Published in final edited form as:
Prostate. 2014 May ; 74(6): 569–578. doi:10.1002/pros.22778.

MSMB Variation and Prostate Cancer Risk: Clues Towards a Possible Fungal Etiology

Siobhan Sutcliffe[1,*], **Angelo M. De Marzo**[2,3], **Karen S. Sfanos**[2], and **Martin Laurence**[4]

[1]Division of Public Health Sciences and the Alvin J. Siteman Cancer Center, Department of Surgery, Washington University School of Medicine, St. Louis, Missouri [2]Department of Pathology, Johns Hopkins Medical Institutions, Baltimore, Maryland [3]Brady Urological Institute and the Sidney Kimmel Cancer Center, Johns Hopkins Medical Institutions, Baltimore, Maryland [4]Shipshaw Labs, Montreal, Quebec, Canada

Abstract

BACKGROUND—With recent advances in high-throughput sequencing technologies, many prostate cancer risk loci have been identified, including rs10993994, a single nucleotide polymorphism (SNP) located near the *MSMB* gene. Variant allele (T) carriers of this SNP produce less prostate secretory protein 94 (PSP94), the protein product of *MSMB*, and have an increased risk of prostate cancer (approximately 25% per T allele), suggesting that PSP94 plays a protective role in prostate carcinogenesis, although the mechanisms for such protection are unclear.

METHODS—We reviewed the literature on possible mechanisms for PSP94 protection for prostate cancer.

RESULTS—One possible mechanism is tumor suppression, as PSP94 has been observed to inhibit cell or tumor growth in in vitro and in vivo models. Another novel mechanism, which we propose in this review article, is that PSP94 may protect against prostate cancer by preventing or limiting an intracellular fungal infection in the prostate. This mechanism is based on the recent discovery of PSP94's fungicidal activity in low-calcium environments (such as the cytosol of epithelial cells), and accumulating evidence suggesting a role for inflammation in prostate carcinogenesis. We provide further details of our proposed mechanism in this review article.

CONCLUSIONS—To explore this mechanism, future studies should consider screening prostate specimens for fungi using the rapidly expanding number of molecular techniques capable of identifying infectious agents from the entire tree of life.

Keywords

prostate secretory protein 94; *MSMB*; prostate cancer; fungi

[*]Correspondence to: Siobhan Sutcliffe, Division of Public Health Sciences and the Alvin J. Siteman Cancer Center, Department of Surgery, Washington University School of Medicine, 660 South Euclid Avenue, Box 8100, Room 208S, St Louis, MO 63110. sutcliffes@wudosis.wustl.edu.

INTRODUCTION

Recent advances in high-throughput sequencing technologies have allowed for the identification of at least 77 genetic loci associated with prostate cancer risk in genome-wide association and replication studies [1]. These recent genetic discoveries offer the potential for risk prediction, targeted prevention and screening, biomarker development, and insight into prostate cancer etiology. Loci identified to date include, most notably, single nucleotide polymorphisms (SNPs) in the 8q24 and 17q12 chromosomal regions, and those related to the *HNF1B* and *MSMB* genes [2]. While SNPs in the 8q24 region have received much attention, our review article focuses on genetic variation related to the *MSMB* gene and proposes a novel hypothesis as to how this variation may inform a fungal etiology of prostate cancer.

MSMB AND PROSTATE CANCER RISK

Two genome-wide association and several replication studies have observed associations between SNP rs10993994, a SNP located 57 base pairs upstream of the first exon of *MSMB* in its proximal promoter region [3], and prostate cancer risk [4–8]. In the largest replication study, CC homozygotes had the lowest risk of prostate cancer, heterozygotes had an intermediate risk (odds ratio [OR] = 1.21; 95% CI = 1.11–1.33), and TT homozygotes had the highest risk of prostate cancer (OR = 1.57; 95% CI = 1.42–1.74) [4]; similar associations were observed in smaller studies and among men of varying races [7–14]. Results from fine-mapping studies further indicate that associations between rs10993994 carrier status and prostate cancer risk were stronger and more significant than those for other local tag SNPs, which, together with observed promoter activity, suggest that rs10993994 is one of the main SNPs responsible for observed associations between *MSMB*-related variation and prostate cancer risk [3,8]. Finally, although rs10993994 carrier status was also associated with levels of mRNA for *NCOA4* (a gene located within 16 kb telomeric of rs10993994) in one study of benign prostate tissue [15], no association was observed for NCOA4 protein levels in the only other study to examine this possible relation [16], suggesting that rs10993994 genetic associations are likely specific to *MSMB*.

While the association between rs10993994 carrier status and prostate cancer risk is certainly strong, reproducible, and likely specific for *MSMB*, one concern for all genetic association studies is the possibility of prostate-specific antigen (PSA) detection bias. This bias occurs when the variant under investigation is associated with prostate cancer detection through its association with elevated PSA levels and the likelihood of prostate biopsy independent of the presence of prostate cancer. Although rs10993994 carrier status is associated with PSA levels [6,12,16–18], we believe that PSA detection bias is unlikely to explain associations between rs10993994 status and prostate cancer risk because similar associations were observed for both cancers more and less likely to be detected purely by PSA (e.g., low-grade, low-stage, and non-palpable disease, and cancers detected after the introduction of PSA screening vs. high-grade, high-stage, palpable, and pre-PSA era disease) in most previous studies [4,5,7–9,11,13], and because no association was observed with the likelihood of a negative prostate biopsy in one further study [18]. African-American men, who have the highest risk of prostate cancer diagnosis and mortality [19], are also more

likely to carry the high-risk T allele (60% in African- American controls [7] vs. 40% in their Caucasian counterparts [5,6]), further arguing against a major influence of detection bias. Thus together, these findings support a causal role for *MSMB*-related variation in prostate carcinogenesis.

PROSTATE SECRETORY PROTEIN 94

MSMB encodes prostate secretory protein 94 (PSP94), a 94-amino acid, 10.7 kDa member of the immunoglobulin binding factor family and one of the three main proteins secreted by prostate epithelial cells into seminal plasma [20]. Over the years, this protein has had several different names and hypothesized functions. It was first identified in semen in the early 1980s and named by two independent groups. One group reported that PSP94 suppressed the secretion of follicle stimulating hormone (FSH), suggesting a role for PSP94 as an inhibin, and named it β-inhibin [21]. Shortly thereafter, however, FSH suppression could not be reproduced [22,23], and the name prostate secretory protein 94 was adopted instead [24]. A second group reported that PSP94 coated the surface of spermatozoa, suggesting a role in reproduction, and named it β-microseminoprotein (β-MSP, MSP, or MSMB) [25]. This potential role for PSP94 is still being explored [26].

