Published in final edited form as:

Am J Mens Health. 2011 May ; 5(3): 272–278. doi:10.1177/1557988310390030.

Association of Obesity and Smoking With PSA and PSA Velocity in Men With Prostate Cancer

Amit M. Algotar, PhD, MBBS¹, Steven P. Stratton, PhD^{1,2}, James Ranger-Moore, PhD^{1,3}, M. Suzanne Stratton, PhD¹, C.H. Hsu, PhD^{1,3}, Frederick R. Ahmann, MD^{1,2}, Raymond B. Nagle, MD, PhD^{1,4}, and Patricia A. Thompson, PhD^{1,5}

¹Arizona Cancer Center, University of Arizona, Tucson, AZ

²Department of Medicine, College of Medicine, University of Arizona, Tucson, AZ

³Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ

⁴Department of Pathology, College of Medicine, University of Arizona, Tucson, AZ

⁵Department of Anatomy and Cell Biology, College of Medicine, University of Arizona, Tucson, AZ

Abstract

Significant number of prostate tumors are slow growing and could probably be left untreated. However, many are aggressive and can spread rapidly causing patient suffering and/or death. Current technology does not allow physicians to differentiate between slow growing and aggressive tumors at diagnosis. Hence, many patients are exposed to invasive treatment and its associated morbidities such as incontinence and impotence. Markers that enable differentiation between slow and fast progressing cancer will allow physicians to prevent unnecessary treatments on men who may not need them, and focus on the men with aggressive disease. A longitudinal study was conducted ($N = 140$) using mixed effects regression models to determine the association of obesity and smoking toward prostate cancer progression. These models account for correlation because of repeated measures over time, thus, using maximum amount of information provided by the subject. Estimates thus obtained are more robust and reliable than those obtained using data from a single time point. Rate of change of prostate-specific antigen (PSA) over time (PSA velocity) was used as a measure of prostate cancer progression. Results indicate that PSA velocity of overweight and obese subjects (0.59 and 1.05 ng/mL/year) was not significantly different as compared with normal weight subjects (p values .91 and .31, respectively). For men in the highest tertile of pack-years of smoking, PSA velocity was significantly higher as compared with never smokers 1.57 ng/mL/year ($p = .04$). Further studies with larger sample sizes and study designs specific to above exposures are needed before recommendations can be made to reduce weight or reduce/quit smoking.

Corresponding Author: Amit M. Algotar, Arizona Cancer Center, University of Arizona, 2504 East Elm Street, P.O. Box 245170, Tucson, AZ 85716, USA algotar@email.arizona.edu.

Declaration of Conflicting Interests The author(s) declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

Keywords

obesity; smoking; prostate cancer; PSA; PSA velocity

Introduction

Prostate cancer (PCa) is the most common nonskin cancer (28% of all cancers) and second most common cause of cancer-related deaths (11% of all cancer deaths) among men in the United States (American Cancer Society, 2010). Lifetime risk of PCa in the United States has been estimated to be 8% (Bostwick et al., 2004). Incidence of PCa is higher for men who are older than 65 years, are African American, or have a familial predisposition (American Cancer Society, 2010). Although the majority of PCa cases present as slow growing disease, in others, PCa can progress rapidly causing significant morbidity and mortality. Of the total number of men first diagnosed with PCa, as many as 75% are diagnosed with localized disease with a sizable fraction presenting with a relatively indolent, non or slow progressing form (Lamb et al., 2007). The identification of risk factors for disease progression, particularly those that may be modifiable, is an important and largely underexploited area for improving patient care and disease-specific outcomes (Bostwick et al., 2004).

