2-9-2021

Fitness and prostate cancer screening, incidence, and mortality: Results from the Henry Ford Exercise Testing (FIT) Project

Cara Reiter-Brennan

Omar Dzaye

Mouaz H. Al-Mallah

Zeina Dardari

Clinton A. Brawner
Henry Ford Health, cbrawne1@hfhs.org

See next page for additional authors

Recommended Citation

Reiter-Brennan C, Dzaye O, Al-Mallah MH, Dardari Z, Brawner CA, Lamerato LE, Keteyian SJ, Ehrman JK, Blaha MJ, Visvanathan K, and Marshall CH. Fitness and prostate cancer screening, incidence, and mortality: Results from the Henry Ford Exercise Testing (FIT) Project. Cancer 2021.

Authors

Cara Reiter-Brennan, Omar Dzaye, Mouaz H. Al-Mallah, Zeina Dardari, Clinton A. Brawner, Lois E. Lamerato, Steven J. Keteyian, Jonathan K. Ehrman, Michael J. Blaha, Kala Visvanathan, and Catherine H. Marshall

Original Article

Fitness and Prostate Cancer Screening, Incidence, and Mortality: Results From the Henry Ford Exercise Testing (FIT) Project

Cara Reiter-Brennan[1,2]; Omar Dzaye, MD, PhD[1,2,3]; Mouaz H. Al-Mallah, MD, MSc[4]; Zeina Dardari, MS[1]; Clinton A. Brawner, PhD[5]; Lois E. Lamerato, PhD[6]; Steven J. Keteyian, PhD[5]; Jonathan K. Ehrman, PhD[5]; Michael J. Blaha, MD, MPH[1]; Kala Visvanathan, MBBS, MHS[7]; and Catherine H. Marshall, MD, MPH [1,7]

BACKGROUND: The relation between cardiorespiratory fitness (CRF) and prostate cancer is not well established. The objective of this study was to determine whether CRF is associated with prostate cancer screening, incidence, or mortality. **METHODS:** The Henry Ford Exercise Testing Project is a retrospective cohort study of men aged 40 to 70 years without cancer who underwent physician-referred exercise stress testing from 1995 to 2009. CRF was quantified in metabolic equivalents of task (METs) (<6 [reference], 6-9, 10-11, and ≥12 METs), estimated from the peak workload achieved during a symptom-limited, maximal exercise stress test. Prostate-specific antigen (PSA) testing, incident prostate cancer, and all-cause mortality were analyzed with multivariable adjusted Poisson regression and Cox proportional hazard models. **RESULTS:** In total, 22,827 men were included, of whom 739 developed prostate cancer, with a median follow-up of 7.5 years. Men who had high fitness (≥12 METs) had an 28% higher risk of PSA screening (95% CI, 1.2-1.3) compared with those who had low fitness (<6 METs. After adjusting for PSA screening, fitness was associated with higher prostate cancer incidence (men aged <55 years, $P = .02$; men aged >55 years, $P \leq .01$), but not with advanced prostate cancer. Among the men who were diagnosed with prostate cancer, high fitness was associated with a 60% lower risk of all-cause mortality (95% CI, 0.2-0.9). **CONCLUSIONS:** Although men with high fitness are more likely to undergo PSA screening, this does not fully account for the increased incidence of prostate cancer seen among these individuals. However, men with high fitness have a lower risk of death after a prostate cancer diagnosis, suggesting that the cancers identified may be low-risk with little impact on long-term outcomes. ***Cancer* 2021;0:1-7**. © *2021 American Cancer Society*.

KEYWORDS: cancer, cardiorespiratory fitness, prostate cancer, prostate-specific antigen.

INTRODUCTION

Although several modifiable cancer risk factors, such as smoking, body weight, and diet, have been associated with many cancers, few have been identified for prostate cancer.[1] High levels of cardiorespiratory fitness (CRF), a measure of peak energy expenditure, are associated with a lower incidence of multiple cancers, including lung cancer, colon cancer, bladder cancer, and pancreas cancer.[2-4] This observation is consistent with data on the benefits of physical activity and these cancers.[5,6] CRF reflects not only the effect of regular physical activity but also the effects of age, genetics, and other host factors, and it is a better predictor of all-cause mortality than physical activity alone.[7-9]

Within cancer, it is thought that the relation between high fitness and better cancer outcomes may be mediated by alterations in hormones, systemic inflammation, and the insulin axis, among others, which also have been reported to be important in prostate cancer.[10-14] Despite this, investigations into the relation of fitness and prostate cancer incidence and mortality have yielded mixed results.[4,15-18] The mixed results regarding CRF (and physical activity) and prostate cancer are thought to be related in part to differential screening practices as well as differences in risk modification based on the type of disease, although this has not been well established.[4,6,19,20] In addition, those studies were limited by relatively homogenous populations.[4,20] The objective of the current study was to examine the associations between fitness and prostate-specific antigen (PSA) screening, prostate cancer incidence, and all-cause mortality among men diagnosed with prostate cancer.