In addition to its possible involvement in reproduction, recent associations between *MSMB*-related variation and prostate cancer risk clearly suggest a role for PSP94 in prostate cancer development. Based on levels of *MSMB* expression among men of varying rs10993994 genotype, this role appears to be protective. Low-risk rs10993994 C allele carriers have the highest levels of promoter activity [3,8] and prostate tissue expression [15,16,27], and the highest concentrations of PSP94 in their blood [13,17], urine [27], and seminal plasma [8,17,27], suggesting that high PSP94 expression may be protective for prostate cancer. Although the protective mechanisms conferred by the rs10993994 C allele are unknown, two previously hypothesized biological functions of PSP94 could explain this effect: tumor suppression [28] and pathogen defense [29]. These two hypothesized functions are reviewed here in detail; a brief review of all hypothesized functions for PSP94 was published by Lazure et al. [30].

Tumor Suppression

In 1992, Lokeshwar et al. investigated the effects of seminal plasma on prostate cancer cells and reported strong inhibition of human PC3 and DU145 cells, as well as rat DT cells, which they attributed to TGF-β_1 (for all three cell types [31]) and PSP94 (for DT cells only [32]). This was the first report, to our knowledge, of PSP94's tumor suppression properties. Thereafter, many studies have continued to explore its tumor suppression properties and those of its derived peptides using in vitro and rodent models [15,28,32–39]. Considering findings from in vitro studies, generally variable results have been observed across models and peptides. Three studies examined the effects of human PSP94 on PC3 cells, two of which reported no growth inhibition [28,37], while a third reported strong inhibition [33]. Another study examined two additional human prostate cancer cell lines, and reported moderate growth inhibition of LNCaP cells and strong inhibition of WPE1-NB26 cells [37]. Finally, one further study suppressed *MSMB* expression in immortalized prostate epithelial cells and found that such suppression promoted anchorage-independent growth [15]. All

additional studies explored the influence of PSP94 or derived peptides on rat prostate cancer cells. One study reported strong growth inhibition by human PSP94 and peptides derived from PSP94 amino acids 31–45, but not amino acids 7–21 and 76–94, on the MLL rat prostate cancer cell line [34,35]; another observed no inhibition by human PSP94 on the MLL cell line [28]; and a third study observed strong inhibition by amino acids 85–94 on rat DT prostate cancer cells [32]. Finally, one further study tested the influence of rat PSP94 on the PAIII rat cancer cell line and reported strong growth inhibition [36].

In contrast to in vitro findings, those from in vivo rodent models have tended to be more consistent. All six in vivo studies reported tumor suppression by subcutaneously injected human PSP94 and derived compounds in rats and mice [28,32–35,38], although only two of these studies were sufficiently similar to allow for a comparison of the minimum dose required for tumor suppression. In these two studies, the minimum dose varied from 25 [28] to 1,000 ng/kg/day [34] for tumor suppression of the MLL rat cancer cell line in male Copenhagen rats, making it difficult to comment on the minimum required dose.

Finally, in addition to findings from in vitro and rodent models, changes in PSP94 expression in the prostate with the development of malignancy may also inform its tumor suppression properties. Compared to normal prostate tissue, lower levels of *MSMB* mRNA and PSP94 expression have been observed consistently in localized prostate cancer lesions, although no further differences were observed by Gleason score in most previous studies [16,40–45]. These findings suggest that high PSP94 expression may influence prostate cancer development, but not prostate cancer cell differentiation, consistent with observed null associations with grade in most genetic studies [4,7,8]. Possible mechanisms that have been proposed to explain all of these findings include suppression of FSH [28,34,46], inhibition of DNA synthesis [32], failed DNA repair [47], inhibition of angiogenesis [39], and increased apoptosis of cancer cells by binding to CRISP-3 [48] or laminin receptors [49].

Beyond tumor development, further observations suggest that PSP94 may also play a role in inhibiting prostate cancer recurrence or metastasis. This role may be relevant to genetic findings for rs10993994 if properties related to prostate cancer recurrence/metastasis overlap with those related to prostate cancer development. Human PSP94 and a peptide derived from amino acids 31–45 reduced microvessel density and experimental skeletal metastases, and inhibited matrix metalloproteinase (MMP-9) mediated metastasis in in vitro and rodent models [34,35,39,50]. Lower expression of *MSMB* mRNA was also observed in prostate cancer metastases than in primary prostate tumors in three human tissue-based studies [51–53], and lower levels of prostatic PSP94 expression were associated with a greater likelihood of prostate cancer recurrence/metastasis in some studies [40,43], while others reported the opposite association [42,45]. These findings suggest that, in addition to suppressing tumor development, PSP94 may also contribute to inhibition of prostate cancer recurrence and metastasis.

Pathogen Defense

Another possible and novel role for PSP94 is pathogen defense, which has only recently been explored. In their study of the anti-microbial properties of semen, Hagerwall et al. [29]

demonstrated potent fungicidal activity against the fungus *Candida albicans* in post-coital seminal plasma. This activity was mediated by PSP94 amino acids 66–76 and was limited to post-coital seminal plasma; PSP94 was not fungicidal in normal seminal plasma, which the authors attributed to selective inhibition by calcium ions at a neutral pH but not at the acidic pH of the post-coital milieu. The authors further demonstrated that porcine PSP94, which shares 51% amino acid sequence identity with human PSP94, was also fungicidal, suggesting that this may be a retained and fundamental property of PSP94. Finally, Hagerwall et al. [29] tested the toxicity of PSP94 against common bacterial uropathogens and human cells, and found it to lack both bactericidal and cytotoxic activity, which they attributed, at least in part, to its observed selective affinity for fungal plasma membranes. In liposome experiments, they found that PSP94 disrupted ergosterol-rich liposomes, which mimic the plasma membranes of most fungi and some protists, but not cholesterol-rich liposomes, which mimic mammalian plasma membranes.

Although Hagerwall et al.'s findings clearly demonstrate that PSP94 is fungicidal in the acidic, calcium ion binding-inhibiting environment of post-coital seminal plasma, whether or not it is also fungicidal in other naturally occurring low-calcium environments is largely unknown. Within the prostate, the only low-calcium ion environment is the cytosol—where calcium ions are all but absent. [54] Unfortunately, few studies have examined the intracellular localization of PSP94 to inform the possibility of cytosolic localization. In their immunoelectron microscopic study of prostate tissue from older men with benign prostatic hyperplasia (BPH) or prostate cancer, Ito et al. [55] observed PSP94 protein staining primarily in the secretory granules, but not the cytosol, of prostate epithelial cells. Similar granular staining was also observed by Doctor et al. [56] in tissue from men with BPH. However, when these investigators examined tissue from young men without prostate disease, they observed diffuse rather than granular PSP94 protein staining throughout the cytoplasm, providing support for cytosolic localization of PSP94 in the non-diseased prostate. This finding is particularly intriguing given accumulating evidence for an inflammatory, and thus possibly an infectious, contribution to prostate cancer [57].

