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Cardiorespiratory fitness and risk of prostate cancer: Findings from the Aerobics Center Longitudinal Study

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Abstract

Objective—To examine the association between cardiorespiratory fitness (CRF) and risk of incident prostate cancer (PrCA).

Methods—Participants were 19,042 male subjects in the Aerobics Center Longitudinal Study (ACLS), ages 20 to 82 years, who received a baseline medical examination including a maximal treadmill exercise test between 1976 and 2003. CRF levels were defined as low (lowest 20%), moderate (middle 40%), and high (upper 40%) according to age-specific distribution of treadmill duration from the overall ACLS population. PrCA was assessed from responses to mail-back health surveys during 1982 to 2004. Cox proportional hazards regression models, adjusted for potential confounders, were used to compute hazard ratios (HRs), 95% confidence intervals (95% CIs), and incidence rates (per 10,000 person-years of follow-up).

Results—A total of 634 men reported a diagnosis of incident PrCA during an average of 9.3 ± 7.1 years of follow-up. Adjusted HRs (95% CIs) in men with moderate and high CRF relative to low CRF were, 1.68 (1.13–2.48) and 1.74 (1.15–2.62), respectively. The positive association between CRF and PrCA was observed only in the strata of men who were not obese, had ≥ 1 follow-up examination, or who were diagnosed ≤ 1995.

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Conflicts of interest statement
None declared.

Conclusions—Rather than revealing a causal relationship, the unexpected positive association observed between CRF and incident PrCA is most likely due to a screening/detection bias in more fit men who also are more health-conscious. Results have important implications for understanding the health-related factors that predispose men to receive PrCA screening that may lead to over-detection of indolent disease.

Keywords

Cardiorespiratory fitness; Prostate cancer; Cohort studies; Attitude to health; Screening/detection bias

1. Introduction

Prostate cancer (PrCA) is the most common cancer among men in the United States. Despite relatively high incidence, PrCA has among the lowest virulence of any cancer [1]. According to the American Cancer Society, over 192,000 new cases of invasive PrCA were diagnosed in 2009, accounting for 25% of all incident cancers in men. Approximately 27,400 men died of PrCA in 2009, accounting for 9% of all male cancer deaths [2]. Though the etiology of PrCA is poorly understood, there are several potential genetic and environmental/lifestyle risk factors associated with the disease, such as familial aggregation, race/ethnicity, genetic variants in candidate genes (e.g., single nucleotide polymorphisms), obesity, tobacco use, diet, and physical inactivity [3–6].

Physical activity may prevent the occurrence of PrCA through several hypothesized mechanisms, including reduced concentration of circulating testosterone [7,8], modifications in androgen receptor [8], obesity-related effects [9,10], reduced inflammation [11,12], and enhanced immune function [13]. Results showing that higher endogenous testosterone levels are associated with increased PrCA risk [14] and that elevated testosterone levels are seen among men with PrCA [15] are consistent with the fact that the vast majority of PrCAs are hormone dependent [7]. Therefore, the observation of acute decreases in testosterone levels after exercise sessions [16], and decreased testosterone among male athletes compared to nonathletes [17] are intriguing. Several prospective studies have suggested that physical activity may reduce the risk of PrCA morbidity and mortality [18–20]. However, null or positive associations between physical activity and risk of PrCA also have been reported [21–26]. This inconsistency may be due to misclassification of exposure or recall bias in physical activity using methods typically employed in large epidemiological studies or problems with outcome ascertainment.

After an extensive literature review by an expert committee charged with reviewing the scientific basis for the 2008 federal physical activity guidelines, there was a lack of evidence to confirm a protective role of physical activity in PrCA prevention [27]. It has been suggested that cardiorespiratory fitness (CRF), an objective marker for physical activity habits, is a stronger predictor of overall mortality than self-reported physical activity [28–30]. We are aware of only one study on the association of CRF with PrCA, an earlier report from the Aerobic Center Longitudinal Study (ACLS) in which we reported a significant reduction in PrCA risk in men with moderate to high CRF [31]. However, there were only 94 incident cases available for analysis at that time, and those data were collected prior to substantial increases in PrCA screening that occurred in the mid-1990s. Thus, the purpose of this study was to extend our earlier work by including a larger number of participants, longer period of follow-up, more incident cases, and better control of potential confounders of the CRF-PrCA association.

