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MSMB gene variant alters the association between prostate cancer and number of sexual partners

Marni Stott-Miller, PhD[1], **Jonathan L. Wright**[1,2], and **Janet L. Stanford, PhD.**[1,3]

[1]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA

[2]Department of Urology, University of Washington School of Medicine, Seattle, WA

[3]Department of Epidemiology, School of Public Health, University of Washington, Seattle, WA

Abstract

Background—Recently, a genetic variant (rs10993994) in the *MSMB* gene associated with prostate cancer (PCa) risk was shown to correlate with reduced prostate secretory protein of 94 amino acids (PSP94) levels. Although the biological activity of PSP94 is unclear, one of its hypothesized functions is to protect prostatic cells from pathogens. Number of sexual partners and a history of sexually transmitted infections (STIs) have been positively associated with PCa risk, and these associations may be related to pathogen-induced chronic prostatic inflammation. Based on these observations, we investigated whether *MSMB* genotype modifies the PCa-sexual history association.

Methods—We estimated odds ratios (OR) and 95% confidence intervals (CI) for the association between number of sexual partners and PCa by fitting logistic regression models, stratified by *MSMB* genotype, and adjusted for age, family history of PCa, and PCa screening history among 1,239 incident cases and 1,232 controls.

Results—Compared with 1–4 female sexual partners, men with ≥15 such partners who carried the variant T allele of rs10993994 were at increased risk for PCa (OR=1.32; 95% CI, 1.03–1.71); no association was observed in men with the CC genotype (OR=1.03; 95% CI, 0.73–1.46; p=0.05 for interaction). Similar estimates were observed for total sexual partners (any T allele OR=1.37; 95% CI, 1.07–1.77; CC genotype OR=1.11; 95% CI, 0.79–1.55; p=0.06 for interaction).

Conclusions—The rs10993994 genotype in the *MSMB* gene modifies the association between number of sexual partners and PCa risk. These findings support a hypothesized biological mechanism whereby prostatic infection/inflammation may enhance risk of PCa.

Keywords

sexual partners; PSP94; MSMB; sexually transmitted infections; prostate cancer; rs10993994

CORRESPONDING AUTHOR: Janet L. Stanford; Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, 1100 Fairview Avenue N, M4-B874, Seattle, WA 98109-1024, Phone: (206) 667-2715; Fax: (206) 667-4787. jstanfor@fhcrc.org.

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Introduction

Prostate secretory protein of 94 amino acids (PSP94) is secreted by prostatic epithelial cells, and is a primary component of semen. Decreased expression of PSP94 has been associated with increased prostate cancer (PCa) risk and disease progression in multiple studies [1–4], and has been suggested as a potential PCa biomarker [1,5]. The PSP94 protein is encoded by the *β-microseminoprotein* (*MSMB*) gene. Several studies, including our own [6], have observed that the variant T allele of SNP rs10993994, which is in the proximal promoter region of the *MSMB* gene, is associated with increased PCa risk and with lower PSP94 protein expression in tissue and urine [7–11].

Despite the observed association between PSP94 and the development of PCa, its biological function remains unclear. A recent hypothesis proposed by Laurence suggests that PSP94 mediates prostatic exposure to pathogens that may be acquired through sexual activity; by blocking or reducing pathogenic effects of sexually transmitted infections (STIs) on prostate epithelial cells, PSP94 may alter subsequent risk of PCa [12]. Persistent STI-associated inflammation within the prostate has been hypothesized to promote development of PCa [13], and Laurence proposes that lower levels of PSP94 within the prostate may provide a microenvironment that facilitates pathogen-induced inflammation and carcinogenesis [12].

A higher relative risk of PCa has been observed among men with a history of STIs (summary relative risk of 1.5; 95% CI = 1.3–1.7) [14]. Strong evidence to implicate a specific pathogen has not emerged, but the relatively consistent associations of multiple STIs with PCa risk [14] suggest the existence of one or more causal infectious agents. Number of sexual partners can serve as a proxy for exposure to STIs and has been associated with PCa risk in several studies (see Dennis and Dawson for a review and meta-analysis; reported summary relative risk of 1.2 for an increase of 20 partners (95% CI, 1.1–1.3) [15]. We previously reported an association between number of sexual partners and risk of PCa [16]. In the present study, we used data from two population-based case-control studies to test the hypothesis that the association between number of sexual partners or history of STIs and PCa risk varies by the *MSMB* rs10993994 SNP genotype.

