Association of Changes in Fitness and Body Composition with Cancer Mortality in Men

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ABSTRACT

ZHANG, P., X. SUI, G. A. HAND, J. R. HÉBERT, and S. N. BLAIR. Association of Changes in Fitness and Body Composition with Cancer Mortality in Men. *Med. Sci. Sports Exerc.*, Vol. 46, No. 7, pp. 1366–1374, 2014. **Introduction**: Both baseline cardiorespiratory fitness and adiposity predict the risk of cancer mortality. However, the effects of changes in these two factors over time have not been evaluated thoroughly. The aim of this study was to examine the independent and joint associations of changes in cardiorespiratory fitness and body composition on cancer mortality. **Methods**: The cohort consisted of 13,930 men (initially cancer-free) with two or more medical examinations from 1974 to 2002. Cardiorespiratory fitness was assessed by a maximal treadmill exercise test, and body composition was expressed by body mass index (BMI) and percent body fat. Changes in cardiorespiratory fitness and body composition between the baseline and the last examination were classified into loss, stable, and gain groups. **Results**: There were 386 deaths from cancer during an average of 12.5 yr of follow-up. After adjusting for possible confounders and BMI, change hazard ratios (95% confidence intervals) of cancer mortality were 0.74 (0.57–0.96) for stable fitness and 0.74 (0.56–0.98) for fitness gain. Inverse dose–response relationships were observed between changes in maximal METs and cancer mortality (P for linear trend = 0.05). Neither BMI change nor percent body fat change was associated with cancer mortality after adjusting for possible confounders and maximal METs change. In the joint analyses, men who became less fit had a higher risk of cancer mortality (P for linear trend = 0.03) compared with those who became more fit, regardless of BMI change levels. **Conclusions**: Being unfit or losing cardiorespiratory fitness over time was found to predict cancer mortality in men. Improving or maintaining adequate levels of cardiorespiratory fitness appears to be important for decreasing cancer mortality in men. **Key Words:** CARDIORESPIRATORY FITNESS CHANGE, ADIPOSITY, CANCER MORTALITY, PROSPECTIVE COHORT STUDY, EPIDEMIOLOGY

EPIDEMIOLOGY

Cancer is a leading cause of death worldwide, contributing to 8.0 million deaths in 2010 and accounting for 15.1% of all deaths (28). Cancer also is associated with heavy economic burdens. There were 12.7 million new cancer cases diagnosed worldwide in 2008, and an estimated 169.3 million years of healthy life were lost because of cancer. Considering population growth and aging, new cancer cases worldwide are projected to reach 21.4 million in 2030 (37).

Worldwide, more than 35% of deaths from cancer are caused by five leading risk factors: tobacco smoking, alcohol use, low fruit and vegetable intake, overweight and obesity (high body mass index [BMI]), and physical inactivity (4,41). All of these lifestyle factors are potentially modifiable, which means at least 35% of cancer deaths could be prevented, and previous studies have shown that lifestyle modification can prevent incident cancer or slow disease progression (18,36).

The majority of the existing literature has demonstrated that physical inactivity or low levels of cardiorespiratory fitness, an objective indicator of habitual physical activity, increase the risk of cancer mortality (15–17,24,26,34). A large body of epidemiological evidence also shows that obesity is directly associated with cancers of the breast, colon, endometrium, kidney, liver, pancreas, esophagus, and gallbladder (3,40). A recent study reported that cancer mortality rates increase by 10% for every 5 $kg \cdot m^{-2}$ increase in BMI (3). However, these previous studies have not evaluated possible changes in cardiorespiratory fitness and obesity over time. The apparent associations between cardiorespiratory fitness, obesity, and cancer outcomes, therefore, might be under- or overestimates of the true relationships.

Only a few previous reports indicate that change in fitness is a strong predictor of all-cause mortality (14) and that improving or maintaining cardiorespiratory fitness is associated with a lower risk of dying (25). Nevertheless, the relationship between change in cardiorespiratory fitness and cancer mortality remains uncertain. A small number of

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studies also have examined the effects of adiposity (using BMI) change on cancer mortality; however, results obtained are controversial (11,13,21). Different measures of adiposity, including BMI (a crude measure of adiposity) and percent body fat (a better measure of adiposity), can more accurately assess the relationship between adiposity change and cancer mortality.

To the best of our knowledge, no study has examined the independent and combined associations among changes in cardiorespiratory fitness and adiposity with cancer mortality. Understanding these relationships can help to inform cancer prevention policy and clinical practice. From a public health perspective, it is important to know whether cardiorespiratory fitness and adiposity changes during adulthood are related to cancer mortality. Therefore, the primary purpose of this study was to examine the independent and joint associations of changes in cardiorespiratory fitness and body composition with subsequent cancer mortality in a large cohort of initially cancer-free men. We addressed three questions: 1) Are changes in cardiorespiratory fitness or body composition related to cancer mortality? 2) Are these relationships reciprocally independent of each other? 3) Do cancer mortality risks vary among the various combinations of changes in cardiorespiratory fitness and body composition?

