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Association Between Smoking Status, and Free, Total and Percent Free Prostate Specific Antigen

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Abstract

Purpose—There are scant data available on the relationship between smoking and total prostate specific antigen, free prostate specific antigen and percent-free prostate specific antigen. Given the high prevalence of smoking and the frequency of prostate specific antigen screening, it is important to determine any association between smoking and prostate specific antigen values using nationally representative data.

Materials and Methods—Included in the final study population were 3,820 men 40 years old or older who participated in the 2001–2006 NHANES (National Health and Nutrition Examination Survey) and met the eligibility criteria for prostate specific antigen testing. The distributions of total, free and percent free prostate specific antigen were estimated by sociodemographic and clinical characteristics. Multivariate linear regression models were fit to determine the adjusted relationship between smoking and total and percent free prostate specific antigen while simultaneously controlling for these characteristics.

Results—For all ages combined the median total and free prostate specific antigen levels were 0.90 (0.81– 0.90) and 0.26 (0.25– 0.28) ng/ml, respectively. Multivariate linear regression analysis showed that total prostate specific antigen was 7.9% and 12.2% lower among current and former smokers, respectively, than among never smokers. High body mass index and diabetes were also statistically significantly associated with a lower total prostate specific antigen. Approximately a third of the men had a percent free prostate specific antigen less than 25%. Current smokers had a significantly lower percent free prostate specific antigen than former smokers.

Conclusions—Our finding that smoking is inversely associated with total prostate specific antigen may have potential implications for the interpretation of prostate specific antigen levels in men who are current or former smokers. Given the high prevalence of smoking, obesity and diabetes, additional research on the combined effect of these health risk factors is warranted.

Keywords

prostatic neoplasms; smoking; prostate-specific antigen; early detection of cancer

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Although the mortality benefit from screening with PSA is uncertain,[1,2] PSA based screening has resulted in a downward stage shift to more organ confined prostate cancer at the time of diagnosis.[3] The often used PSA cut point of greater than 4.0 ng/ml detects the majority of prostate cancers. However, the specificity of the PSA test is low and has led to a high rate of false-positive results, particularly among older men with BPH. Percent-free PSA (the ratio of fPSA-to-tPSA) testing has been used as an adjunct to PSA tests to enhance the specificity and decrease the number of unnecessary biopsies.[4]

It has been recognized that age, race, BPH, prostate size and prostatitis can influence PSA levels.[5,6] Epidemiological studies have also shown that PSA can be affected by several heath characteristics including obesity, diabetes and certain medications such as NSAIDs, statins and thiazide diuretics.[7–9] Scant data exist on the association between smoking and PSA levels. Gelmann et al reported that current and former smokers had a statistically significantly lower PSA and fPSA levels compared with never smokers.[10] Gray et al measured PSA values in New Zealand Europeans, Maori and Pacific Islanders, and concluded that this inverse association was only true for fPSA but not tPSA.[11] Kristal et al reported that current smokers had lower levels of tPSA than nonsmokers and this inverse association was borderline significant.[12] While provocative, these studies produced inconsistent results because potential confounders such as diabetes, BPH and the use of certain medications were not controlled for.

Smoking has been a devastating health concern for decades. In 2010 the U.S. Centers for Disease Control and Prevention reported that nearly a quarter of American men 18 years old or older, approximately 23 million, were current cigarette smokers in 2009.[13] Given the high prevalence of smoking and the frequency of PSA screening, it is important to examine the associations between smoking and PSA level while controlling for key sociodemographic and clinical variables using nationally representative data. Our study may aid in interpreting PSA values more accurately, and may have possible implications for the use of tPSA and %fPSA in recommending further evaluation of abnormal PSA results with a prostate biopsy.

MATERIALS AND METHODS

Study Population

The NHANES is a nationally representative cross-sectional survey of the adult United States noninstitutionalized population. A detailed description of sampling and data collection procedures has been published elsewhere.[14] The overall response rates for the 2001 to 2002, 2003 to 2004 and 2005 to 2006 surveys were 84%, 79% and 80% for the interview component, and 80%, 76% and 77% for the examination component, respectively.

