Cardiorespiratory Fitness and Digestive Cancer Mortality: Findings from the Aerobics Center Longitudinal Study

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Abstract

Although higher levels of physical activity are inversely associated with risk of colon cancer, few prospective studies have evaluated overall digestive system cancer mortality in relation to cardiorespiratory fitness (CRF). The authors examined this association among 38,801 men ages 20 to 88 years who performed a maximal treadmill exercise test at baseline in the Aerobics Center Longitudinal Study (Dallas, TX) during 1974 to 2003. Mortality was assessed over 29 years of follow-up (1974-2003). Two hundred eighty-three digestive system cancer deaths occurred during a mean 17 years of observation. Age-adjusted mortality rates per 10,000 person-years according to low, moderate, and high CRF groups were 6.8, 4.0, and 3.3 for digestive system cancer (P_{trend} < 0.001). After adjustment for age, examination year, body mass index, smoking, drinking, family history of cancer, personal history of diabetes, hazard ratios (95% confidence intervals) for overall digestive cancer deaths for those in the middle and upper 40% of the distribution of CRF relative to those in the lowest 20% were 0.66 (0.49-0.88) and 0.56 (0.40-0.80), respectively. Being fit (the upper 80% of CRF) was associated with a lower risk of mortality from colon [0.61 (0.37-1.00)], colorectal [0.58 (0.37-0.92)], and liver cancer [0.28 (0.11-0.72)] compared with being unfit (the lowest 20% of CRF). These findings support a protective role of CRF against total digestive tract, colorectal, and liver cancer deaths in men. (Cancer Epidemiol Biomarkers Prev 2009;18(4):1111–7)

Introduction

Digestive system cancers include those of the alimentary canal below the neck (e.g., esophagus, stomach, small, and large intestines) and key digestive organs (pancreas, liver, and gallbladder). Considering all digestive cancers together, these constitute the second leading cause of cancer-related mortality of men in the United States (1). Of all digestive tract sites, colon and pancreas account for the majority of deaths (colon because it is so common and pancreas because it has such poor prognosis). The etiology of various digestive cancers is not fully understood. Several potential risk factors including genetic components, diet, smoking, and physical inactivity have been identified for colon cancer (2). However, other than smoking and diabetes (3, 4), few lifestyle factors have been linked to pancreatic cancer. Recent evidence suggests that insulin resistance and abnormal glucose metabolism, without diagnosis of diabetes, also may be risk factors for pancreatic cancer (5, 6).

Although higher levels of physical activity are inversely associated with risk of colon cancer (7, 8), the association between pancreatic cancer and physical activity remains inconclusive. Several studies have found an inverse relationship (9, 10), whereas other studies have reported no association (11-13). Very few cohort studies have reported on physical activity and other sites of digestive system cancer, and the findings are inconsistent (14, 15). No studies have been conducted to assess the association between physical activity and cancers of the liver or small intestine. There is some indication that greater amounts of activity are associated with higher risk of stomach (14) and bladder (15) cancer and lower risk of oral/esophagus cancer (15). It may be that measurement errors inherent in self-reported physical activity are partly responsible for these discrepant findings. Cardiorespiratory fitness (CRF), an objective and more reproducible measure, reflects the functional consequences of physical activity habits of the individual and therefore may provide a better exposure with which to evaluate associations with relevant health outcomes.

To the best of our knowledge, only one study (16) has been conducted on CRF and mortality from cancers of the gastrointestinal system among men. However, this study only examined men with pre-diabetes and diabetes. There is a lack of data in the general population. Because the 5-year survival rate for digestive cancers as a group is very low (~45%; <10% for some sites such as pancreas and esophagus), identification of modifiable risk factors for these deadly cancers may provide important opportunities for reducing overall cancer mortality (17). We therefore examined the association between CRF, objectively measured by maximal exercise test on a treadmill, and overall and site-specific digestive cancer mortality in men from the Aerobics Center

Received 9/10/08; revised 12/30/08; accepted 1/28/09; published OnlineFirst 3/17/09.
Grant support: NIH grants AG06945 and HL62508.
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doi:10.1158/1055-9965.EPI-08-0846

Longitudinal Study (ACLS). We tested the hypothesis that CRF is associated with cancers of the colorectum, pancreas, esophagus, stomach, or gallbladder, for which there is prior evidence of an association (7-10, 14, 15), and generated hypotheses on the association between cancers of the liver or small intestine and either CRF or other measures of physical activity, for which there are no prior data.

