Aus der Klinik für Radiologie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Cardiorespiratory fitness and prostate cancer – analysis of the FIT-Cancer Cohort
Kardiorespiratorische Fitness und das Prostatakarzinom – Analyse der FIT-Cancer Cohort

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

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Datum der Promotion: 30.11.2023

Folgende Daten im Manteltext wurden auch in zwei Abstracts auf dem Annual American Association for Cancer Research (AACR) Congress, im Juni 2020 veröffentlicht. In dem ersten Abstract wurde der Effekt von kardiovaskulärer Fitness auf das Screening-Verhalten im Rahmen des Henry Ford FIT Projekts evaluiert. Der zweite Abstract beschreibt, dass eine niedrigere kardiovaskuläre Fitness vor Diagnose eines Prostata-Karzinoms mit einem höheren Gesamtmortalitätsrisiko assoziiert ist.

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Abbreviations

ACS	American Cancer Society
ADT	Androgen deprivation therapy
BMI	Body mass index
BRCA 1/2	Breast cancer type 1/2 susceptibility protein
CHF	Chronic heart failure
CI	Confidence Interval
CVD	Cardiovascular disease
DRE	Digital rectal examination
EAU	European Association of Urology
ERSPC	European Randomized Study of Screening for Prostate Cancer
FIT	Henry Ford Exercise Testing (FIT) Project
GS	Gleason score
HR	Hazard ratio
IQR	Interquartile range
IRR	Incidence rate ratio
ISUP	International Society for Urological Pathology
MET	Metabolic Equivalent of Task
MI	Myocardial infarction
mpMRI	Multi-spectrum Magnetic resonance imaging
NND	Number needed to diagnose
PI-RADS	Prostate Imaging-Reporting and Data System
PSA	Prostate specific antigen
RR	Risk ratio
SD	Standard deviation
SEER	National Cancer Institute's Surveillance, Epidemiology, and End Results
TRUS	Transrectal ultrasound
US-PLCO	United States based Prostate, Lung, Colorectal, and Ovarian Cancer trial
USPSTF	US Preventive Service Task Force

1. Abstract

1.1. English

Objective: High cardiorespiratory fitness reduces the risk of several cancers. However, the relationship between cardiorespiratory fitness and prostate cancer is not well established. This investigation aims to determine the association between cardiorespiratory fitness with prostate-specific antigen (PSA) screening, incident prostate cancer, and mortality.

Methods: Participants in this retrospective cohort study were 22,827 men aged 40 to 70 years without cancer in the Henry Ford Exercise Testing (FIT) Project, who received a physician-referred exercise stress testing from 1995 to 2009. Participants were grouped in categories of metabolic equivalents of task (METs) (<6 [reference], 6-9, 10-11, and ≥12 METs) achieved during the maximal exercise stress test. PSA testing was evaluated with multivariable-adjusted Poisson regression. Multivariable adjusted cox-proportional hazards models were used to compute hazard ratios (HR), 95% confidence interval (95% CI) of incident prostate cancer, and all-cause mortality among those diagnosed with prostate cancer.

Results: Men with high fitness (METs >=12) were 29% more likely to have undergone PSA screening (95% CI, 1.2-1.3) compared to those with low fitness (<6 METs). Men with high cardiorespiratory fitness were more likely to be diagnosed with prostate cancer after adjusting for PSA screening (men aged <55 years, P = .02; men aged >55 years, P ≤ .01). Cardiorespiratory fitness was not associated with advanced prostate cancer. Among men diagnosed with prostate cancer, high pre-diagnostic fitness was associated with a 60% lower risk of all-cause mortality (95% CI, 0.2-0.9).

Conclusions: While men with high fitness are more likely to undergo PSA screening tests, they are also more likely to be diagnosed with prostate cancers, although high fitness remains predictive of a lower risk of death, even among men diagnosed with prostate cancer. Cardiorespiratory fitness may identify those more likely to be screened and therefore diagnosed with less clinically significant disease, especially in men < 55.

1.2. Deutsch

Einleitung

Eine hohe kardiorespiratorische Fitness wirkt protektiv für zahlreiche Krebserkrankungen. Jedoch ist der Zusammenhang zwischen kardiorespiratorischer Fitness und dem Auftreten eines Prostatakarzinoms umstritten. Vermutlich erschwert der Bias im PSA-Screening bei Männern mit hoher Fitness die Analyse zwischen der Inzidenz von Prostatakarzinomen und kardiorespiratorischer Fitness.

Methodik

Insgesamt wurden 22.827 Männer zwischen 40 und 70 Jahren ohne Krebsdiagnose aus der retrospektiven Kohortenstudie, Henry Ford Exercise Testing (FIT) Project, untersucht. Alle Männer erhielten zwischen 1995 und 2009 einen laufbandergometrischen Belastungstest, um ihre kardiorespiratorische Fitness in *Metabolic Equivalents of Task* (METs) zu quantifizieren. Die Teilnehmer wurden anhand ihres Belastungstests in vier Gruppen eingeteilt: <6 [Referenz-Wert], 6-9, 10-11, und ≥12 METs. Mithilfe multivariabler adjustierter Poisson Regression und Cox Proportional Hazard-Modellen wurde der Zusammenhang zwischen Fitness und jeweils Erhalt eines PSA-Screenings, Prostatakarzinom-Inzidenz und Gesamtmortalität bestimmt.

Ergebnisse

Männer in der höchsten Fitness-Kategorie (METs >=12) hatten eine 29% höhere Wahrscheinlichkeit sich einem PSA-Screening zu unterziehen (95% CI, 1,2-1,3), als Männer in der niedrigsten Fitness-Kategorie (METs <6). Auch nach Adjustierung für PSA-Screening, hatten Männer, die >=12 METs in dem Belastungstest erreichten, ein größeres Risiko für eine Prostatakarzinom-Diagnose als Männer mit niedriger Fitness (Männer <55 Jahre, P = 0,02; Männer >55 Jahre, P ≤ 0,01). Wir konnten keine signifikante Beziehung zwischen fortgeschrittenem Prostatakarzinom und kardiorespiratorischer Fitness feststellen. Unter den Männern, die im Verlauf ein Prostatakarzinom entwickelten und eine hohe kardiorespiratorische Fitness hatten, war das Gesamtmortalitäts-Risiko im Vergleich zu Männern mit niedriger kardiorespiratorischer Fitness um 60% reduziert (95% CI, 0,2-0,9).

Schlussfolgerung

Männer mit einer hohen kardiorespiratorischen Fitness haben eine deutlich höhere Wahrscheinlichkeit sich einem PSA-Screening zu unterziehen als Männer mit niedriger Fitness. Die erhöhte Prostatakarzinom-Inzidenz bei Männern mit einer hohen Fitness konnte sich nicht ganz durch das PSA-Screening-Verhalten erklären. Auch nach dessen Berücksichtigung, hatten Männer mit hoher Fitness ein größeres Risiko für eine Prostatakarzinom-Diagnose als Männer mit niedriger Fitness. Allerdings ist kardiorespiratorische Fitness ein signifikanter Prädiktor für Gesamtmortalität nach einer Prostatakarzinom-Diagnose.

2. Introduction

2.1. Epidemiology

Prostate cancer is the second most frequent cancer in men worldwide, with approximately 1,414,259 new prostate cancer cases and 375,304 prostate cancer deaths reported in 2020. (1) Prostate cancer is the third leading and second leading cause of death in Europe and in the United States, respectively. (1,2) Approximately one man in nine will suffer from a prostate cancer diagnosis during his lifetime. (1) Prostate cancer is predominantly diagnosed in men aged between 65 and 75 years. Two-thirds of prostate cancer deaths occur after 75 years of age, and the median age of death is 80 years. (3) By 2040, the global prostate cancer burden will grow to an estimated 2.3 million cases and cause 740,000 deaths, mainly due to an aging population. (4) Significant international variations in prostate cancer incidence and mortality exist. Differences in prostate cancer susceptibility due to ethnic distributions and access to health care, especially to PSA screening and prostate cancer surgery, are likely to explain these disparities. The highest rates of prostate cancer incidence are found in North America, Oceania, and Northern Europe. (5) While prostate cancer diagnosis surged during 1980-1990 after the uptake of population-based PSA screening in these countries, prostate cancer incidence stabilized or decreased following USPSTF recommendations against routine PSA screening for all men in 2012. (5,6) In contrast, prostate cancer incidence is rising in several Asian and South American, and African countries. (4) By 2040, prostate cancer incidence expects to increase by 108.3% in Africa, 81.4% in Latin America and the Caribbean, and 74.3% in Asia. (4) European incidence of prostate cancer is expected to only increase by 27.6%. (4) Increasing incidence in developing countries is likely due to an increase of PSA testing and prostate cancer diagnosis and better documentation and reporting of cases. Obesity and the prevalence of westernized, unhealthy diets offer an additional explanation for the increase in prostate cancer incidence in these countries. (7,8) North America and Western and Northern Europe have witnessed a steady decline in prostate cancer mortality, most likely as a result of earlier detection and improved treatment. (4)

While currently Africa and Asia report the lowest prostate cancer mortality rates worldwide, by 2040, the mortality rate in Africa is expected to rise by 124%, followed by Asia with an increase of 116.7%. (4) Trinidad, Tobago, and Barbados have the highest prostate cancer mortality rates worldwide, possibly reflecting the high proportion of African descent. (5,9)

2.2. Risk Factors

Age is a well-established risk factor for prostate cancer. (10) In the United States, the lifetime risk of developing prostate cancer in men over 70 years of age is 8.2%, compared to men between 50 and 59 years of age, who only carry a 1.8% lifetime risk of a cancer diagnosis. (1) The risk of prostate cancer is significantly higher among African-American men, partly explained by a higher genetic susceptibility to prostate cancer. (9) Non-Hispanic black men suffer an average annual incidence of prostate cancer of approximately 172 per 100,000 compared to 98 per 100,000 men in non-Hispanic white men. (1) Family history, especially if the relative was diagnosed before the age of 65, is associated with a higher risk of prostate cancer, and risk doubles if a first-line relative has prostate cancer. (11) Known or suspected breast cancer type 1 susceptibility protein 1 (BRCA1) or BRCA2 mutations are additional risk factors. (12) Obesity is a likely risk factor for advanced prostate cancer, and some evidence suggests an elevated risk for men with high consumption of dairy products and calcium. (13–15) Low plasma selenium and alpha-tocopherol concentrations may also increase risk. (16)

Table 1: International Society of Urological Pathology 2014 grades

Low risk	**Intermediate risk**		**High risk**
PSA < 10ng/mL	PSA 10-20ng/mL	PSA >20 ng/mL	Any PSA
GS < 7 (ISUP grade 1)	GS 7 (ISUP Grade 2/3)	Or GS > 7 (ISUP Grade 4/5)	Any GS (any ISUP grade)
cT1-2a	cT2b	cT2c	CT3-4 or cN+
Localized	Localized		Locally advanced

