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Differences in characteristics of men with localised prostate cancer who demonstrate low, intermediate or high prostate-specific antigen velocity

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Abstract

Background—Current diagnostic tools are inadequate for reliable prediction of prostate cancer (PCa) aggressiveness in patients with localised disease. This results in many patients being exposed to potentially unnecessary invasive treatment and its associated morbidities. In order to develop appropriate treatment strategies, it is essential to understand the differences between patients who will develop aggressive disease and those who will not.

Methods—A longitudinal study was conducted in men with localised PCa on active surveillance for their disease in which 140 subjects were followed every 3 months for up to 5 years. Change in prostate-specific antigen (PSA) over time (PSA velocity) was used as a marker for PCa progression. Subjects were categorised as slow, intermediate and fast progressors based on tertiles of PSA velocity. Differences in baseline markers were investigated using logistic regressions. Two approaches were used, slow progressors were compared with fast progressors (model 1) and slow progressors were compared with combination of intermediate and fast progressors (model 2).

Results—Aspirin was negatively associated with high PSA velocity in model 1 (odds ratio (95% confidence interval): 0.24 (0.06, 0.94), *P*-value = 0.04) and model 2 (odds ratio = 0.22 (0.08, 0.59), *P*-value = 0.003), whereas smoking was positively associated with high PSA velocity in model 1 (1.03 (0.92, 1.13), *P*-value = 0.01).

Conclusions—These findings highlight the role of aspirin and smoking in PCa progression. They have potential towards risk stratification as well as PCa prevention and hence need to be investigated further.

Keywords

prostate cancer progression; PSA velocity; aspirin; smoking

Introduction

Prostate cancer is the most commonly diagnosed cancer (28%) and second most common cause of cancer-related deaths (11%) among American men.¹ The American Cancer Society estimates approximately 1 in 6 men will develop prostate cancer during their lifetime and 1 in 34 men will die from it.¹ Although the majority of prostate cancer presents as indolent disease, a subset of cases progress to cause considerable morbidity and mortality. Of the total number of men diagnosed with prostate cancer, as many as 25% are diagnosed with metastatic disease,² and 17–23% at risk of metastasis following the diagnosis of organ-confined disease.^{3,4}

Prostate-specific antigen (PSA) is a commonly used biomarker for early detection and prognosis and also to monitor biochemical recurrence after local therapy for prostate cancer.⁵ Although serum PSA ≥ 4 ng/mL is regarded by most as a cut point for prostate biopsy, cancer foci can be demonstrated in approximately 15% patients with PSA levels <4 ng/mL.⁶ Prevalent use of PSA for early detection has led to an increase in the incidence of prostate cancer and has also led to a ‘stage migration’ in the disease profile. Tumours being diagnosed by PSA are characteristically small in size, low grade and expressing low levels of PSA.⁵ A considerable portion of tumours so diagnosed may never develop into clinically significant cancer.⁷ Various authors have called this ‘over-diagnosis’. Studies have estimated the percentage of over-diagnosis to range from 30% to 56%.^{5,7} A large percentage of patients thus diagnosed may then undergo treatment for prostate cancer. Furthermore, as this treatment was not necessarily needed, they would be subjected to a wide variety of potential side-effects or morbidities, such as urinary incontinence, impotence, radiation proctitis and cystitis, depending on the modality of treatment chosen. This phenomenon can be termed as ‘over-treatment’.

Age, family history and African American race are the only consistent risk factors for prostate cancer. However, using currently available diagnostic tools and markers, accurate prediction of which patients will develop advanced or progressive cancer cannot be made.⁸ Markers that reliably differentiate indolent from aggressive cancer need to be identified so that physicians can determine which patients need aggressive treatment as opposed to those who might do better with conservative management. This increase in predictive ability will reduce overtreatment and its associated morbidities and healthcare cost. Using subjects from the Watchful Waiting (WW) study, we sought to identify differences between patients who will develop aggressive disease and those who will not. Rate of PSA change over time (PSA velocity) was used as a marker of PCa progression in this study. Subjects were categorised as low, intermediate or high based on tertiles of PSA velocity. Differences in baseline variables were investigated using logistic regression models. The low PSA velocity tertile was compared with the high tertile (model 1); and the low PSA velocity tertile was compared with a combination of the intermediate and high tertiles (model 2). Variables selected as potential markers have been shown to be associated with prostate cancer progression in the literature and most are already being collected during routine patient workup and are available to the attending physician. The relationship between PSA velocity and aggressive or progressive prostate cancer remains controversial. However, PSA velocity has been the predominant clinical marker for monitoring progress and prognosis in both the