Materials and Methods

Study Population. The ACLS is an ongoing cohort study of patients who were examined during a preventive medical examination in Dallas, TX, between 1974 and 2003. This study was reviewed and approved by the Cooper Institute Institutional Review Board on an annual basis. The sample for the current analysis was 38,801 primarily White, well-educated, middle-to-upper socioeconomic status men ages 20 to 88 years. The inclusion criteria required that men had no prior history of cancer, ulcer disease, gallbladder trouble, jaundice, hepatitis, cirrhosis, or colon polyps. At baseline, all participants completed a symptom limited treadmill test. The men in the analyses reported here are very similar to the overall ACLS cohort, with only minor differences in some clinical variables. The death rate for the subgroup of men in this analysis is not significantly different from the age, risk factor, health status, and family history-adjusted rates for the overall cohort.

Baseline Examination. Participants arrived for the clinical examination after an overnight fast of at least 12 h and gave their written informed consent to participate in the examination and the follow-up study. Information was collected pertaining to personal and family health histories, fasting blood chemistry analyses, anthropometry, resting blood pressure and electrocardiogram, and a maximal graded exercise test. Examination methods and procedures followed a standard manual of operations as described previously (18). Briefly, body mass index (BMI) was computed from measured height and weight (kg/m^2). Resting blood pressure was recorded as the first and fifth Korotkoff sounds by ausculatatory methods. Serum samples were analyzed for lipids and glucose using standardized automated bioassays by a laboratory that participates in the Centers for Disease Control and Prevention Lipid Standardization Program and meets its quality-control standards. Information on smoking habits (never, past, and current smoker), alcohol intake (number of drinks per week), personal history of diabetes, and family (from parents and siblings; first-degree relatives) history of cancer from all-cause was obtained from a standardized questionnaire. One unit of alcohol is defined as 12 ounces (3.41 dL) of beer, 5 ounces (1.421 dL) of wine, or 1.5 ounces (0.4262 dL) of hard liquor.

We determined CRF at the baseline examination using a maximal exercise test on a treadmill. CRF was assessed as the duration of the exercise test using a modified Balke protocol (18, 19). The treadmill speed was 88 m/min for the first 25 min. During this time, the grade was 0% for the first minute and 2% the second minute and increased 1% for each minute. After 25 min, the grade remained constant while the speed increased 5.4 m/min each minute until test termination. Patients were encouraged to give a maximal effort during the test. Men included in the present analyses reached at least 85% of their age-predicted maximal heart rate [220-age (years) beats per minute] on the test. The duration of the maximal exercise treadmill test on this protocol is highly (and positively) correlated with directly measured maximal oxygen uptake in men (ref. 20; $r = 0.92$), an accepted measure of CRF. Maximal metabolic equivalents (MET; 1 MET = 3.5 mL O_2 uptake/kg/min) were estimated from the final treadmill speed and grade (21). We used our previously published age-specific distribution of treadmill duration from the overall ACLS population to define fitness groups as low (lowest 20%), moderate (middle 40%), and high (upper 40%) to maintain consistency in the study methods and because we have found that a low level of fitness, defined in this way, is an independent predictor of mortality (18, 22) and morbidity (23). The respective cut points for total treadmill time and METs in the low, moderate, and high fitness groups were described in detail in a recent report (23).

Ascertainment of Digestive Cancer Death. All participants were followed from the date of their baseline examination until their date of death or December 31, 2003. The National Death Index was the primary data source for mortality surveillance. The National Death Index has been shown to be an accurate method of ascertaining deaths in observational studies, with high sensitivity (96%) and specificity (100%; ref. 24). 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. Causes of cancer death were identified using *International Classification of Diseases, Ninth Revision* codes for deaths occurring before 1999 and *International Classification of Diseases, Tenth Revision* codes (in parentheses) for deaths during 1999 to 2003. Our primary outcome for this analysis was death from digestive cancers, 150-159 (C15-C26), and our secondary mortality outcomes were esophagus, 150 (C15); stomach, 151 (C16); small intestine, 152 (C17); colon, 153 (C18); rectum, 154 (C19-C21); liver, 155 (C22); gallbladder and intrahepatic bile ducts, 156 (C23-C24); pancreas, 157 (C25); and other and ill-defined digestive organs, 158-159 (C26).