MATERIALS AND METHODS

Study population. The Aerobics Center Longitudinal Study (ACLS) is a prospective observational study of individuals who completed comprehensive medical examinations at the Cooper Clinic in Dallas, Texas (9). Study participants came to the clinic for periodic preventive health examinations and for counseling regarding diet, exercise, and other lifestyle factors associated with increased risk of chronic disease. Many participants were sent by their employers for the examination; others were referred by their physicians or were self-referred.

The current study included adult men (age ≥20 yr at baseline) who received at least two medical examinations from 1974 to 2002. We used the first (baseline) and last examination to assess changes in fitness and body composition, and followed participants for mortality after the last examination. Participants were excluded from the present study if they reported a history of myocardial infarction, stroke, or cancer at baseline (n = 1085); failed to achieve at least 85% of age-predicted maximal heart rate (220 minus age in years) during the treadmill test at baseline or at the last examination (n = 318); or had a BMI <18.5 $kg \cdot m^{-2}$ at baseline (n = 215) (29). Moreover, we excluded participants with <1 yr of mortality follow-up (n = 994), those who answered "yes" to a question about "unexplained weight loss or gain" at the last examination (n = 499), and those with an extreme value of fitness change (>10 METs change per year) or BMI change (>10 $kg \cdot m^{-2}$ change per year) (n = 12). These exclusion criteria were used to minimize potential biases because of underlying or preexisting disease on changes in fitness and BMI and their associations with cancer mortality. The final study population consisted of 13,930 men who were 20 to 82 yr old at the time of their baseline clinical examination.

The participants were mainly (>95%) non-Hispanic white, well educated, and from middle to upper socioeconomic strata. The study protocol was reviewed and approved annually by the Institutional Review Board of the Cooper Institute, and all participants provided written informed consent to participate in the examinations and follow-up study.

Clinical examination. The clinical examination was performed after an overnight fast of at least 12 h and has been described in detail elsewhere (9). In brief, the examination consisted of a physician examination, including a comprehensive preventive medical evaluation and clinical measurements. Height and weight were measured by a standard clinical scale and stadiometer, with light clothing and without shoes. Seated resting blood pressure was determined by standard auscultation method with a mercury sphygmomanometer. Concentrations of fasting serum glucose and total cholesterol were analyzed by automated methods in the Cooper Clinic Laboratory. Resting ECG was done according to a standard manual of operations. Abnormal ECG responses included rhythm and conduction disturbances and ischemic ST-T wave abnormalities. Information about personal health histories, family history of cancer, smoking habits, alcohol drinking habits, physical activity habits, and demographic information was obtained from standardized medical history questionnaires.

Cardiorespiratory fitness. Cardiorespiratory fitness was measured by a maximal treadmill exercise test using a modified Balke protocol (19). In short, the treadmill speed was 88 $m \cdot min^{-1}$ initially, and participants started the test at 0% grade. The grade was increased to 2% for the second minute and was thereafter increased 1% per minute until the 25th minute. After 25 min, the speed was increased 5.4 $m \cdot min^{-1}$ without grade change until test termination. All participants were encouraged to give maximal effort during the test. Participants who had the test stopped by a physician for problematic symptoms and signs, or failed to reach 85% of age-predicted maximal heart rate, were excluded from the analyses to ensure that near maximal effort was obtained. The exercise test performance from this protocol is highly correlated with measured maximal oxygen uptake in men (r = 0.92) (31). Cardiorespiratory fitness in maximal METs was estimated from the final treadmill grade and speed using the following equation from the American College of Sports Medicine: [(speed × 0.1) + (speed × grade × 1.8) + 3.5] / 3.5 (2).

Body composition. BMI was calculated as weight in kilograms divided by the square of height in meters. On the basis of BMI, participants were categorized as normal weight (18.5 ≤ BMI < 25), overweight (25 ≤ BMI < 30), or obese (BMI ≥ 30). Percent body fat was determined by underwater weighing (60%) or skinfold thickness measurements (40%), following standard procedures. These two

measurements were highly correlated ($r > 0.90$) for participants who underwent both measurements (20). According to percent body fat, participants were classified as normal body fat (% body fat <25%) or obese (% body fat ≥25%) (10).

