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ORIGINAL ARTICLE

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Cardiorespiratory fitness is not associated with reduced risk of prostate cancer: A cohort study and review of the literature

Setor K. Kunutsor[1,2] | **Ari Voutilainen**[3] | **Jari A. Laukkanen**[3,4,5]

[1]National Institute for Health Research Bristol Biomedical Research Centre, University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol, Bristol, UK

[2]Translational Health Sciences, Bristol Medical School, Southmead Hospital, University of Bristol, Bristol, UK

[3]Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland

[4]Department of Medicine, Central Finland Health Care District, Jyväskylä, Finland

[5]Department of Medicine, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland

Correspondence
Setor K. Kunutsor, Translational Health Sciences, Bristol Medical School, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Bristol, BS10 5NB, UK.
Email: skk31@cantab.net

Abstract

Background: Cardiorespiratory fitness (CRF) has a strong inverse relationship with several chronic disease outcomes, including some cancers. The association between CRF and prostate cancer is controversial. We aimed to assess the prospective association of CRF with prostate cancer risk using a cohort study and review of the literature.

Material and methods: Cardiorespiratory fitness was assessed using a respiratory gas exchange analyser during exercise testing in 2204 cancer-free middle-aged men. Hazard ratios (HRs) with 95% confidence interval (CIs) were estimated. We corrected for within-person variability in CRF levels using repeat measurements.

Results: During a median follow-up of 24.9 years, 216 prostate cancer cases occurred. The age-adjusted regression dilution ratio of CRF was 0.58 (95% CI: 0.53-0.64). The HR (95% CI) of prostate cancer per 1 standard deviation increase in CRF in age-adjusted analysis was 1.10 (0.95-1.27). The association remained consistent after further adjustment for several risk factors (HR 1.13; 95% CI 0.96-1.33). The corresponding adjusted HRs were 1.24 (95% CI: 0.87-1.77) and 1.28 (95% CI: 0.87-1.88), respectively, when comparing the extreme tertiles of CRF levels. Previous studies mostly reported no evidence of an association or an increased risk of prostate cancer in relation to high CRF. Studies reporting positive associations had short-term follow-up durations (<10 years).

Conclusions: Primary data and a review of previous studies suggest that elevated CRF is not associated with reduced prostate cancer risk. Previous findings of significant evidence of associations could be attributed to increased screening and detection as well as reverse causation bias.

KEYWORDS

cardiorespiratory fitness, cohort study, maximal oxygen uptake, prostate cancer

1 | INTRODUCTION

Cancer is a global health burden, being the leading cause of death worldwide at all income levels.[1] With the ageing population and a steep increase in unfavourable lifestyle habits that predispose to cancer risk, the number of cancer cases and deaths attributed to these are expected to grow rapidly.[1] Prostate cancer is the second most frequently diagnosed cancer among males globally, and it is also one of the leading causes of death from cancer in men. It is commonly associated with factors such as race, age, family history, hereditary factors, infections, hormonal changes and those related to economic development such as excess body weight, physical inactivity and high consumption of animal fats.[2-6] Though these factors explain a large proportion of the risk of prostate cancer, it appears other potential risk factors may be involved, as its pathogenesis is still not fully established. Identification of other modifiable factors that may have causal or predictive significance will increase our knowledge of the aetiology of prostate cancer and help in the development of preventive and management strategies.

A wealth of epidemiologic evidence suggests that physical activity (PA) may protect against several chronic diseases including certain cancers.[7] A protective association between physical activity and prostate cancer has also been reported.[8] Maximal oxygen uptake (VO_{2max}), a cardiopulmonary exercise testing (CPX) parameter[9,10] and commonly used as a measure of cardiorespiratory fitness (CRF), is an index of habitual physical activity.[9] Like PA, CRF has also been consistently shown to be independently and inversely associated with several chronic disease outcomes.[11-13] A number of observational cohort studies have investigated the associations of CRF with the specific outcome of prostate cancer, but their results have been inconsistent. Some studies have reported an increased risk of prostate cancer with high CRF,[14-17] whereas others reported a decreased risk[18] or no evidence of an association.[19-22] Notably, these previous studies employed indirect methods or nonexercise algorithms for estimating CRF rather than the gold standard measure, that is CPX with VO_{2max} measured by ventilatory expired gas analysis.[23] However, there are limitations associated with non-use of the gold standard measure, which include: (a) underestimation and overestimation of CRF at the top and bottom ends of the distribution, respectively,[10] and (b) a particular equation may not be suitable for all populations.[24] The availability of CRF, ascertained with the gold standard measure, within the Kuopio Ischaemic Heart Disease (KIHD) prospective study offered the opportunity to revaluate the nature and magnitude of the association between CRF and prostate cancer in greater detail than in previous studies. To put these findings into context, we also reviewed the literature for previously published evidence on the associations between CRF and prostate cancer risk.

