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Appendix
Questions from the baseline and 1982 Cooper Clinic physical activity questionnaire.

"For the last 3 months, which of the following activities have you performed regularly?"

	YES	NO	
Walking			How many workouts per week? How many miles per workout? Average duration of workout? Average time per mile?
Jogging or Running			How many workouts per week? How many miles per workout? Average duration of workout? Average time per mile?
Treadmill			How many workouts per week? Average duration of workout? Speed? Grade?
Bicycling (outdoors)			How many workouts per week? How many miles per workout? Average duration of workout? Average time per mile?
Stationary Cycling			How many workouts per week? Average duration of workout? Heart rate during exercise?
Swimming Laps			How many workouts per week? How many miles per workout? Average duration of workout? How many months per year?
Aerobic Dance/Floor Exercises			How many workouts per week? Average duration of workout? Heart rate during exercise?
Vigorous Racquet Sports			How many workouts per week? Average duration of workout?
Other Vigorous Sports/Exercise			How many workouts per week? Average duration of workout?

論文名	The association between cardiorespiratory fitness and prostate cancer
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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	男性	( )		( )		( )
	年齢	20-80歳			( )		前向き研究
	対象数	10000以上			( )		( )
調査の方法	実測	( )					
アウトカム	予 防	なし	なし	ガン予防	なし	死亡	( )
	維持・改善	なし	なし	なし	なし	( )	( )

図 表

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

Fitness Level	<13.7 (N = 3826)	13.7–<17.0 (N = 2828)	17.0–<21.0 (N = 3545)	≥21.0 (N = 3575)	
of cases	40	27	21	6	
son-years of follow-up	30,160	26,738	31,144	26,260	
te incidence rate ratio (95% CI)	1.00†	0.76 (0.46–1.23)	0.52 (0.30–0.87)	0.15 (0.08–0.43)	P trend = 0.0001
sted 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.
nfidence interval.

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	
son-years of follow-up	17,357	22,364	12,418	13,295	
ate incidence rate ratio (95% CI)	1.00‡	0.36 (0.17–0.76)	0.52 (0.23–1.36)	0.29 (0.11–0.76)	P trend = 0.7946
usted 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

y level expressed in energy (kcal) expenditure per week.
ent category.
ted for age, body mass index, and smoking status.
nfidence interval.

図表掲載箇所	P101, Table3, Table4
概 要(800字まで)	本研究は、アメリカのThe Aerobics Center Longitudinal Studyに参加した男性12,975名を対象に18年間の追跡調査を行い、全身持久力と前立腺がんとの関連を検討したものである。全身持久力は、最大トレッドミルテストにより最大酸素摂取量を測定し、測定時間により13.7分未満、13.7-17.0分、17.0-21.0分、21.0分以上の4群に分類した。身体活動量は、過去3ヶ月間において、ウォーキング、ジョギング、ランニング、自転車、水泳、エアロビクス、ラケットスポーツ、その他高強度運動/身体活動を行った週当たりの頻度、時間を尋ね、週当たりの消費エネルギー量を算出し、1000kcal/週未満、1000-2000、2000-3000、3000kcal/週以上の4群に分類した。全身持久力に関して、測定時間が13.7分未満の集団と比較すると21.0分以上行えた集団で前立腺がん発症リスクが0.26(95%信頼区間:0.10-0.63)と有意に減少し、量反応的減少がみられた(Ptrend=0.0036)。身体活動に関しては、1000kcal/週未満の集団と比較すると、1000-2000kcal/週の集団と、3000kcal/週以上の集団で、前立腺がん発症リスクがそれぞれ0.37(0.17-0.79)、0.37(0.14-0.98)と有意に減少した。
結 論(200字まで)	全身持久力の向上により、前立腺がん発症リスクを減少させることが示唆され、また、高強度身体活動量の増加は、前立腺がんの予防につながる可能性があることが示唆された。
エキスパートによるコメント(200字まで)	我が国の男性における前立腺がんは、年々増加傾向にあり、その予防は重要な課題である。身体活動を高めることや体力を高めることが前立腺がん予防につながることが示されており、身体活動・体力の重要性をより啓蒙していくことが重要である。

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Physical Activity and Physical Fitness as Predictors of All-Cause Mortality in Korean Men

We examined the associations between physical activity (PA), fitness and all-cause mortality and compared their contributions, taking smoking status into consideration. A retrospective cohort study of 18,775 men was carried out between May 1995 and December 2003. Fitness was measured by maximum oxygen uptake and regular PA was defined as at least three times a week, for more than 30 min of leisure time PA. During the mean 6.4 yr of follow-up, 547 deaths were recorded. The hazard ratio (HR) (95% confidence interval [CI]) of regular PA for all-cause mortality was 0.63 (0.52-0.76). The HRs (95% CIs) for men with middle and highest tertile levels of fitness were decreased by 0.58 (0.47-0.70) and 0.58 (0.45-0.75) in comparison to men with lowest one. The inverse association between fitness and mortality was significant among the men who did not engage in regular PA, but not among those who did (*p* for interaction=0.031). Smoking status did not influence on the associations between regular PA, fitness and mortality. Our result suggested that regular PA and fitness predicted mortality in men. The influence of fitness on mortality was pronounced in the men who did not engage in regular PA.

Key Words : *Motor Activity; Exercise; Physical Fitness; Mortality, Smoking*

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INTRODUCTION

Physical inactivity is an important risk factor for all-cause, cardiovascular (CV) and cancer mortality in both men and women (1, 2). Epidemiologic evidences have shown strong associations between physical fitness (fitness), measured by maximal exercise testing, and survival from CV and non-CV causes (1-4).

Fitness, a physiologic attribute, quantifies the ability of the body to transport and use oxygen and is determined principally by training status and, to some extent, by genetic predisposition (5). Physical activity (PA) is a behavioral attribute and comprises the energy expenditure from volitional or nonvolitional activity throughout the day (5). Whereas fitness can be directly and accurately quantified with graded exercise tests, the measure of PA pattern has relied on cruder methods, such as self-reports, motion detectors (i.e., Caltrac) (6), or structured interviews (7). Although fitness is often used as an indicator of PA, there has been recent debate as to whether daily PA patterns largely determine one's fitness and therefore its inverse association with mortality, or whether fitness level predicts mortality, independent of PA patterns (8). Most of these issues have been evaluated in asymptomatic Caucasians and other ethnic population (9-11) or patients with existing cardiovascular disease (5). It has not been well studied as to whether PA and fitness are independent determinants of all-cause mortality in Korean subjects.

Chronic smoking usually induces elevated myocardial work and reduces exercise capacity and thus impairs overall cardiopulmonary fitness (12). In addition, it is a well established risk factor for mortality. Accordingly, chronic smoking reduces one's fitness level and therefore might influence on the association between physical fitness and mortality. Furthermore, there has been debate as to whether the beneficial effects of physical activity are modified by the smoking status (13, 14). Therefore, the aim of this study was to examine the association between fitness (measured by maximum oxygen uptake [VO_2 max]) and all-cause mortality, independent of regular PA or smoking status in Korean men.

MATERIALS AND METHODS

Subjects

We collected data for 19,410 men who had undergone medical check-ups and graded exercise tests for obtaining VO_2 max at the Health Promotion Center at Seoul National University Hospital from May 1995 to December 2003. Of those, we excluded 148 subjects who had prior histories of cancer (N=78), stroke (N=44) or myocardial infarction (N=26), and 487 subjects who had missing information on regular PA. A total of 18,775 men were included in the final analysis. The institution review board of Seoul National University Hospital reviewed and approved the protocol, retrospectively.

Baseline measurements

Information on age, education level, occupation, income, smoking status, alcohol consumption, regular leisure time PA (light moderate, or vigorous activities for more than 30 min at least three times a week) by a structured self-reported questionnaire, supervised by trained nurse. Smoking status were classified into 3 categories; current, former, or never smokers. Subjects who reported smoking at least one cigarette per day at present time were classified as current smokers. Non-smokers were defined as those who had never smoked. Subjects who reported as not smoking currently but had smoked ever were classified as former smokers. History for alcohol drinking was evaluated by the subject's reported average frequency (times per week) during the month before the screening examination. Regular drinker was defined as drinking alcoholic beverages at least once a week.

Height and weight were measured after an overnight fast while the subject wore a lightweight gown. Blood pressure was measured using an automated blood pressure device (Jawon, Busan, Korea) after the subject had rested for at least 20 min in a sitting position. Blood samples were obtained after an overnight fast of at least 12 hr for chemical analysis. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg at baseline examination, a reported history of previous hypertension, or current uses of antihypertensive medication (15). Diabetes was defined as fasting plasma glucose ≥ 126 mg/dL at enrollment, a reported history of previous diabetes mellitus, or current use of anti-diabetic agents.