Changes in fitness and body composition. Changes in fitness and body composition as continuous variables were calculated as the difference in maximal METs, BMI, and percent body fat between the baseline and the last examination, divided by the duration (number of years) between the two examinations. The mean interval between the baseline and the last examination was 6.2 ± 5.6 yr. Because the intervals between those two examinations varied among individuals in this cohort, we used changes in fitness and body composition per year as our main exposures. Approximately half of participants showed an increase in maximal METs (48%), BMI (57%), and percent body fat (57%), and the others showed a decrease or no change. On the basis of these almost equal distributions, changes in fitness and body composition per year were further divided into thirds to simplify the complex combined associations of changes in fitness and body composition with cancer mortality. The upper third of changes in fitness, BMI, and percent body fat (annual mean increases of 0.84 METs, 0.46 $kg \cdot m^{-2}$, and 1.58%) were classified as "gain"; the middle third (mean changes of −0.04 METs, 0.04 $kg \cdot m^{-2}$, and 0.11%) were classified as "stable"; and the lower third (mean decreases of −0.34 METs, −0.71 $kg \cdot m^{-2}$, and −2.22%) were classified as "loss." We also created nine combinations from the three fitness and BMI change classifications for the joint analyses of changes in fitness and BMI with cancer mortality.

In addition, we examined the associations between cancer mortality and changes in fitness or body composition status according to specific cut points. Using age-specific (20–39, 40–49, 50–59, and ≥60 yr) fifths of treadmill time distribution from the overall ACLS population (8), participants were dichotomized as unfit (lower 20%) or fit (upper 80%) groups. This method for defining fit and unfit is a standardized approach used in the ACLS, and unfit by this definition is an independent predictor of morbidity and mortality (6,8,39). Participants who were fit at both the baseline and the last examination were classified as "remained fit," those who were unfit at both examinations were classified as "remained unfit," those who were unfit at baseline but fit at the last examination were classified as "became fit," and those who were fit at baseline but unfit at the last examination were classified as "became unfit." Because the number of obese participants was small, we combined obese and overweight participants (assessed using BMI). Similarly, participants were classified into one of four BMI status patterns: participants who were normal weight at both the baseline and the last examination were classified as "remained normal BMI," those who were overweight or obese at both examinations were classified as "remained abnormal BMI," those who were overweight or obese at baseline but normal weight at the last examination were classified as "became normal BMI," and those who were normal weight at baseline but overweight or obese at the last examination were classified as "became abnormal BMI." Participants were categorized into one of four body fat status patterns in a similar way.

Finally, changes in maximal METs, percent body fat, and body weight per year were categorized into fifths to investigate the possible dose–response relationship between each of these variables and cancer mortality. Changes in percent body fat and body weight as continuous variables were calculated the same way as change in fitness and BMI.

Mortality surveillance. Study participants were followed from the date of their last examination to the date of death for decedents or to December 31, 2003, for survivors. Participants with less than 1 yr of follow-up were excluded to minimize potential bias.

The National Death Index and death certificates from states in which the death occurred were used to ascertain vital status and cause of death. More than 95% of mortality follow-up was completed by these methods. The National Death Index has been demonstrated to be a precise method for ascertainment of deaths in prospective cohort studies, with high specificity (100%) and sensitivity (96.5%) (38). All-cause cancer mortality was identified using the *International Classification of Diseases, Ninth Revision* codes 140 to 208 before 1999 and the *International Classification of Diseases, Tenth Revision* codes C00 to C97 during 1999 to 2003.

Statistical analysis. Baseline characteristics of the study population were summarized by survival status. The differences between survivors and decedents at baseline were examined using Student's *t*-test for continuous variables and chi-square test for categorical variables.

Cox proportional hazard models were used to estimate the hazard ratios and the 95% confidence intervals for cancer mortality across changes in fitness and body composition groups. Adjustments were made for baseline age, parental history of cancer, BMI, and maximal METs; the combination patterns of medical conditions (hypertension, hypercholesterolemia, diabetes, and abnormal ECG) and lifestyle factors (physical activity, alcohol intake, and smoking status) at the baseline and the last examination; the number of clinic visits between the baseline and the last examination; and the changes in body composition or maximal METs for each other. The combination patterns of each medical condition at the two examinations were defined as one of three classifications, for example, remained nondiabetic, became diabetic, or remained diabetic. Combination patterns of each lifestyle factor were classified into four categories: remained active, became active, became inactive, or remained inactive; remained non–heavy drinker, became non–heavy drinker, became heavy drinker (alcohol drinks >14 wk^{-1}), or remained heavy drinker; and remained nonsmoker, became nonsmoker, became smoker, or remained smoker. The proportional hazards assumption was examined by comparing the cumulative hazard plots grouped on exposure; no appreciable violations were noted. Tests for linear trend of cancer mortality and changes in

TABLE 1. Baseline characteristics by survival status in 13,930 men.