There have been several large studies that have reported obesity as a risk factor for PCa, (Andersson et al., 1997; Engeland, Tretli, & Bjorge, 2003; Parkin, Bray, Ferlay, & Pisani, 2005), though others have reported no association (Nilsen & Vatten, 1999; Veierod, Laake, & Thelle, 1997) or even a protective effect (Giovannucci et al., 2003; Gong et al., 2006; Rodriguez et al., 2007; Schuurman, Goldbohm, Dorant, & van den Brandt, 2000). Obesity and risk of PCa progression, high grade, or advanced disease, including death, has been consistently observed across studies (Giovannucci et al., 2003; Giovannucci, Liu, Platz, Stampfer, & Willett, 2007; Gong et al., 2006; Parkin et al., 2005; Wright et al., 2007). Overall, obesity appears to have protective or null effects on PCa incidence with effects as a risk factor in the development of more aggressive PCa and death due to PCa. As additional evidence supporting a role for obesity in PCa pathogenesis, others have shown protective effects of intentional weight loss (Rodriguez et al., 2007; Schuurman et al., 2000).

Several hypotheses have been proposed to explain the apparent association between obesity and PCa. As a protective factor in incidence, obese individuals have been reported to have lower PSA levels (Buschemeyer & Freedland, 2007) with higher rates of conversion of testosterone to estrogen (Buschemeyer & Freedland, 2007; Calle & Kaaks, 2004). Obese men also have higher plasma volume compared with normal-weight men, which has been suggested to dilute the amount of PSA in plasma, reducing its concentration in plasma (Banez et al., 2007). In addition, obese individuals have been shown to have larger prostates (Buschemeyer & Freedland, 2007), increasing the probability of missing a PCa focus on biopsy or on digital rectal examination.

Similar to obesity, the role of smoking as a risk factor for PCa remains unclear. In reviews by Hickey, Do, and Green (2001), smoking was found to not act as a significant risk factor for PCa incidence in the majority of prospective cohort studies. In contrast, the majority (8

of 12) of prospective studies, where PCa death was the outcome reported, current smoking at baseline was strongly related to worse outcomes.

Biologically, it is unclear how smoking affects PCa development and acceleration. Giovannucci et al. (1999) have speculated that higher mutation in the tumor suppressor gene p53 among smokers may be a mechanism that explains the association between smoking and fatal PCa. Other postulated mechanisms include direct mutagenesis and higher genomic instability as well as adverse effects of smoking on natural killer cell activity and T lymphocyte cell function (Hickey et al., 2001).

A study was conducted to investigate the role of obesity and smoking as risk factors for prostate-specific antigen (PSA) velocity (i.e., rate of PSA change over time) among men participating in a chemoprevention study of selenium for the prevention of PCa progression. PSA velocity has consistently been shown to be associated with aggressive PCa (Carter et al., 1992; Lieberman, 2004; Schroder et al., 2008; Shariat & Karakiewicz, 2008) and was used as an indicator of PCa progression in this study.

Materials and Methods

Study Population

Data for this study were obtained from the active surveillance trial, details of the study design for which have been published earlier (Stratton et al., 2003, 2010). Briefly, this was a randomized, double-blind, placebo-controlled, multicenter, Phase 2 clinical trial designed to investigate the effects of two doses of selenized yeast compared with placebo on the progression of PCa in men with localized cancer. The primary aim of this study was to assess if subjects who were supplemented with selenium demonstrated lower PSA velocity as compared with subjects who received placebo. Eligibility criteria for this study required subjects to have biopsy proven PCa within 48 months prior to beginning the study with a Gleason score less than 8, no metastatic cancer, and not receiving treatment for the PCa. The men also had PSA less than 50 ng/mL, were less than 85 years of age, had a life expectancy of at least 3 years, and agreed not to take more than 50 µg of other selenium supplementation per day. All men selected for this trial had selected WW as a therapeutic modality for their disease in favor of other options such as surgery or radiation. A total of 140 men were randomized 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.

Data Collection and Processing

At the enrollment visit, questionnaires seeking demographic characteristics, medical history, tobacco and alcohol use, selenium toxicity information, and urological symptoms were filled out and eligibility criteria verified by study coordinators. Subjects' height and weight were measured by study coordinators at each study center using standard guidelines. Blood was drawn to assess baseline serum selenium, PSA, chromagranin-A, lycopene, and vitamin E and to obtain a comprehensive metabolic panel. Prostate tissue samples from the subject's qualifying biopsy were requested from the subject's physician and compiled in a tissue

library. Blood samples were collected for serum selenium and PSA at each 3-month visit. Follow-up questionnaires were filled at each follow-up visit to capture any change in information that may have occurred since the enrollment visit.