2 | METHODS

2.1 | Study participants and assessment of covariates and outcomes

Reporting of the study conforms to broad EQUATOR guidelines[25] and was conducted according to STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting observational studies in epidemiology (Table S1).[26] The study population were participants in the KIHD risk factor study, a prospective population-based cohort study designed to investigate risk factors for vascular disease and other chronic outcomes. The cohort comprised of middle-aged men aged 42-61 years who were recruited from Kuopio in eastern Finland. The study design and recruitment methods have been described in detail previously.[27] Following exclusion of those who did not respond to the invitation and declined to give informed consent, the final cohort comprised of 2682 participants who had baseline measurements performed between March 1984 and December 1989. The present analysis included a cohort of 2204 cancer-free men at baseline, with complete information on CRF, relevant confounders and incident prostate cancer cases. The study was approved by the Research Ethics Committee of the University of Eastern Finland, and each participant provided written informed consent. All study procedures were conducted according to the Declaration of Helsinki. Maximal oxygen uptake was used as a measure of CRF and was measured using a respiratory gas exchange analyser during a maximal symptom-limited cycle ergometer exercise tolerance test.[28] Repeat measurements of VO_{2max} were performed 11 years after the baseline measurements, during the follow-up period in a random subset of participants. We included all incident cases of prostate cancer that occurred from study enrolment through 2014.[29] Cases were derived from the population-based Finnish Cancer Registry (FCR). Every diagnosed cancer case in the healthcare system has been reported in a countrywide and population-based manner in Finland since 1953. The coverage of FCR is complete, and there were no losses to follow-up.[30]

2.2 | Statistical analysis

Baseline characteristics of participants were summarised using descriptive analyses. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazard models. Cardiorespiratory fitness was modelled as per 1 standard deviation (SD) increase and as tertiles. Hazard ratios were adjusted for age (Model 1) and for age, smoking status, history of type 2 diabetes, fasting plasma glucose (FPG), total cholesterol, triglycerides, alcohol consumption, total energy intake, socioeconomic status (SES), total physical activity and high

sensitivity C-reactive protein (hsCRP) (Model 2). Because prostate cancer has a long latency period (subclinical phase), this could cause declines in levels of CRF long before definite diagnosis (ie, reverse causation bias). To account for this potential bias, sensitivity analysis involved limiting analysis to participants with at least 10 years of follow-up. The 10-year threshold was chosen for consistency with previous studies reporting on outcomes with long latency periods[19,31] Analyses restricted to the first 10 years of follow-up could not be conducted due to a low number of events in this time window. Due to measurement errors in exposure estimation, ageing and lifestyle changes in long-term prospective cohort studies, analysis using only baseline measurements of an exposure could underestimate the true strength of any association between exposure and outcome (ie, 'regression dilution bias'[32]). To address this issue, we used repeat measurements of VO_{2max} taken 11 years apart in a random subset of 551 men to correct for the effect of this regression dilution bias. This was achieved by estimating adjusted regression dilution ratios (RDRs), calculated by regressing available repeat measurements on baseline values[33] as reported in previous studies.[34-36] All statistical analyses were conducted using Stata version MP 16 (Stata Corp.).

2.3 | Literature review

A search was conducted in MEDLINE from inception to 13 January 2021, to identify observational cohort studies (with at least one year of follow-up) that had evaluated the association between CRF and prostate cancer risk in general populations. The computer-based searches used a combination of keywords or terms relating to the exposure ('cardiorespiratory fitness', 'aerobic fitness') and outcome ('prostate cancer'). We did not conduct a meta-analysis as it would be inappropriate to do this, given the excessive variation in the assessment of CRF measures, follow-up periods and results. With regard to follow-up for cancer outcomes, combining findings from short-term follow-up studies and those of long-term follow-up studies will yield biased estimates, due to the long latency period for cancers.

