predictor of an increased risk of death from any cause was peak exercise capacity, followed by a history of congestive heart failure, history of myocardial infarction, pack-years of smoking, left ventricular hypertrophy on electrocardiography while at rest, pulmonary disease, and exercise-induced ST-segment depression. According to the model for the total group, every 1-MET increase in exercise capacity conferred a 12 percent improvement in survival.

The age-adjusted relative risks of death for subjects with each of the major risk factors among those achieving a peak exercise capacity of less than 5 MET and 5 to 8 MET, as compared with the fittest subjects (those achieving a peak of more than 8 MET), are shown in Figure 1. For subjects with any of these risk factors, the relative risk of death from any cause increased significantly as exercise capacity decreased. The age-adjusted relative risks of death from any cause for subjects in each quintile of fitness in each group are shown in Figure 2. In both groups, subjects with lower exercise capacity had a higher risk of death. The relative risk for the subjects in the lowest quintile of exercise capacity, as compared with those in the highest quintile, was 4.5 among the normal subjects and 4.1 among those with a history of cardiovascular or pulmonary disease, abnormal results on exercise testing, or both.

TABLE 3. AGE-ADJUSTED RISK OF DEATH, ACCORDING TO CLINICAL AND EXERCISE-TEST VARIABLES.*

VARIABLE	HAZARD RATIO FOR DEATH (95% CI)	P VALUE
Normal subjects		
Peak exercise capacity (for each 1-MET increment)	0.84 (0.79–0.89)	<0.001
Pack-yr of smoking (for each 10-yr increment)	1.09 (1.03–1.14)	<0.001
History of hypertension	0.75 (0.56–1.02)	0.07
Diabetes	1.30 (0.84–2.00)	0.24
Total cholesterol level >220 mg/dl (5.7 mmol/liter)	1.21 (0.88–1.64)	0.25
Left ventricular hypertrophy	1.22 (0.57–2.63)	0.61
Exercise-induced ventricular arrhythmia	1.14 (0.64–2.01)	0.66
Maximal heart rate (for each increment of 10 beats/min)	1.00 (0.92–1.08)	0.93
Subjects with cardiovascular disease		
Peak exercise capacity (for each 1-MET increment)	0.91 (0.88–0.94)	<0.001
History of congestive heart failure	1.67 (1.37–2.04)	<0.001
History of myocardial infarction	1.60 (1.35–1.90)	<0.001
Pack-yr of smoking (for each 10-yr increment)	1.05 (1.02–1.08)	0.001
Left ventricular hypertrophy	1.50 (1.13–1.99)	0.005
Pulmonary disease	1.34 (1.06–1.68)	0.01
ST-segment depression	1.22 (1.03–1.44)	0.02
Total cholesterol level >220 mg/dl (5.7 mmol/liter)	0.88 (0.74–1.04)	0.14
Maximal heart rate (for each increment of 10 beats/min)	0.97 (0.93–1.01)	0.17
Exercise-induced ventricular arrhythmia	1.19 (0.92–1.53)	0.18
Diabetes	0.90 (0.69–1.16)	0.41
History of hypertension	1.07 (0.90–1.25)	0.47

*Data are from the Cox proportional-hazards model. Metabolic equivalents (MET) were calculated from the peak speed and grade of the treadmill and were evaluated as a continuous variable. Left ventricular hypertrophy was defined according to electrocardiographic criteria in a resting patient. Exercise-induced arrhythmia was defined as three or more premature ventricular contractions in succession, premature ventricular contractions that accounted for 10 percent or more of total beats during exercise, or both. Maximal heart rate was measured at peak exercise. ST-segment depression was defined as an exercise-induced change of 1.0 mm or more. CI denotes confidence interval.

Absolute Exercise Capacity versus Percentage of Age-Predicted Value

Absolute peak exercise capacity (with or without adjustment for age) predicted survival more accurately than the percentage of age-predicted values achieved when entered into the proportional-hazards model. In addition, the area under the receiver-operating-characteristic curve was greater for absolute exercise capacity than for the percentage of age-predicted values (0.67 vs. 0.62, $P<0.01$), indicating that the absolute value had greater discriminatory power. For subjects over 65 years of age, however, the areas under the receiver-operating-characteristic curves were similar (0.60). The survival curves for normal subjects who achieved an exercise capacity of less than 5 MET, 5 to 8 MET, and more than 8 MET are shown in Figure 3A; the survival curves for normal subjects who achieved an exercise capacity of less than 50 percent, 50 to 74 percent, 75 to 100 percent, and more than 100 percent of the age-predicted value are shown in Figure 3B. The corresponding curves for the subjects with cardiovascular disease are shown in Figures 3C and 3D. For both the absolute exercise capacity and the percentage of the age-predicted value, there were significant differences in mortality rate among groups defined according to exercise level ($P<0.001$), although the curves were shifted downward in the group with cardiovascular or pulmonary disease.

Effect of Beta-Blockade

There was no interaction between the use or nonuse of beta-blockade and the predictive power of the peak exercise capacity; this was the case throughout the typical range of values for exercise capacity (2 to 10 MET). The results were similar when subjects were included in the beta-blockade subgroup only if they were taking a beta-blocker and had a blunted heart-rate response to exercise (a peak heart rate of less than 85 percent of the age-predicted value). The results were also similar (i.e., beta-blockade had no effect) when the survival curves were based on various cut-