Reproduced with permission of the EAU Guidelines Office. N. Mottet et al. 2021, Table 4.2, Place published: Arnhem, The Netherlands. Available from: https://uroweb.org/guideline/prostate-cancer/ (17)

2.3. Prostate cancer risk groups and prognosis

Due to the different therapeutic options dependent on the stage of localized prostate cancer, men with localized prostate cancer are divided into risk groups. (Table 1) With the International Society of Urological Pathology's risk group table designed initially by D'Amici et al, the risk of biochemical recurrence of patients treated with radiotherapy or prostatectomy can be estimated. (17) Prostate cancer is associated with a highly favorable prognosis, with a 5-year survival rate of 97.8% across all cancer stages. (18) Localized cancer is disease confined to the primary site and associated with a 5-year survival approaching 100%. Localized cancers account for 76% of all diagnoses, while 13% of cancers are regional diseases spread to regional lymph nodes. (18) Distant cancers, also known as metastatic prostate cancer, are rare, comprising 6% of all prostate cancers. (18) The prognosis of distant prostate cancer is significantly worse, with a 5-year survival rate of 30.2%. (18)

2.4. Early detection of prostate cancer

Prostate cancer screening and early detection are predominantly driven by prostate-specific antigen (PSA) based screening and digital rectal examination (DRE), followed by a saturation biopsy for histopathological verification. PSA is synthesized by the prostate gland and found in semen and blood. Higher PSA levels increase the likelihood of prostate cancer. (Table 2) While malignancy can elevate PSA, non-cancerous enlargements of the prostate, prostatitis, or certain urologic procedures can also increase serum PSA and cause a false-positive screening result. The definition of an abnormal PSA value used in the original seminal articles advocating for PSA screening, - > 4.0 ng/mL, remains the standard definition of a pathological PSA level. (19) Some physicians argue for a lower PSA threshold due to reports of microscopic evidence of prostate cancer, despite PSA values below 4.0 ng/mL. (20) For example, in an investigation of 855 men with unsuspicious DRE and PSA levels <= 4.0ng/ml, 23% had biopsy-detected prostate cancer lesions, of which 20% were high grade (Gleason sum >=7). (21) Reports suggest that aggressive prostate cancer can already be found within a PSA range of 3-3.9ng/ml. (23) While lowering the PSA threshold would allow earlier detection of aggressive cancers and increase overall prostate cancer diagnosis,

this would also inevitably consequent in higher biopsy rates and diagnosis of clinically insignificant disease. (22) Due to imperfect PSA thresholds, physicians should interpret PSA as a continuous parameter relative to previous values. (17) While many propositions exist to define better a pathological (abnormal) PSA value (e.g., age-specific PSA, PSA density, PSA velocity), these are not yet common practices.

The transrectal, ultrasound-guided 12-core systematic needle biopsy of the prostate based on multiple elevated PSA tests or positive DRE is still the primary method of a prostate cancer diagnosis. (23) The biopsy can be performed either via the transrectal or transperineal route, both equally viable approaches and with similar cancer detection rates. (24) The biopsy should be completed under antibiotic prophylaxis and local anesthetic. (17) For a baseline biopsy with no prior imaging, at least eight systematic biopsies are recommended for a prostate of 30cc, while 10-12 core biopsies should be taken for larger prostates. (17)

Multiple diagnostic tools can be used in conjunction with PSA to better differentiate between non-aggressive and clinically significant cancers and reduce unnecessary biopsies and over-diagnosis. Score tests based on algorithms developed from different kallikrein biomarkers and clinical information aim to improve prostate cancer diagnosis. The 4 K Score, Stockholm-3 test, Prostate Health Index and free PSA, are currently available for clinicians in men with elevated PSA levels who may consider biopsy. Urine-based biomarkers include prostate cancer gene 3, a non-coding microRNA biomarker, the SelectMDX test based on mRNA biomarker isolation from urine, and the TMPRSS2-ERG fusion gene. According to current evidence, these urine biomarkers may add some value when discriminating between aggressive and non-aggressive tumors when added to existing diagnostic tests. (25) The 2020 European Association of Urology (EAU) guideline award a weak recommendation for additional serum and urinary-based tests for prostate cancer risk assessment in asymptomatic men. (17) Prediction models estimate individual prostate cancer risk more precisely by considering PSA in addition to DRE and other prostate cancer risk factors (family history, ethnicity, age, previous biopsy results). In a meta-analysis of multiple risk calculators, the European Randomized Study of Screening for Prostate Cancer Risk Calculator 3 and Prostataclass demonstrated the highest discriminative value for the risk of a prostate cancer diagnosis. Both risk calculators had a sensitivity of 44% for prostate cancer detection,

compared to 21% sensitivity of PSA testing assuming a PSA cut-off of >4ng/ml. (26) Multiparametric magnetic resonance imaging (mpMRI) is an additional possible triage tool for prostate biopsy. MpMRI is not recommended as an initial screening tool but rather in men with elevated PSA who may be candidates for biopsy. (17) TRUS-biopsy has low diagnostic accuracy and often underdiagnoses clinically significant cancers while overdiagnosing indolent disease. MpMRI can better visualize clinically significant prostate cancers and facilitate better selection of patients for biopsy and improve targeting lesions during a biopsy. Clinically significant cancer was detected in 38% of MRI-targeted biopsies, compared to 26% of ultrasound-guided random biopsies.(27) The landmark trial, PROMIS, compared mpMRI with systematic transrectal biopsy TRUS-biopsy against a template prostate mapping biopsy as a reference test. (28) In PROMIS, mpMRI was associated with considerably better sensitivity and negative predictive value for clinically significant prostate cancer (defined as Gleason score >=4 + 3 or > ISUP grade 3 or more than 6mm of cancer in a biopsy core) compared to TRUS-biopsy. MpMRI sensitivity and negative predictive value for clinically significant cancer were 93% and 89%, in contrast to 48% and 74%, respectively, for TRUS-biopsy. (28) The authors concluded that mpMRI used as a triage test before prostate biopsy could avoid unnecessary biopsies in approximately a quarter of men and would allow detection of 18% more clinically significant cancers compared to only TRUS-biopsy. (28) However, mpMRI does not detect all cancers. In PROMIS, prostate cancer was found in 10.8% of men with a negative mpMRI through template-biopsy and systematic 12-core biopsy. (28) In another study, 16% of men with negative mpMRI harbored significant prostate cancer. (29) Evidence suggests that the combination of systematic biopsy with mpMRI targeted biopsy is superior in capturing clinically significant cancers than relying on one singular procedure. (29,30) In biopsy naïve patients, guidelines recommend combining targeted biopsy with systematic biopsy if mpMRI is positive (Prostate Imaging-Reporting and Data System (PI-RADS) >=3). (17,31)

Table 2: PSA levels and risk of prostate cancer (20)

PSA level (ng/mL)	Risk of prostate cancer (%)
0.0-0.5	6.6
0.6-1.0	10.1
1.1-2.0	17.0
2.1-3.0	17.0
2.1-3.0	23.0
3.1-4.0	26.9

Reproduced with permission of Massachusetts Medical Society, Thompson IM et al. 2004, p.2239-2246 (20)

2.5. History of PSA testing

Even though PSA-based screening for prostate cancer was introduced three decades ago, PSA testing remains heavily debated. (32) Biochemical prostate cancer screening with the PSA test became standard practice in North America in 1988, after evidence emerged suggesting a correlation between elevated PSA levels and prostate cancer incidence. (33,34) While Germany adopted PSA testing later, both countries witnessed a strong increase in pre-therapeutic PSA testing and, consequently, a rise in prostate cancer incidence. (35) In the United States, the incidence of prostate cancer tripled between 1986 and 1991. (36) Among men 65 years and older, the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program reported an 82% increase in the age-adjusted incident rate of prostate cancer between 1986 and 1991. (37) The uptake of widespread PSA testing coincided with a remarkable 70% decline in the metastatic prostate cancer incidence at diagnosis. (38) In addition, death by prostate cancer decreased by 42% between 1991 and 2005 in men aged 50 - 89 years. (39) To what extent this is attributable to PSA-based screening is debatable, as therapeutic options have also improved since the introduction of PSA screening. Results from modeling studies demonstrate that one-third of mortality decline may result from improved prostate cancer treatment, such as advancements in nerve-sparing radicle prostatectomy and adjuvant hormonal therapy uptake. (39)

The other two-thirds are most likely attributable to PSA screening. (39) In 2009, two landmark trials, the U.S.-based Prostate, Lung, Colorectal, and Ovarian Cancer (US-PLCO) and European Randomized Study of Screening for Prostate Cancer (ERSPC) trial, investigated the effect of PSA screening on prostate cancer-specific and all-cause mortality.

2.5.1. US-PLCO trial

The PLCO trial enrolled 76,693 men aged between 55 and 74 years with no previous personal history of prostate, lung, colorectal, or ovarian cancer. The intervention group received annual PSA and DRE examinations for 6 years while the control group underwent usual care with occasional opportunistic screening. (40) After 13 years of follow-up, no significant difference in prostate cancer mortality was observed between the two groups (4.8 vs. 4.6 deaths per 10 000 person-years, respectively) (Risk ratio (RR) 1.04, 95%CI, 0.87-1.24). (40) However, men in the intervention group had a 12 % higher prostate cancer incidence than the control group. (RR 1.12, 95% CI 1.07-1.17). (40) Results of the PLCO trial are controversial due to the high degree of contamination. By the sixth year of the trial, 52% of the control group had undergone PSA screening, and 86% of men had PSA testing at some point during the trial. (41) As a consequence of the major PSA screening contamination, the PLCO trial is frequently considered a comparison between organized and opportunistic screening. (42) From this perspective, the PLCO trial demonstrated no prostate cancer mortality benefit of organized screening versus opportunistic PSA screening.

