論文名	Cardiovascular fitness as a predictor of mortality in men.
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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	42、48, 54, 60歳	[redacted]		( )		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	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)	目的：心臓血管疾患（CVD）に関連、非CVD関連、および全死亡について、ベースライン時における最大酸素摂取量および負荷テスト持続時間の測定によりそれらから得られた全身持久性体力との関係を調べること。方法：東フィンランドのクオピオ市とその周囲の共同体において、ベースライン時にCVD、呼吸器疾患およびガンをもたない1294名の男性に対する人口ベースのコホート研究。平均10.7年の追跡調査期間中、全体で124名、CVD関連で42名、および非関連で82名の死亡があった。結果：低体力者（最大酸素摂取量が27.6 ml/kg/min以下）における全体死の相対リスクは、年齢、試験年数、喫煙、およびアルコール消費を補正した適合者（最大酸素摂取量が37.1 ml/kg/min以上）と比べ、2.76[1.43-5.33]（95%信頼区間）（P=0.002）であり、同様に、CVD関連の死亡の相対リスクは3.09[1.10-9.56]（95%信頼区間）（P=0.05）であった。低体力者の非CVD関連の死の相対リスクは、全体死とほとんど同じ大きさであった。その上、血清脂質レベル、血圧、血漿フィブリノーゲンレベル、糖尿病、および空腹時血清インスリンレベルによる補正は、これらの関係をほとんど減弱しなかった。また、負荷テスト持続時間は、全体、CVD関連、そして、非CVD関連の死亡率との間に強い負の関係がみられた。弱い全身持久性体力は、死亡の危険因子として重要性の高い最高血圧、喫煙、肥満、および糖尿病を高めた。結論：全身持久性体力には、全体、CVD関連、そして、非CVD関連の死亡との間に、強い、負の相関がみられた。最大酸素摂取量と負荷テスト持続時間は、死亡率の最も強い予測因子の一つであろう。
結 論 (200字まで)	42-60歳の中年男性では最大酸素摂取量が普通：32.3-37.1の水準があることが全ての疾患のによる死亡リスクを低くする。
エキスパートによるコメント (200字まで)	体力が高いことが、循環器疾患による死亡や総死亡のみならず、循環器疾患以外での死亡リスクを減らすことができるという興味深い研究。

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Cardiorespiratory fitness, lifestyle factors and cancer risk and mortality in Finnish men

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ABSTRACT

Background: Physical fitness along with lifestyle factors may have important roles in the prevention of cancer. We examined the relationship between common lifestyle factors such as energy expenditure, physical activity and maximal oxygen uptake (VO_{2max}), nutrition and smoking habits and the risk of cancer.

Methods: A population-based cohort study was carried out in 2268 men from Eastern Finland with no history of cancer. They were followed up for an average of 16.7 years. The outcome measures were cancer incidence ($n = 387$) and cancer mortality ($n = 159$).

Results: Men with VO_{2max} of more than 33.2 mL/kg/min (highest tertile) had 27% (95% confidence interval (CI) 0.56–0.97) decreased cancer incidence and 37% (95% CI 0.40–0.97) reduced cancer mortality than men with VO_{2max} of less than 26.9 mL/kg/min (lowest tertile) after adjustment for age, examination year, alcohol, smoking, socioeconomic status, waist-to-hip ratio and energy, fibre and fat intake. The risk reduction was mainly due to decreased risk of lung cancer in fit men. The adjusted risk of cancer was 0.73 (95% CI 0.55–0.98) among fit ($VO_{2max} \geq 26.9$ mL/kg/min) men with the total energy expenditure of physical activity over 2500 kcal/week. A total of 290 active (energy expenditure >2500 kcal and at least 2 h of physical activity per week) men with a favourable lifestyle (good fitness, balanced diet and non-smoking) had an adjusted relative risk of 0.63 (95% CI 0.46–0.87) for cancer.

Conclusion: Favourable lifestyle including good cardiorespiratory fitness and healthy dietary habits with active and non-smoking lifestyle considerably reduces the risk of cancer.

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1. Introduction

Weight gain is one of the most important factors contributing to the increased risk for certain cancers, but the role of physical fitness, activity level and dietary energy intake in the prevention of cancer is not well defined.[1] Some studies have found that physical activity may reduce the risk of cancer at all sites[2–8] including the risk of colon,[9–14] lung,[3,10,12,15–17] pros-

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tate[3,18–20] and breast cancers[21–23] whereas other epidemiologic studies have observed only a weak or borderline significant association between physical activity and cancer risk.[23–28] It has been reported that total energy expenditure is more important than the type of exercise for reducing overall mortality.[29–31] However, little is known about the duration, intensity and energy expenditure of physical activity needed to reduce the risk of cancer when initial fitness level is taken into account. In general, the dose–response relationship between self-reported physical activity and cancer risk is uncertain but using objective and reliable measure of exercise capacity may help in achieving additional valuable information for its prognostic value.[7,8,28,32]

The latest recommendation suggest that should perform every adult 30 min of moderate-intensity physical activity on 5 d of the week helps to promote health and maintain health.[31] Only few prospective studies have reported the quantity and intensity of physical activity needed to reduce overall mortality.[28,29] Some studies indicate that reduced total mortality among fit men is largely due to reduced mortality from non-cardiovascular causes,[4,33,34] but there are no studies on the relationship between physical fitness and cancer morbidity or mortality.

The aim of the present study was to study the amount of modifiable lifestyle factors such as diet, smoking, physical activity and the level of cardiorespiratory fitness, as measured by maximal oxygen uptake (VO_{2max}), necessary to reduce the risk of morbidity and mortality from common cancers in a population-based sample of men.

2. Methods

2.1. Subjects

The present study is based on Kuopio Ischemic Heart Disease Risk Factor Study which is an ongoing population-based study to investigate various risk factors including physical fitness for atherosclerotic CVD and cancers.[35] The study population is a representative random sample of 2682 men who were 42–60 years of age at baseline examination and exercise data were available for 2361 men. Of these, men who had a history of cancer (93 men) were excluded, and thus, complete data on VO_{2max}, energy expenditure, duration, mean intensity and frequency of physical activity were available for 2268 men. Baseline examinations were conducted between March 1984 and December 1989. The study was approved by the Research Ethics Committee of the University of Kuopio, Kuopio, Finland. Each participant gave written informed consent.

2.2. Measurements

2.2.1. Cardiorespiratory fitness

A maximal symptom-limited exercise tolerance test was performed between 8:00 a.m. and 10:00 a.m. using an electrically braked cycle ergometer. The standardised testing protocol comprised an increase in the workload of 20 W/min. The tests were supervised by an experienced physician with the assistance of an experienced nurse. The electrocardiogram (ECG), blood pressure and heart rate were registered during the exercise stress test.

A detailed description of the measurement of VO_{2max} has been given elsewhere.[36] In short, respiratory-gas exchange was measured for the first 581 men by the mixing-chamber method, and for the other 1687 men by a breath-by-breath method. VO_{2max} was defined as the highest value for or the plateau of oxygen uptake. The MET is the ratio of the metabolic rate during exercise to the metabolic rate at rest. One metabolic equivalent corresponds to oxygen uptake of 3.5 mL/kg/min.

2.2.2. Physical activity

Physical activity was assessed using the 12-month physical activity questionnaire.[37,38] The checklist included the most common physical activities of middle-aged Finnish men, selected on the basis of a previous population-based study in Finland.[39] For each activity performed, the subjects were asked to record the frequency (number of sessions per month), average duration (hours and minutes per session) and intensity (scored as 0 for recreational activity, 1 for conditioning activity, 2 for brisk conditioning activity and 3 for competitive, strenuous exercise). A trained nurse checked and completed the questionnaire in an interview.

The intensity of physical activity was expressed in metabolic units (MET or metabolic equivalents of oxygen consumption). The four categories of intensity of activity were assigned their own metabolic unit values, and revised on the basis of a synthesis of available empirical data.[39] One metabolic unit corresponds to an energy expenditure of approximately 1 kcal/kg of body weight per hour, or an oxygen uptake of 3.5 mL/kg/min.

Physical activity was categorised according to type: (1) conditioning physical activity – walking (mean intensity, 4.2 MET), jogging (10.1 MET), skiing (9.6 MET), bicycling (5.8 MET), swimming (5.4 MET), rowing (5.4 MET), ball games (6.7 MET), and gymnastics, dancing, or weight lifting (5.0 MET); (2) non-conditioning physical activity – crafts, repairs, or building (2.7 MET), yard work, gardening, farming, or snow shovelling (4.3 MET), hunting, picking berries, or gathering mushrooms (3.6 MET), fishing (2.4 MET), and forestry (7.6 MET); and (3) walking (3.5 MET) or bicycling (5.1 MET) to work.

2.2.3. Diet and smoking

Dietary energy intake was assessed using 4-d food recording.[40] Instructions were given and completed food records were checked by a nutritionist. Intake of nutrients was estimated using the NUTRICA software. The data bank of NUTRICA is complied using mainly Finnish value nutrient compositions that take into account possible food preparation losses.

Lifelong exposure to smoking (cigarette pack-years) was estimated as the product of years spent smoking and the number of cigarettes smoked daily at the time of examination.[41] Energy expenditure >2500 kcal/week, physical activity duration >2 h/week (men with healthy lifestyle), $VO_{2max} \geqslant 26.9$ mL/kg/min, energy intake >108.6 kJ/kg/week, lowest tertile and non-smoking were considered as criteria for protective lifestyle factors.

2.2.4. Body mass, other lifestyle factors and biochemical variables

Body mass index (BMI) was computed as weight in kilograms divided by the square of height in metres, and waist-to-hip ra-

tio was computed as the ratio of the circumference of the waist to the hip. Alcohol consumption was assessed using the Nordic Alcohol Consumption Inventory.[12] Socioeconomic status (SES) is as described previously.[42] Blood specimens were collected at baseline and serum lipids and glucose were measured as described elsewhere.[35,41]

2.3. Outcome events

Cancer deaths and overall mortality were ascertained by linkage to the National Death Registry using the Finnish personal identification code. There were no losses to follow-up. Incident cancer cases were derived from the population-based Finnish Cancer Registry. Follow-up was started at the date of baseline measurement and ended at death or on 31st December 2005, whichever was first. Follow-up for cancer incidence was done in an automatic record linkage (based on personal identifier, PID) with the files of the population-based countrywide Finnish Cancer Registry. All residents of Finland have a unique PID which is used in all main registers in Finland.