pre- and post-treatment phases of prostate cancer. Hence, PSA velocity was monitored in this study as an indicator of progression.

Methods

Study population

A detailed description of the study design for the WW study has been published elsewhere.⁹ Briefly, the WW study was a randomised, double-blind, placebo-controlled, multicentre, phase 2b clinical trial conducted among men diagnosed with prostate cancer. It was designed to investigate the effects of two doses of selenised yeast compared with placebo on the progression of clinical prostate cancer, as measured by decrease in PSA velocity. The primary aim of this study was to assess if subjects who were supplemented with selenium would show lower PSA velocity as compared with subjects who received placebo. Subjects were recruited from urology offices at nine sites in the USA (Annapolis, MD; Little Rock, AR; Shreveport, LA; Chicago, IL; Columbus, OH; Palo Alto, CA; Tucson, AZ; Chapel Hill, NC; and Fresno, CA). Recruitment began August 1, 1998 and ended on July 31, 2003.⁹ The trial was stopped in August 2006. Eligibility criteria for this study required subjects to have biopsy-proven prostate cancer within 48 months prior to beginning the study with a Gleason score less than 8, no metastatic cancer and not receiving treatment for the prostate cancer. These men also had serum PSA less than 50 ng/mL, less than 85 years of age, life expectancy of at least 3 years, and agreed not to take more than 50 µg of other selenium supplementation per day. One hundred and forty subjects were randomised to placebo ($n = 46$), selenium 200 µg/day ($n = 47$) or selenium 800 µg/day ($n = 47$) groups after a run-in period of 30 days. Subjects were followed every 3 months for up to 5 years. Median time on study was 35 months and average yearly dropout rate was 10.5%. Results from this trial indicated no effect of selenium supplementation on PCa progression as measured by PSA velocity.⁹

Data collection and processing

At the enrolment visit, questionnaires seeking demographic characteristic, medical history, medication history, selenium toxicity information and urological symptoms were filled out and eligibility criteria verified by study coordinators. Detailed history regarding type of medication, dose, frequency, reason for taking a particular medication, and the start and stop dates for each medication were collected. Blood was drawn to assess selenium chromogranin-A, and PSA at baseline and at subsequent follow-up visits (every 3 months). Pathology reports from the qualifying biopsy were obtained from the patient's pathologist and compiled in a tissue library.

Total selenium content was measured by automated electrothermal atomic absorption spectrophotometer (3030; Perkin-Elmer, Norwalk, CT, USA). Serum PSA levels were measured using Abbott tumour markers assay module on the IMX analyser (Abbott Diagnostics, Abbott Park, IL, USA). In March 2005, Abbott Diagnostics replaced the AxsYM-PSA assay by Total AxsYM-PSA assay, a combined assay for free and bound PSA. Adjustment for changes in the PSA assay techniques was included in the analysis to account for any effects this change might have on PSA values. Both assays were approved

by the Food and Drug Administration in the USA. Serum samples were sent to Dr Deftos's laboratory at University of California-San Diego, La Jolla, California, for estimation of chromogranin-A.

Body mass index was calculated as weight in kilograms divided by height in square metres (kg/m^2). As only 9.42% of subjects reported themselves to be current smokers, subjects were not categorised as current, former or never smokers, instead pack-years of smoking was used as a measure of smoking. Pack-years of smoking was calculated as number of packs of cigarette smoked per day multiplied by the number of years the subject had been smoking at or prior to enrolment. Subjects were categorised as aspirin users if they reported current aspirin use at the time of enrolment in the study. Otherwise they were categorised as non-users. The same approach was taken for categorising statin users and non-steroidal anti-inflammatory drug (NSAID) users. Race was dichotomised as white people or non-white people as only 12% of our subjects were non-white people.