Physical activity and physical fitness assessment

Leisure time PA was determined by assessing the results of a self-administered questionnaire that included questions regarding the subjects' participation in any kind of regular physical exercise or walking, the duration and the frequency of each activity per week over a month prior to the examination. This process was supervised by a trained nurse, and the subjects were encouraged to ask questions if they needed further clarification on any question. The PA of each subject was confirmed by a doctor, face-to-face, just after the completion of the self-administered questionnaire. Those who reported engaging in leisure time PA once a week or more were asked about the average duration and intensity (light, moderate or vigorous) (16) of the activity. In this study, PA was classified into two categories: regular PA, defined as leisure time PA engaged in any intensity of PA for 30 min at least three times a week, and no regular PA group.

Graded exercise tests were performed on a cycle ergometer (Cateye Ergociser, EC 1600, Osaka, Japan), and VO_2 max was estimated by a skilled examiner in order to evaluate the subject's physical fitness level. The subjects exercised to a cardiac frequency of 85% of their predicted maximum until stopping due to dyspnea, fatigue, chest pain or systolic blood pressure greater than or equal to 250 mmHg (17).

Mortality ascertainment

Participants were followed for mortality from baseline examination until death for decedents or until December 31, 2005 for survivors. Death was ascertained through record linkage with the national death certificate files in Korea. Follow-up for deaths was more than 98% complete (18). For all deaths, a computerized search of death certificate data from the National Statistical Office in Korea was performed using personal identification numbers assigned at birth. International Classification of Diseases (ICD) 10th Revision was used for coding the cause of death. Cardiovascular death was defined with codes I00-99 and cancer death was defined with codes C00-C97 (19) at the hospitals.

Table 1. Baseline characteristics of the study subjects according to the regularity of physical activity

	Regular PA (N=7,157)	No regular PA (N=11,618)	*p* value
Age (yr)	58.3 (10.8)	54.0 (11.00)	<0.001
BMI (kg/m²)	24.3 (2.63)	24.0 (2.98)	<0.001
Smoking*			<0.001
Never	1,560 (22.0)	1,968 (17.1)	
Former	2,963 (41.8)	2,997 (26.0)	
Current	2,569 (36.2)	6,572 (57.0)	
Regular drinker*	5,155 (72.7)	8,129 (70.8)	0.004
Total cholesterol (mg/dL)	200.3 (34.29)	199.4 (36.66)	0.102
Glucose (mg/dL)	103.2 (27.75)	101.0 (28.22)	<0.001
Triglyceride (mg/dL)	145.6 (110.4)	162.6 (115.7)	<0.001
Diagnosis of hypertension*	3,004 (42.0)	4,042 (34.8)	<0.001
Diagnosis of diabetes*	957 (13.5)	1,162 (10.1)	<0.001
VO_2 max (mL/kg/min)*	26.0 (15.46)	23.8 (10.34)	<0.001
Low	2,541 (35.5)	4,246 (38.7)	
Moderate	2,114 (29.5)	3,085 (28.1)	
High	2,502 (35.0)	3,639 (33.2)	

Data are mean (SD), *frequency (%).
Chi-square test or Student's t-tests were used (missing information for smoking status=144).
VO_2 max was categorized as low (VO_2 max $\leq$22 mL/kg/min), moderate (23 mL/kg/min $\leq VO_2$ max $\leq$29 mL/kg/min) and high (VO_2 max $\geq$30 mL/kg/min).
Regular drinker means the men drinking alcoholic beverages at least once a week.
VO_2 max, maximum O_2 uptake measured by graded exercise test with bicycle ergometer. Regular physical activity (PA) means 'engaging in light, moderate or vigorous activities for at least 30 min more than three times a week.'
PA, physical activity; BMI, body mass index.

Statistical analysis

SPSS for Windows 12.0 was used for statistical analysis. All analyses were performed after excluding the subjects who died during the first two years of follow-up. The chi-square-tests or Student's t-tests were used to analyze the statistical differences between the characteristics of the study participants according to PA. Cox proportional hazard models were used to calculate the adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) in model for all-cause mortality. Physical fitness level was first classified into tertile in total subjects: low (VO_2 max ≤22 mL/kg/min), moderate (23 mL/kg/min ≤VO_2 max ≤29 mL/kg/min) and high (VO_2 max ≥30 mL/kg/min). Then, fitness was divided into tertile separately according to the regular or no regular PA groups: low (VO_2 max ≤23 mL/kg/min), moderate (24 mL/kg/min ≤VO_2 max ≤29 mL/kg/min) and high (VO_2 max ≥30 mL/kg/min) in the regular PA group; low (VO_2 max ≤22 mL/kg/min), moderate (23 mL/kg/min ≤VO_2 max ≤28 mL/kg/min) and high (VO_2 max ≥29 mL/kg/min) in the no regular PA group. Stratified by the regularity of PA, all-cause, CV and cancer mortality at the different levels of fitness (by each tertile increase) were estimated after adjusting for age, study year, body mass index (BMI), total cholesterol, alcohol consumption, smoking status (never, former, or current) and diagnosis of hypertension or diabetes.

We also examined stratified analyses according to the categories of smoking status in the multivariate analyses to examine whether the associations between regular PA, fitness and mortality were modified by smoking status. p values are 2-sided, and $p<0.05$ was considered to be statistically significant.

RESULTS

During the mean follow-up period of 6.4 yr, 547 deaths were recorded, of which 262 (47.9%) were due to cancer and 101 (18.5%) were due to CV disease. The characteristics of the study subjects according to PA status at baseline were compared (Table 1). The mean (SD) age of the study participants was 55.7 (11.1) yr, and the mean (SD) VO_2 max of the subjects in the regular PA group was 26.0 (15.5) mL/kg/min and that of the subjects in the no regular PA group was

Table 2. Multivariate hazard ratios (HRs) (95% CI) of all-cause, CV and cancer mortality among men

Variables	All-cause mortality HR (95% CI)	CV mortality HR (95% CI)	Cancer Mortality HR (95% CI)
Age	1.08 (1.07-1.09)	1.11 (1.09-1.13)	1.08 (1.06-1.09)
BMI (per 1- unit increment)	0.96 (0.93-1.00)	0.97 (0.93-1.01)	0.94 (0.89-0.99)
Cholesterol (per 1 mg/dL increment)	1.00 (0.99-1.00)	1.01 (1.00-1.01)	1.00 (0.99-1.00)
Regular physical activity			
No	1	1	1
Yes	0.63 (0.52-0.76)	0.42 (0.27-0.68)	0.72 (0.55-0.94)
Regular drinking			
No	1	1	1
Yes	0.75 (0.63-0.90)	0.78 (0.52-1.18)	0.73 (0.57-0.94)
Smoking			
No	1	1	1
Former	1.25 (0.96-1.64)	0.92 (0.47-1.98)	2.08 (1.34-3.25)
Current	1.97 (1.52-2.55)	1.44 (0.85-2.43)	3.00 (1.94-4.63)
Diagnosis of hypertension			
No	1	1	1
Yes	1.44 (1.20-1.72)	2.27 (1.48-3.48)	1.26 (0.97-1.63)
Diagnosis of diabetes			
No	1	1	1
Yes	1.30 (1.04-1.61)	1.16 (0.70-1.93)	1.48 (1.09-2.02)
VO_2 max			
Low	1	1	1
Moderate	0.58 (0.47-0.70)	0.47 (0.29-0.77)	0.60 (0.45-0.80)
High	0.58 (0.45-0.75)	0.64 (0.35-1.19)	0.52 (0.36-0.76)

Regular physical activity (PA) means 'engaging in light, moderate or vigorous activities for at least 30 min more than three times a week.'
VO_2 max was categorized as low (VO_2 max ≤23 mL/kg/min), moderate (24 mL/kg/min ≤VO_2 max ≤29 mL/kg/min) and high (VO_2max ≥30 mL/kg/min) in the regular PA group and low (VO_2 max ≤22 mL/kg/min), moderate (23 mL/kg/min ≤VO_2 max ≤28 mL/kg/min) and high (VO_2max ≥29 mL/kg/min) in the no regular PA group.
Regular drinking means drinking alcoholic beverages at least once a week.
VO_2max, ~; maximum O_2 uptake measured by graded exercise test with bicycle ergometer; CI, confidence interval; CV, cardiovascular; BMI, body mass index.

