Cardiorespiratory Fitness as a Predictor of Cancer Mortality among Men with Pre-Diabetes and Diabetes

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Running Title: Cardiorespiratory fitness, diabetes, cancer

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Received for publication 21 August 2007 and accepted in revised form 20 December 2007.

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ABSTRACT

Objective: 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 (mean age [SD]: 46.3 [9.7] years) from the Aerobics Center Longitudinal Study. We identified 719 cancer deaths during 354,558 man-years of risk. The mean (SD) duration of follow-up was 16.4 (7.8) years (range < 1 yr to 30.0 years).

Results: In men with pre-diabetes, moderate (HR [95% CI]: 0.71 [0.57-0.88]) and high fitness (0.76 [0.60-0.96]) were associated with lower risk 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 body mass index. 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 risk 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 cancers of the gastrointestinal tract, compared with those who had low levels of fitness.
Elevated concentrations of fasting glucose and the presence of diabetes are associated with 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). The results of 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), female breast cancer (12,13). In a review of epidemiological evidence, Freidenreich et al. found 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). In men with diabetes there is a reduced risk of all-cause and CVD mortality accompanying moderate or high levels of cardiorespiratory fitness (fitness) (16-18).

Since 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, the development of diabetes is characterized as a progressive impaired 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 to 199 mg/dL after a 2-hour oral glucose tolerance test are considered to have IGT whereas individuals with a fasting glucose ≥100 mg/dL but <26 mg/dL are considered to have impaired fasting glucose (19). Rates of progression from IGT and IFG to diabetes vary widely but in general the rate of progression is higher for IFG than 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**

**Participants.** 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 to 88 years [mean age (SD): 46.3 (9.7) years] who completed a clinical examination including fitness testing between the years 1974 to 2003. The mean duration of follow-up was 16.4 (7.8) years (range <1 yr to 30 years) with a total of 354 558 person-years of 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 due to the small number of women with pre-diabetes or diabetes in the ACLS cohort. Participants were predominantly (>95%) non-Hispanic white, college graduates, and 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...
Mortality surveillance. We followed participants for mortality from their examination until date of death or until December 31, 2003 for survivors. The primary method of mortality surveillance was the National Death Index (NDI). The underlying cause of death was determined from the NDI report or by a nosologist’s review of official death certificates obtained from the department of vital records in the decedent’s state of residence. 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 International Classification of Diseases 9th revision codes 140 to 239 or 10th revision codes C00 to D48. Cancers of the gastrointestinal (GI) system were identified using ICD-9/10 codes 140.0-157.9/ C00.1-C26.9. Neoplasms of lymphoid, hematologic, and related tissues used ICD-9/10 codes 201.0-205.9, 238.6/C81.0-C96. 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 (18.5 ≤ BMI [body mass index] <25.0 kg/m²), overweight (25.0 ≤ BMI <30.0 kg/m²), and obese (BMI ≥30.0 kg/m²) 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 cases were 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 (22). 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 hrs. 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 (Low; 1.0-140.0 g/wk); Moderate-Intake (Moderate; 140.1-280.0 g/wk); and High-Intake (High; >280 g/wk).

We assessed fitness with a symptom-limited maximal treadmill exercise test using a modified version of the Balke protocol (23). 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 (24). We quantified exercise capacity as maximal metabolic equivalents (METs; 1 MET = 3.5 mL O₂ uptake kg⁻¹ min⁻¹) using a previously validated regression formula [(1.44 • (exercise duration, min) + 14.99) ÷ 3.5] (24). 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 (25,26).

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 the comparison by fitness level. Categorical variables were compared using chi-square. We used Cox proportional hazard models to estimate the hazard ratio (HR) and
95% confidence intervals (CI) of all-cause and cancer mortality. Unless otherwise noted all mortality models included age, examination year, smoking, alcohol use, fasting glucose concentration, self-report 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 (Cary, NC). Data are shown as mean (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-report previous history of cancer were higher in the high fitness categories. Reported insulin use was highest in the high fitness 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 [95% CI]: 1.4 [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 risk of cancer mortality compared with normal weight. Self-report history of previous cancer was associated with greater risk for colorectal cancer (7.7 [2.4-24.4]) and prostate cancer mortality (3.3 [1.0 – 11.2]), but not other site-specific nor of overall cancer mortality (1.8 [0.8 – 2.8]). In individuals with diabetes, insulin use (n=378) was not associated with 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 [95% CI]: 0.71 [0.57 - 0.88]) and high (0.76 [0.60 - 0.96]) fitness groups. In individuals with diabetes, risk was lower in both moderate (0.53 [0.35 - 0.82]) and high fitness (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 the low fit group. In order to account for occult malignancies, we excluded from the analysis men with less than 3 years of follow-up (n = 339 with 27 cancer deaths); however this 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 Insulin 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 to the low fit group.