Statistical analysis

PSA values were transformed using $\ln(\text{PSA} + 1)$ in order to normalise their distribution and to stabilise their variance. PSA velocity (rate of rise of PSA) was estimated using a mixed effects model. This model utilised information from PSA measurements taken at baseline and follow up and the duration of time over which these measurements were made to estimate PSA velocity.¹⁰ This model allowed a random intercept and slope for individual subjects in the study and accounted for the correlated data due to repeated measures over time. Unstructured correlation structure was used to model these data and the model was adjusted for change in PSA assay method. Subjects having PSA measurements for only one time point during the WW study were not included in the analysis ($n = 10$) hence resulting in 130 eligible subjects. Subjects were categorised as low, intermediate or high based on tertiles of PSA velocity.

Differences in baseline variables were investigated using logistic regressions. Analyses were run using two approaches. Low PSA velocity tertile was compared with the high tertile (model 1); and the low PSA velocity tertile was compared with a combination of the intermediate and high tertiles (model 2). As 41 of the 130 subjects had data for free PSA, a sub-analysis was conducted to investigate the association between free PSA and high PSA velocity. These models were adjusted for age, Gleason score, pack-years of smoking, race and aspirin use. Variables were considered to be statistically significant if their P -values were less than 0.05. All analyses were conducted using Stata10 statistical software (Stata-Corp IC, College Station, TX, USA).

Results

Table 1 shows the baseline characteristics of men in the study. The mean age of the men in the study was 73 years and the mean body mass index was 26.8 kg/m^2 . Mean baseline serum selenium, pack-years of smoking and Gleason score were 134.6 ng/mL , 24.8 and 5.7 respectively. Approximately 87% of the men were white, and 12% reported a family history of prostate cancer. Overall, 36% of the men reported aspirin use at baseline, 20% reported using a statin and 14% reported taking an NSAID other than aspirin.

In model 1 (comparing low and high tertiles) or model 2 (comparing low tertile with a combination intermediate and fast tertile), none of the variables was statistically significantly different between the comparison groups, although pack-years in model 1 and free PSA in model 2 demonstrated a *P*-value of 0.05 (Table 1).

In the multiple logistic regression for model 1 (Table 2), smoking was positively associated with a statistically significant higher risk for high PSA velocity (odds ratio (OR) = 1.03, 95% confidence interval (CI): 1.00, 1.05, *P* = 0.01) whereas aspirin use was associated with a statistically significant protective effect for high PSA velocity (OR and 95% CI = 0.28 (0.08, 0.97), *P* = 0.04) after adjusting for other variables in the model. This means the odds of having high PSA velocity increased by 1.03 for 1 pack-year increase in smoking and the odds of having high velocity were 0.28 times higher for aspirin users as compared with non-users. This means that for a 10-pack-year smoking exposure, the odds of a subject having high PSA velocity increased by 30%. Ten-pack-year exposures could happen by smoking 1 pack per day for 10 years or 2 packs per day for 5 years.

In model 2, smoking was associated with a higher odds for having high PSA velocity (OR and 95% CI: 1.02 (1.00, 1.03), *P* = 0.06) while aspirin demonstrated a statistically significant protective effect (OR and 95% CI: 0.22 (0.08, 0.59), *P* = 0.003). In the sub-analysis carried out to assess the association between free PSA and high PSA velocity (Table 3), free PSA was not significantly associated with high PSA velocity after adjusting for other variables in both models (model 1: 0.89 (0.76, 1.05), 0.18, model 2: 0.96 (0.88, 1.05), 0.39).

Discussion

In men with localised prostate cancer on watchful waiting for their disease, aspirin is negatively associated with high PSA velocity in both models (model 1 comparing low PSA velocity tertile with the high PSA velocity tertile and model 2 comparing low PSA velocity tertile with a combination of the intermediate and high tertiles) whereas smoking demonstrates statistically significant positive association with high PSA velocity in model 1.