Methods

Study Population

Data and specimens from two prior population-based case-control studies, as previously described [17,18], were used for these analyses. Study participants were European American and African American residents of King County, Washington. Cases from the first study were 40–64 year old men diagnosed with histologically confirmed PCa between 1993 and 1996. Cases from the second study were 35–74 year old men diagnosed with histologically confirmed PCa between 2002 and 2005. For both studies, cases were identified from the Seattle-Puget Sound population-based tumor registry that is operated as part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. The case participation proportion was 82% and 75% for the first and second study, respectively.

Controls were men without a self-reported physician's diagnosis of PCa, and were recruited by random-digit telephone dialing. In both studies, household census information was obtained, and men within the study age range and without a prior diagnosis of PCa and who agreed to receive study related information, were contacted. Controls were recruited evenly throughout the ascertainment periods for cases, and were frequency matched to cases by 5-year age groups. The overall response proportion for control subjects was 75% and 63% for the first and second study, respectively.

As previously described [17,18], study participants were interviewed using a structured questionnaire eliciting demographic characteristics, medical and lifestyle history, and PCa screening history. Questions on lifetime sexual history included age at first intercourse, sexual orientation, lifetime number of male and female sexual partners, lifetime history of any STI, and type of STI.

Of 753 eligible interviewed cases in the first study, 631 (84%) provided a blood sample, and of 703 eligible interviewed controls, 565 (80%) provided a blood sample. Of 1,001 eligible interviewed cases in the second study, we collected 827 (83%) blood samples, and of 942 eligible interviewed controls, 787 (84%) provided blood samples. There were 1,404 cases and 1,333 controls with sufficient DNA for this study and who were successfully genotyped for the *MSMB* variant. We excluded 2 cases and 6 controls who reported having had no sexual partners, and those with missing data on both male and female sexual partners (22 cases and 16 controls). The allele frequency distribution was substantially different between European American and African American men, so we excluded African Americans in primary analyses (n=220), and conducted separate analyses for this subgroup. Primary analyses were conducted for a total of 1,239 European American cases and 1,232 European American controls.

The Seattle–Puget Sound SEER registry provided information on tumor stage and Gleason score of prostate cancer at diagnosis for cases. The Fred Hutchinson Cancer Research Center's Institutional Review Board approved the studies. Written informed consent was obtained from all study participants prior to participation.

Single Nucleotide Polymorphism Genotyping

A custom designed TaqMan SNP genotyping assay (Applied Biosystems, Foster City, CA) was used to genotype the *MSMB* (rs10993994) SNP on the ABIPrism 7900HT sequence detection system according to the manufacturer's instructions [6].

Data Analysis

The number of lifetime female sexual partners was grouped into tertiles (1–4, 5–14, ≥15) to provide a relatively similar frequency distribution among controls. The total number of lifetime sexual partners (male and female) was calculated by assigning a category based on female partners, and then adjusting a subject's category based on reported male partners.

Genotype frequencies for rs10993994 were consistent ($P > 0.05$) with Hardy-Weinberg equilibrium (HWE) among European American controls. To investigate whether an association between lifetime number of sexual partners and PCa was modified by the *MSMB*

genotype, we stratified subjects according to whether or not they carried the variant T allele. Odds ratios (OR) and 95% confidence intervals (CI) were estimated for the association between number of female and total sexual partners and PCa by fitting unconditional logistic regression models, adjusted for age, family history of PCa, and prostate-specific antigen (PSA) tests or digital rectal examinations (DRE) in the previous 5 years. To statistically assess departures from multiplicative effects, a product term (genotype by number of sexual partners) was included in the stratified analyses, and a log-likelihood ratio test was used to compare logistic models with and without the product term. We repeated these analyses for African American men separately.

We additionally investigated whether there was an association between any history of STIs (yes/no) and PCa risk in our data, and whether this association was modified by the *MSMB* genotype. A product term (genotype by STI history) was included, and a log-likelihood ratio test was used to compare logistic models. Number of episodes and type of STI reported were also investigated.

In exploratory analyses, we investigated whether stratified risk estimates changed with additional adjustment for marital status or income. We also investigated whether adjustment for self-reported history of prostatitis changed the stratified risk estimates, since a hypothesized mechanism for the influence of MSMB genotype on PCa risk is through chronic inflammation. Finally, we investigated whether adjustment for self-reported circumcision status affected the results, as circumcision status has been associated with risk of STIs [19,20], and has recently been associated with decreased risk of PCa [21].

Results

Compared with controls, cases were more likely to report a first-degree family history of PCa (Table 1). Cases were also more likely to have had PSA testing in the five year period before reference date (date of diagnosis for cases and a randomly assigned date for controls that approximated the distribution of diagnosis dates for cases).