Men 40 years old or older were eligible for PSA testing consisting of measured tPSA and fPSA as well as a calculated %fPSA. For the 2001–2006 NHANES 4,869 men were 40 years old or older, of whom 4,589 (94.2%) participated in the NHANES physical examination. Men were excluded from PSA testing if they reported current infection or inflammation of the prostate gland, digital rectal examination in the last week, prostate biopsy in the last 30 days, cystoscopy in the last 30 days, history of prostate cancer or if information was missing for any of those questions (323, 7.0%). In addition, 339 (7.4%)

men refused or did not give permission for the PSA test and 107 (2.3%) eligible men were missing PSA values. The final study population included 3,820 of 4,589 or 83.2% of all examined men 40 years old or older who participated in the NHANES PSA testing.

Statistical Analysis

Smoking status was defined using cotinine level, and the 2 survey questions, "Have you smoked at least 100 cigarettes in your entire life?" and "Do you now smoke cigarettes every day, some days or not at all?" Serum cotinine levels greater than 10 ng/ml are associated with active smoking within the last few days.[15] Respondents with a serum cotinine concentration greater than 10 ng/ml or who had smoked at least 100 cigarettes during their lifetime and, at the time of interview, reported smoking every day or some days were classified as current smokers. Those who responded "not at all" to the latter question were classified as former smokers. Finally, respondents who had smoked fewer than 100 cigarettes in their lifetime were classified as never smokers. Distributions of tPSA, fPSA and %fPSA for the 2001–2006 NHANES were estimated by smoking status as well as other demographic and clinical characteristics. Of those characteristics race/ethnicity was categorized as nonHispanic white, non-Hispanic black, Mexican-American (Mexican or Mexican-American) and other (other Hispanic or other race including multiracial), and tPSA and fPSA were analyzed as continuous variables. In this study medications included statins, thiazide diuretics and NSAIDs. Over the counter NSAIDs were not examined because the NHANES questionnaires did not collect this information. In the descriptive analysis %fPSA was dichotomized to less than 25% vs 25% or greater since less than 25% is typically the cut point for further diagnostic evaluation. Continuous variables were presented as weighted medians and discrete variables as weighted percentages. The 95% CIs for the medians were determined using the Woodruff method.[16] For discrete variables 95% CIs were calculated using a logit transformation. No statistical tests were conducted in the bivariate analysis because statistical testing for differences in medians was not available in software packages for complex sample survey data. CIs around the median were included to provide estimates of the variability and allowed for informal comparisons.

Multivariate linear regression models were fit to determine the adjusted relationship between smoking status and PSA values (tPSA and %fPSA). Independent variables included age, race, BMI, diabetes, BPH and C-reactive protein. We included those medications mentioned in the model because previously published studies showed possible associations between these medications and PSA.[7,17] We excluded a family history of prostate cancer because this information was only included in the 2003–2006 NHANES. The linearity assumption for continuous predictors was assessed in each model using restricted cubic spline functions.[18] The relationship between C-reactive protein and each PSA outcome was nonlinear, and was transformed using a 3-knot restricted cubic spline function. The relationships between the other continuous predictors and each PSA outcome were found to be linear. As such, age and BMI were treated as linear effects in the final models. The dependent variable, tPSA, was log transformed because of nonnormality. Due to the small number of the denominator df, the F-statistic with Satterthwaite correction for the df was used to test significance in each model. Since tPSA was log transformed, the adjusted associations were presented as

the percent change in the tPSA geometric mean. The adjusted associations with %fPSA were presented as the absolute change in %fPSA.

Variance estimates were calculated using Taylor series linearization. Sample weights, which account for the differential probabilities of selection, nonresponse and noncoverage, were incorporated into the variance estimation process. The R Package for Statistical Computing was used to estimate the percentiles and corresponding CIs using the Woodruff method.[19] SAS-Callable SUDAAN® version 9.0 and SAS® version 9.2 were used for the remainder of the analyses including the regression modeling.