Statistical Analysis. Baseline characteristics of the population were calculated for the entire study group and by CRF categories. Differences in covariates were assessed using *F* tests. Kaplan-Meier plots were used to compare survival curves. The crude and multivariate-adjusted log-rank tests were used to determine significance. Cox proportional hazards models were used to estimate adjusted hazard ratios (HR), associated 95% confidence intervals (95% CI), mortality rates (deaths/10,000 person-years of follow-up), and linear trends of mortality for levels of each fitness category. When calculating HR, the low fitness group was used as the reference category. Multivariable-adjusted models controlled for the potential confounding effects of baseline age (years), examination year, smoking (never, past, or current smoker), alcohol intake (drinks per week), and family history of cancer (whether present). Examination year was included as a covariate to control for variation in the length of follow-up in this ongoing study. We

Table 1. Baseline characteristics according to CRF, ACLS, Dallas, TX, 1974-2003

Characteristics	All (n = 38,801)	CRF			P_{trend}
		Low (n = 6,665)	Moderate (n = 15,315)	High (n = 16,821)	
Mean (SD) age (y)	43.8 (9.7)	43.6 (9.4)	44.0 (9.6)	43.6 (9.9)	<0.001
Mean (SD) height (cm)	178.9 (6.9)	178.0 (8.6)	179.0 (6.6)	179.3 (6.5)	<0.001
Mean (SD) BMI (kg/m^2)	26.3 (3.4)	28.6 (4.2)	26.7 (3.2)	24.9 (2.5)	<0.001
Mean (SD) METs achieved during the treadmill test	11.6 (2.5)	8.5 (1.3)	10.7 (1.2)	13.7 (1.9)	<0.001
Mean (SD) treadmill time duration (min)	17.9 (5.2)	11.1 (2.7)	16.0 (2.5)	22.3 (3.5)	<0.001
Mean (SD) lipids (mmol/L)					
Total cholesterol	5.5 (1.1)	5.7 (1.1)	5.5 (1.0)	5.3 (1.2)	<0.001
High-density lipoprotein-cholesterol	1.2 (0.3)	1.0 (0.3)	1.1 (0.3)	1.3 (0.3)	<0.001
Triglycerides	1.6 (1.4)	2.2 (2.1)	1.7 (1.2)	1.2 (1.0)	<0.001
Mean (SD) fasting blood glucose (mmol/L)	5.6 (2.8)	5.8 (1.5)	5.6 (1.0)	5.5 (4.1)	<0.001
Mean (SD) blood pressure (mm Hg)					
Systolic	122 (14)	124 (14)	122 (13)	120 (13)	<0.001
Diastolic	81 (10)	84 (10)	82 (10)	79 (9)	<0.001
Cigarette smoking (%)					
Never	70.8	59.0	68.9	77.2	
Past	10.8	7.4	10.2	12.7	<0.001
Current	18.4	33.6	20.9	10.1	
Mean (SD) alcohol drinking (drinks/wk)	7.9 (11.4)	8.3 (11.5)	8.1 (11.6)	7.5 (11.2)	<0.001
Diabetes* (%)	5.4	10.1	5.7	3.3	<0.001
Family history of cancer (%)	1.0	0.8	1.2	1.1	0.04

*Diabetes was defined as glucose ≥126 mg/dL or history of physician-diagnosed diabetes.

conducted additional analyses that further adjusted for baseline differences in two factors that could plausibly mediate the association between CRF and digestive cancer mortality: BMI (<25 versus ≥25 kg/m^2) and diabetes (whether diagnosed before or at the examination). Unfortunately, we have no information on nonsteroidal anti-inflammatory drug usage to include in the model. Cumulative hazards plots grouped by exposure had no appreciable violations of the proportional hazards assumption.

Next, we conducted Cox regression analyses of CRF stratified by categories of BMI (<25 versus ≥25 kg/m^2). We also examined the risk of total digestive system cancer across increments of METs to assess the shape of the fitness-mortality curve. Finally, we explored the site-specific cancer deaths across fitness levels. Statistical analyses were done using SAS (version 9.1; SAS Institute) software. All P values were calculated based on two-sided hypothesis tests, and 95% CIs were calculated at the 95% level.