2. Materials and methods

2.1. Study population

Between 1976 and 2003, 20,356 men aged 20–82 years received a medical examination, had at least one mail-back survey at the Cooper Clinic in Dallas, TX, and were enrolled in the ACLS, a prospective epidemiological investigation. The study protocol was approved annually by the Institutional Review Board of the Cooper Institute, and all participants gave informed consent to participate in the clinical examination and follow-up study.

Participants were not included in the present analyses if, at baseline, they did not achieve at least 85% of age-predicted maximal heart rate (220-age) during the treadmill test (n=280), they reported history of myocardial infarction (n=70), stroke (n=19), or cancer (n=188), they were underweight (BMI<18.5 kg/m^2) (n=665), or they had any exposure variables missing (n=92). These criteria resulted in 19,042 men, ranging in age from 20–82 years, who were followed up from the date of their baseline examination until their date of PrCA, or the date of their last survey when they reported being free of PrCA. Among these men, 9,092 (47.8%) men also retuned to the Cooper Clinic after their baseline examination to receive one or more follow-up clinical examination. These follow-up examinations were conducted using the same protocols as the baseline examination. A majority of them were white (>95%), approximately 80% were college graduates, and most worked in (or were retired from) professional or executive positions. The participants had no prior history of cancer, heart attack or stroke. Study participants came to the clinic for periodic preventive health examinations and to receive 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; some were referred by their personal physicians; while the rest were self-referred.

2.2. Baseline examination

Each individual underwent a thorough medical evaluation that included personal and family health history, a physical examination, a questionnaire on health habits, anthropometry measurement, fasting blood chemistry analyses, resting blood pressure and electrocardiogram, and a maximal exercise test [32]. Examination methods and procedures followed a standard manual of operations, as described in detail previously [32]. Briefly, body mass and stature were measure using a standard physician's scale and stadiometer, and the body mass index [BMI = weight(kg)/height(m)^2] was calculated. Waist circumference was measured level with the umbilicus. Resting blood pressure was recorded as the first and fifth Korotkoff sounds by ausculatatory methods. Men who reported a history of physician-diagnosed hypertension or who had blood pressures ≥ 140/90 mmHg at the examination were classified as having hypertension. Serum samples were analyzed for lipids and glucose using standardized automated bioassays by a laboratory that participates in and meets quality control standards of the CDC Lipid Standardization Program. Hypercholesterolemia was defined as a fasting total cholesterol level ≥ 240 mg/dL. Diabetes was defined as a fasting plasma glucose level ≥ 126 mg/dL, self-reported physician diagnosed diabetes, or taking insulin. Information on smoking habits (whether a current smoker), alcohol intake (number of drinks per week), leisure-time physical activity, and family history of PrCA was obtained from a standardized questionnaire.

Cardiorespiratory fitness was assessed at the baseline examination as the duration of a symptom-limited maximal treadmill exercise test using a modified Balke protocol [33]. The treadmill speed was 88m · min^{-1} for the first 25 min. During this time the grade was 0% for the first minute, 2% the second minute, and increased 1% each minute until 25 min had elapsed. After 25 min, the grade remained constant while the speed increased 5.4 m · min^{-1}

each minute until test termination. Patients were encouraged to give a maximal effort during the test. All men in the present analyses were able to complete the test to at least 85% of their age-predicted maximal heart rate (220 minus age in years). The duration of the maximal exercise treadmill test on this protocol is highly correlated with directly measured maximal oxygen uptake in men (r = 0.92), an accepted measure of CRF [34]. Maximal metabolic equivalents (METs, 1 MET = 3.5 ml O_2 uptake $\cdot kg^{-1} \cdot min^{-1}$) were estimated from the final treadmill speed and grade [35]. We used our previously published [36] age-specific distributions 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. 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 [36]. Exercise test durations (minutes) for the incremental fifths of fitness categories for men were: < 7.8, 7.8–10.5, 10.5–13.1, 13.1–16.4, and >16.4. In equivalent METs values, the thresholds that defined these categories were 7.2, 8.5, 9.5, and 10.8 METs.

2.3. Ascertainment of incident prostate cancer cases

PrCA incidence was ascertained from responses to mail-back health surveys in 1982, 1990, 1999, and 2004. Thus, men were followed for prostate cancer from 1976 through 2004. The aggregate survey response rate across all survey periods in the ACLS is ≈ 65%. Nonresponse bias, a concern in epidemiological surveillance, has been investigated in the ACLS [37], and found to be unlikely to present a major source of bias. Baseline health histories and clinical measures were similar between responders and nonresponders and between early and late responders [37]. The endpoint was defined as a participant report of physician-diagnosed PrCA and has been described in detail elsewhere [31].