INFLAMMATION AND PROSTATE CANCER

Similar to cancers with known inflammatory or infectious etiologies, inflammation is extremely common in the prostate [58–60]. Of relevance to prostate cancer causation, intraprostatic inflammation is also present in young men before the onset of prostate diseases [59], and is common in the peripheral zone [61], the zone at highest risk of prostate cancer development. Within this zone, inflammation tends to be observed near areas of proliferative atrophy (termed "proliferative inflammatory atrophy" lesions), which have been proposed as signatures of the "field effect" of prostate carcinogenesis (i.e., a field of cells with genomic alterations believed to predispose to prostate cancer), because a subset of these lesions share somatic DNA alterations with prostate cancer precursor lesions (high-grade prostatic intraepithelial neoplasia, HGPIN) and prostate adenocarcinomas, and because they have been observed at times in close proximity or transitioning into HGPIN and small adenocarcinomas [57]. This hypothesis is supported by findings from animal model studies, in which inflammation induced by various means has been shown to lead to epithelial hyperproliferation and atrophy, and occasionally dysplasia/PIN [57,62,63]. It is

also supported by findings from a recent observational study, in which a positive association was observed between intraprostatic inflammation and high-grade prostate cancer among men without indication for biopsy—thus where the positive association between PSA and inflammation should not have influenced findings (Gurel et al. [64]). Weaker or null associations were observed for low-grade prostate cancer in this same study [64] and in another smaller study [65]. Finally, positive associations were observed between tumor-associated intraprostatic inflammation (sometimes accompanied by focal atrophy) and subsequent prostate cancer recurrence or death in most [66–70], but not all [71,72], studies of prostate cancer patients. Thus together, these findings support a role for intraprostatic inflammation in prostate carcinogenesis.

Despite this evidence, responsible causes of asymptomatic intraprostatic inflammation have not been identified, although several possibilities have been proposed. These include urine reflux, which might induce either chemical or physical trauma; trapped spermatozoa; dietary factors, such as heterocyclic amines; estrogens; infectious agents, particularly those that ascend the urethra; or a combination of several of these factors. A break in tolerance to prostate antigens triggered by any of these factors has also been proposed [57]. However, irrespective of the type of proposed inflammatory cause(s)—infectious or otherwise— it must be very common to explain the high prevalence of asymptomatic intraprostatic inflammation [58–60] and prostate cancer precursor lesions [73].

INFECTIONS AND PROSTATE CANCER

Over the past few decades, many epidemiologic studies have investigated infections in relation to prostate cancer, focused primarily on sexually transmitted infections (STIs). Findings from several of these studies have been pooled with combined results suggesting a positive association between ever having had an STI and prostate cancer (OR = 1.44–1.48 [74,75]). However, as many of these studies were case–control in design with retrospective, self-reported assessment of STI history, the possibility of recall bias has been raised (i.e., prostate cancer cases may have been more likely to respond to STI questions truthfully than controls). This concern is supported by recent null cohort study findings for several of these same self-reported STIs [76]. On the other hand, accumulating positive findings for other STIs that tend to be asymptomatic and are thus better assessed by serology than by self-report, such as *Trichomonas vaginalis* and mycoplasma infections [76,77], provide further sup- port for an infectious contribution to prostate cancer risk. These STIs may also be more likely to establish persistent prostate infections than those assessed by self-report because of their frequent lack of symptoms and thus lack of treatment [76]. Recent epidemiologic and/or animal model-based findings for other infectious agents not typically considered to be sexually transmitted, such as *Escherichia coli* and *Propionibacterium acnes*, are also intriguing and warrant further study [78]. However, while each of these infectious leads is promising, none is yet conclusive. It is also possible that no single infectious agent is by itself responsible for prostate cancer risk, but that many may have the potential to contribute to prostate carcinogenesis, depending on their propensity to elicit prostatic inflammation and establish long-term prostate infections.

Given recently observed associations between *MSMB* variation and prostate cancer, as well as the recent discovery of fungicidal activity associated with PSP94 in low-calcium environments such as the cytosol of epithelial cells, we propose that intracellular fungal infections may also be good candidate infections for prostate carcinogenesis. An intracellular infectious etiology is also consistent with the finding of a greater ratio of cytotoxic/suppressor ($CD8^+$) T cells to helper/inducer ($CD4^+$) T cells in the intraepithelial compartment of the prostate than in the stroma [79–81], which Bostwick et al. [80] have proposed may represent the first line of defense against foreign luminal agents. As cytotoxic T cells are known to aid in clearing intracellular pathogens, such pathogens may be promising candidate causes of intraprostatic inflammation and prostate cancer. However, while many studies have examined viral and intracellular bacterial infections [77], very few studies— only one, to our knowledge [82]—have investigated fungal infections in relation to prostate cancer. This paucity of mycotic research is likely due to the low documented occurrence of symptomatic fungal prostate infections. For instance, although *Candida* species, *Aspergillus* species, *Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum*, and *Blastomyces dermatitidis* are possible causes of clinical prostatitis, the fraction of prostatitis cases caused by such infections is very low [83]. These species are also readily culturable; therefore, if they were common asymptomatic pathogens, they would likely have already been identified in at least one large previous study of prostate specimen culture [84].

While findings from this previous culture study make the possibility of a culturable fungal etiology unlikely, the possibility of a fastidious fungal candidate remains plausible. For instance, microsporidia (a phylum of fastidious intracellular fungi) are known to infect healthy individuals asymptomatically [85], some species have been detected in prostate specimens [86] and urine [87], and some are suspected of a sexual route of transmission [85,86,88]. However, no studies, to our knowledge, have investigated microsporidia species in relation to prostate cancer to date, although DNA primers are available for several of these species [89]. Therefore, these microsporidia species could be explored in relation to prostate cancer in future studies.

