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ARTICLE

Levels of Beta-Microseminoprotein in Blood and Risk of Prostate Cancer in Multiple Populations

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Background A common genetic variant (rs10993994) in the 5′ region of the gene encoding β-microseminoprotein (MSP) is associated with circulating levels of MSP and prostate cancer risk. Whether MSP levels are predictive of prostate cancer risk has not been evaluated.

Methods We investigated the prospective relationship between circulating plasma levels of MSP and prostate cancer risk in a nested case–control study of 1503 case subjects and 1503 control subjects among black, Latino, Japanese, Native Hawaiian, and white men from the Multiethnic Cohort study. We also examined the ability of MSP to serve as a biomarker for discriminating prostate cancer case subjects from control subjects. All statistical tests are two-sided.

Results In all racial and ethnic groups, men with lower MSP levels were at greater risk of developing prostate cancer (odds ratio = 1.02 per one unit decrease in MSP, $P < .001$ in the prostate-specific antigen [PSA]–adjusted analysis). Compared with men in the highest decile of MSP, the multivariable PSA-adjusted odds ratio was 3.64 (95% confidence interval = 2.41 to 5.49) for men in the lowest decile. The positive association with lower MSP levels was observed consistently across racial and ethnic populations, by disease stage and Gleason score, for men with both high and low levels of PSA and across all genotype classes of rs10993994. However, we did not detect strong evidence of MSP levels in improving prostate cancer prediction beyond that of PSA.

Conclusions Regardless of race and ethnicity or rs10993994 genotype, men with low blood levels of MSP have increased risk of prostate cancer.

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Although prostate cancer is the most common cancer among men in the United States, risk factors for the disease remain largely unknown. More than 40 common low-risk genetic variants have been discovered through genome-wide association studies of prostate cancer (1–6). One such variant is a single nucleotide polymorphism (rs10993994) in the 5' region of the microseminoprotein-β *(MSMB)* gene, which encodes for β-microseminoprotein (MSP) (2,6). The risk allele (T nucleotide) for prostate cancer has been shown to be strongly associated with lower circulating MSP levels in multiple populations, with the variant accounting for as much as 50% of the variation in MSP levels in blood or seminal fluid (7,8).

MSP is one of the most highly secreted proteins from the prostate, and circulating levels have been shown to be positively correlated (r = approximately 0.2) with both levels of total and free prostate-specific antigen (PSA) (8). In contrast with PSA, whereby risk of prostate cancer increases with higher PSA levels, MSP levels measured in serum, urine, and prostate tissue have been shown to be statistically significantly lower in men with prostate cancer and even lower in men with aggressive disease (9,10). The reproducible association of rs10993994 with prostate cancer risk and circulating MSP levels implicates MSP in the etiology of prostate cancer (11). However, a prospective study has yet to examine MSP levels as a risk factor for incident prostate cancer and as a potentially clinically informative marker for early detection.

To determine the prospective relationship between circulating prediagnostic levels of MSP and prostate cancer risk, we measured MSP and PSA in a nested, multiethnic, case–control study of prostate cancer among men in the Multiethnic Cohort.

Methods

Study Population

The Multiethnic Cohort consists of more than 215 000 men and women in California and Hawaii aged 45 to 75 years at recruitment and comprises mainly five self-reported racial/ethnic populations: black, Japanese, Latino, Native Hawaiian, and white (12).

Between 1993 and 1996, adults enrolled in the study by completing a 26-page mailed questionnaire that asked detailed information about demographic factors, personal behaviors, and prior medical conditions. Potential participants were identified through driver's license files from Departments of Motor Vehicles, voter registration lists, and Health Care Financing Administration data files. Between 1995 and 2006, blood specimens were collected prospectively from approximately 67 000 participants for genetic and biomarker analyses. Information about previous PSA testing was collected at the time of blood draw as well as from a second questionnaire completed between 1999 and 2000. Informed consent was provided by all study participants and the institutional review boards at the University of Southern California and the University of Hawaii approved the study protocol.

