Research Article

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Associations of Lifestyle Factors and Anthropometric Measures with Repeat PSA Levels During Active Surveillance/Monitoring

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Abstract

Background: Assessment of prostate-specific antigen increase with time (PSA growth) is a fundamental component of active surveillance among men with localized prostate cancer. Factors that influence PSA growth, however, are unclear. We evaluated associations of anthropometric and lifestyle factors with age-related PSA growth.

Methods: Repeat PSA measures from 404 men, aged 50 to 69 years, with localized prostate cancer undergoing active monitoring were obtained. From log(PSA) measures, age-specific multilevel mixed effect linear models were developed to predict PSA at age 50 years and yearly increase in postdiagnosis PSA. Baseline anthropometric measures, alcohol consumption, occupational class, smoking status, and physical activity were added to the model as covariates.

Results: The median number of repeat PSAs was 13 (range, 2–40), and the mean duration of follow-up was 4.8 years (SD, 2.3). The basic model of age-related PSA growth in men with localized prostate cancer estimated a mean PSA at age 50 of 3.95 ng/mL [95% confidence interval (CI): 3.55 to 4.39] and a yearly increase of 8.50% (95% CI: 7.90% to 9.10%). PSA at age 50 years was 2.1% lower per unit increase in weighted exercise score (95% CI: −3.3 to −0.8), 5.3% lower per 5 cm increase in height (95% CI: −9.4 to –1.1), and 24.5% higher (95% CI: 4.0 to 49.1) in current smokers than never smokers. Similar associations with PSA growth were seen.

Conclusion: Smoking and exercise are modifiable lifestyle factors that may be associated with PSA levels in men with localized prostate cancer undergoing active monitoring/surveillance.

Impact: These factors may be useful in understanding etiology of progression. *Cancer Epidemiol Biomarkers Prev; 21(10); 1877–85. ©2012 AACR.*

Introduction

Widespread prostate-specific antigen (PSA)–based testing has led to a marked increase in the number of men diagnosed with organ confined, well-differentiated prostate cancers (1, 2). Prostate cancer–specific mortality among clinically detected and PSA-detected localized disease is low (3–5), and there is growing support for active surveillance as an alternative to radical primary intervention for low risk cancers (6–10). Active surveillance includes regular testing for circulating PSA levels: postdiagnosis increases in levels with time (PSA growth) may indicate cancer progression and the need for clinical review (2, 8). The aim is to delay or prevent unnecessary radical treatment in men whose cancer may not progress within their natural lifespan while preserving younger men in a window of curability (8, 11).

PSA levels in individual men vary, and factors other than prostate cancer progression (e.g., age and prostatitis) affect circulating levels (12). Lifestyle factors, including body mass index (BMI) and physical activity, may also influence PSA change (13, 14), but few studies have investigated these factors in men with localized disease. As the numbers of men on active surveillance is increasing, it is important to identify the factors that influence initial PSA levels and PSA growth in such men. We used multilevel models to evaluate associations of anthropometric and lifestyle factors with age-related PSA growth in men with PSA-detected localized prostate cancer undergoing active monitoring.

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Materials and Methods

Study population

Repeat PSA measures were obtained from a cohort of 1,115 men with localized prostate cancer undergoing active monitoring (a program with an active surveillance approach within the ProtecT trial). Briefly, men aged 50 to 69 years from 9 different regions across the United Kingdom were invited for a PSA test between 1999 and 2009. Those with PSA levels of 3 ng/mL or more had a 10-core transrectal ultrasound-guided prostate biopsy. Men with localized (T stage $\leq$2) prostate cancer and a PSA less than 20 ng/mL were randomized or chose by preference in 1 of 3 trial arms: radical prostatectomy, radical radiotherapy, or active monitoring with regular PSA measurement (15).

Evaluation of PSA

Men on active monitoring had their PSA measured every 3 months in the first year and every 6 to 12 months thereafter, using standard methods in the hospital laboratories of each of the 9 study centers. If PSA levels increased by more than 50% in 12 months, or if the participant or clinician were otherwise concerned, men were invited for clinical review and offered radical treatment if appropriate.

