Recreational and occupational physical activity in relation to prostate cancer aggressiveness: the North Carolina-Louisiana Prostate Cancer Project (PCaP)

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Abstract

Purpose To examine associations between recreational and occupational physical activity and prostate cancer aggressiveness in a population-based, case-only, incident prostate cancer study.

Methods Data were analyzed from the cross-sectional North Carolina-Louisiana Prostate Cancer Project of African-American ($n = 1{,}023$) and European-American ($n = 1{,}079$) men newly diagnosed with prostate cancer (CaP). High-aggressive CaP was defined as Gleason sum ≥ 8, or prostate-specific antigen > 20 ng/ml, or Gleason sum ≥ 7 and clinical stage T3–T4. Metabolic equivalent tasks (MET) were estimated from self-reported recreational physical activity in the year prior to diagnosis assessed retrospectively via a validated questionnaire and from occupational physical activity based on job titles. Associations between physical activity variables and high-aggressive prostate cancer were estimated using logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for multiple confounders.

Results There was suggestive evidence that walking for 75–150 min/week for exercise is associated with lower odds of high-aggressive prostate cancer compared to no walking (OR = 0.69, 95% CI 0.47–1.01). Physical activity at the current job was associated with 24% lower odds of high-aggressive prostate cancer (highest vs. lowest tertile OR = 0.76, 95% CI 0.56–1.04). However, total MET-h/week of recreational physical activity and accumulation of high-level physical activity at the longest-held job were not associated with high-aggressive prostate cancer. Results did not vary by race.

Conclusions The odds of high-aggressive prostate cancer were lower among men who walk for exercise and those engaged in occupations with high activity levels.

Keywords Prostate cancer · Physical activity · Recreational physical activity · Leisure time · Occupational physical activity · African American

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Abbreviations

ACS	American Cancer Society
BMI	Body mass index
CI	Confidence interval
DRE	Digital rectal exam
HR	Hazard ratio
IGF-1	Insulin and insulin-like growth factor 1
LSUHSC	Louisiana State University Health Sciences Center
MET	Metabolic equivalent task
NCI-DHQ	National Cancer Institute's Diet History Questionnaire
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PCaP	North Carolina-Louisiana Prostate Cancer Project
PSA	Prostate-specific antigen
RR	Relative risk
SES	Socioeconomic status
UNC-CH	University of North Carolina at Chapel Hill

Introduction

Despite prostate cancer being the most frequently diagnosed invasive cancer and the second leading cause of cancer death in American men, it often presents as an indolent disease with few modifiable risk factors available to inform prevention efforts [1, 2]. Physical activity has been implicated in the etiology of prostate cancer; however, most systematic reviews have reported modest inverse or null associations for risk of any prostate cancer [3–14]. These inconsistent findings may be attributed to failure to distinguish between lethal and indolent forms of prostate cancer or to methodological challenges in the operational definitions and measurement of physical activity in both recreational and occupational domains.

A 2018 meta-analysis reported a summary relative risk (RR) of advanced/aggressive prostate cancer of 0.92 (95% CI 0.80–1.06) for highest versus lowest levels of overall pre-diagnosis physical activity, and an inverse association for long-term regular recreational activity. However, no association was found between long-term occupational physical activity and advanced/aggressive prostate cancer [12]. A pooled analyses of the National Cancer Institute's Cohort Consortium reported an unexpected increased risk of non-advanced prostate cancer for higher pre-diagnosis leisure-time physical activity, but no association with advanced prostate cancer. The authors thought this finding might be explained, in part, by screening bias since prostate cancer screening was not controlled for in the multivariable model [15]. While there is biological evidence linking physical activity and prostate cancer aggressiveness [16], the type, frequency, duration, and intensity of physical activity required to reduce the risk of developing aggressive prostate cancer remain unclear.

Most previous studies that examined associations between physical activity and advanced or aggressive prostate cancer were conducted primarily among persons of European ancestry. By contrast, African-American men have the highest incidence rates of prostate cancer and tend to be diagnosed with more aggressive prostate cancer compared to other racial/ethnic groups [1, 17]. Other concerns of previous literature include inadequate control for confounding and limited evaluation of effect modification, particularly potential confounding by family history of prostate cancer or prostate cancer screening history [12]. Physically active men and men with a family history of prostate cancer may be more likely to screen regularly, and men who screen regularly are more likely to be diagnosed with less aggressive prostate cancer (i.e., earlier clinical stage, lower Gleason sum, and lower prostate-specific antigen (PSA) level at diagnosis) [18, 19]. Only four of 57 studies included in a meta-analysis on physical activity and prostate cancer adjusted for PSA screening [12].

To address these gaps in the literature, associations of carefully measured recreational and occupational physical activity with high-aggressive prostate cancer were examined among African-American and European-American men with incident prostate cancer, adjusting for multiple factors known to be associated with diagnosis of aggressive prostate cancer, including PSA and digital rectal exam (DRE) screening.