A total of 862 cases and 767 controls carried the T allele of rs10993994. Men who carried the variant T allele had a 40% increased risk of PCa compared with men who had the CC genotype, adjusted for age, family history of PCa and PSA/DRE screening history (95% CI, 1.17–1.66). Compared with the reference group (1–4 female sexual partners), a positive association was observed for men reporting ≥15 female sexual partners and PCa risk (OR=1.21; 95% CI, 0.98–1.48). The adjusted risk estimate was slightly stronger for men with ≥15 total (female and male) sexual partners (OR=1.27; 95% CI, 1.04–1.55). We did not observe an association between age at first intercourse and risk of PCa (results not shown).

We then evaluated whether *MSMB* genotype modified the associations with sexual history. Compared with 1–4 female sexual partners, there was a positive association between having ≥15 female sexual partners and PCa among men carrying the T allele (OR=1.32; 95% CI, 1.03–1.71; Table 2), but no association was observed among men with the CC genotype (OR=1.03; 95% CI, 0.73–1.46). A likelihood ratio test for interaction yielded p=0.05. Similarly, compared with 1–4 total sexual partners, men with ≥15 total sexual partners were

at elevated risk of PCa if they carried the variant T allele (OR=1.37; 95% CI, 1.07–1.77; Table 2), but not if they had the CC homozygous wild-type genotype (OR=1.11; 95% CI, 0.79–1.55); p-value for interaction was 0.06.

The number of African American men was too small to draw meaningful conclusions from the analyses. Although confidence intervals were wide, compared with 1–4 total sexual partners, there was a positive association between ≥15 total sexual partners and PCa among African American men with the variant T allele (OR=1.49; 95% CI, 0.55–4.05), and an inverse association among men with the CC genotype (OR=0.57; 95% CI, 0.85–3.76). Neither risk estimate, however, was statistically significant.

There were 1,236 European American cases and 1,232 European American controls with data on a history of STIs (yes/no). We did not observe an overall adjusted association between history of any STI and PCa risk (OR=1.08; 95% CI, 0.84–1.37) and there was no interaction between STI history and *MSMB* genotype (p=0.68). There was also no indication of an association by number of STIs or type of STI (data not shown). We did not observe any meaningful change in the stratified risk estimates after additional adjustment for marital status, income, self-reported history of prostatitis, or self-reported circumcision status (results not shown).

Discussion

These results demonstrate a gene-environment interaction between a genetic variant in the *MSMB* gene (rs10993994) and number of lifetime sexual partners in relation to PCa risk. To the best of our knowledge, the present investigation is the first to examine whether the *MSMB* gene variant modifies the association between sexual history and PCa risk. We observed a moderate positive association between having 15 or more female sexual partners and PCa risk, and this association was stronger among men with the variant T allele. No association between 15 or more female sexual partners and PCa risk was observed among men with the CC genotype. Results were similar for analyses of total (female and male) sexual partners.

A higher number of sexual partners has been associated with increased risk of PCa in several research studies, with a meta-analysis estimating a summary relative risk of 1.2 for an increase of 20 partners (95% CI,1.1–1.3) [15]. Number of sexual partners is a surrogate for potential exposure to STIs, as each partner may lead to exposure to a sexually transmitted pathogen(s).

A summary relative risk of 1.5 (95% CI, 1.3–1.7) for PCa has been estimated for men with a history of STIs [14]. We did not observe an association between history of any STI and risk of PCa; however, the percentage of men who reported a lifetime history of any STI in our data set was only 14%. This prevalence is likely to be an underestimate, as the majority of men will experience an STI at some point in their lifetime [22,23]. This underreporting problem is particularly notable for non-symptomatic STIs such as human papilloma virus (HPV), which has an estimated lifetime risk of 75% [22].

STIs are hypothesized to increase PCa risk by infecting the prostatic epithelium, resulting in an inflammatory immune response [13]. Sexually transmitted organisms, including HPV, herpes simplex virus (HSV), Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis, and Treponema pallidum, have been detected in the prostate [24]. The presence of HPV DNA [25] in prostate tissue and serum antibodies against Trichomonas vaginalis [26] have been associated with an elevation in the relative risk of PCa. No particular pathogen, however, has been confirmed as a causal agent. Moreover, an observed infectious organism may be a proxy for another unidentified pathogen, since co-infections are common.

Following the theory proposed by Laurence [12], the present study provides initial epidemiological support for the hypothesis that the PSP94 protein may inhibit the adverse effects of a sexually transmitted pathogen on prostatic tissue, since men who carry the T allele of rs10993994 have been shown to have lower PSP94 expression in prostate tissue and lower PSP94 concentrations in urine, and are also at increased risk for PCa [6–11]. The biological mechanism by which PSP94 may inhibit an STI is unknown. If PSP94 has anti-infection and anti-inflammatory activity, this may be a plausible mechanism; however, further research is needed to confirm or refute this notion. PSP94 does exhibit strong fungicidal activity [27], and Laurence proposes the novel idea that a candidate STI organism may be fungal in origin [12].

