Cardiorespiratory Fitness as a Predictor of Cancer Mortality Among Men With Pre-Diabetes and Diabetes

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OBJECTIVE — The purpose of this article was to examine the risk of cancer mortality across levels of fitness and to examine the fitness-mortality relation for site-specific cancers in men with pre-diabetes and diabetes.

RESEARCH DESIGN AND METHODS — We examined the fitness-mortality relation for all-cause and site-specific cancer mortality among 18,858 men with pre-diabetes and 2,805 men with diabetes (aged 46.3 ± 9.7 years [mean ± SD]) from the Aerobics Center Longitudinal Study. We identified 719 cancer deaths during 354,558 person-years of risk. The duration of follow-up was 16.4 ± 7.8 years (range <1–30.0 years).

RESULTS — In men with pre-diabetes, moderate (hazard ratio 0.71 [95% CI 0.57–0.88]) and high fitness (0.76 [0.60–0.96]) were associated with lower risks of cancer mortality compared with the low-fit group in a model adjusted for age, examination year, smoking, alcohol use, fasting glucose concentration, previous cancer, and BMI. Similarly, for individuals with diabetes, moderate (0.53 [0.35–0.82]) and high fitness (0.44 [0.26–0.73]) were associated with lower risks of cancer mortality compared with the low-fit group. Among all men, being fit was associated with a lower risk of mortality from gastrointestinal (0.55 [0.39–0.77]), colorectal (0.53 [0.30–0.96]), liver (0.22 [0.07–0.71]), and lung cancer (0.43 [0.30–0.60]).

CONCLUSIONS — In men with pre-diabetes and diabetes, higher levels of cardiorespiratory fitness were associated with lower risk of cancer mortality, particularly as a result of cancers of the gastrointestinal tract, compared with those who had low levels of fitness.

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Elevated concentrations of fasting glucose and the presence of diabetes are associated with an elevated risk for cardiovascular disease (CVD) mortality (1,2) and may alter the risk of cancer mortality (3–6). The presence of diabetes is most consistently associated with increased risk of cancer of the colon (3,7,8), pancreas (3,4,6), and, in men, liver (3,6). Studies also indicate that diabetes is associated with increased risk of kidney (6) and bladder cancer (3). Impaired glucose regulation is associated with an increased risk of esophageal, colon, liver, and pancreatic cancer in men (5,9). Several other studies indicate that there is a possible decreased risk of developing prostate cancer or do not show an association (10).

In individuals without diabetes, regular physical activity is associated with a reduced risk of developing colon cancer (11,12) and, in women, breast cancer (12,13). In reviews of the epidemiological evidence, a probable decrease in prostate cancer risk in physically active men and a possible risk reduction for lung cancer (12,14), as well as reduced overall cancer mortality among men (15), were found. In men with diabetes there is a reduced risk of all-cause and CVD mortality accompanying moderate or high levels of cardiorespiratory fitness (16–18).

Since the time of previous analyses, the continued growth of the Aerobics Center Longitudinal Study (ACLS) cohort and accompanying fatal events now allow us to examine the risk of cancer mortality across levels of fitness and to conduct site-specific cancer analyses. Although diabetes is a clearly defined clinical condition, its development is characterized as a progressive impairment in glucose regulation. Pre-diabetes is a term used to define individuals with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG). Individuals with a blood glucose concentration of 140–199 mg/dl after a 2-h oral glucose tolerance test are considered to have IGT, whereas individuals with a fasting glucose ≥100 mg/dl but <126 mg/dl are considered to have IFG (19). Rates of progression from IGT and IFG to diabetes vary widely, but in general the rate of progression is higher for IFG than for IGT. However, IGT is more common in most populations. All people with diabetes will pass through this intermediate phase of pre-diabetes (19,20). This phase may be a critical point for cancer prevention, detection, and treatment. The primary aims of this study were to *1*) examine the risk of cancer mortality across levels of fitness and 2) examine the fitness-mortality relation for site-specific cancers in men with pre-diabetes and diabetes.