Incident prostate cancer, as well as stage and Gleason score, was identified by linkage of the cohort to the Surveillance, Epidemiology, and End Results cancer registries covering Hawaii and California. Invasive prostate cancer was classified according to the International Classification of Disease for Oncology, Third Edition code C619 (prostate). The nested case–control study of prostate cancer in the Multiethnic Cohort includes 1503 men diagnosed with incident prostate cancer after blood collection and 1503 male control subjects without prostate cancer at the time the case subjects and control subjects were selected (June 2010). Control subjects were matched to case subjects in a 1:1 ratio based on race and ethnicity, location, birth year, year of blood collection, hours of fasting, and time of collection (1005 case subjects were matched on birth year within 5 years, collection date within 0.5 year, hours of fasting time within 2 hours, and collection time within 3 hours).

Laboratory Assays

Measurements of MSP and PSA in blinded samples of ethylenediaminetetraacetic acid anticoagulated blood plasma were performed in H. Lilja's laboratory at Lund University (Malmö, Sweden). In brief, the MSP immunoassay was conducted using the AutoDelfia 1235 automatic immunoassay system (PerkinElmer Life Sciences, Turku, Finland). Production and purification of the polyclonal rabbit anti-MSP antibody and protocols for the biotinylation and Europium labeling of the anti-MSP antibody have been previously described (13). To measure free and total PSA, we used the dual-label DELFIA Prostatus total/free PSA-Assay (PerkinElmer Life Sciences) (14), which is calibrated against the WHO 96/670 (PSA-WHO) and WHO 68/668 (free PSA-WHO) standards. Using two identical AutoDelfia 1235 automated instruments to measure MSP, each sample was run in duplicate with coefficients of variation less than or equal to 9.0% at 22.8 ng/mL and less than or equal to 6.6% at 55 ng/mL of MSP. For the measurements of free PSA, coefficients of variation were 7.3% at 0.14 ng/mL, 3.3% at 0.63 ng/mL, and 5.1% at 2.6 ng/mL; coefficients of variation for measuring total PSA were 10.6% at 0.47 ng/mL, 7.4% at 2.6 ng/mL, and 8.4% at 14.2 ng/mL. For 37 blinded duplicates, the coefficients of variation were 3.6%, 5.2%, and 3.3% for MSP, total PSA, and free PSA, respectively. The detectable ranges were 0.10 to 250 ng/mL for total PSA, 0.04 to 250 ng/mL for free PSA, and 0.2 to 90 ng/mL for MSP; values above the detectable limits were assigned the highest detectable values. Of the 3006 samples, 2999 were analyzed for the MSP and PSA measures.

Statistical Analysis

We excluded men who were determined not to belong to one of the five racial and ethnic populations (n = 22), men missing information about body mass index (BMI) (n = 3), and men with levels below the limits of detection for either total PSA, free PSA, or MSP (n = 12), resulting in 1480 case subjects and 1481 control subjects for analysis. Analysis of variance was used to test for differences in demographic variables and biomarker levels by case–control status, racial and ethnic group, and rs10993994 genotype, adjusted for matching factors (age, area [Hawaii, Los Angeles], hours of fasting, year of collection, and time of collection) and BMI (kg/m^2). MSP and PSA levels were log transformed to better meet the model assumptions, and the results are presented as geometric means. The relationship between free or total PSA levels and MSP levels was summarized using Spearman's rank correlation.

Unconditional logistic regression models of prostate cancer were used to examine its association with MSP levels, adjusted for the matching factors (listed above), BMI, total PSA and free PSA. Total and free PSA were included in the models as linear and squared terms to better capture their associations with prostate cancer risk. MSP was parameterized as indicator variables reflecting quartile and decile membership. Laboratory batch was not adjusted for because it did not influence the results. We assessed heterogeneity in the association of MSP levels and risk by a Wald test of the interaction terms between each covariate and MSP as well as by stratified analysis.

We also examined the association of MSP and the risk of prostate cancer by disease stage (localized, n = 1116; regional and advanced, n = 169) and Gleason score (≥7, n = 640; <7, n = 688). In analyses stratified by stage and Gleason score, odds ratios (ORs) were estimated comparing case subjects in each subgroup with all control subjects. Case subject–only analyses were performed to test for differences by disease subgroup. We also conducted analysis stratified by self-reported PSA testing prior to blood collection.

