

Cardiorespiratory Fitness, Different Measures of Adiposity, and Cancer Mortality in Men

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Abstract

FARRELL, STEPHEN W., GINA M. CORTESE, MICHAEL J. LAMONTE, AND STEVEN N. BLAIR. Cardiorespiratory fitness, different measures of adiposity, and cancer mortality in men. *Obesity*. 2007;15:3140–3149. **Objective:** The purpose was to examine the prospective relationship among cardiorespiratory fitness level (CRF), different measures of adiposity, and cancer mortality in men.

Research Methods and Procedures: Participants were 38,410 apparently healthy men who completed a comprehensive baseline health examination between 1970 and 2001. Clinical measures included BMI, waist circumference (WC), percent body fat, and CRF quantified as duration of a maximal treadmill exercise test. Participants were divided into fifths of CRF, BMI, WC, and percent body fat. Hazard ratios were computed with Cox regression analysis.

Results: During a mean follow-up period of 17.2 ± 7.9 years, 1037 cancer deaths occurred. Adjusted hazard ratios across incremental BMI quintiles were 1.0, 1.23, 1.15, 1.39, and 1.72; those of WC were 1.0, 1.05, 1.03, 1.31, and 1.64; those of percent body fat were 1.0, 1.24, 1.17, 1.23, and 1.50; and those of CRF were 1.0, 0.70, 0.67, 0.70, and 0.49 (trend $p < 0.01$ for each). Further adjustment for CRF eliminated the significant trend in mortality risk across percent body fat groups and attenuated the trend in risk across BMI and WC groups. Adjustment of CRF for adiposity measures had little effect on mortality risk. When grouped into categories of fit and unfit (upper 80% and lower 20% of CRF distribution, respectively), mortality

rates (per 10,000 man-years) were significantly lower in fit compared with unfit men within each stratum of BMI, WC, and percent body fat.

Discussion: Higher levels of CRF are associated with lower cancer mortality risk in men, independently of several adiposity measures.

Key words: body composition, exercise, waist circumference, skinfold thickness, BMI

Introduction

Cancer is the second leading cause of death for U.S. men, accounting for ~285,000 deaths annually (1). In addition to its physical and emotional toll, cancer also is associated with a significant economic burden to society. The NIH has estimated total U.S. healthcare expenditures of \$210 billion for cancer in 2004; approximately \$74 billion in direct costs such as medication, hospital, physician, and nursing services; and approximately \$136 billion in indirect costs related to lost productivity and the like (1).

Traditionally known modifiable risk factors for cancer include tobacco use (2) and poor diet (3), as well as environmental and occupational exposures (4,5). More recently, adiposity (6–9) and low levels of physical activity or cardiorespiratory fitness (CRF)¹ also have been shown to be associated with cancer mortality in men (10–14). Overweight and obesity (15), as well as physical inactivity (16), are highly prevalent in the U.S. population. Most studies on adiposity and cancer mortality have used self-reported or measured BMI as the measure of adiposity (6,7,9,14,17,18). Few studies have reported on associations between cancer mortality and clinical adiposity measures, such as waist circumference (WC) (8) or percent body fat. Studies on physical activity and cancer mortality have relied almost exclusively on self-reported assessment of physical activity habits (7,12,19). There is a paucity of reported data relating an objective measure of CRF with cancer mortality (11,14).

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¹ Nonstandard abbreviations: CRF, cardiorespiratory fitness; WC, waist circumference; ACLS, Aerobics Center Longitudinal Study; HR, hazard ratio; CI, confidence interval.

Even fewer studies have reported on the joint exposures of adiposity and physical activity or fitness with subsequent cancer mortality (14,20). Thus, the primary purpose of this investigation is to examine the relationship among CRF, several measures of adiposity, and cancer mortality in a large cohort of initially cancer-free men who are enrolled in the Aerobics Center Longitudinal Study (ACLS).

Research Methods and Procedures

Study Participants and Measurements

The ACLS is a prospective epidemiological follow-up of patients who have completed a comprehensive health examination at the Cooper Clinic in Dallas, TX (21). Participants in the present study were 38,410 men who completed baseline examinations during the interval between 1970 and 2001. All participants were U.S. residents, and the majority of men were white and from middle to upper socioeconomic strata. After receiving written informed consent from each participant, a clinical evaluation was performed and included an examination by a physician, fasting blood chemistry assessment, personal and family health history, anthropometry, resting blood pressure and electrocardiogram, and a maximal graded treadmill exercise test. Height and weight were measured using a stadiometer and standard physician's scale. BMI was calculated as weight in kilograms divided by height in meters squared. Participants were grouped into fifths of the BMI distribution as follows: BMI <23.50, 23.50 to 25.10, 25.11 to 27.00, 27.01 to 29.80, and >29.80 kg/m². Percent body fat was assessed with hydrostatic weighing, with skinfold measures, or with both following standardized procedures (22). Body fat was estimated from hydrodensitometry using the Siri Equation (23) or from the sum of seven skinfolds using a generalized equation (22). In accord with our previously published study methods (24) and to standardize the body fat estimates, we developed a prediction model for hydrostatically determined percent of body fat from percent of fat determined from the skinfold measures in men who had both assessments ($n = 13,234$). Regression analysis resulted in the following equation: Percent body fat = $1.448 + 0.945 \times \text{skinfold percent fat}$ ($r = 0.83$, standard error of the estimate = 3.77). Men were grouped into fifths of percent body fat distribution as follows: percent body fat <17.50%, 17.50% to 21.50%, 21.51% to 24.60%, 24.61% to 28.00%, and >28.0%. Waist circumference was measured at the level of the umbilicus using a cloth tape measure. The measurement of WC was not included in the clinical examination until the 1980s and, thus, is only available in a subset of study participants ($n = 27,881$). Men were assigned to fifths of the WC distribution as follows: WC <85.00 cm, 85.00 to 90.80 cm, 90.81 to 95.90 cm, 95.91 to 102.00 cm, and >102.00 cm. All procedures were administered by trained technicians who followed standardized measurement protocols.