Corresponding Author: Catherine H. Marshall, MD, MPH, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, 201 N. Broadway, Box 7, Baltimore, MD 21287 (chm@jhmi.edu).

[1]Ciccarone Center for the Prevention of Heart Disease, Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Department of Radiology and Neuroradiology, Charite, Berlin, Germany; [3]Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, Maryland; [4]Houston Methodist DeBakey Heart and Vascular Center, Houston Methodist Hospital, Houston, Texas; [5]Division of Cardiovascular Medicine, Henry Ford Health System, Detroit, Michigan; [6]Henry Ford Health System, Detroit, Michigan; [7]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, Maryland

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.33426, **Received:** August 24, 2020; **Revised:** November 23, 2020; **Accepted:** December 15, 2020, **Published online** Month 00, 2021 in Wiley Online Library (wileyonlinelibrary.com)

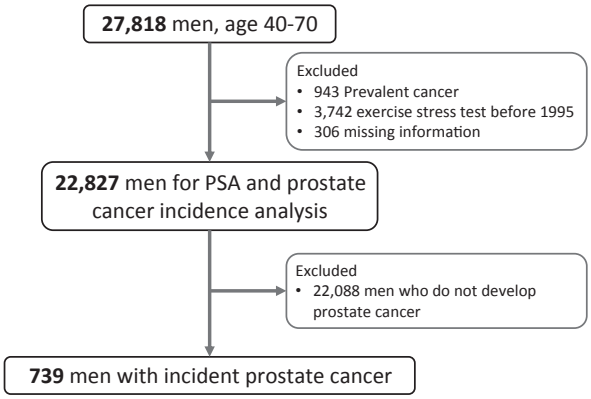

Figure 1. This is a Consolidated Standards of Reporting Trials (CONSORT) diagram of the current study. PSA indicates prostate-specific antigen.

MATERIALS AND METHODS

Patients: The Hendry Ford Exercise Testing Project

The Henry Ford Exercise Testing (FIT) Project is a large, retrospective cohort study of 69,885 adult men and women who underwent physician-referred exercise stress tests using the Bruce protocol at Henry Ford Health System-affiliated hospitals and ambulatory care centers in metropolitan Detroit, Michigan, between 1991 and 2009.[21] The full details of this cohort have been previously described.[21] For the current analysis, the cohort was limited to men aged 40 to 70 years. Those who had prevalent cancers and those who underwent exercise testing before 1995, when PSA testing became widespread and was available in our cohort, were excluded. A Consolidated Standards of Reporting Trials (CONSORT) diagram is shown in Figure 1.

Exposure

Fitness was estimated based on the final speed and elevation achieved while walking on the treadmill and then was calculated in metabolic equivalents of task (METs).[22] Because of the nature of data from the exercise test and to be consistent with other FIT Project studies,[2,21,23] patients were categorized into the following CRF levels; <6 METs, from 6 to 9 METs, from 10 to 11 METs, and ≥12 METs.

Covariates

Demographic data were obtained at the time of exercise testing and were complimented with data from clinical and administrative data sources. Medication use was assessed using the medical record and pharmacy claim files. Body mass index (BMI) was based on weight and height measured at the time of the stress test or, if it was unavailable, was imputed using age, race, and the available values. Comorbid conditions were considered if present at the time of exercise testing. This project was approved by the institutional review boards of the Johns Hopkins School of Medicine and the Henry Ford Health System.

Outcomes

PSA screening

All PSA values beginning January 3, 1995 (the first day available) through May 31, 2010, within Henry Ford Health System were obtained and included in the analysis. A repeat PSA test within 90 days of a previous test was excluded because this was considered likely part of the same evaluation. Among men who ultimately were diagnosed with prostate cancer, a PSA test was considered a screening test if it occurred >6 months before the diagnosis. Among men without a diagnosis of prostate cancer, all PSA tests were considered screening PSAs.