Materials and methods

Data source and study population

Data from the North Carolina-Louisiana Prostate Cancer Project (PCaP) were utilized. PCaP is a large, racially diverse, population-based, case-only study of incident prostate cancer. Details of the study methods and population have been described [20]. Briefly, PCaP consists of North Carolina and Louisiana residents with histologically confirmed, incident adenocarcinoma of the prostate diagnosed between 1 July 2004 and 31 August 2009. Potential research subjects were eligible if they resided within the catchment areas of the study, were between 40 and 79 years of age at the time of diagnosis, self-identified as Black/African American or White/Caucasian/European American, were able to complete the study interview in English, did not live in an institution (e.g., nursing home), and were physically and mentally capable of completing study interview(s). Informed consent was obtained from all individual research subjects included in the study. The study protocols were approved by Institutional Review Boards (IRBs) at the University of North Carolina–Chapel Hill, Louisiana State University Health Sciences Center, Department of Defense Prostate Cancer Research Program, and the University of South Carolina.

PCaP included an extensive evaluation of sociodemographic, individual, biological, and tumor characteristics [20]. PCaP nurses administered structured questionnaires soliciting information including prostate cancer diagnosis, prostate cancer screening history, family history of prostate cancer, occupation, diet, supplement use, and physical activity, among others.

Physical activity assessment

Recreational physical activity in the year prior to cancer diagnosis was assessed retrospectively using a modified questionnaire that had been tested for relative validity among adults age 50–75 years in Washington state (partial Pearson correlation coefficient = 0.68 for average MET-hours per week from questionnaire compared to a detailed interview) [21] and was used in a previous case–control study of prostate cancer [22]. We modified the original questionnaire slightly to inquire about the year prior to diagnosis (the original questionnaire inquired about the past 10 years), removed the separate question about yoga, and separated moderate and vigorous activities into separate questions. The modified version of the questionnaire was not validated. The physical activity questionnaire covered the type, frequency, duration, and intensity of recreational activity. The research subjects were asked "in the 12 months prior to prostate cancer diagnosis, did you: walk for exercise (including walking on a treadmill), lift weights or use weight machines, do light exercise, do moderate exercise, or do vigorous exercise?" For each question, there were three response category options for days per week (1–2, 3–4, or 5–7). There were four response category options for minutes per day (10–25, 30–40, 45–55, or 60 +) with the exception of the light exercise question that had three response category options for hours per day (< 1 h, 1–2 h, or 3+ h). Research subjects who walked for exercise were also asked to indicate the pace: casual (each mile takes 30 min or more), moderate (each mile takes 20–29 min), or fast (each mile takes 19 min or less). In addition to questions on frequency and duration, those research subjects who performed moderate and/or vigorous exercise were asked about the most frequent type of exercise. The research subjects were also asked about the usual frequency of exercise or sports at age 18, 30, and 45 years with the following response choices: none, 1, 2–3, 4–5, or 6–7 days per week.

Occupational physical activity was measured by job titles [23]. Research subjects were asked open-ended questions about their current and longest-held jobs. For current job, research subjects were asked about their current occupational status (employed full time, employed part time, retired, or unemployed), job title (i.e., "what is your current job?"), the name of the company or business where they work, and when they started working their current job. For longest-held job, research subjects were asked "what occupation or line of work have you done the longest?" They also were asked to indicate the total number of years spent at that job and the company or business for which they worked. When a research subject reported having more than one current job or more than one longest-held job, the job with the longest duration (based on number of years on the job) was used in the analyses. The same job title was used for both measures of occupational physical activity when the current job was the same as the longest-held job.

Metabolic equivalent task (MET) values were estimated for the various recreational physical activities and for the current and longest-held job titles using the 2011 *Compendium of Physical Activities* [24]. The Compendium contains estimates of MET values for more than 800 different types of physical activities and job titles. A MET is calculated as a ratio of the metabolic rate for a specified activity divided by the individual's resting metabolic rate [24]. MET-hours/week for specific activities was estimated by multiplying hours per week of the activity (days per week multiplied by minutes per day/60) by the MET value assigned for that activity. Total MET-hours/week was estimated as the sum of MET-hours per week for light, moderate, and vigorous exercise. The actual MET values assigned by the Compendium were used for current job titles. MET-years were calculated as MET*time on the job in years for the longest-held job.

Outcome variable

Medical records related to prostate cancer diagnosis and staging were requested from the diagnosing physician of consenting research subjects and abstracted to obtain clinical stage, Gleason grade, and PSA level at the time of diagnosis, in addition to other information. Quality assurance was maintained by randomly selecting and abstracting duplicate records for approximately 10% of medical records by a second staff member to ensure inter-abstractor consistency with the standardized protocol. Prostate cancer aggressiveness was defined using a combination of Gleason sum, cancer stage, and PSA level at diagnosis and classified as high-aggressive (Gleason sum ≥ 8 or PSA > 20 ng/ml or Gleason sum ≥ 7 and clinical stage T3–T4), low-aggressive (Gleason sum < 7 and clinical stage T1–T2 and PSA < 10 ng/ml), or intermediate-aggressive (all other cases) [20]. A case-case analysis was performed by contrasting high-aggressive prostate cancer with the comparison group of low-/intermediate-aggressive prostate cancer.