CRF was quantified as the duration of a maximal treadmill exercise test using a modified Balke protocol (25). The treadmill test began at a speed of 88 m/min and 0% elevation. At the end of the first minute, elevation was increased to 2%, then by 1% each minute thereafter. After 25 minutes, elevation remained at 25% while speed was increased 5.4 m/min each minute until volitional fatigue. Exercise duration from this protocol has been shown to correlate highly ($r = 0.92$) with directly measured maximal oxygen uptake in men (26). Patients were given verbal encouragement to achieve a maximal effort during the test, and those that did not achieve at least 85% of age-predicted maximal heart rate were excluded from the analyses. To standardize exercise test performance, we computed maximal metabolic equivalent (1 metabolic equivalent = 3.5 mL O₂ uptake/kg/min) levels of CRF based on the final treadmill speed and grade (27).

Smoking history was obtained from a standardized questionnaire and grouped categorically for analysis (never, past, or current smoker). Chronic illness at baseline was defined as the presence of 1) dyslipidemia based on a history of physician-diagnosed high cholesterol or triglyceride, or measured fasting total cholesterol ≥ 240 mg/dL, or triglyceride ≥ 200 mg/dL, or high density lipoprotein <50 mg/dL; 2) diabetes based on a history of physician diagnosis or insulin use, or measured fasting glucose ≥ 126 mg/dL; 3) hypertension based on a history of physician diagnosis, resting systolic blood pressure ≥ 140 or resting diastolic blood pressure ≥ 90 mm Hg; 4) a history of physician diagnosed myocardial infarction or stroke; or 5) an abnormal resting electrocardiogram. Men with previously diagnosed cancer at baseline were excluded from the analyses.

Mortality Surveillance

Vital status was ascertained primarily using the National Death Index. Cancer deaths were identified using the International Classification of Diseases, ninth revision (codes 140–208) for deaths occurring before 1999 and 10th revision (codes C00-C97 for deaths during 1999 to 2003).

Statistical Analyses

We followed study participants for mortality from the date of their examination to the date of death for decedents or to December 31, 2003 for survivors. We computed man-years of exposure as the sum of follow-up time among decedents and survivors. There were 1037 cancer deaths identified during an average of 17.2 ± 7.9 years of follow-up and 660,652 man-years of exposure. Cox proportional hazards regression analysis was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of cancer mortality according to exposure categories. In our primary analysis, each adiposity exposure was grouped according to fifths of the sample-specific distribution as described above. CRF was grouped according to age-standard-

Table 1. Baseline characteristics for all men and by vital status in 38,410 men who were followed an average of 17.2 years: Aerobics Center Longitudinal Study, 1970 to 2003

Characteristic	All	Decedents	Survivors
<i>N</i>	38,410	1037	37,373
Man-years exposure	660,652	16,592	644,060
Age (yrs)	43.8 ± 9.9	50.7 ± 9.2	43.6 ± 9.8*
BMI (kg/m ²)	26.5 ± 3.8	26.5 ± 3.5	26.5 ± 3.8
Waist circumference† (cm)	94.2 ± 10.8	96.6 ± 10.8	94.1 ± 10.8*
Percent body fat‡	22.8 ± 6.4	24.1 ± 6.5	22.8 ± 6.4*
Treadmill time (min)	17.6 ± 5.2	14.6 ± 4.9	17.7 ± 5.2*
Maximal METs	12.2 ± 2.5	10.1 ± 2.3	12.5 ± 2.5*
BMI-defined weight groups (%)			
Normal-weight (18.5 to 24.99 kg/m ²)	38.5	36.5	38.6
Overweight (25 to 29.99 kg/m ²)	46.8	48.8	46.7
Obese (≥30 kg/m ²)	14.5	14.7	14.5
Waist circumference ≥102 cm (%)	21.0	28.0	20.9*
Smoking status (%)			
Never	47.8	31.4	48.3*
Past	33.7	39.3	33.6*
Current	18.5	29.3	18.1*
Chronic illness (%)§	75.1	87.9	74.7*

MET, metabolic equivalent. Data are mean ± standard deviation.