23.8 (10.3) mL/kg/min. The subjects who engaged in regular PA were older and had higher fasting glucose levels and a lower prevalence of current smoker in comparison to those who did not.

The effects of regular PA and physical fitness on mortality

The adjusted HR (95% CI) of regular PA for all-cause mortality was 0.63 (0.52-0.76). The HRs (95% CI) of all-cause mortality for the men with moderate and high levels of fitness decreased to 0.58 (0.47-0.70) and 0.58 (0.45-0.75), respectively, in comparison to the men with a low level of fitness. Engaging in regular PA and higher level of fitness also reduced CV and cancer mortality. The HRs (95% CI) of men who engaged in regular PA was 0.42 (0.27-0.68) for CV mortality and 0.72 (0.55-0.94) for cancer mortality. The adjusted HRs (95% CI) in men with moderate and high levels of fitness, using men with a low level of fitness as reference, were 0.47 (0.29-0.77) and 0.64 (0.35-1.19) for CV mortality and 0.60 (0.45-0.80) and 0.52 (0.36-0.76) for cancer mortality, respectively. Diagnosis of hypertension or Diabetes, BMI, smoking status and alcohol consumption were also significantly related to mortality (Table 2).

Combined effect of regular PA and fitness on mortality

The association between fitness and mortality was significantly stronger among the men who did not engage in regular PA than those who did (p for interaction=0.031 for all-cause mortality, table not shown). When stratified by regularity of PA, the men in higher level of fitness did not show significant reduction of the HRs for total mortality and CV mortality (p for trend=0.15 for total mortality, p for trend=0.63 for CV mortality) compared to men in the lowest level of fitness. Cancer mortality decreased significantly in men with higher level of fitness in the regular PA group (p for trend=0.037) On the other hand, in the no regular PA group, all-cause, CV and cancer mortality decreased significantly with increased fitness level. The adjusted HRs in men with moderate and high levels of fitness, using men with a low level of fitness as reference, were 0.49 and 0.49 (p for trend <0.001) for total mortality, 0.41 and 0.46 (p for trend=0.007) for CV mortality, and 0.57 and 0.42 (p for trend<0.001) for cancer mortality, respectively, after full adjustment for age, study year, total cholesterol, BMI smoking status, alcohol consumption and diagnosis of hypertension or diabetes (Table 3).

The effect of regular PA and fitness on mortality according to smoking status

In the analysis stratified by smoking status, there was statistically significant decrease in all-cause mortality with increased fitness level in all smoking categories in the no regular PA group. In the group of subjects who did not engage in regular PA, the HRs of men with moderate and high levels of fitness in never smokers for all-cause mortality were 0.21 and 0.53 (p for trend=0.007), those of former smokers were 0.58 and 0.45 (p for trend=0.018) and those of current smokers were 0.52 and 0.50 (p for trend<0.001), respectively, in comparison to the men with a low level of fitness in

Table 3. Hazard ratios for all-cause, cardiovascular and cancer mortality according to level of physical fitness and regularity of physical activity

		Physical activity					
		Regular case/person-years	ID	aHR (95% CI)	No regular case/person-years	ID	aHR (95% CI)
All cause mortality	1st tertile	81/16,735	484.02	1.00	240/28,123	853.39	1.00
	2nd tertile	58/14,252	406.96	0.71 (0.49-1.02)	50/20,608	242.62	0.49 (0.37-0.65)
	3rd tertile	35/14,482	241.68	0.77 (0.52-1.12)	43/22,027	195.22	0.49 (0.36-0.67)
				p for trend=0.148			p for trend <0.001
Cardiovascular mortality	1st tertile	13/16,735	77.68	1.00	53/28,123	188.46	1.00
	2nd tertile	8/14,252	56.13	0.62 (0.22-1.73)	14/20,608	67.93	0.41 (0.21-0.79)
	3rd tertile	5/14,482	34.53	1.01 (0.35-2.95)	8/22,027	36.31	0.46 (0.22-0.95)
				p for trend=0.625			p for trend=0.007
Cancer mortality	1st tertile	44/16,735	262.92	1.00	107/28,123	380.47	1.00
	2nd tertile	26/14,252	182.43	0.49 (0.27-0.85)	49/20,608	237.77	0.57 (0.39-0.85)
	3rd tertile	19/14,482	131.20	0.71 (0.41-1.24)	17/22,027	77.18	0.42 (0.26-0.68)
				p for trend=0.036			p for trend<0.001

Adjusting for age, study year, total cholesterol, body mass index, smoking status (never, former, current), regular drinking (drinking alcoholic beverages at least once a week) and diagnosis of hypertension or diabetes.

Regular physical activity (PA) means 'engaging in light, moderate to vigorous activities for at least 30 min more than three times a week.'

VO_2 max was categorized as low (VO_2 max ≤23 mL/kg/min), moderate (24 mL/kg/min ≤VO_2 max ≤29 mL/kg/min) and high (VO_2 max ≥30 mL/kg/min) in the regular PA group and low (VO_2 max ≤22 mL/kg/min), moderate (23 mL/kg/min ≤VO_2 max ≤28 mL/kg/min) and high (VO_2 max ≥29 mL/kg/min) in the no regular PA group.

ID, incidence density (per 100,000 person-years); aHR, adjusted hazard ratio; CI, confidence interval.

Table 4. Hazard ratios for all-cause mortality according to level of physical fitness (VO_2 max) and regular physical activity and smoking status among men

Physical activity	Never smoker	aHR (95% CI) Former smoker	Current smoker
Regular			
Low	1	1	1
Moderate	1.08 (0.43-2.75)	0.85 (0.50-1.82)	0.50 (0.27-0.91)
High	1.47 (0.54-3.96)	0.61 (0.30-1.24)	0.75 (0.41-1.36)
p for trend	0.744	0.379	0.076
No regular			
Low	1	1	1
Moderate	0.21 (0.07-0.59)	0.58 (0.34-0.97)	0.52 (0.36-0.74)
High	0.53 (0.23-1.21)	0.45 (0.23-0.89)	0.50 (0.34-0.73)
p for trend	0.007	0.018	<0.001

Adjusting for age, study year, total cholesterol, fasting glucose, body mass index, regular drinking (drinking alcoholic beverages at least once a week) and diagnosis of hypertension or diabetes.
Regular physical activity (PA) means 'engaging in light, moderate or vigorous activities for at least 30 min more than three times a week.'
VO_2 max was categorized as low (VO_2 max $\leq$23 mL/kg/min), moderate (24 mL/kg/min $\leq VO_2$ max $\leq$29 mL/kg/min) and high (VO_2 max $\geq$30 mL/kg/min) in the regular PA group and low (VO_2 max $\leq$22 mL/kg/min), moderate (23 mL/kg/min $\leq VO_2$ max $\leq$28 mL/kg/min) and high (VO_2 max $\geq$29 mL/kg/min) in the no regular PA group.
aHR, adjusted hazard ratio; CI, confidence interval.

each smoking category (Table 4). The HRs (95% CIs) in men who engaged in regular PA and who were current smokers with moderate and high levels of fitness decreased to 0.50 (0.27-0.91) and 0.75 (0.41-1.36), in comparison to those with a low level of fitness.

DISCUSSION

The results of the present study demonstrated that both regular PA and physical fitness are inversely associated with the risk of death among relatively healthy men.

The extent how much the beneficial effects of PA on health are mediated through one's fitness level has been a matter of debate. The association between PA pattern and fitness was reported with a correlation of 0.3-0.6 (20) and 0.09 (5) in different studies. Roman et al. examined the relationship between VO_2 max and PA energy expenditure using doubly labeled water method in free living older individuals (21). They reported a low order of correlation (r=0.37) and only 13% of shared variance between VO_2 max and PA energy expenditure. They also suggested that fitness and PA may act in a unique and independent manner to improve cardiovascular and metabolic health (21).

Few studies have addressed both fitness and PA in the same study in subjects with clinical data. In this study, the association between fitness and mortality was significant among men who did not engage in regular PA, but not among those who did. We observed that the subjects in the no regular PA group with the highest level of fitness showed a significant 51% risk reduction in all-cause mortality; meanwhile the risk of death in the subjects in the regular PA group with the highest level of fitness was attenuated by 23%, compared to the lowest level of fitness, but this effect was not statistically significant. These finding might be originated from the result that the number of subjects who engaged in regular PA was relatively small (38.1% of total subjects), and the incidence rate of mortality in the men engaging in regular PA was lower than that in the men with no regular PA (484.02 per 100,000 person-years for lowest fitness in regular PA group, 853.39 per 100,000 person-years for lowest fitness in no regular PA group).