Exposures

Before diagnosis, men were invited to complete a questionnaire detailing their diet, health, and lifestyle at recruitment and had their weight and height measured by trained research nurses. If nurse-measured weight (5.9% of men) or height (80.2%) were unavailable, self-reported values were used based on the following questions: How tall are you? What is your weight in light clothing? Inside leg length was self-reported based on the question: What is your inside leg measurement? (If you do not know, please examine a pair of your trousers). Waist and hip circumferences were self-measured: respondents were given a tape measure with detailed instructions and were asked to mark their circumference on the tape and return. The BMI was calculated as weight (kg)/height $(m)^2$. Units of alcohol per week were calculated from self-reported alcohol drunk in the previous 7 days, frequency of drinking over the last year and quantity normally consumed. Self-reported smoking status was defined as "never," "ex," or "current."

Exercise was calculated by applying weights to the frequency of self-reported mild, moderate, and strenuous exercise per week, which were predicted to reflect the metabolic equivalent task value, (mild $\times$ 3) + (moderate $\times$ 5) + (strenuous $\times$ 9), to create a total weekly score. This method was developed by Godin and Shephard (16) to create a simple questionnaire for use in research that could be reliably used to classify people into categories of physical activity. The Godin score has been validated against the percentage body fat from skinfold thickness (16), body fat from hydrostatic weighing (17), maximum oxygen intake (VO_2 max; refs. 16, 17), Caltrac Accelerometer Motion (17, 18), and a graded treadmill exercise test (17). Men were included if they had 2 or more PSA results available. Trent Multicentre Research Ethics Committee approved the study under the auspices of ProMPT (Prostate Mechanisms of Prostate cancer and Treatment; MREC/01/4/061), and all men gave informed consent.

Statistical methods

The PSA measures were log transformed before analysis and transformed back for interpretation. Men who ceased active monitoring were censored at the last PSA measure while on active monitoring. Age, log (PSA) at baseline, and log (mean repeat PSA) were compared between subgroups of baseline variables using the *t* test (2 groups) or one-way ANOVA (>2 groups).

From the repeat PSA measures, age-specific multilevel mixed effect linear models (growth curves; ref. 19) were used to predict log (PSA) at age 50 years and yearly increase in log (PSA). Multilevel models that allow for intraindividual correlations were used because measures from the same individual over time will be more highly correlated than measures from different individuals, but standard multiple regression assumes measures are independent. The multilevel model allowed each man to have their own intercept and their own slope (assumed normally distributed within the population), with measurement error in log (PSA) assumed constant over time. The assumption of a linear relationship between log (PSA) and age was verified (by adding polynomial terms to the model). The first level in the model was the repeat log (PSA) measures and the second was the individual men. To make the intercept meaningful, we made the origin of the time axis age 50 years, which is the lowest age of recruitment. This means that the intercept represents average PSA at age 50. All models were adjusted for age at recruitment to account for the different ages at which baseline variables were measured. An interaction term that allowed age at recruitment clinic to affect yearly increase in log (PSA) was added to each model but was not statistically significant and did not influence the model estimates and so was left out of the final analyses.

Lifestyle factors and anthropometric measures were added to the model as covariates individually, then together in mutually adjusted models, and finally additionally adjusted for Gleason grade, to control for the effects of differences in tumor aggressiveness at diagnosis. Only 404 men had data available on every variable included in the mutually adjusted models; therefore, a sensitivity analysis was conducted in which the age-adjusted models were rerun restricting the analysis to the 404 men with complete data. Models were constructed in which each variable could affect either the log (PSA) at age 50 years (Model 1), yearly increase in log (PSA) (Model 2), or both log (PSA) at age 50 years, and yearly increase in log (PSA) (Model 3). However, due to the high correlation (approximately -0.85) between the slope, yearly increase in log (PSA), and the intercept [log (PSA) at age 50 years], the estimates in Model 3 could not be interpreted with confidence and therefore are not presented here. The best

fitting model was considered the one with the lowest Akaike information criterion (AIC) estimate (20). Gleason score at diagnosis was investigated as a covariate to confirm the ability of PSA growth to indicate aggressive disease. All analyses were repeated including only men with Gleason grade ≤6 and the results compared with those of the whole cohort. All statistical analyses were conducted using Stata v11.2 (StataCorp).

