# Physical activity and prostate tumor vessel morphology: data from the Health Professionals Follow-up Study

**Erin L. Van Blarigan**[#1,2], **John P. Gerstenberger**[#3], **Stacey A. Kenfield**[2,4], **Edward L. Giovannucci**[4,5,6], **Meir J. Stampfer**[4,5,6], **Lee W. Jones**[7], **Steven K. Clinton**[8], **June M. Chan**[#1,2], and **Lorelei A. Mucci**[#4,5]

[1]Dept. of Epidemiology and Biostatistics, University of California San Francisco

[2]Dept. of Urology, University of California San Francisco

[3]School of Medicine, University of California San Francisco

[4]Department of Epidemiology, Harvard School of Public Health

[5]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School

[6]Dept. of Nutrition, Harvard School of Public Health

[7]Dept. of Medicine, Memorial Sloan Kettering Cancer Center

[8]Ohio State University Medical Center and Comprehensive Cancer Center

[#] These authors contributed equally to this work.

## Abstract

Vigorous activity is associated with lower risk of prostate cancer progression, but the biologic mechanisms are unknown. Exercise affects vascularization of tumors in animal models, and small, irregularly shaped vessels in prostate tumors are associated with fatal prostate cancer. We hypothesized that men who engaged in vigorous activity or brisk walking would have larger, more regularly shaped vessels in their prostate tumors. We prospectively examined whether physical activity was associated with prostate tumor microvessel morphology among 571 men in the Health Professionals Follow-up Study using ordinal logistic regression. Vessel size ($\mu m^2$), vessel lumen regularity (perimeter$^2$ / 4 · $\Pi$ · area), and microvessel density (number per high powered field) were ascertained in tumor sections stained for endothelial cell marker CD34. Vigorous activity [metabolic equivalent task (MET) 6], non-vigorous activity (MET <6), and walking pace were assessed a median of 14 months prior to diagnosis. Prostate tumors from men who reported a brisk walking pace (3+ mph) had larger, more regularly shaped blood vessels compared to those of men who walked at a less than brisk pace [vessel regularity odds ratio (OR): 1.59; 95% confidence interval (CI): 1.11, 2.27; *p*-value: 0.01; vessel size OR: 1.48; 95% CI: 1.04, 2.12; *p*-value: 0.03]. Brisk walking was not associated with microvessel density; total vigorous and non-vigorous activities were not associated with vessel size, shape, or number. Brisk walking may be associated

**Corresponding author**: Erin Van Blarigan ScD, UCSF Department of Epidemiology and Biostatistics Box 0560, 550 16th St. 2nd Floor, San Francisco, CA 94158; (415) 476-6179; erin.vanblarigan@ucsf.edu.

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with larger, more regularly shaped vessels in prostate tumors. Additional research elucidating the effect of physical activity on prostate tumor biology is needed.

**Keywords**

physical activity; angiogenesis; vasculature; prostate cancer; blood vessels

## Introduction

Prostate cancer is the second leading cause of cancer death among men in the United States (US) (1). Our group previously identified physical activity as a potential modifiable factor associated with a reduced risk of prostate cancer progression and mortality (2, 3). In animal models, exercise has been shown to suppress solid tumor growth, progression, and metastasis (4-9). However, the underlying biological mechanisms are not well understood.

Modulation of tumor vasculature may be one potential mechanism by which exercise reduces risk of prostate cancer progression. Dysregulation of angiogenesis and the resulting abnormal vasculature have long been understood as characteristic features of malignant tumors (10, 11). Dysfunctional vasculature results in poor tumor perfusion and local hypoxia, inducing a more aggressive phenotype with increased metastatic potential and increased resistance to both the host immune system and therapeutics (12). Additionally, tumor vessels have increased permeability, which may result in an increased propensity for tumor cell shedding and metastasis (12, 13). In the prostate, blood vessels in malignant tissue are smaller and more collapsed compared to normal tissue (14). Our group previously reported that markers of abnormal tumor vasculature, small vessel size and irregular shape, in prostatectomy samples were associated with 6.6- and 17.1-fold increased risks of prostate cancer mortality, respectively (15).