We also evaluated the predictive ability of MSP to discriminate prostate cancer case subjects and control subjects in all subjects and in analyses stratified by case subject characteristics, PSA, and the time between blood draw and diagnosis. In these analyses, area under the curve statistics for receiver operating characteristic curves from logistic regression models were estimated before and after accounting for age, BMI, total and free PSA (linear and squared terms), and MSP. All statistical tests are two-sided. The statistical analyses were conducted using SAS software version 9.2 (SAS Institute Inc, Cary, NC).

Results

The mean age of case subjects and control subjects at blood draw (baseline) was 72.1 and 70.6 years, respectively (Table 1). MSP levels were positively associated with age in case subjects but not in control subjects and were inversely associated with BMI and weight in both case subjects and control subjects (Supplementary Table 1, available online). For case subjects, the mean number of years between blood draw and cancer diagnosis ranged from 3.0 in white case subjects to 3.8 in Native Hawaiian case subjects (subject range: <1 year to 12 years and 2 months).

Table 1. Characteristics of prostate cancer case subjects and control subjects by race and ethnicity*

Characteristic	White, case subjects/ control subjects	Black, case subjects/ control subjects	Latino, case subjects/ control subjects	Japanese, case subjects/ control subjects	Native Hawaiian, case subjects/ control subjects	All groups, case subjects/ control subjects	P‡	P§
No.	288/287	349/345	258/263	499/499	86/87	1480/1481		
Age, y†	70.8 ± 7.9/69.7 ± 8.0	72.9 ± 7.0/70.4 ± 6.5	71.3 ± 6.7/70.0 ± 6.5	73.1 ± 7.7/72.2 ± 7.6	69.0 ± 7.2/66.4 ± 6.3	72.1 ± 7.5/70.6 ± 7.3	<.001	
Body mass index, kg/m²†	26.6 ± 3.9/26.8 ± 4.2	27.4 ± 4.2/27.7 ± 4.1	27.0 ± 3.5/27.2 ± 3.8	25.3 ± 3.4/25.2 ± 3.5	29.3 ± 5.3/27.6 ± 5.8	26.6 ± 4.0/26.6 ± 4.1	.98	
MSP, ng/mL‖	22.7 ± 1.0/24.9 ± 1.1	18.4 ± 0.8/17.5 ± 0.8	21.3 ± 1.0/22.1 ± 1.0	18.4 ± 0.6/20.7 ± 0.7	16.4 ± 1.2/23.2 ± 1.7	19.7 ± 0.4/21.1 ± 0.4	.003	<.001
MSP ng/mL¶	21.1 ± 0.9/26.0 ± 1.1	17.2 ± 0.7/18.9 ± 0.8	20.2 ± 0.9/23.9 ± 1.1	17.4 ± 0.6/21.7 ± 0.7	15.2 ± 1.1/24.5 ± 1.8	18.5 ± 0.4/22.4 ± 0.4	<.001	<.001
Total PSA, ng/mL#	4.2 ± 0.2/1.4 ± 0.08	4.5 ± 0.3/1.4 ± 0.08	4.2 ± 0.3/1.2 ± 0.08	3.9 ± 0.2/1.3 ± 0.06	4.7 ± 0.5/1.2 ± 0.1	4.2 ± 0.1/1.3 ± 0.03	<.001	.37
Free PSA, ng/mL#	0.9 ± 0.04/0.4 ± 0.02	0.9 ± 0.05/0.4 ± 0.02	0.8 ± 0.04/0.4 ± 0.02	0.8 ± 0.03/0.4 ± 0.02	1.0 ± 0.09/0.4 ± 0.04	0.9 ± 0.02/0.4 ± 0.01	<.001	.84
Percent free PSA#	0.2 ± 0.01/0.3 ± 0.01	0.2 ± 0.01/0.3 ± 0.01	0.2 ± 0.01/0.3 ± 0.01	0.2 ± 0.01/0.3 ± 0.01	0.2 ± 0.01/0.3 ± 0.02	0.2 ± 0.002/0.3 ± 0.003	<.001	.001

* MSP = β-microseminoprotein; PSA = prostate-specific antigen.

† Means ± SD at time of blood draw.

‡ *F* test of case–control differences from covariance analysis.

§ *F* test of racial and ethnic differences among control subjects from covariance analysis.

‖ Geometric means (±SE) adjusted by covariance analysis for the matching factors (age, area, hours of fasting, year of collection, time of collection) and body mass index (kg/m²).