2.4. Statistical analysis

Follow-up time among noncases was computed as the difference between the date of the baseline examination and the date of the last returned survey where the participant reported being free of PrCA. Follow-up time among cases was computed as the difference between the baseline examination date and the reported date of the PrCA event. If a diagnosis date was not provided on the survey, we used the midpoint between the date of the case-finding survey and either the baseline examination date or the date of the last returned survey where the participant reported being free of PrCA. The time-axis used in modeling was years. Baseline characteristics of the population were compared according to CRF levels. General linear models and χ^2-tests were used to test mean and frequency differences in covariates, respectively. Cox proportional hazards regression models were used to examine adjusted hazard ratios (HRs), 95% confidence intervals (95% CIs), and incidence rates (cases per 10,000 person-years of follow-up), using men in the lowest CRF level as the reference category. Multivariable-adjusted models included age (yr), examination year (single year), physical activity (low, moderate, high), smoking status (never, former, current), alcohol intake (drinks/week), family history of PrCA (yes, no), diabetes (yes, no), hypertension (yes, no), hypercholesterolemia (yes, no), waist circumference (WC) (cm), and BMI (kg/m^2) as potential confounders. Multicollinearity among independent variables in the models was tested and we found no significant collinearity based on variance inflation factors. Kaplan-Meier survival curves also were constructed to compare the probability of developing incident PrCA across CRF levels. To determine whether the association between CRF and PrCA risk differed by follow-up examinations, PrCA diagnosis year, age, or body weight, we conducted the stratified analyses by follow-up examinations (No vs. Yes), PrCA diagnosis year (≤ 1995 vs. > 1995), age (<55 vs. ≥55 years), waist circumference (≤ 102 vs. >102 cm), and BMI (18.5–29.9 vs. ≥ 30 kg/m^2) categories. All statistical analyses were performed using Statistical Analysis Systems software, version 9.1 (SAS Inc., Cary, NC). All *P* values were 2-sided, and 95% CIs were considered to indicate statistical significance.

3. Results

The baseline characteristics of the participants according to baseline levels of CRF are presented in Table 1. The mean age, CRF (in METs), and BMI of 19,042 men were 45.6 ± 9.7 years, 12.0 ± 2.4 METs, and 26.2 ± 3.5 kg/m^2 respectively. Overall, men with higher CRF level had more favorable baseline characteristics, including lower prevalence of diabetes, hypertension, and hypercholesterolemia ($p_{trend} < 0.0001$). We also examined the characteristics of men, according to the number of follow-up examinations that they had after the baseline examination (Fig 1). Overall, the data indicated that men with more follow-up examinations at the clinic were more likely to have optimal baseline characteristics, including CRF (presented as METs), BMI, alcohol intake, smoking status, and disease prevalence.

There were 634 PrCA cases identified during an average of 9.3 ± 7.1 years of follow-up. After adjusting for age, examination year, significantly higher risks of PrCA were observed in men with higher CRF levels (Table 2). After further adjusting for physical activity, current smoking, alcohol intake, family history of PrCA, diabetes, hypertension, hypercholesterolemia, and BMI, men with moderate and high CRF level had 68% higher risk of being diagnosed with PrCA (HR, 1.68; 95% Confidence Interval, 1.13–2.48) and 74% higher PrCA risk (HR, 1.74; 95% CI, 1.15–2.62), respectively, compared to men with low CRF (*P* trend < 0.05). In a subgroup of men for whom prostate-specific antigen (PSA) test results were available (N=3,003), there was no significant association between CRF and PrCA, without and with adjustment for PSA scores.

To determine whether there was effect modification by several risk factors for PrCA, we examined the association between CRF and risk of PrCA, stratified by age, waist circumference, BMI, and follow-up examination after adjustment for several potential confounders (Table 3). We found borderline significant statistical evidence of qualitative interaction between CRF and BMI ($\chi^2_{df=1} = 3.81$, $P = 0.05$), and follow-up examination ($\chi^2_{df=1} = 2.13$, $P = 0.14$), but no statistical evidence in support of the association between CRF and WC ($\chi^2_{df=1} = 1.53$, $P = 0.21$), and age ($\chi^2_{df=1} = .01$, $P = 0.91$). A statistically significant positive association between CRF and PrCA risk was observed among men who were normal weight or overweight, and among men with follow-up examination, but not among those who were obese, or those without follow-up.