Serum PSA levels were measured using Abbott tumor markers assay module on the IMX analyzer (Abbott Diagnostics, Abbott Park, IL). In March 2005, Abbott Diagnostics replaced the IMX-PSA assay by Total AxSYM-PSA assay. Adjustment for changes in the PSA assay techniques was included in the random coefficient model to account for any effects this change might have had on PSA velocity. Both assays were approved by the Food and Drug Administration in the United States.

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Subjects were categorized as normal ($\text{BMI} \geq 18$ and $\text{BMI} < 25$), overweight ($\text{BMI} \geq 25$ and $\text{BMI} < 30$), and obese ($\text{BMI} \geq 30$) according to the criteria specified by the World Health Organization and National Institutes of Health (Buschemeyer & Freedland, 2007). There were no underweight ($\text{BMI} < 18$) subjects in the study population. Since only 9.42% of subjects reported themselves for being current smokers, pack-years of smoking were used as a measure of smoking. Pack-years of smoking were calculated as number of packs of cigarette smoked per day multiplied by the number of years the subject had been smoking at that level prior to enrollment. The pack-years variable was then categorized into four categories: never smokers ("0") and then by tertiles of the smokers' pack-years with low (0.15 to 20 pack-years), medium (21.5 to 48 pack-years), and high (49 to 117.5 pack-years). Race was dichotomized as Caucasian or non-Caucasian.

Statistical Analysis

Frequencies and mean values were calculated for all variables and differences between BMI and smoking groups were compared using ANOVA or Fisher's exact tests. PSA values were transformed using $\ln(\text{PSA} + 1)$ to correct for right skewed distribution and to stabilize variance. Multiple linear regression modeling was used to evaluate the potential associations between baseline PSA level and baseline BMI as well as baseline PSA and pack-year smoking history. Race, age, and Gleason score were included in the models as potential confounders based on previous literature.

PSA velocity (rate of change in PSA over time) was used as an indicator of PCa progression. Mixed effects models (Laird & Ware, 1982) with patient level random effects were used to assess the effect of BMI and pack-years on PSA velocity. This model allowed random intercept and slope for individual subjects in the study and accounted for correlated data because of repeated measures over time. An interaction term between BMI and the time on study was created to derive PSA velocity for each BMI category. Statistical significance of this interaction term was used as a measure of the impact of the particular BMI category with the trajectory of PSA (i.e., PSA velocity). If an interaction was deemed to be statistically significant ($p < 0.05$), then the trajectories of participants in a particular BMI category (overweight or obese) were considered to be significantly different as compared the trajectories of participants in the reference category (normal weight category). Similar principles were applied to a model using BMI as a continuous variable. An unstructured correlation structure was used to model these data. The unstructured correlation structure

does not impose any assumptions on the data, and hence, it was chosen to use it for these analyses. The correlations modeled by using this correlation structure correspond to repeated measurements of PSA within the subject.

Separate models were evaluated using BMI as a continuous or categorical variable. Models were adjusted for race, age, pack-years of smoking at baseline, and Gleason score based on previous literature. Models were also adjusted for type of assay used to estimate PSA to account for any effect that change in the PSA assay might have had on the PSA values. A similar analytic approach was used to assess the effect on smoking at baseline and on PSA velocity. All smoking models were adjusted for BMI along with other variables mentioned above. Statistical significance was assessed at $p < .05$. All analyses were conducted using Stata10 statistical software (StataCorp Inc., College Station, TX).

Results

The baseline characteristics of men participating in the WW Study by BMI categories and smoking histories are presented in Tables 1 and 2, respectively. The mean age of the men in this population was 73 years and the majority of the men (49%) were overweight, with a mean BMI of 26.9 kg/m². Mean baseline serum PSA, serum selenium, and Gleason score were 8.0 ng/mL, 134.6 ng/mL, and 5.7, respectively. Approximately 88% of subjects were Caucasian and the ethnic-racial distribution was approximately equal across categories of BMI and pack-years. Smoking history increased with BMI category, with obese men reporting higher mean pack-years of smoking as compared with normal weight subjects ($F = 6.19$, $p = .01$). This statistically significant association (higher BMI for subjects with higher pack-years of smoking) was also noted by categories of pack-years ($F = 3.96$, $p = .001$).