Beyond microsporidia, it is also possible that an as-yet-undiscovered, fastidious fungal species may be involved. While not specific to fungi, as early as 12 years ago, Strickler and Goedert [90] proposed a “yet unrecognized” sexually transmissible infectious etiology for prostate cancer. This hypothesis was based on the similarity between the low estimates of association for various STIs with prostate cancer and the low estimates of association for herpes simplex virus and other STIs with cervical cancer, which was eventually attributed to their frequent co-acquisition with human papillomaviruses, the actual causal agents of cervical cancer. While this hypothesis led to many viral and bacterial screens of prostate specimens [77], no studies, to our knowledge, screened for a broad spectrum of fungi. Such screens are possible, as demonstrated recently by Ghannoum et al. [91] who used molecular techniques to identify fungi in the oral cavity of healthy individuals; these authors found 85 fungal genera of which 11 were non-culturable. These same molecular techniques could be applied to prostate specimens. However, even the consensus primers used by Ghannoum et al. cannot detect all fungal phyla (for instance, these primers do not detect microsporidia or

Pneumocystis jiroveci). Therefore, newly developed techniques that can identify infectious agents from the entire tree of life (viruses, bacteria, protists, and fungi) should also be considered [92,93].

CONCLUSION

In summary, we propose a second mechanism to explain the consistent association between variation in *MSMB*, the gene that encodes PSP94, and prostate cancer risk [2]—in addition to PSP94's purported tumor suppression properties. Specifically, we propose that PSP94 may protect against prostate cancer by preventing or limiting an intracellular fungal (or possibly protistan) infection in the prostate, based on the recent discovery of PSP94's fungicidal activity in low-calcium environments, such as the cytosol of epithelial cells [29], and accumulating evidence suggesting a role for inflammation in prostate carcinogenesis [57,63]. While we have yet to test for the presence of such infectious agents in prostate specimens, some support for this idea comes from recent epidemiologic findings from the King County prostate cancer case–control study. This study observed a positive association between lifetime number of sexual partners, a marker of cumulative STI exposure, and prostate cancer among high-risk rs10993994 T allele carriers, but no association among C allele homozygotes, which produce the greatest amount of PSP94 [94]. Future studies should consider screening prostate specimens for fungi and protists, particularly fastidious ones, using the rapidly expanding number of molecular techniques capable of identifying infectious agents from the entire tree of life. These types of investigations are critical because the discovery of an infectious etiology of prostate cancer could have tremendous influence on rates of this common malignancy; such a discovery would offer the potential for primary prevention strategies using existing or newly developed anti-microbial therapies, such as pharmaceutical drugs targeting ergosterol.

Acknowledgments

Dr. Sutcliffe was funded by the Barnes-Jewish Hospital Foundation.

REFERENCES

1. Eeles RA, Olama AA, Benlloch S, Saunders EJ, Leongamornlert DA, Tymrakiewicz M, Ghoussaini M, Luccarini C, Dennis J, Jugurnauth-Little S, Dadaev T, Neal DE, Hamdy FC, Donovan JL, Muir K, Giles GG, Severi G, Wiklund F, Gronberg H, Haiman CA, Schumacher F, Henderson BE, Le Marchand L, Lindstrom S, Kraft P, Hunter DJ, Gapstur S, Chanock SJ, Berndt SI, Albanes D, Andriole G, Schleutker J, Weischer M, Canzian F, Riboli E, Key TJ, Travis RC, Campa D, Ingles SA, John EM, Hayes RB, Pharoah PD, Pashayan N, Khaw KT, Stanford JL, Ostrander EA, Signorello LB, Thibodeau SN, Schaid D, Maier C, Vogel W, Kibel AS, Cybulski C, Lubinski J, Cannon-Albright L, Brenner H, Park JY, Kaneva R, Batra J, Spurdle AB, Clements JA, Teixeira MR, Dicks E, Lee A, Dunning AM, Baynes C, Conroy D, Maranian MJ, Ahmed S, Govindasami K, Guy M, Wilkinson RA, Sawyer EJ, Morgan A, Dearnaley DP, Horwich A, Huddart RA, Khoo VS, Parker CC, Van As NJ, Woodhouse CJ, Thompson A, Dudderidge T, Ogden C, Cooper CS, Lophatananon A, Cox A, Southey MC, Hopper JL, English DR, Aly M, Adolfsson J, Xu J, Zheng SL, Yeager M, Kaaks R, Diver WR, Gaudet MM, Stern MC, Corral R, Joshi AD, Shahabi A, Wahlfors T, Tammela TL, Auvinen A, Virtamo J, Klarskov P, Nordestgaard BG, Roder MA, Nielsen SF, Bojesen SE, Siddiq A, Fitzgerald LM, Kolb S, Kwon EM, Karyadi DM, Blot WJ, Zheng W, Cai Q, McDonnell SK, Rinckleb AE, Drake B, Colditz G, Wokolorczyk D, Stephenson RA, Teerlink C, Muller H, Rothenbacher D, Sellers TA, Lin HY, Slavov C, Mitev V, Lose F,

Srinivasan S, Maia S, Paulo P, Lange E, Cooney KA, Antoniou AC, Vincent D, Bacot F, Tessier DC, Consortium P, KoteJarai Z, Easton DF. Initiative CO-CRUG-E, Australian Prostate Cancer B, Oncology UKGPCSCBAoUSSo, Collaborators, UKPS. Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. Nat Genet. 2013; 45(4):385–391. 91e1–91e2. [PubMed: 23535732]