Because of the dramatic increase in the use of the PSA test after it was introduced to the public in 1986 [38], we sought to determine whether a period effect existed. Therefore, we examined the association between CRF and PrCA by diagnosis year (Table 3). We chose 1995 as our cut-point year because the incidence of PrCA increased dramatically after 1986 when PSA test was introduced to the public, peaked about 1992–1993, and then leveled off about 1995 [38]. We found a significant direct association between CRF and PrCA, which showed that men with moderate CRF level had an HR of 3.00 (95% CI, 1.38–6.55) and those with high CRF level had and HR of 3.17 (95% CI, 1.41–7.10); i.e., three times higher PrCA incidence than men with low CRF level among men who were diagnosed with PrCA up to 1995. However, there was a suggestion of a negative association among men who were diagnosed with PrCA after 1995. The Kaplan-Meier curves showing PrCA incidence rates according to CRF level are shown in Figure 2.

4. Discussion

In the current study, we found an unexpected positive association between CRF, as measured by a maximal treadmill exercise test, and risk of PrCA. These results, obtained after adjusting for potential confounders such as smoking, alcohol intake, obesity, and other

disease (i.e., co-morbid) status, were at odds with hypothesized mechanisms, some of the published literature on physical activity and PrCA (in particular, several large cohort studies have shown a benefit of physical activity on PrCA risk [18–20]) and previous findings from this study, published in 1996 showing 74% and 63% lower risk of PrCA among men in the highest quartile of CRF and physical activity, respectively [31]. As such, they point out the need to exercise caution in the interpretation of study results, especially in areas of research that are affected by changes in the public's perception of the utility of tests used for cancer screening.

Inconsistent findings from previous reports may be due to limited sample sizes (including our own earlier study in this cohort [31]), imprecise assessments of physical activity, variation in the control for confounding, or residual confounding by unknown factors which need further investigation. There exist several possible explanations for our findings that underline the importance of understanding the role of potential confounders and the unconventional ways in which they might work in relation to incident PrCA:

First, men with moderate-to-high CRF may be more likely to participate in the study. Such men also may be more likely to return more surveys over time. On the other hand, men with low CRF may be less likely to participate and also have more co-morbidities that may diminish their enthusiasm for PSA screening, hence resulting in a lower probability for a PrCA diagnosis. Similarly, they may not have enough longevity to develop PrCA because they are at significantly greater risk of mortality from other causes than are men with moderate-to-high CRF [32]. In our data, men with moderate-to-high CRF had longer average follow-up time than men with low CRF (7.9 years vs. 9.4 years). Therefore, defining PrCA incidence via mail-back survey may be one of the sources of bias in the current study.

Second, although we adjusted for numerous potential confounders in the analysis, there is possibility of confounding by other unmeasured factors, such as endogenous hormones, diet (especially fat intake), and genetic variants, which is always a concern in an observational study. Though it is possible that one or more such factors is operative, it is unlikely that any combination of exposure-related factors could explain such a large change in the direction and magnitude of the observed effect in the period before 1995 vs. afterward.

Third, men with moderate-to-high CRF probably are more health-conscious in general. Thus, they may have been more likely to avail themselves of widely accessible opportunities to be diagnosed with PrCA and be more likely to obtain PSA screening. PrCA is primarily an indolent cancer whose apparent incidence increased as an artifact of the wide availability and increased use of PSA screening from the late 1980s through the mid-1990s [38]. The observed higher prostate cancer incidence may be a result of increased health consciousness and screening in men with high CRF than in men with low CRF. This is supported by our observation that men with moderate-to-high CRF had better baseline health profiles and lower prevalence of diseases. Also, men with moderate or high CRF were more likely to revisit the clinic (49.3% vs. 34.3%), be screened for PSA (16.2% vs. 12.3%), and be diagnosed with PrCA (3.5% vs. 1.5%) compared to men who were in the low CRF level.