Table 3 presents the regression coefficients for the associations of BMI and pack-years of smoking with PSA at baseline. BMI and pack-years of smoking were not significantly associated with PSA at baseline but age, Gleason score, and race other than Caucasian were significantly and positively associated with baseline PSA. Longitudinal analysis using mixed effects models was carried out to determine the association between baseline BMI and baseline smoking with PSA velocity. Separate mixed models were evaluated using BMI and pack-years of smoking. Results of these analyses are shown in Tables 4 and 5. Table 4 demonstrates the results of analyses using obesity and smoking as continuous variables, whereas Table 5 presents them in a categorical format. For Table 5, PSA velocity was derived using back-transformation. Compared with normal weight subjects, PSA velocity of men in the overweight and obese categories was not statistically significantly different (PSA velocities and p values, 0.59 ng/mL/year and .92 and 1.05 ng/mL/year and .37, respectively). For smoking, the PSA velocity of men in the lower two tertiles was not statistically significantly different as compared with the never smokers (PSA velocities and p values, 0.58 ng/mL/year and .99 and 0.74 ng/mL/year and .85, respectively). However, PSA velocity of men in the highest tertile of smoking was statistically significantly higher as compared with PSA velocity of never smokers (1.57 ng/mL/year and $p = .04$). These models were adjusted for baseline age, baseline selenium, race, and Gleason score. The smoking models were also adjusted for BMI, and the BMI models were adjusted for smoking status.

In this study, the average number of PSA measurements per subject was 11 with range being from 1 to 22. Since number of PSA measurements per subject could have an influence on results, a sensitivity analysis was carried out to compare results of a model with data from all subjects (full model) and those with 11 or more PSA measurements (reduced model). Sensitivity analysis was carried out for obesity as well as smoking data separately and yielded comparable results for both the full and reduced models demonstrating robustness of results.

Discussion

Among men with localized PCa on WW, neither baseline BMI nor baseline smoking were associated with serum PSA levels at baseline. In contrast, BMI was not significantly associated with PSA velocity, but pack-years of smoking remained independently associated with PSA velocity in a model that included the known predictors of PSA velocity (maximum follow-up time: 60 months). These results suggest that BMI is not a major determinant of PSA levels among men with localized cancer or of PSA velocity in the immediate interval following PCa diagnosis in this sample. In contrast, pack-years of smoking conferred a significantly increased risk for PSA velocity and potentially PCa progression.

The BMI results for PSA velocity in this study are consistent with results from previous studies. Kristal et al. (2006) reported an inverse association between baseline BMI and baseline PSA (p for trend $< .0001$), but no effect of BMI on PSA velocity (p for trend = .84) among the 3,341 subjects in the placebo arm of the Prostate Cancer Prevention Study. Baillargeon et al. (2005) also studied the association between BMI and PSA using a nested case-control design in subjects from the San Antonio Center for Biomarkers of Risk of Prostate Cancer (SABOR) cohort study. They reported a statistically significant reduction in mean PSA with increasing categories of BMI (p value for trend $< .0005$).

Results for the smoking analyses also are consistent with previous reports (Giovannucci et al., 2007; Plaskon, Penson, Vaughan, & Stanford, 2003). As reviewed (Hickey et al., 2001; Wolk, 2005), the majority of studies conducted to date report no association between smoking and diagnosis of PCa but do support an association between smoking and increased risk for advanced or fatal PCa. In a recent publication, Giovannucci et al. (2007) noted that smoking was not associated with incident PCa (odds ratio [OR] = 0.98, 95% confidence interval [CI]: 0.89–1.07) for men in the Health Professional Follow-up Survey, but was associated with increased odds of developing fatal or more aggressive disease (OR = 1.41, 95% CI: 1.04–1.91). In contrast, Kristal et al. (2006) reported significantly lower PSA velocity for current smokers compared with nonsmokers (2.5 ng/mL vs. 3.2 ng/mL, $p = .045$). Although the reason for inconsistencies between our study and the Kristal study are unknown, we found that pack years was associated with PSA velocity in contrast to the Kristal study. Subjects in the Kristal study were categorized as current smokers and nonsmokers based on their self-reported status at the time of enrollment in the PCPT study. Our findings that lifetime smoking was an apparent risk factor for disease progression is consistent with a potential effect of tobacco exposure on tumor biology and behavior (i.e., p53 mutation, chromosomal instability) as suggested by Giovannucci et al. (2007).