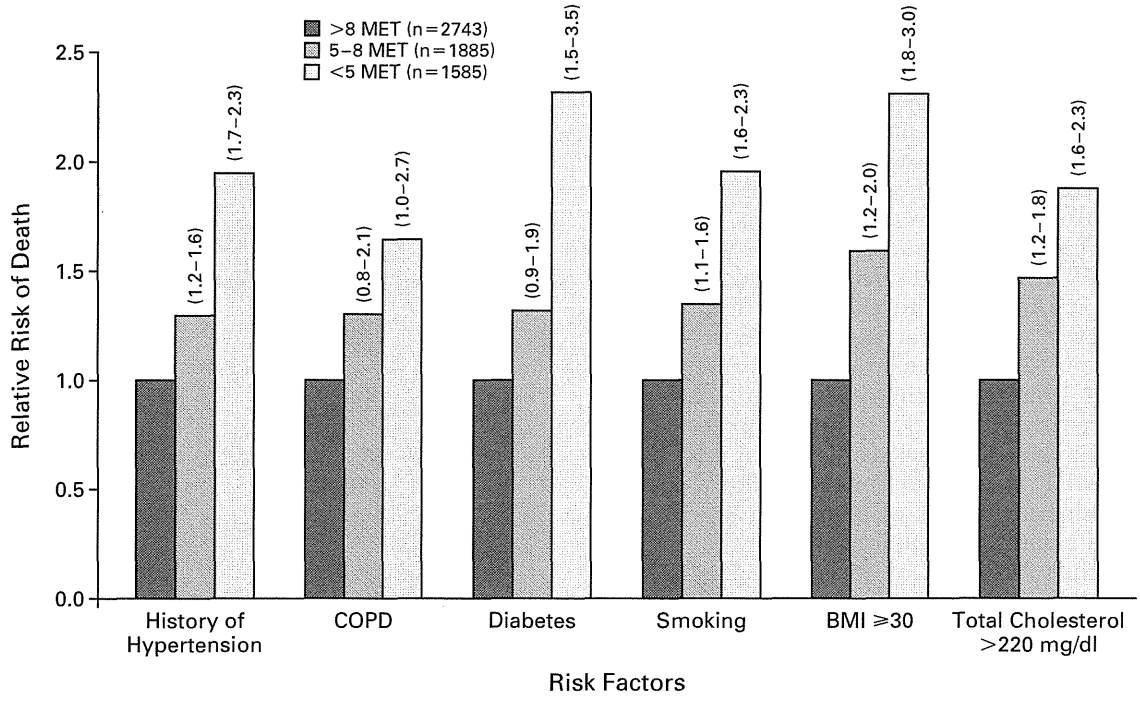

Figure 1. Relative Risks of Death from Any Cause among Subjects with Various Risk Factors Who Achieved an Exercise Capacity of Less Than 5 MET or 5 to 8 MET, as Compared with Subjects Whose Exercise Capacity Was More Than 8 MET.

Numbers in parentheses are 95 percent confidence intervals for the relative risks. BMI denotes body-mass index, and COPD chronic obstructive pulmonary disease.

off points for the percentage of age-predicted exercise capacity achieved (e.g., 50 percent or 75 percent of age-predicted values).

DISCUSSION

Our results demonstrate that exercise capacity is a strong predictor of the risk of death in patients referred for exercise testing for clinical reasons. The importance of exercise capacity, physical-activity status, or both in predicting survival has been reported in asymptomatic populations such as those of the Framingham Study,[11] the Aerobics Center Longitudinal Study,[8,9] the Lipid Research Clinics Trial,[7] and the Harvard Alumni study.[24] Our population was unique in that it afforded us the opportunity to assess subjects both with and without documented cardiovascular disease. Whereas the above-mentioned studies involved generally healthy populations, our data demonstrate that exercise capacity is a similarly important marker of risk in a clinically referred population and among men both with and without existing cardiovascular disease. Unlike the estimates of activity status or the submaximal exercise tests used in many studies, the maximal exercise testing used in the present study provided an objective measure of physical fitness.[25]

In both healthy subjects and those with cardiovascular disease, the peak exercise capacity achieved was a stronger predictor of an increased risk of death than clinical variables or established risk factors such as hypertension, smoking, and diabetes, as well as other exercise-test variables, including ST-segment depression, the peak heart rate, or the development of arrhythmias during exercise. Our data also confirm the protective role of a higher exercise capacity even in the presence of other risk factors.[7-9,24,25] In all subgroups defined according to risk factors, the risk of death from any cause in subjects whose exercise capacity was less than 5 MET was roughly double that of subjects whose exercise capacity was more than 8 MET (Fig. 1).

Poor physical fitness is a modifiable risk factor, and improvements in fitness over time have been demonstrated to improve prognosis.[2,9] Our observation that every 1-MET increase in treadmill performance was associated with a 12 percent improvement in survival underscores the relatively strong prognostic value of exercise capacity. In addition, it confirms the presence of a graded, inverse relation between exercise capacity and mortality from any cause.[7-11] Recent long-term findings from the National Exercise and Heart Disease Project[26] among patients who had had a myocardial

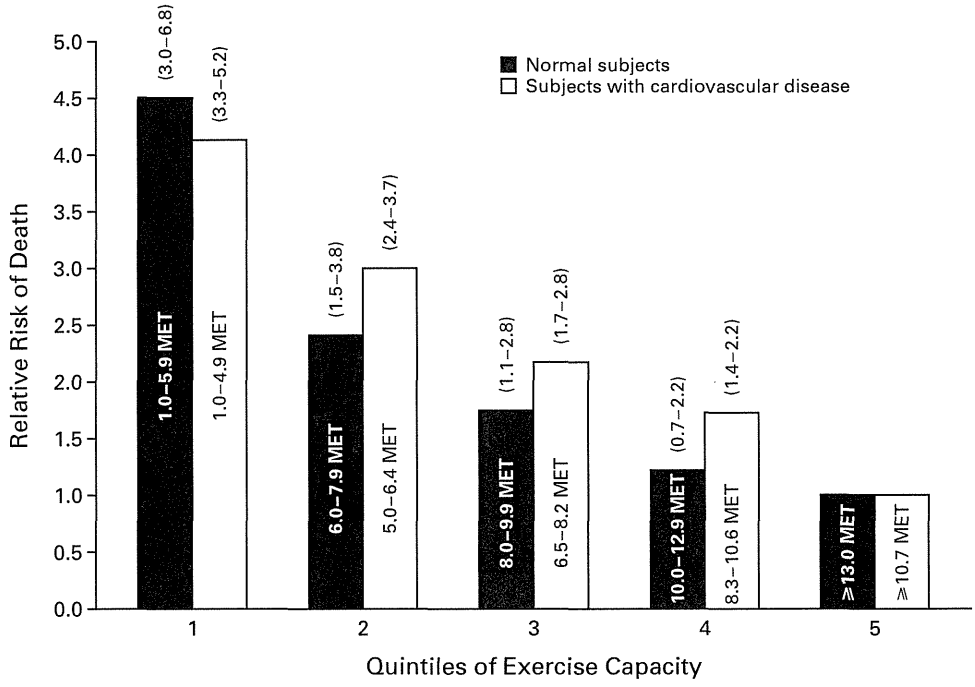

Figure 2. Age-Adjusted Relative Risks of Death from Any Cause According to Quintile of Exercise Capacity among Normal Subjects and Subjects with Cardiovascular Disease.