Regular PA in this study was defined as leisure time PA (engaging in any kind of leisure time PA for 30 min at least three times a week) over one month prior to the assessment of fitness. All subjects not included in the regular PA group were included in the no regular PA group. Regular PA in this study reflected regularly spent leisure time PA-related energy expenditure regardless of intensity of leisure time PA. In regular PA, strength and power training like indoor golf or weight lifting and stretching exercise like yoga were all included based upon the frequency and duration of activity. These activities are not enough to increase fitness level, but enough to spend PA-related energy expenditure and reduce total mortality related to non-CV causes such as fall, fracture and depression etc. Although there is a genetic component to fitness, the major modifiable determinant of fitness is physical activity intense enough to increase heart rate above resting levels and deliver more oxygen to the tissue.

Our study showed that all-cause mortality was affected by regular PA than fitness level. Regular PA is known to influence not only metabolic health including improving insulin sensitivity and reducing body fatness, but also improving cardiopulmonary fitness (22). They also reported that PA-related energy expenditure, or the total dose of physical activity is more important for health benefits than is the specific type of PA performed (e.g., walking, running, cycling) (22).

In general, the dose-response relationship between fitness and activity and the risk of death showed a relatively greater benefit in the lower fitness group than in the higher fitness group (23-24). In Korea, the 2001 Korean National Health and Nutrition Survey performed with a representative sample of 7,838 subjects who completed questionnaires on PA and were over 20 yr old showed that 71.8% of the subjects did not exercise at all (25). However, the public transportation system and walkways in Korea are well developed, and people in Korea spend an average 65.8 ($\pm$73.6) min per day walking (25). Therefore regardless of regularity of leisure time PA, Korean people might spend much time walking on average. This phenomenon might explain why the effect of fitness level on mortality was attenuated in subjects in the regular PA group.

We also assessed the influence of smoking status on the association between fitness level, regular PA and all-cause mortality. The risk of mortality in men who did not engage in regular PA with higher level of fitness, compared to the lowest level of fitness, was significantly reduced in all smoking categories. In the regular PA group, an increased fitness level seemed to have a protective effect on death risk reduction, but this was statistically significant only in the current smokers.

Smoking is widely recognized as a major risk factor for all-cause mortality, as is physical inactivity (26). Cigarette smoking has been known to contain more than 4,000 toxic substances, and engaging in physical activities that are intense enough to increase one's fitness level would increase their body heat and eliminate the water-soluble toxic substances found in cigarettes from their body by heat dissipation (sweating). Even the detrimental effect of smoking on all-cause mortality might be preventable with strenuous physical activity. Physical activity also provides the advantages of increased body fluid for heat dissipation (sweating) and thermoregulatory stability as well as a larger vascular volume for greater cardiac filling and stroke volume and cardiovascular stability during exercise and orthostatic challenges (27). Therefore, PA and fitness may be protective against reduced blood volume and the subsequent development of disease associated with aging. These findings suggest that human beings might be born with an innate need to be physically active to live healthy. We observed that physical fitness reduced the risk of all-cause mortality, especially in the high-risk group, such as those who did not engage in regular PA. According to our study results, men who do not engage in regular PA could reduce their mortality risk by engaging in daily activities that are intense enough to increase their fitness level.

Our study has several limitations. The study population was composed of relatively healthy people and did not include women because the number of female smokers was too small. Although the sample size of this study was not small, the number of deaths may not have been large enough to obtain enough statistical power to demonstrate the health benefit of increased the fitness level of healthy subjects who engage in regular PA. Because the cause-specific mortality has been classified accurately since 2000, it might have chance of being misclassified between 1995 and 1999.

However, our study results are not different from those of previous studies that investigated physical fitness or activity separately (28-30). Few researches have focused on the association between fitness level and all-cause mortality according to smoking status, mostly in former and current smokers. To the best of our knowledge, this is the first large study to directly measure VO_2 max by graded exercise testing in order to assess physical fitness in Korean men.

In conclusion, we observed that regular PA and physical fitness, as assessed by VO_2 max, were inversely associated with all-cause, CV and cancer mortality in Korean men. In this study, the regular PA is more important than fitness in predicting the mortality. The combined effect of fitness and PA on mortality was more pronounced in the subjects who did not engage in regular PA. Our study suggested that even in the current smokers especially who did not engage in regular PA, increasing one's fitness level by participating intense activities such as running, fast walking or climbing stairs during normal daily activities, might provide health benefits to reduce the risk of mortality. Further studies are needed to investigate the association between free living PA and fitness on all-cause and cause-specific mortalities.

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対象の内訳		ヒト	動物	地 域	アジア	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	男性	(　　)		(　　)		(　　)
	年齢	55.7(±11.1)歳	[redacted]		(　　)		前向き研究
	対象数	10000以上			(　　)		(　　)
調査の方法	実測	(　　)					

アウトカム							
	予 防	心疾患予防	なし	ガン予防	なし	死亡	(　　)
	維持・改善	なし	なし	なし	なし	(　　)	(　　)

図 表

Table 2. Multivariate hazard ratios (HRs) (95% CI) of all-cause, CV and cancer mortality among men

Variables	All-cause mortality HR (95% CI)	CV mortality HR (95% CI)	Cancer Mortality HR (95% CI)
Age	1.08 (1.07-1.09)	1.11 (1.09-1.13)	1.08 (1.06-1.09)
BMI (per 1- unit increment)	0.96 (0.93-1.00)	0.97 (0.93-1.01)	0.94 (0.89-0.99)
Cholesterol (per 1 mg/dL increment)	1.00 (0.99-1.00)	1.01 (1.00-1.01)	1.00 (0.99-1.00)
Regular physical activity			
No	1	1	1
Yes	0.63 (0.52-0.76)	0.42 (0.27-0.66)	0.72 (0.55-0.94)
Regular drinking			
No	1	1	1
Yes	0.75 (0.63-0.90)	0.78 (0.52-1.18)	0.73 (0.57-0.94)
Smoking			
No	1	1	1
Former	1.25 (0.96-1.64)	0.92 (0.47-1.98)	2.08 (1.34-3.25)
Current	1.97 (1.52-2.55)	1.44 (0.85-2.43)	3.00 (1.94-4.63)
Diagnosis of hypertension			
No	1	1	1
Yes	1.44 (1.20-1.72)	2.27 (1.48-3.48)	1.26 (0.97-1.63)
Diagnosis of diabetes			
No	1	1	1
Yes	1.30 (1.04-1.61)	1.16 (0.70-1.93)	1.48 (1.09-2.02)
VO_2 max			
Low	1	1	1
Moderate	0.58 (0.47-0.70)	0.47 (0.29-0.77)	0.60 (0.45-0.80)
High	0.58 (0.45-0.75)	0.64 (0.35-1.19)	0.52 (0.36-0.76)

Regular physical activity (PA) means 'engaging in light, moderate or vigorous activities for at least 30 min more than three times a week.'
VO_2 max was categorized as low (VO_2 max ≦23 mL/kg/min), moderate (24 mL/kg/min ≦VO_2 max ≦29 mL/kg/min) and high (VO_2max ≧30 mL/kg/min) in the regular PA group and low (VO_2 max ≦22 mL/kg/min), moderate (23 mL/kg/min ≦VO_2 max ≦28 mL/kg/min) and high (VO_2max ≧29 mL/kg/min) in the no regular PA group.
Regular drinking means drinking alcoholic beverages at least once a week.
VO_2max, –; maximum O_2 uptake measured by graded exercise test with bicycle ergometer; CI, confidence interval; CV, cardiovascular; BMI, body mass index.