In animal models, tumor blood flow increases two-fold during acute endurance exercise, and chronic physical activity modulates vasculature, increasing tumor perfusion and oxygenation and decreasing the propensity for distant metastasis (4, 5, 16, 17). We hypothesized that physical activity induces a physiologic normalization of tumor vasculature in men with prostate cancer. No prior study has investigated the association between physical activity and morphological characteristics of prostate tumor vasculature in humans.

Thus, we examined the association between physical activity and tumor vessel size, shape, and density among 571 men with prostate cancer in the Health Professionals Follow-up Study. Based on our prior findings of improved clinical outcomes associated with brisk walking and 3+ hours per week of vigorous physical activity (2, 3), we expected to observe larger, more regularly shaped vessels in tumors of men reporting 3+ hours per week of vigorous physical activity or a brisk walking pace prior to diagnosis. Due to the lack of association between microvessel density and prostate cancer-specific mortality in our study population (15), we hypothesized that vigorous physical activity and walking pace would not be associated with the number of vessels in the prostate tumors.

## Materials and Methods

### Study population

The Health Professionals Follow-up Study is a prospective cohort study initiated in 1986 among 51,529 US male health professionals 40-75 years of age. The baseline questionnaire asked men to report on medical history, medication use, body weight, physical activity, smoking behavior, and diet. Data on medical diagnoses, medications, weight, physical activity, and smoking have been updated every two years, and the average questionnaire response rate exceeds 90%.

This study was conducted among men in the Health Professionals Follow-up Study diagnosed with prostate cancer and treated via prostatectomy or trans-urethral resection of the prostate (TURP) between 1986 and 2000. Of the 1,593 men meeting these criteria, archival formalin-fixed paraffin-embedded specimens were obtained from 1,023 men (64%). The size, shape, and density of the tumor vasculature were assessed on a random sample of 572 men; the clinical characteristics of these men were representative of all men who donated tissue samples. These men represent the same study population as our previous report on the association between tumor vessel morphology and prostate cancer-specific mortality (15). One man was missing data on physical activity prior to diagnosis, leaving 571 men available for analysis.

The Institutional Review Board at the Harvard School of Public Health approved this investigation; all participants provided informed consent.

### Physical activity assessment

Participants completed a validated physical activity questionnaire at baseline and every two years thereafter (18). The baseline questionnaire asked men to report the average time per week during the past year spent performing the following activities: walking or hiking outdoors (including walking at golf); jogging (slower than 10 min/mile); running (10 min/mile or faster); bicycling (include stationary machine); lap swimming; tennis; squash or racket ball; and calisthenics or rowing. Responses were collected in 10 categories ranging from none to 11+ hours/week. Heavy outdoor work (e.g. digging, chopping) was added to the questionnaire in 1988 and weightlifting or Nautilus was added in 1990. Participants also reported how many flights of stairs they climbed daily in five categories ranging from two or fewer to 15 or more. Lastly, participants reported their usual walking pace in four categories: easy, casual (less than 2 mph); normal, average (2 to 2.9 mph); brisk pace (3 to 3.9 mph); and very brisk, striding (4 mph or faster).

Given the short time between diagnosis and surgery for patients who undergo radical prostatectomy as their primary treatment for prostate cancer, we used physical activity reported on the questionnaire just prior to diagnosis as our primary exposure. If a man was missing data from the questionnaire immediately preceding diagnosis, we carried forward his physical activity information from the most recent available pre-diagnostic questionnaire. The median time from physical activity assessment to diagnosis was 14 months (interquartile range: 8-22 months).