2.5.2. ERSPC trial

In the ERSPC trial, 182,000 men of 7 European underwent a PSA screening test every 4 years (every 2 years in Sweden) with three reports after 9, 11, and 13 years of follow-up. (43–45) In all reports, the primary analysis was focused on participants aged 55-69 years. A 21% relative risk reduction in death by prostate cancer was observed in this age group after 13 years of follow-up (RR 0.79, 95% CI 0.69–0.91, p=0.001). (43) The trial demonstrated that 781 men had to be screened, and 27 men would have to be treated for 1 fewer death by prostate cancer. (43) The report, after 11-years of follow-up, yielded similar results. (44) However, after 13 years of follow-up, the absolute mortality reduction of 1.28 per 1000 men screened increased from 1.07 per 1000 men randomized after 11 years of follow-up. (44) In an updated report of the ERSPC trial with an extended follow-up of 16 years, prostate cancer-specific mortality results remained unchanged from the primary analysis. (46) No

reduction of all-cause mortality by screening was observed in any version of the ERSPC trial. The four ERSPC trial sites which evaluated PSA screening on long-term risk of metastatic prostate cancer reported a 30% lower chance of metastatic disease in the screening group after 12-years of follow-up. (47) This is equivalent to an absolute reduction of 3.1 cases of metastatic prostate cancer per 1000 men screened. (47)

The contradictory results of the PLCO and ERPC trials most likely stem from differences in methodology. The PLCO trial suffered from low compliance to biopsy protocol. Despite a clear recommendation for a sextant biopsy for PSA values >=4 ng/ml or an abnormal DRE, the decision to biopsy was ultimately left to the physician's discretion. (48) Adherence to biopsy indication was about twice as high in the ERSPC trial. (48) The high degree of contamination in the PLCO trial made detection of a difference in prostate cancer mortality between screening and control arm unlikely. Even though not evaluated in the ERSPC trial, the extent of PSA screening before randomization was most likely negligible as PSA-based prostate screening was uncommon in Europe during the time. (48) In addition, the authors of the ERSPC trial stated that the reduced mortality associated with PSA screening came at a high cost of overdiagnosis and overtreatment with subsequent side effects. Approximately 40-50% of screen-detected cancers on the ERSPC trial were overdiagnosed. (49) After 13-years of follow-up, an additional 1,301 prostate cancer cases were diagnosed more than in the control group (7,408 vs. 6,107). (43) In other words, to prevent one prostate cancer death, 34 prostate cancers had to be detected. (43) Models predicted that a continuation of the screening rate from the year 2000 would consequent in 710,000 – 1,120,000 overdiagnosed prostate cancers from 2013 – 20205. (50) In a controversial decision statement, the US Preventive Service Task Force (USPSTF) acknowledged PSA screening benefits but argued that the harms associated with screening outweighed the possible protective effects. The USPSTF denounced PSA screening for men over 75 years of age in 2008 and recommended against routine-based PSA screening for all men in 2012. (51,52)

2.6. Harms of screening

A pathological PSA screening result is not unusual, with approximately 100 – 120 elevated PSA values for every 1,000 men tested. (52) However, most men referred for a biopsy because of an abnormal PSA result will not have prostate cancer. (43,53) Of biopsies performed in the PLCO and ERSPC, 67.7% and 75.8% were false positive, respectively. (45,53) The Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) trial investigated the effect of low-intensity, single PSA testing on prostate cancer mortality in 419,582 men with 10 years of follow-up. (54) In this trial, 60.6% of biopsies performed did not result in a prostate cancer diagnosis. (54)

Biopsy-associated side effects were an additional argument for the USPSTF recommendations against non-selective prostate cancer screening. The most common complications are hematuria and hematospermia, with large discrepancies in incidence rates. Hematuria is observed 14-50% of the time, while hematospermia is reported in 10-70% of cases after biopsy. (55,56) Among the men in the PLCO trial who underwent biopsy, 2.0% experienced complications such as bleeding, infection, or difficulties urinating. Of the 8,313 men who underwent at least one biopsy in the Veterans Affair Cohort, 5.6% reported complications after biopsy, including urinary incontinence in 13.6% of men and erectile dysfunction in 13.7%. (57) Other estimates suggest that for every 1000 men screened, one will be hospitalized for sepsis, three will suffer from urinary incontinence, and 25 more will report erectile dysfunction. (58)

Screening may detect disease which would have remained indolent for the duration of the man's life if not for early detection. (52) Overdiagnosis is one of the most significant harms of PSA-based prostate cancer screening. Asymptomatic prostate cancer is prevalent in the screening population. Autopsy studies detected prostate cancer in 32% of men in their 4th decade, 55% of men in their 5th decade, and 64% of men in their 70th decade. (59) An estimated 40% of all screen-detected cancers are overdiagnosed and occur particularly to those with little treatment benefits, such as older men or those with lower PSA values. (60,61)

Overtreatment as a direct consequence of overdiagnosis has a significant impact on quality of life due to treatment-induced bowel damage, urinary and sexual function. (62) This is particularly relevant as prostate cancer is characterized by a long, symptom-free lead time, while early treatment has immediate side effects. The harms of overtreatment are especially apparent in the United States, where low-risk prostate cancer is frequently treated aggressively, even in men with short life-expectancies. Approximately one in four diagnoses of prostate cancers are indolent cancers, but 90% of all men diagnosed are treated. (63,64) Despite newer technologies, adverse effects of prostate cancer treatment are common. After 2-years of follow-up, patients undergoing radical prostatectomy in the Prostate Cancer Intervention Versus Observation Trial (PIVOT) trial had a 43% higher risk of erectile dysfunction and 11% higher risk of incontinence. (65) Bowel dysfunction was observed in 12% of patients. (65) Physicians should neither underestimate the possible psychological consequences of screening, biopsy, and prostate cancer diagnosis. (66,67)

2.7. Guideline recommendations on PSA screening

The recent availability of more long-term evidence with extended follow-up added new understandings of prostate cancer screening's long-term risks and benefits. (10) After the USPSTF recommendation against PSA-based prostate screening in 2012, screening declined by approximately 20-30%. (68) Simultaneously, the incidence of metastatic cancer rose significantly. Data from Surveillance, Epidemiology, and End Results (SEER) suggests that the incidence of advanced cancer at diagnosis increased by approximately 6% among men over 75 years of age between 2004 and 2013. (35) By contrast, Schröder et al. observed a 30% risk reduction of advanced prostate cancer among men screened every four years in the ERSPC trial with 12 years of follow-up. (47) PSA-based screening benefits are possibly underestimated as follow-up times in most PSA screening trials are modest relative to the long lead time of prostate cancer. (60) In a natural history study of prostate cancer, Johansson et al. observed a 25% decline in prostate cancer survival after 15 years of follow-up compared to the first 15 years of follow-up. (69) Despite the ERSPC trial's relatively long follow-up of 16 years, the median follow-up from diagnosis was only 5.4 years in the control

group and 8.8 years in the screening group. (46) Schröder et al. remark that the number needed to diagnose (NND) to prevent 1 prostate cancer declined from 48 after 9 years to 18 after 16 years of follow-up and is expected to regress further with extended follow-up. (46) In addition, the harms of overtreatment induced by PSA screening are mitigated by heavier reliance on active surveillance of low-risk cancers. (70) Side effects such as erectile dysfunction or urinary incontinence were reduced by 65% in cases treated with active surveillance in men with low or intermediate-risk prostate cancer. (71) The implementation of risk calculators, serum biomarkers, and MRI imaging into clinical practice has resulted in a more favorable balance between PSA-based prostate cancer screening harms and benefits. (72)

As a result of these new considerations, the USPSTF upgraded their recommendation statement in 2018 from a grade D (no recommendation for PSA screening for prostate cancer) to a grade C, which proposes a shared-decision making model for the decision on PSA screening. (70) The USPSTF acknowledge that decision on screening cannot be answered by evidence from randomized trials alone but has to accommodate each individual's preferences and situation. (70) According to the 2018 recommendation statement, men aged 55 – 75 years should have the opportunity to discuss the risks and benefits of PSA-based prostate cancer screening with a clinician. (70) The authors argue that PSA-based screening's net benefit is determined by each man's assessment of the harms and benefits of screening. Men who are highly concerned with avoiding complications from biopsy and treatment are likely to abstain from PSA screening, while men who weigh even a slight prostate cancer risk reduction highly will likely choose screening. The USPSTF decision statement does not recommend PSA-based screening for men over the age of 70, as there is little proof of the benefits of screening among this age group. (70) The shift to an individualized, risk-adapted prostate cancer screening strategy is also evident in other guidelines and recommendation statements. The 2020 EAU guideline does not recommend PSA screening without prior counseling on screening risks and benefits. (17) PSA testing should be suggested to well-informed men with a higher risk of prostate cancer, such as men over 50 years of age, men over 45 years and with a family history of prostate cancer or of African descent, or men over 40 years of age and BRCA2 mutation. (17) The guidelines

emphasize that men with less than 15 years of life expectancy are unlikely to benefit from PSA screening. (17) The ACS similarly recommends communicating information about potential risks and benefits of screening to facilitate informed decision-making. (73) Screening discussions are recommended for men 50 years of age with an average risk of prostate cancer and a life expectancy of at least 10 or more years. Men 45 years of age with a high risk of prostate cancer, such as African-Americans or first degree relatives with prostate cancer, and men 40 years of age with a very high risk (those with more than one first degree relative with prostate cancer) should be offered a screening discussion. (73)

2.8. Cardiorespiratory fitness in preventive medicine

Preventive medicine in prostate cancer is primarily based on PSA screening as a form of secondary prevention. Primary and tertiary prevention programs for prostate cancer, however, are ill-defined. In many cancers and other chronic conditions, cardiorespiratory fitness is a highly established lifestyle strategy to prevent disease and improve outcome. (74–76) In a dose-response analysis, a 1-MET increase in maximal aerobic capacity reduced the risk of all-cause mortality by 13% and coronary heart disease and cardiovascular disease (CVD) by 15%. (77) Individuals with higher fitness have a significantly reduced risk of multiple cancers compared to their unfit counterparts. In the Cooper Center Longitudinal Study, high cardiorespiratory fitness was associated with a reduction of lung and colorectal cancer risk of 55% and 44%, respectively. (74) Similar evidence exists for lung, pancreas, bladder cancer, liver, and breast cancer. (78–80) Cardiorespiratory fitness may also protect against cancer-specific mortality and reduce all-cause mortality. Evidence from a meta-analysis of 71,654 participants revealed that in comparison to individuals with low fitness, those with moderate and high fitness had a 20% and 45% lower risk of cancer-specific and all-cause mortality, respectively. (81)

2.9.Measurement of cardiorespiratory fitness

While physical activity questionnaires are the most common approach for assessing activity status, there is often a substantial misclassification of self-reported physical activity, as not all relevant activities are captured or activity is reported inaccurately. (82) In comparison, assessments of cardiorespiratory fitness is a highly reproduceable and objective measurement of physical fitness. Self-reported physical activity and cardiorespiratory fitness are correlated, but directly measured fitness is more strongly associated with cardiovascular risk factors than self-reported activity. (83) Cardiorespiratory fitness reflects the body's circulatory and respiratory systems to sustain oxygen supply during physical exertion and is denoted in metabolic equivalents of task (METs). (84) While cardiorespiratory fitness can be measured directly and more precisely through the maximal oxygen consumption (V02 max), it is more easily estimated from the peak work rate reached on a cycle ergometer or treadmill. (84) In addition to measuring physical activity, cardiorespiratory fitness reflects age, genetics and other host factors and can thereby better assess the general health of an individual. (76,83)

2.10. Cardiorespiratory fitness and prostate cancer

Despite much evidence on the benefit of cardiorespiratory fitness for a broad range of chronic conditions, data on the relationship between fitness and prostate cancer is inconclusive. Most studies do not measure cardiorespiratory fitness but rather rely on self-reported physical activity or questionaries. Some studies report a small protective effect of physical activity. (85–87) A meta-analysis of 19 cohort studies and 24 case-control studies observed that occupational physical activity was associated with a 19% risk reduction of prostate cancer (RR 0.81, 95% CI, 0.73-0.91; $p<0.001$), while recreational physical activity was associated with a marginally statistically significant 5% risk reduction (RR 0.95, 95% CI, 0.89-1.00 $p=0.07$). (85) Protective factors induced by exercise, such as modulation of immune response (88) and enhanced antioxidant defense mechanisms (89), may reduce prostate cancer risk. Exercise decreases endogenous hormones mediating prostate cancer development, such as testosterone (90), insulin-like growth factors (91,92), insulin (93) and androgens (94). Obesity may facilitate more aggressive prostate cancer development through

altered levels of hormones and greater production of inflammatory mediators. (95) In particular, a high circulating level of insulin-like growth factor, often elevated in individuals with obesity, may promote the development of advanced prostate cancer. (96,97) Weight control through exercise may also play a role in high-risk prostate cancer prevention, as a weak association between obesity and aggressive prostate cancer has been noted. (98) However, other studies have reported no association between prostate cancer and fitness. (99–101) Some authors even reported an increased risk of non-advanced prostate cancer at higher levels of leisure-time physical activity. (102) These conflicting results between cardiorespiratory fitness (and physical activity) and prostate cancer incidence and mortality may stem from differential screening practices. Men with high cardiorespiratory fitness are more likely health-conscious and engage in more intensive prostate cancer screening and have a higher chance of a localized prostate cancer diagnosis. Screening bias may explain the different findings for localized versus advanced prostate cancer. PSA testing is more likely to diagnose indolent, localized cancers than advanced cancers, as these become symptomatic earlier on. Additionally, the inconsistency of physical activity classification in many studies impedes the assessment of the association between fitness and prostate cancer. Inconsistent physical activity classification also makes evaluation of a dose-response effect of physical activity and prostate cancer risk difficult.