Case-control studies of genetic variants are susceptible to bias from race/ethnicity differences [28]. To mitigate this problem, we elected to confine analyses to European American men, based on differences in *MSMB* allele frequency between the European American and African American men in our population. Another limitation of the present study is potential differential misclassification caused by reporting bias due to the sensitive nature of questions about sexual behavior. However, we have no reason to believe that this would differ between cases and controls, and all structured interviews were conducted by trained male interviewers. In addition, biased main effects for environmental factors do not necessarily imply biased estimates of gene-environment interactions [29]. Poor recall might have resulted in non-differential misclassification, possibly attenuating main effects; although this would not be expected to impact estimates of interaction. Finally, we were limited by the use of number of sexual partners as a proxy for exposure to specific STIs, and lack of data on levels of PSP94.

Nevertheless, the present study makes use of a well-characterized population-based group of men with comprehensive demographic, lifestyle and screening information. The implications of the gene-environment interaction that we observed for a SNP in the *MSMB* gene and number of lifetime sexual partners is currently unknown. However, these findings lend some support to a biological mechanism that has been proposed to link STIs and PCa risk [12], and emphasize the need for further research.

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Table 1

Distributions for selected characteristics among European American prostate cancer cases and controls, King County, Washington

Characteristic	Cases (n=1,239)		Controls (n=1,232)	
	N	%	n	%
Age at reference date (years)				
35–49	96	7.8	107	8.7
50–54	183	14.8	172	14.0
55–59	306	24.7	336	27.3
60–64	371	29.9	323	26.2
65–69	145	11.7	156	12.7
70–74	138	11.1	138	11.2
MSMB rs10993994 genotype				
CC	377	30.4	465	37.7
CT	621	50.1	599	48.6
TT	241	19.5	168	13.6
First-degree family history of prostate cancer				
No	968	78.1	1,093	88.7
Yes	271	21.9	139	11.3
PSA/DRE testing[a]				
None	130	10.5	161	13.1
DRE only	208	16.8	469	38.1
PSA	901	72.7	602	48.9
PSA level (ng/mL)[b]				
0 – 3.9	168	13.6	1,145	92.9
4 – 9.9	681	55.0	71	5.8
10 – 19.9	177	14.3	14	1.1
20+	116	9.4	2	0.2
Missing	97	7.8		
Stage of disease				
Local	966	78.0		
Regional	241	19.5		
Distant	32	2.6		
Gleason score				
2–4	63	5.1		
5–6	644	52.0		
7 (3+4)	338	27.3		
7 (4+3), 8–10	190	15.3		
Missing	4	0.3		

[a] In the 5 years before reference date. PSA=prostate specific antigen; DRE=digital rectal examination.

[b] PSA at diagnosis in cases and at interview in controls.

Table 2

Odds ratios of prostate cancer associated with lifetime number of sexual partners, stratified by *MSMB* rs10993994 genotypes, King County, Washington[a]

Sexual Partners	Cases (n=1,239)		Controls (n=1,232)				
	n	%	n	%	OR	(95% CI)	P (interaction)
Number of female sexual partners:							
MSMB CC genotype							
1–4	178	(47.2)	197	(42.4)	1.00	(referent)	0.05
5–14	83	(22.0)	137	(29.5)	0.68	(0.48–0.98)	
≥ 15	111	(29.4)	128	(27.5)	1.03	(0.73–1.46)	
N/A[b]	5	(1.3)	3	(0.7)			
MSMB CT or TT genotype							
1–4	375	(43.5)	356	(46.4)	1.00	(referent)	
5–14	247	(28.7)	215	(28.0)	1.14	(0.89–1.47)	
≥ 15	230	(26.7)	188	(24.5)	1.32	(1.03–1.71)	
N/A[b]	10	(1.2)	8	(1.0)			
Number of total sexual partners:							
MSMB CC genotype							
1–4	175	(46.4)	197	(42.4)	1.00	(referent)	0.06
5–14	84	(22.3)	138	(29.7)	0.70	(0.49–0.99)	
≥ 15	118	(31.3)	130	(28.0)	1.11	(0.79–1.55)	
MSMB CT or TT genotype							
1–4	361	(41.9)	349	(45.5)	1.00	(referent)	
5–14	248	(28.8)	214	(27.9)	1.17	(0.91–1.50)	
≥ 15	253	(29.4)	204	(26.6)	1.37	(1.07–1.77)	

[a] Adjusted for age at reference date, first-degree family history of prostate cancer, and PSA/DRE tests within the previous 5 years before reference date.

[b] Reported male sexual partners only.