図表掲載箇所	P15, Table2
概 要（800字まで）	本研究は、韓国で健康診断を受けたコホートのうち体力測定を行った男性18,775名を対象に、平均6.4年間の追跡調査を行い、体力や余暇身体活動が総死亡、心血管疾患死亡、がん死亡に与える影響について検討したものである。質問紙により、1回30分以上の余暇身体活動を少なくとも週3回以上実施している者を習慣者とし、それ未満を非習慣者と分類した。また、自転車エルゴメータによる最大下漸増負荷試験により最大酸素摂取量(全身持久力)を測定し、低:22mL/kg/min以下、中:23-29mL/kg/min、高:30mL/kg/min以上の3群に分類した。運動非習慣者と比較すると、運動習慣者で総死亡、心血管疾患死亡、がん死亡リスクがそれぞれ、0.63(95%信頼区間:0.52-0.76)、0.42(0.27-0.68)、0.72(0.55-0.94)と有意に低下した。また、全身持久力低の集団と比較すると、中、高の集団でそれぞれ、総死亡リスクが0.58(0.47-0.70)、0.58(0.45-0.75)、心血管疾患死亡リスクが0.47(0.29-0.77)、0.64(0.35-1.19)、がん死亡リスクが0.60(0.45-0.80)、0.52(0.36-0.76)と有意に低下した。また、体力と余暇身体活動の複合効果として、非習慣者のうち全身持久力低の集団と比較すると、総死亡、心血管疾患死亡、がん死亡全てで量反応的にリスクが低下することが明らかとなった(総死亡、がん死亡Ptrend<0.001、心血管疾患死亡Ptrend=0.007)。
結 論（200字まで）	韓国人男性コホートにおいて、余暇時間の定期的な身体活動と体力は、総死亡、心血管疾患死亡、がん死亡リスクを有意に低下させることが明らかとなった。それら死亡リスクにおいて、身体活動の実施状況が強力な予測因子であった。また、体力と身体活動の死亡リスクに対する複合効果は、運動非習慣者において顕著であった。
エキスパートによるコメント（200字まで）	身体活動基準の策定に用いられた研究の1つである。死亡のリスクに対する体力と身体活動の複合的影響を見た論文である。身体活動量が多く、体力も高いことでより大きな死亡リスクの減少が認められていることは、単に身体活動量の増大を図るだけでなく、体力を高めることを意図した支援をすることの重要性を支持するものである。

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A Prospective Study of Cardiorespiratory Fitness and Breast Cancer Mortality

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[1]Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, SC; [2]Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC; [3]Statewide Cancer Prevention and Control Program, University of South Carolina, Columbia, SC; [4]Center for Health Services and Policy Research, University of South Carolina, Columbia, SC; and [5]Department of Kinesiology, Health Promotion, and Recreation, University of North Texas, Denton, TX

ABSTRACT

PEEL, J. B., X. SUI, S. A. ADAMS, J. R. HÉBERT, J. W. HARDIN, and S. N. BLAIR. A Prospective Study of Cardiorespiratory Fitness and Breast Cancer Mortality. *Med. Sci. Sports Exerc.*, Vol. 41, No. 4, pp. 742–748, 2009. **Purpose**: Physical activity may protect against breast cancer. Few prospective studies have evaluated breast cancer mortality in relation to cardiorespiratory fitness (CRF), an objective marker of physiologic response to physical activity habits. **Methods**: We examined the association between CRF and risk of death from breast cancer in the Aerobics Center Longitudinal Study. Women (N = 14,811), aged 20 to 83 yr with no prior breast cancer history, received a preventive medical examination at the Cooper Clinic in Dallas, Texas, between 1970 and 2001. Mortality surveillance was completed through December 31, 2003. CRF was quantified as maximal treadmill exercise test duration and was categorized for analysis as low (lowest 20% of exercise duration), moderate (middle 40%), and high (upper 40%). At baseline, all participants were able to complete the exercise test to at least 85% of their age-predicted maximal heart rate. **Results**: A total of 68 breast cancer deaths occurred during follow-up (mean = 16 yr). Age-adjusted breast cancer mortality rates per 10,000 woman-years were 4.4, 3.2, and 1.8 for low, moderate, and high CRF groups, respectively (trend P = 0.008). After further controlling for body mass index, smoking, drinking, chronic conditions, abnormal exercise ECG responses, family history of breast cancer, oral contraceptive use, and estrogen use, hazard ratios (95% CI) for breast cancer mortality across incremental CRF categories were 1.00 (referent), 0.67 (0.35–1.26), and 0.45 (0.22–0.95) (trend P = 0.04). **Conclusions**: These results indicate that CRF is associated with a reduced risk of dying from breast cancer in women. **Key Words**: EPIDEMIOLOGY, PREVENTION, DEATH FROM BREAST CANCER, PHYSICAL ACTIVITY

Breast cancer is the second leading cause of cancer death and the most frequently diagnosed form of cancer among women in the United States. According to the most recent publication from the American Cancer Society, in 2008, an estimated 182,462 new cases of invasive breast cancer will be diagnosed among women, and approximately 40,480 women are expected to die from this disease. The etiology of breast cancer remains to be fully explained, with less than 50% of the cases attributed to known risk factors (1). Several potential risk factors including genetic components, diet, smoking, alcohol intake, and physical activity, have been identified (28).

It has been suggested that physical activity, one of the few established modifiable breast cancer risk factors, may protect against both the development of the disease (9,36,37,39) and the progression after diagnosis (19,27). A recent systematic review by Monninkhof et al. (30) found evidence of an extreme inverse association between physical activity and breast cancer in postmenopausal women; that is, equivalent to a 20–80% decrease in risk of incident disease. Differences in risk estimates may result from imprecise physical activity assessment collected from self-report instruments, especially in women (3). In addition, most of previous studies have reported on either physical activity and incident (9,37) or combined fatal/nonfatal (36,39) breast cancer. Because physical activity protects against incident breast cancer (9,12,18,37), it might be reasonable to expect that physical activity would confer

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protection against fatal breast cancer. However, this inference cannot confidently be drawn from studies of combined nonfatal/fatal events or studies solely reliant on nonfatal outcomes. To the best of our knowledge, no study has been conducted on cardiorespiratory fitness (CRF), an objective and reproducible measure that reflects the functional consequences of physical activity habits, short-term effects of disease status (e.g., respiratory tract infections), and genetics (21). We therefore examined the association between CRF, objectively measured by maximal exercise test on a treadmill, and breast cancer mortality in women from the Aerobic Center Longitudinal Study (ACLS).

METHODS

Study sample. The population for the current analysis was composed of primarily white (>99%), married, well-educated women with no prior history of breast cancer. These women, ranging in age from 20 to 83 yr, received a preventive medical examination at the Cooper Clinic in Dallas, Texas, between 1970 and 2001 ($N = 14{,}811$). Study participants came to the clinic for periodic preventive health examinations and to receive counseling regarding diet, exercise, and other lifestyle factors associated with increased risk of chronic disease. Many participants were sent by their employers for the examination, some were referred by their personal physicians, and the rest were self-referred. At baseline, all participants were able to complete an exercise stress test to at least 85% of their age-predicted maximal heart rate (220 minus age in years). The study protocol was approved annually by the Institutional Review Board of the Cooper Institute.

Baseline examination. The baseline clinical examination was performed after receiving written informed consent from each participant and included fasting blood chemistry analyses, personal and family health history, anthropometry, resting blood pressure and ECG, and a maximal graded exercise test. Examination methods and procedures followed a standard manual of operations, as described previously (6). Briefly, body mass index [BMI = weight (kg) / height $(m)^2$] was computed from measured height and weight. Resting blood pressure was recorded as the first and the fifth Korotkoff sounds by auscultatory methods. Serum samples were analyzed for lipids and glucose using standardized automated bioassays by a laboratory that participates in and meets quality control standards of the CDC Lipid Standardization Program. Information on smoking habits (whether a current smoker), alcohol intake (number of drinks per week), personal history of cardiovascular disease (myocardial infarction or stroke), hypertension and diabetes, family history of breast cancer, oral contraceptive use, and exogenous estrogen use was obtained from a standardized questionnaire.

CRF was assessed at the baseline examination as the duration of a symptom-limited maximal treadmill exercise test using a modified Balke protocol (5,6). 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 whereas the speed increased 5.4 $m \cdot min^{-1}$ each minute until test termination. Patients were encouraged to give a maximal effort during the test. The mean (SD) percentage of age-predicted maximal heart rate achieved during exercise was 100.0 (6.3). The duration of the maximal exercise treadmill test on this protocol is highly correlated with directly measured maximal oxygen uptake in women ($r = 0.94$), an accepted measure of CRF (32). Maximal METs (1 MET = 3.5 mL O_2 uptake$\cdot kg^{-1} \cdot min^{-1}$) were estimated from the final treadmill speed and grade (4). We used our previously published age-specific distribution of treadmill duration from the overall ACLS population to define fitness groups as low (lowest 20%), moderate (middle 40%), and high (upper 40%) to maintain consistency in the study methods and because we have found that a low level of fitness, defined in this way, is an independent predictor of mortality (6) and morbidity (38). The respective cut points for total treadmill time and METs in the low, moderate, and high fitness groups were described in detail in a recent report (38).

Abnormal exercise ECG responses were broadly defined as rhythm and conduction disturbances and ischemic ST-T wave abnormalities as described in detail elsewhere (13). We have found 90% agreement between the ECG interpretation recorded in our database and that of a group of three physicians who read a random sample of 357 patient records (13).