	All (n = 13,930)	Survivors (n = 13,544)	Decedents (n = 386)	P
Age (yr)	43.8 ± 9.2	43.6 ± 9.2	50.0 ± 9.0	<0.001
Body weight (kg)	83.5 ± 12.2	83.5 ± 12.2	83.5 ± 12.5	0.995
BMI (kg·m^{-2})	26.0 ± 3.3	26.0 ± 3.3	26.0 ± 3.2	0.757
18.5–24.9 (%)	41.9	42.0	39.4	0.514
25.0–29.9 (%)	47.2	47.1	50.0	
≥30 (%)	10.9	10.9	10.6	
Percent body fat (%)	20.8 ± 6.4	20.7 ± 6.3	22.0 ± 6.6	<0.001
<25% (%)	75.9	76.1	72.0	0.092
≥25% (%)	24.1	23.9	28.0	
Cardiorespiratory fitness (maximal METs)	11.9 ± 2.4	11.9 ± 2.4	10.8 ± 2.2	<0.001
Systolic blood pressure (mm Hg)	121.1 ± 13.2	121.0 ± 13.1	124.4 ± 15.0	<0.001
Diastolic blood pressure (mm Hg)	80.7 ± 9.4	80.7 ± 9.4	81.4 ± 10.0	0.121
Hypertension (%)[a]	29.5	29.3	38.1	<0.001
Total cholesterol (mmol·L^{-1})	5.5 ± 1.2	5.5 ± 1.2	5.5 ± 1.0	0.284
Hypercholesterolemia (%)[b]	25.9	26.0	22.5	0.142
Fasting glucose (mmol·L^{-1})	5.6 ± 4.4	5.6 ± 4.5	5.6 ± 0.7	0.915
Diabetes (%)[c]	5.4	5.2	10.1	<0.001
Abnormal ECG (%)[d]	6.9	6.8	11.4	0.001
Physically inactive (%)[e]	28.3	28.1	36.5	<0.001
Heavy drinker (%)[f]	6.3	6.4	4.1	0.094
Current smoker (%)	16.5	16.3	23.1	0.001
Parental cancer (%)	0.7	0.7	0.0	0.118

Data are presented as mean ± SD unless otherwise indicated. Data of percent body fat was from 11900 men.
[a]Defined as systolic or diastolic blood pressure ≥140/90 mm Hg or physician's diagnosis.
[b]Defined as total cholesterol ≥6.2 mmol·L^{-1} or physician's diagnosis.
[c]Defined as fasting glucose ≥6.1 mmol·L^{-1}, current therapy with insulin, or physician's diagnosis.
[d]Defined as abnormal resting or exercise ECG.
[e]Defined as no leisure-time physical activity in the 3 months before the examination.
[f]Defined as >14 alcohol drinks per week.

fitness or body composition across three exposure categories were computed using Cox regression models.

We also assessed the joint associations of changes in fitness and body composition with cancer mortality using interaction terms in the Cox regression. There were no significant interactions among exposure groups. All analyses were performed using the Statistical Package for the Social Sciences (version 17.0; SPSS Inc., Chicago, IL). All P values were derived from two-tailed tests, and $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Table 1 summarizes the baseline characteristics of 13,930 adult men. There were 386 deaths from cancer during follow-up of 12.5 ± 7.6 yr. Among these decedents, 110 died from digestive system cancer, 97 died from lung cancer, 16 died from prostate cancer, and the others died from other types of cancers such as neoplasm of lymphoid, hematologic, and related tissues. Survivors were younger and fitter than decedents at baseline. They were more likely to lead a healthy lifestyle. Compared with decedents, survivors were more active and the percentage of smokers was lower. In addition, survivors had more advantageous profiles for medical conditions, such as lower systolic blood pressure, and lower percentages of hypertension and diabetes. Overall, participants were middle age (mean age = 43.8 ± 9.2 yr), relatively fit (mean maximal METs = 11.9 ± 2.4), and slightly overweight (mean BMI = 26.0 ± 3.3 kg·m^{-2}) at baseline.

Table 2 shows the independent associations of changes in cardiorespiratory fitness or body composition with cancer mortality. Compared with those subjects who lost fitness, participants who improved their fitness had a 29% lower risk of cancer mortality (P = 0.02), and participants who maintained fitness had a 27% lower risk of cancer mortality (P = 0.01), after adjusting for possible baseline confounders and changes in medical conditions and lifestyle factors (model 1). When we further adjusted for BMI change

TABLE 2. Hazard ratios of cancer mortality by changes in fitness and body composition in 13,930 men.