The subgroup of subjects with the highest exercise capacity (quintile 5) was used as the reference category. For each quintile, the range of values for exercise capacity represented appears within each bar; 95 percent confidence intervals for the relative risks appear above each bar.

infarction demonstrated that every 1-MET increase in exercise capacity after a training period was associated with a reduction in mortality from any cause that ranged from 8 percent to 14 percent over the course of 19 years of follow-up. In a study involving serial evaluations in nearly 10,000 men, Blair et al.[9] observed a 7.9 percent reduction in mortality for every one-minute increase in treadmill time (roughly equivalent to the 1-MET change in our study).

In combination, these findings demonstrate that both a relatively high degree of fitness at base line and an improvement in fitness over time yield marked reductions in risk. The relative weight of exercise capacity in the model for assessing risk in both normal subjects and those with cardiovascular or pulmonary disease in our study, along with the fact that an improvement in exercise capacity lowers the risk of death,[9,26] suggests that health professionals should incorporate into their practices strategies for promoting physical activity, in addition to the routine treatment of hypertension and diabetes, the encouragement of smoking cessation, and the like.

Our findings in normal subjects are similar to those of other studies[8,27,28] in that we observed the most striking difference in mortality rates between the least-fit quintile and the next-least-fit quintile. This observation concurs with the consensus (reflected in the recommendations of the Centers for Disease Control and Prevention and the American College of Sports Medicine[2] and the report of the Surgeon General on physical activity and health[29]) that the greatest health benefits are achieved by increasing physical activity among the least fit. Among subjects with cardiovascular disease, however, we observed a nearly linear reduction in risk with increasing quintiles of fitness. Since most studies assessing the relation between fitness and mortality have excluded subjects with cardiovascular disease,[30] these findings require confirmation.

Few studies have similarly assessed the prognostic value of exercise tolerance among patients specifically referred for exercise testing for clinical reasons. Roger et al.[31] retrospectively assessed 2913 men and women from Olmsted County, Minnesota, and reported that among exercise-test variables, exercise capacity had the strongest association with overall mortality and cardiac events among subjects of both sexes. More recently, this group addressed the association between clinical and exercise-test variables among young and elderly subjects in Olmsted County and observed that the peak workload achieved was the only treadmill-test

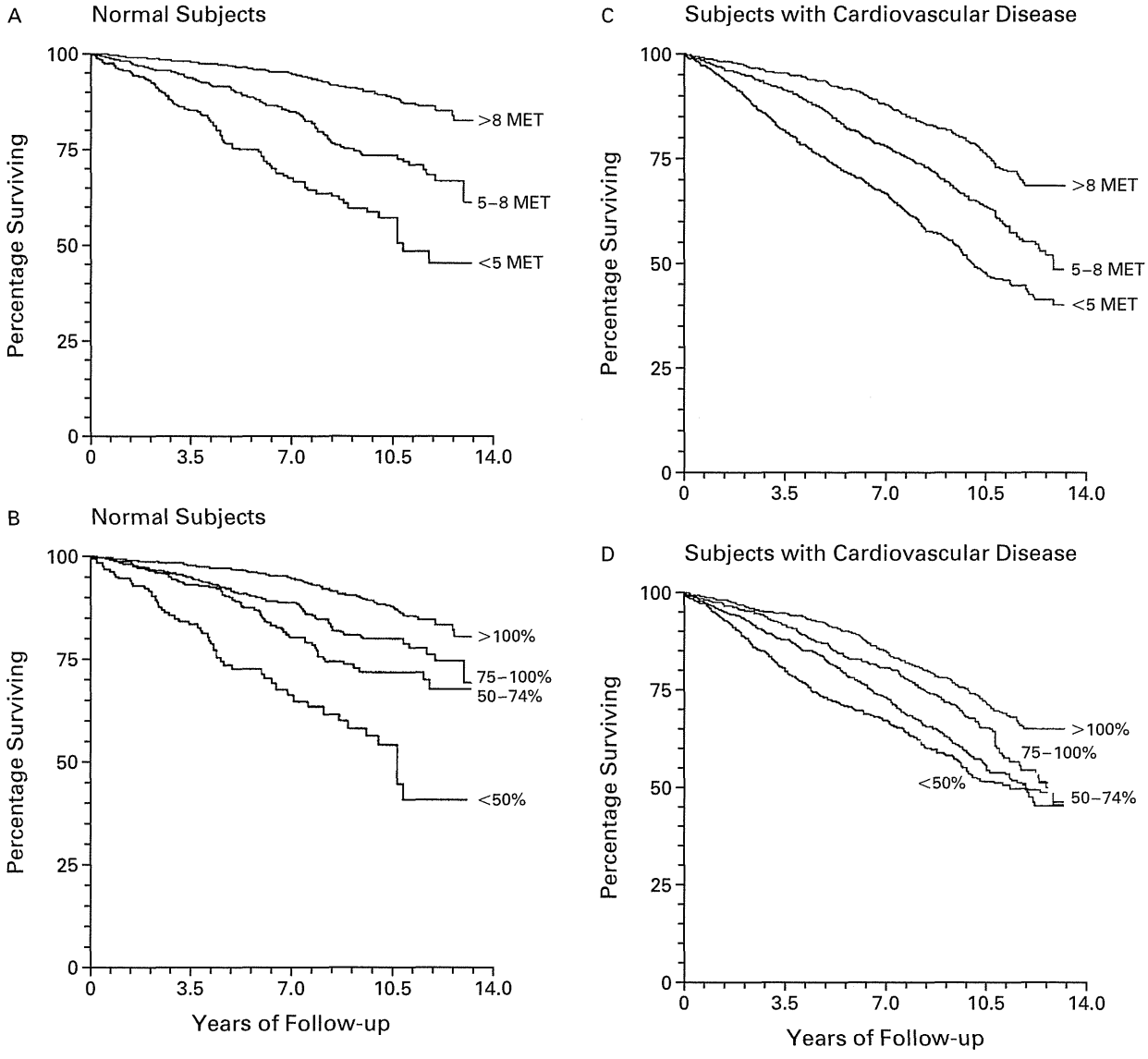

Figure 3. Survival Curves for Normal Subjects Stratified According to Peak Exercise Capacity (Panel A) and According to the Percentage of Age-Predicted Exercise Capacity Achieved (Panel B) and Survival Curves for Subjects with Cardiovascular Disease Stratified According to Peak Exercise Capacity (Panel C) and According to the Percentage of Age-Predicted Exercise Capacity Achieved (Panel D).