Based on the previous studies, we considered three measures of physical activity in this analysis: duration of vigorous physical activity, duration of non-vigorous physical activity, and walking pace (2, 3). Each activity was assigned a metabolic equivalent task (MET) value, which represents the amount of energy required to perform that activity relative to the resting metabolic rate (19). Activities with MET values of six or higher were considered vigorous and activities with MET values less than six were considered non-vigorous (19). These standard cut-points are based on data from healthy adults, and activities with lower MET values may be relatively vigorous for older men. Thus, we also considered walking pace as a measure of intensity of activity, because walking is the most common form of physical activity among men with prostate cancer (2, 3). Very few men reported walking at an easy [<2 mph; n=30 (5%)] or very brisk [ 4 mph; n=24 (4%)] pace, therefore we analyzed walking pace as a dichotomous variable: less than brisk (<3 mph) vs. brisk ( 3 mph).

The physical activity questionnaire was validated among 238 participants in the Health Professionals Follow-up Study (18). After completing the physical activity questionnaire in 1990, these men completed a 1-week physical activity diary every three months for one year (1991-1992), followed by the 1992 administration of the physical activity questionnaire. The de-attenuated correlation between the 1992 questionnaire and the average of the diaries was 0.58 for vigorous physical activity and 0.28 for non-vigorous activity. The question on walking pace has not been validated.

### Assessment of Tumor Vessel Morphology

The methods used to assess tumor vessel morphology in the prostate tumor specimens have been previously described (15). A study pathologist identified all prostatectomy blocks that contained cancer. Immunohistochemistry was then performed on blocks containing cancer (1-9 blocks per case) to ascertain protein expression of endothelial cell marker CD34. CD34 is a myeloid progenitor cell antigen detectable in all types of endothelium. Microvascularity in the prostate, as determined by CD34 staining, is higher in malignant versus benign or hyperplastic tissue and is positively associated with risk of prostate cancer recurrence and mortality (15, 20-22). Semi-automated image analysis (Image ProPlus 4.5 software, Media Cybernetics, MD) was conducted under the supervision of the pathologist to measure vessel size and architecture. Three measures were used to characterize tumor angiogenesis: vessel size ($\mu m^2$), regularity of the vessel lumen (perimeter$^2$ / 4 · $\Pi$ · area), and microvessel density (number of vessels per high powered field). For regularity of the vessel lumen, values of 1.0 indicate a perfect circle and higher values indicate less regular vessels. If a case had more than one measure available, we used the average value to characterize each case. The correlations between the tumor vasculature measures in this population have been previous reported: microvessel density and vessel size (−0.15), microvessel density and regularity (−0.07), and vessel size and regularity (−0.31) (15).

### Statistical analysis

We used ordinal logistic regression to examine vigorous physical activity, non-vigorous physical activity, and walking pace in relation to vessel area, regularity of the vessel lumen, and microvessel density in the prostate tumor. We used ordinal logistic regression with the

dependent variables categorized in quartiles for interpretability and consistency with our prior report examining tumor vessel morphology markers in relation to risk of lethal prostate cancer (15). The odds ratio (OR) represents the relative odds for a 1-unit increase in the exposure of interest of being in the 4th vs. 3rd-1st, 4th-3rd vs 2nd-1st, or 4th-2nd vs. 1st quartile of the outcome. For interpretability, the lowest quartile (smallest vessels, lowest microvessel density) was used as the reference for vessel size and microvessel density and the highest quartile (least regular vessels) was used as the reference for vessel regularity. Thus, OR greater than 1 are interpreted intuitively as increased odds of larger vessels, greater microvessel density, or more regularly shaped vessels.

We categorized activity levels based on our prior report and the distribution in the population as follows: vigorous activity, <1, 1 to <3, 3 h/wk; non-vigorous activity, <1.5, 1.5 to <3.5, 3.5 to <7, 7 h/wk, and walking pace, <3, 3 mph (2, 3). We analyzed the categories using indicator variables with the lowest level as the reference, and tested for evidence of a linear trend across categories by modeling the median value of each category as a continuous term.