* $p < 0.05$ with decedents.

† Waist circumference: $n = 27,881$ (489 deaths).

‡ Percent body fat: $n = 36,885$ (960 deaths).

§ Chronic illness was defined as the presence of 1) dyslipidemia (history of physician-diagnosed high cholesterol or triglyceride or measured fasting total cholesterol >240 mg/dL, or triglyceride >200 mg/dL or high-density lipoprotein <50 mg/dL); 2) diabetes (history of physician diagnosis or use of insulin or measured fasting glucose >126 mg/dL); 3) hypertension (history of physician diagnosis or resting systolic blood pressure ≥140 or diastolic blood pressure ≥90); 4) prevalent cardiovascular disease (history of physician-diagnosed myocardial infarction or stroke); or 5) an abnormal resting echocardiogram.

ized quintiles of maximal exercise duration as described elsewhere (21). Multivariable analyses included age (years), examination year, smoking status (never, past, current smoker), and chronic illness at baseline (present or not). These four factors will henceforth be referred to as covariables. Tests of linear trends in mortality rates and risk estimates across exposure categories were computed using ordinal scoring. We also examined the joint associations of adiposity and CRF exposures with cancer mortality. In these analyses, adiposity exposure groups were based on standardized definitions for BMI (normal-weight 18.50 to 24.99, overweight 25.0 to 29.99, and obese ≥30 kg/m²), WC (normal <102 and abdominal obesity ≥102 cm), and percent body fat (normal <25% and obese ≥25%) (28). CRF was grouped as fit and unfit based on the upper 80% and lower 20% of the age-standardized CRF distribution, as previously reported in the ACLS (24). We assessed interaction among exposure groups using likelihood ratio tests of

nested models. All p values are 2-sided, and $p < 0.05$ was regarded as statistically significant.

Results

Baseline characteristics of the overall cohort and according to vital status are presented in Table 1. On average, decedents were older and had greater levels of adiposity, lower CRF, and a higher prevalence of smoking and chronic illness than survivors. With the exception of age, each of the other baseline characteristics was significantly ($p < 0.001$ each) associated with categories of CRF (Table 2). Rates of cancer mortality according to exposure groups are presented in Table 3. Significant positive associations with cancer mortality were seen across incremental categories of adiposity measures and of age (p for trend = 0.001 each). Mortality rates also were significantly higher in current and past smokers compared with non-smokers (p for trend <0.001) and in men who had chronic illness at baseline

Table 2. Baseline characteristics by cardiorespiratory fitness quintiles for 38,410 men who were followed an average of 17.2 years: Aerobics Center Longitudinal Study, 1970 to 2003

Characteristic	Cardiorespiratory fitness quintiles					<i>p</i> trend
	1 (low)	2	3	4	5 (high)	
<i>N</i>	7220	7820	7536	8009	7825	
Man-years	138,624	139,857	130,373	128,945	122,853	
Age (yrs)	43.6 ± 9.5	43.5 ± 9.7	44.6 ± 9.7	43.8 ± 10.0	43.5 ± 10.3	0.87
BMI (kg/m ²)	29.3 ± 5.1	27.1 ± 3.5	26.3 ± 3.0	25.5 ± 2.7	24.3 ± 2.3	<0.0001
Waist circumference (cm)	104.3 ± 13.1	97.8 ± 9.8	94.9 ± 8.7	91.7 ± 8.0	86.9 ± 7.1	<0.0001
Percent body fat	27.2 ± 6.3	24.7 ± 5.6	23.3 ± 5.5	21.3 ± 5.4	18.2 ± 5.3	<0.0001
Treadmill time (min)	11.0 ± 2.7	14.8 ± 2.2	17.1 ± 2.2	19.9 ± 2.3	24.4 ± 3.0	<0.0001
Maximal METs	8.4 ± 1.3	10.2 ± 1.0	11.2 ± 1.0	12.5 ± 1.1	14.9 ± 1.9	<0.0001
BMI-defined weight groups (%)						<0.0001
Normal-weight (18.5 to 24.99 kg/m ²)	18.6	27.9	34.4	45.4	65.1	
Overweight (25 to 29.99 kg/m ²)	44.3	53.5	53.9	48.9	33.6	
Obese (≥30 kg/m ²)	36.9	18.7	11.7	5.7	1.3	
Waist circumference ≥102 cm (%)	54.6	32.2	20.6	10.4	2.5	<0.0001
Smoking status (%)						<0.0001
Never	36.7	43.6	47.8	53.2	56.8	
Past	31.7	32.8	34.5	34.3	35.3	
Current	31.6	23.7	17.7	12.6	7.9	
Chronic illness (%)*	91.8	83.6	77.9	68.6	55.1	<0.0001
Deaths (%)	4.4	2.8	2.4	1.9	1.5	<0.0001

MET, metabolic equivalent. Data are mean ± standard deviation.