In all the analyses, the stratification according to exercise capacity discriminated among groups of subjects with significantly different mortality rates — that is, the survival rate was lower as exercise capacity decreased ($P<0.001$).

variable that was significantly associated with mortality from any cause.[32] These investigators also observed that each 1-MET increment in the peak treadmill workload was associated with a 14 percent reduction in cardiac events among younger subjects (those less than 65 years old) and an 18 percent reduction among elderly subjects.

In recent years, questions have been raised about which variable has superior prognostic power: exercise capacity relative to age- and sex-predicted standards or absolute exercise capacity.[33-35] We found that exercise capacity expressed as a percentage of the age-predicted value was not superior to the absolute peak exercise capacity in terms of predicting survival. Other studies in this area have focused only on patients with congestive heart failure and have had conflicting findings.[33-35]

We were also interested in whether our results

would be affected by beta-blockade, given that such treatment favorably influences survival and is known to either improve or inhibit exercise tolerance, depending on the presence or absence of symptoms during exercise, among other factors. Previous data in this area, although sparse, have demonstrated that beta-blockade does not interfere with the prognostic power of a finding of a low exercise capacity.[36,37] Approximately 19 percent of the subjects in our study underwent exercise testing while receiving beta-blocker therapy, and the overall survival rate was slightly lower among those taking beta-blockers (18.4 percent vs. 21.0 percent among those not taking such drugs, $P=0.03$). Subjects achieving an exercise capacity of 5 MET or more had a higher survival rate than those achieving an exercise capacity of less than 5 MET, and this remained true when subjects were stratified according to the use or nonuse of a beta-blocker. Similarly, beta-blockade had no effect on survival within groups of subjects stratified according to exercise capacity within the clinically relevant range (2 to 10 MET). This issue has rarely been addressed in previous studies, although presumably a substantial proportion of subjects were taking beta-blockers in the Coronary Artery Surgery Study,[38] the Olmsted County Study,[31,32] the Kuopio Ischemic Heart Disease Risk Factor Study,[10] and other follow-up studies that quantified exercise tolerance and survival.

Our findings are applicable only to men, which is noteworthy, given that exercise-test results have been shown to differ significantly between men and women.[39] In addition, we had information only on death from any cause; we did not know the specific causes of death, nor were we able to censor data at the time of cardiovascular interventions. Finally, our exercise-capacity data were estimated on the basis of the speed and grade of the treadmill. Although this type of estimate is the most common clinical measure of exercise tolerance, directly measured exercise capacity (peak oxygen consumption) is known to be a more accurate and reproducible measure of exercise tolerance,[40] as well as a more robust predictor of outcomes.[34,35]

The present results confirm the prognostic usefulness of exercise capacity in men. The prognostic power of exercise capacity is similar among apparently healthy persons and patients with cardiovascular conditions who are referred for exercise testing and similar among subjects who are taking beta-blockers and those who are not taking beta-blockers. Expressing exercise capacity as a percentage of the age-predicted value does not improve its prognostic power. Our findings demonstrate an association between exercise capacity and overall mortality, not necessarily a causal relation. Nevertheless, given the high prognostic value of exercise capacity relative to other markers of risk in this and other recent studies, clinicians who are reviewing exercise-test results should encourage patients to improve their exercise capacity. In terms of reducing mortality from any cause, improving exercise tolerance warrants at least as much attention as other major risk factors from physicians who treat patients with or at high risk for cardiovascular disease.

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対象の内訳		ヒト	動物	地 域	欧米	研究の種類	縦断研究
	対象	空白	空白		( )		コホート研究
	性別	男性	( )		( )		( )
	年齢	59歳、健常:55.5歳、循環器病あり:61.5歳			( )		前向き研究
	対象数	5000～10000	空白		( )		( )
調査の方法	実測	( )					
アウトカム	予 防	な し	な し	な し	な し	(死亡)	( )
	維持・改善	な し	な し	な し	な し	( )	( )

図 表	
図表掲載箇所	
概 要 (800字まで)	背景:運動能力は、心血管疾患をもつ患者の重要な予後の因子であることが知られているが、それが健常者の中でも等しく適切に死亡率を予測できるかどうかは不明確である。また、運動能力の予測に関して、他の臨床および運動テストにおける変数に比例しているという点においても不明確である。方法: 我々は、平均で6.2±3.7年の追跡調査期間において、臨床所見の有無についてトレッドミル運動負荷テストを用いて連続してテストを受けた合計6213名の男性を調査した。対象は2つのグループに分類された: 3679名は、運動負荷テストにおいて異常な所見あるいは心血管疾患、または両方の既往があり、2534名は、運動負荷テストの結果は正常であり、またいかなる心血管疾患の既往も存在しなかった。総死亡をエンドポイントとした。結果:追跡期間中において、1256名の死亡があり、一年平均で2.6%の死亡率をもたらした。死亡した者は、生存しかつ低い最大心拍数、低い最大収縮期および拡張期血圧、低い運動能力を有する者より高齢であった。年齢による補正後、代謝当量(MET)により測定された最大運動能は、正常な者と心血管疾患を有する者の双方の死亡リスクとして最も強い予測因子となった。β 遮断薬の使用もしくは不使用と運動能力の予測力との間にいかなる交互作用も存在しなかった。運動能力各々の1METsの増加は、生存における12%の改善をもたらした。結論:運動能力は、男性においては、他の確立された心血管疾患による危険因子より死亡率の強力な予測因子である。
結 論 (200字まで)	約60歳時に8メッツ以上に心肺体力を維持すれば、総死亡リスクを減らすことができる。
エキスパートによるコメント (200字まで)	心血管疾患のリスクのある者とない者の両方で、心肺体力が最も強力な総死亡の予測因子であることを示し、リスクの有無にかかわらず、適切な管理の下で運動を行い、体力維持することの重要性を示唆している。