Prostate cancer incidence

Prostate cancer incidence was determined through May 2010 by linkage with the Henry Ford Cancer Institute tumor registry. The *International Classification of Diseases for Oncology, Third Edition* guidelines was used to categorize the cancer type according to the Surveillance, Epidemiology, and End Results program.[24] Only men with newly diagnosed prostate cancer were considered for this study. Advanced prostate cancer was further defined if there was a diagnosis of prostate cancer with regional or distant spread.

All-cause mortality

Among men diagnosed with prostate cancer, those who were diagnosed at autopsy or who had missing clinical information were excluded. All-cause mortality data were obtained from the Social Security Death Index Master File and were censored in June 2013.

Statistical Analysis

Because PSA testing was common in this cohort, to determine the association between fitness and PSA screening, we used multivariable adjusted Poisson regression. Sensitivity analyses were done among those who were considered healthy (the reason for a stress test was preoperative or screening/research) and among those who had a prior myocardial infarction (MI), congestive heart failure (CHF), or diabetes. Analyses were adjusted for age, race, and the presence of prior MI, CHF, or diabetes. The

TABLE 1. Demographics Overall and by Peak Metabolic Equivalents of Task Achieved

Variable	Overall N = 22,827	Peak METs Achieved <6 N = 1931	6-10 N = 4735	10-11 N = 9108	≥12 N = 7053
Age: Mean ± SD, y	53.8 ± 7.9	58.2 ± 7.9	57.1 ± 7.8	53.7 ± 7.6	50.4 ± 6.8
Race/ethnicity, no. (%)					
White	15,640 (69)	1072 (56)	3035 (64)	6201 (68)	5332 (76)
Black	5410 (24)	766 (40)	1423 (30)	2102 (23)	1119 (16)
Other	1777 (8)	93 (5)	277 (6)	805 (9)	602 (9)
Smokers, %	49.0	52.0	54.0	51.0	43.0
BMI: Mean ± SD, kg/m^2	29.4 ± 6.0	30.2 ± 8.0	30.6 ± 6.0	29.7 ± 5.0	27.9 ± 5.0
Medication use, %					
Statin use	26.0	31.0	33.0	27.0	19.0
Aspirin	24.0	35.0	29.0	23.0	17.0
Past medical history, %					
Myocardial infarction	13.0	38.0	20.0	9.0	5.0
Diabetes	21.0	38.0	31.0	20.0	10.0
Congestive heart failure	2.0	15.0	3.0	1.0	<1.0
Follow-up: Median [range], y	7.5 [5-11]	7.5 [4-11]	7.2 [4-11]	7.2 [5-11]	8 [5-11]
Reason for exercise stress test: Top 3 causes, %					
Chest pain	42.0	26.0	37.0	45.0	45.0
Rule out ischemia	12.0	10.0	12.0	13.0	12.0
Shortness of breath	10.0	16.0	11.0	9.0	10.0
≥1 PSA test, %	84.0	74.0	84.0	85.0	85.0

Abbreviations: BMI body mass index; METs, metabolic equivalents of task; PSA, prostate-specific antigen.

PSA at time of diagnosis was considered to be the PSA value that was before, but closest to, the date of diagnosis (within 6 months). Median values across fitness groups were compared using the nonparametric test for trend across ordered groups developed by Cuzick.[25]

Multivariable Cox proportional hazard models were developed to evaluate the association between fitness and incident prostate cancer, advanced prostate cancer, and all-cause mortality. Incidence models were adjusted for age, race, BMI, and statin use,[26] with the time scale beginning at the date of the exercise test. Mortality models were adjusted for age at prostate cancer diagnosis; race; BMI; aspirin and statin use (at the time of the stress test); smoking history; hypertension; prior MI, CHF, or diabetes; time from the exercise test to prostate cancer diagnosis; cancer stage (local, regional, distant) at diagnosis; and year of cancer diagnosis.

The α level was .05. Stata version 15 was used for all analyses.[27]

RESULTS

The analytic population included 22,827 men with a mean ± SD age of 53.8 ± 7.9 years; 69% of men were White, 24% were Black, and 8% were of other races (Table 1). At the time of the stress test, 31% of the cohort had at least 1 other comorbid disease (13% had previous MI, 2% had previous CHF, and 21% had previous diabetes). The median number of PSA tests during follow-up was 4 (interquartile range [IQR], 1-8 PSA tests). The median follow-up was 7.5 years (IQR, 5-11 years).