Results

The cohort was mainly Caucasian (1,134/1,155; 98.8%), and 46.5% (528) were of managerial occupational class. A total of 221 (19.1%) had a Gleason score ≥7 at diagnosis, and 73 (8.1%) reported a history of prostate cancer in a father or brother. The median PSA at diagnosis was 4.51 ng/mL (range, 3.0–19.4 ng/mL). The mean number of repeat PSAs was 13.7 (SD, 6.1; range, 2–40), and the mean duration of follow-up was 4.77 years (SD, 2.33; range 0.34–11.57 years). The baseline characteristics of the cohort by questionnaire response status are displayed in Table 1. A total of 335 (29.0%) men did not return their questionnaire (nonresponders); these men were less likely to be Caucasian and more likely to be of working occupational class but were otherwise similar to responders.

Supplementary Tables S1 and S2 describe the distribution of baseline demographic, lifestyle, anthropometric, and missing data by age, recruitment PSA, and repeat PSA measures in the total 1,155 men included in this study. It should be noted that median repeat PSA values presented in Supplementary Tables S1 and S2 should be interpreted with caution as they will be affected by men dropping out of monitoring. Alcohol intake, height, and inside leg length were lower in men who were older at baseline, and age was positively associated with working occupational class. Baseline PSA was higher in older men and men with higher (≥7) Gleason score. Log (mean repeat PSA) level was higher in older men, current smokers, men with Gleason score ≥7, shorter men, and men who reported a family history of prostate cancer.

The multilevel model without covariates estimated a mean PSA at age 50 of 3.95 ng/mL [95% confidence interval (CI): 3.55 to 4.39] and a yearly increase of 8.50% (95% CI: 7.90 to 9.10). Age-adjusted models were constructed using all available PSA measures (Supplementary Table S3), and also restricted to measures only from

Table 1. Baseline characteristics of participants

	Questionnaire responders ($N = 820$)			Nonresponders ($N = 335$)		
	N	**Mean**	**SD**	***N***	**Mean**	**SD**
Age, y	820	62.5	5.0	335	62.2	5.0
Gleason score	820	6.2	0.5	335	6.2	0.5
Height (cm)	814	176.3	6.6	142	175.6	6.8
Weight (kg)	818	83.6	12.2	298	84.0	12.7
BMI (kg/m^2)	812	26.9	3.6	128	26.3	3.8
Waist circumference (cm)	733	95.7	9.4	NA		
Hip circumference (cm)	721	102.4	7.4	NA		
Inside leg length (cm)	797	76.9	4.7	NA		
	N	**Median**	**IQR**	***N***	**Median**	**IQR**
PSA at baseline (ng/mL)	820	4.5	3.5–6.5	335	4.7	3.6–6.8
Mean repeat PSA (ng/mL)	820	5.7	4.3–8.2	335	5.7	4.3–8.3
Exercise (10 weighted scores per week)	515	2.5	0.6–4.9	NA		
Alcohol (units per week)	752	12.0	6.0–26.3	NA		
	N	%		*N*	%	
Family history (total)	655			248		
Yes	52	7.9		21	8.5	
Ethnicity (total)	813			335		
Caucasian	806	99.1		328	97.9	
Smoking (total)	747			NA		
Current	96	12.9		NA		
Ex	357	47.8		NA		
Never	294	39.4		NA		
Occupational class (total)	806			330		
Managerial	389	48.3		139	42.1	
Intermediate	130	16.1		55	16.7	
Working	287	35.6		136	41.2	

Abbreviations: IQR, interquartile range; NA, not applicable.