* Chronic illness was defined as the presence of 1) dyslipidemia (history of physician-diagnosed high cholesterol or triglyceride or measured fasting total cholesterol >240 mg/dL, or triglyceride >200 mg/dL or high-density lipoprotein <50 mg/dL); 2) diabetes (history of physician diagnosis or use of insulin or measured fasting glucose >126 mg/dL); 3) hypertension (history of physician diagnosis or resting systolic blood pressure ≥140 or diastolic blood pressure ≥90); 4) prevalent cardiovascular disease (history of physician-diagnosed myocardial infarction or stroke); or 5) an abnormal resting echocardiogram.

(*p* = 0.048). A significant inverse gradient of cancer mortality rates was seen across incremental CRF categories (*p* < 0.0001).

We next computed HRs and 95% CIs as measures of the strength of association for adiposity and CRF exposure categories with cancer mortality (Table 4). After adjusting for covariables, HRs of cancer mortality across incremental quintiles of CRF were 1.0, 0.71, 0.69, 0.73, and 0.53; *p* for trend <0.0001. Further adjustment for BMI, WC, or percent body fat had little effect on the pattern or strength of association. Table 4 also shows the risk of cancer mortality across quintiles of BMI, WC, and percent body fat. When adjusted for covariables, a significant trend for higher mortality risk was seen across incremental levels of BMI (HRs = 1.0, 1.23, 1.09, 1.31, and 1.60; *p* for trend <0.0001), WC (HRs = 1.0, 1.02, 0.95, 1.19, and 1.51; *p* for trend = 0.001), and percent body fat (HRs = 1.0, 1.23, 1.13, 1.16, and 1.41; *p* for trend <0.01). After further

adjustment for CRF, mortality risk was attenuated across BMI and WC levels and was no longer significant across levels of percent body fat (*p* = 0.81). Restricting the analyses to men who had at least 3 years of follow-up did not materially change the strength or patterns of the above associations (data not shown). Furthermore, restricting analyses on BMI and cancer mortality to only non-smokers and only apparently healthy men did not strengthen the CRF-adjusted association between BMI and mortality (data not shown).

To place our findings into a more clinically relevant perspective, we jointly regressed mortality rates on adiposity and CRF exposures grouped according to standardized definitions (Figures 1 to 3). Cancer mortality rates were significantly lower in fit compared with unfit men within each stratum of adiposity exposure, including men with BMI-defined obesity and with abdominal obesity. As shown in Figure 1, cancer mortality rates (per 10,000 man-years)

Table 3. Rates of cancer mortality according to exposure groups in 38,410 men followed an average of 17.2 years: Aerobics Center Longitudinal Study, 1970 to 2003

	Man-years	Deaths	Rate* (per 10,000 man-years)
BMI (kg/m²) quintiles			
<23.5	145,625	176	12.3
23.50 to 25.10	139,467	223	15.2
25.11 to 27.00	153,020	230	14.1
27.01 to 29.80	109,263	185	17.1
>29.80	115,140	223	21.1
<i>p</i> linear trend			<0.0001
Waist circumference† (cm) quintiles			
<85.00	74,280	59	10.2
85.00 to 90.80	91,873	94	10.7
90.81 to 95.90	81,703	88	10.3
95.91 to 102.00	75,885	111	13.4
>102.00	77,365	137	16.7
<i>p</i> linear trend			<0.0001
Percent body fat‡ quintiles			
<17.50	136,375	142	12.6
17.50 to 21.50	131,718	189	15.6
21.51 to 24.60	122,186	182	14.8
24.61 to 28.00	117,426	194	15.5
>28.00	116,095	253	18.9
<i>p</i> linear trend			<0.001
Treadmill time§ (min) quintiles			
<13.50	138,624	314	21.9
13.50 to 16.10	139,978	216	15.3
16.11 to 19.00	130,373	203	14.6
19.01 to 22.30	128,945	185	15.3
>22.30	122,853	119	10.7
<i>p</i> linear trend			<0.0001
Age (yrs)			
18 to 30	44,324	6	1.2
30 to 40	211,895	106	4.5
40 to 50	241,197	369	14.6
50 to 60	128,917	382	29.6
60+	35,301	174	56.9
<i>p</i> linear trend			<0.001
Smoking status			
Never	301,169	326	11.6
Past	233,064	407	15.3
Current	128,474	304	25.8
<i>p</i> linear trend			<0.001
Chronic illness			
No	146,359	126	13.4
Yes	516,308	911	16.3
<i>p</i> difference			0.048

* Adjusted for age and examination year.

† Waist circumference: *n* = 27,881 (489 deaths).

‡ Percent body fat: *n* = 36,885 (960 deaths).

§ Quintiles of fitness were based on the distribution of treadmill exercise duration standardized to the following age groups: 18 to 39 years, 40 to 49 years, 50 to 59 years, and 60+ years in the overall Aerobics Center Longitudinal Study population of men. The tabulated values reflect the average value for the men included in this analysis. The associated metabolic equivalent (MET) ranges for each fitness quintile were <9.9, 9.9 to 10.8, 10.9 to 12.6, 12.7 to 14.0, and >14.0.