Fitness and PSA Testing

When adjusted for age, race, and the presence of a prior MI, CHF, or diabetes, those who had high fitness (≥12 METs) were 29% more likely to have undergone PSA screening compared with those who had low fitness (<6 METs) (incident rate ratio [IRR], 1.29; 95% CI, 1.25-1.33; *P* for trend <.01) (Fig. 2). Among the *healthy* men, those who had high fitness were 35% more likely to undergo PSA screening (IRR, 1.35; 95% CI, 1.22-1.50; *P* for trend <.01), and this also was observed among men who had a prior MI, CHF, or diabetes (IRR, 1.30; 95% CI 1.25-1.35; *P* for trend <.01).

Fitness and Prostate Cancer Incidence

Because of an interaction with age within the entire group (*P* = .007), we split the group into 2o cohorts: those aged ≤55 years and those aged >55 years at the time of the exercise test.

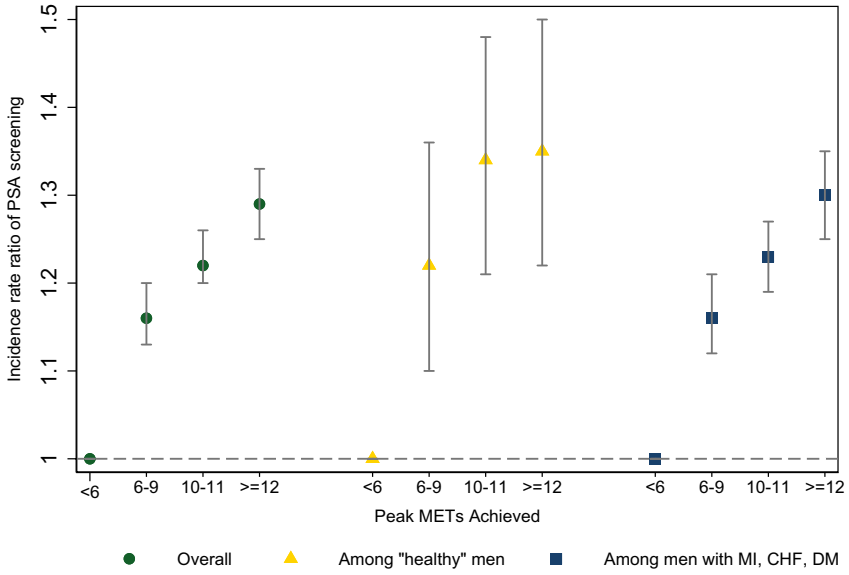

Figure 2. Incident rate ratios are illustrated for having ≥1 screening prostate-specific antigen (PSA) test. The analysis was adjusted for age, race, and comorbid conditions (prior myocardial infarction [MI], congestive heart failure [CHF], diabetes [DM]). METs indicates metabolic equivalents of task.

TABLE 2. Multivariable Adjusted Hazard Ratios of Incident Prostate Cancer, Adjusted for Age, Race, Body Mass Index, Statin Use, and Prostate-Specific Antigen Screening and Stratified by Age

Peak METs Achieved	Men Aged ≤55 Years, n = 13,082					Men Aged >55 Years, n = 9745				
	No. of Men	No. of Events	HR	95% CI	*P* for Trend	No. of Men	No. of Events	HR	95% CI	*P* for Trend
<6	654	10	Ref		.02	1277	56	Ref		<.01
6-9	1856	27	1.15	0.55-2.38		2879	158	1.40[a]	1.03-1.91[a]	
10-11	5251	80	1.46	0.75-2.84		3857	230	1.78[a]	1.32-2.40[a]	
≥12	5321	82	1.77	0.90-3.47		1732	96	1.80[a]	1.27-2.54[a]	

Abbreviations: HR, hazard ratio; METs, metabolic equivalents of task; Ref, reference category.
[a]These values indicate a statistically significant difference.

Among men aged ≤55 years (n = 13,082), after adjusting for age, race, BMI, statin use, and ever undergoing PSA screening, there was a significant trend toward an increased risk of being diagnosed with prostate cancer associated with higher fitness (*P* for trend = .02) (Table 2). This also was observed without the adjustment for PSA screening test (see Supporting Table 1). Among men aged > 55 years (n = 9745), there was a significant trend toward increased risk of being diagnosed with prostate cancer associated with higher fitness (*P* for trend <.01). Compared with men in the lowest fitness group (peak METs, <6), those who achieved from 6 to 9 METs had a 40% increased hazard of being diagnosed with prostate cancer (hazard ratio [HR], 1.40; 95% CI, 1.03-1.91), those who achieved 10 to 11 METs had a 78% increased hazard of being diagnosed (HR, 1.78; 95% CI, 1.32-2.40), and those who achieved ≥12 METs had an 80% increased hazard of being diagnosed (HR, 1.80; 95% CI, 1.27-2.54) (Table 2). This was similar to what was seen without an adjustment for PSA screening (see Supporting Table 1).