Our first model was adjusted for age at diagnosis (years). Our primary multivariate model was additionally adjusted for body mass index at diagnosis (BMI; <25, 25-29.9, 30 kg/m$^2$), smoking at diagnosis (current, former, never), regular aspirin use at diagnosis (yes/no), and quartiles of intake of lycopene and vitamin E. These lifestyle factors have previously been associated with prostate cancer mortality, and we hypothesized may also be associated with markers of tumor vessel morphology (23). Vigorous activity, non-vigorous activity, and walking pace were also adjusted for one another. To examine whether the associations were independent of clinical prognostic factors, we examined our multivariate model additionally adjusted for pathologic stage (T1/T2 v. T3/T4/N1/M1), pathologic Gleason sum (<7, 7, 7), and prostate specific antigen (PSA) level at diagnosis (ng/ml), and ran a sensitivity analysis excluding men diagnosed with advanced stage disease (T3/T4/N1/M1). Clinical stage and biopsy Gleason sum data were used for the 49 men treated via TURP. Additionally, we performed a sensitivity analysis restricting to the 522 (91%) men treated via radical prostatectomy. Lastly, because the etiologically relevant exposure window is unknown, we conducted an analysis examining the relation between physical activity at baseline (1986) and features of the tumor vasculature.

SAS v. 9.3 was used for all statistical analyses, and *p*-values <0.05 were considered statistically significant.

## Results

Clinical and sociodemographic characteristics of the 571 men by level of vigorous physical activity and walking pace approximately one year prior to diagnosis are presented in **Table 1**. Brisk walking was reported by 46% of the men and 18% reported engaging in 3 hours of vigorous activity per week. At diagnosis, men who reported engaging in more vigorous activity or walking at faster pace were younger, had a lower BMI, and were less likely to be current smokers. In addition, more active men were less likely to have Gleason sum 8-10 or regional/distant disease.

Men who reported walking at a brisk walking pace had larger, more regularly shaped vessels in their prostate tumors than men who reported walking at a less than brisk pace (**Table 2**). Men who walked briskly had 52% greater odds of having more regular vessel lumens [OR: 1.52; 95% confidence interval (CI): 1.10, 2.09; *p*-value: 0.01]. Adjustment for pathologic stage, Gleason sum, and diagnostic PSA slightly strengthened this association (OR: 1.59; 95% CI: 1.11, 2.27; *p*-value: 0.01). There was also a positive association between walking pace and vessel size. Men who reported walking at a brisk pace had 24% higher odds of having larger vessels (OR: 1.24; 95% CI: 0.90, 1.71; *p*-value: 0.18), and this association became stronger and statistically significant after adjusting for clinical prognostic factors (OR: 1.48; 95% CI: 1.04, 2.12; *p*-value: 0.03). As hypothesized, walking pace was not associated with microvessel density.

There was no association between duration of vigorous or non-vigorous physical activity and vessel size, shape, or density in prostate tumor specimens. In sensitivity analyses, the observed associations remained the same when excluding the 79 (14%) men diagnosed with stage T3b, T4, N1, or M1 disease and became stronger when restricting to the 522 (91%) men treated via radical prostatectomy (brisk walking and tumor vessel regularity OR: 1.62; 95% CI: 1.16, 2.26; *p*-value: 0.005). Lastly, the relation between brisk walking pace and regularity of the vessel lumen in the tumors was slightly attenuated when examining baseline walking pace (OR: 1.32; 95% CI: 0.93, 1.88), suggesting recent brisk walking may have a greater impact on tumor vasculature than past activity levels.

## Discussion

In this prospective study of 571 men with prostate cancer, we observed larger more regularly shaped blood vessels in prostate tumors of men who reported a brisk walking pace approximately one year before diagnosis. Walking pace was not associated with the number of vessels in prostate tumors, and vigorous and non-vigorous physical activities were not associated with vessel size, shape, or density.