Some previous epidemiologic studies have reported increased risk of PrCA among more physically active men compared to their inactive counterparts [21,23–26]. In addition, these studies examined whether the association between physical activity and PrCA differed among subgroups according to age, overweight/obese, PSA screening, and PrCA stage (i.e., localized vs. advanced or tumor aggressiveness) [21,23–25]. This is consistent with results from a hospital-based case-control study [39] and cohort studies reporting a positive association between occupational physical activity [40], non-occupational physical activity

and sports participation [25], sports play [26], and leisure-time and home maintenance physical activity [21]. The overall range of increased relative risks or odds ratios in those studies was from 1.63 to 2.16, and the reported associations in subgroups were not consistent across these studies. However, due to heterogeneity of study design, physical activity measurement, and categorization of physical activity as exposure, it is difficult to compare our study with previous ones reporting a positive association.

It is interesting to note that two of the cohort studies [41,42] that showed a positive association between physical activity and PrCA risk also showed inverse (protective) associations between levels of physical activity and all-cause mortality, similar to what we found in the ACLS cohort [32].

Consistent with the secular trend toward vastly increased use of the PSA test from the late 1980s through the mid-1990s [38], we also examined whether the association between CRF and PrCA varied according to diagnosis year (≤ 1995 vs. >1995) to gauge the potential for PSA-screening bias that the association between CRF and PrCA differs by period of widespread adoption of the PSA test for screening. Our finding of a positive association between CRF and PrCA among men who were diagnosed with PrCA up to 1995, versus a suggestive of a negative association in men who were diagnosed with PrCA after 1995, supports the hypothesis that the observed result in the earlier period is an artifact resulting from an “early-adopter” effect. That is, the most health-conscious men were the ones both most likely to be fit and to be early users of the PSA test (and therefore be more likely to have a diagnosis of incident PrCA).

There is some support for this alternate explanation in that when analyses were restricted only to men with PSA screening results, we observed no association between CRF and PrCA risk. Another way to minimize the effect of screening bias would be to examine only fatal prostate cancer. Unfortunately we did not have enough data to further explore this, because only 19 men died from PrCA during this period.

On balance, we believe that the most likely explanation of the unexpected association observed in this study can be ascribed to an early-adopter effect in more fit men. This, in turn, is related to a dramatic increase of incident PrCA known to be associated with PSA screening, which became popular in the United States from late 1980s and increased reported incidence through the mid-1990s [38]. Even though the early detection in PrCA is encouraged by some groups, it has been suggested that overdiagnosis from PrCA screening is not uncommon [43,44]. It is interesting to note that more recent studies such as in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort conducted in Europe where PSA screening is less popular than in the US, are broadly consistent with what we found in the ACLS in this latter period (i.e., after 1995) [45].

In summary the unexpected association we observed is most likely due to a screening/detection bias in more fit men, rather than a causal association. It most likely reflects an overdiagnosis of PrCA cases compared to what was available in our previous work [31], which used data obtained primarily in the period prior to the upsurge in PSA screening.

This study has several strengths and limitations that should be considered. Strengths include its prospective study design, relatively large sample, long follow-up period, and extensive baseline examination including objective maximal treadmill test for CRF and identified potential confounders. In addition, no previous study, except for the one conducted previously in the same cohort, has examined the relationship between PrCA and CRF [32].

It has been suggested that the relationship of physical activity with PrCA risk may vary by PSA screening and stage of PrCA [20,23]. Therefore, a major weakness is that we did not

have complete data on PSA screening, which limited these analyses to 3,003 men. It is unlikely, however, that such factors could explain much of the positive association observed in the earlier (i.e., pre-1995) period. Due to the widespread geographic distribution of participants evaluated at the Cooper Clinic we were unable to verify all reported PrCA cases. However, the ACLS population is well-educated and based on the relatively high agreement between participant's self-reported history such as hypertension [46,47], heart attack [36], stroke [48], or diabetes [49–51] and their medical records, we also suspect that there was an acceptable level of accuracy for self-reported PrCA. Vigorous attempts to reach all participants could not be implemented before the undertaking of the present analysis; therefore, we did not have the ability to separate true nonresponders from those who never received the mail survey and thus did not have the opportunity to respond. Finally, generalizability of findings from this study is limited to well-educated European Americans of middle-to-upper socioeconomic status.

In conclusion, there is inconsistency in the literature regarding the association between physical activity and PrCA risk. We found a positive association between CRF and risk of PrCA, which does not support the inverse association with moderate-to-high CRF that we observed from our previous work in the same cohort. It is most likely that screening bias due to more health-conscious behavior among men with moderate-to-high CRF, leading to increased diagnosis of PrCA in these groups, played a role in these results. The results from this study underline the importance of considering outcome ascertainment bias, especially for a condition such as PrCA, which has been the center of so much debate, controversy, and variations in use over time [43,52–54].