2.11. Objective

This investigation aims to analyze the impact of cardiorespiratory fitness on PSA screening, prostate cancer incidence, and all-cause mortality in men diagnosed with prostate cancer. (110) Currently, it is unknown precisely how PSA screening behavior varies by fitness level. No studies, as we are aware of, have adequately adjusted for PSA testing when analyzing the relationship between fitness and prostate cancer incidence. (110) We hypothesize that individuals of higher fitness levels engage in more PSA screening. After accounting for PSA screening behavior, we expect an inverse association between cardiorespiratory fitness and prostate cancer incidence. Finally, we hypothesize that all-cause mortality in those diagnosed with prostate cancer decreases with fitness level. The results of the following dissertation were published in „Cancer. Fitness and prostate cancer screening, incidence, and mortality: Results from the Henry Ford Exercise Testing (FIT) Project. Reiter-Brennan C, Dzaye O, Al-Mallah MH, Dardari Z, Brawner CA, Lamerato LE, Keteyian SJ, Ehrman JK, Blaha MJ, Visvanathan K, Marshall CH. 2021 Feb 9."

3. Materials and Methods

3.1.Patients

3.1.1. The FIT-Cancer Cohort

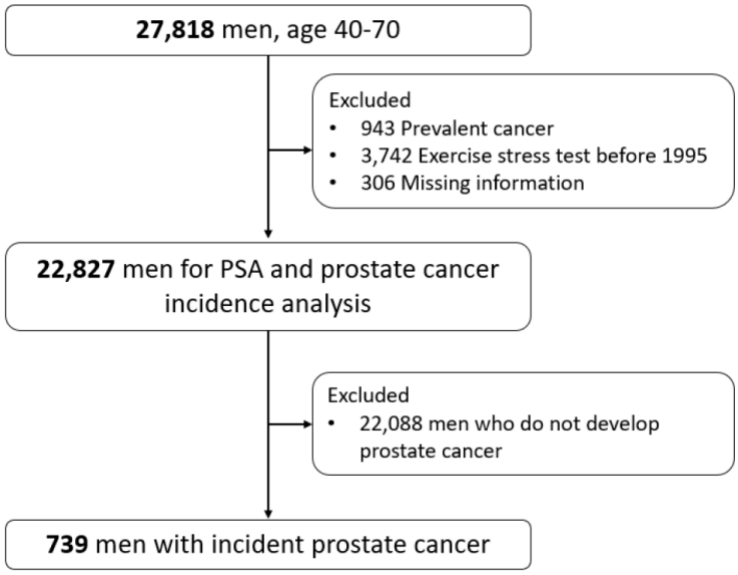
The FIT-Cancer Cohort is a novel data set created from the linkage of the Henry Ford Exercise Testing (FIT) Project with data of the Henry Ford Health System tumor registry. The Henry Ford Health System tumor registry contains cancer incidence reports from 1991 until May 2010 at Henry Ford Health System-affiliated medical centers. (76) The FIT Project is a large, retrospective cohort study of 69,885 adult men and women at Henry Ford Health System-affiliated hospitals and ambulatory care centers in metropolitan Detroit, Michigan, between 1991 and 2009. (103)(110) This single-center cohort study aimed to evaluate the association between cardiorespiratory fitness and clinical events in a racially diverse population. (103) As one of the largest studies of physical fitness, the FIT Project is unique in its heterogeneous population and long follow-up. Other large fitness cohort studies, such as the Aerobic Longitudinal Study of the Lipids Research Clinic Cohort, primarily include white and healthy participants with a lower risk-factor burden than the general population. (103,104) The Henry Ford Health System-affiliated hospitals are located in a large urban area, which allows the inclusion of 30% Africa-American patients, a population often underrepresented in cohort studies. Other studies on cardiorespiratory fitness are limited by modest cohort sizes (usually no more than 25,000 participants) and intermediate follow-up times (< 10 years). (103) In comparison, 50% of patients in the FIT project were followed for more than 10 years. (103) The FIT Project leverages multiple electronic data sources (electronic medical records, pharmacy records, laboratory data, insurance claims data, and administrative claims data) to generate a large healthcare database for epidemiological research. (103) The FIT Project can answer important questions on cardiorespiratory fitness and long-term clinical outcomes through the combination of a comprehensive database with directly measured exercise data. All individuals participated in a physician referred, symptom-limited treadmill stress tests, adhering to the Bruce protocol. (103,105) Reasons for stress testing were noted on the requisition form presented by the referring clinician and categorized by common indications such as palpitations, dizziness, shortness of breath, chest pain, rule out ischemia, or prior abnormal stress test. (103) Asymptomatic patients were

categorized as “risk factors only” if major cardiovascular risk factors were present and “research screening” if there were no risk factors. If individuals underwent repeated stress testing, only the first test was included in the database. Stress testing was terminated at the attending physician’s discretion for life-threatening reasons, such as clinically significant arrhythmias, atypical hemodynamic responses, chest pain, severe shortness of breath, or if the participant could not continue. (103) Medical history, including sex, ethnicity, age, cardiovascular risk factors, and medication use, was self-reported directly before the stress test. Missing data was supplemented by a retrospective search of the electronic medical record and pharmacy claim files for patients enrolled in the systems integrated health plan. Follow-up for nondeath outcomes lasted until May 2010. Data for cardiovascular outcomes were acquired from the electronic medical record, and administrative databases shared between subsidiaries with the same medical system. Nondeath outcomes were censored at the date of the last contact with the Henry Ford Health System when continuous coverage with the health system could not be confirmed to limit bias associated with loss to follow-up or follow-up in centers outside the Henry Ford Health System. (103) For all-cause mortality, participants were followed from baseline to the date of death or April 2013, using an algorithm for searching the Social Security Death Index Death Master File. While many studies leveraged data from the FIT project to answer questions on fitness and outcomes, the data from the FIT-Cancer Cohort was used for the first time in the publication “Cardiorespiratory fitness and incident lung and colorectal cancer in men and women: Results from the Henry Ford Exercise Testing (FIT) Cohort” by Handy Marshall et al., which discusses the relationship between cardiorespiratory fitness and lung and colorectal cancer. (76) The effect of fitness on prostate cancer was not analyzed in this publication due to the lack of PSA data in the FIT-Cancer Cohort’s initial version. To augment the FIT-Cancer Cohort for this publication, PSA values beginning January 3, 1995, through May 31, 2010, were abstracted from the Henry Ford Health System electronic medical record and recorded in a separate PSA data set. (110) Variables of the PSA data set were re-coded and standardized, and combined with the FIT-Cancer Cohort. As a result, the FIT-Cancer Cohort is now a combination of data from the FIT Project, the Henry Ford tumor registry, and PSA data abstracted from the Henry Ford Health System electronic medical records. This analysis is based on this updated version of the FIT-Cancer Cohort.

3.1.2. Population

This population is limited to men aged 40 to 70 years. (110) This age range was chosen because current prostate cancer screening guidelines recommend PSA screening only for this age group. (70,73,106,107) Those with prevalent cancers were excluded, as this would influence the number of PSA tests received. Men with a date of stress test before 1995 were omitted, as PSA testing only became widespread and was available for this cohort after 1995. (108,109) Those missing information in the data set were excluded from the analysis. A consort diagram is shown in Figure 1.

Figure 1: Consort diagram



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3.2. Exposure

Participants' fitness levels were estimated by calculating the METs based on the final speed and elevation achieved while walking on the treadmill. (111) Consistent with the 2002 recommendations of the American College of Cardiology/American Heart Association guidelines, decisions when to stop the stress test was taken by the attending clinicians (i.e., physician, registered nurse, or clinical exercise physiologist). (112) In order to conform with other FIT Project studies, patients were grouped into four respective cardiorespiratory fitness categories; < 6 METs, 6 to 9 METs, 10 to 11 METs, and >= 12 METs. (71,81,82) The category <6 METs was chosen as the reference group in order to be consistent with other FIT Project studies.

3.3. Covariates

Participants' demographic data were obtained during exercise testing and supplemented with other clinical and administrative sources. Medication use was based on medical records and pharmacy claim files. Body mass index (BMI) was based on weight and height measured at the time of the stress test. (110) If BMI was unavailable, values were imputed using multiple imputations by linear regression. Imputation was based on available BMI data, age, sex, and race. (110) Any conditions present at the time of the stress test were recorded and listed as comorbid conditions. Covariates for models for prostate cancer incidence and all-cause mortality were chosen based on risk factors for prostate cancer and all-cause mortality. For example, there is evidence that statin use may be associated with a lower risk of incident prostate cancer, so this was included in the incident model. (113) While long-term, low-dose aspirin use is estimated to reduce cancer mortality, there is conflicting evidence about its effect on prostate cancer risk. (114,115) Hence aspirin was included in the all-cause mortality model but not in the incidence model.

3.4. Outcomes

3.4.1. PSA Screening

All PSA values recorded in the Henry Ford Health System from January 3, 1995, to May 31, 2010, were incorporated in the analysis. PSA tests recorded within 90 days of the previous test were considered a repeat test of the same assessment and excluded from the analysis. In this investigation, we distinguished between screening and monitoring PSA tests. A PSA test was considered a screening test if it occurred more than 6 months prior to prostate cancer diagnosis. (110) All PSA tests were considered screening PSAs among men without a diagnosis of prostate cancer. (110) Monitoring PSA tests were defined as such if administered less than 6 months before or after a prostate cancer diagnosis. Monitoring PSA tests were not the subject of this analysis, as we sought to evaluate the relationship between PSA screening and cardiorespiratory fitness.