2.4. Statistical analysis

For the descriptive purposes, the associations of VO_{2max} with the possible risk factors for cancer were examined using covariate analysis. Risk factors for cancer were analysed using multivariate Cox model. The levels of VO_{2max} were entered as dummy variables into forced SPSS Cox proportional hazards models. In these models, VO_{2max} was categorised according to tertiles. If possible, covariates were entered uncategorised into the Cox models. Two different sets of covariates were used: (1) age and examination year and (2) age, examination year, smoking, alcohol consumption, waist-to-hip ratio, SES and total caloric, fibre and fat intake.

In additional Cox models, fit ($VO_{2max} \geqslant 26.9$ mL/kg/min, lowest tertile) and unfit ($VO_{2max} < 26.9$ mL/kg/min) men were categorised according to physical activity; energy intake and smoking as reference group consisted of unfit men with other risk predictors of interest. On the basis of previous results,[43,44,48,49] the protective factors were combined to find out the optimal levels of factors that help in the reduction of cancer risk. Relative hazards, adjusted for risk factors, were estimated as antilogarithms of coefficients from multivariable models. Tests for statistical significance were two-sided. Statistical analyses were performed using the SPSS 14.0 for Windows (SPSS, Inc., Chicago, Illinois).

3. Results

3.1. Baseline characteristics

At the beginning of the follow-up, the median VO_{2max} was 30.0 mL/kg/min (range 16.0–65.4 mL/kg/min). The distribu-

Table 1 – Means (and standard deviations) of 2268 men in Eastern Finland according to tertiles of maximal oxygen uptake.

	Tertiles of maximal oxygen uptake				
	All men Mean (SD)	Lowest (1) Mean (SD)	Middle (2) Mean (SD)	Highest (3) Mean (SD)	P-value
Age	52.8 (5.1)	55.0 (4.1)	52.7 (4.8)	50.6 (5.3)	<0.001
Total physical activity					
Energy expenditure (kcal/week)	2603 (2343)	2473 (2517)	2573 (2325)	2764 (2169)	0.049
Mean intensity (METs)[a]	4.53 (1.18)	4.28 (1.05)	4.41 (1.06)	4.90 (1.32)	<0.001
Duration (h/week)	2.15 (2.65)	2.24 (2.99)	1.92 (2.45)	2.28 (2.48)	0.01
Diet					
Total energy intake (kJ/day)	9969 (2602)	9372 (2497)	9854 (2404)	10681 (2727)	<0.001
Total fat intake (g)	102.6 (33.8)	97.6 (33.7)	101.9 (31.4)	108.3 (35.4)	<0.001
Total fibre intake (g)	25.1 (8.3)	23.6 (7.7)	24.5 (8.2)	27.1 (8.7)	<0.001
	161.7 (83.8)	166.7 (87.8)	163.7 (85.0)	154.8 (78.1)	<0.001
Fruits and vegetable intake (sum g) intake (g/day)	121.2 (136.5)	121.9 (151.9)	114.7 (124.1)	126.9 (132.0)	0.218
Cigarette smoking (pack-years[b])	8.1 (16.2)	11.1 (19.6)	8.3 (15.2)	5.0 (12.4)	<0.001
Alcohol consumption (g/week)	73.8 (121.2)	80.6 (144.5)	77.4 (120.9)	63.3 (91.7)	0.01
Body mass index (kg/m^2)	26.8 (3.4)	28.2 (3.9)	26.9 (3.2)	25.5 (2.7)	<0.001
Waist-to-hip ratio	0.95 (0.06)	0.97 (0.06)	0.95 (0.06)	0.92 (0.06)	0.001
Blood glucose (mmol/L)	4.8 (1.2)	5.0 (1.5)	4.8 (1.2)	4.6 (0.8)	<0.001
Serum polyunsaturated to saturated fatty acid ratio	1.19 (0.23)	1.13 (0.25)	1.19 (0.22)	1.24 (0.21)	<0.001
Serum total cholesterol (mmol/L)	5.91 (1.07)	5.98 (1.08)	5.95 (1.06)	5.79 (1.04)	0.001
Serum insulin level (mmol/L)	11.56 (6.91)	13.99 (8.8)	11.30 (6.0)	9.40 (4.3)	<0.001
Cancer in family (%)	25.0	26.3	26.7	21.8	0.051
Use of PG-inhibitors (%)[c]	10.9	15.0	9.5	7.7	<0.001

Tertile 1 $\leqslant$ 26.9 mL/kg/min, tertile 2 = 26.9–33.2 mL/kg/min, and tertile 3 $\geqslant$ 33.2 mL/kg/min.

a MET denotes metabolic equivalents of oxygen consumption. The metabolic unit is the ratio of metabolic rate during exercise to the metabolic rate at rest. One MET corresponds to approximately 1 kcal/kg of body weight per hour and an oxygen uptake of 3.5 mL/kg/min.

b Pack-years denotes the lifelong exposure to smoking which was estimated as the product of years smoked and the number of cigarette smoked daily at the time of examination.[42]

c Regular use of prostaglandin inhibitors.

Table 2 – Risk factors for lung, GI-tract and prostate cancers in 2268 men without cancer diagnosed at baseline.

Risk factor	Lung cancer risk (52 cases)		GI-tract cancer risk (92 cases)		Prostate cancer risk (127 cases)	
	Relative risk[b] (95% CI)	P-value	Relative risk[b] (95% CI)	P-value	Relative risk[b] (95% CI)	P-value
Age (years)	1.07 (0.99–1.15)	0.781	1.04 (0.99–1.10)	0.130	1.11 (1.05–1.16)	<0.001
Smoking (cigarette pack-years per 10 years)[a]	1.36 (1.24–1.48)	<0.001	1.08 (0.95–1.23)	0.245	0.94 (0.82–1.09)	0.425
Body mass index (per 5 kg/m^2 increment)	0.62 (0.39–0.93)	0.045	1.04 (0.76–1.43)	0.816	0.96 (0.71–1.23)	0.766
Physical fitness (per 1 MET increase)	0.80 (0.69–0.93)	0.001	0.88 (0.79–0.99)	0.032	1.03 (0.94–1.12)	0.599
Alcohol consumption (per 10 g/week)[c]	1.01 (1.00–1.02)	0.029	1.01 (0.99–1.02)	0.086	1.01 (0.99–1.03)	0.277

CI = confidence interval and MET = metabolic equivalent of oxygen consumption.

a Pack-years is divided by 10, and cigarette pack-years denotes the lifelong exposure to smoking which was estimated as the product of years spent smoking and the number of cigarettes smoked daily at the time of examination.[42]

b Relative risks are adjusted for all other risk factors shown in the table in addition to fat, fibre and energy intake.

c Risk factor is expressed as a one standard deviation increment in the value.

tions of the energy expenditure, duration and mean intensity of total physical activity and other baseline characteristics according to tertiles of VO_{2max} are shown in Table 1.

3.2. *Outcomes events*

A total of 593 deaths occurred during an average follow-up of 16.7 years (range 0.4–21.8 years), and 159 deaths were due to cancers. There were 387 cancer events during the follow-up. Most common types of incident cancers were cancers of the prostate ($n = 127$), lung ($n = 52$), colo-rectum ($n = 49$), urinary bladder or kidney ($n = 36$), skin ($n = 27$), cerebrum ($n = 15$), upper gastro-intestinal (GI) tract ($n = 19$), liver ($n = 7$), pancreas ($n = 18$) and lymphoid tissues ($n = 9$).

3.3. *Risk factors for cancer*

The significant risk factors were smoking, body mass index, VO_{2max} and alcohol consumption for lung cancer, VO_{2max} for GI-tract cancers and age for prostate cancer. Alcohol consumption was a significant predictor of prostate cancer when not adjusted for serum fatty acid and dietary factors. One MET increase in VO_{2max} (3.5 mL/kg/min) amounted to a 20% decrease in lung cancer risk and 12% decrease in GI-tract cancer risk (Table 2a). Physical fitness was not independently related to prostate cancer risk but the interaction between age and VO_{2max} was almost statistically significant ($p = 0.07$).

In the multivariate analysis, the significant risk factors for overall cancer incidence were age, smoking, VO_{2max} and alcohol consumption and the risk predictors for cancer mortality were age, smoking, VO_{2max}, dietary energy intake and socioeconomic status. One MET increase in physical fitness was related to 6% decreased risk of cancer incidence (relative risk, RR 0.94, 95% confidence interval (CI) 0.89–0.99, $p = 0.026$) and cancer mortality by 12% (0.88(0.80–0.96), $p = 0.002$).

Smoking was one of the most significant predictors for cancer mortality and morbidity for lung cancer. The RR of fit non-smokers compared with that of unfit smokers was 0.43 (95% CI 0.31–0.59) for cancer incidence and 0.37 (95% CI 0.23–0.60) for cancer mortality, after adjustment for age, examination year and confounders. The adjusted risk of cancer incidence was lower (RR = 0.68, 95% CI 0.49–0.94) in fit smokers than in unfit smokers. No statistically significant interaction existed between smoking or non-smoking and the predictive power of physical fitness. VO_{2max} was related to the risk of cancer among both smokers and non-smokers.

3.4. *Physical fitness and cancer risk*

Men with VO_{2max} of more than 33.2 mL/kg/min (highest tertile) had 28% decreased cancer incidence and 45% reduced cancer mortality than men in the lowest tertile after adjustment for age and examination year (Table 3). The respective risk reductions were 27% and 37% after further adjustment for smoking, alcohol consumption, waist-to-hip ratio, SES and total caloric, fibre and fat intake. The results did not change substantially although fruits, vegetables and meat intake, family history of cancer and the regular use of prostaglandin inhibitors were controlled with the tertiles of VO_{2max}. The adjusted RR of overall death was 0.42 (95% CI

Table 3 – Relative risks of cancer according to physical fitness in 2268 men with no history of cancer at baseline.