2. Goh CL, Schumacher FR, Easton D, Muir K, Henderson B, Kote-Jarai Z, Eeles RA. Genetic variants associated with predisposition to prostate cancer and potential clinical implications. J Intern Med. 2012; 271(4):353–365. Epub 2012/02/09. eng. [PubMed: 22308973]
3. Lou H, Yeager M, Li H, Bosquet JG, Hayes RB, Orr N, Yu K, Hutchinson A, Jacobs KB, Kraft P, Wacholder S, Chatterjee N, Feigelson HS, Thun MJ, Diver WR, Albanes D, Virtamo J, Weinstein S, Ma J, Gaziano JM, Stampfer M, Schumacher FR, Giovannucci E, Cancel-Tassin G, Cussenot O, Valeri A, Andriole GL, Crawford ED, Anderson SK, Tucker M, Hoover RN, Fraumeni JF Jr, Thomas G, Hunter DJ, Dean M, Chanock SJ. Fine mapping and functional analysis of a common variant in MSMB on chromosome 10q11.2 associated with prostate cancer susceptibility. Proc Natl Acad Sci USA. 2009; 106(19):7933–7938. [PubMed: 19383797]
4. Kote-Jarai Z, Easton DF, Stanford JL, Ostrander EA, Schleutker J, Ingles SA, Schaid D, Thibodeau S, Dork T, Neal D, Donovan J, Hamdy F, Cox A, Maier C, Vogel W, Guy M, Muir K, Lophatananon A, Kedda MA, Spurdle A, Steginga S, John EM, Giles G, Hopper J, Chappuis PO, Hutter P, Foulkes WD, Hamel N, Salinas CA, Koopmeiners JS, Karyadi DM, Johanneson B, Wahlfors T, Tammela TL, Stern MC, Corral R, McDonnell SK, Schurmann P, Meyer A, Kuefer R, Leongamornlert DA, Tymrakiewicz M, Liu JF, O'Mara T, Gardiner RA, Aitken J, Joshi AD, Severi G, English DR, Southey M, Edwards SM, Al Olama AA, Consortium P, Eeles RA. Multiple novel prostate cancer predisposition loci confirmed by an international study: The PRACTICAL Consortium. Cancer Epidemiol Biomarkers Prev. 2008; 17(8):2052–2061. [PubMed: 18708398]
5. Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, Orr N, Yu K, Chatterjee N, Welch R, Hutchinson A, Crenshaw A, Cancel-Tassin G, Staats BJ, Wang Z, Gonzalez-Bosquet J, Fang J, Deng X, Berndt SI, Calle EE, Feigelson HS, Thun MJ, Rodriguez C, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Giovannucci E, Willett WC, Cussenot O, Valeri A, Andriole GL, Crawford ED, Tucker M, Gerhard DS, Fraumeni JF Jr, Hoover R, Hayes RB, Hunter DJ, Chanock SJ. Multiple loci identified in a genome-wide association study of prostate cancer. Nat Genet. 2008; 40(3):310–315. [PubMed: 18264096]
6. Eeles RA, Kote-Jarai Z, Giles GG, Olama AA, Guy M, Jugurnauth SK, Mulholland S, Leongamornlert DA, Edwards SM, Morrison J, Field HI, Southey MC, Severi G, Donovan JL, Hamdy FC, Dearnaley DP, Muir KR, Smith C, Bagnato M, Ardern-Jones AT, Hall AL, O'Brien LT, Gehr-Swain BN, Wilkinson RA, Cox A, Lewis S, Brown PM, Jhavar SG, Tymrakiewicz M, Lophatananon A, Bryant SL, Horwich A, Huddart RA, Khoo VS, Parker CC, Woodhouse CJ, Thompson A, Christmas T, Ogden C, Fisher C, Jamieson C, Cooper CS, English DR, Hopper JL, Neal DE, Easton DF. Multiple newly identified loci associated with prostate cancer susceptibility. Nat Genet. 2008; 40(3):316–321. [PubMed: 18264097]
7. Chang BL, Spangler E, Gallagher S, Haiman CA, Henderson B, Isaacs W, Benford ML, Kidd LR, Cooney K, Strom S, Ingles SA, Stern MC, Corral R, Joshi AD, Xu J, Giri VN, Rybicki B, Neslund-Dudas C, Kibel AS, Thompson IM, Leach RJ, Ostrander EA, Stanford JL, Witte J, Casey G, Eeles R, Hsing AW, Chanock S, Hu JJ, John EM, Park J, Stefflova K, Zeigler-Johnson C, Rebbeck TR. Validation of genome-wide prostate cancer associations in men of African descent. Cancer Epidemiol Biomarkers Prev. 2011; 20(1):23–32. [PubMed: 21071540]
8. Chang BL, Cramer SD, Wiklund F, Isaacs SD, Stevens VL, Sun J, Smith S, Pruett K, Romero LM, Wiley KE, Kim ST, Zhu Y, Zhang Z, Hsu FC, Turner AR, Adolfsson J, Liu W, Kim JW, Duggan D, Carpten J, Zheng SL, Rodriguez C, Isaacs WB, Gronberg H, Xu J. Fine mapping association study and functional analysis implicate a SNP in MSMB at 10q11 as a causal variant for prostate cancer risk. Hum Mol Genet. 2009; 18(7):1368–1375. [PubMed: 19153072]
9. Camp NJ, Farnham JM, Wong J, Christensen GB, Thomas A, Cannon-Albright LA. Replication of the 10q11 and Xp11 prostate cancer risk variants: Results from a Utah pedigree-based study. Cancer Epidemiol Biomarkers Prev. 2009; 18(4):1290–1294. [PubMed: 19336566]
10. Gudmundsson J, Sulem P, Gudbjartsson DF, Blondal T, Gylfason A, Agnarsson BA, Benediktsdottir KR, Magnusdottir DN, Orlygsdottir G, Jakobsdottir M, Stacey SN, Sigurdsson A, Wahlfors T, Tammela T, Breyer JP, McReynolds KM, Bradley KM, Saez B, Godino J, Navarrete

S, Fuertes F, Murillo L, Polo E, Aben KK, van Oort IM, Suarez BK, Helfand BT, Kan D, Zanon C, Frigge ML, Kristjansson K, Gulcher JR, Einarsson GV, Jonsson E, Catalona WJ, Mayordomo JI, Kiemeney LA, Smith JR, Schleutker J, Barkardottir RB, Kong A, Thorsteinsdottir U, Rafnar T, Stefansson K. Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility. Nat Genet. 2009; 41(10):1122–1126. [PubMed: 19767754]