3 | RESULTS

3.1 | Observational cohort analysis

The mean (SD) of age and CRF of study participants at baseline were 53 (5) years and 30.3 (8.0) mL/kg/min, respectively (Table 1). During a median (interquartile range) follow-up of 24.9 (17.3-27.0) years, 216 cases of prostate cancer occurred, corresponding to an annual rate of 4.54/1000 person-years at risk (95% CI: 3.98 to 5.19). The HR for prostate cancer per 1 SD increase in CRF in analysis adjusted for age was 1.10 (95% CI: 0.95-1.27), which remained consistent in analyses additionally adjusted for several risk factors (smoking status, history of type 2 diabetes, FPG, total cholesterol, triglycerides, alcohol consumption, total energy intake, SES, total physical activity and hsCRP) and 1.13 (95% CI: 0.96-1.33) (Table 2). The corresponding adjusted HRs were 1.24 (95% CI: 0.87-1.77) and 1.28 (95% CI: 0.87-1.88), respectively, when comparing the top versus bottom tertiles of CRF levels. The overall age-adjusted RDR of CRF was 0.58 (95% CI: 0.53-0.64), which suggests that if there was a significant association between CRF and prostate CA, using one-off or baseline measurements of CRF could underestimate the risk by $[(1/0.58) - 1] \times 100 = 72\%$. The HRs were more extreme following correction for within-person variability in CRF levels (Table 2). In sensitivity analyses, results were consistent in analyses limited to participants with at least 10 years of follow-up (Table S2).

TABLE 1 Baseline participant characteristics

	Mean (SD) or median (IQR) or n (%)
CRF (mL/(kg.min))	30.3 (8.0)
Questionnaire/Prevalent conditions	
Age at survey (years)	53 (5)
Alcohol consumption (g/week)	31.8 (6.4-90.8)
Total energy intake, kJ/d	9655 (8148-11 332)
Socioeconomic status	8.41 (4.23)
History of type 2 diabetes	76 (3.5)
Current smokers	683 (30.9)
Physical measurements	
BMI (kg/m^2)	26.9 (3.5)
SBP (mm Hg)	134 (17)
DBP (mm Hg)	89 (10)
Total physical activity (kcal/d)	1212 (637-1990)
Blood-based biomarkers	
Total cholesterol (mmol/L)	5.91 (1.07)
HDL-C (mmol/L)	1.29 (0.30)
Triglycerides (mmol/L)	1.09 (0.79-1.53)
Fasting plasma glucose (mmol/L)	5.33 (1.21)
High sensitivity CRP (mg/L)	1.23 (0.69-2.37)

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation.

3.2 | Literature review findings

We identified eight population-based prospective cohort studies reporting on the associations between CRF and prostate cancer risk, which were published from 1996 to

2020 (Table 3).[14-21] The average age at baseline ranged from approximately 18.0 to 59.2 years. Four studies were based in North America (USA) and four in Europe (Denmark, Norway, Sweden and UK). Average duration of follow-up ranged from 5.0 to 44 years. All studies employed indirect methods for the assessment of CRF, which were based on submaximal or maximal treadmill/bicycle exercise tests. Four studies with follow-up durations ranging from 5.0 to 9.3 years reported an increased risk of prostate cancer with high CRF levels.[14-17] Three studies with follow-up durations ranging from 12.7 to 44.0 years reported no evidence of an association.[19-21] Only one study, which was published in 1996, reported a decreased risk of prostate cancer with increased CRF levels.[18]

TABLE 2 Association between cardiorespiratory fitness and risk of prostate cancer