担当者　宮地 劉

The association between cardiorespiratory fitness and prostate cancer

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ABSTRACT

SUSAN A. OLIVERIA, HAROLD W. KOHL III, DIMITRIOS TRICHOPOULOS, and STEVEN N. BLAIR. The association between cardiorespiratory fitness and prostate cancer. *Med. Sci. Sports Exerc.*, Vol. 28, No. 1, pp. 97–104, 1996. We conducted a prospective study to assess the association between cardiorespiratory fitness and prostate cancer. The subjects were men, aged 20–80 yr, who received a preventive medical exam at the Cooper Clinic in Dallas, TX, during 1970–1989 and provided information on cardiorespiratory fitness and prostate cancer (N = 12,975). Cardiorespiratory fitness was assessed at a baseline examination between 1971 and 1989 using a maximal exercise treadmill test. Questionnaires were mailed to the men in 1982 and 1990 to ascertain incident cases of prostate cancer. Ninety-four cases of incident prostate cancer were identified. Higher cardiorespiratory fitness levels were inversely associated with the probability of development of incident prostate cancer after controlling for age, body mass index, and smoking habits; adjusted estimates of the incidence rate ratio declined from 1.1 (95% CI 0.63–1.77) to 0.73 (95% CI 0.41–1.29) to 0.26 (95% CI 0.10–0.63) across increasing quartiles of fitness (P for trend <0.004). This protective effect was limited to participants <60 yr old. Also, an inverse association was observed between physical activity and prostate cancer. Compared with expending <1000 kcal·wk^{-1}, participants who expended 1000-<2000, 2000–<3000, or ≥3000 kcal·wk^{-1} had adjusted incidence rate ratios of 0.37 (95% CI 0.17–0.79), 0.62 (95% CI 0.27–1.41), and 0.37 (95% CI 0.14–0.98), respectively. The results suggest that cardiorespiratory fitness and physical activity levels may protect against the development of incident prostate cancer.

EXERCISE, MAXIMAL EXERCISE TREADMILL TEST, MEN, NEOPLASMS, PHYSICAL ACTIVITY, PROSPECTIVE STUDY

Prostate cancer is the second leading cause of death from cancer among men in the U.S.; during 1993, prostate cancer accounted for 13% of all male cancer deaths (14). An estimated 165,000 cases are being diagnosed in the U.S. each year, making prostate cancer the most frequently diagnosed cancer among men (14). Blacks in the U.S. have the highest incidence rates of prostate cancer, followed by whites from North America (53). The etiology of prostate cancer is unknown. Studies have been conducted examining potential risk factors such as diet, venereal diseases, sexual habits, smoking, occupational exposures, and physical activity; however, the results have been inconsistent (21,53).

It has been suggested that physical activity may protect against the development of prostate cancer through reduction of levels of endogenous testosterone (24,44). Male athletes have been shown to have lower levels of circulating testosterone than nonathletes, and men who exercise have reduced testosterone levels immediately after an exercise session (1,20,26,27,37,49,51). The physical activity-prostate cancer hypothesis is compatible with the fact that the standard treatment for prostate cancer is antitestosterone therapy in which the circulating androgen, testosterone, is essentially reduced to levels observed after castration (24). Furthermore, some studies have shown that men with prostate cancer have higher levels of endogenous testosterone compared with nondiseased men, and cancerous tissue has been reported to have higher levels of testosterone compared with normal tissue (2,22,25,28,31).

Despite these hypothesized mechanisms, previous studies have provided inconclusive findings on the relationship between physical activity and prostate cancer (4,17,33,34,40,42,47,50,52). An inverse association between physical activity and prostate cancer was found in six studies (4,17,33,47,50,52), while three studies (34, 40,42) revealed a positive association. No data exist on the relationship between cardiorespiratory fitness and prostate cancer. Fitness level is likely to represent the end result of physical activity and may be considered a good

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indicator of long-term physical activity participation (6). No gold standard exists for the measurement of physical activity; however, cardiorespiratory fitness can be measured validly using a maximal exercise treadmill test to provide estimates of maximal oxygen uptake (10,13).

The purpose of this paper is to report our prospective observations of the association between cardiorespiratory fitness and incident prostate cancer.

METHODS

Study Population

The total population at the Cooper Clinic is composed of 28,072 subjects. The population for analysis was composed of 12,975 primarily white (>99%), married, college-educated men, aged 20–80 yr, with no history of prostate cancer, who received a voluntary, preventive medical examination at the Cooper Clinic in Dallas, TX, during 1971–1989 and who provided information on cardiorespiratory fitness and prostate cancer. Fifty percent of the men in this cohort were over the age of 42 yr, with 25% over the age of 50. This baseline examination included a physical examination: a questionnaire on demographic characteristics, physical activity, and health habits; a personal and family health history; anthropometric measures; resting and exercise electrocardiography; blood chemistry tests; blood pressure measurements; and a maximal exercise treadmill test to determine cardiorespiratory fitness. Written informed consent was obtained from the participants. Examination methods and procedures followed a standard manual of operations and have been previously described (10,11,13).

Fitness Measurement

Cardiorespiratory fitness was assessed at the baseline examination with a maximal exercise treadmill test using the Balke protocol (7). The treadmill speed was 88 $m \cdot min^{-1}$ for the first 25 min. During this time the grade was 0% for the first minute, 2% the second minute, and increased 1% each minute until 25 min had elapsed. After 25 min, the grade remained constant while the speed increased 5.4 $m \cdot min^{-1}$ each minute until test termination (10). The outcome of interest was total treadmill time in minutes. The duration of the maximal exercise treadmill test is highly correlated with measured maximal oxygen uptake in men ($r = 0.92$), an accepted measure of cardiorespiratory fitness (43). Fitness levels were created by categorizing total treadmill time in minutes by quartiles.

Prostate Cancer Measurement

Questionnaires were mailed to the men in 1982 and 1990 for the purposes of periodic health status updates and monitoring. A series of case finding questions were included on each questionnaire. Cases of incident prostate cancer were ascertained by asking each individual whether he had ever been diagnosed with prostate cancer. If the answer was affirmative, the year of diagnosis was also obtained. Fatal cases of prostate cancer were ascertained by mortality surveillance using Social Security Administration files, Departments of Motor Vehicles, nationwide credit bureau network, National Death Index, and local area telephone directories. Further details of this mortality surveillance have been described elsewhere (10,13). Vital status through 1989 is 93% complete. However, only six prostate cancer cases were fatal due to the limited duration of follow-up. Therefore, all analyses included only the incident prostate cancer cases. All participants with existing prostate cancer at their first visit were eliminated. The remaining participants were followed from their baseline examination to the outcome of interest, newly diagnosed prostatic cancer, death from other causes, loss to follow-up due to administrative difficulties or operational limitations, or until the end of the study period. Vigorous attempts to reach all participants could not be implemented before the undertaking of the present analysis; therefore, we did not have the ability to separate true nonresponders from those who never received the mail survey and thus did not have the opportunity to respond. Information was obtained on cancer occurrence from 47% ($N = 12,975$) of the participants.