Mortality surveillance. All participants were followed from the date of their baseline examination until their date of death or December 31, 2003. The National Death Index (NDI) was the primary data source for mortality surveillance. The underlying cause of death was determined from the NDI report or by a nosologist's review of official death certificates obtained from the department of vital records in the decedent's state of residence. Breast cancer mortality was defined by the *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes 174 to 175 before 1999 and *Tenth Revision* (*ICD-10*) codes C50 during 1999–2003. We computed woman-years of exposure as the sum of follow-up time among decedents and survivors.

Statistical analysis. Baseline characteristics of the population were calculated for the entire cohort and by CRF groups. Differences in covariates were assessed using *F*-tests. Kaplan–Meier plots were used to compare survival curves, and Cox proportional hazards models were used to estimate adjusted hazard ratios (HR), associated 95% confidence intervals (CI), mortality rates (deaths/10,000 woman-years of follow-up), and linear trends of breast cancer mortality for levels of each fitness category. When calculating HR, the low fitness group was used as the reference category. Multivariable-adjusted models controlled for the potential confounding effects of baseline age (yr), BMI ($kg \cdot m^{-2}$), smoking (current smoker or not),

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TABLE 1. Baseline characteristics according to cardiorespiratory fitness (CRF) in the Aerobics Center Longitudinal Study, 1970–2001.

Characteristic	All (N = 14,811)	CRF Low (n = 2117)	CRF Moderate (n = 5397)	CRF High (n = 7297)	P for Trend
Age (yr)	43.0 ± 10.5	42.9 ± 10.1	42.8 ± 10.4	43.1 ± 10.7	0.36
BMI (kg·m^{-2})	23.0 ± 4.1	25.9 ± 6.0	23.4 ± 4.0	21.9 ± 2.9	<0.0001
Maximal METs	9.5 ± 2.2	6.7 ± 0.9	8.5 ± 1.0	11.1 ± 1.8	<0.0001
Treadmill time duration (min)	13.3 ± 4.7	7.2 ± 1.9	11.2 ± 2.2	16.7 ± 3.7	<0.0001
Lipids (mmol·L^{-1})					
Total cholesterol	5.20 ± 1.07	5.40 ± 1.04	5.28 ± 1.04	5.08 ± 1.08	<0.0001
HDL-C	1.59 ± 0.42	1.42 ± 0.37	1.53 ± 0.37	1.66 ± 0.45	<0.0001
Triglycerides	1.05 ± 0.85	1.28 ± 0.87	1.10 ± 0.78	0.95 ± 0.87	<0.0001
Fasting blood glucose (mmol·L^{-1})	5.27 ± 4.68	5.41 ± 1.10	5.23 ± 0.75	5.27 ± 6.51	0.42
Blood pressure (mm Hg)					
Systolic	113 ± 15	117 ± 16	113 ± 14	111 ± 14	<0.0001
Diastolic	75 ± 10	78 ± 10	76 ± 10	75 ± 9	<0.0001
Current smoker (%)	1591 (10.7)	367 (17.3)	687 (12.7)	537 (7.4)	<0.0001
Alcohol drinker (≥5 drinks per week) (%)	2844 (19.2)	424 (20.0)	1133 (21.0)	1287 (17.6)	<0.0001
Hypertension (%)*	1384 (9.3)	339 (16.0)	501 (9.3)	544 (7.5)	<0.0001
Diabetes (%)†	319 (2.2)	66 (3.1)	106 (2.0)	147 (2.0)	0.004
Cardiovascular disease (%)‡	63 (0.4)	17 (0.8)	23 (0.4)	23 (0.3)	0.01
Oral contraceptive use (%)	3908 (26.4)	347 (16.4)	1356 (25.1)	2205 (30.2)	<0.0001
Estrogen use (%)	2832 (19.1)	371 (17.5)	1041 (19.3)	1420 (19.5)	0.13
Family history of breast cancer (%)	331 (2.2)	18 (0.9)	85 (1.6)	228 (3.1)	<0.0001
Abnormal exercise ECG (%)	683 (4.6)	133 (6.3)	237 (4.4)	313 (4.3)	0.0004

Data shown as means ± SD unless specified otherwise.
* Hypertension was defined as systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg, or history of physician-diagnosed hypertension.
† Diabetes was defined as glucose ≥126 mg·dL^{-1} or history of physician-diagnosed diabetes.
‡ Cardiovascular disease was defined as history of physician-diagnosed myocardial infarction or stroke.
METs, maximal metabolic equivalents achieved during the treadmill test; HDL-C, high-density lipoprotein cholesterol.

alcohol intake (five or more drinks per week or not), chronic conditions (cardiovascular disease, hypertension or diabetes, present or not for each), family history of breast cancer (present or not), abnormal exercise ECG responses (present or not), oral contraceptive use (yes or no), and estrogen use (yes or no). Cumulative hazard plots grouped by exposure suggested no appreciable violations of the proportional hazards assumption.

We also conducted Cox regression analyses of CRF stratified by categories of age, BMI, oral contraceptive use, and estrogen use to assess whether the associations were stronger in particular subgroups. Tests for multiplicative interaction between an increment of 1 min of MET of exercise capacity and other risk factors in relation to risk of breast cancer death were assessed using likelihood ratio tests comparing the models with or without interaction terms. We examined the risk of breast cancer across increments of METs to assess the shape of the fitness–breast cancer curve. Statistical analyses were performed using SAS (version 9.1, SAS Institute, Cary, NC) software. All P values were calculated from two-sided hypothesis tests, and CI were calculated at the 95% level.

RESULTS

At baseline, the mean (SD) age of the study participants was 43.0 (10.5) yr, the mean (SD) treadmill test duration was 13.3 (4.7) min, and the mean (SD) maximal METs was 9.5 (2.2). The distribution of participant characteristics for several breast cancer risk factors is given in Table 1 across categories of CRF. Women in the high fitness group were more likely to have a lower BMI, to have a more favorable lipid and blood pressure profile, to have a healthier lifestyle (as reflected by smoking and alcohol intake), and to have a lower rate of chronic conditions (as reflected by cardiovascular disease, hypertension, diabetes, and abnormal exercise ECG) as compared with low CRF.

In a mean length of 16.4 yr (range = 1.01–33.7 yr) follow-up and 242,900 woman-years of observation, 68 breast cancer deaths were identified. A steep inverse

TABLE 2. Rates and HR for breast cancer mortality by cardiorespiratory fitness (CRF) groups in 14,811 women.

	Low CRF	Moderate CRF	High CRF	P Value for Trend
No. of deaths	20	31	17	
No. of woman-years	42,488	96,714	103,554	
Rate*	4.4	3.2	1.8	0.008
Age-adjusted HR (95% CI)	1.00	0.72 (0.41–1.27)	0.42 (0.22–0.80)	0.008
Multivariate HR (95% CI)†	1.00	0.67 (0.35–1.26)	0.45 (0.22–0.95)	0.04

* Rate is expressed as per 10,000 woman-years and adjusted for age.
† Adjusted for age, BMI (kg·m^{-2}), current smoking (yes or not), alcohol intake (≥5 drinks per week, or not), chronic conditions (hypertension, diabetes, or cardiovascular disease present or not for each), family history of breast cancer (present or not), abnormal exercise ECG responses (present or not), oral contraceptive use (yes or no), and estrogen use (yes or no).
HR, hazard ratio; CI, confidence interval; CRF, cardiorespiratory fitness.

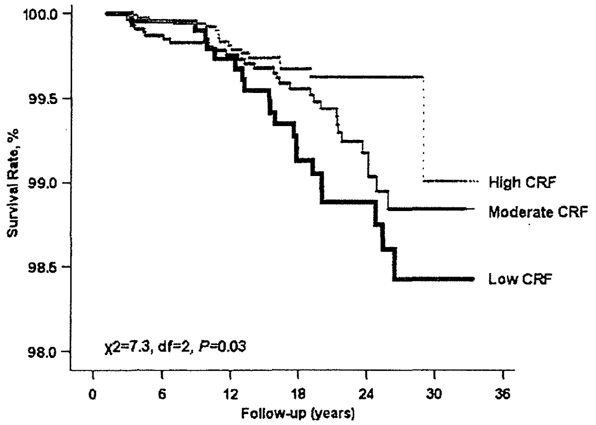

FIGURE 1—Survival free of breast cancer across cardiorespiratory fitness (CRF) status in a mean 16-yr follow-up study of 14,811 women.