CRF (mL/(kg.min))	Events/ Total	Model 1 HR (95% CI)	*P*-value	Model 2 HR (95% CI)	*P*-value
Baseline CRF					
Per 1 SD increase	216/2204	1.10 (0.95-1.27)	.19	1.13 (0.96-1.33)	.16
T1 (6.36-26.87)	56/735	ref		ref	
T2 (26.88-33.24)	79/735	1.25 (0.88-1.77)	.21	1.22 (0.86-1.75)	.26
T3 (33.25-65.40)	81/734	1.24 (0.87-1.77)	.23	1.28 (0.87-1.88)	.22
Usual CRF[a]					
Per 1 SD increase	216/2204	1.18 (0.92-1.52)	.19	1.23 (0.93-1.63)	.16
T1 (6.36-26.87)	56/735	ref		ref	
T2 (26.88-33.24)	79/735	1.47 (0.81-2.67)	.21	1.42 (0.77-2.62)	.26
T3 (33.25-65.40)	81/734	1.45 (0.79-2.68)	.23	1.52 (0.78-2.97)	.22

Note: Model 1: Adjusted for age. Model 2: Model 1 plus smoking status, history of type 2 diabetes, fasting plasma glucose, total cholesterol, triglycerides, alcohol consumption, total energy intake, socioeconomic status, total physical activity and high sensitivity C-reactive protein.

Abbreviations: CI, confidence interval; CRF, cardiorespiratory fitness; HR, hazard ratio; ref, reference; SD, standard deviation; T, tertile.

[a]Indicates correction for within-person variability in values of CRF, that is the extent to which an individual's CRF measurements vary around a long-term average value ('usual CRF values').

TABLE 3 Baseline characteristics of published prospective cohort studies (1996-2020)

Author, year of publication	Study name	Country	Baseline year	Mean/median age (yrs)	Follow-up (yrs)
Oliveria, 1996	Copper Clinic	USA	1970-1989	44.2	~10.0
Byun, 2011	ACLS	USA	1976-2003	45.6	9.3
Lakoski, 2015	CCLS	USA	1971-2009/1999-2009	49.0	6.5
Jensen, 2017	Copenhagen Male Study	Denmark	1970-1971	48.8	44.0
Robsahm, 2017	Oslo Ischemia Study	Norway	1972-1975	49.8	26.2
Vainshelboim, 2017	VETS	USA	1987-2012	59.2	12.7
Steell, 2019	UK Biobank	UK	2007-2010	40-69[a]	5.0
Crump, 2020	—	Sweden	1972-1985	18.0	—

Abbreviations: ACLS, Aerobics Center Longitudinal Study; CCLS, Cooper Center Longitudinal Study; VETS, Veterans Exercise Testing Study.

[a]Age range; CA, cancer; CRF, cardiorespiratory fitness; MET, metabolic equivalent; NR, not reported; VO_2max, maximal oxygen uptake.

4 | DISCUSSION

In this new study which examines the prospective association between objectively measured CRF and risk of prostate cancer in a general population-based cohort of middle-aged Caucasian men who were followed over two decades, the results did not suggest evidence of an association. Our results are in line with some earlier studies that have evaluated the association. Of the eight studies identified in the literature review, three of the studies which were all published in 2017, involved middle-aged men and with average follow-up durations ranging from 12.7 to 44.0 years, demonstrated no evidence of an association between CRF and prostate cancer.[19-21] Contrary to these findings, the majority of previously published studies reported an increased risk of prostate cancer with high CRF levels.[14-17]

A consistent relationship has been demonstrated between high CRF and lower risk of all-cause and some site-specific cancers.[15,19,37] Chronic inflammation has been reported to play a major role in prostate carcinogenesis,[4,38] and multiple factors suggested to contribute to the chronic inflammation process include infections, dietary factors and hormonal changes.[4] Increased testosterone levels and hyperglycaemia are also known to contribute to prostate carcinogenesis.[39,40] The protective effect of CRF on cancer may be attributed to the role of PA, which is well established to influence CRF levels.[41] Regular PA may exert a protective effect on prostate cancer via dampening of inflammatory responses, tumour growth suppression, decrease in excessive levels of testosterone, increased insulin sensitivity and immunological mechanisms.[42-44] Given the evidence, it would seem our null findings are unexpected. However, the associations between CRF and some site-specific cancers have been especially strong and consistent for lung and colorectal cancers,[15,37,45] whereas findings for CRF and prostate CA risk have been inconsistent. More surprisingly, the majority of published studies have demonstrated evidence of an increased risk of prostate cancer with high CRF levels.[14-17] These findings have been attributed to increased healthcare awareness and screening and early detection (diagnostic bias).[15,19] Jensen et al[19] report that due to these factors, prostate cancer mortality may be a more sensitive outcome measure of the association between CRF and prostate cancer. This is consistent with the fact that CRF is strongly and inversely associated with all-cause mortality.[46] In addition to factors above, evidence of associations demonstrated by previous studies may have been influenced by reverse causation bias, as many cancers (including prostate cancer) have a long subclinical development which may cause PA and CRF to decline in the early stages of follow-up. Consistent with this hypothesis, significant findings have been demonstrated predominantly in studies with short-term follow-up durations (average of 5-10 years),[14-17] with no evidence of associations for long-term follow-up studies.[19-21] The null association observed between CRF and prostate cancer may reflect important differences between CRF and the aetiopathogenesis of prostate cancer and other site-specific cancers such as lung and colorectal cancers. Hence, it is possible that the lack of an association between CRF and prostate CA may actually be a true association. In a recent comprehensive review of 48 cohort and 24