Results

At baseline, the mean (SD) age of the study participants was 43.8 (9.7) years, the mean treadmill test duration was 17.9 (5.2) min, and the mean CRF measure was 11.6 (2.5) METs. The distribution of participant characteristics for several digestive cancer risk factors is given in Table 1 across categories of CRF. Men in the high fitness group were more likely to have a lower BMI, to have more favorable lipid and blood pressure profiles, to be nonsmokers, and to have less diabetes compared with men with low CRF. The Kaplan-Meier plot depicts the total digestive cancer death rates by fitness group (Fig. 1). After adjusting for all the risk factors, the resulting log-rank test did not change materially (χ^2 = 14.9; P < 0.001).

In a mean length of 17 years of follow-up and 661,169 person-years of observation, 283 total digestive cancer deaths were identified. A steep inverse gradient (P_{trend} < 0.001) of total digestive cancer mortality rates was observed across CRF groups (Table 2). After adjusting for potential confounders (age, examination year, smoking status, alcohol intake, and family history of cancer), men with moderate and high CRF had 37% and 49% lower risk of death from digestive cancers, respectively, than did men with low CRF (P_{trend} < 0.001). Additional adjustment for BMI and personal history of diabetes did not materially change the magnitude or the pattern of the association.

To explore possible effect modification of the association between CRF and total digestive cancer by BMI, we stratified the analysis according to BMI category (<25 and ≥25 kg/m^2; Table 2). The age-adjusted death rate was inversely related to CRF within the normal weight (18.5 < BMI < 25 kg/m^2; P_{trend} = 0.009) and overweight/obese [BMI ≥ 25 kg/m^2; P_{trend} = 0.003; because of the small number of deaths (only 1 death) in

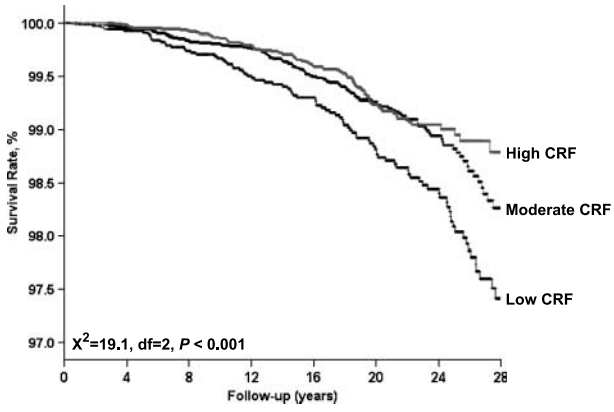

Figure 1. Kaplan-Meier plots for mortality due to total digestive system cancer, ACLS, Dallas, TX, 1974-2003.

Table 2. Rates and HR for digestive system cancer mortality by CRF groups, ACLS, Dallas, TX, 1974-2003

	Deaths from digestive system cancer	Mortality rate*	HR† (95% CI†)	HR‡ (95% CI‡)
All men (n = 38,801)				
Low CRF	90	6.8	1.00 (reference)	1.00 (reference)
Moderate CRF	110	4.0	0.63 (0.47-0.85)	0.66 (0.49-0.88)
High CRF	83	3.3	0.51 (0.37-0.70)	0.56 (0.40-0.80)
P_{trend}		<0.001	<0.001	0.001
Men with BMI < 25 kg/m^2 (n = 15,422)				
Low CRF	18	5.7	1.00 (reference)	
Moderate CRF	37	3.8	0.75 (0.42-1.37)	
High CRF	40	2.7	0.51 (0.28-0.94)	
P_{trend}		0.009	0.02	
Men with BMI ≥ 25 kg/m^2 (n = 23,379)				
Low CRF	72	7.2	1.00 (reference)	
Moderate CRF	73	4.1	0.60 (0.42-0.85)	
High CRF	43	4.2	0.62 (0.418-0.94)	
P_{trend}		0.003	0.01	

*Rate is expressed as per 10,000 person-years and adjusted for age.
†Model 1: adjusted for age, examination year, smoking status (never, past, or current), alcohol intake (drinks per week), and family history of cancer (present or not).
‡Model 2: adjusted for all variables in model 1 plus BMI (<25 versus ≥ 25 kg/m^2) and personal history of diabetes (present or not).

obese (BMI ≥ 30 kg/m^2) men with high CRF, we combined the overweight and obese groups]. Similar patterns of association were noted after adjusting for confounders.