men with data available on all other variables (404 men, Tables 2 and 3). Although the CIs for the larger models were slightly narrower, the material conclusions were unchanged. For consistency, the restricted models results are reported and discussed here. By a small margin, the best fitting model for all anthropometric measures and lifestyle factors was Model 1, in which variables were only allowed to affect log (PSA) at age 50 years (see Table 2 and Supplementary Table S3 for model results). Most of the anthropometric measures, alcohol consumption, and occupational class were not strongly associated with log (PSA) at age 50 years. There was weak evidence that height was associated with a 5.30% decrease in log (PSA) at age 50 years per 5 cm increase in height, which remained upon adjustment for other covariates (−6.80%; 95% CI, −12.80 to −0.40; $P = 0.04$), and Gleason score (−7.50; 95% CI, −13.40 to −1.30; $P = 0.02$). There was strong evidence that a 10 unit increase in weighted exercise score was associated with an approximately 2% lower PSA at age 50 years (95% CI; −3.30 to −0.80; $P = 0.001$), which remained unchanged after controlling for other covariates and Gleason score. There was also evidence that current smokers had 24.50% higher PSA levels at age 50 years than never 95% CI, 4.00 to 49.10, p for heterogeneity by smoking status = 0.058), which remained essentially unchanged after controlling for other covariates and Gleason score, although the CI widened.

Exercise and height also seemed to be associated with a lower yearly increase in PSA (0.20% lower PSA per 10 unit increase in exercise score; 95% CI, −0.20% to −0.10%; $P = 0.001$ and −0.40% per 5 cm increase in height; 95% CI, −0.70 to 0.10; $P = 0.018$) and current smoking with higher yearly increase in PSA (2.30% higher; 95% CI, 1.00% to 3.70%; $P = 0.002$, even after mutual adjustment and adjustment for Gleason score (Table 3). However, these associations may have been the consequence of the association with PSA at age 50 years, which is related to yearly increase–men with higher PSA levels at 50 years have steeper yearly increase in PSA. Models allowing factors to be associated with both intercept and slope had wide CIs, including the possibility of no association. Height was more strongly associated with PSA at age 50 and yearly increase in PSA in the restricted model than the model based on the full dataset. Therefore this may be a spurious finding.

In separate analyses, men with Gleason score ≥7 had 24.5% higher PSA at age 50 years (95% CI, 14.3% to 35.6%; $P < 0.001$) and 1.9% higher yearly increase in PSA (95% CI;

Table 2. PSA at age 50 (expressed as % difference in baseline PSA)

	Age-adjusted				Mutually adjusted[a]				Gleason score adjusted[b]			
Covariate	**%Change**	**LCI**	**UCI**	***P***	**%Change**	**LCI**	**UCI**	***P***	**%Change**	**LCI**	**UCI**	***P***
Height (per 5 cm)	−5.30	−9.40	−1.10	0.015	−6.80	−12.80	−0.40	0.039	−7.50	−13.40	−1.30	0.019
Weight (per kg)	−0.30	−0.70	0.20	0.31	0.00	−1.00	1.00	0.96	0.00	−1.00	1.00	0.94
BMI (per kg/m^2)	0.30	−1.40	2.00	0.75	1.20[c]	−1.70	4.30	0.42	1.60[c]	−1.40	4.60	0.30
Waist circumference (per 5 cm)	0.10	−3.00	3.30	0.94	3.50	−2.40	9.70	0.25	3.00	−2.70	9.10	0.31
Hip circumference (per 5 cm)	−2.30	−6.20	1.60	0.24	−5.10	−11.60	1.90	0.15	−4.70	−11.20	2.10	0.17
Inside leg (per 5 cm)	−5.00	−11.20	1.80	0.15	4.20	−5.40	14.70	0.40	4.10	−5.30	14.40	0.40
Occupational class												
Managerial	−6.70	−20.40	9.50		−5.10	−18.80	10.90		−5.10	−18.60	10.70	
Intermediate	Reference				Reference				Reference			
Working	2.30	−14.00	21.60	0.34	−2.50	−17.90	15.90	0.78	−2.50	−17.70	15.50	0.78
Smoking status												
Never	Reference				Reference				Reference			
Ex	5.80	−6.10	19.20		7.20	−4.90	20.70		4.90	−6.80	18.00	
Current	24.50	4.00	49.10	0.058	21.70	1.50	45.80	0.097	20.20	0.60	43.60	0.13
Alcohol (per 10 units a week)	−2.10	−4.90	0.90	0.18	−2.10	−5.00	0.80	0.16	−2.20	−5.10	0.70	0.13
Exercise (per 10 weighted scores a week)	−2.10	−3.30	−0.80	0.001	−1.90	−3.20	−0.70	0.003	−2.00	−3.30	−0.80	0.002

Abbreviations: LCI, lower 95% confidence interval; UCI, upper 95% confidence interval.