We previously reported that smaller vessel area and more irregular shape (markers of abnormal vasculature) at the time of prostatectomy were associated with increased risk of prostate cancer-specific mortality, independent of other clinical prognostic factors (smaller vessel area hazard ratio (HR): 4.0, 95% CI: 1.2-13.3; irregular shape HR: 10.9, 95% CI: 1.5-81.4, Q1 vs Q4) (15). We also previously reported in a distinct study population that men who walked briskly after diagnosis had a 48% decreased risk of prostate cancer recurrence compared to men who walked at an easy pace (HR: 0.52, 95% CI: 0.29, 0.91; Ptrend = 0.01) (2). Here, we report that men with a walking pace 3 mph approximately one year prior to diagnosis had larger, more normal shaped blood vessels in their prostate tumors. This finding adds evidence to support the hypothesis that brisk walking reduces the risk of developing lethal prostate cancer, and suggests a potential biologic mechanism by which brisk walking may inhibit prostate cancer progression.

Dysfunctional tumor vasculature results in increased permeability and local hypoxia, which may increase tumor cell shedding and activate pathways promoting metastasis, inhibition of immune-mediated tumor cell destruction, and increased therapeutic resistance (12). Animal

models of breast and prostate cancer have shown that chronic exercise training increases tumor perfusion (4, 5, 24). For example, Betof et al. recently reported that mice implanted with murine breast cancer cells that were able to exercise had significantly improved vessel function and maturity, lower hypoxia, and more uniform and centralized perfusion in their tumors compared to sedentary control mice (4). Here we report for the first time that exercise may also have a beneficial effect on tumor vasculature in men with prostate cancer.

Contrary to our hypothesis, we observed no association between vigorous physical activity and characteristics of the tumor vasculature. In a prior report, we observed that men who engaged in 3 h/wk of vigorous physical activity after diagnosis had a 61% lower risk of prostate cancer-specific mortality compared to men engaging in <1 h/wk (HR: 0.39, 95% CI: 0.18, 0.84) (3). In that analysis, the inverse relation only appeared at the highest levels of vigorous physical activity; there was no difference in risk of prostate cancer-specific mortality comparing men who reported 1 to <3 h/wk of vigorous activity to men who reported <1 h/wk. In the current study population, only 101 men (18%) reported engaging in 3 h/wk of vigorous activity. Thus, we may have lacked sufficient statistical power to detect an association between vigorous activity and markers of tumor vasculature due to low participation in vigorous activity in our study sample. In contrast, 265 (46%) of our population reported engaging in brisk walking. Brisk walking is a relatively vigorous activity for many elderly men, and data suggest that brisk walking lowers risk of prostate cancer recurrence (2). Thus, brisk walking may be sufficient for eliciting biologic changes in prostate tumors. It is also possible that men may more accurately report their usual walking pace compared to time spent in leisure-time activities, which could in part explain the lack of association between vigorous activity and tumor vessel morphology. Nevertheless, further research in larger study populations is clearly needed to improve our understanding of the complex and pleiotropic effects of physical activity, both before and after diagnosis, in the development and progression of prostate cancer.

This was an observational study, and we cannot rule out the potential for unmeasured or residual confounding. Our results were robust when controlling for clinical and lifestyle factors associated with prostate cancer progression, but predictors of tumor vessel morphology have not been well studied and therefore it is possible that an unknown confounder was not accounted for. A randomized controlled trial is needed to definitively determine whether engaging in brisk walking changes the shape or size of vasculature in prostate tumors. In addition, we also relied on self-reported physical activity, and our measure of walking pace has not been validated. However, our assessment was collected prospectively and therefore we expect that the error in our exposure assessment was non-differential. Future studies using a combination of self-reported and objective measures of physical activity in relation to biological endpoints in men with prostate cancer would be of interest. Lastly, it is possible that the associations we observed between walking pace and tumor vessel size and shape are due to chance. We did not adjust for multiple testing because this was the first study to examine this question in humans and we had a clear *a priori* hypothesis based on preclinical data, but replication is necessary in future studies.