¶ Geometric means (± SE) adjusted by covariance analysis for the matching factors (age, area, hours of fasting, year of collection, time of collection), body mass index (kg/m²), total PSA (log transformed), free PSA (log transformed), and, race and ethnicity (n = 5 groups) in the pooled analysis.

Geometric means (±SE) adjusted by covariance analysis for the matching factors (age, area, hours of fasting, year of collection, time of collection), body mass index (kg/m²), MSP, and race and ethnicity (n = 5 groups) in the pooled analysis.

The levels of both total and free PSA measured at the time of blood draw were statistically significantly higher ($P < .001$) in men who were subsequently diagnosed with prostate cancer than in men who did not develop prostate cancer (Table 1; Supplementary Figure 1, A–C, available online). In contrast, mean plasma levels of MSP at baseline were statistically significantly lower in case subjects than in control subjects ($P = .003$) (Table 1; Supplementary Figure 1, D, available online). We found statistically significant, yet modest, correlations between PSA measures and MSP at baseline (correlation coefficients = 0.23–0.26, $P < .001$, in case subjects and control subjects). Although there were no statistically significant differences in the levels of total or free PSA across racial and ethnic populations, among control subjects, black men had the lowest mean MSP levels at baseline ($P < .001$ for differences by race and ethnicity) (Table 1).

Given the lower levels of MSP in prostate cancer case subjects compared with control subjects, and the positive correlation of MSP and PSA, the difference in mean MSP levels between case subjects and control subjects was statistically significantly greater following adjustment for PSA ($P < .001$) (Table 1). In analyses adjusted for total and free PSA, lower MSP levels were strongly associated with greater prostate cancer risk (OR = 1.02 per unit decrease in MSP, $P < .001$ adjusted for PSA; OR = 1.01, $P = .006$ unadjusted for PSA) (Figure 1). Compared with men in the highest quartile of MSP, the PSA-adjusted odds ratio was 1.58 (95% confidence interval [CI] = 1.23 to 2.03) for men in the third quartile, 1.77 (95% CI = 1.37 to 2.27) for men in the second quartile, and 2.08 (95% CI = 1.61 to 2.68) for men in the lowest quartile (Table 2). The PSA-adjusted odds ratio was 3.64 (95% CI = 2.41 to 5.49) for men in the lowest decile, when compared with men in the highest decile of MSP (Figure 1). We observed evidence of heterogeneity in the MSP–risk association by racial and ethnic group ($P = .04$), with statistically significant differences noted between white subjects and black subjects (P for interaction = .008), white subjects and Latino subjects (P for interaction = .02), and black subjects and Native Hawaiian subjects (P for interaction = .02). We did not observe evidence of heterogeneity of the association by age, disease stage or Gleason score, PSA levels, the number of years between providing a blood sample and a subsequent prostate cancer diagnosis (Supplementary Table 2, available online), or prior PSA testing (Supplementary Table 3, available online).

Among the 1221 case subjects and 1230 control subjects with rs10993994 genotype information available from previous studies in the Multiethnic Cohort (8,15), we confirmed the strong association between the prostate cancer risk variant and MSP levels in each population (Supplementary Table 4, available online), with the genotype accounting for 46% to 58% of the variation in circulating MSP levels in control subjects. We detected evidence of heterogeneity of the association between MSP and prostate cancer risk by rs10993994 genotype ($P = .03$ for interaction). Stratified analysis shows that the association is strongest for men with the CC genotype (Table 3). An association was observed for the lowest compared with the highest quartile of MSP levels for each genotype group; the trend was statistically significant both for men with the TT genotype, which is associated with higher risk of prostate cancer, and for men with the low-risk CC genotype, indicating that the association of MSP on risk is independent of genotype.