Other study variables

Data on potential confounders including demographics, family history of prostate cancer, medical history, and lifestyle factors were collected from interviewer-administered questionnaires. PCaP nurses obtained standardized anthropometric measures that included weight and height at the in-home visit. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters and categorized as < 25 (referent group), 25–29 (overweight), or ≥ 30 (obese) kg/m^2. Research subjects were asked if they ever had a routine PSA blood test or DRE other than any exams that were done recently as part of their diagnosis, the date of their first PSA and/or DRE, and how many times they had the PSA or DRE, not counting the recent exams as part of their diagnosis. Information on previous PSA and DRE screening was combined to create a previous prostate cancer screening variable. A modified National Cancer Institute's Diet History Questionnaire (NCI-DHQ) [25] was used to obtain information on usual dietary habits over the year prior to prostate cancer diagnosis. Total energy intake and alcohol intake were calculated from the NCI-DHQ responses. Research subjects with extreme energy intake (< 500 or > 6,000 kcals/day) were excluded from the analyses.

Statistical analyses

The physical activity variables examined included walking for exercise (yes *vs*. no), minutes walked for exercise (0, 1–74, 75–150, or > 150 min/week), and the American Cancer Society (ACS)-recommended minutes of physical activity for cancer prevention (< 150 min/week of moderate physical activity or < 75 min/week of vigorous physical activity *vs*. ≥ 150 min/week of moderate physical activity or ≥ 75 min/week of vigorous physical activity) [26]. The ACS-recommended level of physical activity plus weightlifting also was examined (≥ 150 min/week of moderate physical activity plus weightlifting for exercise or ≥ 75 min/week of vigorous physical activity plus lifting weights for exercise vs. those who do not meet this requirement). The other measures of physical activity were MET-hours/week from walking for exercise; total MET-hours/week of recreational physical activity; MET-hours/week of light, moderate or vigorous physical activity; and days/week of physical activity earlier in life at ages 18, 30, and 45 years. MET-hours were categorized into tertiles based on their distribution in the low-/intermediate-aggressive prostate cancer group, with lower tertiles as the referent groups. For occupational activity, current job MET was categorized as no job as the referent and two other categories defined by less than or greater than the median (2.3 METs) of low-/intermediate-aggressive cases who were currently working, and longest-held job activity was categorized into tertiles based on the low-/intermediate-aggressive cases.

Twenty-two subjects had missing data on frequency and duration of physical activity among those who engaged in light, moderate, or vigorous physical activity. For these research subjects, data were imputed using the most frequent response for these variables based on the individual subject's age (± 2 years), race/ethnicity, and prior responses to questions on light, moderate, and vigorous physical activity. For example, if a research subject answered "yes" to light, moderate, and vigorous physical activity but had missing data on days/week or minutes/day for any of these activities, the missing information was replaced with the most frequent response on days/week or minutes/day for men of similar age and the same race as the research subject. In sensitivity analyses, the 22 research subjects were excluded for which one or more of the physical activity variables were imputed and analyses were repeated.

Descriptive statistics (means, frequencies, and percentages) of the study variables were reported overall and by level of prostate cancer aggressiveness. ORs and 95% CIs were estimated using unconditional logistic regression. The minimally adjusted models included adjustment for age and race. Multivariable models included additional potential confounders that were selected from review of the literature including age (continuous); race (African American or European American); study site (UNC or LSUHSC); family history of prostate cancer (none or at least one affected first-degree relative); education (graduate/professional degree, some college or college graduate, high school graduate or vocational/technical school, or less than high school education); screening history (none, previous PSA or DRE but not both, or previous history of both PSA and DRE); smoking status (non-smoker, former smoker, or current smoker); BMI (continuous); total energy intake (kcals/day, continuous); alcohol intake (servings/day, continuous); NSAIDs use (no or yes); and Charlson comorbidity index (none, 1–3 comorbidities, or > 3 comorbidities).

Tests for linear trend (p_{trend}) were represented by the *p*-values for the continuous variables. Stratified analyses were conducted, and *p*-values for multiplicative interaction terms were used to examine whether associations varied by race, BMI categories, PSA and DRE screening history, and NSAIDs use. Joint effects of walking for exercise and current occupational physical activity were examined using the common referent group of < 75 min/week walking and no current job. The 204 research subjects who were excluded due to missing data or outlier energy intakes were compared to those who were included in the analyses using descriptive statistics.

PCaP research subjects have been followed through December 2019 in LA and through February 2021 in NC for mortality outcomes through linkage with the National Death

Index and state cancer registries and state vital offices. There were 61 research subjects who were initially diagnosed with low- or intermediate-aggressive prostate cancer based on the aggressiveness definition above but who later died of prostate cancer. In sensitivity analyses, we reclassified these research subjects as high-aggressive and reran the multivariable models using this new outcome definition.

All statistical analyses were performed using SAS version 9.4 (SAS Inc, Cary, NC, USA), with statistical significance set at $\alpha = 0.05$ (two-tailed).