3.4.2. Prostate cancer incidence

Prostate cancer incidence was determined with the Henry Ford Cancer Institute tumor registry through May 2010 and compounded with the FIT data set. (110) Cancer types were categorized according to the Surveillance, Epidemiology, and End Results (SEER) program with the *International Classification of Diseases for Oncology, Third Edition* (ICD-O-3) guidelines. (116) Men with prevalent prostate cancers were excluded, and only newly diagnosed prostate cancer was the subject of this study. Prostate cancer cases were classified by localized, regional, and distant disease. Advanced prostate cancer was defined as prostate cancer spread to regional or distant lymphnodes.

3.4.3. All-cause mortality

Men diagnosed with prostate cancer at autopsy or with missing clinical information were excluded. Data on all-cause mortality was procured from the Social Security Death Index Master File and censored in June 2013. (110)

3.5.Statistical Analysis

The PSA test within 6 months of the date of diagnosis was considered the PSA test at the time of diagnosis. Since PSA is a non-normally distributed, right-shifting variable, we compared median PSA values across fitness groups using the nonparametric test for trends across ordered groups developed by Cuzick. (110)

Initially, we used multi-variable adjusted ordinal logistic regression to determine if fitness was associated with PSA screening. We also used multi-variable adjusted logistic regression to evaluate the relationship between fitness and being a high PSA screener (men with >4 PSA screening tests). However, after much deliberation with coauthors, we decided to change the statistical analysis of PSA screening from logistic regression to multi-variable adjusted Poisson regression. The value of odds ratios determined by logistical regression models and incidence rate ratios (IRR) determined by Poisson regression are similar when the outcome is rare. However, the outcome, PSA screening, is not a rare event. To measure the risk of common outcomes, odds ratios calculated by Poisson regression is the appropriate analytical tool. When analyzing a common outcome, such as a PSA test with logistical regression, point estimates are too high. For example, in our initial analysis, the multi-variable adjusted odds of having at least one PSA screening test amongst the highest fitness group was 2.68 (95% CI 2.23 – 3.22), compared to the lowest fitness group. In our current and more accurate analysis, men achieving >=12 METs are associated with an IRR of 1.35 (95% CI 1.22-1.50) of having undergone at least one PSA test, compared to men with low fitness.

The relationship between fitness and incident prostate cancer, advanced prostate cancer, and all-cause mortality was evaluated with multi-variable cox proportional hazard models. (110) Prostate cancer incidence models were adjusted for age, race, BMI, and statin use. (113) The time scale of incident models began at the time of stress test until the date of prostate cancer diagnosis. Mortality models were adjusted for race, aspirin and statin use (at time of stress test), BMI, age at prostate cancer diagnosis, smoking history, hypertension, prior myocardial infarction (MI), congestive heart failure (CHF), or diabetes, cancer stage (local, regional, distant) at diagnosis, year of cancer diagnosis and time from exercise test to prostate cancer

diagnosis. (110) Mortality models were adjusted for time, as two time periods need to be accounted for when evaluating all-cause mortality of men with a prostate cancer diagnosis; date of stress test to prostate cancer diagnosis and date of prostate cancer diagnosis to the date of death. The alpha level was .05. All analyses were completed with Stata version 15. (117)

4. Results

A total of 22,827 men with a mean age of 53.8 years (standard deviation (SD) 7.9 years) were included in the analytic population. (Table 3) This was a racially diverse cohort consisting of 69% White, 24% Black, and 8% other races. (110) At the time of the stress test, at least one comorbid disease was recorded in 31% of the study population. Amongst these patients, 13% reported previous MI, 2% CHF, and 21% were diagnosed with diabetes. Incidence of comorbidities was numerically lower in men with high fitness than men achieving <6 METs in the stress test. Concurrently, medication use was lowest in the men achieving >=12 METs and highest in men achieving <6 METs in the fitness test. Men underwent a median of 4 PSA tests during follow-up (Interquartile range (IQR) 1-8), and median follow-up time was 7.5 years (IQR 5-11). For 442 men (60%), a PSA test result was available at diagnosis. The median time from the PSA test to the date of prostate cancer diagnosis was 57 days (IQR 32-86). (110)

Table 3. Demographics, overall and by peak METs achieved

		Peak METs Achieved			
	Overall	<6	6-10	10-11	>=12
	N=22,827	N=1,931	N=4,735	N=9,108	N=7,053
Mean Age (SD), y	53.8 (7.9)	58.2 (7.9)	57.1 (7.8)	53.7 (7.6)	50.4 (6.8)
Race/ethnicity					
White, no. (%)	15,640 (69)	1,072 (56)	3,035 (64)	6,201 (68)	5,332 (76)
Black, no.(%)	5,410 (24)	766 (40)	1,423 (30)	2,102 (23)	1,119 (16)
Other, no.(%)	1,777 (8)	93 (5)	277 (6)	805 (9)	602 (9)
Smokers, %	49	52	54	51	43
Mean BMI (SD), kg/m^2 categories of BMI (nl, overweight, obese)	29.4 (6)	30.2 (8)	30.6 (6)	29.7 (5)	27.9 (5)
Medication use					
Statin use, %	26	31	33	27	19
Aspirin use, %	24	35	29	23	17
Past medical history					
Myocardial infarction, %	13	38	20	9	5
Diabetes, %	21	38	31	20	10
Congestive heart failure, %	2	15	3	1	<1
Median follow-up, in years (IQR)	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	26	37	45	45
Rule out ischemia, %	12	10	12	13	12
Shortness of breath	10	16	11	9	10

Table 4: PSA descriptor overall and by METs achieved

	Peak METs achieved				
	Overall	< 6	6-9	10-11	≥12
	N=22,827	N=1,931	N=4,735	N=9,108	N=7,053
PSA density (n)					
0 PSA tests	3,570	502	718	1,332	1,309
1-2 PSA tests	4,452	421	876	1,700	4,455
3-5 PSA tests	5,544	398	1,141	2,256	1,749
>= 6 PSA tests	9,261	610	2,000	3,820	2,831
Men with at least one PSA test (%)	84	74	84	85	85
Mean total number of abnormal PSA screening tests (> 4 ng/ml)	0.29	0.36	0.37	1.40	1.39
Mean number of PSA screening tests 10 years after stress test	2.88	2.41	2.88	2.81	2.99
Mean number of PSA screening tests within 5 years of stress test (+/- 5yrs of date of stress test)	0.81	0.71	0.82	0.83	0.82
Median PSA at diagnosis, ng/mL (IQR)	5.1 (4.1-7.1)	5.6 (4.4 – 10.5)	5.3 (4.3 – 8.0)	4.9 (4.1 – 6.7)	5.0 (3.8 – 6.0)

Table not previously published and created only for this dissertation

Table 4 summarizes PSA screening behavior in the overall population and by peak METs achieved. This data was collected during the initial exploratory analysis examining the relationship between PSA testing and fitness. Apart from the median PSA at diagnosis, this data was not included in the paper for publication. PSA screening is prevalent in this population, as 84% of men underwent at least one PSA screening test. In the highest fitness group (>=12 METs), 85% of men underwent at least one PSA screening test, while 74% of men in the low fitness group (<6 METs) had at least one screening test (p for trend <0.01).

As time confounds the total number of PSA tests received, we calculated the mean number of PSA screening tests 10 years after the date of the exercise stress test and within 5 years of stress test (5 years before and 5 years after the date of stress test). Most PSA screening tests were completed 10 years after the stress test. On average, a man underwent 2.88 PSA screening tests within 10 years after the stress test. Men with high fitness (>= 12 METs) underwent an average of 2.99 PSA screening tests within 10 years after the stress test. The mean number of screening tests 5 years prior or 5 years after the stress test was 0.81 for the overall population. Men of higher fitness achieving 10-11 METs or >=12 METs during stress test had the highest mean number of abnormal PSA screening tests (> 4ng/ml), 1.40 and 1.39, respectively. The mean number of abnormal PSA screening tests in the overall population was 0.29. The median PSA value at diagnosis was 5.1 ng/mL (IQR 4.1-7.1), and the median time from PSA to diagnosis was 57 days (IQR 32-86). The median PSA at diagnosis was 5.6 (IQR 4.4-10.5) for men in the lowest fitness group (<6 METs), 5.3 ng/mL (IQR 4.3-8.0) in men achieving 6-9 METs, 4.9 (IQR 4.1-6.7) in men achieving 10-11 METs and 5.0 (IQR 3.8-6.0) among men in the highest fitness group (≥12 METs). (110)

Table 5: Total number of new prostate cancer cases and prostate cancer stage

New prostate cancer cases		Number of cases (n)
Total		739
Cancer stage	Localized (%)	599 (81)
	Regional (%)	118 (16)
	Distant (%)	7 (1)
	Unknown (%)	15 (2)

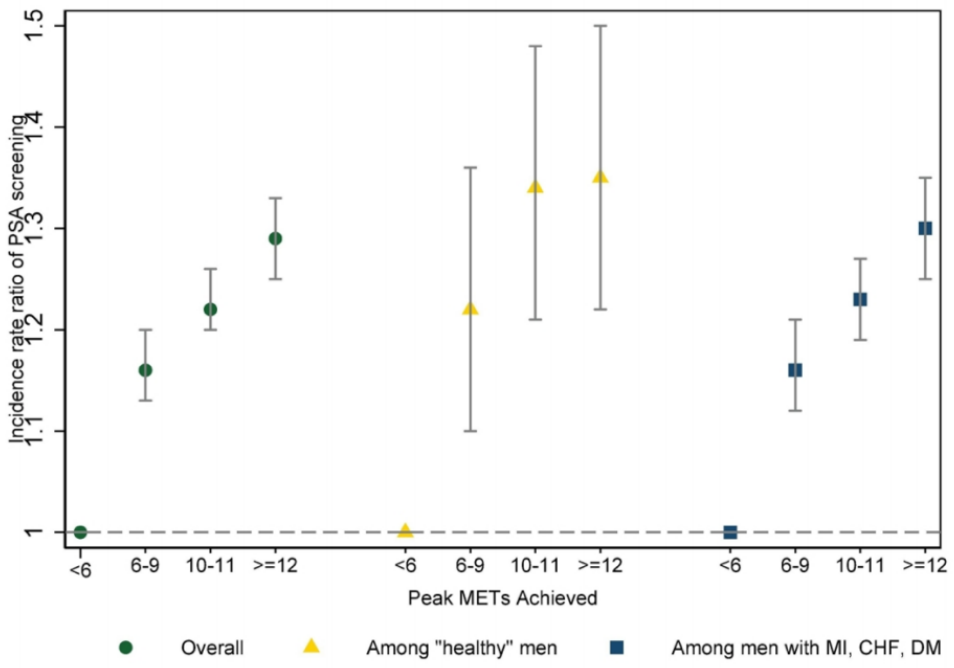
Table not previously published and created only for this dissertation

A total of 739 new prostate cancer cases were detected in men without any previous cancers during follow-up. (Table 5) Among these, 81% were localized disease, 16% regional disease and 1% distant disease.