Among the 739 men who were diagnosed with prostate cancer, 81% were diagnosed with localized disease, 16% were diagnosed with regional disease, and 1% were diagnosed with distant disease (2% unknown). PSA values at diagnosis (within 180 days) were available for 442 men (60%). The median PSA level at diagnosis was 5.1 ng/mL (IQR, 4.1-7.1 ng/mL), and the median time from PSA test to diagnosis was 57 days (IQR, 32-86 days). The median PSA level at diagnosis was 5.6 ng/mL (IQR, 4.4-10.5 ng/mL) for men in the lowest fitness group (peak METs achieved, <6; n = 42),

TABLE 3. Multivariable Adjusted Hazard Ratio of Mortality by Fitness After Prostate Cancer Diagnosis, Adjusted for Age at Prostate Cancer Diagnosis, Race, Body Mass Index, Statin Use, Aspirin Use, Hypertension, Smoking, Comorbid Disease (Prior Myocardial Infarction, Congestive Heart Failure, or Diabetes), Time to Prostate Cancer Diagnosis, Stage at Diagnosis, and Year of Prostate Cancer Diagnosis

Peak METs Achieved	No. of Men	No. of Events	HR	95% CI	*P* for Trend
<6	66	21	Ref		<.01
6-9	185	47	0.94	0.55-1.59	
10-11	310	34	0.40[a]	0.23-0.72[a]	
≥12	178	13	0.40[a]	0.19-0.86[a]	

Abbreviations: HR, hazard ratio; METs, metabolic equivalents of task; Ref, reference category.
[a]These values indicate a statistically significant difference.

5.3 ng/mL (IQR, 4.3-8.0 ng/mL) in men who achieved 6 to 9 METs (n = 106), 4.9 ng/mL (IQR, 4.1-6.7 ng/mL) in men who achieved 10 to 11 METs (n = 192), and 5.0 ng/mL (IQR, 3.8-6.0 ng/mL) among men in the highest fitness group (peak METs achieved, ≥12; n = 102; *P* for difference <.01). In a subset analysis, the risk of advanced prostate cancer was not associated with fitness (HR, 1.53; 95% CI. 0.74, 3.17; *P* for trend = .27).

Fitness and All-Cause Mortality Among Men Diagnosed With Prostate Cancer

The median age at diagnosis of prostate cancer was 61 years (IQR, 55-67 years), with a mean ± SD of 7.6 ± 3.9 years from exercise test to prostate cancer diagnosis. There were 115 deaths during follow-up. After adjusting for age at prostate cancer diagnosis; race; BMI; statin and aspirin use; hypertension; smoking history; the presence of prior MI, CHF, or diabetes; time between exercise test and prostate cancer diagnosis; stage at diagnosis; and year of prostate cancer diagnosis, there was a significant inverse relation between fitness and the risk of all-cause mortality (*P* for trend <.01) (Table 3). Compared with <6 METs, 6 to 9 METs were associated with a 6% lower hazard of death (HR, 0.94; 95% CI, 0.55-1.59), and both 10 to 11 METs and ≥12 METs were associated with a 60% lower hazard of death (10-11 METs: HR, 0.40; 95% CI, 0.23-0.72; ≥12 METs: HR, 0.40; 95% CI, 0.19-0.86) (Table 3).

DISCUSSION

In a cohort of racially diverse adult men who completed a physician-referred exercise stress, we observed that PSA testing was more prevalent among men who had higher fitness levels, where those with high fitness (peak METs, ≥12) had a 29% increased likelihood of undergoing testing compared with those who had low fitness (<6 METs). This was similar among men who had a diagnosis of prior MI, CHF, or diabetes and among those who might be considered healthy because they did not have symptoms or disease as the major reason for the exercise stress test. In this cohort, we also observed that, among men aged >55 years, high fitness was associated with an 80% higher risk of being diagnosed with prostate cancer (*P* for trend <.01), and a similar trend was observed among younger men. Interestingly, PSA screening did not seem to fully account for the increased risk observed in incident prostate cancer. However, there was no significant association between fitness and advanced prostate cancer. Importantly, higher fitness, measured before a diagnosis of prostate cancer, was associated with a lower risk of mortality even after a prostate cancer diagnosis. Men who had high fitness (≥12 METs) had a 60% lower risk of death after a prostate cancer diagnosis compared with men who had low fitness (≤6 METs).