	Cancer incidence			Cancer mortality			Overall mortality		
	Relative risk (95% CI)	P-value	No. of events	Relative risk (95% CI)	P-value	No. of deaths	Relative risk (95% CI)	P-value	No. of deaths
Maximal oxygen uptake (mL/kg/min)	387 Events			159 Deaths			593 Deaths		
Follow-up time from baseline to outcome events									
<26.9, <8.3 METs (n = 756)	1.00 (reference)		150	1.00 (reference)		58	1.00 (reference)		306
26.9–33.2, 8.3–9.5 METs (n = 756)	0.87 (0.67–1.11)[a]	0.249	133	0.79 (0.55–1.12)[a]	0.030	55	0.58 (0.49–0.70)[a]	<0.001	183
	0.87 (0.68–1.10)[b]	0.292		0.84 (0.56–1.21)[b]	0.340		0.64 (0.53–0.77)[b]	<0.001	
>33.2, >9.5 METs (n = 756)	0.72 (0.56–0.94)[a]	0.015	104	0.55 (0.36–0.83)[a]	0.005	36	0.34 (0.27–0.43)[a]	<0.001	104
	0.73 (0.56–0.97)[b]	0.028		0.63 (0.40–0.97)[b]	0.037		0.42 (0.33–0.54)[b]	<0.001	
	P = 0.0016 for linear trend			P < 0.001 for linear trend			P < 0.001 for linear trend		
	P = 0.012 for linear trend[c]			P = 0.014 for linear trend[c]			P < 0.001 for linear trend[c]		
	363 Events			137 Deaths			489 Deaths		
Follow-up time from 5 years after baseline to outcome events									
<26.9, <8.3 METs	1.00 (reference)		62	1.00 (reference)		35	1.00 (reference)		240
26.9–33.2, 8.3–9.5 METs	0.90 (0.71–1.16)[a]	0.421	45	0.83 (0.56–1.23)[a]	0.354	19	0.62 (0.51–0.76)[a]	<0.001	156
	0.90 (0.70–1.16)[b]	0.415		0.88 (0.59–1.31)[b]	0.524		0.67 (0.54–0.82)[b]	<0.001	
>33.2, >9.5 METs	0.77 (0.59–1.00)[a]	0.053	35	0.62 (0.40–0.96)[a]	0.033	13	0.38 (0.30–0.49)[a]	<0.001	93
	0.79 (0.59–1.05)[b]	0.100		0.72 (0.45–1.15)[b]	0.165		0.46 (0.35–0.59)[b]	<0.001	
	P = 0.029 for linear trend			P = 0.007 for linear trend			P < 0.001 for linear trend		
	P = 0.092 for linear trend[c]			P = 0.043 for linear trend[c]			P < 0.001 for linear trend[c]		

a Model 1: RRs are adjusted for age and examination year.

b Model 2: RRs are further adjusted for age and examination year, cigarette smoking, alcohol consumption, waist-to-hip ratio, SES and total caloric, fibre and fat intake.

c P for linear trend across the tertiles of maximal oxygen uptake from adjusted Cox model.

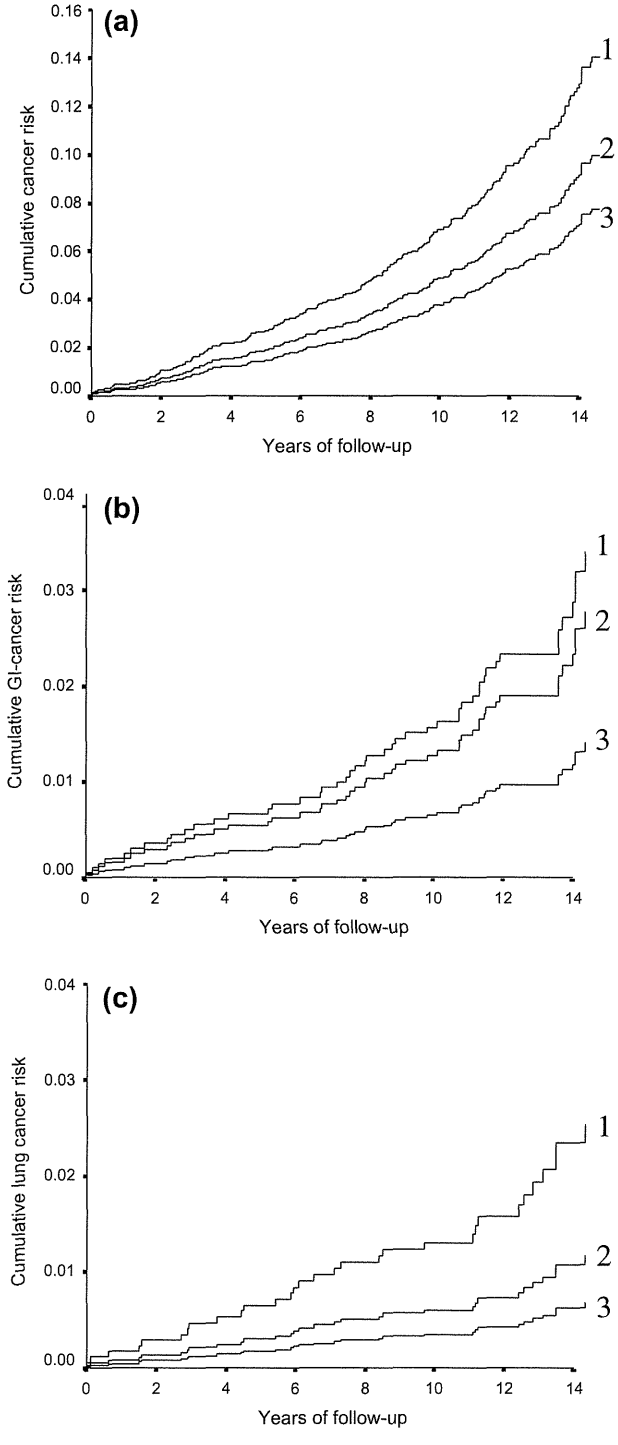

Fig. 1 – Multivariable-adjusted cumulative overall cancer (a), GI-cancer (b) and lung cancer (c) incidence during an average follow-up of 12 years in men according to tertiles of maximal oxygen uptake (1st group < 26.9 mL/kg/min, 2nd group = 26.9–33.2 mL/kg/min and 3rd group > 33.2 mL/kg/min).

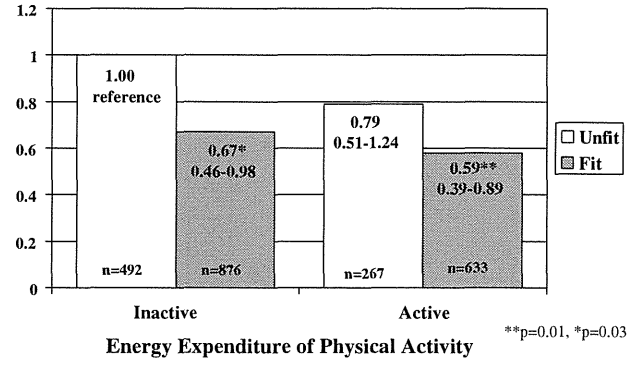

Fig. 2 – The multivariate-adjusted (age, examination year, cigarette smoking, alcohol consumption, waist-to-hip ratio, SES and total caloric, fibre and fat intake) relative risks of cancer during an average of 12 years of follow-up in 2268 men classified according to maximal oxygen uptake and the energy expenditure of total physical activity. Unfit men included those with maximal oxygen uptake less than 26.9 mL/kg/min and fit men included those with maximal oxygen uptake of at least 26.9 mL/kg/min. Active = energy expenditure of physical activity over 2500 kcal/week and inactive = energy expenditure of physical activity over 2500 kcal/week.

0.33–0.54, $p < 0.001$) among men with the highest VO_{2max} (>33.2 mL/kg/min). Some of the relative risks presented in Table 3 are not significant after full adjustment.

In order to reduce selection bias due to ill health the association between VO_{2max} and cancer risk was estimated excluding cancer cases that occurred during the first 5 years of follow-up (Table 3). In this restricted analysis, VO_{2max} was related to a decreased age-adjusted risk of cancer and overall mortality after exclusion. Cumulative curves for the incidence of GI-tract, lung and overall cancers according to three groups of VO_{2max} are presented in Fig. 1.

3.5. *Physical fitness, physical activity, and cancer risk*

The total energy expenditure of physical activity of over 2500 kcal/week among fit men was related to an additional risk reduction. The multivariate-adjusted risks were 0.82 (95% CI 0.67–1.03) for any cancer, 0.51 (95% CI 0.26–0.99) for lung cancer, 0.61 (95% CI 0.39–0.96) for GI-tract cancers and 0.61 (95% CI 0.43–0.86) for cancer death in fit men ($VO_{2max} \geqslant 26.9$ mL/kg/min) with moderate intensity (>4 METs) of physical activity ($n = 1026$) than in all other counterparts. Fig. 2 shows the multivariate-adjusted relative risks of cancer during an average of 12 years of follow-up in 2268 men classified according to maximal oxygen uptake and the energy expenditure of total physical activity. Fit men who accumulated over 2 h of physical activities weekly also had a 16% and a 26% reduced risk of non-fatal and fatal cancer events, after adjustment for age and examination year and confounders. The frequency of physical activity was not independently related to the risk of cancer showing that frequency was a less important component of physical activity for reducing cancer risk.

3.6. *The combination of protective lifestyle factors and cancer risk*

A total of 290 (12.8%) active (energy expenditure >2500 kcal/week and physical activity duration >2 h/week) men with a healthy lifestyle ($VO_{2max} \geqslant 26.9$ mL/kg/min, energy intake

>108.6 kJ/kg/week; lowest tertile, non-smoking) had markedly reduced (RR = 0.63, 95% CI 0.46–0.87) risk of cancer incidence than all other study participants, after adjustment for age examination year, alcohol consumption, SES, waist-to-hip ratio and fibre and fat intake. Among men with a combination of favourable lifestyle factors no lung cancer occurred and only one rectal cancer event occurred. A total of 362 (16.0%) men with the above-mentioned protective lifestyle factors combined with moderate-intensity physical activity expending of over 2500 kcal/week had a decreased (RR = 0.71, 95% CI 0.52–0.96) risk of cancer incidence, after adjustment for confounders.

4. Discussion

This prospective population-based study shows that good cardiorespiratory fitness including active lifestyle and reasonable high dietary energy intake may be vital modifiable factors that help in decreasing cancer risk in middle-aged men. The combination of the favourable lifestyle factors provides maximal protection against the risk of cancer. In our study, VO_{2max} has an inverse dose-response association with cancer incidence and death through its whole range.