	Cancer Mortality Hazard Ratios (95% CI)	
	Model 1[a]	Model 2[b]
Fitness change		
Loss (n = 4643)	1.00	1.00
Stable (n = 4643)	0.73 (0.56–0.95)	0.74 (0.57–0.96)
Gain (n = 4644)	0.71 (0.55–0.94)	0.74 (0.56–0.98)
P for linear trend	0.024	0.045
Per 1-MET increase	0.95 (0.89–1.01)	0.95 (0.89–1.01)
BMI change		
Loss (n = 4643)	1.00	1.00
Stable (n = 4643)	1.39 (1.08–1.78)	1.35 (1.04–1.74)
Gain (n = 4644)	1.16 (0.89–1.50)	1.10 (0.85–1.43)
P for linear trend	0.040	0.070
Per 1-BMI increase	1.04 (1.00–1.07)	1.04 (1.00–1.07)
Body fat change		
Loss (n = 3967)	1.00	1.00
Stable (n = 3966)	1.10 (0.82–1.46)	1.07 (0.81–1.43)
Gain (n = 3967)	1.07 (0.83–1.38)	1.04 (0.80–1.36)
P for linear trend	0.794	0.884
Per 1% body fat increase	1.01 (0.98–1.03)	1.01 (0.99–1.03)

[a]Adjusted for age, parental cancer, BMI, and maximal METs at baseline; the combination patterns of medical conditions (hypertension, hypercholesterolemia, diabetes, and abnormal ECG) and lifestyle factors (physical activity, alcohol intake, and smoking status) at the baseline and the last examinations; and the number of clinic visits between the baseline and the last examinations.
[b]Adjusted for model 1 plus BMI change (for fitness change) or maximal METs change (for BMI change and body fat change) between the baseline and the last examinations.

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(model 2), the observed associations remained virtually unchanged. Every 1-MET improvement in fitness was marginally associated with a 5% lower risk of cancer mortality ($P = 0.10$) after adjusting for possible confounders and BMI change (model 1 and model 2). Nevertheless, compared with participants whose BMI decreased, participants whose BMI was stable or increased had a higher risk of cancer mortality (P for linear trend = 0.04) after adjusting for possible confounders (model 1). When we also adjusted for maximal METs change (model 2), these associations were attenuated (P for linear trend = 0.07); however, participants whose BMI was stable had a higher risk of cancer mortality ($P = 0.02$). Every unit increase in BMI was associated with a 4% higher risk of cancer mortality ($P = 0.05$), after adjusting for possible confounders and maximal METs change (model 1 and model 2). In addition, body fat change was not significantly associated with cancer mortality after adjusting for possible confounders and maximal METs change (model 1 and model 2).

Table 3 demonstrates the independent relationships between changes in fitness status or body composition status and cancer mortality when using standard clinical cut points. Compared with participants who remained unfit, participants who became fit or remained fit had 41% and 37% lower risk of cancer mortality ($P = 0.03$), respectively, after adjusting for possible baseline confounders and changes in medical conditions and lifestyle factors (model 1). These associations remained approximately the same after further adjusting for BMI change (model 2). Participants who became obese (assessed using body fat) evinced increased risk of cancer mortality ($P = 0.03$) compared with those who maintained normal body fat, after adjusting for possible confounders and maximal METs change (model 1 and model 2). Nonetheless, BMI status change was not significantly associated with cancer mortality after adjusting for possible confounders and maximal METs change (model 1 and model 2).

TABLE 3. Hazard ratios of cancer mortality by changes in fitness status and body composition status in 13,930 men.

	Cancer mortality hazard ratios (95% CI)	
	Model 1[a]	Model 2[b]
Fitness status change[c]		
Remained unfit ($n = 617$)	1.00	1.00
Became unfit ($n = 339$)	1.16 (0.62–2.21)	1.15 (0.61–2.18)
Became fit ($n = 1226$)	0.59 (0.37–0.94)	0.61 (0.38–0.97)
Remained fit ($n = 11,748$)	0.63 (0.42–0.96)	0.64 (0.43–0.97)
BMI status change		
Remained normal BMI ($n = 4458$)	1.00	1.00
Became normal BMI ($n = 842$)	0.88 (0.56–1.36)	0.91 (0.58–1.42)
Became abnormal BMI ($n = 1381$)	0.94 (0.62–1.44)	0.92 (0.60–1.41)
Remained abnormal BMI ($n = 7249$)	1.21 (0.95–1.53)	1.20 (0.95–1.52)
Body fat status change		
Remained normal body fat ($n = 7642$)	1.00	1.00
Became normal body fat ($n = 1107$)	0.85 (0.58–1.25)	0.85 (0.58–1.25)
Became obese ($n = 1386$)	1.54 (1.12–2.11)	1.52 (1.10–2.09)
Remained obese ($n = 1765$)	1.22 (0.89–1.66)	1.21 (0.88–1.65)

[a]Adjusted for age, parental cancer, and BMI (for fitness status change) or maximal METs (for BMI status change and body fat status change) at baseline; the combination patterns of medical conditions (hypertension, hypercholesterolemia, diabetes, and abnormal ECG) and lifestyle factors (physical activity, alcohol intake, and smoking status) at the baseline and the last examinations; and the number of clinic visits between the baseline and the last examinations.