These results demonstrate that aspirin seems to be negatively associated with high PSA velocity or faster PCa progression. The protective effect of aspirin has been demonstrated in several large studies^{11–14} and also by studies by our group using the same study population.¹⁵ Aspirin is hypothesised to act on prostate cancer through its anti-inflammatory effect by blocking the cyclooxygenase enzyme and preventing generation of pro-inflammatory prostaglandins.^{13,14}

Pack-years of cigarettes smoked during the patient's lifetime was used as a measure of smoking for this analysis as only 9.42% of subjects reported themselves to be current smokers. Using it as a continuous variable allowed us to account appropriately for the subject's smoking exposure that might have occurred at the time of enrolment or before it. Previous studies have shown inconsistent association between smoking and prostate cancer risk, but have shown more consistent association of smoking with aggressive prostate cancer. In a review by Hickey *et al.*, 26 out 36 studies using incident prostate cancer as an

outcome did not report an association between with smoking whereas 8 out of 12 studies using death from prostate cancer as an outcome found positive association with smoking.¹⁶ Biologically, it is unclear how smoking acts on prostate cancer development and progression. Authors have speculated that mutation in the tumour suppressor gene p53 may be a mechanism through which smoking influences prostate cancer.¹⁷ Other postulated mechanisms include direct mutagenesis and higher genomic instability, hormonal imbalances as well as adverse effects of smoking on natural killer cell activity and T lymphocyte cell function.¹⁶

Most of the variables used in this analysis were self-reported by subjects during enrolment in the WW study. Because of this, the reliability of these data is not very high, as in the case for any other study where data are collected through self-report. As this is a prospective analysis, the effect of recall bias is likely to be non-differential. A limitation of the study was the study population, which was at low risk for disease progression (PSA < 50 ng/mL, age < 85 years, life expectancy > 3 years, Gleason score < 8 and no evidence of metastatic cancer) as they were on watchful waiting for their disease. The median PSA doubling times for subjects having 'good risk' prostate cancer have been reported as 3 years or above.¹⁸ The median PSA doubling time observed in the current study population was 5.54 years. Actual PSA velocities noted at the end of the study were much lower than what was expected when the study was designed. Also the WW study was designed to follow subjects for 5 years, but the median follow-up time at the end of the study was 3.2 years. Both these factors lowered the ability to detect differences if any existed.

Strengths of the current study design and analysis include use of mixed effects model to derive PSA velocities, using pack-years as a variable for smoking exposure, categorising subjects into low, intermediate and high PSA velocity tertiles and using multiple approaches to analyse data. The mixed effects model accounts for correlation due to repeated measures and allows independent random intercept and random coefficient for each subject and uses maximum information provided by the subject to estimate PSA velocity. Other methods used to estimate PSA velocity include best line fit or first and last observation methods.¹⁹ In both these methods, PSA velocity is computed by using only limited numbers of PSA measurements from a single patient. Because of a high degree of biologic variation in PSA values, the velocity estimations obtained from these methods may not provide a reliable description of the patient's PSA profile. Thus the mixed effects model avoids the instability associated with other methods for calculating PSA velocity and provides a more reliable estimate of PSA velocity.¹⁹

Categorising subjects into low, intermediate and high PSA velocity categories allowed us to compare variables between these groups. Using two different approaches for analyses (low PSA velocity tertile compared with the high tertile (model 1), and low PSA velocity tertile compared with a combination of the intermediate and high tertiles (model 2)) allowed us to contrast results. In model 1, we compared the extremes and hence we had high sensitivity to detect differences if any existed, but lower power as this reduced sample size. In model 2, we had higher power as we could use the full study population, but had lower sensitivity to detect statistically significant differences if any existed.