[a]All covariates included in the same model, accept BMI (due to colinearity with weight and height).

[b]As[a], but additionally adjusted for Gleason score.

[c]All other covariates included in the model, accept height and weight (due to colinearity).

Based on repeat PSA measures from 404 men with complete covariate data.

Table 3. Yearly increase in PSA (expressed as %change in yearly increase in PSA)

	Age-adjusted				Mutually adjusted[a]				Gleason score adjusted[b]			
Covariate	**%Change**	**LCI**	**UCI**	***P***	**%Change**	**LCI**	**UCI**	***P***	**%Change**	**LCI**	**UCI**	***P***
Height (per 5 cm)	−0.40	−0.70	−0.10	0.018	−0.50	−1.00	0.00	0.032	−0.60	−1.10	−0.10	0.011
Weight (per kg)	0.00	−0.10	0.00	0.41	0.00	−0.10	0.10	0.88	0.00	−0.10	0.10	0.98
BMI (per kg/m^2)	0.00	−0.10	0.20	0.63	0.10[c]	−0.10	0.30	0.45	0.10[c]	−0.10	0.30	0.30
Waist circumference (per 5 cm)	0.00	−0.20	0.30	0.87	0.20	−0.20	0.60	0.36	0.20	−0.20	0.60	0.43
Hip circumference (per 5 cm)	−0.10	−0.40	0.20	0.47	−0.20	−0.80	0.30	0.38	−0.20	−0.70	0.30	0.45
Inside leg (per 5 cm)	−0.40	−0.90	0.10	0.15	0.30	−0.40	1.00	0.36	0.40	−0.30	1.00	0.29
Occupational class												
Managerial	−0.70	−1.80	0.50		−0.60	−1.70	0.50		−0.60	−1.60	0.50	0.30
Intermediate	Reference				Reference				Reference			
Working	−0.10	−1.30	1.20	0.29	−0.40	−1.60	0.80	0.596	−0.40	−1.60	0.80	0.59
Smoking status												
Never	Reference				Reference				Reference			
Ex	0.50	−0.30	1.40		0.60	−0.20	1.50		0.40	−0.40	1.30	
Current	2.30	1.00	3.70	0.002	2.20	0.80	3.50	0.005	2.00	0.70	3.30	0.008
Alcohol (per 10 units a week)	−0.20	−0.40	0.10	0.14	−0.20	−0.40	0.10	0.14	−0.20	−0.40	0.10	0.15
Exercise (per 10 weighted scores a week)	−0.20	−0.20	−0.10	0.001	−0.10	−0.20	0.00	0.005	−0.10	−0.20	0.00	0.003

Abbreviations: LCI, lower 95% confidence interval; UCI, upper 95% confidence interval.

[a]All covariates included in the same model, excluding BMI (due to colinearity with weight and height).

[b]As[a], but additionally adjusted for Gleason score.

[c]All other covariates included in the model, accept height and weight (due to colinearity).

Based on repeat PSA measures from 404 men with complete covariate data.

1.3% to 2.4%; $P < 0.001$) than men with Gleason score ≤6. The best fitting model for Gleason score was Model 2, in which Gleason score could affect the yearly increase in PSA, suggesting that increased PSA growth is a marker of poorer tumor differentiation. The associations of PSA growth with smoking, exercise, and height have been modeled in Figs. 1, 2, and 3, for an "average" study man, ages 60 years at recruitment (estimates are from age-adjusted, PSA at age 50 models—Table 2). Analyses were repeated excluding men with Gleason ≥7 ($n = 221$), and