[b]Adjusted for model 1 plus BMI change (for fitness status change) or maximal METs change (for BMI status change and body fat status change) between the baseline and the last examinations.

[c]Unfit was defined as the least fit 20%, and fit was defined as the most fit 80% of maximal treadmill time.

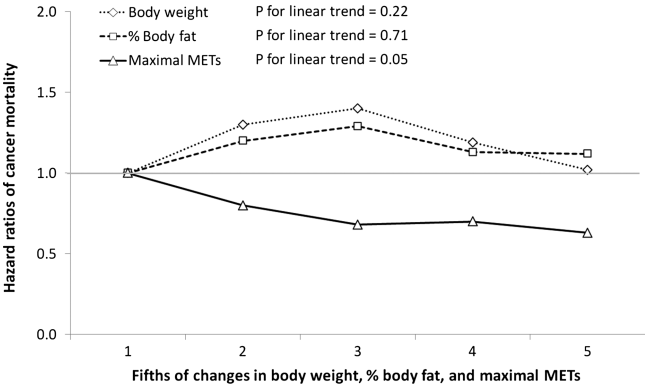

FIGURE 1—Hazard ratios of cancer mortality by fifths of changes in body weight, percent body fat, and maximal METs in 13,930 men. *Adjusted for age, parental cancer, baseline maximal METs, and baseline BMI (for maximal MET change); the combination patterns of medical conditions (hypertension, hypercholesterolemia, diabetes, and abnormal ECG) and lifestyle factors (physical activity, alcohol intake, and smoking status) at the baseline and the last examinations; and the number of clinic visits between the baseline and the last examinations. The first fifth of changes in body weight, percent body fat, or maximal METs was used as reference. Then, hazard ratios of cancer mortality by fifths of changes were 1.30, 1.40, 1.19, and 1.02 in body weight; 1.20, 1.29, 1.13, and 1.12 in percent body fat; and 0.80, 0.68, 0.70, and 0.63 in maximal METs, respectively.

Figure 1 illustrates the associations of quintiles of change in maximal METs, body weight, and percent body fat with cancer mortality. There were significant inverse dose–response relationships across quartiles of change in maximal METs and cancer mortality (P for linear trend = 0.05), whereas no significant trend was observed for cancer mortality by quintiles of change in either percent body fat or body weight.

In the joint analyses of changes in fitness and BMI with cancer mortality (Fig. 2), participants who lost fitness had a higher risk of cancer mortality (P for linear trend = 0.03), compared with the reference group, participants who improved fitness and decreased BMI. There was no significant association between cancer mortality and increased BMI in individuals who improved or maintained fitness.

DISCUSSION

There are three main findings from the current study. First, improving fitness or maintaining fitness, compared with losing fitness, was significantly associated with a lower risk (26%) of cancer mortality in men, independent of possible baseline confounders, changes in medical conditions, lifestyle factors, and BMI. Moreover, quintiles of change in maximal METs were significantly inversely related to cancer mortality. Also, men who remained fit or became fit had

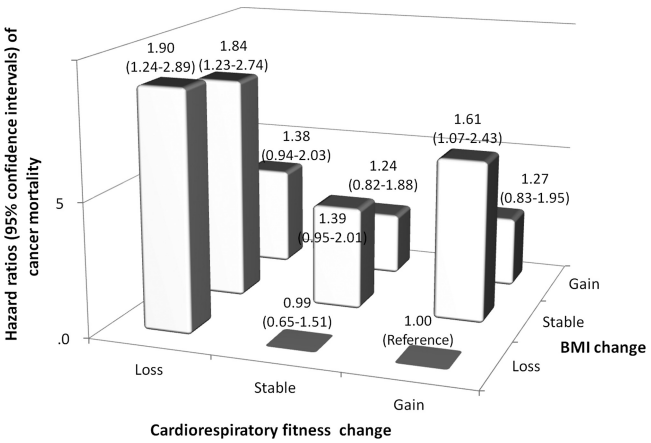

FIGURE 2—Hazard ratio (95% confidence intervals) of cancer mortality by combinations of changes in fitness and BMI in 13,930 men. *Adjusted for age, parental cancer, BMI, and maximal METs at baseline; the combination patterns of medical conditions (hypertension, hypercholesterolemia, diabetes, and abnormal ECG) and lifestyle factors (physical activity, alcohol intake, and smoking status) at the baseline and the last examinations; and the number of clinic visits between the baseline and the last examinations. The number of men (number of cancer deaths) in the fitness loss, stable, and gain groups were 680 (33), 1208 (31), and 2755 (80) in the BMI loss group; 1667 (47), 2077 (54), and 899 (34) in the stable BMI group; and 2296 (44), 1358 (33), and 990 (30) in the BMI gain group, respectively.