The negative findings for obesity as a risk factor for PCa progression in men with low-risk disease in our study could reflect the lack of any such association or reflect limitations in our study population to address this question. Our study population was selected for active surveillance based on eligible subject's low risk for disease progression (PSA < 50 ng/mL, age <85 years, life expectancy ≥ 3 years, Gleason's score <8, and no evidence of metastatic cancer). Other studies have shown median PSA doubling times for subjects with "low risk" PCa as ≥ 3 years (Klotz, 2005). The median PSA doubling time for our study population was estimated to be 5.54 years, reflecting the inherent low-risk nature of our study cohort. Although the planned duration of follow-up for men in the selenium intervention was 5 years, the median follow-up time was 3.2 years. The length of follow-up may have been insufficient to detect an effect of BMI.

Strengths of the current study include use of the mixed effects regression models to derive PSA velocity and availability of pack-years as an estimate of lifetime smoking exposure. The mixed effects models allowed us to account for correlation because of repeated measurement of PSA and allowed for independent random intercept and random coefficient for each subject, thus using the maximum amount of information provided by the subject to derive an estimate of PSA velocity. This approach also avoids the instability associated with other methods for calculating PSA velocity, such as Best Line Fit or First and Last Observation methods, and provides a more reliable estimate of PSA velocity (Svatek, Shulman, Choudhary, & Benaim, 2006). Because of the self-reported nature of the smoking data, there is potential for underreporting of the exposure levels as with any other study that uses such data.

The finding of a significant association of smoking with PSA velocity, despite a population of men at low risk of progression, is important and warrants additional attention. If corroborated, consideration of tobacco history in otherwise low-risk men might warrant more intensive surveillance or consideration of more aggressive intervention. Long-term prospective studies based on the subject's exposure status (i.e., cumulative tobacco exposure) with larger sample sizes sufficient to detect a statistical and clinically significant effect are needed to definitively answer the question of the association between lifestyle factors such as obesity and smoking and PCa progression.

Acknowledgments

Funding The author(s) disclosed receipt of the following financial support for the research and/or authorship of this article:

This work was supported by PHS CA079080 and CA023074.

References

- American Cancer Society. Cancer facts and figures 2010. Author; Atlanta, GA: 2010.
- Andersson SO, Wolk A, Bergstrom R, Adami HO, Engholm G, Englund A, Nyren O. Body size and prostate cancer: A 20-year follow-up study among 135006 Swedish construction workers. *Journal of the National Cancer Institute*. 1997; 89:385–389. [PubMed: 9060961]
- Baillargeon J, Pollock BH, Kristal AR, Bradshaw P, Hernandez J, Basler J, Thompson I. The association of body mass index and prostate-specific antigen in a population-based study. *Cancer*. 2005; 103:1092–1095. [PubMed: 15668913]