Table 4. Risk of cancer mortality by quintiles of cardiorespiratory fitness, BMI, waist circumference, and percent body fat: Aerobics Center Longitudinal Study, 1970 to 2003

	Exposure quintiles					p trend
	1 (low)	2	3	4	5 (high)	
Cardiorespiratory fitness						
Adjusted for covariables*	1.00 (referent)	0.71 (0.60 to 0.85)	0.69 (0.58 to 0.83)	0.73 (0.61 to 0.89)	0.53 (0.43 to 0.67)	<0.0001
+ BMI†	1.00 (referent)	0.73 (0.62 to 0.88)	0.72 (0.60 to 0.87)	0.79 (0.65 to 0.97)	0.59 (0.47 to 0.76)	<0.001
+ waist circumference†	1.00 (referent)	0.68 (0.52 to 0.90)	0.63 (0.48 to 0.85)	0.74 (0.56 to 0.99)	0.53 (0.38 to 0.75)	0.004
+ percent body fat†	1.00 (referent)	0.68 (0.57 to 0.83)	0.65 (0.54 to 0.79)	0.70 (0.58 to 0.87)	0.50 (0.39 to 0.65)	<0.0001
BMI						
Adjusted for covariables	1.00 (referent)	1.23 (1.01 to 1.49)	1.09 (0.89 to 1.32)	1.31 (1.10 to 1.60)	1.60 (1.30 to 1.91)	<0.0001
+ cardiorespiratory fitness	1.00 (referent)	1.19 (0.98 to 1.46)	1.03 (0.84 to 1.26)	1.20 (0.97 to 1.49)	1.40 (1.13 to 1.50)	<0.01
Waist circumference						
Adjusted for covariables	1.00 (referent)	1.02 (0.74 to 1.42)	0.95 (0.68 to 1.32)	1.19 (0.87 to 1.60)	1.51 (1.10 to 2.18)	0.001
+ cardiorespiratory fitness	1.00 (referent)	0.98 (0.71 to 1.37)	0.88 (0.63 to 1.23)	1.07 (0.77 to 1.50)	1.25 (0.89 to 1.80)	0.09
Percent body fat						
Adjusted for covariables	1.00 (referent)	1.23 (0.98 to 1.52)	1.13 (0.90 to 1.41)	1.16 (0.93 to 1.53)	1.41 (1.12 to 1.80)	<0.01
+ cardiorespiratory fitness	1.00 (referent)	1.15 (0.92 to 1.43)	1.00 (0.80 to 1.26)	0.98 (0.78 to 1.24)	1.11 (0.88 to 1.40)	0.81

Data are hazard ratio (95% confidence interval).

* Age, examination year, smoking status, and chronic illness at baseline.

† BMI, waist circumference, and percent body fat were separately entered into a model with cardiorespiratory fitness and the covariables.

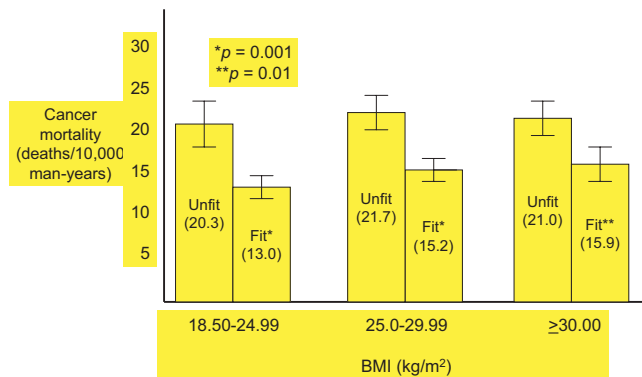


Figure 1: Joint association of CRF and BMI with the age- and examination year-adjusted rates of cancer mortality: ACLS, 1970 to 2003. Error bars represent standard error. Likelihood ratio test for interaction, $\chi^2, df_1 = 0.43, p = 0.51$. Numbers shown in bars represent cancer mortality rates.

were significantly higher in unfit (20.3, 21.7, and 21.0, respectively) than fit men (13.0, 15.2, and 15.9, respectively) across incremental BMI categories ($p = 0.01$). As shown in Figure 2, mortality rates were also significantly higher in unfit (15.6 and 20.9, respectively) than fit men (10.4 and 13.8, respectively) across incremental categories of WC ($p = 0.02$). Finally, as shown in Figure 3, mortality rates were significantly higher in unfit (19.6 and 25.0, respectively) than fit men (12.2 and 16.3, respectively) across incremental categories of percent body fat ($p = 0.001$). There was no statistical evidence of interaction between CRF and the adiposity measures (BMI, $\chi^2 df_1 =$