11. Waters KM, Le Marchand L, Kolonel LN, Monroe KR, Stram DO, Henderson BE, Haiman CA. Generalizability of associations from prostate cancer genome-wide association studies in multiple populations. Cancer Epidemiol Biomarkers Prev. 2009; 18(4):1285–1289. [PubMed: 19318432]
12. Wiklund F, Zheng SL, Sun J, Adami HO, Lilja H, Hsu FC, Stattin P, Adolfsson J, Cramer SD, Duggan D, Carpten JD, Chang BL, Isaacs WB, Gronberg H, Xu J. Association of reported prostate cancer risk alleles with PSA levels among men without a diagnosis of prostate cancer. Prostate. 2009; 69(4):419–427. [PubMed: 19116992]
13. Xu B, Wang J, Tong N, Mi Y, Min Z, Tao J, Li P, Cheng G, Li J, Wang M, Tang J, Song N, Zhang Z, Zhang W, Wu H, Hua L, Feng N. A functional polymorphism in MSMB gene promoter is associated with prostate cancer risk and serum MSMB expression. Prostate. 2010; 70(10):1146–1152. [PubMed: 20333697]
14. Xu Z, Bensen JT, Smith GJ, Mohler JL, Taylor JA. GWAS SNP replication among African American and European American men in the North Carolina-Louisiana prostate cancer project (PCaP). Prostate. 2011; 71(8):881–891. [PubMed: 21456070]
15. Pomerantz MM, Shrestha Y, Flavin RJ, Regan MM, Penney KL, Mucci LA, Stampfer MJ, Hunter DJ, Chanock SJ, Schafer EJ, Chan JA, Tabernero J, Baselga J, Richardson AL, Loda M, Oh WK, Kantoff PW, Hahn WC, Freedman ML. Analysis of the 10q11 cancer risk locus implicates MSMB and NCOA4 in human prostate tumorigenesis. PLoS Genet. 2010; 6(11):e1001204. [PubMed: 21085629]
16. FitzGerald LM, Zhang X, Kolb S, Kwon EM, Liew YC, Hurtado- Coll A, Knudsen BS, Ostrander EA, Stanford JL. Investigation of the relationship between prostate cancer and MSMB and NCOA4 genetic variants and protein expression. Hum Mutat. 2012; 34(1):149–156. [PubMed: 22887727]
17. Xu X, Valtonen-Andre C, Savblom C, Hallden C, Lilja H, Klein RJ. Polymorphisms at the microseminoprotein-beta locus associated with physiologic variation in beta-microseminoprotein and prostate-specific antigen levels. Cancer Epidemiol Biomarkers Prev. 2010; 19(8):2035–2042. [PubMed: 20696662]
18. Gudmundsson J, Besenbacher S, Sulem P, Gudbjartsson DF, Olafsson I, Arinbjarnarson S, Agnarsson BA, Benediktsdottir KR, Isaksson HJ, Kostic JP, Gudjonsson SA, Stacey SN, Gylfason A, Sigurdsson A, Holm H, Bjornsdottir US, Eyjolfsson GI, Navarrete S, Fuertes F, Garcia-Prats MD, Polo E, Checherita IA, Jinga M, Badea P, Aben KK, Schalken JA, van Oort IM, Sweep FC, Helfand BT, Davis M, Donovan JL, Hamdy FC, Kristjansson K, Gulcher JR, Masson G, Kong A, Catalona WJ, Mayordomo JI, Geirsson G, Einarsson GV, Barkardottir RB, Jonsson E, Jinga V, Mates D, Kiemeney LA, Neal DE, Thorsteinsdottir U, Rafnar T, Stefansson K. Genetic correction of PSA values using sequence variants associated with PSA levels. Sci Transl Med. 2010; 2(62): 62ra–92.
19. Siegel R, Naishadham D, Jemal A. Cancer statistics 2012 CA. Cancer J Clin. 2012; 62(1):10–29.
20. Lilja H, Abrahamsson PA. Three predominant proteins secreted by the human prostate gland. Prostate. 1988; 12(1):29–38. [PubMed: 3347596]
21. Seidah NG, Arbatti NJ, Rochemont J, Sheth AR, Chretien M. Complete amino acid sequence of human seminal plasma beta-inhibin. Prediction of post Gln-Arg cleavage as a maturation site. FEBS Lett. 1984; 175(2):349–355. Epub 1984/10/01. eng. [PubMed: 6434350]
22. Kohan S, Froysa B, Cederlund E, Fairwell T, Lerner R, Johansson J, Khan S, Ritzen M, Jornvall H, Cekan S, Diczfalusy E. Peptides of postulated inhibin activity. Lack of in vitro inhibin activity of a 94-residue peptide isolated from human seminal plasma, and of a synthetic replicate of its C-terminal 28-residue segment. FEBS Lett. 1986; 199(2):242–248. Epub 1986/04/21. eng. [PubMed: 3084296]
23. Gordon WL, Liu WK, Akiyama K, Tsuda R, Hara M, Schmid K, Ward DN. Beta-microseminoprotein (beta-MSP) is not an inhibin. Biol Reprod. 1987; 36(4):829–835. Epub 1987/05/01. eng. [PubMed: 3109514]

24. Dube JY, Frenette G, Paquin R, Chapdelaine P, Tremblay J, Tremblay RR, Lazure C, Seidah N, Chretien M. Isolation from human seminal plasma of an abundant 16-kDa protein originating from the prostate, its identification with a 94-residue peptide originally described as beta-inhibin. J Androl. 1987; 8(3):182–189. Epub 1987/05/01. eng. [PubMed: 3610813]
25. Akiyama K, Yoshioka Y, Schmid K, Offner GD, Troxler RF, Tsuda R, Hara M. The amino acid sequence of human betamicroseminoprotein. Biochim Biophys Acta. 1985; 829(2):288–294. Epub 1985/06/10. eng. [PubMed: 3995056]
26. Anahi Franchi N, Avendano C, Molina RI, Tissera AD, Maldonado CA, Oehninger S, Coronel CE. Beta-microseminoprotein in human spermatozoa and its potential role in male fertility. Reproduction. 2008; 136(2):157–166. [PubMed: 18469041]
27. Whitaker HC, Kote-Jarai Z, Ross-Adams H, Warren AY, Burge J, George A, Bancroft E, Jhavar S, Leongamornlert D, Tymrakiewicz M, Saunders E, Page E, Mitra A, Mitchell G, Lindeman GJ, Evans DG, Blanco I, Mercer C, Rubinstein WS, Clowes V, Douglas F, Hodgson S, Walker L, Donaldson A, Izatt L, Dorkins H, Male A, Tucker K, Stapleton A, Lam J, Kirk J, Lilja H, Easton D, Cooper C, Eeles R, Neal DE. The rs10993994 risk allele for prostate cancer results in clinically relevant changes in microseminoprotein-beta expression in tissue and urine. PLoS ONE. 2010; 5(10):e13363. [PubMed: 20967219]
28. Garde S, Sheth A, Porter AT, Pienta KJ. Effect of prostatic inhibin peptide (PIP) on prostate cancer cell growth in vitro and in vivo. Prostate. 1993; 22(3):225–233. [PubMed: 8488155]
29. Hagerwall AME, Rydengard V, Fernlund P, Morgelin M, Baumgarten M, Cole AM, Malmsten M, Kragelund BB, Sorensen OE. Beta-microseminoprotein endows post coital seminal plasma with potent candidacidal activity by a calcium- and pH-dependent mechanism. PLoS Pathog. 2012; 8(4):e1002625. [PubMed: 22496651]
30. Lazure C, Villemure M, Gauthier D, Naude RJ, Mbikay M. Characterization of ostrich (*Struthio camelus*) beta-microseminoprotein (MSP): Identification of homologous sequences in EST databases and analysis of their evolution during speciation. Protein Sci. 2001; 10(11):2207–2218. Epub 2001/10/18. eng. [PubMed: 11604528]
31. Lokeshwar BL, Block NL. Isolation of a prostate carcinoma cell proliferation-inhibiting factor from human seminal plasma and its similarity to transforming growth factor beta. Cancer Res. 1992; 52(20):5821–5825. Epub 1992/10/15. eng. [PubMed: 1394210]
32. Lokeshwar BL, Hurkadli KS, Sheth AR, Block NL. Human prostatic inhibin suppresses tumor growth and inhibits clonogenic cell survival of a model prostatic adenocarcinoma, the dunning R3327G rat tumor. Cancer Res. 1993; 53(20):4855–4859. [PubMed: 8402673]
33. Garde SV, Basrur VS, Li L, Finkelman MA, Krishan A, Wellham L, Ben-Josef E, Haddad M, Taylor JD, Porter AT, Tang DG. Prostate secretory protein (PSP94) suppresses the growth of androgen-independent prostate cancer cell line (PC3) and xenografts by inducing apoptosis. Prostate. 1999; 38(2):118–125. [PubMed: 9973097]
34. Shukeir N, Arakelian A, Kadhim S, Garde S, Rabbani SA. Prostate secretory protein PSP-94 decreases tumor growth and hypercalcemia of malignancy in a syngenic in vivo model of prostate cancer. Cancer Res. 2003; 63(9):2072–2078. [PubMed: 12727822]
35. Shukeir N, Arakelian A, Chen G, Garde S, Ruiz M, Panchal C, Rabbani SA. A synthetic 15-mer peptide (PCK3145) derived from prostate secretory protein can reduce tumor growth, experimental skeletal metastases, and malignancy-associated hypercalcemia. Cancer Res. 2004; 64(15):5370–5377. [PubMed: 15289344]
36. Cadieux PA, Mikolajczak SA, Reeves J, Strathdee C, Reid G, Panchal CJ, Clarke MW. Rat PSP94 inhibits the growth and viability of the rat adenocarcinoma cell line PAIII in vitro. Cancer Invest. 2006; 24(3):246–255. [PubMed: 16809150]
37. Pathak BR, Breed AA, Nakhawa VH, Jagtap DD, Mahale SD. Growth inhibition mediated by PSP94 or CRISP-3 is prostate cancer cell line specific. Asian J Androl. 2010; 12(5):677–689. Epub 2010/08/03. eng. [PubMed: 20676114]
38. Garde S, Fraser JE, Nematpoor N, Pollex R, Morin C, Forte A, Rabbani S, Panchal C, Gupta MB. Cloning, expression, purification and functional characterization of recombinant human PSP94. Protein Expr Purif. 2007; 54(2):193–203. Epub 2007/05/01. eng. [PubMed: 17468008]
39. Lamy S, Ruiz MT, Wisniewski J, Garde S, Rabbani SA, Panchal C, Wu JJ, Annabi B. A prostate secretory protein 94-derived synthetic peptide PCK3145 inhibits VEGF signalling in endothelial