On the basis of previous studies energy expenditure from physical activity has been inversely associated with overall incidence of cancer and cancer mortality.[14] It is suggested that the total energy expenditure of physical activity is more important than the type, duration, frequency or intensity of physical activity with respect to reduced mortality.[31] In the Multiple Risk Factor Intervention Trial[30] moderate amounts of total leisure-time physical activity (energy expenditure of 1000–2300 kcal/week) were sufficient to reduce overall mortality, but there was no further risk reduction at higher amounts of physical activity. In the Harvard Alumni Health Study,[29] subjects spending 500–3500 kcal in total leisure-time physical activity per week had decreased overall mortality but above this level the all-cause death rates became relatively stable. The risk reduction in active men is not only due to reduced risk of CVDs,[29,30,40] but it may also be partly due to decreased risk of death from cancer. Consistent with our previous study,[34] the strong risk reduction for overall morality among fit men is likely due to reduced risk for both cancer and CVD mortality. Our finding that 1-MET increase in exercise capacity was related to a 6–20% decreased risk of overall, GI-tract and lung cancers is similar to that reported in previous studies.[33,46]

There was an inverse association between cardiorespiratory fitness and lung and GI-cancers, although no independent relation between fitness and prostate cancer was observed in our study. Advancing age and serum fatty acids were related to the increased prostate cancer risk, and they may be important contributing factors in the association between fitness and prostate cancer.[1,18,19] Our results show that fit men expending ⩾1000 kcal and spending ⩾2 h by performing moderate-intensity physical activity weekly have a slightly reduced cancer risk, but a higher amount of energy expenditure may provide further risk reduction. In few previous studies, moderate to high amounts of physical activity have been related to decreased risk of the lung,[15–17] breast[22] and colon[11,12,14,47] cancers and some other site-specific cancers such as prostate[8,19] and kidney[48] cancers. However, rather convincing evidence exists only for an association between physical activity and colon and breast cancers with the relationship to other site-specific cancers being not clear.[8,28] Cardiorespiratory fitness has been related inversely to mortality from cancer of combined sites,[33] both smoking- and non-smoking-related cancers and prostate cancer incidence.[20] In Aerobics Center Longitudinal Study, on the other hand, there was no independent association between physical activity and prostate cancer incidence or mortality in the US physician,[49] Harvard Alumni[50] and Health professional[51] studies, which is consistent with our recent findings based on cardiorespiratory fitness and prostate cancer. We did not take into account professional energy expenditure in the present study.

Some underlying non-specific mechanisms during the initiation or later stages of cancer development have been proposed. First, physical activity and good cardiorespiratory fitness may help to block initiators of cancer if exercise has been performed regularly at a relatively young age.[7,43] Second, physical activity may counter promoters of cancer cell replication, so that regular exercise and good cardiorespiratory fitness when combined with optimal diet during later stages of the neoplastic process may be vital in decreasing or preventing the development of clinically significant disease.[43,44] Therefore, physical inactivity during the lifespan may be a key factor in the initiation of cancer development. It is possible that exercise training can improve functioning of the immune system including monocytes, macrophages and natural killer (NK) cells that are thought to be the primary line of defence against the development of malignancies. Some studies have shown high NK cell activity at rest after a period of exercise training.[52–54] Regular physical exercise has been found to improve the decreased antioxidant defence that occurs normally with ageing. Our results show that reasonable energy intake among fit men who had active lifestyle may have decreased GI-cancers risk. This indicates that energy balance, which includes body mass, energy intake and energy expenditure, is importantly related to GI-tract cancers, especially to colon cancer.[14,59] Exercise increases gut motility and prostaglandins levels that decrease the gastro-intestinal transit time thereby reducing the contact time between faecal carcinogenesis and the colonic mucosa and hence allow less opportunity for initiation of carcinogenesis, colonic cell division and proliferation.[7,11–14,43,45,60] Additionally, it has been observed that exercise may decrease the risk of colon and prostate cancers through its impact on insulin metabolism.[58,61] Insulin is a growth factor for tumour cells. Factors such as sedentary lifestyle, abdominal obesity and diets rich in refined sugar increase insulin resistance and decrease production of insulin-like growth factor binding globulins which may increase the risk of colon and prostate cancers.[28,55–57] Furthermore, high intake of saturated fat has been associated with increased prostate and colon cancers,[58] thus, it is possible that aerobic exercise alters the metabolism of fat by increasing the utilisation of free fatty acids and by decreasing hyperinsulinaemia.

Protection against lung cancer related to cardiorespiratory fitness is likely to be due to non-smoking lifestyle because smoking is also related to reduced physical fitness.[17] Good cardiorespiratory fitness may be related to lung function and may also help in the prevention of lung cancer through

an independent pathway. On the other hand, cardiorespiratory fitness and exercise increase the functional capacity of the lungs and their antioxidant enzyme activities and decrease concentrations of possible carcinogenesis, and may thereby decrease the risk of lung cancer.[8,15,16] Furthermore, smoking is inter-related with unfavourable lifestyle such as increased alcohol consumption, unhealthy diet and sedentary lifestyle.[7,8] Therefore, one explanation for our main results is that fit men also have a good dietary habit with non-smoking lifestyle. Cardiorespiratory fitness has been related to several factors, such as age, gender, heredity, prevalent cardiovascular disease, use of medications, quantity and quality of physical activity, cigarette smoking, obesity and nutrition.[62] One of the possible explanations for the differences between unfit and fit men may be genetic predisposition.[63] Furthermore, maximal oxygen uptake (VO_{2max}) is an accurate measurement of the functional capacity of the cardiovascular system.

To our knowledge, this is the first population-based study on physical fitness with reliable measure of VO_{2max} and cancer risk. Strengths of the study include the measurement of VO_{2max} which is not dependent on the type of exercise. Second, we have reliable data on mortality because deaths were ascertained by Finnish National Death and Cancer Registry using personal identification codes, supplemented with reliable data on health status, physical activity, nutritional measurements and alcohol consumption. It is impossible to know whether cardiorespiratory fitness decreased or increased during follow-up because of the probable changes in the exercise and other health habits of the subjects. It is difficult to distinguish an increased risk of cancer or death due to a low level of cardiorespiratory fitness from an increased risk because of prevalent asymptomatic or preexisting heart or lung disease. The exclusion of the first 5 years of follow-up did not substantially change the results.

In conclusion, the present study supports the latest recommendations on physical activity and health outcomes that moderate amount of physical activity and good cardiorespiratory fitness decrease the risk of cancer. A healthy lifestyle including good dietary habits with an active lifestyle considerably reduces the risk of cancer in middle-aged men.

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Conflict of interest statement

None declared.

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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	52.8(±5.1)歳			( )		前向き研究
	対象数	1000～5000			( )		( )
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

Table 3 – Relative risks of cancer according to physical fitness in 2268 men with no history of cancer at baseline.

	Cancer incidence			Cancer mortality			Overall mortality		
	Relative risk (95% CI)	P-value	No. of events	Relative risk (95% CI)	P-value	No. of deaths	Relative risk (95% CI)	P-value	No. of deaths
Maximal oxygen uptake (mL/kg/min)			387 Events			159 Deaths			593 Deaths
Follow-up time from baseline to outcome event:									
<26.9, <8.9 METs (n = 756)	1.00 (reference)		150	1.00 (reference)		58	1.00 (reference)		306
26.9–33.2, 8.9–9.5 METs (n = 756)	0.87 (0.67–1.01)[a]	0.249	135	0.79 (0.55–1.12)[a]	0.050	55	0.68 (0.49–0.76)[a]	<0.001	183
	0.87 (0.68–1.10)[b]	0.236		0.84 (0.56–1.12)[b]	0.340		0.64 (0.53–0.77)[b]	<0.001	
>33.2, >9.5 METs (n = 756)	0.73 (0.56–0.94)[a]	0.015	104	0.55 (0.36–0.83)[a]	0.005	46	0.34 (0.27–0.43)[a]	<0.001	104
	0.73 (0.56–0.97)[b]	0.028		0.63 (0.40–0.97)[b]	0.057		0.42 (0.33–0.54)[b]	<0.001	
	P = 0.0016 for linear trend			P < 0.001 for linear trend			P < 0.001 for linear trend		
	P = 0.012 for linear trend[c]			P = 0.004 for linear trend[c]			P < 0.001 for linear trend[c]		
		365 Events			137 Deaths			489 Deaths	
Follow-up time from 5 years after baseline to outcome event:									
<26.9, <8.9 METs	1.00 (reference)		63	1.00 (reference)		35	1.00 (reference)		240
26.9–33.2, 8.9–9.5 METs	0.80 (0.73–0.96)[a]	0.425	45	0.83 (0.56–1.23)[a]	0.364	19	0.62 (0.51–0.76)[a]	<0.001	156
	0.90 (0.70–1.16)[b]	0.415		0.88 (0.59–1.32)[b]	0.524		0.67 (0.54–0.82)[b]	<0.001	
>33.2, >9.5 METs	0.77 (0.59–0.99)[a]	0.053	33	0.62 (0.40–0.96)[a]	0.033	13	0.38 (0.30–0.49)[a]	<0.001	93
	0.79 (0.59–1.05)[b]	0.100		0.72 (0.45–1.15)[b]	0.165		0.46 (0.35–0.60)[b]	<0.001	
	P = 0.029 for linear trend			P = 0.007 for linear trend			P < 0.001 for linear trend		
	P = 0.092 for linear trend[c]			P = 0.048 for linear trend[c]			P < 0.001 for linear trend[c]		

a Model 1: RRs are adjusted for age and examination year.
b Model 2: RRs are further adjusted for age and examination year, cigarette smoking, alcohol consumption, waist-to-hip ratio, SBP, and total cellulose, fibre and fat intakes.
c P for linear trend across the tertiles of maximal oxygen uptake from adjusted Cox model.