RESEARCH DESIGN AND METHODS

The ACLS is a prospective cohort study composed of patients who received preventive medical examinations at Cooper Clinic in Dallas, Texas. The current analysis included 21,637 men aged 20–88 years (aged 46.3 ± 9.7 years [mean ± SD]) who completed a clinical examination including fitness testing between the years 1974 and 2003. The mean duration of follow-up was 16.4 ± 7.8 years (range <1–30 years) with a total of 354,558 person-years of

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Abbreviations: ACLS, Aerobics Center Longitudinal Study; CVD, cardiovascular disease; IFG, impaired fasting glucose; IGF, insulin-like growth factor; IGT, impaired glucose tolerance.

risk. During this period there were 2,033 deaths of which 719 (35.4%) were from cancer. Men with pre-diabetes and type 1 or type 2 diabetes were included in the analysis. The present study sample was limited to men because of the small number of women with pre-diabetes or diabetes in the ACLS cohort. Participants were predominantly (>95%) non-Hispanic white college graduates who were employed or previously employed in professional or executive occupations. Participants provided written informed consent to participate in the examination and follow-up study. The study protocol was approved annually by The Cooper Institute Institutional Review Board.

Mortality surveillance

We followed participants for mortality from their examination until date of death or until 31 December 2003 for survivors. The primary method of mortality surveillance was the National Death Index. The underlying cause of death was determined from the National Death Index report or by a nosologist's review of official death certificates obtained from the department of vital records in the decedent's state of residence. Cancer mortality was defined if the primary cause of death or if any of the five underlying causes of death were listed as cancer, using the ICD-9 codes 140–239 or ICD-10 codes C00–D48. Cancers of the gastrointestinal system were identified using ICD-9/10 codes 140.0–157.9/C00.1–C26.9. For neoplasms of lymphoid, hematologic, and related tissues, ICD-9/10 codes 201.0–205.9 and 238.6/C81.0–C96 were used. For cancer in specific sites, the following ICD-9/10 codes were used: colon, 153.0–153.9/C18.0–C18.9; pancreas, 157.0–157.9/C25.0–C25.9; lung, 162.2–163.0/C34.0–C34.9; liver, 155.0–155.9/C22.0–C22.9; and prostate, 186.0–186.9/C61.0–C61.9.

Clinical examination

The comprehensive health evaluation is described in detail elsewhere (16,17). Briefly, measured height and weight were used to assign men to normal weight (BMI ≤18.5 to <25.0 kg/m^2), overweight (BMI ≤25.0 to <30.0 kg/m^2), and obese (BMI ≥30.0 kg/m^2) categories (21). Pre-diabetes was defined as fasting glucose ≥100 mg/dl (≥5.6 mmol/l) but <126 mg/dl (7.0 mmol/l). Diabetes was defined as men who reported taking insulin, had a physician-diagnosed history of diabetes, or had a fasting plasma glucose concentration ≥126 mg/dl (≥7.0 mmol/l) at baseline (19). An antecubital venous blood sample was obtained, and glucose was determined with automated bioassays in the morning after an overnight fast of at least 12 h. Serum samples were analyzed in a laboratory that participates in and meets the quality control standards of the Centers of Disease Control and Prevention Lipid Standardization Program. Health histories and medication use were obtained from a self-administered questionnaire and verified by a physician during the examination. Based on self-report, smoking was defined as never smoked, past smoker, and current smoker, and four levels of alcohol intake were used to categorize participants: nondrinkers, low intake (1.0–140.0 g/week), moderate intake (140.1–280.0 g/week), and high intake (>280 g/week).

We assessed fitness with a symptom-limited maximal treadmill exercise test using a modified version of the Balke protocol (22). Specific details on the treadmill speed and grade of each exercise stage are described elsewhere (16,17). Exercise duration on this protocol is highly correlated (r = 0.92) with measured maximal oxygen uptake (23). We quantified exercise capacity as maximal METs (1 MET = 3.5 ml O_2 uptake · kg^{-1} · min^{-1}) using a previously validated regression formula [(1.44 × [exercise duration in minutes] + 14.99) ÷ 3.5] (23). Fitness was defined categorically as low (lowest 20%), moderate (middle 40%), or high (upper 40%) according to the previously published age-specific distribution of maximal exercise duration from the ACLS population (24,25).