Results

Data on 2,258 PCaP research subjects were considered initially for analyses. Research subjects were excluded for missing information on prostate cancer aggressiveness ($n = 85$), extreme energy intake ($n = 71$), missing physical activity questionnaires ($n = 26$), or missing data on education ($n = 1$), NSAIDs use ($n = 2$), or BMI ($n = 19$), which left a final sample size of 2,054 for analyses. Distributions of demographic and lifestyle characteristics are presented overall and stratified by prostate cancer aggressiveness (Table 1) (low-/intermediate-aggressive, $n = 1{,}700$; high-aggressive, $n = 354$). African-American men were more likely than European-American men to be diagnosed with high-aggressive prostate cancer (55% vs. 45%, respectively). Compared to research subjects with low-/intermediate-aggressive prostate cancer at diagnosis, those with high-aggressive prostate cancer were more likely to have no family history of prostate cancer, less than a high school education, no previous screening for prostate cancer, be current smokers, or to have at least one comorbidity. Average physical activity measures tended to be lower among research subjects with high-aggressive prostate cancer as compared to low-/intermediate-aggressive (Supplemental Table 1).

The 204 research subjects who were excluded were compared to those who were included in the analyses (Supplemental Table 2). Excluded and included research subjects were similar in average age, BMI, and number of comorbidities. Among those excluded, a higher proportion were African Americans, had lower educational attainment, reported no previous prostate cancer screening, or were current smokers than in the included research subjects.

Associations of recreational physical activity and prostate cancer aggressiveness are presented in Table 2. A modest, non–statistically significant inverse association was observed in the adjusted model (OR = 0.89, 95% CI 0.70–1.13) for those who reported walking for exercise compared to those who did not. When duration and frequency were considered, men who walked 75–150 min/week for exercise had a non-statistically significant 31% lower odds of high-aggressive prostate cancer when compared to those who did not walk for exercise (OR = 0.69, 95% CI 0.47–1.01). Walking for more than 150 min/week was not associated with high-aggressive prostate cancer (OR = 0.89, 95% CI 0.64–1.23). MET-hours/week from walking for exercise also was inversely associated with high-aggressive prostate cancer, although the association was not statistically significant (highest *vs*. lowest tertile OR = 0.77, 95% CI 0.57–1.05; $p_{\text{trend}} = 0.48$).

Total MET-hours/week for recreational activity, a function of frequency, duration, and intensity of light, moderate, and vigorous physical activity, was not associated with high-aggressive prostate cancer (highest *vs*. lowest tertile OR = 1.06, 95% CI 0.79–1.43), and neither were light ($p_{\text{trend}} = 0.71$) or moderate ($p_{\text{trend}} = 0.33$) physical activity (Table 2). Vigorous physical activity was associated with a non-statistically significant lower odds of high-aggressive prostate cancer (highest *vs*. lowest tertile OR = 0.65, 95% CI 0.39–1.09). No associations were observed between ACS-recommended minutes of moderate to vigorous physical activity or ACS-recommended minutes plus weightlifting and prostate cancer aggressiveness. In sensitivity analyses, the results were similar after excluding the 22 research subjects for whom imputation of one or more physical activity variables was performed (Supplemental Table 3).

No associations were observed for reported physical activity at ages 18, 30, or 45 years and high-aggressive prostate cancer (Supplemental Table 4). Additionally, there was no evidence of interaction by race ($p_{\text{interaction}} = 0.87$), BMI ($p_{\text{interaction}} = 0.47$), screening history ($p_{\text{interaction}} = 0.49$), or NSAIDs use ($p_{\text{interaction}} = 0.17$) on the association between minutes walked for physical activity/week and prostate cancer aggressiveness (Table 3). However, associations between walking for > 75 min/week and high-aggressive prostate cancer were strongest among categories of obese research subjects, those with a previous history of both PSA and DRE screening, and those who were regular users of NSAIDs within five years prior to prostate cancer diagnosis compared to associations among other strata of these three variables.

Table 4 presents associations between occupational physical activity and prostate cancer aggressiveness. Higher physical activity at current job was associated with a non-statistically significant 24% lower odds of high-aggressive prostate cancer (highest *vs*. lowest tertile OR = 0.76, 95% CI 0.56–1.04). A higher level of occupational physical activity accumulated at the longest-held job (MET-years) was not associated with prostate cancer aggressiveness (highest *vs*. lowest tertile OR = 1.05, 95% CI 0.77–1.44). Within the joint association analyses (Table 5), the strongest reduced odds of high-aggressive prostate cancer were observed among research subjects who walked for exercise ≥ 75 min per week and had current job titles with ≤ 2.3 MET values (OR = 0.51, 95% CI 0.27–0.96), though reduced odds were observed for

Table 1 Distribution of study population characteristics in the North Carolina-Louisiana Prostate Cancer Project (PCaP) and by prostate cancer aggressiveness[a]