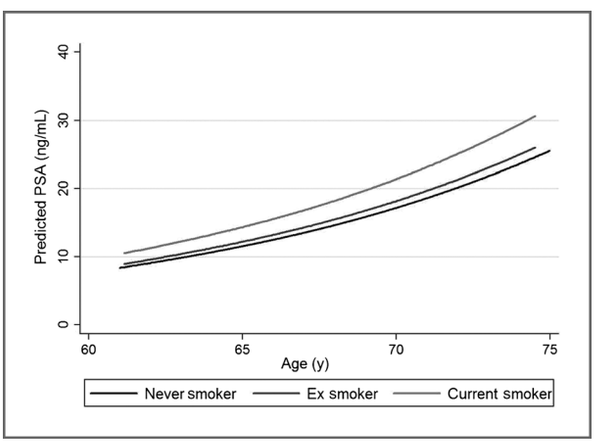

Figure 1. Predicted PSA Growth by Smoking Status, age adjusted, PSA at age 50 model (Model 1).

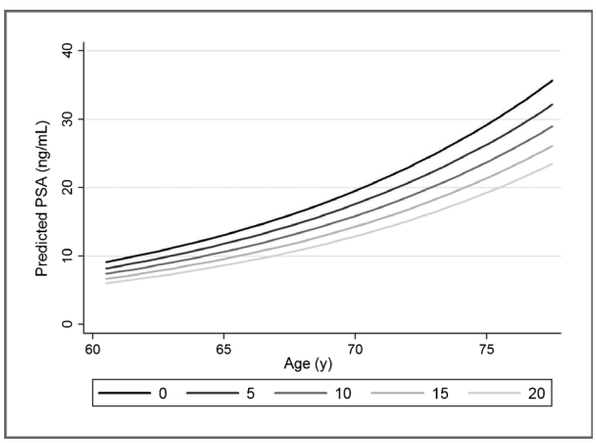

Figure 2. Predicted PSA Growth by Exercise (weighted score), age adjusted, PSA at age 50 model (Model 1).

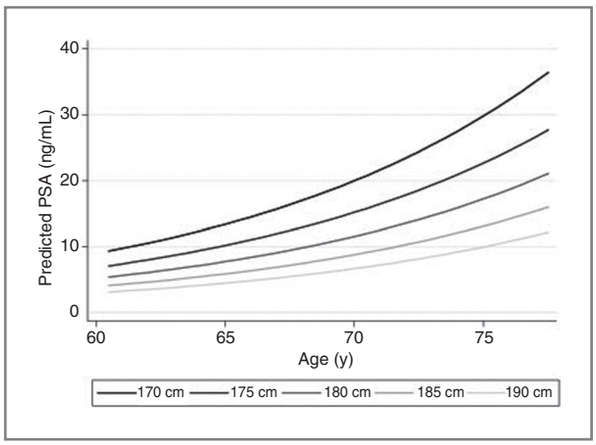

Figure 3. Predicted PSA Growth by Height, age adjusted, PSA at age 50 model (Model 1).

the results were not materially different (results available from authors).

Discussion

In this cohort of men with localized prostate cancer diagnosed as a result of PSA testing and followed up by active monitoring, there was evidence that exercise and smoking status were associated with variations in PSA levels. Increased exercise was associated with lower PSA at age 50 years and lower yearly increases in postdiagnosis PSA. Current smokers had higher PSA levels and higher yearly increases in PSA than never-smokers. Height also seemed to be associated with lower PSA at age 50 years and lower yearly increase in PSA, although the evidence was weaker. For exercise, smoking, and height the PSA at age 50 years model gave the best fit, and as PSA at diagnosis and PSA growth are correlated, it is possible the associations of these variables with steeper yearly increases in PSA were a consequence of higher PSA levels at recruitment. Higher Gleason score was associated with a higher PSA at age 50 and steeper yearly increase in PSA. There was no strong evidence that other anthropometric measures, alcohol consumption, and occupational class were associated with either PSA at age 50 years or PSA growth in this cohort.