- Banez LL, Hamilton RJ, Partin AW, Vollmer RT, Sun L, Rodriguez C, Freedland SJ. Obesity-related plasma hemodilution and PSA concentration among men with prostate cancer. *Journal of the American Medical Association*. 2007; 298:2275–2280. [PubMed: 18029831]
- Bostwick DG, Burke HB, Djakiew D, Euling S, Ho SM, Landolph J, Timms B. Human prostate cancer risk factors. *Cancer*. 2004; 101:2371–2490. [PubMed: 15495199]
- Buschemeyer WC III, Freedland SJ. Obesity and prostate cancer: Epidemiology and clinical implications. *European Urology*. 2007; 52:331–343. [PubMed: 17507151]
- Calle EE, Kaaks R. Overweight, obesity and cancer: Epidemiological evidence and proposed mechanisms. *Nature Reviews Cancer*. 2004; 4:579–591. [PubMed: 15286738]
- Carter HB, Morrell CH, Pearson JD, Brant LJ, Plato CC, Metter EJ, Walsh PC. Estimation of prostatic growth using serial prostate-specific antigen measurements in men with and without prostate disease. *Cancer Research*. 1992; 52:3323–3328. [PubMed: 1375867]
- Engeland A, Tretli S, Bjorge T. Height, body mass index, and prostate cancer: A follow-up of 950000 Norwegian men. *British Journal of Cancer*. 2003; 89:1237–1242. [PubMed: 14520453]
- Giovannucci E, Liu Y, Platz EA, Stampfer MJ, Willett WC. Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. *International Journal of Cancer*. 2007; 121:1571–1578.
- Giovannucci E, Rimm EB, Ascherio A, Colditz GA, Spiegelman D, Stampfer MJ, Willett WC. Smoking and risk of total and fatal prostate cancer in United States health professionals. *Cancer Epidemiology, Biomarkers & Prevention*. 1999; 8(4 Part 1):277–282.
- Giovannucci E, Rimm EB, Liu Y, Leitzmann M, Wu K, Stampfer MJ, Willett WC. Body mass index and risk of prostate cancer in U.S. health professionals. *Journal of the National Cancer Institute*. 2003; 95:1240–1244. [PubMed: 12928350]
- Gong Z, Neuhauser ML, Goodman PJ, Albanes D, Chi C, Hsing AW, Kristal AR. Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial. *Cancer Epidemiology, Biomarkers & Prevention*. 2006; 15:1977–1983.
- Hickey K, Do KA, Green A. Smoking and prostate cancer. *Epidemiologic Reviews*. 2001; 23:115–125. [PubMed: 11588835]
- Klotz L. Active surveillance with selective delayed intervention using PSA doubling time for good risk prostate cancer. *European Urology*. 2005; 47:16–21. [PubMed: 15582244]
- Kristal AR, Chi C, Tangen CM, Goodman PJ, Etzioni R, Thompson IM. Associations of demographic and lifestyle characteristics with prostate-specific antigen (PSA) concentration and rate of PSA increase. *Cancer*. 2006; 106:320–328. [PubMed: 16342294]
- Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. 1982; 38:963–974. [PubMed: 7168798]
- Lamb DS, Slaney D, Smart R, Nacey JN, Russell G, Scott B, Delahunt B. Prostate cancer: The new evidence base for diagnosis and treatment. *Pathology*. 2007; 39:537–544. [PubMed: 18027255]
- Lieberman R. Evidence-based medical perspectives: the evolving role of PSA for early detection, monitoring of treatment response, and as a surrogate end point of efficacy for interventions in men with different clinical risk states for the prevention and progression of prostate cancer. *American Journal of Therapeutics*. 2004; 11:501–506. [PubMed: 15543092]
- Nilsen TI, Vatten LJ. Anthropometry and prostate cancer risk: a prospective study of 22,248 Norwegian men. *Cancer Causes & Control*. 1999; 10:269–275. [PubMed: 10482485]
- Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA: A Cancer Journal for Clinicians*. 2005; 55(2):74–108. [PubMed: 15761078]
- Plaskon LA, Penson DF, Vaughan TL, Stanford JL. Cigarette smoking and risk of prostate cancer in middle-aged men. *Cancer Epidemiology, Biomarkers & Prevention*. 2003; 12:604–609.
- Rodriguez C, Freedland SJ, Deka A, Jacobs EJ, McCullough ML, Patel AV, Calle EE. Body mass index, weight change, and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiology, Biomarkers & Prevention*. 2007; 16:63–69.
- Schroder FH, Carter HB, Wolters T, van den Bergh RC, Gosselaar C, Bangma CH, Roobol MJ. Early detection of prostate cancer in 2007 Part 1: PSA and PSA kinetics. *European Urology*. 2008; 53:468–477. [PubMed: 17997011]