図表掲載箇所	P359, Table3
抄録和訳	
概 要 (800字まで)	本研究は、Kuopio Ischemic Heart Disease Risk Factor Studyに参加したフィンランド人男性2,268名を対象に平均16.7年間の追跡調査を行い、全身持久力や生活習慣とがん発症/死亡との関連を検討したものである。自転車エルゴメータ負荷試験により測定された最大酸素摂取量を26.9mL/kg/min未満、26.9-33.2mL/kg/min、33.2mL/kg/min以上の3群に分類している。最大酸素摂取量が26.9mL/kg/min未満の集団と比較して、33.2mL/kg/min以上の集団におけるがん発症リスクは0.73(95%信頼区間:0.56-0.97)に減少し、がんによる死亡リスクは0.63(0.40-0.97)と有意に減少した。また、26.9-33.2mL/kg/min、33.2mL/kg/min以上の集団における総死亡リスクは、それぞれ、0.64(0.53-0.77)、0.42(0.33-0.54)と量反応的に有意に減少することが明らかとなった。肺がん、消化管がん、前立腺がんにおけるリスク因子はそれぞれ、喫煙・BMI・体力、年齢であることが示唆された。
結 論 (200字まで)	最大酸素摂取量は、がん発症またはがんによる死亡のリスクにおいて逆相関を示しており、総死亡リスクに関しても同様の結果が得られた。
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。がんの発症/死亡に対して、体力を保つことの有効性を示した重要な研究である。また、体力を最大酸素摂取量により数値化することで、がん予防のための体力の基準値を示すことが可能となり、非常に意義深い。

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Cardiorespiratory fitness and smoking-related and total cancer mortality in men

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ABSTRACT

LEE, C. D., and STEVEN N. BLAIR. Cardiorespiratory fitness and smoking-related and total cancer mortality in men. *Med. Sci. Sports Exerc.*, Vol. 34, No. 5, pp. 735–739, 2002. **Purpose:** We investigated the association between cardiorespiratory fitness and smoking-related, nonsmoking-related, and total cancer mortality in men. **Methods:** We followed 25,892 men, age 30–87 yr, who had a preventive medical evaluation, including a maximal exercise test and self-reported health habits. There were 335 cancer deaths (133 from smoking-related cancer, 202 from nonsmoking-related cancer) during an average of 10 yr of follow-up (259,124 man-yr). **Results:** After adjustment for age, examination year, smoking habits, alcohol intake, body mass index, and diabetes mellitus, there was an inverse association between cardiorespiratory fitness levels and smoking-related ($P < 0.001$ for trend), nonsmoking-related ($P = 0.001$ for trend), and total cancer mortality ($P < 0.001$ for trend). Moderate and high levels of cardiorespiratory fitness were associated with lower risk of smoking-related and nonsmoking-related cancer mortality when compared with low fitness in men. We also observed that smoking-related mortality rates were progressively lower across low, moderate, and high fitness groups in former ($P = 0.06$ for trend) and current ($P = 0.04$ for trend) smokers. **Conclusion:** We conclude that cardiorespiratory fitness may provide protection against cancer mortality in men. **Key Words:** PHYSICAL FITNESS, CANCER MORTALITY

Although some studies show benefits of physical activity or fitness in smokers in preventing cardiovascular disease mortality (10,23), there has been little research on the association of physical activity and smoking in relation to cancer mortality. Physical activity or cardiorespiratory fitness may provide protection against the risk of smoking-related cancer mortality. Exercise may reduce risk of lung cancer by enhancing immune function and reducing concentration of carcinogenic agents in the airways (13,28). Another plausible mechanism of protection from smoking-related carcinoma may include the effects of physical activity on leukocyte count and antioxidant defense and DNA repair systems. Better pulmonary function is inversely associated with leukocyte count, a specific marker of inflammation that contributes to carcinogenesis, and is positively associated with antioxidant defense and DNA repair systems that may inhibit tumor formation (7,8,11,20,31). However, there has been little research on the association of physical activity or fitness in relation to smoking-related cancer mortality. A few studies show an inverse association between physical activity and lung cancer events (13,28), or report no association between physical activity and pancreatic cancer events (13,27). Moreover, the relation of physical activity to nonsmoking-related cancer events needs more clarification. Although several prospective studies show good agreement for lower risk of colon cancer in active individuals, the association of activity to prostate and breast cancer needs further evaluation (1,4,9,12,13,15,19,22,26). We, therefore, examined the relation of cardiorespiratory fitness levels to smoking-related, nonsmoking-related, and total cancer mortality in men from the Aerobics Center Longitudinal Study. We also assessed the health effects of cardiorespiratory fitness in never, former, and current smokers in relation to smoking-related cancer mortality.

MATERIALS AND METHODS

Subjects and measurements. Subjects were 25,892 men, ages 30–87 yr, who had a preventive medical evaluation between 1970 and 1994 at the Cooper Clinic in Dallas, Texas. All study participants were United States residents and had no personal history of myocardial infarction, stroke, or cancer at baseline.

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The study protocol was reviewed and approved annually by the Institutional Review Board. All participants gave their informed written consent for the medical evaluation and registration in the follow-up study. The medical evaluation, performed after an overnight fast of at least 12 h, included a physical examination, anthropometry, electrocardiogram, blood chemistry analysis, blood pressure assessment, a maximal exercise treadmill test, self-report of health habits, and demographic characteristics. Additional details of examination procedures are published elsewhere (3).

Body weight and stature were measured with a standard physician's scale and stadiometer. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared ($kg \cdot m^{-2}$) and was classified as underweight (<18.5 $kg \cdot m^{-2}$), normal weight (18.5 to <25 $kg \cdot m^{-2}$), overweight (25 to <30 $kg \cdot m^{-2}$), or obese (≥ 30 $kg \cdot m^{-2}$). Serum samples were analyzed by automated techniques in a laboratory that participates in the Centers for Disease Control and Prevention Lipid Standardization Program. Diabetes mellitus was defined as fasting plasma glucose levels $\geq$ 126 $mg \cdot dL^{-1}$ (7 $mmol \cdot L^{-1}$) or a history of physician-diagnosed diabetes mellitus.

Cardiorespiratory fitness was measured by a maximal treadmill exercise test using the Balke protocol (2). The treadmill speed was 88 $m \cdot min^{-1}$ for the first 25 min. The grade was 0% for the first minute, 2% the second minute, and increased 1% each minute until 25 min. After 25 min, the grade remained constant while the speed increased 5.4 $m \cdot min^{-1}$ until the subject reached exhaustion or was stopped by the supervising physician for medical reasons. All subjects achieved at least 85% of their age-predicted maximal heart rate (220 minus age in years) during the treadmill test. Total treadmill endurance time was used as an index of aerobic power, with time on treadmill with this protocol correlated highly ($r = 0.92$) with maximal oxygen uptake ($\dot{V}O_{2max}$) (25). Data are presented as maximal METs (metabolic equivalents) attained on the exercise test. METs are multiples of resting metabolic rate (RMR), which is taken as 3.5 mL of $oxygen \cdot kg^{-1} \cdot min^{-1}$. Men in the least-fit 20% of each age group were classified as low fit, the next 40% as moderately fit, and the remaining 40% as high fit (3).

Cigarette smoking habit and alcohol intake were assessed with self-report on a medical history questionnaire. Smoking status was classified as never smoker, former smoker, or current smoker based on responses to questions at the baseline examination: "Do you currently use tobacco?" and "Have you used any of the following (cigarettes, cigars, pipe, etc.) in the past but do not use them now?" Current and former smokers also were asked to provide information on how long they had smoked and on the number of cigarettes they smoked per day, but there were much missing data on this variable. Current smokers were further classified as smoking <20, 20 to <40, and $\geq$ 40 cigarettes per day. Alcohol consumption was classified as none, light (<15 $units \cdot wk^{-1}$), moderate (15 to $\leq$ 30 $units \cdot wk^{-1}$), and heavy (≥ 31 $units \cdot wk^{-1}$). One unit of alcohol intake was defined as a bottle/can of beer (12 oz), a glass of wine (5 oz), or 1.5 oz of hard liquor.

Ascertainment of mortality. Participants were followed for mortality from the baseline examination to the date of death or to December 31, 1994. We identified deaths among study subjects from the National Death Index, and obtained official death certificates from the departments of vital records of the various states. A nosologist determined the underlying cause of death according to the *International Classification of Diseases, Ninth Revision,* with cancer defined as codes 140 to 239. Smoking-related cancers (codes 141–149, 150, 157, 161, 162, 188, and 189) included cancers of lung, trachea, bronchus, oral cavity, larynx, esophagus, pancreas, bladder, and kidney (6). Nonsmoking-related cancers included cancers of colon, rectal, digestive, pleura, bone/connective tissue, skin, breast, prostate, brain/nervous system, thyroid, myeloma, lymphoma, leukemia, and unspecified (codes 151, 152, 155, 156, 158, 159, 163, 170–176, 185, 191–193, 200–208, 239).

Statistical analyses. We used proportional hazards regression to examine the relation of cardiorespiratory fitness levels to smoking-related, nonsmoking-related, and total cancer mortality, respectively (5). Relative risks (RRs) and 95% confidence intervals (CIs) were estimated after adjustment for age and examination year, and also after further adjustment for smoking habits (never, former, or current [<20, 20 to <40, or $\geq$ 40 $cigarettes \cdot d^{-1}$]), alcohol intake (none, light, moderate, or heavy), body mass index (BMI; <18.5, 18.5 to <25, 25 to <30, and ≥ 30 $kg \cdot m^{-2}$), and diabetes mellitus (yes/no). Low-fit men were the reference category. Inspection of empirical cumulative hazard plots [$-\ln-\ln$ (survival function) versus time t by cardiorespiratory fitness levels (low, moderate, and high)] indicated that the proportional hazards assumption was justified. We also examined the associations among cardiorespiratory fitness, smoking habits, and smoking-related cancer mortality. Trends across fitness levels were tested by treating fitness categories as an ordinal scale. Population attributable risks (PAR), $Pe \times (RR - 1)/1 + Pe \times (RR - 1)$, were also estimated for low cardiorespiratory fitness and current smokers, where Pe is the proportion of the exposed population and relative risk (RR) is adjusted RR for the exposure (14). All statistical analyses were performed using Statistical Analysis Systems software (SAS Institute, Cary, NC).

RESULTS

During an average of 10 yr of follow-up (259,124 man-yr), we observed 335 cancer (133 from smoking-related cancer, 202 from nonsmoking-related cancer) deaths. Table 1 provides baseline descriptive characteristics of all men by cardiorespiratory fitness levels. In general, high-fit men had a lower prevalence of physical inactivity, type 2 diabetes, and current smoking habit.

Table 2 shows the RRs of smoking-related, nonsmoking-related, and total cancer mortality by cardiorespiratory fitness levels in men. There was an inverse association between cardiorespiratory fitness levels and

TABLE 1. Baseline characteristics[a] by cardiorespiratory fitness levels in men, Aerobics Center Longitudinal Study.