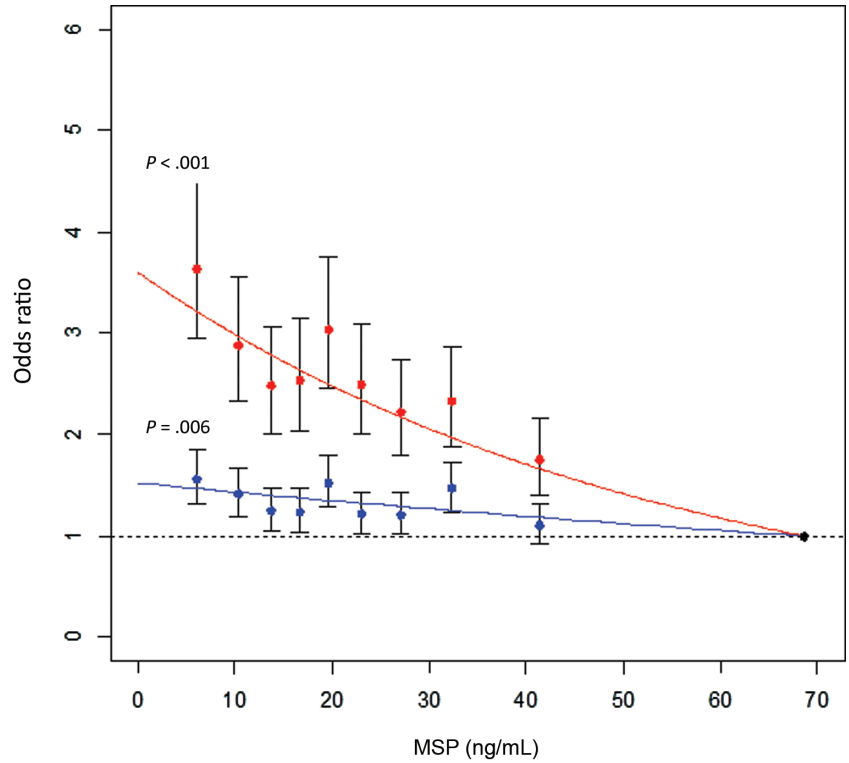

Figure 1. The association of β-microseminoprotein (MSP) levels in the blood with risk of prostate cancer diagnosis is shown. The **red circles** are prostate-specific antigen (PSA)–adjusted odds ratios (bars show 95% confidence intervals) for each decile of MSP compared with the highest decile (**black circle**, reference). The **blue circles** are PSA-unadjusted odds ratios (**bars** show 95% confidence intervals) for each decile of MSP compared with the highest decile (**black circle**, reference). The **red and blue lines** show the linear association from each model starting from the highest decile of MSP. The *P* values are for the linear association of MSP with prostate cancer risk.

Table 2. The association of β-microseminoprotein levels (quartiles) with prostate cancer risk by race and ethnicity*

Population	Q4† (highest)	Q3	Q2	Q1 (lowest)	*P*§
White					
Odds ratio (95% CI)‡	1.0 (referent)	4.74 (2.48 to 9.06)	5.13 (2.66 to 9.91)	4.31 (2.16 to 8.58)	<.001
Black					
Odds ratio (95% CI)‡	1.0 (referent)	1.23 (0.76 to 1.98)	1.49 (0.92 to 2.44)	1.20 (0.73 to 1.98)	.05
Latino					
Odds ratio (95% CI)‡	1.0 (referent)	1.42 (0.75 to 2.68)	1.75 (0.94 to 3.26)	1.81 (0.95 to 3.43)	.11
Japanese					
Odds ratio (95% CI)‡	1.0 (referent)	1.50 (0.96 to 2.35)	1.48 (0.94 to 2.32)	2.20 (1.42 to 3.40)	<.001
Native Hawaiian					
Odds ratio (95% CI)‡	1.0 (referent)	2.88 (0.70 to 11.78)	2.64 (0.57 to 12.23)	6.94 (1.77 to 27.18)	.01
All groups					
Odds ratio (95% CI)‖	1.0 (referent)	1.58 (1.23 to 2.03)	1.77 (1.37 to 2.27)	2.08 (1.61 to 2.68)	<.001
P_{Het}¶					.04
All groups					
Odds ratio (95% CI)#	1.0 (referent)	1.09 (0.88 to 1.34)	1.17 (0.95 to 1.44)	1.27 (1.03 to 1.57)	.006

* CI = confidence interval; Q = quartile.

† Quartiles are based on the distribution in each control population and for all control subjects in the pooled analysis.

‡ Odds ratios were adjusted for the matching factors (age, area, hours of fasting, year of collection, time of collection), body mass index (kg/m^2), total prostate-specific antigen (PSA) (linear and squared terms), and free PSA (linear and squared terms).