Future studies with complete PSA information, and detailed information on stage and histopathological grade (i.e., Gleason score) of PrCA will be helpful to understand the inconsistent association between CRF and PrCA risk that we observed. Because PrCA is generally (>80%) not fatal [1] and concern is well placed regarding overdiagnosis of indolent disease that will never kill a man [52,55], increased effort would be well advised to identify and utilize very large cohorts capable of analyzing mortality as an outcome. Likewise, increased focus on African-American men who are more likely to be diagnosed with aggressive PrCA [56–58] and to die of the disease [1] would help to advance our understanding. Future work also should focus on the combined role of diet and PA while addressing potential biases in outcome ascertainment.

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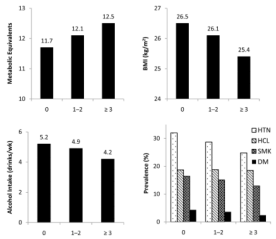

Figure 1.

Characteristics according to number of follow-up examination. Horizontal axis represents number of follow-up examinations at the clinic after baseline examination. HTN, Hypertension; HCL, Hypercholesterolemia; SMK, Smoking; DM, Diabetes Mellitus.

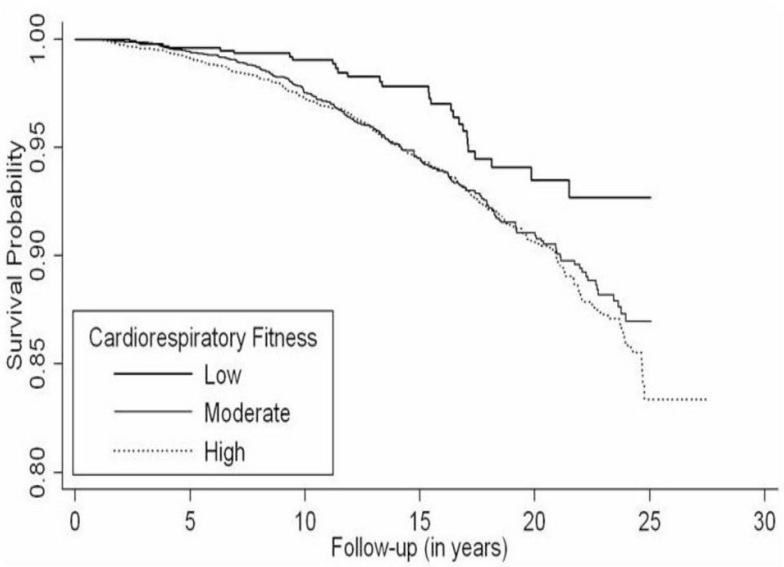

Figure 2.
Kaplan-Meier curves for prostate cancer incidence rate by cardiorespiratory fitness level in men.

Table 1

Baseline characteristics of the study participants across CRF levels

Characteristic	All	Cardiorespiratory fitness			*P* for difference
		Low	Moderate	High	
No. of participants	19042	1931	7037	10074	
Age (y)	45.6±9.7	44.4±9.3	45.4±9.5	45.9±9.9	<0.0001
Maximal metabolic equivalents (METs)[a]	12.0±2.4	8.6±1.2	10.7±1.2	13.6±2.0	<0.0001
Body mass index (kg/m^2)	26.2±3.5	29.8±5.1	26.9±3.2	25.0±2.5	<0.0001
Waist circumference (cm)	92.9±10.2	103.4±13.0	95.6±9.3	89.0±7.9	<0.0001
Current smoker (%)	15.3	29.8	19.8	9.5	<0.0001
Alcohol intake (drinks/wk)	4.9±6.5	4.3±7.0	4.7±6.8	5.2±6.6	<0.0001
HDL cholesterol (mg/dL)	46.3±11.7	40.6±10.1	43.8±10.6	49.2±11.9	<0.0001
Total cholesterol (mg/dL)	208.1±39.0	218.5±42.4	212.2±39.5	203.2±37.2	<0.0001
Triglyceride (mg/dL)	131.2±100.7	189.7±154.8	148.5±109.7	108.0±68.3	<0.0001
Hypercholesterolemia[b] (%)	18.7	27.4	21.8	14.8	<0.0001
Fasting glucose (mg/dL)	99.7±16.1	105.1±27.1	100.4±16.3	98.2±12.5	<0.0001
Diabetes (%)[c]	3.7	8.5	4.3	2.3	<0.0001
Systolic blood pressure (mmHg)	121.0 ± 13.4	123.6 ± 13.9	121.2 ± 13.1	120.4 ± 13.3	<0.0001
Diastolic blood pressure (mmHg)	81.1 ± 9.4	84.1 ± 9.7	82.0 ± 9.3	79.8 ± 8.8	<0.0001
Hypertension (%)[d]	29.6	43.2	33.3	24.3	<0.0001
PSA screening (%)	15.8	12.3	15.9	16.3	<0.0001