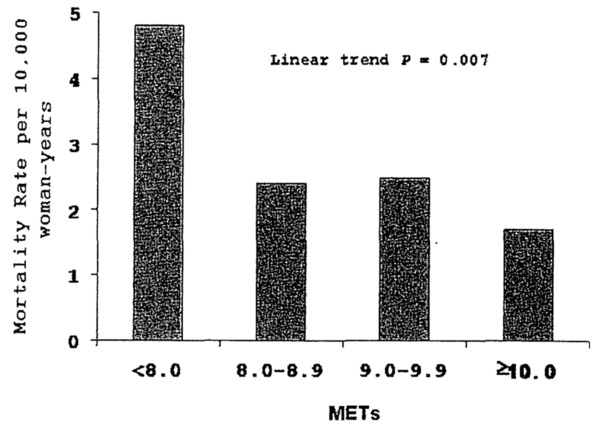

FIGURE 2—Age-adjusted mortality rates (per 10,000 woman-years) of breast cancer by CRF levels quantified in 1 MET increments obtained during a maximal treadmill test in women. Number at risk (and number of cases) in <8.0, 8.0–8.9, 9.0–9.9, and ≥10 was 3345 (34), 3805 (15), 2304 (8), and 5357 (11).

gradient (P_{trend} = 0.008) of breast cancer mortality rates was observed across CRF groups (Table 2). After adjusting for covariates (age, BMI, current smoking, alcohol intake, chronic conditions, family history of breast cancer, abnormal exercise ECG, and oral contraceptive and estrogen use), women with moderate and high CRF had 33% and 55% lower breast cancer risk, respectively, than did women with low CRF (P_{trend} = 0.04). The Kaplan–Meier plot depicts the breast cancer death rates by fitness group (Fig. 1).

We next examined whether other risk predictors modified the association between CRF and breast cancer death (Table 3). After adjustment for age, we observed significantly lower risk of death per 1 MET increment in exercise capacity among younger women (P_{trend} = 0.004), women who were normal weight (P_{trend} = 0.03), and women who never used oral contraceptives (P_{trend} = 0.03) or estrogen replacement (P_{trend} = 0.01). The test for interaction was not significant in the subgroups (P for interaction >0.40 for each). These associations between CRF and breast cancer mortality risk according to categories of other risk factors attenuated after controlling each of the other variables shown in the table. The inverse association remained significant only among women who were younger than 55 yr old and those who never used estrogen.

To further examine the dose–response characteristics between CRF levels and breast cancer mortality in our population of women, we computed the age-adjusted death rates (per 10,000 woman-years) for categories of CRF defined by increments of 1 MET across the range of 8 to 10 METs (Fig. 2). An exercise capacity of less than 8 METs was associated with a nearly threefold higher risk of breast cancer mortality compared with women having a capacity of 10 METs and greater (P_{trend} = 0.007). The inverse association remained significant after multivariate adjustment (P_{trend} = 0.02).

DISCUSSION

In this study, we observed an inverse association between CRF and the risk of breast cancer mortality. Women in the moderate and high CRF groups demonstrated a 33% and 55% lower risk, respectively, of dying of breast cancer. This association persisted after adjustment of other available potential confounders. Women with an exercise capacity less than 8 METs had a nearly threefold higher risk of dying

TABLE 3. HR for breast cancer death per 1 MET increment in maximal exercise capacity in different subgroups of women.

	No. of Deaths	HR*	95% CI*	P Value	HR†	95% CI†	P Value
Age (yr)							
<55	55	0.81	0.70–0.94	0.004	0.76	0.64–0.91	0.002
≥55	13	0.72	0.50–1.05	0.08	0.83	0.56–1.24	0.36
BMI ($kg \cdot m^{-2}$)							
<25	53	0.84	0.72–0.99	0.03	0.87	0.74–1.02	0.08
≥25	15	0.87	0.61–1.25	0.45	0.86	0.60–1.22	0.40
Oral contraceptive use							
Never	58	0.84	0.72–0.99	0.03	0.82	0.68–0.98	0.10
Ever	10	0.85	0.60–1.22	0.38	0.89	0.61–1.32	0.57
Estrogen use							
Never	60	0.83	0.71–0.96	0.01	0.81	0.68–0.96	0.02
Ever	8	1.02	0.67–1.56	0.92	1.04	0.63–1.70	0.88

* Adjusted for age.
† Adjusted for age and each of the other variables in the table.
HR, hazard ratio; CI, confidence interval.

of breast cancer compared with those with higher METs level (≥8). These data suggest that an exercise capacity of at least 8 METs may be needed to provide substantially protective benefits.

To the best of our knowledge, this is the first prospective cohort study to assess the association of CRF to risk of dying of breast cancer. It is important to note that the vast majority of the literature on breast cancer has focused on incidence and not on mortality of disease. Mortality reflects the combination of incidence with a variety of prognostic factors relating primarily to disease-related characteristics such as stage at diagnosis and grade as well as lifestyle and other factors that might influence outcome. Despite this, death registration is excellent in countries such as the United States, and mortality is a "hard" outcome that we have used with great success in the past (16). It is also important to note that there are literatures relating factors such as diet, physical activity, and relative body weight to both breast cancer incidence (9,10,15,22) and mortality (8,31,40).

Previous cohort studies using self-reported physical activity show lower risks for incident (9,37) or combined fatal/nonfatal (30,36,39) breast cancer ranging from 15% to 40%. However, other studies have reported no association (24,25,34) between physical activity and incident breast cancer. The varying range of effects and the inconsistency of results may be due to the imprecise assessment of physical activity derived from the questionnaires, population differences in the study cohorts, differences in breast cancer end points used, duration of follow-up after the baseline exposure measurement, or some combination of these.

Beyond a CRF level of 8 METs (Fig. 2), it did not appear that there were substantial decreases in risk of breast cancer death. This finding of an apparent CRF threshold adds insight into the relationship between CRF and breast cancer death. A systematic review of physical activity and breast cancer end points (including occurrence and mortality) indicates that approximately half of the selected studies observed a dose–response relationship (30). Thune et al. (39) found that compared with being sedentary, being moderately active during leisure time was associated with a 7% lower breast cancer mortality. Being regularly active during leisure time was associated with a 37% lower breast cancer incidence. These findings indicate an incremental dose–response relationship between self-reported physical activity and breast cancer end points rather than the threshold phenomenon between CRF and breast cancer observed in the present study. It is unclear what contributes to this difference, although the differing approaches to measuring physical activity exposures (i.e., self-reported physical activity vs the more objective CRF) likely account for some of the variability. Future studies are needed to confirm our findings.

A functional capacity of 8 METs is considered a low to moderate level of CRF for women across the adult age spectrum (6,38). Most women can attain this level of CRF by participating in moderate and/or vigorous intensity physical activities for 30 min or more on most days of the week (14). Although CRF has a genetic component (21), it is clear that usual physical activity habits are the primary determinant of fitness. Recently, Church et al. (7) reported that women with an activity level as low as 4 $kcal{\cdot}kg^{-1}{\cdot}wk^{-1}$ level (approximately 72 $min{\cdot}wk^{-1}$ of moderate intensity walking) had a significant improvement in CRF compared with women in the nonexercise control group. Therefore, CRF can be enhanced in most individuals through participation in a modest amount of moderate intensity physical activity.

Several biological mechanisms have been proposed to explain how increased physical activity may protect against breast cancer, including the reduction of endogenous reproductive hormone levels, decreases in body weight and adiposity, changes in circulating levels of insulin and insulin-like growth factors, and enhanced immune function (12,17). Unfortunately, we do not have data related to these variables. Therefore, we cannot evaluate these biological mechanisms directly. Due to the unique cohort design of this study, however, our investigation has several properties that enable examination of fitness and physical activity in relation to breast cancer mortality. It is rare to have a measure of fitness in a study of breast cancer and rarer still to obtain that measure before a breast cancer diagnosis. One possible hypothesis is that women maintained their level of fitness after their diagnosis, which then resulted in decreased mortality in the high fitness group. However, previous research among cancer survivors demonstrates that physical activity typically decreases after a cancer diagnosis (26). Thus, observational data do not support this supposition. An alternative hypothesis is that "prediagnosis" fitness could result in a better breast cancer prognosis (i.e., women are diagnosed with less aggressive disease), which could then favorably impact breast cancer mortality. There is some indirect support for this hypothesis from the literature, which has demonstrated a protective effect of physical activity on markers of breast cancer prognosis such as estrogen and progesterone receptor status (2,11). In these studies, physical activity was protective for estrogen and progesterone receptor-negative breast cancer, which is known to be associated with the poorest prognosis and survival. Examination of the relationship of fitness or physical activity with other breast cancer prognostic indicators could be an interesting avenue for future study.