Physical Activity Measurement

Physical activity was assessed in a subsample of the total Cooper Clinic population ($N = 28,072$) at baseline and in the 1982 mail survey by inquiring about participation in various sports and activities. The subsample available for analysis consisted of men who provided information on physical activity, prostate cancer, age, body mass index, and smoking status ($N = 7570$). A self-administered questionnaire, which included a checklist of aerobic activities (Appendix) was provided to the subject during the baseline examination and in the 1982 mail survey. Each person was asked "For the last 3 months which of the following activities have you performed regularly?" Individuals provided information about participation, frequency per week, the intensity level, and duration per workout for the sports and activities on the checklist. This information was then used to create a physical activity index to estimate the total energy in kilocalories (kcal) expended in sport or activity each week, by multiplying the MET score (3.5) by the duration of the workout, body weight in kilograms, and frequency per week engaged in the sport or activity. Total weekly energy expenditure was calculated by summing $kcal \cdot wk^{-1}$ expended for each sport or activity. Physical activity levels were created by categorizing total weekly energy expenditure as follows: <1000, 1000–<2000, 2000–<3000, and ≥3000 $kcal \cdot wk^{-1}$. The cutpoints were defined *a priori* based upon published work (33).

ata Analysis

Descriptive analyses were performed to characterize e study population. Subsequently, the association be-een cardiorespiratory fitness and incident prostate can-r was assessed using proportional hazards regression 8,19). This technique allows estimation of the inci-ence rate ratio while controlling for available potential onfounding variables. Baseline values of age, body mass dex, and smoking status were potential confounding ariables adjusted in the multivariate analyses. The Sta-stical Analysis System (SAS) was used for all analyses 6).

The duration of the maximal exercise treadmill test in inutes was used to define quartiles of baseline cardio-espiratory fitness, <13.7, 13.7-<17.0, 17.0-<21.0, and ≥21.0 min on treadmill test. These categories were en-ered into the multivariate model as indicator variables, vith the lowest level representing the referent category. Person-time was assigned to the appropriate fitness cat-gories according to the baseline fitness level.

We also evaluated physical activity as a risk factor for incident prostate cancer, although information on physi-cal activity was available for only a subsample of the study cohort, men who provided fitness and prostate cancer information. The two physical activity measures (assessed at baseline and 1982 survey) were used to create an average physical activity variable with four levels of energy expenditure (N = 12,098). If an indi-vidual only provided one measure of physical activity at the initial visit or in the 1982 survey, then the single measure was used as the average measure. For those participants whose single 1982 physical activity measure was used as the average measure, we eliminated them if there was any prior evidence of prostate cancer. Fol-low-up information on prostate cancer was available for 63% (N = 7,570) of the participants who had at least one measure of physical activity.

To assess confounding, we included each potential confounder in the model and compared its effect on the incidence rate ratio with that of the model without the potential confounder. The final model was selected based on the change in the estimate of effect produced by including the potential confounder in the model and the *a priori* biological importance of the potential con-founder (45). A 10% change was the minimum criterion deemed necessary for confounding variable inclusion. The potential confounders were categorized and entered into the model as indicator variables. We examined age categorized in groups: 60–64, 65–69, and 70–80 yr old. Because prostate cancer rarely occurs in younger men, the age group composed of 20- to 59-yr-olds was the referent category. The effect of age was also examined by stratifying young (<60 yr old) versus old (≥60 yr old) and assessing the association between fitness and cancer. Body mass index was dichotomized at the median, and we compared those above the median to those below the median. To control for smoking status, we classified participants as current, past, or never smokers based upon responses to questions asked at the baseline examination. The category composed of never smokers was the referent group.

Follow-up studies of clinical diseases with potentially long latency periods must account for the frequently uncertain temporality between the exposure and the outcome of interest. Latent or subclinical disease could be responsible for a level of the hypothesized exposure. To address the concern of bias that could be due to latent disease, we analyzed the data with 1, 3, and 5 yr of person-time follow-up removed after the time of the initial questionnaire.

The results of all the regression analyses are presented in the form of mutually adjusted incidence rate ratios and 95% confidence intervals.

RESULTS

Demographic and anthropometric data of the study population (N = 12,975) by fitness level are detailed in Table 1. Age, weight, and body mass index were lower in men with higher levels of fitness. Men with higher levels of fitness were more likely to have never smoked compared with those men with a low level of fitness, who were more likely to be current smokers.

There were 14,849 participants lost to follow-up from the initial cohort of 28,072. We examined loss to follow-up by levels of fitness and found virtually no difference between the groups. Subjects lost to follow-up had similar baseline characteristics compared with subjects with follow-up information (Table 2). Of the subjects successfully followed, 24% included in the analysis for fitness were followed for the entire study period and there were 4,719 (36%) followed from baseline through 1982.

Because the results comparing the estimates among analyses with 1, 3, or 5 yr of person-time removed were similar, we excluded only 1 yr of person-time from the final analyses to maximize the amount of person-time available. Exclusion of first year cases is done to avoid confusion by subtle changes of exposure variables in response to incipient disease (33). In addition to the baseline exclusions, subjects with less than 1 yr of follow-up were excluded from the analyses (N = 248).

The data in Table 3 show results on cardiorespiratory fitness. Higher cardiorespiratory fitness levels were inversely associated with the probability of development of prostate cancer. Relative to the least fit group, crude incidence rate ratios changed from 0.76 to 0.52 to 0.18 across levels of fitness (P for trend = 0.0001). The adjusted point estimates changed from about 1 in the first two categories to 0.73 and 0.26 in the categories of the more fit individuals (P for trend = 0.0036). When the data were stratified by young (<60 yr old) versus old

TABLE 1. Characteristics of study participants by cardiorespiratory fitness level* at baseline examination; Aerobics Center Longitudinal Study, 1971–1989.