There is increasing evidence across many cancer types suggesting the beneficial effects of high fitness.[2-4] However, this has not been the case for prostate cancer, in which the results have been mixed, potentially because of unknown influences of PSA screening, with differential PSA screening habits among men who have higher fitness.[4-6,19] In line with our results, findings from the Aerobics Center Longitudinal Study demonstrated that men who had high CRF, compared those who had low CRF, were more likely to be screened for PSA (16.2% vs 12.3%) and be diagnosed with prostate cancer (3.5% vs 1.5%).[15] Similarly, Lakoski et al reported a 20% higher risk of prostate cancer among men with high CRF within the Cooper Center Longitudinal Study.[4] This is consistent with the healthy screening bias, in which healthier individuals are more likely to undergo screening tests.[28,29] Another consideration is that there may be differences in the risk of low-grade and advanced prostate cancer, as was observed in the relation between obesity and prostate cancer, in which obesity was associated with a higher risk of aggressive disease but not total or low-risk disease.[30,31] Although

it has been hypothesized that exercise like bike riding increases PSA levels through direct trauma to the perineum and prostate, it is not considered a likely cause of increasing PSA.[32] There is some suggestion that vigorous exercise like marathon running might lead to an increased PSA level in some men.[33] It is worth noting that there was a lower median PSA level at diagnosis among men in the highest fitness group. This suggests that men with high fitness may be undergoing additional testing at lower PSA values than men with low fitness. Taken together, this may result in increased downstream testing of men with high fitness leading to a diagnosis of prostate cancer.

Similar to what has been reported in other cancers, higher fitness levels were associated with lower risk of death after a prostate cancer diagnosis.[2] This is not surprising because cardiovascular disease is the leading cause of death in men diagnosed with prostate cancer, and it highlights the importance of high fitness levels for patients with prostate cancer.[34]

The current study is limited in that we cannot rule out PSA screening done elsewhere, especially in the setting of screening programs that are conducted in the community or outside of the health care system, and we do not have information on insurance coverage or socioeconomic status, which may affect screening rates. Furthermore, longer term follow-up may be needed in younger men to determine whether there will be a differential effect of fitness on prostate cancer incidence. Our study also does not address how or whether changing fitness affects prostate cancer incidence or mortality, and there may be other unmeasured factors, like family history, that are confounding this relation. In addition, we were limited by the number of men who were diagnosed with advanced prostate cancer, and more research is needed to determine the effect of fitness on lethal prostate cancer. Nevertheless, this cohort represents real-world data, with a large, non-White patient group, and may be helpful in adding to the interpretation of data already obtained for clinical purposes. Furthermore, to our knowledge, this is the first study to consider PSA screening habits in the models for prostate cancer incidence and also to consider mortality among those diagnosed with prostate cancer.

Conclusions

In one of the largest cohorts to date, we observed that men who have high fitness are more likely to undergo PSA screening and subsequently are more likely to be diagnosed with prostate cancer. However, the risk of death remains lower among men with high fitness after a prostate cancer diagnosis. This should be a consideration when counseling patients about lifestyle habits and engaging in shared decision making around prostate cancer screening and diagnoses. Future studies should further explore whether fitness influences subtypes of prostate cancer and whether changing fitness affects these results.

FUNDING SUPPORT

This work was supported in part by the National Institutes of Health (Cancer Center Support Grant P30CA006973) and the Maryland Cigarette Restitution Fund.

CONFLICT OF INTEREST DISCLOSURES

Lois E. Lamerato reports grants from AstraZeneca, Pfizer, Merck, Policy Analysis Inc, and the National Cancer Institute, outside the submitted work. Michael J. Blaha reports grants from the National Institutes of Health, the US Food and Drug Administration, the American Heart Association, Aetna Foundation, and Amgen; and personal fees from Amgen, Sanofi, Regeneron, Novartis, Novo Nordisk, Bayer, Akcea, 89Bio, Inozyme, Kaleido, and Kowa, outside the submitted work. Catherine H. Marshall reports personal fees from Bayer Pharmaceuticals, Dava Oncology, Dendreon Pharmaceutical Company, and McGraw-Hill Publishing Company, outside the submitted work. The remaining authors made no disclosures.