§ *P* value for the linear association of β-microseminoprotein modeled as a continuous variable.

‖ Odds ratios were adjusted for the matching factors (age, area, hours of fasting, year of collection, time of collection), body mass index (kg/m^2), total PSA (linear and squared terms), free PSA (linear and squared terms), and race and ethnicity (n = 5 groups).

¶ *P* value for heterogeneity across racial and ethnic groups.

Odds ratios were adjusted for the matching factors (age, area, hours of fasting, year of collection, time of collection), body mass index (kg/m^2), and race and ethnicity (n = 5 groups).

Table 3. The association of β-microseminoprotein (MSP) levels (quartiles) and prostate cancer risk by rs10993994 genotype*

rs10993994 Genotype	Q4†	Q3	Q2	Q1	*P*‡	*P*§
TT genotype						
MSP, ng/mL, case subjects/control subjects‖	21.5/22.1	11.4/11.9	7.8/7.7	4.5/5.1		
No. case subjects/control subjects	71/70	92/72	79/72	77/72	.04	
Odds ratio (95% CI)¶	1.00 (referent)	1.45 (0.83 to 2.53)	1.77 (1.00 to 3.15)	2.04 (1.10 to 3.80)		
CT genotype						
MSP, ng/mL, case subjects/control subjects‖	39.8/38.6	22.6/22.6	17.2/17.0	12.0/13.0		
No. case subjects/control subjects	180/146	166/146	120/146	122/147		
Odds ratio (95% CI)¶	1.00 (referent)	1.59 (1.08 to 2.32)	1.42 (0.94 to 2.16)	1.75 (1.14 to 2.69)	.16	
CC genotype						
MSP, ng/mL, case subjects/control subjects‖	64.4/65.2	36.3/37.6	28.5/28.6	20.3/19.8		
No. case subjects/control subjects	64/89	92/90	82/89	76/91		
Odds ratio (95% CI)¶	1.00 (referent)	2.82 (1.56 to 5.08)	3.14 (1.71 to 5.77)	3.02 (1.56 to 5.85)	<.001	.03

* CI = confidence interval.

† Quartiles are defined separately for each genotype class.

‡ *P* value for the linear association of MSP modeled as a continuous variable.

§ *P* value for test of heterogeneity in the linear association of MSP and prostate cancer risk by genotype.

‖ Geometric means adjusted by covariance analysis for the matching factors (age, area, hours of fasting, year of collection, time of collection), body mass index (kg/m^2), total prostate-specific antigen (PSA) (log transformed), free PSA (log transformed), and race and ethnicity (n = 5 groups).

¶ Odds ratios were adjusted for the matching factors (age, area, hours of fasting, year of collection, time of collection), body mass index (kg/m^2), total PSA (linear and squared terms), free PSA (linear and squared terms), and race and ethnicity (n = 5 groups).

Despite the highly statistically significant association of MSP and prostate cancer risk, MSP levels did not importantly enhance discrimination of prostate cancer case subjects from control subjects above that of PSA. Among all case subjects and control subjects, the area under the curve changed from 0.839 to 0.843 when MSP was included in models that included total and free PSA. Similar small increases in the areas under the curve were noted when MSP was added in models that included free and total PSA for each ethnic group, by disease stage and Gleason score, and for men at increased prostate cancer risk based on their total PSA level at baseline (Supplementary Table 5, available online).

Discussion

In this prospective study, we provide evidence that lower circulating levels of MSP are associated with increased risk of prostate cancer. An association with the biomarker levels was observed in all racial and ethnic populations, in all rs10993994 genotypes, and irrespective of levels of total or free PSA. However, we found little evidence that circulating MSP levels improve prostate cancer prediction beyond that of total and free PSA.