Statistical analyses

Descriptive statistics were used to summarize baseline characteristics based on fitness level with grouping by diabetes status. Continuous variables were compared using Student's t test for comparison by survival status and ANOVA for comparison by fitness level. Categorical variables were compared using a χ^2 test. We used Cox proportional hazard models to estimate the hazard ratio (HR) and 95% CI of all-cause and cancer mortality. Unless otherwise noted, all mortality models included age, examination year, smoking, alcohol use, fasting glucose concentration, self-reported previous history of cancer, and BMI category.

The proportional hazards assumption was confirmed by examining the log cumulative survival plots for exposure categories. P values are two-sided, and P < 0.05 was accepted as statistically significant. All analyses were performed using SAS (version 9.0; SAS Institute, Cary, NC). Data are shown as means ± SD unless otherwise noted.

RESULTS — The baseline characteristics of participants across levels of fitness are described in Table 1. In individuals with pre-diabetes or diabetes, BMI and fasting glucose were lower, and prevalence of never smoking, regular alcohol use, and self-reported previous history of cancer were higher in the high-fit categories. Reported insulin use was highest in the high-fit category of individuals with diabetes.

In examining the risk associated with the potentially confounding variables, there was a higher risk of cancer death for both past smokers (HR 1.4 [95% CI 1.2–1.7]) and current smokers (2.2 [1.8–2.7]) compared with never smokers (adjusted for age and examination year). The BMI categories of obese (1.5 [1.2–1.9]) and overweight (1.2 [1.0–1.4]) were associated with higher risks of cancer mortality compared with normal weight. Self-reported history of previous cancer was associated with greater risk for colorectal (7.7 [2.4–24.4]) and prostate cancer mortality (3.3 [1.0–11.2]), but for no other site-specific or overall cancer mortality (1.8 [0.8–2.8]). In individuals with diabetes, insulin use (n = 378) was not associated with a higher risk of cancer mortality (1.4 [0.4–4.7]).

The risk of cancer mortality is lower across levels of fitness for individuals with diabetes, pre-diabetes, and a combined group compared with the low-fit group (Table 2). Among men with pre-diabetes, risk was lower in the moderate- (HR 0.71 [95% CI 0.57–0.88]) and high- (0.76 [0.60–0.96]) fit groups. In individuals with diabetes, risk was lower in both the moderate- (0.53 [0.35–0.82]) and high-fit (0.44 [0.26–0.74]) groups. In the combined group, moderate (0.67 [0.57–0.82]) and high fitness (0.70 [0.56–0.86) were again both associated with lower risk of cancer mortality compared with that for the low-fit group. To account for occult malignancies, we excluded from the analysis men with <3 years of follow-up (n = 339 with 27 cancer deaths); however, this exclusion had no substantial effect on the fitness-cancer mortality association nor did removing individuals with a reported history of previous cancer (n = 545 with 11 cancer deaths) or insu-

Table 1—*Baseline characteristics of 21,663 men with elevated blood glucose grouped by diabetic status and fitness level, ACLS, 1973–2003*