Due to the small number of cases 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 (Figure 2 1). Further the moderate and high fitness groups were combined (fit) and the low fitness group (unfit) used as the reference group. Only specific cancer sites where at least 15 deaths occurred were considered in this analysis. The adjusted risk associated with being fit for all-cancer mortality was 0.68 (0.57 - 0.82). Being fit was associated with a lower risk of mortality from any GI 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 GI cancers. Being fit was associated with lower risk of colorectal (0.54 [0.30 -
Cardiorespiratory fitness, diabetes, cancer

The association between fitness with pancreatic cancer did not reach statistical significance (0.57 [0.31-1.04], P = 0.07) though the data suggested a reduced risk.

Among all men, we examined the risk of cancer mortality in fit individuals compared to unfit individuals within sub-groups of BMI, smoking, and age. Within normal weight (n = 7,192, with 247 deaths) (HR [95% CI]: 0.52 [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 did not achieve statistical significance. Within 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 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 did not achieve statistical significance. The interaction between fitness and age (individuals <55yr v. ≥55yrs 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 lower risk for cancer mortality in men with pre-diabetes or diabetes. The cancer mortality-fitness association was in large measure due to lower incidence of fatal GI and lung cancers in men with higher levels of fitness. While a large number of reports have found physical activity to be associated with lower risk of a variety of cancers and cancer mortality in non-diabetic 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. While 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 impaired glucose tolerance and insulin resistance, are associated with a higher risk of cancer (27,28). 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 (28). Potential mechanisms that are associated with physical activity, which leads to higher fitness, that are specific to GI health include decreased GI transit time, lower bile secretion, altered prostaglandin synthesis, and gut flora (28).

Our findings confirm numerous studies in non-diabetic populations that have reported that overweight and obesity are associated with higher risk of cancer incidence, reoccurrence, and cancer mortality (29). Our findings that moderate and high levels of fitness were associated with approximately 30% lower risk for all-cause cancer mortality after adjustment for BMI are in accord with other reports that the higher risk of cancer mortality associated with having diabetes or glucose intolerance is independent of BMI (30,31). Several studies have reported that the risk for pancreatic cancer death increased with increasing duration of diabetes compared to individuals without diabetes (31,32). Bowker et al reported that in type 2 diabetes the use of sulfonylureas or insulin was associated with higher risk of cancer-related
mortality (33). We did not find insulin use to be associated with 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. reported that among diabetic women in the Nurses Health Study, insulin users did not have a higher risk of CVD event when compared to non-insulin users within the same fitness stratum. (34) 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. While the prevalence of IGT, IFG and diabetes is higher among African American 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 (35,36). A recent report from Albano et al. showed that cancer death rates vary by level of education as well as by race. Caucasian and African American men with less than 8 years of education had all-cancer death rates 2.7 and 3.5 times higher than Caucasian and African American men with >17 y 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 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 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 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 due to disease progression. Although we did identify inverse associations between fitness and some site-specific cancers, the findings should be interpreted cautiously due to 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 minutes per week of moderate intensity physical activity and should be a strong recommendation given to individuals with pre-diabetes or diabetes (37).

ACKNOWLEDGMENTS

This study was supported in part by U.S. Public Health Service research grant AG06945 from the National Institute on Aging, Bethesda, Md. and by the Communities Foundation of Texas on recommendation of Nancy Ann and Ray L. Hunt.
We thank our participants, Kenneth Cooper, MD, for establishing the Aerobics Center Longitudinal Study, and the Cooper Clinic physicians, technicians, and staff.
REFERENCES


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<td>106.7 (5.8)</td>
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Data are reported as mean values (SD) unless otherwise noted. 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 (Blair, 1989).

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Data are reported as mean values (SD) unless otherwise noted.
* Age-adjusted death rate (per 10 000 man-years)
We used Cox proportional hazard models to estimate the hazard ratio including age, examination year, smoking, alcohol use, fasting glucose level, self-report previous history of cancer, and body mass index category as covariates.
FIGURE LEGEND

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 hazard ratio which included age, examination year, smoking, alcohol use, fasting glucose level, self-reported previous history of cancer, and body mass index category as covariates. The error bars represent the 95% confidence intervals.