In conclusion, we observed that walking pace prior to diagnosis was associated with having larger, more regular shaped vessels in prostate tumors. Our data support the hypothesis that

normalization of tumor vasculature is one mechanism by which brisk walking may reduce the risk of prostate cancer progression. Future work is needed to confirm our findings and further elucidate the biologic mechanisms by which physical activity may reduce risk of prostate cancer progression.

## Acknowledgements

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**Table 1**

Characteristics of 571 men diagnosed with prostate cancer in the Health Professionals Follow-up Study, by level of vigorous physical activity and walking pace prior to diagnosis (median time from assessment to diagnosis: 14 months).

| | Vigorous Activity | | | Walking Pace | |
|---|---|---|---|---|---|
| | <1 h/wk | 1 to <3 h/wk | 3 h/wk | <3 mph | 3 mph |
| No. of participants | 328 | 142 | 101 | 307 | 264 |
| Age at diagnosis, y, mean ± SD | 66 ± 6 | 65 ± 6 | 64 ± 6 | 66 ± 6 | 65 ± 6 |
| BMI, kg/m², mean ± SD | 26 ± 3 | 25 ± 3 | 25 ± 2 | 26 ± 3 | 25 ± 3 |
| Smoking behavior, N (%) | | | | | |
| Never | 147 (45) | 60 (42) | 54 (53) | 118 (38) | 143 (54) |
| Former | 138 (42) | 70 (49) | 37 (37) | 150 (49) | 95 (36) |
| Current | 29 (9) | 8 (6) | 5 (5) | 29 (9) | 13 (5) |
| Missing | 14 (4) | 4 (3) | 5 (5) | 10 (3) | 13 (5) |
| T-stage, N (%) | | | | | |
| T1 N0 M0 | 13 (4) | 3 (2) | 2 (2) | 12 (4) | 6 (2) |
| T2 N0 M0 | 214 (65) | 92 (65) | 74 (73) | 193 (63) | 187 (71) |
| T3 N0 M0 | 79 (24) | 37 (26) | 20 (20) | 78 (25) | 58 (22) |
| T4 N0 M0 | 2 (1) | 1 (1) | 1 (1) | 3 (1) | 1 (0) |
| N1 M0 | 15 (5) | 4 (3) | 3 (3) | 14 (5) | 8 (3) |
| M1 (N0 or N1) | 5 (2) | 5 (4) | 1 (1) | 7 (2) | 4 (2) |
| Gleason sum, N (%) | | | | | |
| 2-6 | 83 (25) | 29 (20) | 23 (23) | 82 (27) | 53 (20) |
| 7 | 175 (53) | 87 (61) | 62 (61) | 160 (52) | 164 (62) |
| 8-10 | 65 (20) | 23 (16) | 15 (15) | 61 (20) | 42 (16) |
| Missing | 5 (2) | 3 (2) | 1 (1) | 4 (1) | 5 (2) |
| PSA at diagnosis (ng/ml), median (range) | 7.3 (0.4, 135.0) | 6.4 (1.3, 49.6) | 6.4 (1.6, 77.0) | 7.2 (0.4, 77.0) | 6.9 (1.1, 135.0) |
| Radical prostatectomy, N (%) | 297 (91) | 129 (91) | 96 (95) | 273 (89) | 249 (94) |
| Regular aspirin use, N (%) | 148 (45) | 82 (58) | 48 (48) | 152 (50) | 126 (48) |
| Lycopene, mg/d, mean ± SD | 6.8 ± 5.0 | 7.4 ± 4.7 | 7.3 ± 4.5 | 6.5 ± 4.2 | 7.6 ± 5.4 |
| Vitamin E, mg/d, mean ± SD | 101 ± 176 | 117 ± 155 | 133 ± 207 | 105 ± 179 | 117 ± 176 |