Characteristics	Low-/intermediate-aggressive ($n=1700$)		High-aggressive ($n=354$)		All included PCaP research subjects ($n=2054$)	
	Mean (SD)		Mean (SD)		Mean (SD)	
Age, years	63 (8)		65 (8)		63 (8)	
Body mass index, kg/m^2	29.1 (5.1)		30.1 (6.0)		29.3 (5.3)	
Energy intake, kcals/day	2453.5 (1018.1)		2635.8 (1136.4)		2484.9 (1041.5)	
Alcoholic drinks, servings/day	1.1 (2.5)		1.3 (3.0)		1.1 (2.6)	
	n	%	*n*	%	*n*	%
Race						
African American	794	47	195	55	989	48
European American	906	53	159	45	1065	52
Study site						
UNC	815	48	155	44	970	47
LSUHSC (pre & post Katrina)	885	52	199	56	1084	53
Family history of prostate cancer						
No affected 1st-degree relative	1279	75	285	81	1564	76
At least 1 affected 1st-degree relative	421	25	69	19	490	24
Education						
Graduate/professional degree	256	15	35	10	291	14
Some college or college graduate	605	36	118	33	723	35
High school grad or voc/tech school	530	31	96	27	626	31
Less than high school education	309	18	105	30	414	20
Screening history						
No previous screening history	182	11	78	22	260	12
Previous PSA or DRE, but not both	317	19	87	25	404	20
Previous history of both PSA and DRE	1201	71	189	53	1390	68
Smoking status						
Non-smoker	599	35	96	27	695	34
Former smoker	871	51	185	52	1056	51
Current smoker	230	14	73	21	303	15
NSAIDs use						
No	656	39	134	38	790	38
Yes	1044	61	220	62	1264	62
Charlson Comorbidity Index						
No comorbidities	861	51	163	46	1024	50
1–3 comorbidities	733	43	163	46	896	44
> 3 comorbidities	106	6	28	8	134	6

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[a]Prostate cancer aggressiveness defined by a combination of Gleason sum, clinical stage, and PSA level at diagnosis and classified as follows: high-aggressive (Gleason sum ≥ 8 or PSA > 20 ng/ml or Gleason sum ≥ 7 AND clinical stage T3–T4); and low-/intermediate-aggressive (all other cases)

each combination of walking for exercise and current job activity compared to the lowest joint categories of each.

In sensitivity analyses when the high-aggressive outcome variable was modified to include research subjects who were originally diagnosed with low- or intermediate-aggressive prostate cancer who later died of prostate cancer, associations with walking for exercise strengthened slightly (OR = 0.64, 95% CI 0.45–0.93 for walking 75–150 min/week), while the association with current job activity was slightly attenuated (Supplemental Table 5).

Table 2 Associations between recreational physical activity and high-aggressive prostate cancer in PCaP

	High-/low-intermediate-aggressive cases	Minimally adjusted model[a]			Adjusted model[b]		
		OR	95% CI	p_{trend}	OR	95% CI	p_{trend}
Walked for exercise							
No	177/760	1.00	(ref)		1.00	(ref)	
Yes	177/940	0.79	0.63–0.99		0.89	0.70–1.13	
Minutes/week walked for exercise							
0	177/760	1.00	(ref)		1.00	(ref)	
1–74	70/325	0.93	0.69–1.27		1.07	0.78–1.47	
75–150	40/271	0.61	0.42–0.88		0.69	0.47–1.01	
> 150	67/344	0.80	0.58–1.09	0.60	0.89	0.64–1.23	0.62
MET-hours/week from walking for exercise							
0	177/760	1.00	(ref)		1.00	(ref)	
1–5.7	99/452	0.92	0.70–1.20		1.01	0.76–1.34	
> 5.7	78/488	0.67	0.50–0.90	0.15	0.77	0.57–1.05	0.48
Total MET-hours/week							
< 7.2	128/551	1.00	(ref)		1.00	(ref)	
7.2–20.7	116/566	0.95	0.71–1.25		1.07	0.79–1.43	
> 20.7	110/583	0.89	0.67–1.18	0.39	1.06	0.79–1.43	0.94
MET-hours/week for light physical activity							
0	98/437	1.00	(ref)		1.00	(ref)	
1–4.5	104/577	0.88	0.65–1.20		1.03	0.75–1.42	
> 4.5	152/686	1.06	0.80–1.41	0.99	1.23	0.91–1.65	0.71
MET-hours/week for moderate physical activity							
0	159/700	1.00	(ref)		1.00	(ref)	
1–7.4	114/592	0.93	0.71–1.21		1.04	0.78–1.39	
> 7.4	81/408	0.95	0.71–1.28	0.93	1.16	0.85–1.59	0.33
MET-hours/week of vigorous physical activity							
0	287/1275	1.00	(ref)		1.00	(ref)	
1–13	48/253	0.94	0.67–1.31		1.08	0.76–1.55	
> 13	19/172	0.56	0.34–0.91	0.07	0.65	0.39–1.09	0.28
ACS-recommended minutes of physical activity[c]							
L1	257/1185	1.00	(ref)		1.00	(ref)	
L2	97/515	0.96	0.74–1.25		1.11	0.84–1.46	
ACS-recommended level of physical activity, including weight lifting[d]							
L1	329/1531	1.00	(ref)		1.00	(ref)	
L2	25/169	0.83	0.53–1.29		0.96	0.60–1.51	