a significantly lower risk (36% and 39%, respectively) of cancer mortality compared with men who remained unfit, independent of possible confounders. Second, there was no significant association between weight-related variables (BMI, percent body fat, and body weight) and cancer mortality after adjusting for possible confounders. Third, analyses on the combined associations between changes in fitness and BMI and cancer mortality showed that men who became less fit had a higher risk of cancer mortality irrespective of BMI change compared with the reference group, that is, men who decreased BMI and became more fit. Nevertheless, sustaining or developing fitness attenuates the potentially negative effects of BMI increase on cancer mortality. We believe this is the first prospective study that thoroughly evaluates these relationships.

These findings indicate that maintaining or improving cardiorespiratory fitness may reduce the risk of cancer deaths. In terms of a public health message, the findings indicate that health and medical professionals should recommend that individuals participate in regular physical activity to gain or maintain cardiorespiratory fitness. Thus, policy and clinical interventions should focus not only on decreasing BMI or body weight, which is a current focus, but also on maintaining cardiorespiratory fitness in those who are fit or increasing cardiorespiratory fitness in those who are not.

There is convincing evidence from prospective epidemiologic studies that higher level of baseline cardiorespiratory fitness is associated with a diminished risk of dying from cancer in various populations, independent of individuals' weight status (15–17,24). However, little information is available on the long-term effect of change in cardiorespiratory fitness on subsequent cancer mortality. Only one previous cohort study investigated if change in physical activity would modify risk of cancer mortality. According to that study, physical activity change was not associated with colon cancer mortality (42). One limitation of that study was using questionnaire to assess physical activity change. Because of the inherent self-report nature of the questionnaire, a mixture of social desirability bias and bias of estimating duration and frequency of physical activity (1,33), the effect of physical activity change on cancer mortality may have been over- or underestimated. Our study is unique in that it measured cardiorespiratory fitness by maximal exercise testing with a standardized protocol, which provides a quantitative estimate of recent physical activity habits, and therefore is a more objective measure of physical activity than self-reported questionnaires. The present study supports the hypothesis that cardiorespiratory fitness change is a predictor of cancer mortality and suggests that cardiorespiratory fitness change had an inverse dose–response relationship with cancer mortality. Our results expand the evidence supporting the relationship between change in fitness and longevity (14).

With the increasing prevalence of obesity worldwide, there is growing evidence of a link between obesity, defined using BMI, and cancer mortality (3,40). However, most studies include only a single measurement of BMI at baseline; very few studies have examined the effect of BMI change on cancer mortality (11,13,21). Two previous studies showed no significant relationship between BMI change and cancer mortality (13,21). One earlier study demonstrated that percent change in BMI from age 50 to baseline was positively associated with the risk of prostate cancer (11). All of these studies had some limitations because of insufficient lifestyle and medical information. In our study, all participants took part in the comprehensive medical examinations and completed standardized medical history questionnaires that included information on personal and family health histories and personal lifestyle habits. Therefore, not only were we able to exclude the effects of potential underlying or preexisting disease on associations between BMI change and cancer mortality, but we also were able to adjust for changes in lifestyle habits and medical conditions between baseline and follow-up examinations. After controlling for these confounders, BMI change was significantly associated with cancer mortality. However, after cardiorespiratory fitness change was taken into account, this association was attenuated. The results of our study indicated that the association of BMI change with cancer mortality may be modified by changes of cardiorespiratory fitness.

We also examined the effect of change in percent body fat, a better measure of body composition than BMI, on cancer mortality. Results of the present study indicated that individuals who became obese (assessed using body fat) had a higher risk of cancer mortality, which was somewhat different from BMI. When using BMI as the adiposity exposure, individuals who transitioned to becoming overweight

or obese (assessed using BMI) did not have a higher risk of cancer mortality. Because there are no other studies that examined the relationship between change in percent body fat and cancer mortality, we could not compare our results with other research. Additional studies in more diverse population samples of men and women with determination of cardiorespiratory fitness, BMI, and percent body fat are needed to better understand this complex issue.