Variables	Cardiorespiratory Fitness Levels			All Men
	Low (N = 4,577)	Moderate (N = 10,603)	High (N = 10,712)	(N = 25,892)
Age (yr)	43.0 ± 9.0	44.4 ± 9.0	44.2 ± 9.1	44.2 ± 9.0
Height (cm)	178.1 ± 6.6	178.8 ± 6.6	179.0 ± 6.3	178.8 ± 6.5
Weight (kg)	91.7 ± 17.2	84.8 ± 11.8	79.4 ± 9.6	83.8 ± 12.9
Aerobic power (METs)	8.9 ± 1.1	10.9 ± 1.0	13.5 ± 1.4	11.6 ± 2.1
Body mass index (kg·m^{-2})	28.8 ± 4.8	26.5 ± 3.2	24.7 ± 2.4	26.2 ± 3.6
Inactive (%)	67.8	43.2	13.6	35.3
Current smoker (%)	31.6	20.3	9.5	17.8
Former smoker (%)	34.3	37.7	41.2	38.6
Never smoker (%)	5.9	10.3	16.4	12.1
Heavy drinker (%)	3.3	3.1	2.7	3.0
Type 2 diabetes (%)	8.9	4.2	1.9	4.1

[a] Mean ± SD or prevalence (%).

smoking-related cancer mortality ($P < 0.001$ for trend). Proportional hazards regression analyses, adjusted for age and examination year, showed that high-fit men had 66% ($P < 0.001$) and moderate-fit men 43% ($P = 0.001$) lower risk of smoking-related cancer mortality when compared with low-fit men. This relation remained after further adjustment for smoking habits, alcohol intake, body mass index, and diabetes mellitus ($P < 0.001$ for trend). There was also an inverse association between cardiorespiratory fitness levels and nonsmoking-related cancer mortality ($P = 0.001$ for trend). After adjustment for multiple risk factors, high-fit men had 46% ($P = 0.001$) and moderate-fit men had 34% ($P = 0.01$) lower risk of nonsmoking-related cancer mortality when compared with low-fit men, respectively. We also found similar results for overall cancer mortality. After adjustment for all risk factors, cardiorespiratory fitness levels were inversely associated with total cancer mortality ($P < 0.001$ for trend). High-fit men had 55% ($P < 0.001$) and moderate-fit men 38% ($P < 0.01$) lower risk of overall cancer mortality when compared with low-fit men, respectively.

Although there was no significant interaction of cardiorespiratory fitness levels with smoking categories, we examined the interrelations among cardiorespiratory fitness, smoking habits, and smoking-related cancer mortality. Figure 1 shows that, after adjustment for multiple risk factors, high-fit never-smokers had the lowest smoking-related cancer mortality, whereas low-fit current smokers had the highest smoking-related cancer mortality. Mortality rates were progressively lower across low, moderate, and high fitness groups in current ($P = 0.04$ for trend) and former ($P = 0.06$ for trend) smokers, and somewhat weaker for never smokers ($P = 0.14$ for trend).

Table 3 presents estimates of PAR for low cardiorespiratory fitness and current smoking in men. Smoking-related cancer mortality in this population might have been reduced by 13% if they had been fit (moderate or high fitness levels), and might have been reduced by 25% if they had not been cigarette smokers.

DISCUSSION

We investigated the health effects of cardiorespiratory fitness in relation to smoking-related, nonsmoking-related, and total cancer mortality in 25,892 men, ages 30–87 yr. Our major finding was that men with moderate or high levels of cardiorespiratory fitness had low risk of smoking-related cancer mortality when compared with low fit men. This association persisted in former and current smokers.

This is the first prospective study to evaluate the relation of cardiorespiratory fitness to smoking-related cancer mortality. Our findings are consistent with Harvard alumni and Norwegian studies in which there was an inverse association between physical activity and lung cancer incidence or mortality (13,28). However, the relation of physical activity or fitness in relation to other smoking-related cancer

TABLE 2. Relative risks (RR) of cancer mortality by cardiorespiratory fitness levels in men, Aerobics Center Longitudinal Study.

Variables	Cardiorespiratory Fitness Levels			P for Trend
	Low	Moderate	High	
Subjects (N)	4,577	10,603	10,712	–
Man years of follow-up (%)	53,940 (21)	110,269 (42)	94,915 (37)	–
Smoking-related cancer mortality				
No. of deaths	47	58	28	
RR (95% CI)[a]	1.00	0.57 (0.39, 0.84)	0.34 (0.21, 0.55)	<0.001
Multivariate RR (95% CI)[b]	1.00	0.58 (0.39, 0.85)	0.34 (0.21, 0.55)	<0.001
Nonsmoking-related cancer mortality				
No. of deaths	64	85	53	
RR (95% CI)[a]	1.00	0.65 (0.47, 0.90)	0.53 (0.37, 0.77)	<0.001
Multivariate RR (95% CI)[b]	1.00	0.66 (0.48, 0.92)	0.54 (0.37, 0.79)	0.001
Total cancer mortality				
No. of deaths	111	143	81	
RR (95% CI)[a]	1.00	0.62 (0.48, 0.79)	0.45 (0.33, 0.60)	<0.001
Multivariate RR (95% CI)[b]	1.00	0.62 (0.49, 0.80)	0.45 (0.34, 0.61)	<0.001

[a] Adjusted for age (single year) and examination year.
[b] Adjusted for age (single year), examination year, smoking habits (never, former, or current [<20, 20 to <40, or ≥40 cigarettes/d^{-1}]), alcohol intake (none, light, moderate, or heavy), body mass index (BMI; <18.5, 18.5 to <25, 25 to <30, and ≥30 kg·m^{-2}), and diabetes mellitus (yes/no).

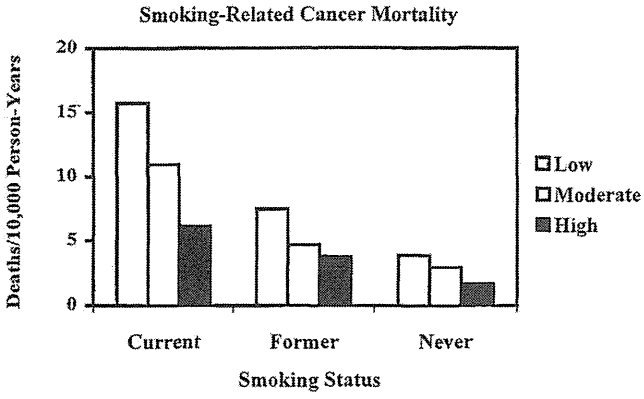

FIGURE 1—Cardiorespiratory fitness, smoking habits, and smoking-related cancer mortality (10,000 person-yr) in men. Adjusted for age (single year), examination year, alcohol intake (none, light, moderate, or heavy), body mass index (BMI; <18.5, 18.5 to <25, 25 to <30, and ≥30 kg·m^{-2}), and diabetes mellitus (yes/no).

incidence or mortality remains less clear. A few studies show no relation between physical activity and pancreatic cancer mortality in men (13,27). In our study, lung, pancreas, kidney, and esophagus were frequent smoking-related cancers, whereas colon, prostate, and leukemia were frequent nonsmoking-related cancers. Our data indicate that moderate and high levels of cardiorespiratory fitness may provide some protection against the risk of smoking-related cancer mortality. We observed this inverse association with or without adjustment for cigarette smoking. Cigarette smoking was a significant risk factor for smoking-related ($P < 0.001$) but not for nonsmoking-related ($P = 0.27$) cancer mortality, whereas cardiorespiratory fitness was an independent risk factor for both smoking-related ($P < 0.001$) and nonsmoking-related ($P < 0.001$) cancer mortality.

Our data also show that there is an inverse association between cardiorespiratory fitness and nonsmoking-related cancer mortality. In general, a recent meta-analysis and other systematic reviews document that active individuals had low risk of colon, prostate, and breast cancers when compared with sedentary individuals (4,19,22,26), although the findings are sometimes inconsistent, especially for prostate and breast cancers (1,9,12,13,15). For example, the Nurses' Health study shows an inverse association between physical activity and colon cancer incidence (18), whereas the Harvard alumni and Physicians' health studies show no relation between physical activity and colon cancer incidence or mortality (12,13). Moreover, there was no association between physical activity and prostate cancer incidence or mortality in the U.S. physicians, Harvard alumni, and Health professionals follow-up studies (9,13,15), although the Aerobics Center Longitudinal Study shows an inverse association between cardiorespiratory activity or fitness and incident prostate cancer (21). The reason for these discrepancies is unknown but may be due to inconsistent physical activity assessment by different cohort studies or imprecise measurement of self-reported physical activity within populations. Further studies are needed to determine whether the objective marker of cardiorespiratory fitness is associated with site-specific cancer incidence or mortality.

In our study, men with moderate and high levels of cardiorespiratory fitness had low risk of smoking-related cancer mortality in former and current smokers. In fact, former smokers are at higher risk of cancer mortality when compared with never-smokers and require a range from 10 to 20 yr before returning the similar RRs of lung, tobacco-related, or total cancer as individuals who had never smoked (16,32). Some biopsy studies also document molecular damages in the bronchial epithelium in former smokers who had stopped smoking for 1–48 yr (17,29). Our data show that former smokers had a lower risk of smoking-related cancer mortality in moderate and high levels of cardiorespiratory fitness. These data suggest that cardiorespiratory fitness may enhance longevity after smoking cessation. We also observed a lower risk of cancer mortality in high-fit current smokers when compared with low-fit current smokers. Moderate and high cardiorespiratory fitness may provide health benefits in current smokers with modest possible protection from fitness.

It is plausible that increased pulmonary function may reduce smoking-related cancer mortality. Better pulmonary function is associated with better immune and antioxidant defense systems that may inhibit smoking-related tumor formation (11,24,30). In fact, aerobic exercise increases natural killer cells and cytotoxic activity of T cells (24,30), and enhances activities of glutathione peroxidase, superoxide dismutase, and catalase (11) that may degrade carcinogenesis from oxidative stress. Another possible mechanism is the inverse association between pulmonary function and leukocyte count (20,31), in which an elevated leukocyte count contributes to carcinogenesis (8,31). Furthermore, high pulmonary function may also positively influence DNA repair systems, although the mechanism is unknown (7).

Mechanisms for physical activity to decrease nonsmoking-related cancers such as colon and prostate cancer have been previously reported (4,19,22). It is possible that improvements in physical activity may decrease prostate cancer risk by decreasing testosterone levels, a risk marker

TABLE 3. Estimated relative and population attributable risks (PAR) for smoking-related cancer mortality by cardiorespiratory fitness levels[a] and smoking status in men, Aerobics Center Longitudinal Study.

		Smoking-Related Cancer Mortality[b]		
Risk factors	Prevalence (man-years, %)	Deaths (*N*)	Relative Risk (RR)	PAR, % (95% CI)
Current smokers	48,672 (19)	49	2.77 (1.90, 4.03)	25.2 (14.6, 36.5)
Low fitness	53,940 (21)	47	1.73 (1.19, 2.52)	13.3 (3.8, 24.2)

[a] Cardiorespiratory fitness level (fit or unfit) from ref. 3.
[b] RR and PAR estimates adjusted for age (single year), examination year, alcohol intake (none, light, moderate, or heavy), body mass index (BMI; <18.5, 18.5 to <25, 25 to <30, and ≥30 kg·m^{-2}), and diabetes mellitus (yes/no).

for prostate cancer (22). It is also possible that high levels of physical activity may decrease colon cancer by reducing gastrointestinal transit time, thereby reducing colonic exposure to carcinogens in the fecal stream (4). Larger studies are needed to determine whether physical activity or fitness is related to other specific smoking-related cancers, including pancreas, bladder, and kidney.