[a]Adjusted for age and race

[b]Adjusted for age, race, study site, family history of prostate cancer, education, PSA and DRE screening history, smoking status, BMI, total energy intake, alcohol intake, NSAIDs use, and Charlson comorbidity index

[c]ACS- and American College of Sports Medicine/American Heart Association-recommended minutes of physical activity for cancer prevention: L1 < 150 min/week of moderate physical activity or < 75 min/week of vigorous physical activity. L2 ≥ 150 min/week of moderate physical activity or ≥ 75 min/week of vigorous physical activity

[d]ACS-recommended level of physical activity including weightlifting: L2 ≥ 150 min/week of moderate physical activity or ≥ 75 min/week of vigorous physical activity AND lifts weight for exercise; L1 = all other cases

Discussion

This population-based, case-only study with similar numbers of African-American and European-American men provides suggestive evidence that walking for exercise and occupational physical activity are inversely associated with high-aggressive prostate cancer. Walking for 75–150 min/week for exercise in the year prior to diagnosis was associated with

Table 3 Adjusted[a] ORs for associations between minutes walked per week for exercise and high-aggressive prostate cancer stratified by race, obesity status, screening history, and NSAIDs use in PCaP

	Minutes/week walked	High-/low-intermediate-aggressive cases	OR	95% CI
Main effect	< 75	247/1085	1.00	(ref)
	≥ 75	107/615	0.80	0.62–1.04
Race				
African American	< 75	136/516	1.00	(ref)
	≥ 75	59/278	0.77	0.54–1.10
European American	< 75	111/569	1.00	(ref)
	≥ 75	48/337	0.75	0.51–1.11
	p (interaction by race) = 0.87			
BMI categories[b]				
Normal weight	< 75	42/212	1.00	(ref)
	≥ 75	18/114	0.87	0.46–1.66
Overweight	< 75	90/462	1.00	(ref)
	≥ 75	46/280	0.85	0.57–1.29
Obese	< 75	115/411	1.00	(ref)
	≥ 75	43/221	0.67	0.45–1.00
	p (interaction by BMI) = 0.47			
Screening history				
No previous screening history	< 75	55/128	1.00	(ref)
	≥ 75	23/54	0.94	0.51–1.73
Previous PSA or DRE, but not both	< 75	61/210	1.00	(ref)
	≥ 75	26/107	0.82	0.48–1.41
Previous history of both DRE and PSA	< 75	131/747	1.00	(ref)
	≥ 75	58/454	0.72	0.51–1.01
	p (interaction by screening history) = 0.49			
NSAIDs use[c]				
No	< 75	88/426	1.00	(ref)
	≥ 75	46/230	0.95	0.63–1.44
Yes	< 75	159/659	1.00	(ref)
	≥ 75	61/385	0.68	0.49–0.95
	p (interaction by NSAIDs) = 0.17			

[a]Adjusted for age, race (in race-unstratified groups), study site, family history of prostate cancer, education, PSA and DRE screening history (in screening-unstratified groups), smoking status, BMI (in BMI-unstratified groups), total energy intake, alcohol intake, NSAIDs use (in NSAIDs use-unstratified groups), and Charlson comorbidity index

[b]BMI categories: normal weight (BMI < 25 kg/m^2); overweight (BMI = 25–29 kg/m^2); obese (BMI ≥ 30 kg/m^2)

[c]Use of NSAIDs within 5 years prior to diagnosis

31% (95% CI 0.47, 1.01) reduced odds of high-aggressive prostate cancer. Total MET-hours from physical activity and light and moderate physical activity intensity levels were not associated with prostate cancer aggressiveness. However, there was a suggestive inverse association with vigorous physical activity. No associations were observed for ACS-recommended levels of physical activity or physical activity earlier in life at age 18, 30, or 45 years and prostate cancer aggressiveness. While there was no evidence for statistical interaction with race, BMI, screening history, or NSAIDs use, the inverse associations with walking were strongest among obese, highly screened, and users of NSAIDs compared to associations among the other groups. A higher level of physical activity at current job was inversely related to high-aggressive prostate cancer, while there was no association with physical activity at the longest-held job.

The current study suggests a link between walking for exercise and decreased risk of high-aggressive prostate cancer and is supported by limited research, most of which is related to risk of overall prostate cancer rather than advanced or aggressive prostate cancer [12]. In a population-based prospective study in Sweden, Orsini et al. [27] observed a 26% lower risk (RR = 0.74, 95% CI 0.59–0.92) of developing advanced prostate cancer among men with

Table 4 Associations between occupational physical activity and high-aggressive prostate cancer in PCaP

	High-/low-intermediate-aggressive cases	Minimally adjusted model[a]			Adjusted model[b]		
		OR	95% CI	p_{trend}	OR	95% CI	p_{trend}
Current job, MET tertiles[c]							
T1	217/815	1.00	(ref)		1.00	(ref)	
T2	61/425	0.67	0.49–0.93		0.81	0.57–1.14	
T3	75/459	0.71	0.53–0.96	0.59	0.76	0.56–1.04	0.73
Longest-held job, MET-years tertiles[d]							
T1	97/463	1.00	(ref)		1.00	(ref)	
T2	92/446	0.93	0.68–1.27		0.91	0.66–1.26	
T3	116/459	1.10	0.82–1.50	0.16	1.05	0.77–1.44	0.39