It is worth noting that the current study was the first to investigate the combined association of cardiorespiratory fitness change and BMI change with cancer mortality. Our results revealed that men who lost cardiorespiratory fitness had a higher risk of cancer mortality than those who improved cardiorespiratory fitness, regardless of BMI change. In the Lipid Research Clinics Mortality Follow-up Study, no significant interactions were found between cardiorespiratory fitness and obesity (assessed using BMI) in predicting cancer mortality for men and women (15). In addition, two previous ACLS studies provided information on the joint associations between baseline cardiorespiratory fitness and BMI on cancer mortality. Earlier results from ACLS indicated that fit men and women had lower rates of cancer mortality than their unfit peers, irrespective of baseline BMI status (16,17). Our findings further confirm and expand upon the independent effect of cardiorespiratory fitness and BMI on cancer mortality; the effects of both baseline cardiorespiratory fitness and cardiorespiratory fitness change on cancer mortality were independent of baseline BMI and BMI change.

Many health benefits result from habitual physical activity and several plausible biological mechanisms may explain the protective association of maintaining and improving cardiorespiratory fitness. First, habitual physical activity may exert a beneficial effect on insulin metabolism by improving insulin sensitivity (30) and inhibiting excess secretion of insulin. One class of possible mechanisms between physical inactivity and cancer risk is that physical inactivity may cause insulin resistance and chronic hyperinsulinemia. Chronically elevated insulin levels may augment cancer development either directly by functioning as a growth factor, or indirectly by raising bioactivity of insulin-like growth factor 1 (IGF-1) through the downregulation of IGF-binding proteins (5). Second, habitual physical activity increases levels of antioxidant enzymes that may play a vital role in protecting against carcinogenesis from oxygen free radicals (12). DNA damage from oxygen free radicals may lead to cancer initiation through mutagenesis. By upregulating the activities of the antioxidant defense system, habitual physical activity may increase DNA-repair activity and diminish DNA damage (32). Third, habitual physical activity may play a protective role against cancer deaths by regulating some risk factors in cancer development, including decreasing levels of endogenous sexual hormones (testosterone, estradiol, and estrone) and increasing generation of sex hormone-binding globulin (22). Fourth, habitual physical activity can improve functioning of the immune system, contributing to protection against cancer development. Habitual physical activity may decrease the level of resting high-sensitivity C-reactive protein; increase the activity of macrophages, natural killer cells, and lymphokine-activated killer cells; and augment the secretion of interleukins 1 and 2 (23,35).

This study has several strengths. It included a large sample of men who ranged in age across the adult life span. The relatively long follow-up time (mean = 12.5 yr) allowed us to accumulate sufficient fatal cancer end points to evaluate the joint associations between changes in exposures and cancer mortality. Our mortality data were reliable because cancer deaths were ascertained by the National Death Index and death certificates from states in which participant death occurred. The extensive physical examination at baseline and follow-up allowed thorough evaluation of the presence or absence of lifestyle and disease conditions. Cardiorespiratory fitness was measured by a standardized exercise test on the treadmill in the laboratory, and BMI was calculated from laboratory-measured height and weight, which provided objective data for the analysis. We also had exposure data on percent body fat to include in the analyses.

This study also has limitations. A major limitation is that participants in the cohort were predominantly white and well-educated men from middle to upper socioeconomic strata. Therefore, the generalization of study findings to other groups should be done with caution. However, physiological characteristics of the ACLS population are similar to other representative populations of North American residents (7). The homogeneity of sociodemographic factors in our sample strengthens the internal validity of our findings by reducing potential confounding by unmeasured factors related to socioeconomic status, such as income or occupation. We did not have information about whether changes in cardiorespiratory fitness and body composition were intentional; thus, a cautious interpretation of these results is necessary. Nonetheless, to minimize potential confounding by unintentional changes in cardiorespiratory fitness and body composition due to disease, we excluded participants with subclinical conditions and various chronic diseases before follow-up. Also, by excluding individuals who had the test stopped by a physician for problematic symptoms and signs, or failed to reach 85% of age-predicted maximal heart rate, results may be biased against the hypothesis that fitness is inversely associated with cancer-related mortality. In addition, we did not have adequate data about dietary intake to include in this analysis. Nevertheless, a recent study showed that the relationship between physical activity and lung carcinoma was not changed after adjusting for intake of fruit, vegetables, and red meat (27). We have insufficient data to comment on cancer incidence among the survivors. Because of a limited number of women with at least two examinations, we were unable to conduct a meaningful parallel analysis in women. Therefore, women were excluded from this study.

In conclusion, cardiorespiratory fitness change was an important predictor of cancer mortality in men. Losing

cardiorespiratory fitness was associated with a higher risk of premature deaths from cancer in men, regardless of BMI change. Improving or maintaining cardiorespiratory fitness was associated with a reduction in risk of cancer death. In addition, improving or maintaining cardiorespiratory fitness may attenuate some potentially negative effects of BMI gain on cancer mortality. Thus, more efforts need to be taken to maintain or increase cardiorespiratory fitness, which may also lead to a healthy lifestyle and longevity.

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