To examine the dose-response characteristics between CRF levels and total digestive cancer mortality in our population of men, we computed the age-adjusted death rates (per 10,000 person-years) for categories of CRF defined by increments of 1 MET across the range of 7 to 14 METs (Fig. 2). An exercise capacity of <8 METs was associated with >3-fold higher risk of total digestive cancer mortality compared with men having a capacity of ≥11 METs (P_{trend} < 0.001). Across incremental MET levels (from <7.0 to ≥14.0 METs), the covariates (including BMI and diabetes)-adjusted HR (95% CI) of mortality were 1.0, 0.75 (0.43-1.30), 0.48 (0.30-0.76), 0.39 (0.23-0.66), 0.43 (0.26-0.71), 0.36 (0.21-0.63), 0.38 (0.21-0.69), 0.28 (0.15-0.53), and 0.38 (0.19-0.76; P_{trend} < 0.001). Excluding the first 5-year of follow-up did not materially change the magnitude and the pattern of the association (P_{trend} < 0.001).

Because of the small number of site-specific cancer deaths and the similar trends in total digestive cancer mortality across fitness levels, the moderate- and high-fit groups were combined into one group (fit) and the low-fit group (unfit) was used as the reference (Fig. 3). For all digestive system cancers combined, the adjusted mortality risk associated with being fit was 0.62 (95% CI, 0.47-0.82). Being fit was associated with a lower risk of mortality from colon cancer [0.61 (0.37-1.00)], colorectal cancer [0.58 (0.37-0.92)], and liver cancer [0.28 (0.11-0.72)]. The associations between fitness and small intestine, gallbladder, and pancreatic cancer were suggestive of a reduced risk, but the HR (95% CI) did not reach statistical significance [0.36 (0.02-6.61), 0.83 (0.09-7.74), and 0.75 (0.45-1.24), respectively].

Because baseline age may influence results, we conducted additional sensitivity analyses by repeating the above analysis in men with baseline age 35 to 74 years (n = 32,137). The patterns of the association between fitness and digestive cancer mortality across different baseline age ranges were similar (data not shown).

Discussion

In this study, we observed an inverse association between CRF and risk of total digestive cancer mortality, with men in the moderate and high CRF groups showing 34% and 44% lower risk, respectively, of dying of digestive cancers after adjustment of confounding by age, smoking, drinking, and family history of cancer. Excluding men with pre-diabetes and diabetes did not materially change the results. Men with an exercise capacity <8 METs had >3-fold higher risk of dying of digestive cancer compared with those with higher MET level (≥11). These data suggest that an exercise capacity of at least 8 METs may be needed to provide substantially protective benefits.

To the best of our knowledge, only one previous study has assessed the association of CRF with risk of dying of

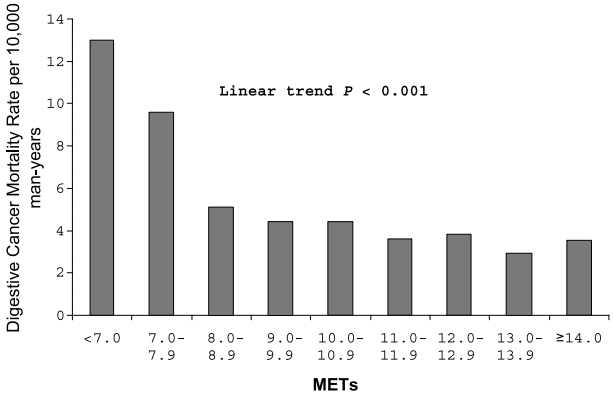

Figure 2. Age-adjusted mortality rates (per 10,000 man-years) of total digestive system cancer by CRF levels quantified in 1-MET increments obtained during a maximal treadmill test in men, ACLS, Dallas, TX, 1974-2003. Number at risk (number of cases) in <7.0, 7.0 to 7.9, 8.0 to 8.9, 9.0 to 9.9, 10.0 to 10.9, 11.0 to 11.9, 12.0 to 12.9, 13.0 to 13.9, and ≥14.0 was 859 (33), 1,096 (27), 4,465 (53), 4,135 (33), 6,014 (44), 5,827 (30), 5,180 (25), 5,872 (20), and 5,353 (18).