RESULTS

For all ages combined the median (95% CI) tPSA and fPSA was 0.90 (0.81– 0.90) ng/ml and 0.26 (0.25–0.28) ng/ml, respectively (table 1). tPSA and fPSA increased with age and decreased with increasing BMI. Lower values of tPSA were observed for current smokers (0.80 [0.80–0.90] ng/ml) than for former smokers (0.95 [0.83–1.01] ng/ml). The fPSA in current smokers (0.24 [0.23– 0.25] ng/ml) was lower than that in former smokers (0.28 [0.27–0.30] ng/ml) and never smokers (0.27 [0.25– 0.29] ng/ml). Men with BPH had higher tPSA and fPSA levels than those without BPH. Overall 34.2% of men had a %fPSA less than 25%. Current smokers had a higher %fPSA less than 25% (38.3%) than former smokers (31.3%) and never smokers (33.1%). Diabetic men had a higher %fPSA less than 25% than nondiabetic men. Interestingly we found that %fPSA less than 25% increased with increasing C-reactive protein.

The results of the multivariate linear regression model predicting tPSA are shown in table 2. The predicted geometric mean of tPSA was 7.9% and 12.2% lower among current and former smokers, respectively, compared with never smokers. A 5-year increase in age was associated with a significant 13.7% increase in the geometrical mean of tPSA. However, a 5 kg/m^2 increase in BMI was associated with a significant 6.9% decrease in tPSA. Diabetes was associated with a 14.8% decrease in tPSA compared with nondiabetics, while BPH was associated with a 16.5% increase in tPSA. The predicted geometric mean of tPSA was 14.1% higher among non-Hispanic black vs nonHispanic white men. Comparing medication use and the geometric mean of tPSA, no statistically significant association was found. C-reactive protein had a significant nonlinear relationship with tPSA.

Results of the multivariate linear regression predicting %fPSA are presented in table 3. Current smokers had a statistically significantly lower %fPSA compared with former smokers (change in %fPSA −2.4; 95% CI −3.8, −0.9; comparison not shown). Diabetes was associated with a higher %fPSA (change in %fPSA 3.8; 95% CI 1.4, 6.2) while increased age was associated with a significant decrease in %fPSA (change in %fPSA −0.3; 95% CI −0.5, −0.05 for 5-year increase). Mexican-Americans had a lower %fPSA compared with nonHispanic whites (change in %fPSA −3.2; 95% CI −4.8, −1.7). There was also a significant nonlinear relationship between C-reactive protein and %fPSA.

DISCUSSION

Using nationally representative data and adjusting for multiple confounders, we found that current and former smokers had a statistically significantly lower tPSA compared with never smokers, and current smokers had a significantly lower %fPSA than former smokers. Gelmann et al examined the relationship between smoking and PSA using the study cohort of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.[10] The authors found that tPSA and fPSA levels were significantly lower among current and former smokers, respectively, compared with never smokers. Similarly an analysis of the 2001–2002 NHANES data demonstrated that men who had ever smoked had a lower PSA than those who had not.[17] The underlying causes for the inverse associations between smoking and tPSA levels are largely unknown. It has been reported that male smokers had an increased level of circulating sex hormone-binding globulin, which might reduce the synthesis of PSA.[20] To our knowledge our study finding that current smokers had a significantly lower %fPSA than former smokers has not been reported in the literature. Additional research is needed to verify this finding.