[a]Adjusted for age and race

[b]Adjusted for age, race, study site, family history of prostate cancer, education, PSA and DRE screening history, smoking status, BMI, total energy intake, alcohol intake, NSAIDs use, and Charlson comorbidity index

[c]Current job: T1 = no current job; T2 ≤ 2.3 MET; T3 > 2.3 MET

[d]Longest-held job tertiles: 0 ≤ T1 ≤ 52.5; 52.5 < T2 ≤ 93; T3 > 93 MET-years

Results represent PCaP research subjects with non-missing data; hence, the total number for each category may not sum up to total number of research subjects

Table 5 Joint effects of walking for exercise and current occupational physical activity in relation to prostate cancer aggressiveness[a]

Current job MET tertiles[b]	Minutes/week walked for exercise					
	< 75			≥ 75		
	High-/low-intermediate-aggressive cases	OR	95%CI	High-/low-intermediate-aggressive cases	OR	95%CI
T1	146/475	1.00	(ref)	71/340	0.72	0.52–1.00
T2	48/290	0.80	0.54–1.19	13/135	0.51	0.27–0.96
T3	53/319	0.68	0.47–0.98	22/140	0.68	0.41–1.13

[a]Adjusted for age, race, study site, family history of prostate cancer, education, PSA and DRE screening history, smoking status, BMI, total energy intake, alcohol intake, NSAIDs use, and Charlson comorbidity index

[b]Current job: T1 = no current job; T2 ≤ 2.3 MET; T3 > 2.3 MET

a lifetime walking or cycling average of > 60 min/day which is notably higher activity than the majority of men in PCaP. A meta-analysis reported a summary RR of 0.91 (95% CI 0.81–1.02) for the association between walking and/or biking and any prostate cancer based on five individual studies though an association with advanced prostate cancer was not reported [12]. We did not find differences between African-American and European-American men for the association between walking for exercise and high-aggressive prostate cancer. One review suggests comparable associations with advanced prostate cancer between African-American and European-American men for various risk factors, which included physical activity, although the number of previous studies was small [17]. In PCaP, the association between walking for exercise and prostate cancer aggressiveness was evident in various sub-populations including obese men, those with previous screening history, and NSAID users. The link between walking and aggressive prostate cancer warrants further investigation, particularly in other racially diverse study populations.

Total MET-hours/week of recreational physical activity was not associated with prostate cancer aggressiveness in PCaP. In contrast, in the American Cancer Society's Cancer Prevention Study II Nutrition Cohort, Patel et al. [28] observed a 31% lower risk of aggressive prostate cancer (defined as a combination of later clinical stage and higher grade, i.e., Gleason sum) in men who engaged in > 35 metabolic equivalent hours (MET-hours)/week of recreational physical activity compared to those who did not [RR = 0.69, 95% CI 0.52–0.92]. In a 2018 systematic review and meta-analysis, high versus low recreational physical activity was associated with reduced risk of advanced/aggressive prostate cancer, although results were based on only two previous studies [12]. Differences in the design of the studies, study populations, and overall range or variability in physical activity level in the populations may explain the different results obtained for total recreational physical activity.

In PCaP, an inverse association, though not statistically significant, was observed for vigorous physical activity and prostate cancer aggressiveness. Four other studies reported similar findings [29–32], but another found no association [33]. In the Health Professionals Follow-up Study, lower risks of advanced and lethal prostate cancers were observed in men who engaged in the highest quintile of vigorous physical activity compared to those in the lowest quintile [29, 32]. In another study, a higher summary score representing higher frequency, duration, and intensity was associated with reduced risk of advanced prostate cancer but not any prostate cancer [30]. Similarly, a meta-analysis concluded that there was no association between vigorous physical activity and overall prostate cancer [12], which indicates the importance of examining associations for advanced or aggressive prostate cancer separately from less aggressive phenotypes. Additionally, men who engage in vigorous physical activity may have other healthy lifestyle practices, such as healthy dietary patterns and regular health screenings [34] that could have confounded the associations and could lead to mixed results across studies with varying covariate adjustment.

The effects of physical activity earlier in life at potentially etiologically important windows of exposure were investigated since prostate cancer typically has a long induction period. However, no significant associations were observed. There is a scarcity of studies reporting associations between early life physical activity and advanced or aggressive prostate cancer. One study reported no association between sport or exercise frequency during adolescence and advanced or fatal prostate cancer [33]. Findings have been mixed among the studies that examined associations of physical activity in earlier life and any prostate cancer [22, 27, 35–37]. A meta-analysis reported no association between physical activity at age < 20 years and any prostate cancer, and a modest reduced risk of any prostate cancer for higher activity at ages 20–45 years [8]. Poor recall accuracy and subsequent misclassification of exposure may play a role in these inconsistent findings.