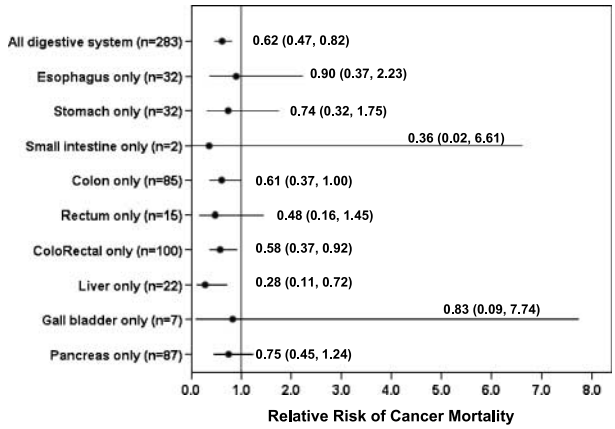

Figure 3. Risk of site-specific digestive cancer mortality associated with being fit (the upper 80% of the distribution of CRF) as defined by achieving at least a moderate level of fitness during maximal exercise testing, ACLS, Dallas, TX, 1974-2003. The reference group was the unfit group (the lowest 20% of the distribution of CRF). We used Cox proportional hazards models to estimate the HR, which include age, examination year, smoking, alcohol intake, personal history of diabetes, family history of cancer, and BMI as covariates. *Bars,* 95% CI.

digestive cancer (16). However, that article examined the role of CRF and risk of fatal digestive cancer events in men with pre-diabetes or diabetes, whereas our article examined a much broader male population. Our results were similar to the previous article's findings and show that higher levels of CRF are associated with substantially lower risk of dying from digestive cancers (including colorectal and liver cancers). In that study, Thompson et al. (16) found men who were fit, as defined by achieving at least a moderate level of fitness during a maximal exercise test, had a 45% lower risk of digestive cancer mortality. In our study, we found that men with at least a moderate fitness level had a 34% lower digestive cancer risk than did men with low CRF. In our study, it appeared that, beyond a CRF level of 8 METs (Fig. 2), there were no substantial decreases in risk of digestive cancer death. This finding of an apparent CRF threshold adds insight into the association between CRF and digestive cancer death. Although CRF has a genetic component (25-40%; refs. 25, 26), it is clear that usual physical activity habits are the primary determinant of fitness. CRF can be enhanced in most individuals through participation in moderate and vigorous physical activities, such as brisk walking, bicycling, and jogging, for ≥30 min on most days of the week (~8 kcal/kg/wk; ref. 27). This consensus public health recommendation will produce a maximal capacity of at least 8 METs in most individuals.

Our finding of an inverse association between physical activity and colorectal cancer risk is consistent with evidence from previous studies (28-30). A previous meta-analysis estimated ~20% to 40% lower risk of colon cancer for high versus low leisure-time physical activity (29). In our study, we found men with at least a moderate fitness level had a 42% lower risk of death from colorectal cancer than did men with low CRF.

We did not observe a significant inverse association between CRF and mortality from pancreatic cancer, a finding that is consistent with many studies (12, 13, 16, 31-35) but discrepant from others (9, 10, 36). However, we did observe a 25% reduction in mortality at this site among more fit men, but the small number of deaths limited the precision of our estimates. Given that the strength of the CRF-pancreatic cancer association was somewhat weaker than the risk estimates we observed for colorectal and liver cancer mortality (HR, 0.28-0.58), it may be that the association between pancreatic cancer and activity-related exposure is weaker. Because physical activity is a complex behavior and often imprecisely measured in epidemiologic studies, the combination of exposure measurement error and a weaker association may account for the heterogeneity in previous reports using self-reported physical activity as the exposure. We speculate that these two factors may be contributing to the inconsistency in previous findings. Future studies will be warranted to further explore this issue and confirm the present findings.

Little information is available on the association between physical activity or CRF and other types of digestive cancer. In this study, higher fitness was shown to be associated with significantly lower risk of liver cancer. This is consistent with the findings among men with pre-diabetes and diabetes (16). The findings with regard to stomach cancer have not been consistent. We found an inverse trend on stomach cancer as well as in men with diabetes (16), although the trend was not statistically significant possibly due to the small number of deaths. The British Regional Heart Study found the same nonsignificant inverse trend between physical activity and stomach cancer (15). In contrast, the Japanese Hawaiian Cancer Study found increased activity to be associated with higher risk of stomach cancer, but the results were preliminary (14). Only one previous study reported a lower risk of oral/esophagus cancer with moderate vigorous activity (15). We observed a similar trend. Regarding bladder cancer, neither the Japanese Hawaiian Cancer Study (14) nor the current study found any association between activity and urinary bladder cancer; however, the British Regional Heart Study (15) showed significant increase in risk of bladder cancer among men who were vigorously active. Finally, we observed a nonstatistically significant lower risk of small intestine cancer among men with high fitness. Despite the absence of a prior hypothesis for the sites shown in Fig. 3, fitness appeared to be protective overall. These findings may provide clues for future research, in studies having larger sample sizes and employing rigorous methods of measuring fitness (such as were available to us).