A limitation of our study is that we did not measure cancer incidence; thus, the causal relation of cardiorespiratory fitness to cancer events may be limited. For instance, fitness may improve survival from cancer rather than prevent or delay its occurrence. It also could be that people prone to cancer are less capable of exercising or becoming fit. Another limitation of the present study is that we were not able to adjust for diet or other potential confounding variables, such as passive smoking. A strength of this study is that it represents the largest published cohort study of objectively measured cardiorespiratory fitness to smoking-related, nonsmoking-related, and total cancer mortality. In addition, our study population is homogeneous on race, education, and occupation, which reduces the likelihood of confounding by these important sociodemographic characteristics.

In conclusion, we found that men with moderate or high levels of cardiorespiratory fitness had reduced risk of cancer mortality when compared with low fit men.

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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	30-87歳(44.2歳)			( )		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)	( )
	維持・改善	な し	な し	な し	なし	(	( )

図 表

TABLE 2. Relative risks (RR) of cancer mortality by cardiorespiratory fitness levels in men, Aerobics Center Longitudinal Study.

Variables	Cardiorespiratory Fitness Levels			P for Trend
	Low	Moderate	High	
Subjects (N)	4,577	10,603	10,712	–
Man years of follow-up (%)	53,940 (21)	110,269 (42)	94,915 (37)	–
Smoking-related cancer mortality				
No. of deaths	47	58	28	
RR (95% CI)*	1.00	0.57 (0.39, 0.84)	0.34 (0.21, 0.55)	<0.001
Multivariate RR (95% CI)†	1.00	0.58 (0.39, 0.85)	0.34 (0.21, 0.55)	<0.001
Nonsmoking-related cancer mortality				
No. of deaths	64	85	53	
RR (95% CI)*	1.00	0.65 (0.47, 0.90)	0.53 (0.37, 0.77)	<0.001
Multivariate RR (95% CI)†	1.00	0.66 (0.48, 0.92)	0.54 (0.37, 0.79)	0.001
Total cancer mortality				
No. of deaths	111	143	81	
RR (95% CI)*	1.00	0.62 (0.48, 0.79)	0.45 (0.33, 0.60)	<0.001
Multivariate RR (95% CI)‡	1.00	0.62 (0.49, 0.80)	0.45 (0.34, 0.61)	<0.001

*Adjusted for age (single year) and examination year.
†Adjusted for age (single year), examination year, smoking habits (never, former, or current [<20, 20 to <40, or ≥40 cigarettes/d^{-1}]), alcohol intake (none, light, moderate, or heavy), body mass index (BMI; <18.5, 18.5 to <25, 25 to <30, and ≥30 kg·m^{-2}), and diabetes mellitus (yes/no).

図表掲載箇所	P737, Table2
概 要 (800字まで)	30-87歳の25,892名の男性を対象に、10年間の追跡調査を行い、心肺体力と、喫煙関連ガンによる死亡、総死亡との関連について検討を行った。心肺体力はBalke protocolを用いて最大酸素摂取量により評価された。最大酸素摂取量を元に、Low(8.9±1.1METs)、Miderate(10.9±1.0METs)、High(13.5±1.4METs)に分類した。喫煙関連のガンによる死亡では、Lowと比較して、Moderate、Highにおけるリスクは、それぞれ0.58(0.39-0.85)、0.34(0.21-0.55)と有意な関連を示した。またガンの総死亡については、Lowと比較して、Moderate、Highにおけるリスクは、それぞれ0.62(0.49-0.8)、0.45(0.34-0.61)であり、有意な関連を示した。また、現在の喫煙者、過去喫煙者においても、最大酸素摂取量は喫煙関連のガン死亡と関連していた。
結 論 (200字まで)	体力(最大酸素摂取量)を高く保つことは、喫煙関連のガン死亡や総ガン死亡のリスクを低下させ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)	喫煙に関連するガンの一つに肺がんが挙げられるが、我が国においても肺がんによる死亡は多く、これらが体力を高く保つことで予防的効果があることが示されたことは非常に意義深い。また、喫煙者、過去喫煙者のどちらにおいても予防効果があることは重要である。

担当者 村上晴香

Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men[1–3]

Chong Do Lee, Steven N Blair, and Andrew S Jackson

ABSTRACT

Background: Cardiorespiratory fitness and body fatness are both related to health, but their interrelation to all-cause and cardiovascular disease (CVD) mortality is unknown.

Objective: We examined the health benefits of leanness and the hazards of obesity while simultaneously considering cardiorespiratory fitness.

Design: This was an observational cohort study. We followed 21 925 men, aged 30–83 y, who had a body-composition assessment and a maximal treadmill exercise test. There were 428 deaths (144 from CVD, 143 from cancer, and 141 from other causes) in an average of 8 y of follow-up (176 742 man-years).

Results: After adjustment for age, examination year, cigarette smoking, alcohol intake, and parental history of ischemic heart disease, unfit (low cardiorespiratory fitness as determined by maximal exercise testing), lean men had double the risk of all-cause mortality of fit, lean men (relative risk: 2.07; 95% CI: 1.16, 3.69; $P = 0.01$). Unfit, lean men also had a higher risk of all-cause and CVD mortality than did men who were fit and obese. We observed similar results for fat and fat-free mass in relation to mortality. Unfit men had a higher risk of all-cause and CVD mortality than did fit men in all fat and fat-free mass categories. Similarly, unfit men with low waist girths (<87 cm) had greater risk of all-cause mortality than did fit men with high waist girths (≥99 cm).

Conclusions: The health benefits of leanness are limited to fit men, and being fit may reduce the hazards of obesity. *Am J Clin Nutr* 1999;69:373–80.

KEY WORDS

Body composition, cardiorespiratory fitness, epidemiology, mortality, cardiovascular disease mortality, all-cause mortality, fat mass, fat-free mass, waist girth, men

INTRODUCTION

Obesity is a public health problem in the United States (1) and the prevalence of obesity has increased substantially over the past few decades (2). However, the health effects of body fatness in relation to longevity are unclear. Many studies show increased mortality in the leanest as well as the most obese individuals (3–6), but others do not observe this trend (7–9). Manson et al (9) suggest that findings of high mortality rates in individuals with low weight-for-height are associated with methodologic limitations such as failure to control for cigarette smoking, failure to eliminate early mortality due to preexisting disease, and inappropriate control for obesity-related biological factors. Nonetheless, a recent meta-analysis documented elevated mortality in association with leanness after accounting for smoking and preexisting disease (10).

Another unexplored methodologic limitation in obesity research is that body mass index (BMI; in kg/m^2) is commonly used to examine the obesity-mortality association even though BMI is not an accurate measure of obesity. Rather, it mainly indicates overweight for height but does not discriminate between fat mass and fat-free mass (FFM). Some studies show higher death rates in individuals with low BMIs and high waist-to-hip circumference ratios (WHRs), but not in those with high BMIs and low WHRs (11–13). The health effects of overweight on height and body composition in relation to cardiovascular disease (CVD) risk factors need further research (14, 15). There has been little research on the relation between measured body fatness and mortality (16).

We believe that cardiorespiratory fitness should also be considered in examining the relation between body composition and mortality. Cardiorespiratory fitness is a powerful predictor of all-cause and CVD mortality (17–19) and appeared to attenuate the relation between BMI and mortality in an earlier study (20). However, the health effects of body fatness and cardiorespiratory fitness in relation to longevity remain unexplored. Therefore, the purpose of this study was to examine the health consequences of body fatness and cardiorespiratory fitness in relation to all-cause and CVD mortality in men. We also assessed the associations of fat mass, FFM, and waist circumference to mortality after taking cardiorespiratory fitness into account.

SUBJECTS AND METHODS

Subjects and measurements

Subjects were 21 925 men aged 30–83 y who had complete preventive medical evaluations between 1971 and 1989 at the

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Cooper Clinic in Dallas. All subjects were residents of the United States and had no personal history of myocardial infarction, stroke, or cancer at baseline. All received body composition assessments and reached ≥85% of their age-predicted maximal heart rate [220 − age (in y)] during their treadmill tests.

The study protocol was reviewed and approved annually by the Institutional Review Board. All subjects gave their informed, written consent for the medical evaluation and subsequent registration in the follow-up study. The medical evaluation, performed after subjects had fasted overnight for ≥12 h, included a physical examination, anthropometric measurements, electrocardiogram, blood chemistry analyses, blood pressure assessment, maximal exercise treadmill test, self-report of health habits, and recording of demographic characteristics. Additional details of examination procedures are published elsewhere (17–19).

Serum samples were analyzed by automated techniques in a laboratory that participates in the Centers for Disease Control and Prevention Lipid Standardization Program, and blood pressure was measured by auscultatory methods with a mercury sphygmomanometer. Body weight and stature were measured with a standard physician's scale and stadiometer. In a subgroup of 14 043 men, waist circumference was measured at the level of the umbilicus with a plastic tape measure. Body composition was assessed either by hydrostatic weighing, by skinfold-thickness measurements, or both following a standard procedure (21). We determined percentage body fat in men by hydrodensitometry using Siri's (22) two-component model. We also measured the sum of 7 (Σ7) skinfold thicknesses and estimated skinfold fat using a generalized body density equation (23).

Not all subjects underwent both hydrostatic weighing and skinfold-thickness measurements; 9655 were measured for skinfold thickness only, 7180 for hydrostatic weight only, and 5090 for both measurements. To standardize these measurements, we developed a prediction model for hydrostatistically determining percentage body fat from percentage fat (%fat) estimated by Σ7 skinfold thicknesses from the 5090 men who provided both Σ7 skinfold thicknesses and hydrostatic weighing data. A regression analysis provided the following equation:

$$\text{Percentage body fat} = 1.511843 + 0.905469 \times \%\text{fat} \quad (1)$$

(SEE = 3.78; $r = 0.82$). We applied this prediction model to the skinfold data for the men who did not undergo hydrostatic weighing to estimate their percentage body fat. We further calculated fat mass and FFM (in kg) as follows:

$$\text{Fat mass (kg)} = \text{wt (kg)} \times (\%\text{fat}/100) \quad (2)$$
$$\text{FFM (kg)} = \text{wt (kg)} - \text{fat mass (kg)} \quad (3)$$

We assigned subjects to categories of lean, normal, or obese. These categories correspond to <25th, 25th to <75th, and ≥75th percentile scores. We also classified subjects as having low, moderate, and high categories of fat mass, FFM, and waist circumference by using these same percentile scores cutoff points.