[a] Maximal metabolic equivalent tasks achieved during treadmill test.

[b] Hypercholesterolemia was defined as total cholesterol ≥240 mg/dL.

[c] Diabetes was defined by self-report, taking insulin or glucose>=126 mg/dL.

[d] Hypertension defined as history or blood pressure>140/90 mmHg.

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TABLE 2

Hazard ratios of prostate cancer associated with CRF

	No. of cases	Person-years of observation	Rate[a]	Model 1[b] HR (95% CI)	Model 2[c] HR (95% CI)
Cardiorespiratory fitness					
Low	29	15,398	3.4	1.00 (Reference)	1.00 (Reference)
Moderate	216	62,267	5.8	1.68 (1.14–2.47)	1.68 (1.13–2.48)
High	389	98,722	5.9	1.72 (1.12–2.51)	1.74 (1.15–2.62)
P for linear trend				< 0.05	<0.05

[a] Age-adjusted prostate cancer incidence rate per 10,000 person-years.

[b] Hazard ratio (HR) adjusted for age (single year), and examination year.

[c] Hazard ratio (HR) adjusted for age (single year), examination year, physical activity, current smoking, alcohol intake, family history of prostate cancer, diabetes, hypertension, hypercholesterolemia, and BMI.

TABLE 3

Hazard ratios prostate cancer associated with CRF, according to subgroups of men.

	Cardiorespiratory fitness			
	Low HR (95% CI)[c]	**Moderate HR (95% CI)**	**High HR (95% CI)**	***P* for interaction**
Follow-up examination[a]				
No	1.00 (Reference)	1.25 (0.75–2.07)	1.26 (0.74–2.15)	0.14
Number of cases	19	90	137	
Yes	1.00 (Reference)	2.36 (1.23–4.53)	2.48 (1.27–4.85)	
Number of cases	10	126	252	
PrCA diagnosis year[b]				
≤ 1995	1.00 (Reference)	3.00 (1.38–6.55)	3.17 (1.41–7.10)	<0.001
Number of cases	7	89	141	
> 1995	1.00 (Reference)	0.72 (0.45–1.16)	0.85 (0.52–1.40)	
Number of cases	22	127	248	
Age (yr)				
<55	1.00 (Reference)	1.26 (0.76–2.01)	1.43 (0.84–2.43)	0.91
Number of cases	19	113	223	
≥55	1.00 (Reference)	2.25 (1.18–4.32)	1.98 (1.05–3.83)	
Number of cases	10	103	166	
Waist circumference (cm)				
≤ 102	1.00 (Reference)	2.08 (1.18–3.65)	2.11 (1.20–3.73)	0.21
Number of cases	13	172	362	
> 102	1.00 (Reference)	1.12 (0.62–1.97)	1.45 (0.71–2.76)	
Number of cases	16	44	27	
Body mass index (kg/m^2)				
18.5–29.9	1.00 (Reference)	1.91 (1.18–3.14)	2.00 (1.21–3.30)	0.05
Number of cases	2	67	240	
≥30.0	1.00 (Reference)	0.92 (0.45–1.89)	0.53 (0.171.62)	
Number of cases	27	149	149	

[a] Follow-up examination defined as men who had at least one follow-up examination (Yes) or men who had no follow-up examination (No) after baseline examination.

[b] PrCA diagnosis year defined as men who were diagnosed PrCA up to 1995 (≤1995) or after 1995 (> 1995).

[c] Hazard ratio (HR) adjusted for age (single year), examination year, physical activity, current smoking, alcohol intake, family history of prostate cancer, diabetes, hypertension, hypercholesterolemia, WC (for BMI), and BMI (for WC).