cells: Implication in tumor angiogenesis. Int J Cancer. 2006; 118(9):2350–2358. [PubMed: 16331603]

40. Hyakutake H, Sakai H, Yogi Y, Tsuda R, Minami Y, Yushita Y, Kanetake H, Nakazono I, Saito Y. Beta-microseminoprotein immunoreactivity as a new prognostic indicator of prostatic carcinoma. Prostate. 1993; 22(4):347–355. [PubMed: 8497429]
41. Tsurusaki T, Koji T, Sakai H, Kanetake H, Nakane PK, Saito Y. Cellular expression of beta-microseminoprotein (β-MSP) mRNA and its protein in untreated prostate cancer. Prostate. 1998; 35(2):109–116. [PubMed: 9568674]
42. Sakai H, Tsurusaki T, Kanda S, Koji T, Xuan JW, Saito Y. Prognostic significance of beta-microseminoprotein mRNA expression in prostate cancer. Prostate. 1999; 38(4):278–284. [PubMed: 10075007]
43. Bjartell AS, Al-Ahmadie H, Serio AM, Eastham JA, Eggener SE, Fine SW, Udby L, Gerald WL, Vickers AJ, Lilja H, Reuter VE, Scardino PT. Association of cysteine-rich secretory protein 3 and beta-microseminoprotein with outcome after radical prostatectomy. Clin Cancer Res. 2007; 13(14):4130–4138. [PubMed: 17634540]
44. Imasato Y, Xuan JW, Sakai H, Izawa JI, Saito Y, Chin JL, Moussa M. PSP94 expression after androgen deprivation therapy: A comparative study with prostate specific antigen in benign prostate and prostate cancer. J Urol. 2000; 164(5):1819–1824. [PubMed: 11025776]
45. Girvan AR, Chang P, van Huizen I, Moussa M, Xuan JW, Stitt L, Chin JL, Yamasaki Y, Izawa JI. Increased intratumoral expression of prostate secretory protein of 94 amino acids predicts for worse disease recurrence and progression after radical prostatectomy in patients with prostate cancer. Urology. 2005; 65(4):719–723. [PubMed: 15833515]
46. Porter AT, Ben-Josef E. Humoral mechanisms in prostate cancer: A role for FSH. Urol Oncol. 2001; 6(4):131–138. [PubMed: 11418318]
47. Rinckleb AE, Surowy HM, Luedeke M, Varga D, Schrader M, Hoegel J, Vogel W, Maier C. The prostate cancer risk locus at 10q11 is associated with DNA repair capacity. DNA Repair. 2012; 11(8):693–701. [PubMed: 22677538]
48. Whitaker HC, Warren AY, Eeles R, Kote-Jarai Z, Neal DE. The potential value of microseminoprotein-beta as a prostate cancer biomarker and therapeutic target. Prostate. 2010; 70(3):333–340. [PubMed: 19790236]
49. Annabi B, Currie JC, Bouzeghrane M, Dulude H, Daigneault L, Garde S, Rabbani SA, Panchal C, Wu JJ, Beliveau R. Contribution of the 37-kDa laminin receptor precursor in the anti-metastatic PSP94-derived peptide PCK3145 cell surface binding. Biochem Biophys Res Commun. 2006; 346(1):358–366. Epub 2006/06/09. eng. [PubMed: 16759641]
50. Annabi B, Bouzeghrane M, Currie JC, Hawkins R, Dulude H, Daigneault L, Ruiz M, Wisniewski J, Garde S, Rabbani SA, Panchal C, Wu JJ, Beliveau R. A PSP94-derived peptide PCK3145 inhibits MMP-9 secretion and triggers CD44 cell surface shedding: Implication in tumor metastasis. Clin Exp Metastasis. 2005; 22(5):429–439. [PubMed: 16283486]
51. LaTulippe E, Satagopan J, Smith A, Scher H, Scardino P, Reuter V, Gerald WL. Comprehensive gene expression analysis of prostate cancer reveals distinct transcriptional programs associated with metastatic disease. Cancer Res. 2002; 62(15):4499–4506. [PubMed: 12154061]
52. Stanbrough M, Bubley GJ, Ross K, Golub TR, Rubin MA, Penning TM, Febbo PG, Balk SP. Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer. Cancer Res. 2006; 66(5):2815–2825. [PubMed: 16510604]
53. Vanaja DK, Cheville JC, Iturria SJ, Young CY. Transcriptional silencing of zinc finger protein 185 identified by expression profiling is associated with prostate cancer progression. Cancer Res. 2003; 63(14):3877–3882. Epub 2003/07/23. eng. [PubMed: 12873976]
54. Clapham DE. Calcium signaling. Cell. 2007; 131(6):1047–1058. Epub 2007/12/18. eng. [PubMed: 18083096]
55. Ito Y, Tsuda R, Kimura H. Ultrastructural localizations of betamicroseminoprotein, a prostate-specific antigen, in human prostate and sperm: Comparison with gamma-seminoprotein, another prostate-specific antigen. J Lab Clin Med. 1989; 114(3):272–277. [PubMed: 2475560]
56. Doctor VM, Sheth AR, Simha MM, Arbatti NJ, Aaveri JP, Sheth NA. Studies on immunocytochemical localization of inhibin-like material in human prostatic tissue: Comparison