	Fitness level							
	Individuals with pre-diabetes (n = 18,858)				Individuals with diabetes (n = 2,805)			
	Low	Moderate	High	*P* value	Low	Moderate	High	*P* value
n	3,299	7,333	8,226		857	1,147	801	
Age (years)*	44.6 ± 9.3	45.8 ± 9.5	46.3 ± 9.7	<0.001	48.6 ± 10.0	50.1 ± 9.3	50.6 ± 9.9	<0.001
BMI (kg/m^2)*	29.8 ± 5.2	27.1 ± 3.3	25.3 ± 2.6	<0.001	31.0 ± 5.7	27.7 ± 3.7	25.1 ± 2.7	<0.001
Fasting glucose (mg/dl)	108.0 ± 6.3	106.7 ± 5.8	105.5 ± 5.1	0.002	150.0 ± 60.0	131.4 ± 45.0	125.6 ± 48.9	0.94
Previous cancer	63 (1.9)	144 (2.0)	250 (3.0)	<0.001	24 (2.8)	33 (2.9)	32 (4.0)	0.28
Alcohol use	2,414 (73.2)	5,697 (77.7)	6,387 (77.7)	<0.001	612 (71.4)	838 (73.1)	618 (77.2)	0.02
Insulin use	NA	NA	NA	NA	54 (6.3)	153 (13.3)	171 (21.4)	<0.001
Cigarette smoking								
Never	1,067 (32.3)	3,077 (41.9)	4,220 (51.3)	<0.001	268 (31.3)	498 (43.4)	437 (54.6)	<0.001
Past	1,167 (35.4)	2,743 (37.4)	3,182 (38.7)		325 (37.9)	458 (39.9)	296 (36.9)	
Current	1,065 (32.2)	1,513 (20.6)	824 (10.0)		264 (30.8)	191 (16.7)	68 (8.5)	

Data are reported as means ± SD or *n* (%). Fitness was defined categorically as low (lowest 20%), moderate (middle 40%), or high (upper 40%) of the previously published age-specific distribution of maximal exercise duration from the ACLS population (24). NA, not applicable.

lin users (n = 378 with 1 cancer death). Similarly, excluding individuals who died of lung cancer (n = 170) did not affect the association in the moderate- (0.71 [0.57–0.88]) or the high- fit group (0.75 [0.59–0.95]) compared with the low-fit group.

Because of the small number of individuals for some of the site-specific cancer deaths and the similar trends in all-cause cancer mortality across fitness levels, the pre-diabetic and diabetic groups were combined to examine site-specific cancer mortality (Fig. 1). Further, the moderate- and high-fit groups were combined (fit) and the low-fit group (unfit) was used as the reference group. Only specific cancer sites for which at least 15 deaths occurred were considered in this analysis. The adjusted risk associated with being fit for all-cancer mortality was 0.68 (95% CI 0.57–0.82). Being fit was associated with a lower risk of mortality from any gastrointestinal cancers (0.55 [0.39–0.77]) and lung cancer (0.43 [0.30–0.60]). Although the numbers of deaths were limited, we conducted preliminary analyses for site-specific gastrointestinal cancers. Being fit was associated with lower risks of colorectal (0.54 [0.30–0.96]) and liver (0.22 [0.07–0.71]) cancer mortality. The association between fitness and pancreatic cancer did not reach statistical significance (0.57 [0.31–1.04], P = 0.07), although the data suggested a reduced risk.

Among all men, we examined the risk of cancer mortality in fit individuals compared with unfit individuals within subgroups of BMI, smoking, and age. Within normal weight (n = 7,192 with 247 deaths; HR 0.52 [95% CI 0.37–0.73]) and overweight individuals (n = 10,632 with 356 deaths; 0.75 [0.59–0.97]), being fit was associated with lower risk of cancer mortality. For obese individuals (n = 3,813 with 114 deaths), there was a similar pattern of lower risk for fit men (0.76 [0.51–1.12]), but this value did not achieve statistical significance. For former smokers (n = 8,166 with 338 deaths; 0.75 [0.56–0.97]) and current smokers (n = 3,919, with 200 deaths; 0.66 [0.48–0.87]), being fit was associated with a lower risk of cancer mortality. Among never-smokers (n = 9,552 with 179 deaths), being fit was associated with a reduced risk (0.69 [0.46–1.04]), but this value did not achieve statistical significance. The interaction between fitness and age (individuals <55 years vs. ≥55

Table 2—*Relation between fitness and all-cause and cancer mortality in 21,663 men grouped by diabetic status, ACLS, 1973–2003*