4.1. Fitness and PSA testing

Figure 2 describes the rate ratios of PSA screening according to peak METs achieved in the physician referred stress test in the overall population and the subgroups. In the overall population, men with high fitness (METs ≥ 12) were 29% more likely to have undergone PSA screening compared to those with low fitness (<6 METs) after adjustment for age, race, and the presence of a prior MI, CHF, or diabetes (IRR 1.29 95% CI 1.25-1.33; P for trend <0.01). (110) (Figure 2) In this analysis, we defined men whose reason for stress test was pre-operative or screening/research as "healthy" compared to the population of men with comorbidities. The "healthy" men with high fitness were 35% (IRR 1.35; 95% CI 1.22-1.50) more likely to undergo PSA screening (P for trend <0.01) than healthy men with low fitness (METS <6). This trend was also seen among men with comorbid diseases. Men with prior MI, CHF, or diabetes who achieved >= 12 METs in the stress test were 30% more likely to undergo PSA screening than men with low fitness (IRR 1.30; 95% CI 1.25-1.35; P for trend <0.01). (110)

Figure 2: PSA screening incidence rate ratios by peak METs achieved



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4.2. Fitness and prostate cancer incidence

The interaction between age and peak METs achieved was statistically significant (p=0.007) for prostate cancer incidence. Therefore, we split the population into two cohorts: those 55 years and younger and those older than 55 years of age at the time of the stress test. Age 55 was selected as the cut point because it was the midpoint between the age group included (40-70 years), and there was no interaction between age and peak METs achieved within those two age groups.

Men 55 years and younger (n=13,082) with high fitness were associated with a significantly higher risk of being diagnosed with prostate cancer after adjusting for age, race, BMI, statin use, and ever having PSA screening (P for trend, 0.02). (110) (Table 6) Men achieving => 12 METs in the fitness test were associated with a 77% increased hazard of a prostate cancer diagnosis compared to men in the lowest fitness group (<6 METs) (HR 1.77 95% CI 0.90 – 3.47). Men achieving 10-11 METs had a 46% higher hazard of incident prostate cancer than men in the lowest fitness category (HR 1.46, 95% CI 0.75-2.84).

A similar trend was observed among men over 55 years of age (n=9,745) after adjusting for confounding variables. Men in this age group with high fitness were associated with a significantly higher risk of prostate cancer diagnosis (p for trend <0.01). Those who achieved 6-9 METs had a 40% increased hazard of being diagnosed with prostate cancer compared to men in the lowest fitness group (<6 METs) (HR 1.40, 95% CI 1.03-1.91). (110) Men who achieved 10-11 METs had a 78% increased hazard of being diagnosed, and those who achieved at least 12 METs had an 80% increased hazard of being diagnosed compared to men in the lowest fitness category (HR 1.78, 95% CI 1.32-2.40 for 10-11 METs, HR 1.80, 95% CI 1.27-2.54 for >=12 METs). (110)

A similar trend was observed without adjustment for PSA screening. (Supplemental Table 1) When adjusted for age, race, BMI, and statin use but not PSA screening, men 55 years and younger achieving >=12 peak METs in the fitness test had a 93% increased hazard of prostate cancer diagnosis compared to men achieving only <6 peak METs (HR 1.93, CI 0.99-3.78). (110) This was similar to the observation among men over 55 years of age (P for trend

<0.01). Compared to men in the lowest fitness group (<6 METs), men who achieved 6-9 METs had a 41% increased risk in prostate cancer diagnosis (HR 1.41, 95% CI 1.04 – 1.92), those who achieved 10-11 METs had a 79% increased risk of diagnosis (HR 1.79, 95% CI 1.33 – 2.41) and those in the highest fitness category, who achieved >=12 METs had an 81% increased hazard of prostate cancer diagnosis (HR 1.81, 95% CI 1.29 – 2.56). (110)

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 0.27). (110) We did not have enough power to calculate the risk of advanced cancer by peak METs achieved.

Table 6. Multi-variable adjusted hazard ratios of incident prostate cancer, adjusted for age, race, BMI, statin use, and PSA screening, stratified by age.

Peak METs achieved	Men 55 years and younger (n=13,082)					Men over 55 years (n=9,745)				
	N	# events	HR	95% CI	P for trend	N	# events	HR	95% CI	P for trend
<6	654	10	Ref		.02	1,277	56	Ref		<0.01
6-9	1,856	27	1.15	0.55, 2.38		2,879	158	1.40	1.03,1.91	
10-11	5,251	80	1.46	0.75,2.84		3,857	230	1.78	1.32,2.40	
>=12	5,321	82	1.77	0.90,3.47		1,732	96	1.80	1.27,2.54	

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Supplemental Table 1: Multi-variable adjusted hazard ratios of incident prostate cancer, adjusted for age, race BMI, statin use, stratified by age (without PSA screening adjustment)

Peak METs achieved	Men 55 years and younger (n=13,082)					Men over 55 years (n=9,745)				
	N	# events	HR	95% CI	P for trend	N	# events	HR	95% CI	P for trend
<6	654	10	Ref		.01	1,277	56	Ref		<0.01
6-9	1,856	27	1.19	0.58, 2.47		2,879	158	1.41	1.04,1.92	
10-11	5,251	80	1.56	0.80, 3.02		3,857	230	1.79	1.33, 2.41	
>=12	5,321	82	1.93	0.99, 3.78		1,732	96	1.81	1.29, 2.56	

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4.3. Fitness and all-cause mortality among men diagnosed with prostate cancer

During follow-up, a total of 115 deaths were recorded. The mean time from exercise stress test to prostate cancer diagnosis was 7.6 years (SD 3.9) and the median age at diagnosis was 61 years (IQR 55-67). We observed a significant inverse relationship between fitness and the risk of all-cause mortality. (Table 7) After adjusting for age at prostate cancer diagnosis, race, BMI, statin and aspirin use, hypertension, smoking history, presence of prior MI, CHF, or diabetes, the time between exercise test and prostate cancer diagnosis, stage at diagnosis, and year of prostate cancer diagnosis, men achieving >=12 METs in the stress test were at lower risk of death compared to men in the lowest fitness category <6 METs (P for trend <0.01). (110) Men achieving >=12 and 10-11 peak METs during the stress test were both had a 60% lower hazard of death compared to men in the lowest fitness category (HR 0.40, 95% CI 0.23-0.72 for METs 10-11 and HR 0.40, 95% CI 0.19, 0.86 for METs >=12). Men who achieved 6-9 METs during the stress test had a 6% lower risk of death (HR 0.94, 95% CI 0.55-1.59) in comparison to men achieving <6 METs. (110)

Table 7: Mortality by fitness after prostate cancer diagnosis, adjusted for age at prostate cancer diagnosis, race, BMI, statin, aspirin, HTN, smoking, comorbid disease (prior MI, CHF, or diabetes), time to prostate cancer diagnosis, stage at diagnosis, year of prostate cancer diagnosis.

Peak METs	N	# of events	HR	95% CI	P for trend
<6	66	21	Ref		<0.01
6-9	185	47	0.94	0.55, 1.59	
10-11	310	34	0.40	0.23, 0.72	
>=12	178	13	0.40	0.19, 0.86	

5. Discussion

In this analysis, men with high fitness engaged in significantly more PSA screening tests than men with low fitness. Men who achieved >=12 peak METS in the physician-referred exercise stress test were 29% more likely to undergo PSA testing compared to men in the lowest fitness category (<6 METs). In the subgroup analysis, this trend was also observed among men with prior MI, CHF, or diabetes and among men without significant comorbidities, whose reason for stress test was pre-operative or research. (110)

Across cancer types, high fitness is associated with reduced incidence and improved outcomes. (74,76,78) Unfortunately, with fitness, as seen with physical activity, this has not been observed in prostate cancer, although undoubtedly, this relationship is confounded by PSA screening habits. (74,102,118,119) Without adjusting for PSA screening, high fitness was associated with an elevated risk of a prostate cancer diagnosis. Even after adjusting for PSA screening, men in the highest fitness category (>= 12 METs) in both age groups were significantly more likely to be diagnosed with prostate cancer. This trend was particularly pronounced in men 55 years and older, who were associated with an 80% higher risk of a prostate cancer diagnosis. However, we found no significant association between fitness and the incidence of advanced prostate cancer.

We observed an inverse relationship between cardiorespiratory fitness and all-cause mortality among men with prostate cancer. Those with high pre-diagnostic fitness (>=12 and 10-11 METs) had a 60% decreased risk of death compared to those with low fitness (<6 METs).

5.1. Prostate cancer incidence and fitness

Our results are similar to the observations from the Aerobics Center Longitudinal Study, in which men with high cardiorespiratory fitness were more likely to undergo PSA screening than men with low cardiorespiratory fitness (16.2% vs. 12.3%) and were at higher risk of prostate cancer diagnoses (3.5% vs. 1.5%). (120) In the Cooper Center Longitudinal Study, men with high cardiorespiratory fitness were 22% more likely to be diagnosed with prostate cancer but were 55% and 44% less likely to be diagnosed with lung and colorectal cancer, respectively. (74) In a cohort study of 2268 Finnish men, a 1-MET increase in cardiorespiratory fitness was associated with a small, non-significant increase in prostate cancer risk (HR 1.03, 95% CI: 0.94-1.12) but reduced risk of lung and GI-tract cancer. (121) These observations stand in line with the healthy screening bias, in which healthier men participate in PSA screening more often than the general population and therefore have a higher risk of a prostate cancer diagnosis. (122) This is supported in our study, as more men in the low fitness group had comorbidities than in the high fitness group, suggesting that those achieving a higher peak workload in their stress test are more health-conscious. In the Aerobics Center Longitudinal Study, prostate cancer risk was only positively associated with cardiorespiratory fitness in men diagnosed before 1995, shortly after the introduction of PSA-base prostate cancer screening in 1987. (120) This may point towards an "early adopter effect," as health-conscious and physically fit men are more likely to be early users of PSA screening. (120) By contrast, the authors observed a negative association between prostate cancer and cardiorespiratory fitness after 1995, when PSA testing was more widely spread amongst all population groups in the United States. Other unmeasured factors related to screening may contribute to the higher risk of prostate cancer incidence observed in this study. While bike riding most likely does not affect PSA, there is some evidence that vigorous exercise like marathon running may elevate PSA. (123,124) Detection bias could have occurred if men with higher fitness were more likely to undergo a biopsy after an elevated PSA test than men with lower fitness. Among men diagnosed with prostate cancer in this study, the median PSA is numerically lower by the level of fitness. This suggests that the decision to biopsy may be at a lower PSA threshold for men with higher fitness levels. The association between biopsy rate and fitness in the current literature is unclear.