Fitness Level	<13.7 (N = 3026)	13.7–<17.0 (N = 2828)	17.0–<21.0 (N = 3546)	≥21.0 (N = 3575)
Age (mean ± SD) (yr)	50.0 (10.0) (N = 3015)	44.9 (9.4) (N = 2815)	42.5 (8.9) (N = 3525)	40.2 (8.6) (N = 3516)
Weight (mean ± SD) (kg)	87.0 (14.1) (N = 2991)	84.0 (11.1) (N = 2821)	81.4 (10.3) (N = 3540)	77.5 (9.0) (N = 3556)
Height (mean ± SD) (m)	1.77 (0.06) (N = 3024)	1.78 (0.06) (N = 2828)	1.79 (0.06) (N = 3541)	1.79 (0.06) (N = 3571)
Body Mass Index† (mean ± SD)	27.6 (3.9) (N = 2990)	26.3 (2.9) (N = 2821)	25.3 (2.6) (N = 3536)	24.1 (2.3) (N = 3555)
Energy expenditure per week (mean ± SD) (kcal)	1476.5 (1287.3) (N = 1090)	1611.0 (1305.9) (N = 1311)	1793.9 (1390.0) (N = 2228)	2542.4 (1716.0) (N = 2945)
Smoking status				
% current	39.0	34.1	25.8	14.7
% past	58.2	58.7	66.1	70.4
% never	2.8	7.2	8.0	14.9

* Fitness level expressed in treadmill time (min).
† Quetelet Index = wt(kg) · ht^{-2}(m).
Within each category of fitness the total number of subjects for each variable may not equal the total for the category due to missing data.

TABLE 2. Characteristics of study participants by lost to follow-up status*; Aerobics Center Longitudinal Study, 1971–1989.

	Successfully Followed (N = 13,223)	Lost to Follow-up (N = 14,849)
Age (mean ± SD) (yr)	44.2 (9.9) (N = 13,118)	42.1 (9.8) (N = 14,628)
Weight (mean ± SD) (kg)	82.2 (11.7) (N = 13,156)	84.3 (12.8) (N = 14,707)
Height (mean ± SD) (m)	1.79 (0.06) (N = 13,212)	1.79 (0.07) (N = 14,822)
Body Mass Index* (mean ± SD)	25.7 (3.2) (N = 13,150)	26.4 (3.6) (N = 14,702)
Treadmill time (mean ± SD) (min)	17.6 (5.2) (N = 13,223)	17.1 (5.5) (N = 14,849)
Energy expenditure per week (mean ± SD) (kcal)	2007.2 (1561.7) (N = 7746)	1670.7 (1356.6) (N = 4528)
Smoking status		
% current	16.9	22.2
% past	38.0	34.8
% never	5.6	5.5

* Quetelet Index = wt(kg)/height^2 (m).
The total number of subjects for each variable may not equal the total lost to follow-up due to missing data.

(≥60 yr old), the protective effect of fitness on prostate cancer was limited to the younger group. The adjusted estimates ranged from 0.75 to 0.11 for increasing levels of fitness in the group <60 yr of age. These results should be interpreted with caution due to the small number of cases in the older group, $N = 33$. There were no significant interactions for body mass index or smoking status.

Incidence rate ratios for prostate cancer and activity level in the subcohort with information on physical activity and prostate cancer are presented in Table 4. Crude and adjusted estimates show an inverse association between physical activity and prostate cancer, comparing increased levels of physical activity to the referent. The data do not support a linear trend; however, the results are based on a small number of cases that may lead to imprecise estimates. The results in Table 4 were not altered when the cutpoints for the physical activity levels were changed to <1000, 1000–<2500, 2500–<3000, and ≥3000 kcal·wk^{-1}.

The validity of the physical activity measure and the consistency of fitness and activity levels over time were assessed by comparing total weekly energy expenditure in sports or activities to the results of the maximal treadmill exercise test. Participants who have high levels of total energy expenditure are expected to have better fitness. A significant correlation between self-reported physical activity levels and maximal exercise treadmill time was observed. The correlation coefficient was r = 0.41 for baseline physical activity level and maximal exercise treadmill time and for the correlation between 1982 activity level and treadmill time, r = 0.32. The correlation between baseline physical activity and 1982 physical activity levels was r = 0.35. In other analyses we found that the incidence of prostate cancer was similar in individuals who did not provide physical activity information as in those who did. We also established that the basic assumption of the proportional hazards model (e.g., hazards are proportional over time) was appropriate for our data.

DISCUSSION

These results provide support for the hypothesis that cardiorespiratory fitness is inversely associated with risk of incident prostate cancer. The upper two quartiles of fitness levels were associated with reduced risks of prostate cancer compared with the lowest quartile of fitness. An age interaction was evident with the protective effect limited to the young age group. Energy expenditure ≥1000 kcal·wk^{-1}, was consistently associated with reduced risks of prostate cancer compared with energy expenditure levels less than 1000 kcal·wk^{-1}. Adjustment for available potential confounders did not substantially alter this association. The point estimates for the 2000–<3000 kcal·wk^{-1} category were higher than the adjusted estimates for the other activity categories. This is likely due to chance because of the small number of cases

3. Estimates of the association between fitness level* at baseline and prostate cancer; Aerobics Center Longitudinal Study, 1971–1989.

Fitness Level	<13.7 (N = 3026)	13.7–<17.0 (N = 2828)	17.0–<21.0 (N = 3546)	≥21.0 (N = 3575)	
of cases	40	27	21	6	
son-years of follow-up	30,160	26,738	31,144	26,260	
de incidence rate ratio (95% CI)	1.00†	0.76 (0.46–1.23)	0.52 (0.30–0.87)	0.18 (0.08–0.43)	*P* trend = 0.0001
isted incidence rate ratio‡ (95% CI)	1.00†	1.1 (0.63–1.77)	0.73 (0.41–1.29)	0.26 (0.10–0.63)	*P* trend = 0.0036

s level expressed in treadmill time (min).
ent category.
ted for age, body mass index, and smoking status.
onfidence interval.

4. Estimates of the association between activity level* and prostate cancer, physical activity measured as an average of the baseline and 1982 measures; Aerobics Center dinal Study, 1971–1989.

Activity Level	<1000 (N = 2070)	1000–<2000 (N = 2600)	2000–<3000 (N = 1407)	≥3000 (N = 1493)	
. of cases	21	10	8	5	
rson-years of follow-up	17,367	22,364	12,418	13,295	
ıde incidence rate ratio (95% CI)	1.00†	0.36 (0.17–0.76)	0.52 (0.23–1.16)	0.29 (0.11–0.76)	*P* trend = 0.7946
justed incidence rate ratio‡ (95% CI)	1.00‡	0.37 (0.17–0.79)	0.62 (0.27–1.41)	0.37 (0.14–0.98)	*P* trend = 0.8263

ty level expressed in energy (kcal) expenditure per week.
ent category.
sted for age, body mass index, and smoking status.
onfidence interval.

his is the first study reporting on fitness level and risk rostate cancer. Fitness is clearly correlated with ha- l physical activity and represents a characteristic that be relevant to the occurrence of chronic disease, pared with short-term physical activity that may vary nding on transient motivation and opportunity or curate reporting. These data on fitness concern the lity of the population enrolled in the study, and al- gh 53% of the subjects eventually did not provide rmation on prostate cancer outcome, there was no lence in these data to suggest that nonresponse was *ly* associated with fitness and prostate cancer (a condition for bias). This is further supported by the ilarity of the proportion of subjects with prostate cer information in those who have only fitness data l in those with both fitness and physical activity data l by the similar incidence of prostate cancer among se with and those without physical activity informa- n. Furthermore, the data on physical activity are es- ntially compatible with the fitness results and they pear to be in agreement with the weight of the existing idence.