	All-cause mortality			Cancer mortality		
	Deaths	Rate*	HR (95% CI)	Deaths	Rate*	HR (95% CI)
Pre-diabetes						
Low fit	482	48.6	1.0	157	24.4	1.0
Moderate fit	598	29.5	0.61 (0.54–0.69)	220	17.3	0.71 (0.57–0.88)
High fit	474	24.8	0.51 (0.44–0.59)	216	18.6	0.76 (0.60–0.97)
Diabetes						
Low fit	220	168.6	1.0	53	42.3	1.0
Moderate fit	170	87.4	0.52 (0.42–0.64)	45	22.5	0.53 (0.35–0.82)
High fit	92	61.4	0.36 (0.28–0.48)	28	18.6	0.44 (0.26–0.73)
Combined						
Low fit	707	92.6	1.0	210	27.0	1.0
Moderate fit	768	53.3	0.58 (0.52–0.64)	265	18.2	0.67 (0.56–0.82)
High fit	566	43.0	0.46 (0.41–0.53)	244	18.8	0.70 (0.56–0.86)

We used Cox proportional hazard models to estimate the HR including age, examination year, smoking, alcohol use, fasting glucose level, self-reported previous history of cancer, and BMI category as covariates. *Age-adjusted death rate (per 10,000 person-years).

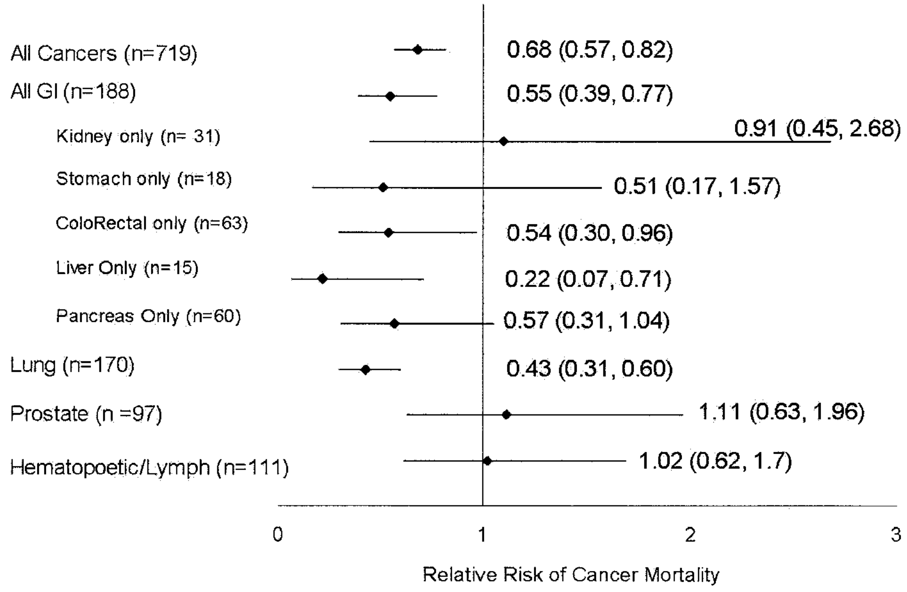

Figure 1—*Data from the combined cohort of 21,637 men. The figure depicts the risk of site-specific cancer mortality associated with being fit as defined by achieving at least a moderate level of fitness during maximal exercise testing. The reference group was the low-fit group (unfit). We used Cox proportional hazard models to estimate the HR, which included age, examination year, smoking, alcohol use, fasting glucose level, self-reported previous history of cancer, and BMI category as covariates. The error bars represent the 95% CIs. GI, gastrointestinal.*

years of age) was not statistically significant, although the data suggested a modest benefit from being fit.

CONCLUSIONS— The primary finding of this study was that higher levels of fitness were associated with a lower risk of cancer mortality in men with pre-diabetes or diabetes. The fitness-cancer mortality association was in large measure due to lower incidence of fatal gastrointestinal and lung cancers in men with higher levels of fitness. Although a large number of reports have shown physical activity to be associated with lower risk of a variety of cancers and cancer mortality in nondiabetic populations, to our knowledge this is the first report that examines the role of cardiorespiratory fitness and risk of fatal cancer events in individuals with pre-diabetes or diabetes. Whereas CVD is generally considered the primary cause of death in individuals with diabetes, it is noteworthy that 35.4% of the 2,033 deaths observed during this observational period were due to cancer.