5.2. Aggressive prostate cancer

No significant association between advanced prostate cancer and fitness was observed in this study. Most previous reports observed either no association or an inverse association between advanced prostate cancer and cardiorespiratory fitness or self-reported physical fitness. A recent population-based cohort study of Swedish military conscripts reported that high cardiorespiratory fitness during late adolescence was not associated with the incidence of aggressive prostate cancer, defined as clinical stage T3 or T4, Gleason score >=8 or PSA >=20ng/mL later in life. (125) Several reports suggest a reduced risk of advanced disease in men with high self-reported physical activity. (126–128) In a prospective population-based study of 29,110 Norwegian men with 17 years of follow-up, participants were categorized into activity levels by self-reported duration, frequency, and physical exercise intensity. (126) Those with the highest level of physical exercise had a 36% lower risk of advanced prostate cancer than men who reported no activity. (126) This study did not adjudicate for possible differences in PSA screening habits across categories of physical activity, but a follow-up study restricted to a period before 1993 (prior to widespread PSA testing in Norway) reported similar results. (129) A comparable trend is observed with occupational physical activity, as The European Prospective Investigation into Cancer and Nutrition (EPIC) Cohort demonstrated an inverse association between advanced prostate cancer risk and physically strenuous occupation. (130) PSA data was not available for this study, but overall PSA screening rates at the time point of the investigation in Europe were quite low (e.g., 6% in England(131), 10% in Spain(132)).(130) The lack of association between high fitness and risk of advanced prostate cancer suggests that lower risk cancers drive the increased risk of total prostate cancer with high fitness. PSA screening disproportionally augments the detection of low-grade and possible inconsequential cancers, as advanced tumors are more likely to become symptomatic and are diagnosed without screening. (133) A similar relationship exists with obesity and prostate cancer, where obesity is associated with high-grade prostate cancer but not low-grade cancer or overall disease. (15,134) As an alternative hypothesis, fitness may reduce factors related to tumor progression rather than carcinogenesis and reduce the risk of advanced cancer, but not overall risk. (86,126)

5.3. All-cause mortality

Among men diagnosed with prostate cancer, fitness remains a powerful predictor of all-cause mortality, consistent with other studies of men (74,135) and other cancer types. (74,76,78) For example, in a previous report from the Henry Ford FIT Cohort, patients with high cardiorespiratory fitness diagnosed with lung and colorectal cancer had a 44% and 89% decreased risk of death, compared to patients with low pre-diagnostic fitness (HR, 0.56 95% CI, 0.32-1.00 and HR, 0.11 95% CI, 0.03-0.37).(76) A possible explanation for this observation is that most prostate cancer patients die of non-prostate cancer competing causes of death, for which low cardiorespiratory fitness is a strong risk factor. A Swedish nationwide register-based cohort study evaluated the cause of death in non-curatively treated men with prostate cancer from 1991 to 2009. (136) After 15 years following diagnosis, men with low-risk disease had a 9% cumulative risk of prostate cancer death, while men with distant metastatic disease had a 70% cumulative risk of death by prostate cancer. (136) The risk of death by other causes increased with age. Men with low-risk cancer had a 29% risk of dying of other causes at 10 years after diagnosis, compared to 50% at 15 years after diagnosis. (136) Amongst patients who did not die of prostate cancer, CVD was accountable for almost half of deaths across all cancer risk groups. (136) Data from the SEER registry similarly confirms CVD as the main cause of death among prostate cancer survivors in the United States. (137) This double disease burden is well documented in other cancers, as an estimated 13-21% of patients with breast, testis, endometrium, larynx and Hodgkin lymphoma also suffer from CVD. (138) Shared risk factors such as smoking, obesity, old age, and dyslipidemia may contribute to the higher risk of CVD among prostate cancer patients. (139–142) However, to what extent prostate cancer treatment impacts CVD risk is controversial, in part because of a healthy screening bias. Prostate cancer survivors are more likely to undergo routine PSA screening and, in conjunction with this health-seeking behavior, participate in medical cardiovascular preventive care programs more often and have lower CVD risk. (143,144) Concerning the cardiovascular risk of prostate cancer therapy, the current understanding is that radiotherapy and surgery do not elevate CVD risk. (144) Studies on androgen deprivation therapy (ADT) have yielded conflicting results, most likely due to different types and duration of ADT and differences in history of CV events. (144–146) PRONOUNCE is the first prospective cardiovascular outcome trial with sufficient

power to assess primary cardiovascular endpoints in men with prostate cancer and hopefully shed more light on the cardiovascular morbidity associated with ADT. (147) While evidence on the baseline cardiovascular risk after ADT is unclear, men with preexisting CVD seem to have a higher risk of CVD mortality after ADT (148), as well as men with a high number of cardiovascular risk factors. (149) Thus, urologists should be particularly vigilant of CVD development in post-ADT prostate cancer survivors and consider cardiac preventive care programs for these patients.

5.4. Clinical Relevance

5.4.1. Lifestyle interventions

The results of this investigation are relevant when counseling patients on lifestyle-based prevention of prostate cancer. Cardiovascular fitness as a form of tertiary prevention should be propagated in men with prostate cancer to mitigate their substantially higher risk of competing causes of death, in particular CVD. The American Society of Clinical Oncology recommends 150 minutes of weekly physical activity for prostate cancer survivors in their Key Recommendations for Prostate Cancer Survivorship Care. (150) Regular exercise was also shown to improve cancer-related fatigue, reduce prostate cancer treatment-related side effects, and increase overall quality of life indicators. (151,152) Adoption of an active lifestyle may feel unattainable for predominantly sedentary patients, so the compliance with exercise regimes is enhanced if patients understand that easily achievable, small increases in cardiorespiratory fitness can reap significant health benefits. The categorical nature of our study did not allow for a dose-response analysis between fitness and all-cause mortality after a prostate cancer diagnosis, but there is comparable evidence in other studies. In an investigation of healthy men and women below 60 years of age, Nes et al. observed that a 1-MET increase in cardiorespiratory fitness was associated with a 21% reduced risk of CVD mortality and 8-14% reduction of all-cause mortality. (153) Other studies similarly report a 10 – 20% risk reduction of CVD-specific and all-cause mortality for each 1-MET increase in exercise capacity. (154,155) Patients should be aware that such small improvements in cardiorespiratory fitness can already be achieved after 12 weeks. (156) Apart from

cardiovascular fitness, patients should engage in other lifestyle modifications to reduce CVD risk and thereby prostate cancer mortality. A unified guideline on the prevention of chronic diseases, such as cancer and CVD is still lacking. However, the "Nutrition and physical activity guidelines for cancer prevention" of the ACS emulate those for prevention of CVD, by recommending a healthy, plant-based eating pattern, limiting alcohol consumption, maintaining healthy body weight, and engaging in 150-300 minutes of moderate-intensity exercise per week. (157) Participants in the Cancer Prevention Study-II Nutrition Cohort who adhered to the ACS Cancer Prevention Guidelines on BMI, diet, alcohol, and physical activity had a significantly lower risk of dying from CVD, cancer, or all causes combined. (158)

5.4.2. Risk reclassification

Cardiorespiratory fitness significantly improves reclassification of cardiovascular risk and mortality when added to established risk scores. (84) The English and Scottish Health Survey evaluated the value of cardiorespiratory fitness to assess CVD mortality risk in 14,650 men and 17,669 women aged 35 to 70 years with a mean follow-up of 9 years. The addition of cardiorespiratory fitness to standard risk factors resulted in a net reclassification index for CVD mortality of 27.2% and 21.0% for men and women, respectively. (159) The discriminatory value of cardiorespiratory fitness is comparative to other widely used and validated risk scores. For instance, a 1-MET increase in fitness and a 1% increase in the European Risk Score were associated with a 15% and 16% risk reduction for all-cause mortality, respectively. (155)

Information from cardiac stress testing could inform the risk of cancer and the risk of death after a cancer diagnosis. PSA screening is discouraged in men with limited life expectancy and where the risk of death from competing comorbid conditions is higher than cancer mortality. Assessment of fitness can provide valuable information on the risk of death of comorbidities and identify which men would benefit most from screening. While direct measures of cardiorespiratory fitness are expensive and time-consuming, and thereby impractical in most clinical settings, non-exercise testing models can estimate cardiorespiratory fitness with reasonable accuracy and are more easily incorporated in medical examinations. (159)

5.4.3. Reducing overdiagnosis

Despite more risk-adapted and personalized screening strategies, the potential of overdiagnosis through PSA-based prostate cancer screening and consequent overtreatment of indolent cancers is still substantial. In this analysis, men with high cardiorespiratory fitness were more likely to undergo PSA testing and had an increased risk of prostate cancer diagnosis, indicating the possibility of overdiagnosis in this population. Active surveillance can break the link between overdiagnosis and overtreatment, but consensus on inclusion and intervention criteria for active surveillance are still unclear. (160) After 15-years of follow-up, an estimated 45% of men with active surveillance regimes still undergo definitive treatment. (161) To generate a better understanding of which men profit from active surveillance, the worldwide cohort study, Movember Global Action Plan Prostate Cancer Active Surveillance initiative (GAP3), gathers data of men with low-risk prostate cancer on active surveillance. (160) The GAP3 project aims to help create a global consensus guideline on selecting and monitoring men on active surveillance therapy. (160) The European Commission has recently proposed an early prostate cancer detection algorithm that combines mpMRI and risk calculators to reduce unnecessary biopsies and increase the early detection of clinically significant cancers. (162) Men with an elevated PSA are first categorized as low or high risk by a multivariable risk prediction model. A biopsy can be avoided if the risk calculator identifies the patient as low risk. (162) Men classed as high risk should proceed to mpMRI imaging. In general, men with a mpMRI PI-RADS 4-5 lesions should be offered a systematic and targeted biopsy. Men with PI-RADS 1-2 and 3 lesions can safely avoid biopsy if no additional risk factors for clinically significant prostate cancer, such as family history, DRE, or age, are present. (162) Underdiagnosis is limited, as men with negative mpMRI but a high risk of prostate cancer still obtain a biopsy. The combination of biomarkers and mpMRI may further refine pre-diagnostic risk assessment in men with elevated PSAs. (163,164)

5.5. Limitations

This is the first investigation we are aware of accounting for PSA screening habits when analyzing the relationship between cardiorespiratory fitness and prostate cancer incidence. As one of the largest studies of physical fitness, the FIT-Cancer Cohort is unique in its heterogeneous population and extended follow-up and generalizability of fitness data to the general patient population are encountered in clinical practice. However, there are several limitations to address. The FIT-Cancer Cohort is limited to health centers around Detroit and may not be representative of populations outside the United States. We did not evaluate how cardiorespiratory fitness affects prostate cancer-specific mortality. Confounders, such as family history or lifestyle factors like alcohol consumption and diet, were not measured and may have impacted these results. Prostate cancer has a long lead time; thus, long-term exposure to such lifestyle risk factors may significantly impact prostate cancer risk. The FIT-Cancer Cohort lacked information on insurance coverage or socioeconomic status, which may affect screening habits. (110) In addition, we cannot eliminate unrecorded PSA screening done elsewhere outside the healthcare system. Fitness levels may change over time, but we only captured a single baseline assessment in the stress test. Few advanced prostate cancer cases were diagnosed in this investigation, limiting our analysis of the relationship between lethal cancer and fitness. Finally, more investigations with younger men and longer follow-up are necessary to evaluate the differential effects of fitness in this population.