Recent reports have raised questions about the reliability of the association between PSA velocity and adverse prostate pathology,²⁰ but selection bias, an important consideration in designing active surveillance cohorts, may have caused undue influence.²¹ Several studies have demonstrated a strong association between high PSA velocity and aggressive prostate cancer or adverse disease outcome. D'Amico *et al.* have successfully demonstrated that men with PSAV greater than 2.0 ng/mL/year have a higher likelihood of death due to prostate cancer despite undergoing radical prostatectomy or radiation therapy.^{22,23} Carter *et al.* also described a statistically significant association between high PSA velocity and death due to prostate cancer.²⁴ Using data from three clinical trials, Rozhansky *et al.* concluded that the association between PSA velocity and aggressive disease profile was strong and hence PSA velocity can be used as a surrogate end point for disease progression.²⁵ In the most definitive study yet, Klotz *et al.* presented an analysis of data from 450 men on an active surveillance.²⁶ Those men with a doubling time of ≤ 3 years had a highly increased risk of biochemical failure following definitive treatment (OR and 95% CI: 8.5 (4.8, 14.9)). This Canadian Surveillance Trial is to date the largest published prospective cohort to date, and supports the association between PSA velocity and aggressive disease. PSA velocity is not ideal, but it has been the predominant clinical marker for monitoring progress and prognosis in both the pre- and post-treatment phases of prostate cancer. Its association with disease progression or aggressive disease has been demonstrated in observational studies and clinical trials.

We do recognise the small sample size reduced further by categorising into tertiles hampers the generalisability of these results. But this is an exploratory attempt using a unique population and dataset at identifying the factors that may be associated with prostate cancer progression. To the best of our knowledge, this is a unique population where data on subjects with localised prostate cancer on active surveillance were collected every 3 months for up to 5 years. The goal of these analyses was to provide physicians with tools to better assess the patient's risk of progression in order to develop a treatment plan that may be best suited for the patient. The variables selected for this analysis have shown to be associated with prostate cancer progression in previous literature and most of the variables are currently collected as part of routine patient workup or can be easily calculated and are thus readily available to the physician. An important current unmet need in the field of prostate cancer is to identify reliable markers of prostate cancer progression that would help clinicians determine which patients need aggressive treatment as opposed to those who might do well using a conservative approach. If these are modifiable risk factors, such as aspirin or smoking, they could potentially contribute towards designing new strategies to prevent or suppress prostate cancer progression.

Conclusion

In men with localised prostate cancer on watchful waiting for their disease, pack-years of smoking and aspirin show association with PSA velocity. These findings highlight the role of aspirin and smoking in PCa progression, and can be used to develop new PCa risk stratification models. This study indicates that these lifestyle factors may be an important component of PCa prevention that should be investigated further in more definitive studies.

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Table 1

Baseline characteristics of the total study population by tertiles of PSA velocity

Variable	Total study population (n = 130)	Low PSA velocity (n = 44)	Intermediate PSA velocity (n = 43)	High PSA velocity (n = 43)	P-value for model 1	P-value for model 2
Age (years)	73.1 (6.0)	72.2 (5.5)	73.4 (6.8)	73.7 (5.7)	0.21	0.15
BMI (kg/m ²)	26.8 (3.9)	26.7 (4.0)	26.7 (3.5)	27.1 (4.3)	0.69	0.73
Pack-years of smoking	24.8 (30.5)	21.4 (28.9)	18.6 (28.2)	34.8 (32.6)	0.05	0.24
Gleason score	5.6 (1.1)	5.6 (1.1)	5.6 (1.2)	5.7 (1.0)	0.51	0.61
Baseline selenium (ng/mL)	134.8 (42.7)	131.8 (23.1)	137.9 (54.1)	134.8 (45.8)	0.70	0.33
Family history	16 (12.3%)	8 (18.2%)	6 (14.0%)	2 (4.7%)	0.09	0.15
White people	113 (86.9%)	38 (86.4%)	41 (95.4%)	34 (79.1%)	0.41	0.89
Baseline aspirin use	47 (36.2%)	19 (43.2%)	14 (32.6%)	14 (32.6%)	0.31	0.11
Baseline statin use	26 (20.0%)	9 (20.5%)	9 (20.9%)	8 (18.6%)	0.83	0.93
Baseline other NSAID use	18 (13.9%)	7 (15.9%)	6 (14.0%)	5 (11.6%)	0.76	0.56
Baseline chromogranin-A (ng/mL)	53.0 (77.6)	42.1 (30.3)	65.0 (97.5)	52.7 (89.7)	0.47	0.63
Baseline free PSA (ng/mL)	1.4 (1.8)	1.5 (1.0)	1.4 (2.6)	1.3 (0.9)	0.72	0.05