Two potential mechanisms that may explain the lower risk of cancer mortality seen with higher levels of fitness in this population include concentrations of circulating insulin and insulin-like growth factor (IGF). Both insulin and IGF-1 are mitogenic, and many conditions associated with increased exposure to insulin and/or IGF-1, such as IGT and insulin resistance, are associated with a higher risk of cancer (26,27). Other potential mechanisms associated with higher levels of fitness include reduced exposure to sex hormones, inflammatory molecules/markers, reduced visceral fat, and improved antioxidant defense (27). Potential mechanisms that are associated with physical activity, which leads to higher fitness, and are specific to gastrointestinal health include decreased gastrointestinal transit time, lower bile secretion, altered prostaglandin synthesis, and gut flora (27).

Our findings confirm the results of numerous studies in nondiabetic populations that have shown that overweight and obesity are associated with higher risks of cancer incidence, reoccurrence, and mortality (28). Our findings that moderate and high levels of fitness were associated with ~30% lower risk for all-cause cancer mortality after adjustment for BMI are in accord with those of other reports showing that the higher risk of cancer mortality associated with having diabetes or glucose intolerance is independent of BMI (6,29). Several studies have shown that the risk for pancreatic cancer death increased with increasing duration of diabetes compared with that for individuals without diabetes (6,30). Bowker et al. (31) reported that in type 2 diabetes the use of sulfonylureas or insulin was associated with a higher risk of cancer-related mortality. We did not find insulin use to be associated with the risk of cancer mortality. The reason for the discrepancies in the two reports is unclear; however, in the ACLS population the moderate- and high-fit groups have a much higher prevalence of insulin use than the low fit population. In a subanalysis, we found that insulin users within each fitness stratum did not have higher mortality rates than men not using insulin within that fitness category. Hu et al. (32) reported that among diabetic women in the Nurses' Health Study, insulin users did not have a higher risk of CVD events compared with noninsulin users within the same fitness stratum. Thus, it is possible, although speculative, that any risk associated with the use of insulin may be negated by higher fitness levels.

This study has a number of limitations that deserve mention. Although the prevalence of IGT, IFG, and diabetes is higher among African Americans and Hispanic Americans, this cohort is male, predominantly Caucasian, well-educated, and middle-to-upper class, limiting the ability to generalize the study results but not affecting the internal validity. There is no reason to assume that the benefits of fitness would be diminished in other populations. Other reports on activity or fitness and health outcomes show similar patterns of association in other populations (33,34). A recent report from Albano et al. (35) showed that cancer death rates vary by level of education as well as by race. Caucasian and African-American men with <8 years of education had all-cancer death rates 3.5 and 2.7 times higher, respectively, than those of Caucasian and African-American men with >17 years of education. Therefore, our cohort may represent the group with the greatest chance of cancer survival. That we saw a significant difference in cancer mortality by fitness group is significant because this finding indicates that even those men with the best chance of survival have poorer outcomes if they have lower fitness versus men with increased fitness levels. IGT was not measured in this population. The use of IFG alone allowed us to identify 18,858 men with pre-diabetes; however, by using IGT alone or in addition to IFG, we would surely have identified a much greater number of men at risk of progressing to diabetes. Our results may underestimate the true impact of impaired glucose regulation on cancer outcomes. We lack detailed information about medication use, particularly insulin and sulfonylureas, which prevented us from examining potential differences in medication dose or duration across fitness groups. We also lacked detailed dietary data and time since diabetes diagnosis. However, given that adjusting for BMI did not diminish the fitness-cancer mortality relation, it is unlikely that accounting for dietary behaviors would have a major influence on the results. Duration of diabetes may be an important factor to consider in examining the BMI-mortality association, as it has been noted that individuals who have had diabetes for a long period may begin to lose weight over time owing to disease progression. Although we did identify inverse associations between fitness and some site-specific cancers, the findings should be interpreted cautiously because of the small number of site-specific cancer deaths in our cohort.

The present study provides additional support for the consensus public health guideline to obtain 150 min/week of moderate-intensity physical activity and supports that a strong recommendation be given to individuals with prediabetes or diabetes (36).

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