AUTHOR CONTRIBUTIONS

Cara Reiter-Brennan: Formal analysis, writing–original draft, and writing–review and editing. **Omar Dzaye:** Supervision and writing–review and editing. **Mouaz H. Al-Mallah:** Data curation and writing–review and editing. **Zeina Dardari:** Data curation, formal analysis, methodology, and writing–review and editing. **Clinton A. Brawner:** Data curation and writing–review and editing. **Lois E. Lamerato:** Data curation and writing–review and editing. **Steven J. Keteyian:** Data curation and writing–review and editing. **Jonathan K. Ehrman:** Data curation and writing–review and editing. **Michael J. Blaha:** Conceptualization, data curation, formal analysis, funding acquisition, methodology, supervision, and writing–review and editing. **Kala Visvanathan:** Conceptualization, formal analysis, methodology, supervision, and writing–review and editing. **Catherine H. Marshall:** Conceptualization, data curation, formal analysis, funding acquisition, methodology, supervision, writing–original draft, and writing–review and editing.

REFERENCES

1. Algotar AM, Cress A. Prostate cancer prevention. In: Alberts DS, Hess LM, eds. Fundamentals of Cancer Prevention. Springer International Publishing; 2019:607-628.doi:10.1007/978-3-030-15935-1_17
2. Marshall CH, Al-Mallah MH, Dardari Z, et al. Cardiorespiratory fitness and incident lung and colorectal cancer in men and women: results from the Henry Ford Exercise Testing (FIT) cohort. *Cancer*. 2019;125:2594-2601.doi:10.1002/cncr.32085
3. Robsahm TE, Falk RS, Heir T, et al. Cardiorespiratory fitness and risk of site-specific cancers: a long-term prospective cohort study. *Cancer Med*. 2017;6:865-873.doi:10.1002/cam4.1043
4. Lakoski SG, Willis BL, Barlow CE, et al. Midlife cardiorespiratory fitness, incident cancer, and survival after cancer in men: the Cooper Center Longitudinal Study. *JAMA Oncol*. 2015;1:231-237. doi:10.1001/jamaoncol.2015.0226
5. Liu L, Shi Y, Li T, et al. Leisure time physical activity and cancer risk: evaluation of the WHO's recommendation based on 126 high-quality epidemiological studies. *Br J Sports Med*. 2016;50:372-378. doi:10.1136/bjsports-2015-094728
6. Moore SC, Lee IM, Weiderpass E, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. *JAMA Intern Med*. 2016;176:816-825.doi:10.1001/jamainternmed.2016.1548