To date the U.S. Preventive Services Task Force does not recommend or advise against routine screening for prostate cancer for men 50 to 74 years old.[21,22] The American Urological Association recommends starting a discussion about prostate cancer screening with men who are at average risk at age 40 years to establish a baseline PSA.[23] While adjusting for other potential confounders, our study showed that there was an approximate 8% to 12% decrease in tPSA among current and former smokers. Thus, men who have ever smoked are less likely to have an abnormal result on PSA screening and diagnostic biopsy, possibly resulting in fewer screen detected prostate cancers than in those who have never smoked. In this study we excluded men with prostate cancer, prostatic infection or inflammation. In this relatively healthy population the median tPSA was 0.9 ng/ml. Loeb et al showed that a baseline PSA between 0.7 and 2.5 ng/ml in men 40 to 49 years old was associated with a 14.6-fold increased risk of prostate cancer.[24] In addition to the often used PSA cut point of greater than 4.0 ng/ml, age specific reference ranges for PSA have been demonstrated as a useful approach to improve PSA sensitivity and specificity.[25]

A survival analysis using data from the National Institutes of Health-American Association of Retired Persons Diet and Health Study suggested that current and former smokers might be at decreased risk for prostate cancer diagnosis, primarily localized disease.[26] A meta-analysis of 24 cohort studies also suggested that current smokers were not at increased risk for incident prostate cancer.[27] These findings may be partially attributable to detection bias resulting from the inverse relationship between smoking and PSA. If smoking substantially alters the relationship between PSA and any potential underlying prostate cancer, we may need to modify, according to smoking status, the often used PSA cutoff points that signal the necessity of further evaluation with prostate biopsy. Such a modification may help to interpret screening results more accurately.

Biologically the mechanisms of initiating or accelerating prostate cancer by smoking have been postulated, including exposure to carcinogenic compounds, modulation of male hormones and genetic mutations in suppressor genes.[28] Despite the demonstrated links

between smoking and several types of solid tumors, the role of smoking in the development of prostate cancer is inconclusive. However, studies have consistently shown that current smokers have an increased risk of fatal prostate cancer.[27,29] Delayed detection of prostate cancer due to the effects of smoking on PSA may contribute in part to worse health outcomes of prostate cancer among smokers.

It has been widely reported that obesity and diabetes have inverse associations with PSA levels.[8,9,11] These findings were also confirmed by our study. Interestingly we did not find any statistically significant association between PSA and the use of NSAIDs, statins or thiazide diuretics as found by Chang et al.[7] Different ways of defining smoking status, and various sociodemographic, clinical factors and medications examined in these 2 studies may partially account for this difference. Although inverse associations between PSA and the use of NSAIDs and statins have been reported,[7,17] a recent study suggested that use of NSAIDs (excluding aspirin) and statins was not associated with PSA, and only aspirin users had a statistically significantly lower PSA than nonusers among men who had never smoked.[30]

A major strength of this study is that it was based on nationwide, population based sampling survey data. However, it has at least 3 limitations. 1) Smoking status was defined based on self-report and serum cotinine levels. Self-report smoking status was subject to misclassification errors. The use of cotinine level in defining current smokers should help reduce the misclassification of self-reported smoking status. 2) This study was cross-sectional, and the temporal relationship of associations between smoking and PSA cannot be assessed. 3) The NHANES did not collect information on nonprescription medication use so the effects of any nonprescription medications cannot be examined.

CONCLUSIONS

Men who had ever smoked had an 8% to 12% decrease in tPSA compared with those who had never smoked. Although the magnitude of the inverse association between smoking status and PSA alone may not be substantial, the joint effect of smoking, obesity and diabetes associated with PSA may have greater clinical implications given the high prevalence of these conditions. Additional research on the combined effect of these and other health risk factors on PSA is needed. Further studies to better understand the biological role of smoking in the development of prostate cancer are also warranted.

Acknowledgments

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Abbreviations and Acronyms

%fPSA	percent free prostate specific antigen
BMI	body mass index
BPH	benign prostatic hyperplasia

fPSA	free prostate specific antigen
NSAIDs	nonsteroidal anti-inflammatory drugs
PSA	prostate specific antigen
tPSA	total prostate specific antigen