Strengths of the current study include its prospective design, extensive baseline examinations to detect subclinical disease, careful measurement of risk factors (as opposed to self-report), maximal exercise testing to quantify CRF, and a hard end point of breast cancer mortality as the study outcome. A limitation is the inability to adjust for dietary factors and menopausal status due to the lack of data in the current study. However, a recent study that has adjusted for daily caloric intake and percentage of calories from fat found that these adjustments did not significantly change conclusions (29). Although there is evidence that dietary fat may be a stronger risk factor for postmenopausal breast cancer than for premenopausal breast cancer (20), Kushi et al. (23) only found a nonsignificant positive association between dietary fat and risk of postmenopausal breast cancer. According to the latest clinical trial results from the Women's Health Initiative, women following a recommended eating pattern including a reduction in total fat did not experience reduced breast cancer incidence (33). It is possible that residual confounding may exist, although it seems unlikely that it would account for all of the observed association between CRF and breast cancer. Another limitation of the present study is that the hormone receptor status (estrogen or progesterone) and the tumor stage (including *in situ*) and grade were not available. A recent report from the California Teachers Study shows an inverse association between self-reported physical activity and risk of both invasive and *in situ* breast cancer in women and an inverse association on estrogen-negative but not estrogen-positive breast cancer (9). Additional research is needed to further understand the specificity of associations between CRF (or physical activity) and breast cancer subtypes. The current findings are limited to European-American women in the middle and upper socioeconomic strata; the results may not be generalizable to other adult populations. Finally, we had no data on the use of mammography screening and current cancer and treatment. Future studies need to include this information to confirm our findings reported here. Given that the cohort was comprised of well-educated women of a high socioeconomic standing, we estimate that the majority of the women were seeking regular mammography screening (35). Thus, we would not anticipate a change in our findings upon adjustment for screening.

In summary, we found an inverse association between CRF and risk of breast cancer mortality in this cohort of US women and that a certain, relatively low, threshold of CRF may be needed. Given the public health burden of breast cancer, future research needs to determine the specific biological aspects of exercise related to breast cancer risk and if a dose–response relationship exists.

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Conflicts of interest: None declared.

BASIC SCIENCES

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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	-83歳（平均43歳	[redacted]		( )		前向きコホート
対象数	10000以上			( )		( )

調査の方法	実測	( )				
アウトカム 予 防	なし	なし	ガン予防	なし	(死亡)	( )
アウトカム 維持・改善	な し	な し	な し	なし	(	( )

図 表

TABLE 2. Rates and HR for breast cancer mortality by cardiorespiratory fitness (CRF) groups in 14,811 women.

	Low CRF	Moderate CRF	High CRF	*P* Value for Trend
No. of deaths	20	31	17	
No. of woman-years	42,488	96,714	103,554	
Rate*	4.4	3.2	1.8	0.008
Age-adjusted HR (95% CI)	1.00	0.72 (0.41–1.27)	0.42 (0.22–0.80)	0.008
Multivariate HR (95% CI)†	1.00	0.67 (0.35–1.26)	0.45 (0.22–0.95)	0.04

* Rate is expressed as per 10,000 woman-years and adjusted for age.
† Adjusted for age, BMI ($kg \cdot m^{-2}$), current smoking (yes or not), alcohol intake (≥5 drinks per week, or not), chronic conditions (hypertension, diabetes, or cardiovascular disease present or not for each), family history of breast cancer (present or not), abnormal exercise ECG responses (present or not), oral contraceptive use (yes or no), and estrogen use (yes or no).
HR, hazard ratio; CI, confidence interval; CRF, cardiorespiratory fitness.

図表掲載箇所	P744, 表2
概 要 (800字まで)	本研究は，全身持久力と乳癌による死亡リスクとの関連を明らかにすることを目的としたエアロビクスセンターの縦断研究（ACLS）である．14811名の乳癌のない女性を対象とし，平均16.4年間追跡された．全身持久力は修正版Balkeトレッドミルプロトコルによって評価された．年齢特異的な分布を考慮し，低体力：下位20%（6.7メッツ），中体力：次の40%（8.5メッツ），高体力：最も高い40%（11.1メッツ）の3つにカテゴリー化し，解析された．全身持久力が最も低い群と比較して，中体力群の調整ハザード比は0.67(95%CI:0.35-1.26)，高体力群では0.45(0.22-0.35)であり，全身持久力が高いものは乳癌による死亡リスクが低いことが示され，量反応関係が認められた（trend P=0.04）．
結 論 (200字まで)	全身持久力が高い人は，女性の乳癌による死亡リスクが低いことが示された．
エキスパートによるコメント (200字まで)	アメリカのエアロビクスセンターで行われたコホート研究により，全身持久力と乳癌による死亡リスクとの関連について明らかにしたものである．全身持久力を高めるような有酸素運動を推奨する上で重要ななエビデンスのひとつである．

担当者　川上諒子

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Cardiorespiratory Fitness and Digestive Cancer Mortality: Findings from the Aerobics Center Longitudinal Study

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Abstract

Although higher levels of physical activity are inversely associated with risk of colon cancer, few prospective studies have evaluated overall digestive system cancer mortality in relation to cardiorespiratory fitness (CRF). The authors examined this association among 38,801 men ages 20 to 88 years who performed a maximal treadmill exercise test at baseline in the Aerobics Center Longitudinal Study (Dallas, TX) during 1974 to 2003. Mortality was assessed over 29 years of follow-up (1974-2003). Two hundred eighty-three digestive system cancer deaths occurred during a mean 17 years of observation. Age-adjusted mortality rates per 10,000 person-years according to low, moderate, and high CRF groups were 6.8, 4.0, and 3.3 for digestive system cancer (P_{trend} < 0.001). After adjustment for age, examination year, body mass index, smoking, drinking, family history of cancer, personal history of diabetes, hazard ratios (95% confidence intervals) for overall digestive cancer deaths for those in the middle and upper 40% of the distribution of CRF relative to those in the lowest 20% were 0.66 (0.49-0.88) and 0.56 (0.40-0.80), respectively. Being fit (the upper 80% of CRF) was associated with a lower risk of mortality from colon [0.61 (0.37-1.00)], colorectal [0.58 (0.37-0.92)], and liver cancer [0.28 (0.11-0.72)] compared with being unfit (the lowest 20% of CRF). These findings support a protective role of CRF against total digestive tract, colorectal, and liver cancer deaths in men. (Cancer Epidemiol Biomarkers Prev 2009;18(4):1111–7)

Introduction

Digestive system cancers include those of the alimentary canal below the neck (e.g., esophagus, stomach, small, and large intestines) and key digestive organs (pancreas, liver, and gallbladder). Considering all digestive cancers together, these constitute the second leading cause of cancer-related mortality of men in the United States (1). Of all digestive tract sites, colon and pancreas account for the majority of deaths (colon because it is so common and pancreas because it has such poor prognosis). The etiology of various digestive cancers is not fully understood. Several potential risk factors including genetic components, diet, smoking, and physical inactivity have been identified for colon cancer (2). However, other than smoking and diabetes (3, 4), few lifestyle factors have been linked to pancreatic cancer. Recent evidence suggests that insulin resistance and abnormal glucose metabolism, without diagnosis of diabetes, also may be risk factors for pancreatic cancer (5, 6).

Although higher levels of physical activity are inversely associated with risk of colon cancer (7, 8), the association between pancreatic cancer and physical activity remains inconclusive. Several studies have found an inverse relationship (9, 10), whereas other studies have reported no association (11-13). Very few cohort studies have reported on physical activity and other sites of digestive system cancer, and the findings are inconsistent (14, 15). No studies have been conducted to assess the association between physical activity and cancers of the liver or small intestine. There is some indication that greater amounts of activity are associated with higher risk of stomach (14) and bladder (15) cancer and lower risk of oral/esophagus cancer (15). It may be that measurement errors inherent in self-reported physical activity are partly responsible for these discrepant findings. Cardiorespiratory fitness (CRF), an objective and more reproducible measure, reflects the functional consequences of physical activity habits of the individual and therefore may provide a better exposure with which to evaluate associations with relevant health outcomes.

To the best of our knowledge, only one study (16) has been conducted on CRF and mortality from cancers of the gastrointestinal system among men. However, this study only examined men with pre-diabetes and diabetes. There is a lack of data in the general population. Because the 5-year survival rate for digestive cancers as a group is very low (~45%; <10% for some sites such as pancreas and esophagus), identification of modifiable risk factors for these deadly cancers may provide important opportunities for reducing overall cancer mortality (17). We therefore examined the association between CRF, objectively measured by maximal exercise test on a treadmill, and overall and site-specific digestive cancer mortality in men from the Aerobics Center

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