7. Minder CM, Shaya GE, Michos ED, et al. Relation between self-reported physical activity level, fitness, and cardiometabolic risk. *Am J Cardiol*. 2014;113:637-643.doi:10.1016/j.amjcard.2013.11.010
8. Aadahl M, Kjaer M, Kristensen JH, Mollerup B, Jorgensen T. Self-reported physical activity compared with maximal oxygen uptake in adults. *Eur J Cardiovasc Prev Rehabil*. 2007;14:422-428.doi:10.1097/HJR.0b013e3280128d00
9. Sassen B, Cornelissen VA, Kiers H, Wittink H, Kok G, Vanhees L. Physical fitness matters more than physical activity in controlling cardiovascular disease risk factors. *Eur J Cardiovasc Prev Rehabil*. 2009;16:677-683.doi:10.1097/HJR.0b013e3283312e94
10. Winzer BM, Whiteman DC, Reeves MM, Paratz JD. Physical activity and cancer prevention: a systematic review of clinical trials. *Cancer Causes Control*. 2011;22:811-826.doi:10.1007/s10552-011-9761-4
11. Campbell JP, Turner JE. Debunking the myth of exercise-induced immune suppression: redefining the impact of exercise on immunological health across the lifespan. *Front Immunol*. 2018;9:648. doi:10.3389/fimmu.2018.00648
12. Duggal NA, Pollock RD, Lazarus NR, Harridge S, Lord JM. Major features of immune senescence, including reduced thymic output, are ameliorated by high levels of physical activity in adulthood. *Aging Cell*. 2018;17:e12750. doi:10.1111/acel.12750
13. Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent regulation of the tumour microenvironment. *Nat Rev Cancer*. 2017;17:620-632.doi:10.1038/nrc.2017.78
14. Thomas RJ, Kenfield SA, Jimenez A. Exercise-induced biochemical changes and their potential influence on cancer: a scientific review. *Br J Sports Med*. 2017;51:640-644.doi:10.1136/bjsports-2016-096343
15. Byun W, Sui X, Hebert JR, et al. Cardiorespiratory fitness and risk of prostate cancer: findings from the Aerobics Center Longitudinal Study. *Cancer Epidemiol*. 2011;35:59-65.doi:10.1016/j.canep.2010.07.013
16. Jensen MT, Holtermann A, Bay H, Gyntelberg F. Cardiorespiratory fitness and death from cancer: a 42-year follow-up from the Copenhagen Male Study. *Br J Sports Med*. 2017;51:1364-1369.doi:10.1136/bjsports-2016-096860
17. Pozuelo-Carrascosa DP, Alvarez-Bueno C, Cavero-Redondo I, Morais S, Lee IM, Martinez-Vizcaino V. Cardiorespiratory fitness and site-specific risk of cancer in men: a systematic review and meta-analysis. *Eur J Cancer*. 2019;113:58-68.doi:10.1016/j.ejca.2019.03.008
18. Steell L, Ho FK, Sillars A, et al. Dose-response associations of cardiorespiratory fitness with all-cause mortality and incidence and mortality of cancer and cardiovascular and respiratory diseases: the UK Biobank cohort study. *Br J Sports Med*. 2019;53:1371-1378.doi:10.1136/bjsports-2018-099093
19. Vainshelboim B, Muller J, Lima RM, et al. Cardiorespiratory fitness and cancer incidence in men. *Ann Epidemiol*. 2017;27:442-447.doi:10.1016/j.annepidem.2017.06.003
20. Pernar CH, Ebot EM, Pettersson A, et al. A prospective study of the association between physical activity and risk of prostate cancer defined by clinical features and TMPRSS2:ERG. *Eur Urol*. 2019;76:33-40.doi:10.1016/j.eururo.2018.09.041
21. Al-Mallah MH, Keteyian SJ, Brawner CA, Whelton S, Blaha MJ. Rationale and design of the Henry Ford Exercise Testing Project (the FIT Project). *Clin Cardiol*. 2014;37:456-461.doi:10.1002/clc.22302
22. Riebe D, Ehrman JK, Liguori G, Magal M; American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription. 10th ed. Wolters Kluwer; 2018.
23. Hung RK, Al-Mallah MH, Qadi MA, et al. Cardiorespiratory fitness attenuates risk for major adverse cardiac events in hyperlipidemic men and women independent of statin therapy: the Henry Ford Exercise Testing Project. *Am Heart J*. 2015;170:390-399.doi:10.1016/j.ahj.2015.04.030
24. Surveillance, Epidemiology and End Results Program (SEER), National Cancer Institute. SEER ICD-O-3 Coding Materials. Accessed September 22, 2019. https://seer.cancer.gov/icd-o-3/
25. Cuzick J. A Wilcoxon-type test for trend. *Stat Med*. 1985;4:87-90.doi:10.1002/sim.4780040112
26. Alfaqih MA, Allott EH, Hamilton RJ, Freeman MR, Freedland SJ. The current evidence on statin use and prostate cancer prevention: are we there yet? *Nat Rev Urol*. 2017;14:107-119.doi:10.1038/nrurol.2016.199
27. StataCorp. Stata Statistical Software: Release 15. StataCorp; 2017.
28. Weiss N, Rossing M. Healthy screenee bias in epidemiologic studies of cancer incidence. *Epidemiology*. 1996;7:319-322.
29. Zhu X, van Leeuwen PJ, Holmberg E, et al. Efficacy vs. effectiveness study design within the European screening trial for prostate cancer: consequences for cancer incidence, overall mortality and cancer-specific mortality. *J Med Screen*. 2012;19:133-340.
30. Barrington WE, Schenk JM, Etzioni R, et al. Difference in association of obesity with prostate cancer risk between US African American and non-Hispanic white men in the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA Oncol*. 2015;1:342-349.doi:10.1001/jamaoncol.2015.0513
31. Vidal AC, Howard LE, Moreira DM, Castro-Santamaria R, Andriole GL, Freedland SJ. Obesity increases the risk for high-grade prostate cancer: results from the REDUCE study. *Cancer Epidemiol Biomarkers Prev*. 2014;23:2936-2942.doi:10.1158/1055-9965.EPI-14-0795
32. Jiandani D, Randhawa A, Brown RE, et al. The effect of bicycling on PSA levels: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis*. 2015;18:208-212.doi:10.1038/pcan.2015.16
33. Kratz A, Lewandrowski KB, Siegel AJ, et al. Effect of marathon running on total and free serum prostate-specific antigen concentrations. *Arch Pathol Lab Med*. 2003;127:345-348.doi:10.1043/0003-9985(2003)127<0345:EOMROT>2.0.CO;2
34. Sturgeon KM, Deng L, Bluethmann SM, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. *Eur Heart J*. 2019;40:3889-3897.doi:10.1093/eurheartj/ehz766