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Table 1

PSA levels by study population characteristics

	Sample Size	Median ng/ml tPSA (95% CI)	Median ng/ml fPSA (95% CI)	Median %fPSA Less Than 25% (95% CI)
Total	3,820	0.90 (0.81–0.90)	0.26 (0.25–0.28)	34.2 (31.6–36.9)
Age:				
40–49	1,115	0.70 (0.70–0.75)	0.21 (0.20–0.23)	31.8 (28.5–35.3)
50–59	827	0.90 (0.80–0.95)	0.26 (0.24–0.27)	35.3 (31.9–38.9)
60–69	840	1.20 (1.08–1.35)	0.33 (0.31–0.36)	39.2 (34.8–43.8)
70+	1,038	1.70 (1.58–1.90)	0.48 (0.45–0.52)	32.8 (28.2–37.9)
Race/ethnicity:				
NonHispanic white	2,205	0.90 (0.80–0.94)	0.27 (0.25–0.28)	33.6 (30.9–36.5)
NonHispanic black	709	0.90 (0.80–1.00)	0.27 (0.25–0.30)	34.0 (29.9–38.4)
Mexican-American	695	0.90 (0.80–0.97)	0.24 (0.22–0.25)	40.1 (34.8–45.7)
Other	211	0.80 (0.70–1.00)	0.24 (0.20–0.28)	36.7 (26.3–48.4)
Family history of prostate Ca:*				
No	2,073	0.85 (0.80–0.90)	0.26 (0.25–0.27)	31.7 (28.8–34.7)
Yes	199	0.97 (0.73–1.30)	0.31 (0.25–0.35)	31.0 (23.9–39.1)
Smoking status:				
Current smoker	1,188	0.80 (0.80–0.90)	0.24 (0.23–0.25)	38.3 (34.6–42.1)
Former smoker	1,359	0.95 (0.83–1.01)	0.28 (0.27–0.30)	31.3 (27.3–35.6)
Never smoker	1,270	0.90 (0.80–0.94)	0.27 (0.25–0.29)	33.1 (29.4–37.0)
BMI (kg/m^2):				
Normal (less than 25)	905	1.00 (0.90–1.10)	0.30 (0.28–0.33)	35.2 (31.2–39.3)
Overweight (25–less than 30)	1,621	0.90 (0.80–0.95)	0.27 (0.25–0.28)	33.5 (30.2–36.9)
Obese (30+)	1,187	0.80 (0.76–0.89)	0.25 (0.23–0.25)	34.3 (30.2–38.6)
Diabetes:				
No	3,253	0.90 (0.84–0.91)	0.26 (0.25–0.27)	35.0 (32.4–37.7)
Yes	564	0.80 (0.73–0.90)	0.27 (0.25–0.29)	27.7 (21.7–34.5)
BPH:				
No	3,114	0.86 (0.80–0.90)	0.26 (0.25–0.27)	33.7 (30.9–36.6)
Yes	468	1.27 (1.00–1.50)	0.35 (0.33–0.38)	37.9 (31.5–44.9)
Statin use:				
No	2,900	0.90 (0.80–0.90)	0.26 (0.25–0.27)	34.4 (31.3–37.7)
Yes	769	0.97 (0.83–1.00)	0.28 (0.26–0.30)	33.6 (29.4–38.1)
NSAID use:†				
No	3,419	0.90 (0.82–0.90)	0.26 (0.25–0.27)	34.2 (31.6–36.9)
Yes	401	0.90 (0.74–1.00)	0.28 (0.26–0.30)	34.4 (27.8–41.7)
Thiazide diuretic use:				
No	3,426	0.90 (0.80–0.90)	0.26 (0.25–0.27)	34.9 (32.2–37.6)
Yes	394	1.00 (0.82–1.10)	0.29 (0.25–0.33)	27.7 (21.1–35.5)
Cotinine level (ng/ml):				

	Sample Size	Median ng/ml tPSA (95% CI)	Median ng/ml fPSA (95% CI)	Median %fPSA Less Than 25% (95% CI)
10 or Less	2,668	0.90 (0.86–1.00)	0.28 (0.26–0.29)	32.7 (29.8–35.8)
Greater than 10	1,142	0.80 (0.78–0.90)	0.24 (0.22–0.25)	37.6 (33.8–41.6)
C-reactive protein (mg/dl):				
Less than 1.0	3,499	0.90 (0.80–0.90)	0.26 (0.25–0.27)	33.6 (31.0–36.3)
1.0–3.0	261	0.84 (0.73–1.15)	0.25 (0.22–0.31)	40.1 (31.9–48.9)
Greater than 3.0	60	1.16 (1.00–1.40)	0.30 (0.21–0.40)	53.7 (36.3–70.3)

[*] Only available for the NHANES 2003–2006.