6. Summary

Cardiorespiratory fitness is an independent risk factor for many chronic conditions, but the findings on the relationship between fitness and prostate cancer remain inconclusive. Variations in PSA screening behaviors represent a challenge for this line of research. The purpose of this investigation was to analyze PSA screening behavior relative to level of cardiorespiratory fitness. We then sought to observe the relationship between fitness and prostate cancer incidence accounting for PSA screening. Finally, we examined the relationship between fitness and all-cause mortality among those diagnosed with prostate cancer.

We obtained data for this analysis from the Henry Ford FIT cohort, a retrospective cohort study of men aged 40-70 years who underwent a physician-referred stress test from 1995 to 2009. Cardiorespiratory fitness was measured by a symptom-limited, maximal exercise stress test. Poisson regression and multivariable hazard models were used to model the relationship between fitness, PSA testing, prostate cancer incidence, and all-cause mortality.

Men with high cardiorespiratory fitness had a 28% higher likelihood of undergoing PSA testing than men with low fitness. Even after accounting for PSA screening, high fitness was associated with prostate cancer incidence but not advanced prostate cancer. The risk of all-cause mortality was 60% lower amongst men with prostate cancer who achieved >=12 METs in the stress test, compared to those with low fitness. Our results stand in line with those of other investigations.

In this investigation, PSA screening did not account for the higher incidence of prostate cancer amongst men with high fitness. However, the lower hazard of all-cause mortality associated with high fitness suggests that PSA screening predominantly detects low-risk cancers with little impact on life expectancy. Men with prostate cancer most likely die of CVD rather than prostate cancer, which explains the lower hazard of death among men with high fitness. Public health communication would benefit from a unified health message on the prevention of prevalent chronic diseases. Improvement of cardiorespiratory fitness should be advocated as a highly effective strategy to prevent CVD and cancer incidence and mortality.

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Eidesstattliche Versicherung

„Ich, Cara Reiter-Brennan, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Cardiorespiratory fitness and prostate cancer – analysis of the FIT-Cancer Cohort“ / „Kardiorespiratorische Fitness und das Prostatakarzinom – Analyze des FIT-Cancer Cohorts, selbstständig“ und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum 26.8.2021 Unterschrift

Anteilserklärung an erfolgter Publikation

Cara Reiter-Brennan's contribution to the following publication:

Publication 1: Reiter-Brennan C, Dzaye O, Al-Mallah MH, Dardari Z, Brawner CA, Lamerato LE, Keteyian SJ, Ehrman JK, Blaha MJ, Visvanathan K, Marshall CH. Fitness and prostate cancer screening, incidence, and mortality: Results from the Henry Ford Exercise Testing (FIT) Project. Cancer. 2021 Feb 9. doi: 10.1002/cncr.33426. Epub ahead of print. PMID: 33561293.

- Background literature analysis on prostate cancer, PSA modelling and PSA score in relation to cardiorespiratory fitness
- Completion of intensive data analysis course and STATA introduction course at the Johns Hopkins School of Public Health in preparation for the statistical analysis in this project
- Completion of Institutional Review Board (IRB) online training modules to attain IRB certification to be able to work with the FIT-Cancer Cohort data set
- Standardization of variables and cleaning of data set in order to harmonizing PSA data set with FIT-Cancer Cohort data set
- Statistical analysis of updated version of FIT-Cancer Cohort data set with STATA in consultation with supervisor and statistician
- Preparation of tables (table 1, 2, and 3) and figures (figure 1 and 2) and editing after feedback from supervisor and co-authors
- Drafting first version of manuscript and abstract
- Editing manuscript and abstract after review from supervisors and co-authors
- Preparing manuscript for journal
- Editing manuscript after journal response and drafting rebuttal letter

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Unterschrift des Doktoranden/der Doktorandin

Auszug aus der Journal Summary List (ISI Web of Knowledge SM)

Journal Data Filtered By: **Selected JCR Year: 2019** Selected Editions: SCIE,SSCI
Selected Categories: **"ONCOLOGY"** Selected Category Scheme: WoS
Gesamtanzahl: 244 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	CA-A CANCER JOURNAL FOR CLINICIANS	39,917	292.278	0.093460
2	Nature Reviews Clinical Oncology	12,384	53.276	0.035980
3	NATURE REVIEWS CANCER	52,053	53.030	0.066030
4	LANCET ONCOLOGY	53,592	33.752	0.143420
5	JOURNAL OF CLINICAL ONCOLOGY	155,297	32.956	0.261940
6	Cancer Discovery	18,093	29.497	0.069280
7	CANCER CELL	41,064	26.602	0.095430
8	JAMA Oncology	13,794	24.799	0.064650
9	ANNALS OF ONCOLOGY	45,813	18.274	0.107060
10	Molecular Cancer	15,448	15.302	0.023990
11	Journal of Thoracic Oncology	18,136	13.357	0.038200
12	JNCI-Journal of the National Cancer Institute	36,018	11.577	0.045450
13	Trends in Cancer	2,351	11.093	0.010140
14	SEMINARS IN CANCER BIOLOGY	8,310	11.090	0.011730
15	Journal of Hematology & Oncology	6,732	11.059	0.015550
16	NEURO-ONCOLOGY	12,950	10.247	0.029050
17	CLINICAL CANCER RESEARCH	85,288	10.107	0.131520
18	Journal for ImmunoTherapy of Cancer	4,557	9.913	0.016030
19	CANCER RESEARCH	135,753	9.727	0.118680
20	Liver Cancer	1,131	9.720	0.002660

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
21	Journal of the National Comprehensive Cancer Network	6,912	9.316	0.020020
22	CANCER TREATMENT REVIEWS	9,427	8.885	0.017800
23	Cancer Immunology Research	6,969	8.728	0.026440
24	LEUKEMIA	25,819	8.665	0.048640
25	Blood Cancer Journal	2,800	8.023	0.010400
26	ONCOGENE	66,303	7.971	0.068320
27	Clinical and Translational Medicine	1,349	7.919	0.003280
28	npj Precision Oncology	500	7.717	0.001520
29	BIOCHIMICA ET BIOPHYSICA ACTA-REVIEWS ON CANCER	5,650	7.365	0.007800
30	CANCER LETTERS	34,162	7.360	0.044450
31	EUROPEAN JOURNAL OF CANCER	32,241	7.275	0.048170
32	Gastric Cancer	5,525	7.088	0.010730
33	JOURNAL OF EXPERIMENTAL & CLINICAL CANCER RESEARCH	9,316	7.068	0.014540
34	Therapeutic Advances in Medical Oncology	1,894	6.852	0.004260
35	Molecular Oncology	6,378	6.574	0.013820
36	CANCER AND METASTASIS REVIEWS	6,247	6.400	0.005940
37	Cancers	10,442	6.126	0.018740
38	Oncogenesis	2,775	6.119	0.007750
39	STEM CELLS	20,554	6.022	0.024110
40	npj Breast Cancer	814	6.000	0.003590
41	JOURNAL OF PATHOLOGY	16,307	5.979	0.017910

Selected JCR Year: 2019; Selected Categories: "ONCOLOGY"

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
42	OncoImmunology	10,116	5.869	0.029410
43	INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS	44,197	5.859	0.042160
44	CRITICAL REVIEWS IN ONCOLOGY HEMATOLOGY	8,477	5.833	0.014250
45	BRITISH JOURNAL OF CANCER	46,406	5.791	0.051560
46	Chinese Journal of Cancer	2,330	5.760	0.003700
47	CANCER	66,520	5.742	0.065520
48	NEOPLASIA	7,453	5.696	0.008200
49	Cancer Communications	465	5.627	0.000860
50	MOLECULAR CANCER THERAPEUTICS	19,457	5.615	0.028690
51	CANCER IMMUNOLOGY IMMUNOTHERAPY	8,390	5.442	0.011550
52	Cancer Biology & Medicine	1,389	5.432	0.003640
53	Annual Review of Cancer Biology-Series	318	5.413	0.001270
54	ESMO Open	1,286	5.329	0.004150
55	BIODRUGS	1,803	5.313	0.002980
56	CELLULAR ONCOLOGY	1,719	5.304	0.002220
57	Advances in Cancer Research	2,711	5.235	0.004050
58	American Journal of Cancer Research	5,531	5.177	0.012170
59	INTERNATIONAL JOURNAL OF CANCER	53,177	5.145	0.064950
60	Translational Lung Cancer Research	1,922	5.132	0.005660
61	Cancer & Metabolism	922	5.033	0.002770
62	Clinical Epigenetics	3,787	5.028	0.010640
63	ONCOLOGIST	12,944	5.025	0.020980

Selected JCR Year: 2019; Selected Categories: "ONCOLOGY"

Originalpublikation

Reiter-Brennan, C, Dzaye, O, Al-Mallah, MH, Dardari, Z, Brawner, CA, Lamerato, LE, Keteyian, SJ, Ehrman, JK, Blaha, MJ, Visvanathan, K, Marshall, CH. Fitness and prostate cancer screening, incidence, and mortality: Results from the Henry Ford Exercise Testing (FIT) Project. Cancer. 2021. https://doi.org/10.1002/cncr.33426

Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Danksagung / Acknowledgements

An erster Stelle danke ich Dr. Dominik Geisel und Dr. Omar Dzaye für die einmalige Möglichkeit diese Dissertation fertigzustellen und mir den bereichernden Forschungsaufenthalt an der Johns Hopkins University zu ermöglichen. Speziell möchte ich Dr. Omar Dzaye für die Idee und Umsetzung dieses Johns Hopkins Forschungsprogramms und die Einbindung in so viele weitere Projekte danken. Dr. Dominik Geisel danke ich besonders für die wertvolle Betreuung und zuverlässige Unterstützung, insbesondere in der letzten Phase der Dissertation.

Ebenfalls danke ich dem Biomedical Science Exchange Programm für die finanzielle Unterstützung die diese Promotionsvorhaben ermöglicht hat.

I would like to especially thank Prof. Dr. Mike Blaha for making my incredible stay at Johns Hopkins University possible and for supporting me in every conceivable way throughout my dissertation and after. I also owe a tremendous thanks to Dr. Catherine Handy-Marshall for making the FIT-Cancer cohort project possible and her exceptional mentorship. This dissertation would not have been realized without her strong guidance and limitless support. I also would like to specially thank the Ciccarone Center Team for so warmly welcoming and supporting me during my stay at Hopkins. Thank you Dr. Funmi Obisesan and Dr. Miguel Cainzos-Achirica for being such kind and fun desk neighbors, for lessons in epidemiology and guiding me through STATA frustrations.

Meinen Freunden dank ich für die vielen ermunternden Gespräche und konstruktive Diskussionen. Mein größter Dank gilt jedoch meinen Eltern für ihre bedingungslose und unerschöpfliche Unterstützung, Zuspruch und Motivation.