|  | Vigorous Activity | | | Walking Pace | |
| --- | --- | --- | --- | --- | --- |
|  | <1 h/wk | 1 to <3 h/wk | 3 h/wk | <3 mph | 3 mph |
| Vigorous activity, h/wk, mean ± SD | 0.1 ± 0.2 | 1.7 ± 0.6 | 6.4 ± 3.6 | 1.5 ± 2.9 | 1.7 ± 2.7 |
| Non-vigorous activity, h/wk, mean ± SD | 5.4 ± 6.4 | 6.9 ± 8.1 | 4.6 ± 4.8 | 5.1 ± 5.8 | 6.3 ± 7.5 |

Abbreviations: hours (h), week (wk), miles per hour (mph), standard deviation (SD), body mass index (BMI), prostate specific antigen (PSA).

**Table 2**

Relative odds of having more regular vessel lumens, larger vessel area, or higher microvessel density in the prostate tumor by level of physical activity at diagnosis among 571 men in the Health Professionals Follow-up Study.

**Regularity of Vessel Lumen**

| Walking pace | <3 mph | 3 mph | P-trend[1] |
|---|---|---|---|
| Model 1[2] | 1.0 (ref.) | 1.52 (1.13, 2.05) | 0.006 |
| Model 2[3] | 1.0 (ref.) | 1.52 (1.10, 2.09) | 0.01 |
| Model 3[4] | 1.0 (ref.) | 1.59 (1.11, 2.27) | 0.01 |

| Vigorous Physical Activity | <1 h/wk | 1 to <3 h/wk | 3 h/wk | P-trend |
|---|---|---|---|---|
| Model 1[2] | 1.0 (ref.) | 1.32 (0.93, 1.89) | 0.93 (0.62, 1.39) | 0.87 |
| Model 2[3] | 1.0 (ref.) | 1.24 (0.86, 1.81) | 0.78 (0.51, 1.20) | 0.36 |
| Model 3[4] | 1.0 (ref.) | 1.17 (0.78, 1.75) | 0.89 (0.56, 1.41) | 0.68 |

| Non-vigorous Physical Activity | <1.5 h/wk | 1.5 to <3.5 h/wk | 3.5 to <7 h/wk | 7 h/wk | P-trend |
|---|---|---|---|---|---|
| Model 1[2] | 1.0 (ref.) | 0.90 (0.59, 1.38) | 1.22 (0.79, 1.89) | 1.00 (0.65, 1.54) | 0.85 |
| Model 2[3] | 1.0 (ref.) | 0.91 (0.59, 1.41) | 1.14 (0.72, 1.80) | 0.86 (0.55, 1.35) | 0.53 |
| Model 3[4] | 1.0 (ref.) | 0.71 (0.43, 1.15) | 0.86 (0.52, 1.42) | 0.75 (0.46, 1.25) | 0.55 |

**Vessel Area**

| Walking pace | <3 mph | 3 mph | P-trend |
|---|---|---|---|
| Model 1[2] | 1.0 (ref.) | 1.24 (0.93, 1.67) | 0.15 |
| Model 2[3] | 1.0 (ref.) | 1.24 (0.90, 1.71) | 0.18 |
| Model 3[4] | 1.0 (ref.) | 1.48 (1.04, 2.12) | 0.03 |

| Vigorous Physical Activity | <1 h/wk | 1 to <3 h/wk | 3 h/wk | P-trend |
|---|---|---|---|---|
| Model 1[2] | 1.0 (ref.) | 0.98 (0.69, 1.40) | 0.87 (0.58, 1.31) | 0.52 |
| Model 2[3] | 1.0 (ref.) | 0.92 (0.63, 1.33) | 0.82 (0.54, 1.26) | 0.36 |
| Model 3[4] | 1.0 (ref.) | 0.83 (0.55, 1.24) | 0.70 (0.44, 1.11) | 0.12 |