Observational studies of this nature have the potential r bias. The maximal exercise treadmill test, used to sess fitness, is an accepted and validated measure of diorespiratory fitness (43). Any misclassification of is exposure would be random since prostate cancer tcome was not known at the time of treadmill testing. ur results are not subject to recall bias because of the spective nature of the study.

Cases of prostate cancer were identified using self- ported data. No validation of self-reported prostate ncer has been accomplished; however, self-report of other diseases such as myocardial infarction, stroke, and hypertension were validated in this population (13). Self-reported hypertension had a sensitivity of 98% and a specificity of 99% in a study conducted in this population by Blair et al. (13). In a study conducted by Giovannucci et al. (23), in a different population, self-reported prostate cancer was validated by review of medical and pathology records and a diagnosis of adenocarcinoma was confirmed in 99.4% of the men.

There is potential for bias in this study if there was differential diagnosis of prostate cancer between fitness levels. However, subjects who are fit are *more* health conscious. There is a body of literature indicating that physically active subjects are more likely to have contact with physicians and the health care system than subjects who are not physically active (8,9,32,35,48). This difference would create an increased likelihood of diagnosis of prostate cancer in those men with increased levels of fitness and thus would reduce the strength of an inverse association between fitness and prostate cancer. Therefore, if diagnostic bias occurred in this study, the observed estimates are likely to be an underestimate of the true strength of the association between fitness and prostate cancer. It would be important to have information on the stage of diagnosis of the tumor to predict what implications fitness may have on the future progression of the tumor, but such data are not available.

Loss to follow-up was defined as a nonresponse to both the 1982 and 1990 questionnaires. Loss to follow-up could have generated biased results only if nonresponse was correlated with both fitness level and prostate cancer. However, a substantial amount of bias would need to exist to explain the strong inverse associations observed

in these data. We examined loss to follow-up by levels of fitness and found virtually no difference between the groups. Subjects lost to follow-up had similar baseline characteristics compared with subjects with follow-up information. We believe the high percentage of loss to follow-up was due in part to the mobility of the population, and our inability to maintain current addresses on some of the men. Thus, many nonresponders did not have the opportunity to answer the mail survey because they did not receive it.

We were unable to control for the potential confounding effects of diet in our analyses. A positive association between fat intake and prostate cancer has been observed in some case-control and cohort studies (39,41). For diet to be confounding the observed association between fitness and prostate cancer, active men would have to consume a diet composed of less fat. There are no data available on the association between diet and fitness levels, and no association has been observed between physical activity level and dietary composition (9,12,15, 36). The results of Lee et al. (33) showed increased caloric intake in highly active men compared with those who were less active, but the proportion of calories from fat consumed was the same across inactive, moderately active, and highly active groups.

Also, we were unable to control for some other potential risk factors: venereal disease, sexual habits, and occupational exposures. The results of previous studies examining these factors have been inconsistent (21,39, 53). It is unlikely that one or more of these factors is strongly associated with both fitness and prostate cancer incidence, and could cause substantial confounding.

Varying amounts of person-time after completion of the baseline questionnaire were eliminated to assess the effect of latent disease, which may have affected fitness levels in diseased individuals. If participants with existing disease had altered fitness results, then the association between fitness and prostate cancer could be spurious. Eliminating 1, 3, or 5 yr of person-time follow-up, however, did not substantially alter the results.

The mechanism behind the protective effect of fitness on prostate cancer may be related to the sex hormone testosterone. The prostate is a secondary sex gland that is affected by hormonal stimulation. The growth and development of the organ relies on the presence of sex hormones. Testosterone was singled out as a possible cause of prostate cancer as early as 1941 when androgen deprivation was used as therapy in advanced prostatic cancer (30). Currently, metastatic prostate cancer is treated with antitestosterone therapy or adrenal androgen blockage (24). Animal studies have shown that prostate cancer can be induced in rats by the administration of exogenous testosterone (16,29,38). In studies involving humans, prostate cancer cases appear to have higher levels of endogenous testosterone compared with nondiseased men (2,22,31). This evidence seems to implicate thermore, athletes have been shown to have lower levels of testosterone, and individuals who exercise may have a temporary decrease in post-exercise levels of testosterone (1,20,26,27,37,49,51). If fit individuals have lower levels of endogenous testosterone and lower levels of testosterone are associated with decreased incidence of prostate cancer, it should be expected that men who are more physically fit or active would be at a lower risk of developing prostate cancer compared with men who are inactive.

It should be noted highly trained athletes have been observed to have lower basal circulating testosterone, whereas men who exercise experience a more acute and temporary drop in testosterone levels. It would seem that a continued decrease of testosterone levels would be more important in influencing a decreased prostate cancer risk compared with a transient change due to an exercise session. We observed a protective effect on prostate cancer across all levels of increased fitness and physical activity.

There are no previously reported data concerning cardiorespiratory fitness and prostate cancer. Epidemiological studies on the association between prostate cancer and physical activity are not entirely consistent. Increased exercise in the form of occupational activity, recreational exercise, or household work has been observed to be protective for prostate cancer in six studies (4,17,33,47,50,52). Conversely, three studies have shown an increased risk of prostate cancer with increasing levels of physical activity (34,40,42). In two of the studies, participation in college athletics was the exposure of interest (40,42). In the third study, an inverse association was found between risk of prostate cancer and the proportion of life spent in occupations involving only sedentary or light work (34). It may be that college athletics participation is too remote in time to be etiologically relevant for prostate cancer or may not be related to lifetime fitness and that the proportion of time spent in sedentary occupation is a poor indicator of overall fitness.

These results suggest that moderate to high levels of cardiorespiratory fitness may protect against the incidence of prostate cancer. This study supports the physical activity-prostate cancer hypothesis and provides evidence that cardiorespiratory fitness may be a better predictor of prostate cancer risk than physical activity.

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