Higher level of physical activity at the longest-held job was not associated with prostate cancer aggressiveness, even though an association with physical activity at current job was observed. The inverse association between physical activity at current job and high-aggressive prostate cancer is in agreement with previous literature that suggests a modest reduced risk [12]. For example, Johnsen et al. [38] observed that occupational physical activity, such as standing and manual work, was inversely related to advanced prostate cancer in the European Prospective Investigation into Cancer and Nutrition cohort ($p_{\text{trend}} = 0.02$). The current null finding for longest-held job activity in PCaP may be influenced by confounding from unmeasured factors such as exposure to carcinogenic chemicals in higher labor jobs. Although education was adjusted for in the model, residual confounding by socioeconomic status (SES) may have been related to health care access and other sociodemographic attributes that affect risk of high-aggressive prostate cancer. The longest-held job may have been many years prior to prostate cancer diagnosis, and thus, current job or employment status may be more relevant to recent physical activity behaviors or may more accurately define the continuously active person. Of note, we found limited concordance between the cross tabulations of joint categories of occupational and recreational physical activity as shown in Table 5.

Several lines of evidence suggest that physical activity may influence prostate cancer through endogenous hormone regulation, immune function, decreased adiposity, antioxidant defense, and regulation of apoptosis and angiogenesis [3, 4, 16]. Men who exercise regularly tend to have lower levels of androgens, particularly testosterone, which has been associated with prostate cancer risk and aggressiveness in some studies [39–42]. Physical activity may modify prostate cancer risk by reducing circulating levels of serum insulin and insulin-like growth factor I (IGF-I) which promote tumor proliferation [43–46]. Regular physical activity reduces inflammation and enhances immune function, thus offering protection against prostate cancer by inducing and promoting the activities of natural killer cells and modifying the effects of cytokines on the prostate gland [42]. Adipose tissue, which is generally lower in physically fit men, may promote prostate cancer by promoting inflammation or acting as a storage site for potential carcinogens [4, 47, 48], and obesity has been associated with increased odds of high-aggressive prostate cancer in PCaP [49]. Regular exercise may mediate prostate cancer aggressiveness by upregulating the production of reactive oxygen species scavenger enzymes to bolster antioxidant defense against oxidative stress [50–52].

Despite biologically plausible mechanisms by which physical activity may influence prostate cancer, evidence from epidemiologic studies has been largely inconsistent [12, 13], perhaps because of inherent methodological limitations of these observational studies. One challenge of observational studies in the area of physical activity research is how to measure physical activity exposure accurately, reliably, with appropriate metrics (i.e., type, frequency, duration, and intensity), and at biologically relevant time periods earlier in life [3, 4]. Additionally, associations between physical activity and prostate cancer may be modulated by a wide range of confounders and effect modifiers, such as prostate cancer screening [32]. However, few studies adjusted for PSA testing when examining the association between physical activity and prostate cancer [12]. The current study addressed these methodological concerns by controlling for the confounding effects of sociodemographic, lifestyle, and clinical attributes of prostate cancer and evaluating effect modification by race, BMI, PSA and DRE screening history, and NSAIDs use.

Several limitations of the current study should be noted. The use of self-reported information on past exercise patterns, especially pertaining to distant recall of physical activity earlier in life, may have resulted in imprecise measurements. This factor was mitigated by using a slightly modified version of a previously validated questionnaire [21, 22] that provided specific examples of various types of activities to help prompt memory and improve recall. Recall bias is a possible limitation since disease severity (and potentially preclinical disease in the year prior to diagnosis) may result in a reduction in physical activity levels that could affect recall of activity in the year prior to diagnosis. While job category classification has been used as a proxy for occupational physical activity [23], it is a relatively crude measure for examination of the effects of physical activity on disease status. The focus of our questionnaire was on recent physical activity (in the year prior to diagnosis) as the primary exposure, so we were unable to evaluate more detailed information on long-term physical activity that may be etiologically important. Finally, residual confounding and chance findings due to multiple comparisons cannot be ruled out in observational studies.

In conclusion, walking for 75–150 min/week for exercise in the year prior to diagnosis was associated with lower odds of high-aggressive prostate cancer. Occupational physical activity at current job also was inversely associated with high-aggressive prostate cancer. Further research in this area is needed, particularly intervention trials involving prostate cancer biomarker endpoints to help clarify the etiological relationship between physical activity and prostate cancer aggressiveness. Future studies in racially diverse populations should consider objective measurements of physical activity (e.g., activity monitors) and consider more extensive measures of occupational physical activity.

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Data availability The data that support the findings of this study are available from the North Carolina-Louisiana Prostate Cancer Project. Data are available from the authors upon reasonable request and with permission of the North Carolina-Louisiana Prostate Cancer Project.

Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocols were approved by Institutional Review Boards (IRBs) at the University of North Carolina–Chapel Hill, Louisiana State University Health Sciences Center, Department of Defense Prostate Cancer Research Program, and the University of South Carolina.

Consent to participate Informed consent was obtained from all individual research subjects included in the study.

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