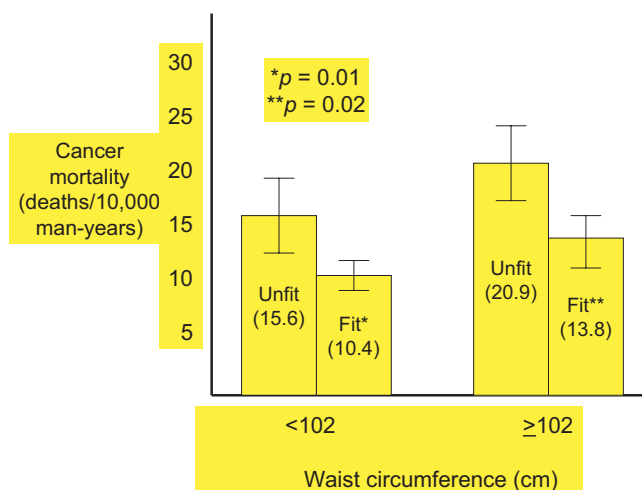


Figure 2: Joint association of CRF and waist circumference with the age- and examination year-adjusted rates of cancer mortality: ACLS, 1970 to 2003. Error bars represent standard error. Likelihood ratio test for interaction, $\chi^2, df_1 = 0.07, p = 0.78$. Numbers shown in bars represent cancer mortality rates.

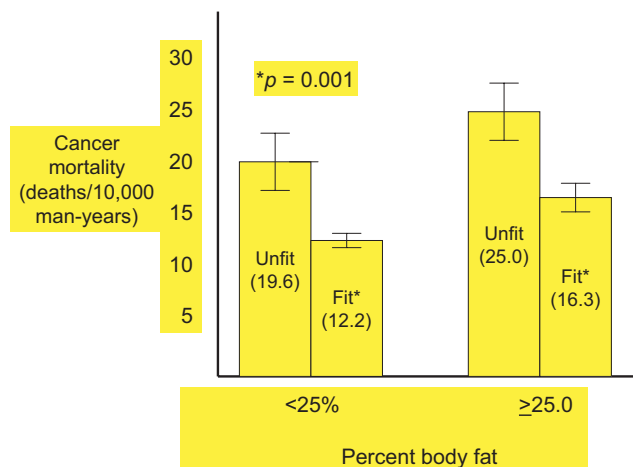


Figure 3: Joint association of CRF and percent body fat with the age- and examination year-adjusted rates of cancer mortality: ACLS, 1970 to 2003. Error bars represent standard error. Likelihood ratio test for interaction, $\chi^2, df_1 = 0.09, p = 0.77$. Numbers shown in bars represent cancer mortality rates.

0.43, $p = 0.51$; WC $\chi^2 df_1 = 0.07, p = 0.78$; and, percent body fat, $\chi^2 df_1 = 0.09, p = 0.77$).

Discussion

In the present study, rates of cancer mortality were positively associated with BMI, WC, and percent body fat. The association persisted after adjusting for baseline differences in age, smoking, and health status. However, further adjustment for CRF attenuated the significant mortality risk associated with BMI to only men in the highest BMI quintile, attenuated the association between cancer mortality and WC, and eliminated the associations between cancer mortality and percent body fat. CRF was inversely associated with cancer mortality independently of several confounding factors, including each of the adiposity measures. Based on joint regression analysis, men with low CRF and high adiposity experienced the highest rates of cancer mortality, whereas men who were fit had lower rates of mortality than their unfit peers, irrespective of adiposity levels. Our findings are consistent with and expand on an earlier report from the ACLS (11) and a more recent report on CRF, BMI, and cancer mortality in the Lipid Research Clinics Mortality Follow-up Study (14). In the Lipid Research Clinics Mortality Follow-up Study, a significantly lower risk of cancer mortality was seen only in men in the highest CRF quintile. The somewhat different findings seen in the Lipid Research Clinics Mortality Follow-up Study and the present study may be explained, in part, by differences in the distribution of CRF, BMI, and baseline health status among men in the 2 studies. In the present study, the reduction in cancer mortality risk across quintiles of CRF was materially unchanged after adjustment for BMI, WC, and percent body

fat. Furthermore, cancer mortality rates were much lower among fit vs. unfit men within each stratum of BMI, WC, and percent body fat. These findings suggest that higher CRF levels can significantly attenuate the association between adiposity and cancer mortality in men.

CRF is positively correlated to levels of physical activity. There are many health benefits that result from physical activity, some of which may explain the protective association between CRF and cancer mortality that was seen in the present study. For example, there is convincing evidence that physical activity increases anti-tumor immune defenses and antioxidant defenses. There is also convincing evidence that levels of circulating insulin, insulin-like growth factors, and glucose decrease while levels of insulin-like growth factor-binding protein-3 increase as a result of physical activity (29).

The mechanisms by which adiposity contributes to cancer development may be similar to some of those that are potentially associated with low levels of physical activity. For instance, excess body fat has been shown to increase circulating levels of insulin-like growth factors, insulin, glucose, and sex hormones. Additionally, adipocytes produce estrogen and can store carcinogens (30,31).