| Non-vigorous Physical Activity | <1.5 h/wk | 1.5 to <3.5 h/wk | 3.5 to <7 h/wk | 7 h/wk |
|---|---|---|---|---|

| | <3 mph | 3 mph | | | p-trend[1] |
|---|---|---|---|---|---|
| Model 1[2] | 1.0 (ref.) | 1.11 (0.72, 1.70) | 1.04 (0.68, 1.61) | 0.90 (0.58, 1.39) | 0.40 |
| Model 2[3] | 1.0 (ref.) | 1.13 (0.73, 1.76) | 0.95 (0.60, 1.49) | 0.78 (0.50, 1.23) | 0.12 |
| Model 3[4] | 1.0 (ref.) | 1.18 (0.72, 1.92) | 0.93 (0.57, 1.54) | 0.86 (0.52, 1.42) | 0.31 |

**Microvessel Density**

| **Walking pace** | <3 mph | 3 mph | | | |
|---|---|---|---|---|---|
| Model 1[2] | 1.0 (ref.) | 1.10 (0.82, 1.47) | | | 0.55 |
| Model 2[3] | 1.0 (ref.) | 1.02 (0.74, 1.41) | | | 0.89 |
| Model 3[4] | 1.0 (ref.) | 1.07 (0.75, 1.53) | | | 0.70 |
| **Vigorous Physical Activity** | <1 h/wk | 1 to <3 h/wk | 3 h/wk | | |
| Model 1[2] | 1.0 (ref.) | 1.48 (1.04, 2.12) | 0.95 (0.63, 1.42) | | 0.97 |
| Model 2[3] | 1.0 (ref.) | 1.53 (1.05, 2.22) | 0.99 (0.64, 1.51) | | 0.87 |
| Model 3[4] | 1.0 (ref.) | 1.55 (1.03, 2.32) | 1.03 (0.65, 1.64) | | 0.76 |
| **Non-vigorous Physical Activity** | <1.5 h/wk | 1.5 to <3.5 h/wk | 3.5 to <7 h/wk | 7 h/wk | |
| Model 1[2] | 1.0 (ref.) | 0.91 (0.59, 1.39) | 0.74 (0.48, 1.15) | 0.97 (0.63, 1.50) | 0.85 |
| Model 2[3] | 1.0 (ref.) | 0.92 (0.59, 1.42) | 0.73 (0.47, 1.16) | 0.92 (0.58, 1.44) | 0.89 |
| Model 3[4] | 1.0 (ref.) | 0.79 (0.49, 1.29) | 0.61 (0.37, 1.01) | 0.80 (0.48, 1.31) | 0.68 |

[1] p-trend calculated by modeling the median of the exposure categories as a continuous term.

[2] Model 1: Ordinal logistic regression with the dependent variable categorized in quartiles and adjusted for age at diagnosis.

[3] Model 2: Model 1 adjusted for body mass index at diagnosis (<25, 25-29.9, 30+ kg/m$^2$), smoking status at diagnosis (never, former, current), tissue source (radical prostatectomy, trans urethral resection of the prostate), lycopene intake at diagnosis (quartiles), vitamin E intake at diagnosis (quartiles), and regular aspirin use at diagnosis (yes/no). Additionally, the types of activity are adjusted for one another. Model 2 includes the 546 men who had complete data on all covariates included in the model.

[4] Model 3: Model 2 adjusted for pathologic stage (T1/T2 vs. T3/T4), Gleason sum (2-6, 7, 8-10), and diagnostic prostate specific antigen level (ng/ml). Model 3 includes 465 men who had complete data on all covariates included in the model.