Alcohol use, cigarette smoking habit, and parental history of ischemic heart disease (IHD; either parent died of IHD) were assessed by self-report on a medical history questionnaire. Alcohol consumption was classified as none, light (<15 units/wk), moderate (15–30 units/wk), and heavy (≥31 units/wk). One unit of alcohol intake was defined as a bottle or can of beer [355 mL (12 oz)], a glass of wine [148 mL (5 oz)], or 44 mL (1.5 oz) of hard liquor. Smoking status was classified as never smoked, former smoker, or current smoker. Current smokers were further classified as smoking <20, 20 to <40, and ≥40 cigarettes/d.

Cardiorespiratory fitness was measured by using a maximal treadmill exercise test as described previously (17). Total treadmill endurance time was used as an index of aerobic power; time on treadmill with this protocol correlated highly ($r = 0.92$) with

TABLE 1
Baseline characteristics of 21 925 men across body fatness and cardiorespiratory fitness categories[1]

	Lean (<16.7% BF)		Normal (16.7 to <25.0% BF)		Obese (≥25.0% BF)		
	Fit (n = 5093)	Unfit (n = 327)	Fit (n = 9255)	Unfit (n = 1851)	Fit (n = 3217)	Unfit (n = 2182)	All men (n = 21 925)
Age (y)	40.6 ± 8.0[2]	40.3 ± 8.3	44.5 ± 8.7	42.6 ± 8.2	48.0 ± 9.1	44.4 ± 8.6	43.8 ± 8.9
Height (cm)	178.9 ± 6.3	178.2 ± 6.9	178.9 ± 6.3	177.9 ± 6.4	178.9 ± 6.5	178.2 ± 6.6	178.7 ± 6.4
Weight (kg)	75.6 ± 8.5	77.3 ± 10.4	82.0 ± 9.1	83.9 ± 10.8	90.9 ± 12.0	96.8 ± 16.5	83.4 ± 12.4
Treadmill time (min)	22.0 ± 4.3	12.5 ± 2.5	18.5 ± 3.7	11.9 ± 2.4	15.8 ± 3.1	10.8 ± 2.6	17.5 ± 5.1
Systolic BP (mm Hg)	118.5 ± 13.1	119.8 ± 13.8	120.5 ± 13.2	121.7 ± 13.4	123.6 ± 13.9	126.6 ± 14.3	121.2 ± 13.6
Diastolic BP (mm Hg)	78.0 ± 9.0	80.3 ± 8.9	80.5 ± 9.2	81.9 ± 9.7	83.1 ± 9.3	85.1 ± 9.9	80.9 ± 9.5
Triacylglycerol (mmol/L)	1.1 ± 0.8	1.9 ± 3.0	1.5 ± 1.2	2.1 ± 1.7	1.7 ± 1.2	2.2 ± 1.7	1.6 ± 1.3
Serum glucose (mmol/L)	5.4 ± 0.7	5.7 ± 1.7	5.5 ± 0.7	5.7 ± 1.1	5.7 ± 0.9	5.9 ± 1.5	5.6 ± 0.9
Total cholesterol (mmol/L)	5.2 ± 0.9	5.5 ± 1.1	5.6 ± 1.3	5.7 ± 1.1	5.8 ± 1.0	5.8 ± 1.1	5.5 ± 1.2
BMI (kg/m^2)	23.6 ± 2.0	24.3 ± 2.6	25.6 ± 2.2	26.5 ± 2.7	28.3 ± 3.1	30.4 ± 4.6	26.1 ± 3.4
Percentage BF (%)	12.9 ± 3.0	13.5 ± 3.0	20.7 ± 2.3	21.5 ± 2.3	28.3 ± 3.4	30.1 ± 4.6	20.9 ± 6.4
Inactive (%)	20.9	77.4	28.7	70.5	39.3	70.0	36.8
Systolic BP ≥140 mm Hg (%)	7.4	10.1	9.3	11.4	13.2	20.1	10.7
Fasting glucose ≥6.7 mmol/L (%)	1.6	3.7	3.6	6.2	6.2	11.6	4.5
Abnormal electrocardiogram (%)	4.2	9.5	5.9	9.7	9.2	9.6	6.7
Family history of IHD (%)	23.5	22.9	29.6	27.9	32.2	31.6	28.5
History of hypertension (%)	9.4	14.5	14.9	20.2	20.6	29.6	16.4
History of diabetes (%)	1.8	4.9	1.8	5.5	2.8	5.1	2.6
Current smoker (%)	15.3	46.5	17.9	39.1	17.0	31.9	20.8
Past smoker (%)	26.1	13.2	30.3	19.3	32.7	24.2	27.9

[1] BF, body fat; BP, blood pressure; IHD, ischemic heart disease.
[2] $\bar{x}$ ± SD.

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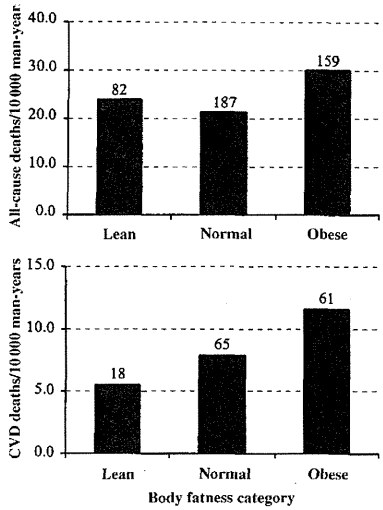

FIGURE 1. All-cause (top) and cardiovascular disease (CVD; bottom) death rates per 10 000 man-years of follow-up, adjusted for age (single year) and examination year, across body fatness categories. Body fatness categories were, in percentage body fat, lean (<16.7%), normal (16.7% to <25.0%), and obese (≥25.0%). Numbers atop the bars represent the number of deaths.

maximal oxygen uptake ($\dot{V}O_2$max) (24). Men in the least-fit 20% of each age group were classified as physically unfit, and all others as physically fit (18). We also calculated $\dot{V}O_2$max in mL·kg FFM^{-1}·min^{-1} and classified men in the lowest quartile of oxygen uptake in each age group as physically unfit, and all others as physically fit. All subjects were cross-tabulated by cardiorespiratory fitness levels across body fatness categories as follows: *1*) fit and lean, *2*) unfit and lean, *3*) fit and normal, *4*) unfit and normal, *5*) fit and obese, and *6*) unfit and obese. We also cross-tabulated by cardiorespiratory fitness levels across fat mass, FFM, and waist circumference categories.

All subjects were followed for mortality from the baseline examination to the date of death or to December 31, 1989. Deaths among study subjects were identified from the National Center for Health Statistics National Death Index and official death certificates from the departments of vital records of the various states. The underlying cause of death was determined by a nosologist according to the *International Classification of Diseases,* Ninth Edition, with CVD defined as codes 390 to 449.9.

Statistical analysis

All-cause and CVD death rates per 10 000 man-years (for which a man-year is 1 man followed for 1 y) of follow-up, adjusted for age and examination year, were calculated across body fatness and waist circumference categories. Proportional hazards regression was used to examine the associations among cardiorespiratory fitness, body fatness, and all-cause and CVD mortality (25). We also examined the associations among cardiorespiratory fitness, fat mass, FFM, and waist circumference to all-cause and CVD mortality. The relative risks (RRs) of all-cause and CVD mortality were estimated after adjustment for age and examination year and further adjustment for cigarette smoking, alcohol intake, and parental history of IHD. Physically fit men in the lowest quartile of each body composition variable were the reference category. The 95% CIs were calculated for each RR. All statistical procedures were performed with SAS software (26).

RESULTS

During an average of 8 y of follow-up (176 742 man-years), there were 428 deaths: 144 from CVD, 143 from cancer, and 141 from other causes. Baseline descriptive characteristics of the subjects across body fatness categories and cardiorespiratory fitness level are shown in **Table 1**. Unfit men had a slightly higher degree of body fatness than did their fit counterparts within lean, normal, and obese categories [0.6%, 0.8%, and 1.8% higher, respectively ($P < 0.001$)]; treadmill times were progressively lower in unfit men, indicating lower cardiorespiratory fitness, across lean, normal, and obese categories. Fit, lean men had the highest average estimated maximal aerobic power [13.4 metabolic equivalents (METs); 1 MET = $\dot{V}O_2$ (3.5 mL·kg^{-1}·min^{-1})], whereas unfit, obese men had the lowest average maximal aerobic power (8.7 METs). We tested differences between groups with a two-factor analysis of variance (continuous data) or log linear models (categorical data). The main effects for both fitness and fatness were highly significant ($P < 0.001$) for all variables except that height was not related to fatness. We also tested fitness and

TABLE 2
Body fatness and relative risks (RR) of all-cause and cardiovascular disease mortality by cardiorespiratory fitness level in men[1]

Body fatness category and cardiorespiratory fitness level	Man-years of follow-up	All-cause mortality			Cardiovascular disease mortality		
		Deaths	RR of death (95% CI)[2]	Multivariate RR of death (95% CI)[3]	Deaths	RR of death (95% CI)[2]	Multivariate RR of death (95% CI)[3]
	man-y (%)	*n*			*n*		
Lean (<16.7% body fat)							
Fit (n = 5093)	41 854 (23.7)	68	1.00	1.00	13	1.00	1.00
Unfit (n = 327)	3883 (2.2)	14	2.06 (1.15, 3.66)	2.07 (1.16, 3.69)	5	3.18 (1.13, 8.96)	3.16 (1.12, 8.92)
Normal (16.7 to <25.0% body fat)							
Fit (n = 9255)	68 546 (38.8)	127	0.80 (0.59, 1.08)	0.80 (0.59, 1.08)	43	1.43 (0.76, 2.66)	1.43 (0.77, 2.67)
Unfit (n = 1851)	19 669 (11.1)	60	1.61 (1.14, 2.28)	1.62 (1.15, 2.30)	22	2.91 (1.47, 5.79)	2.94 (1.48, 5.83)
Obese (≥25.0% body fat)							
Fit (n = 3217)	21 874 (12.4)	65	0.93 (0.65, 1.31)	0.92 (0.65, 1.31)	19	1.35 (0.66, 2.77)	1.35 (0.66, 2.76)
Unfit (n = 2182)	20 916 (11.8)	94	1.92 (1.40, 2.62)	1.90 (1.39, 2.60)	42	4.08 (2.18, 7.61)	4.11 (2.20, 7.68)

[1] Cardiorespiratory fitness level (fit or unfit) from reference 18.
[2] Adjusted for age (single year) and examination year.
[3] Adjusted for age (single year), examination year, smoking habit, alcohol intake, and parental history of ischemic heart disease.

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