An important point to consider when interpreting the joint associations of CRF and measures of adiposity with cancer mortality is the method in which CRF was grouped for this analysis. Currently, there is not a widely accepted method of defining CRF levels for use in clinical or public health research. In the ACLS, we have standardized the definition of low fitness (unfit) according to the bottom 20% of the age-standardized distribution of maximal exercise duration within the overall ACLS population; individuals in the remaining 80% of the distribution are considered to be fit (10,21). By our definition, it would thus seem that even modest levels of CRF are associated with lower risk of cancer mortality. For example, a 50- to 59-year-old man would need to achieve a maximal metabolic equivalent (MET) level of 8.9 or higher to qualify for the fit category. This is equivalent to covering ~1.2 miles in the Cooper 12 Minute Run-Walk Test (32) or achieving a treadmill time of ~8.5 minutes on a standard Bruce Treadmill Test (27). This level of CRF can be achieved by many, perhaps even most, apparently healthy adults through moderate amounts and intensities of regular physical activity such as brisk walking (33). In a study comparing the effects of weight loss and aerobic exercise training on coronary artery disease risk factors in sedentary, obese middle-aged and older men, Katznel et al. (34) showed a 17% mean increase ($p < 0.001$) in maximal oxygen consumption in 49 subjects who completed 9 months of moderate aerobic training. In a supervised setting, subjects used treadmills and stationary bicycles with an initial training load of 30 minutes, 3 days per week at 50% to 60% of heart rate reserve. The group progressed to performing 45 minutes of cycling, 3 days per

week at 70% to 80% of heart rate reserve. The significant increase in maximal oxygen consumption in the aerobic training group occurred in the absence of weight loss, showing that the increase in CRF was due to a true training effect and not simply due to weight loss.

An issue that arises in prospective studies of apparently healthy individuals is the possibility of undetected subclinical disease at baseline. Including such individuals in the present study could potentially confound the relation between CRF, adiposity, and cancer mortality because participants with subclinical disease might also have lower exercise test performance and higher levels of adiposity. In contrast to most other epidemiological cohort studies on this topic is the extensive baseline clinical examination including a physician-given examination, detailed health history interview, and other tests that make it less likely that undetected subclinical disease was present in our study participants. When we performed additional analyses restricted only to those men with three or more years of follow-up, the primary findings were materially unchanged. This enhances our confidence that our primary observations were not explained entirely by undetected disease at baseline.

Among the strengths of the current study is a large and well-characterized cohort of men, an extensive follow-up with a relatively large number of cancer deaths for analysis, and the use of objective measures for CRF and adiposity exposures. This study also has limitations. The cohort is primarily white and from middle to upper socioeconomic strata; therefore, our findings must be cautiously interpreted when generalized to other populations. However, the homogeneity of socio-demographic factors in our population sample strengthens the internal validity of our findings by reducing potential confounding by these issues. We did not have sufficient data for dietary intake and medication use to include in this analysis. Dietary intake is an important determinant of cancer risk (3), and we hope to include a measure of this important exposure in future studies. We did not have more extensive information on smoking habits, such as number of pack-years. Although it is possible that residual confounding by smoking exists in the present analyses, it is not likely to account for all of the observed associations. We examined deaths from all types of cancer in the present study. There is evidence that CRF and adiposity may differentially affect mortality risk associated with specific cancers (7,13). At present, we were unable to examine associations of CRF, adiposity, and cause-specific cancer mortality. Future studies including work in the ACLS cohort should attempt to address issues pertaining to site-specific cancer mortality.

Our group has previously shown that CRF is a stronger predictor than adiposity for all-cause (35) and cardiovascular disease mortality (24) in non-diabetic men as well as for

all-cause mortality in men with type 2 diabetes (36). The results of the current study underscore the need for health professionals to place at least as much emphasis on enhancing physical activity as on weight management when counseling individuals on healthy lifestyle habits that may lower cancer mortality risk.

In summary, CRF is significantly and inversely associated with cancer mortality in men. This association is steep, graded, and relatively unchanged after adjustment for adiposity. While each adiposity measure was significantly and directly associated with cancer mortality, this association was attenuated or eliminated after adjustment for CRF. When regressed jointly, mortality rates were significantly lower in fit compared with unfit men within stratum of standard clinical groupings for BMI, WC, and percent body fat. These data suggest that attaining a moderate to high level of CRF may attenuate some of the cancer mortality risks associated with increased adiposity. A strong emphasis should be placed on encouraging sedentary individuals of all adiposity levels to become at least moderately active, presumably thereby increasing their CRF level to decrease the risk of cancer mortality.