- Schuurman AG, Goldbohm RA, Dorant E, van den Brandt PA. Anthropometry in relation to prostate cancer risk in the Netherlands Cohort Study. *American Journal of Epidemiology*. 2000; 151:541–549. [PubMed: 10733035]
- Shariat SF, Karakiewicz PI. Screening for prostate cancer in 2007: The PSA era and its challenges are not over. *European Urology*. 2008; 53:457–460. [PubMed: 18079050]
- Stratton MS, Algotar AM, Ranger-Moore J, Stratton SP, Slate EH, Hsu CH, Thompson PA, Clark LC, Ahmann FR. Oral selenium supplementation has no effect on prostate-specific antigen velocity in men undergoing active surveillance for localized prostate cancer. *Cancer Prev Res (Phila)*. 2010; 3:1035–1043. [PubMed: 20647337]
- Stratton MS, Reid ME, Schwartzberg G, Minter FE, Monroe BK, Alberts DS, Ahmann FR. Selenium and inhibition of disease progression in men diagnosed with prostate carcinoma: Study design and baseline characteristics of the “Watchful Waiting” Study. *Anticancer Drugs*. 2003; 14:595–600. [PubMed: 14501381]
- Svatek RS, Shulman M, Choudhary PK, Benaim E. Critical analysis of prostate-specific antigen doubling time calculation methodology. *Cancer*. 2006; 106:1047–1053. [PubMed: 16456812]
- Veierod MB, Laake P, Thelle DS. Dietary fat intake and risk of prostate cancer: A prospective study of 25,708 Norwegian men. *International Journal of Cancer*. 1997; 73:634–638.
- Wolk A. Diet, lifestyle and risk of prostate cancer. *Acta Oncologica*. 2005; 44:277–281. [PubMed: 16076700]
- Wright ME, Chang SC, Schatzkin A, Albanes D, Kipnis V, Mouw T, Leitzmann MF. Prospective study of adiposity and weight change in relation to prostate cancer incidence and mortality. *Cancer*. 2007; 109:675–684. [PubMed: 17211863]

Table 1

Selected Baseline Descriptive Characteristics by BMI Categories for Subjects in the Watchful Waiting Study

Characteristic	All Men (N = 140)	Baseline BMI Categories			p Value ^a
		Normal (N = 45, 32.1%)	Overweight (N = 69, 49.3%)	Obese (N = 26, 18.6%)	
Age in years					
Mean (SD)	72.8 (6.7)	74.1 (5.5)	71.9 (7.6)	72.9 (5.8)	.22
Age groups; n (%)					
65	16 (11.4)	2 (4.4)	11 (15.9)	3 (11.54)	.47
65–75	71 (50.7)	23 (51.1)	34 (49.2)	14 (53.9)	
>75	53 (37.9)	20 (44.4)	24 (34.7)	9 (34.6)	
Caucasians; n (%)	123 (87.9)	38 (84.4)	64 (92.8)	21 (80.8)	.16
BMI in kg/m ² ; mean (SD)	26.9 (4.1)	23.1 (1.5)	26.8 (1.4)	33.4 (3.4)	NA
PSA in ng/mL; mean (SD)	8.0 (6.1)	9.37 (7.5)	7.1 (5.3)	8.0 (5.3)	.22
Smoking history					
Pack-years; mean (SD)	23.3 (29.8)	17.0 (24.5)	21.2 (28.4)	39.4 (36.3)	.01
Never smokers; n (%)	51 (36.7)	18 (40.9)	29 (42.7)	4 (15.4)	.07
Former smokers; n (%)	74 (53.6)	20 (45.5)	34 (50.0)	20 (76.9)	
Current smokers; n (%)	13 (9.42)	6 (13.6)	5 (7.35)	2 (7.7)	
Gleason score; mean (SD)	5.7 (1.0)	5.6 (1.0)	5.6 (1.0)	6.0 (0.6)	.17
Selenium in ng/mL; mean (SD)	134.5 (41.5)	142.2 (65.6)	130.4 (21.7)	132.0 (23.8)	.32

Note: BMI = body mass index; PSA = prostate-specific antigen; SD = standard deviation.

^aFor test of significance between BMI groups using analysis of variance or Fisher's exact test for categorical variables.