CRF measure	CRF assessment	No. of participants	No. of prostate CA cases	Risk comparison	Risk estimate (95% CI)
Treadmill time	Maximal or symptom-limited treadmill exercise test	12 975	94	Top vs bottom quartile	0.26 (0.10-0.63)
Maximal METs	Symptom-limited exercise treadmill testing	19 042	634	High vs Low	1.74 (1.15-2.62)
Peak METs	Incremental treadmill test (indirect method)	13 949	1310	High vs Low	1.22 (1.02-1.46)
Maximal oxygen consumption (VO_2max)	Bicycle ergometer test (indirect method)	5131	373	Per 10 mL/kg/min increase	0.91 (0.77-1.06)
Maximal aerobic workload	Incremental bicycle exercise test (indirect method)	1997	213	High vs Low	1.20 (0.83-1.74)
Peak METs	Maximal treadmill exercise test	4920	337	High vs Low	0.97 (0.68-1.40)
Maximal METs	Submaximal cycle ergometer test	73 259	—	High vs Low	1.16 (1.02-1.32)
Maximal aerobic workload	—	699 125	10 782	High vs Low	1.10 (1.03-1.19)

case-control studies, Benke and colleagues demonstrated no evidence of an association between overall PA and prostate cancer incidence.[47] Though these null findings may appear not to be useful for future research on CRF and prostate cancer risk, it does clarify the existing uncertainties regarding the association; especially given the body of evidence on the strong inverse associations between CRF and some site-specific cancers such as lung and colorectal cancers.[15,37,45] Though all-cause and site-specific cancers share some common risk factors, there are risk factors that are specific to some cancers; it is, therefore, expected that the aetiogenesis of site-specific cancers may differ. Mechanistic studies are needed to delineate the pathways underlying the relationship between PA, CRF and the development of specific cancers.

4.1 | Strengths and limitations

The strengths of this evaluation include (a) the large-scale population-based prospective cohort design; (b) zero loss to follow-up; (c) reliable ascertainment of prostate cancer outcomes using a validated national cancer registry; (d) use of the gold standard measure for CRF assessment; (e) the follow-up period which was sufficiently long to ascertain the risk for prostate cancer; (f) ability to correct for within-person variability in CRF levels due to availability of repeat assessments in a subset of individuals; and (g) comprehensive review of previously published studies on the topic. The findings should be interpreted in light of the inability to (a) generalise the results to other populations, (b) evaluate the impact of CRF on cancer prognosis due to unavailability of data on cancer stages, (c) address causality due to the observational study design; and (d) pool the results of identified studies due to wide variation in study methods, exposures and outcomes.

5 | CONCLUSIONS

Primary data based on a cohort of middle-aged Caucasian male population and a review of previously published studies suggest that elevated CRF is not associated with reduced prostate cancer risk. The overall findings suggest that previous results showing evidence of associations could be attributed to increased screening and detection as well as reverse causation bias.

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CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

AUTHOR CONTRIBUTIONS

SKK contributed to study design, data analysis and interpretation, drafting manuscript, revising manuscript content and approving final version of manuscript. AV contributed to study design and conduct, responsibility for the patients and data collection and approving final version of manuscript. JAL contributed to study design and conduct, responsibility for the patients and data collection, revising manuscript content and approving final version of manuscript.

ORCID

Setor K. Kunutsor https://orcid.org/0000-0002-2625-0273

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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