[†] Prescription only.

Table 2

Multivariate model predicting geometric mean of tPSA

	% Change in Predicted Geometric Mean (95% CI)		p Value*
Age (per 5-yr increase)	13.7	(12.1, 15.4)	<0.001
Race/ethnicity:			0.098
NonHispanic white	0	(reference)	
NonHispanic black	14.1	(3.8, 25.3)	
Mexican-American	10.1	(−0.7, 22.1)	
Other	0.4	(−13.7, 16.7)	
Smoking status:			0.015
Current smoker	−7.9	(−15.1, −0.1)	
Former smoker	−12.2	(−20.5, −3.0)	
Never smoker	0	(reference)	
BMI (per 5 kg/m^2 increase)	−6.9	(−9.3, −4.4)	<0.001
Diabetes:			0.003
No	0	(reference)	
Yes	−14.8	(−23.2, −5.4)	
BPH:			0.016
No	0	(reference)	
Yes	16.5	(3.1, 31.7)	
Statin use:			0.274
No	0	(reference)	
Yes	−4.3	(−11.6, 3.6)	
NSAID use:†			0.217
No	0	(reference)	
Yes	−6.3	(−15.6, 4.0)	
Thiazide diuretic use:			0.470
No	0	(reference)	
Yes	−4.6	(−16.1, 8.6)	
C-reactive protein‡	Nonlinear (nonlinear)		0.001

All variables included in the model are shown in the table.

*Based on the F-statistic with Satterthwaite correction for the degrees of freedom from the simultaneous test that all coefficients for a given variable are equal to 0.

†Prescription only.

‡Increasing C-reactive protein was associated with higher tPSA for C-reactive protein values up to 0.6 mg/dl. Above this level C-reactive protein did not have a significant effect on tPSA.

Table 3

Multivariate model predicting % fPSA

	Change in Predicted %fPSA Mean (95% CI)		p Value*
Age (per 5-yr increase)	−0.3	(−0.5, −0.05)	0.021
Race/ethnicity:			0.048
NonHispanic white	0	(reference)	
NonHispanic black	−0.4	(−1.8, 0.9)	
Mexican-American	−3.2	(−4.8, −1.7)	
Other	−1.3	(−4.4, 1.7)	
Smoking status:			0.015
Current smoker	−1.2	(−2.8, 0.4)	
Former smoker	1.2	(−0.1, 2.5)	
Never smoker	0	(reference)	
BMI (per 5 kg/m^2 increase)	0.0	(−0.6, 0.5)	0.926
Diabetes:			0.003
No	0	(reference)	
Yes	3.8	(1.4, 6.2)	
BPH:			0.145
No	0	(reference)	
Yes	−1.4	(−3.4, 0.5)	
Statin use:			0.812
No	0	(reference)	
Yes	−0.2	(−1.6, 1.2)	
NSAID use:†			0.287
No	0	(reference)	
Yes	1.2	(−1.0, 3.4)	
Thiazide diuretic use:			0.151
No	0	(reference)	
Yes	1.5	(−0.6, 3.7)	
C-reactive protein‡	Nonlinear (nonlinear)		<0.001

All variables included in the model are shown in the table.

*Based on the F-statistic with Satterthwaite correction for the degrees of freedom from the simultaneous test that all coefficients for a given variable are equal to 0.

†Prescription only.

‡Increasing C-reactive protein was associated with a decrease in %fPSA for levels up to 0.7 mg/dl. Above this level there was no relationship between C-reactive protein and %fPSA.