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References

1. **American Cancer Society.** *Cancer Facts & Figures 2006*. Atlanta, GA: American Cancer Society; 2006.
2. **Koop CE, Luoto J.** The health consequences of smoking: cancer, overview of a report of the Surgeon General. *Public Health Rep.* 2006;121(Suppl 1):269–75.
3. **Byers T, Nestle M, McTiernan A, et al.** American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention. *CA Cancer J Clin.* 2002;52:92–119.
4. **Boffetta P, Nyberg F.** Contribution of environmental factors to cancer risk. *Br Med Bull.* 2003;68:71–94.
5. **Jarup L.** Hazards of heavy metal contamination. *Br Med Bull.* 2003;68:167–82.
6. **Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ.** Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med.* 2003;348:1625–38.
7. **Patel AV, Rodriguez C, Bernstein L, Chao A, Thun MJ, Calle EE.** Obesity, recreational physical activity and risk of pancreatic cancer in a large U.S. cohort. *Cancer Epidemiol Biomarkers Prev.* 2005;14:459–66.
8. **Moore LL, Bradlee M, Singer MR, et al.** BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. *Int J Obes Relat Metab Disord.* 2004;28:559–67.
9. **Garfinkel L.** Overweight and cancer. *Ann Intern Med.* 1985;103:1034–6.
10. **Lee CD, Blair SN.** Cardiorespiratory fitness and smoking-related and total cancer mortality in men. *Med Sci Sports Exerc.* 2002;34:735–9.
11. **Kampert JB, Blair SN, Barlow CE, Kohl HW.** Physical activity, physical fitness, and all-cause and cancer mortality: a prospective study of men and women. *Ann Epidemiol.* 1996;6:452–7.
12. **Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC.** Physical activity, obesity, and risk for colon cancer and adenoma in men. *Ann Intern Med.* 1995;122:327–34.
13. **Thune I, Lund E.** The influence of physical activity on lung cancer risk: a prospective study of 81,516 men and women. *Int J Cancer.* 1997;70:57–62.
14. **Evenson KR, Stevens J, Cai J, Thomas R, Thomas O.** The effect of cardiorespiratory fitness and obesity on cancer mortality in women and men. *Med Sci Sports Exerc.* 2003;35:270–7.
15. **Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM.** Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA.* 2006;295:1549–55.
16. **NIH Consensus Conference.** Physical activity and cardiovascular health. *JAMA.* 1996;276:241–6.
17. **Ajani UA, Lotufo PA, Gaziano JM, et al.** Body mass index and mortality among US male physicians. *Ann Epidemiol.* 2004;14:731–9.
18. **Baik I, Ascherio A, Rimm EB, et al.** Adiposity and mortality in men. *Am J Epidemiol.* 2000;152:264–71.
19. **Patel AV, Rodriguez C, Jacobs EJ, Solomon L, Thun MJ, Calle EE.** Recreational physical activity and risk of prostate cancer in a large cohort of U.S. men. *Cancer Epidemiol Biomarkers Prev.* 2005;14:275–9.
20. **Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA.** Physical activity and survival after breast cancer diagnosis. *JAMA.* 2005;293:2479–86.
21. **Blair SN, Kohl HW, Paffenbarger RS, et al.** Physical fitness and all-cause mortality: a prospective study of healthy men and women. *JAMA.* 1989;262:2395–401.
22. **Jackson AS, Pollock ML.** Practical assessment of body composition. *Physician Sports Med.* 1985;13:76–90.
23. **Siri WE.** Body composition from fluid spaces and density. In: Brozek J, Hanschel A, eds. *Techniques for Measuring Body Composition*. Washington, DC: National Academy of Science; 1961, pp. 223–4.
24. **Lee CD, Jackson AS, Blair SN.** Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. *Am J Clin Nutr.* 1999;69:373–80.
25. **Balke B, Ware RW.** An experimental study of physical fitness in Air Force personnel. *US Armed Forces Med J.* 1959;10:675–88.
26. **Pollock ML, Bohannon RL, Cooper KH, et al.** A comparative analysis of four protocols for maximal treadmill stress testing. *Am Heart J.* 1976;92:39–46.
27. **American College of Sports Medicine.** *Guidelines for Exercise Testing and Prescription*. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.
28. **Bray GA.** Fat distribution and body weight. *Obes Res.* 1993;1:203–5.

29. **Friedenreich C.** Physical activity and cancer prevention: from observational intervention research. *Cancer Epidemiol Biomarkers Prev.* 2001;59:287–301.
30. **Friedenreich CM, Orenstein MR.** Physical activity and cancer prevention: etiologic evidence and biological mechanisms. *J Nutr.* 2002;132(suppl):3456–64.
31. **Frezza EE, Wachtel MS, Chiriva Internati M.** Influence of obesity on the risk of developing colon cancer. *Gut.* 2006; 55:285–91.
32. **Cooper KH.** A means of assessing maximal oxygen intake: correlation between field and treadmill testing. *JAMA.* 1968; 203:201–4.
33. **Stofan JR, DiPietro L, Davis D, Kohl HW, Blair SN.** Physical activity patterns associated with cardiorespiratory fitness and reduced mortality: the Aerobics Center Longitudinal Study. *Am J Public Health.* 1998;88:1807–13.
34. **Katzel LI, Bleecker ER, Colman EG, Rogus EM, Sorkin JD, Goldberg AP.** Effects of weight loss vs. aerobic exercise training on risk factors for coronary disease in healthy obese, middle-aged and older men: a randomized controlled trial. *JAMA.* 1995;274:1915–21.
35. **Barlow CE, Kohl HW, Gibbons LW, Blair SN.** Physical fitness, mortality and obesity. *Int J Obes.* 1995;19(Suppl 4): 41–4.
36. **Church TS, Cheng YJ, Earnest CP, et al.** Exercise capacity and body composition as predictors of mortality among men with diabetes. *Diabetes Care.* 2004;27:83–8.