Several biological mechanisms have been proposed to explain how higher levels of physical activity may protect against cancer in general and cancers of the digestive tract in particular. Physical activity is known to affect cancer development through immune system function, insulin sensitivity, and growth factor levels (37-39). It is unclear which mechanisms are important for different sites of digestive cancer. Any or all of these mechanisms may influence general susceptibility to cancer (38). There are links between colorectal cancer and central obesity (40, 41) and insulin and the insulin-like growth factor-I axis (42). Biologically, it appears that insulin resistance and abnormal glucose metabolism may

be related to increased risk of pancreatic cancer. We specifically examined two potential obesity-related mediators of the association (BMI and diabetes) in our sequential models and found that adjustment for these factors had relatively little influence on the strength of associations observed. This finding suggests adiposity and diabetes, as measured in our study, are not strong mediators of the associations of interest. Evidence suggests that higher plasma glucose level after an oral glucose load is predictive of pancreatic cancer mortality (5) as is a diagnosis of diabetes (4). However, little is known about the specific mechanisms between physical activity and stomach, small intestine, liver, bladder, and other digestive tract cancers. Potential mechanisms, specific to gastrointestinal health, include decreased fecal transit time, reduced bile secretion, altered prostaglandin synthesis, and gut flora (43). Additional research is needed to clarify the complicated association between activity and digestive tract cancers.

This large prospective study with a long follow-up interval has several strengths that should be considered. First, it is rare to have a measure of fitness in a prospective study of digestive cancer mortality. Second, our extensive baseline examination to evaluate health status (such as cancer and diabetes), careful measurement of body size, and other lifestyle factors addresses the potential for confounding by these factors to influence our results. Our study also has limitations that should be considered. First, we are unable to adjust for dietary factors such as fiber and saturated fat intake in the current study. Second, although we had a hard endpoint of digestive cancer mortality, it is not possible to determine completely whether higher levels of CRF protected men against developing cancer or whether it aided their survival after their diagnosis. However, the low 5-year survival rates for many of these cancers (especially pancreatic and liver cancer) make incidence and mortality essentially interchangeable (as virtually everyone diagnosed with the cancer dies of the cancer; ref. 44). Fitness also appeared to be protective against esophagus, stomach, small intestine, and gallbladder cancer mortality, although statistical significance was not achieved because of the small number of deaths associated with these sites. Third, few studies have examined the relationship between physical activity and cancer risk in anatomic segments of the colon with conflicting results (45). Unfortunately, we do not have data regarding specific subsite colon cancer risk. Another limitation to the current findings is that the study population consists mainly of White men in the middle and upper socioeconomic strata; thus, results may not be generalizable to other adult populations but should not affect the internal validity of our findings. In terms of exposure assessment, we classified men at study enrollment, but in the present analysis we were unable to evaluate the effect of changes in fitness over time on our outcomes. It is possible, but not very likely, that many low-fit men increased their fitness levels at some point in the follow-up interval. Additionally, others may have experienced decreases in this component. Therefore, we cannot examine whether changes in fitness and other exposures occurred during follow-up. However, such misclassification of exposure would likely underestimate the magnitude of the association observed in the present study. We had insufficient information to assess the effect of aspirin and other nonsteroidal anti-inflammatory drugs on outcome. Future studies should include such information whenever possible.

In summary, the findings from this study provide evidence supporting a protective role of CRF on risk of digestive cancer mortality and that a relatively low threshold of CRF may be needed. The consensus public health guideline to obtain 150 min/wk of moderate-intensity physical activity will improve fitness levels and produce this threshold in most individuals. Given the public health burden of digestive cancer, future research needs to determine the specific biological characteristics of exercise related to digestive cancer risk and if a dose-response relationship exists.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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We thank Dr. Kenneth H. Cooper for establishing the ACLS, the Cooper Clinic physicians and technicians for collecting the baseline data, and the staff at the Cooper Institute for data management.

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