Together with PSA, MSP is one of the most abundantly expressed proteins from the prostate (16,17) and one of the most abundant secreted proteins in human seminal fluid (18). Serum MSP levels have been shown to be lower in men with aggressive prostate cancer (9) as well as in men with a prostate cancer recurrence after radical prostatectomy (19). Urinary MSP levels have also been shown to be lower in men with prostate cancer than in men with no history of prostate cancer (10). In the prostate, MSP expression is lower in malignant tissue than in benign prostate tissue, with levels found to be even lower in men with more aggressive tumors (10,20,21). It is not clear whether the lower expression in malignant tissue and the lower levels observed in the blood and in the urine are a reflection of the disease or whether the change is an etiologic event that is important in the pathogenesis of the cancer. All previous studies to examine MSP as a marker of risk have been cross-sectional, with urinary or blood measurements taken among case subjects already diagnosed with prostate cancer. Here we show that a lower level of MSP measured in blood drawn 5 years before diagnosis is associated with a statistically significantly increased risk of subsequent diagnosis of prostate cancer. The inverse association that we detected was not influenced by the duration of time between blood draw and a diagnosis, which suggests that the lower levels in case subjects is unlikely to be the result of undiagnosed disease. However, one limitation of our study is the length of time of follow-up. Given the long latency period for prostate cancer, longer follow-up of the cohort will be required to better assess the impact of potentially undiagnosed disease on our findings.

The biological function of MSP in the prostate is not known. It is also unclear why MSP levels decrease (in contrast with PSA) during tumor progression. MSP has been implicated to have a role in regulating cellular growth in the prostate through apoptosis as well as to function as a suppressor of tumor growth (22). Silencing of MSP expression in prostate tumor tissue has been associated with promotor methylation of the gene mediated by a polycomb group member protein, enhancer of zeste homolog-2 (EZH2) (23). MSP has the capacity to form very high-affinity complexes with cysteine-rich secretory protein-3 (CRISP3) in seminal fluid (24), a protein implicated through structural similarity of the C-terminal domain to possibly function as a potassium-channel inhibitor (25); however, the functional significance or biological role of MSP alone or bound to CRISP3 is not currently known.

Consistent with numerous prior reports (26,27), the level of total PSA in blood was a remarkably strong predictor of prostate cancer risk in our study. The increase in the effect size associated with lower MSP levels after adjustment for PSA is consistent with

negative confounding due to a modest positive correlation between these markers and the very strong association of PSA and prostate cancer risk. Both accurate measurement of PSA and modeling of its relationship with prostate cancer are important because residual and unaccounted for negative confounding would conceal the true strength of the association of MSP with prostate cancer risk.

Genome-wide association studies have been criticized because the variants identified have modest associations, account for only a small fraction of disease heritability, and have yet to translate into mechanisms that are successful, beyond those currently available, to effectively identify, prevent, or treat disease. The counter to this criticism is that the risk loci are providing biological insights into genes and pathways that are unambiguously important in disease etiology. Whereas previous studies have focused on MSP as a biomarker of potential utility in screening (9,10,19), the identification of a common risk variant at the MSP locus from genome-wide association studies (2,6) and subsequent studies showing that this variant is involved in the regulation of the protein (7,8) has highlighted the protein as directly involved in the pathogenesis of the disease. Our investigation of MSP as a biomarker and risk factor for the disease was based on the risk association with the genetic locus and demonstrates the value of genome-wide association studies in revealing and strengthening biological links with disease, which in the case of prostate cancer is important given how little is known about factors that influence individual risk.

Despite the highly statistically significant association of MSP with prostate cancer risk, we found little evidence that circulating MSP levels improve prostate cancer prediction beyond that of total and free PSA. Findings from our prospective analysis are consistent with the cross-sectional study of Nam et al. (9) which also found no improvement by considering MSP in prostate cancer prediction among men with PSA greater than four or an abnormal digital rectal examination. However, in contrast with this previous report (9), we observed no improvement in distinguishing aggressive vs nonaggressive disease when MSP was combined with total PSA and free PSA. This difference may be due to the association of PSA being artificially inflated in our study because of verification bias, which is another potential limitation of our study. Prostate cancer is more likely to be detected among men with elevated PSA levels because this is an indication for biopsy in the United States. Indeed, the area under the curve for PSA and prostate cancer (0.822) was much higher than typically reported (26,27). Accordingly, we suggest additional studies to determine the value of MSP in predicting outcome of biopsy after an elevated PSA level as well as studies to address the specificity of MSP for lethal disease.

In summary, our data provide strong evidence in support of an association between the MSP protein measured in blood and prostate cancer risk across multiple racial and ethnic populations. However, this study does not contribute definitive evidence as to whether MSP levels can importantly enhance prostate cancer prediction beyond that of total and free PSA

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Notes

H. Lilja holds patents for assays for free PSA and intact PSA.

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