Table 2

Selected Baseline Descriptive Statistics by Categories of Smoking for Subjects in the Watchful Waiting Study

Characteristic	All Men (<i>N</i> = 140)	Smoking Categories				<i>p</i> Value ^a
		Never Smokers (<i>N</i> = 54, 38.6%)	Pack-Years Tertile 1 (<i>N</i> = 29, 20.7%)	Pack-Years Tertile 2 (<i>N</i> = 29, 20.7%)	Pack-Years Tertile 3 (<i>N</i> = 28, 20.0%)	
Age in years; mean (<i>SD</i>)	72.8 (6.7)	72.2 (7.0)	74.1 (8.3)	73.6 (6.4)	71.8 (3.8)	.47
BMI in kg/m ² ; mean (<i>SD</i>)	26.9 (4.1)	25.9 (3.0)	26.1 (4.5)	26.9 (3.4)	29.5 (4.9)	.001
PSA; ng/mL; mean (<i>SD</i>)	8.0 (6.1)	7.6 (5.3)	6.5 (4.1)	10.0 (8.4)	8.2 (6.4)	.22
Smoking pack-years; mean (<i>SD</i>)	23.3 (29.8)	0.0 (0.0)	9.3 (6.8)	33.0 (9.5)	72.5 (22.8)	NA
Gleason score; mean (<i>SD</i>)	5.7 (1.0)	5.7 (0.9)	5.6 (0.7)	5.6 (1.2)	5.8 (1.1)	.86
Baseline selenium in ng/mL; mean (<i>SD</i>)	134.6 (41.8)	142.8 (59.9)	137.3 (28.1)	122.2 (15.0)	129.8 (21.4)	.18
Caucasians; <i>n</i> (%)	123 (87.9)	46 (85.2)	25 (86.2)	25 (86.2)	27 (96.4)	.49

Note: BMI = body mass index; PSA = prostate-specific antigen; *SD* = standard deviation.^aFor test of significance between smoking groups, using analysis of variance or Fisher's exact test for categorical variables.

Table 3

Relationship Between ln(PSA + 1) at Baseline and Baseline Demographic Characteristics of Men in the Watchful Waiting Study

Variable	Regression Coefficient	<i>p</i> Value	95% Confidence Intervals
BMI (per 5 kg/m ²)	−0.03	.30	−0.21, 0.07
Age (per 5 years)	0.12	.001	0.06, 0.22
Pack-years of smoking (per 5 years)	0.01	.13	−0.004, 0.03
Race other than Caucasian	0.37	.04	0.02, 0.72
Gleason score	0.16	.007	0.043, 0.272

Note: PSA = prostate-specific antigen; BMI = body mass index.

Table 4

Association Between Baseline BMI, Baseline Smoking, and PSA Trajectory Using BMI and Pack-Years of Smoking as Continuous Variables

Model	Variable	Coefficient	95% Confidence Intervals	p Value
Obesity	BMI (per 5 kg/m ²)	−0.05	−0.19, 0.08	.46
	Time (per 5 years)	0.10	−0.63, 0.83	.79
	BMI × Time (per 25 kg-years/m ²)	0.06	−0.07, 0.19	.37
Smoking	Pack-years (per 5 years)	0.02	−0.002, 0.03	.09
	Time (per 5 years)	0.33	0.19, 0.46	<.001
	Pack-years × Time (per 25 years ²)	0.02	0.004, 0.04	.018

Note: BMI = body mass index; PSA = prostate-specific antigen.

Table 5

Association Between Baseline BMI, Baseline Smoking, and PSA Velocity

Model	Variable	Mean PSA Velocity (ng/mL/year)	p Value	p Value for Trend
Obesity	Normal weight subjects	0.76	Reference	
	Overweight subjects	0.59	.92	.28
	Obese subjects	1.05	.37	
Smoking	Never smokers	0.66	Reference	
	Pack-years tertile 1	0.58	.99	.88
	Pack-years tertile 2	0.74	.85	
	Pack-years tertile 3	1.57	.04	

Note: BMI = body mass index; PSA = prostate-specific antigen.