There were several strengths to this study. We used multilevel modeling, which takes into account natural age-related increases in PSA. Additionally, the repeated measurement of PSA avoids the issue of day-to-day fluctuations in PSA levels. As the men were undergoing active monitoring, the natural history of localized prostate cancer could be investigated. Many low risk prostate cancers are found through PSA testing, and active surveillance is recommended as an alternative to radical treatment for these types of cancers (21, 22). This study is representative of this important and expanding fraction of men. Our study involves a large number of men followed for a mean 4.77 years. This is much larger than the only other similar study that has been conducted (23), and therefore has more power to detect smaller associations.

There are some limitations. Only men with PSA of 3.0 to 19.9 ng/mL at recruitment were biopsied and subsequently included in this sample, therefore the PSA data will be missing not at random and so associations could be under- or overestimated in this PSA-selected sample compared with the overall population. This means that these associations only apply to men with PSA-detected cancer. Covariates were measured once and may not have been representative of the man over the duration of follow-up. For example, there is evidence that a cancer diagnosis acts as a stimulus for lifestyle and behavioral change (Kerry Avery; unpublished data). This would influence interpretation of the findings if the etiology of progression was to be considered, but not if baseline covariates are to form indicators of risk of progression. In addition, smoking and exercise may be proxies for unmeasured exposures, such as diet; therefore, quitting smoking and/or increasing exercise alone may not affect PSA growth. The cohort is of white ethnicity and from higher occupational class backgrounds, so may not be representative of all men at risk in the population. Many variables were self-reported, which may increase measurement error, thus attenuating associations. However, a validation study carried out on ProtecT pilot phase data based on 4,708 men found a correlation of 0.96 for measured versus self-reported height and no systematic misreporting (24). There are also substantial missing data in the covariates. However, provided PSA levels are not related to missingness and all variables related to missingness are included in the model, these missing data should not bias results (25). Variables were coded as missing or not missing and regressed against initial and mean repeat PSAs to check for any relationships–none were seen. Censoring should not bias the multilevel models used provided the data are missing at random, that is, that censoring (missingness) is related to observed data. Men are censored when they cease active monitoring, and this could potentially lead to bias if the decision to cease active monitoring depends on variables, which are unobserved/not included in these models.

Although, the PSA kinetics are frequently used as indicators of prostate cancer progression, few studies have looked at the influence of lifestyle and demographic factors on initial PSA levels and PSA growth in men with PSA-detected localized prostate cancer. This is the largest study of this kind to the best of the authors' knowledge. In contrast, to our finding of no association of PSA with BMI, Loeb and colleagues (26) found weak evidence that obese men were more likely to have a PSA velocity greater than 2 ng/mL/year and higher PSA at diagnosis. However, PSA velocity was based on 2 PSA measures taken in the year before diagnosis, a total of 1,174 prediagnosis observations over 587 person-years. In contrast, our BMI models are based on 13,087, mainly postdiagnosis, observations over 4,230 person-years. Algotar and colleagues (23) used multilevel mixed effects regression models in a study involving 140 men undergoing watchful waiting. Similarly to our results, no strong association

between BMI and either baseline PSA or PSA velocity was observed. They found a positive association between pack-years of smoking and PSA velocity but not baseline PSA.

Kristal and colleagues (12) also used multilevel models to examine smoking, body mass, and physical activity in relation to mean PSA and PSA velocity in a large cohort of 3,341 cancer-free men. In conflict with our findings in men with prostate cancer, PSA velocity was lower in smokers than nonsmokers, and the authors found little evidence that physical activity was associated with PSA levels or growth. Also, in contrast to the studies involving men with prostate cancer [(refs. 26, 23, and our study], Kristal and colleagues found that BMI was associated with lower mean PSA (but not with PSA velocity). There is some evidence that the presence of prostate cancer may attenuate any inverse BMI–PSA association (13). However, using multilevel models, Bosch and colleagues (27) did not find evidence of an association between BMI and PSA or PSA velocity in 1,439 cancer-free men (although, prostate volume did appear to increase with increasing BMI). In a study of cancer-free men designed to explore factors that may be involved in the BMI–PSA relationship, Wright and colleagues (28) added various factors into a BMI–PSA linear regression model. Age, benign prostate hyperplasia, statin use, and nonsteroidal anti-inflammatory use were all found to be independently associated with both BMI and PSA and explained the apparent inverse BMI–PSA association. It should be noted that substantial evidence indicates that increased BMI is associated with biochemical recurrence following primary treatment (29), prostate cancer progression (30, 31), and prostate cancer mortality (32). However, no evidence was found in this cohort of men with PSA-detected localized prostate cancer that BMI was associated with PSA growth.