Table presents mean (SD) for continuous variables and n (%) for categorical variables. Model 1 compares low PSA velocity tertile with high PSA velocity tertile. Model 2 compares low PSA velocity tertile with intermediate and high PSA velocity tertiles. T-tests used to compare continuous variables, χ^2 -tests used to compare categorical variables. Data included in this study come from subjects recruited from multiple sites and followed between 1998 and 2006. Please refer to the *Methods* section for details regarding subject recruitment and follow up.

BMI, body mass index; NSAID, non-steroidal anti-inflammatory drug; PSA, prostate-specific antigen.

Table 2

Odds ratios and 95% CI from multiple logistic regression for models 1 and 2

Variable	Model 1 (OR (95% CI))	P-value	Model 2 (OR (95% CI))	P-value
Age	1.08 (0.98–1.18)	0.12	1.05 (0.98–1.13)	0.19
BMI	0.95 (0.82–1.09)	0.44	0.99 (0.87–1.12)	0.86
Pack-years of smoking	1.03 (1.006–1.05)	0.01	1.02 (1.00–1.04)	0.06
Gleason score	1.28 (0.76–2.18)	0.35	0.98 (0.63–1.51)	0.93
Baseline selenium	1.00 (0.98–1.02)	0.82	1.01 (1.00–1.02)	0.32
Family history	0.17 (0.03–1.17)	0.07	0.29 (0.07–1.10)	0.07
White people	0.41 (0.09–1.91)	0.26	1.02 (0.28–3.80)	0.97
Baseline aspirin use	0.28 (0.08–0.97)	0.04	0.22 (0.08–0.59)	0.003
Baseline statin use	0.86 (0.19–3.91)	0.84	0.87 (0.27–2.75)	0.81
Baseline other NSAID use	0.38 (0.06–1.17)	0.31	0.93 (0.23–3.76)	0.93
Baseline chromogranin-A	1.00 (0.99–1.01)	0.53	1.00 (0.99–1.00)	0.71

Odds ratios (OR) adjusted for other variables in table. Model 1 compares low PSA velocity tertile with high PSA velocity tertile. Model 2 compares low PSA velocity tertile with intermediate and high PSA velocity tertiles. Data included in this study come from subjects recruited from multiple sites and followed between 1998 and 2006. Please refer to the *Methods* section for details regarding subject recruitment and follow up.

BMI, body mass index; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; PSA, prostate-specific antigen.

Table 3

Odds ratios and 95% CI from multiple logistic regression from categories of PSA velocity on free PSA adjusted for other variables

Variable	Model 1	P-value	Model 2	P-value
Age	1.19 (0.79, 1.88)	0.82	0.98 (0.82, 1.16)	0.53
Pack-years of smoking	1.04 (0.97, 1.12)	0.21	1.02 (0.99, 1.05)	0.07
Gleason score	1.09 (0.24, 4.93)	0.90	1.02 (0.57, 1.81)	0.96
Baseline aspirin use	0.003 (3.10e ⁻⁶ , 2.25)	0.21	0.22 (0.02, 2.27)	0.01
Baseline free PSA (ng/mL)	0.89 (0.76, 1.05)	0.18	0.96 (0.88, 1.05)	0.39

Odds ratios (OR) adjusted for other variables in table. Model 1 compares low PSA velocity tertile with high PSA velocity tertile. Model 2 compares low PSA velocity tertile with intermediate and high PSA velocity tertiles. Data included in this study come from subjects recruited from multiple sites and followed between 1998 and 2006. Please refer to the *Methods* section for details regarding subject recruitment and follow up.

BMI, body mass index; CI, confidence interval; PSA, prostate-specific antigen.