Oremek and colleagues (14) investigated the relationship between exercise and PSA by assigning 301 cancer-free men to 15 minutes on a bicycle ergometer. The authors found that PSA levels increased from 2 to 3.3 times following the ergometer test, in proportion to the age of the participant. Although this result seems to conflict with our results, our exercise variable was an indication of general weekly exercise, which may have differing effects on PSA than the immediate effect of cycling-based physical activity.

Our results suggest that height and the modifiable lifestyle factors, exercise and smoking, may be associated with PSA levels in men being followed-up by active monitoring. It is important to define the factors that influence initial PSA levels and PSA growth in men with localized prostate cancer for several reasons; first, if a factor is associated with higher PSA levels, then individuals with higher levels are more likely to be referred for prostate biopsy. If that factor does not increase the individual's risk of clinically relevant prostate cancer, then this is potentially harmful, as biopsies are associated with risks to health including scarring and sepsis (9). Second, if a factor decreases PSA levels but not the risk of aggressive prostate cancer, this may prevent clinically important cancers being identified at an early curative stage.

Identification of factors that affect PSA growth may provide insight into the etiology of prostate cancer progression. There is recent evidence that smoking is associated with increased risk of fatal prostate cancer (33), and that vigorous physical activity is associated with decreased risk (34). In contrast to our findings of an inverse association between height and PSA growth, there is consistent evidence that increasing height is weakly associated with prostate cancer risk (31, 35) and more strongly with advanced/aggressive prostate cancer (35, 36). It is plausible that taller men may have lower PSA levels, and therefore their cancers are missed at an early, more curable stage through PSA testing. Our findings do support the observational evidence linking smoking and exercise with lethal prostate cancer and provide further support of a casual interpretation. However, to verify if these factors are associated with prostate cancer progression in this cohort, longer follow-up to progression-specific outcomes would be needed. Several biologic mechanisms have been proposed linking smoking to prostate cancer progression, including increased plasma levels of carcinogenic compounds (in particular nitrosamines and cadmium), nicotine stimulation of angiogenesis, aberrant DNA methylation, and increased plasma testosterone (33). Physical activity may influence prostate cancer progression via the insulin/insulin-like growth factor (IGF) axis (34). This is also the pathway suggested to mediate the association between prostate cancer progression and height (35). Physical activity increases insulin sensitivity, affects bioavailable IGF-1 and has an anti-inflammatory affect on cytokine production (34), which may protect against progression. If inactivity or smoking are associated with risk of progression and this association is causal, then clinicians could advise patients on lifestyle changes that would reduce their risk, such as increasing weekly exercise. Cancer survivors often have a strong interest in making lifestyle changes and clinician-provided lifestyle guidance has been found to have a powerful effect on cancer survivor behavior (37, 38). Regular physical activity and adoption of other health-promoting lifestyle changes, such as smoking cessation and increased fruit and vegetable consumption also reduces psychological distress and increases health-related quality of life in cancer survivors (38). In addition to the points mentioned earlier, measurement of these factors could be used in prognostic models to predict the risk of progression and therefore need for radical treatment.

In conclusion, the modifiable lifestyle factors smoking and exercise may influence PSA levels in men with localized prostate cancer undergoing active monitoring. Further research is needed to identify the magnitude of this association and its potential role in etiology of progression.

Disclosure of Potential Conflicts of Interest

The authors declare to the Editors-in-Chief, Deputy Editors, Senior Editors, and Scientific Editors that there are no relationships that they believe could be construed as resulting in an actual, potential, or perceived conflict of interest with regard to the manuscript they have submitted for review. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health. No potential conflicts of interest were disclosed.

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