of its distribution in normal, benign and malignant prostates. Br J Cancer. 1986; 53(4):547–554. [PubMed: 2423106]

57. De Marzo AM, Platz EA, Sutcliffe S, Xu J, Gronberg H, Drake CG, Nakai Y, Isaacs WB, Nelson WG. Inflammation in prostate carcinogenesis. Nat Rev Cancer. 2007; 7(4):256–269. [PubMed: 17384581]
58. Kohnen PW, Drach GW. Patterns of inflammation in prostatic hyperplasia: A histologic and bacteriologic study. J Urol. 1979; 121(6):755–760. Epub 1979/06/01. eng. [PubMed: 88527]
59. Bennett B, Culberson D, Petty C, Gardner W. Histopathology of prostatitis. J Urol. 1990; 143:265A.
60. Blumenfeld W, Tucci S, Narayan P. Incidental lymphocytic prostatitis. Selective involvement with nonmalignant glands. Am J Surg Pathol. 1992; 16(10):975–981. Epub 1992/10/01. eng. [PubMed: 1415905]
61. Nickel JC, True LD, Krieger JN, Berger RE, Boag AH, Young ID. Consensus development of a histopathological classification system for chronic prostatic inflammation. BJU Int. 2001; 87(9): 797–805. Epub 2001/06/20. eng. [PubMed: 11412216]
62. Bernoulli J, Yatkin E, Laakso A, Anttinen M, Bosland M, Vega K, Kallajoki M, Santti R, Pylkkanen L. Histopathological evidence for an association of inflammation with ductal pin-like lesions but not with ductal adenocarcinoma in the prostate of the noble rat. Prostate. 2008; 68(7): 728–739. [PubMed: 18302197]
63. Sfanos KS, De Marzo AM. Prostate cancer and inflammation: The evidence. Histopathology. 2012; 60(1):199–215. [PubMed: 22212087]
64. Gurel B, Lucia MS, Thompson IM Jr, Goodman PJ, Tangen CM, Kristal AR, Parnes HL, Lippman SM, Sutcliffe S, Peskoe SB, Drake CG, Nelson WG, De Marzo AM, Platz EA. Chronic inflammation in benign prostate tissue is associated with higher-grade prostate cancer in the placebo arm of the Prostate Cancer Prevention Trial. Submitted.
65. Delongchamps NB, de la Roza G, Chandan V, Jones R, Sunheimer R, Threatte G, Jumbelic M, Haas GP. Evaluation of prostatitis in autopsied prostates—Is chronic inflammation more associated with benign prostatic hyperplasia or cancer? J Urol. 2008; 179(5):1736–1740. [PubMed: 18343414]
66. Irani J, Goujon JM, Ragni E, Peyrat L, Hubert J, Saint F, Mottet N. High-grade inflammation in prostate cancer as a prognostic factor for biochemical recurrence after radical prostatectomy. Pathologist Multi Center Study Group. Urology. 1999; 54(3):467–472. [PubMed: 10475356]
67. Karja V, Aaltomaa S, Lipponen P, Isotalo T, Talja M, Mokka R. Tumour-infiltrating lymphocytes: A prognostic factor of PSA-free survival in patients with local prostate carcinoma treated by radical prostatectomy. Anticancer Res. 2005; 25(6C):4435–4438. [PubMed: 16334122]
68. Davidsson S, Fiorentino M, Andren O, Fang F, Mucci LA, Varenhorst E, Fall K, Rider JR. Inflammation, focal atrophic lesions, and prostatic intraepithelial neoplasia with respect to risk of lethal prostate cancer. Cancer Epidemiol Biomarkers Prev. 2011; 20(10):2280–2287. [PubMed: 21953116]
69. Nonomura N, Takayama H, Nakayama M, Nakai Y, Kawashima A, Mukai M, Nagahara A, Aozasa K, Tsujimura A. Infiltration of tumour-associated macrophages in prostate biopsy specimens is predictive of disease progression after hormonal therapy for prostate cancer. BJU Int. 2011; 107(12):1918–1922. [PubMed: 21044246]
70. Nonomura N, Takayama H, Nishimura K, Oka D, Nakai Y, Shiba M, Tsujimura A, Nakayama M, Aozasa K, Okuyama A. Decreased number of mast cells infiltrating into needle biopsy specimens leads to a better prognosis of prostate cancer. Br J Cancer. 2007; 97(7):952–956. [PubMed: 17848955]
71. Vesalainen S, Lipponen P, Talja M, Syrjanen K. Histological grade, perineural infiltration, tumour-infiltrating lymphocytes and apoptosis as determinants of long-term prognosis in prostatic adenocarcinoma. Eur J Cancer. 1994; 30A(12):1797–1803. [PubMed: 7880609]
72. Shimura S, Yang G, Ebara S, Wheeler TM, Frolov A, Thompson TC. Reduced infiltration of tumor-associated macrophages in human prostate cancer: Association with cancer progression. Cancer Res. 2000; 60(20):5857–5861. [PubMed: 11059783]

73. Powell IJ, Bock CH, Ruterbusch JJ, Sakr W. Evidence supports a faster growth rate and/or earlier transformation to clinically significant prostate cancer in black than in white American men, and influences racial progression and mortality disparity. J Urol. 2010; 183(5):1792–1796. Epub 2010/03/20. eng. [PubMed: 20299055]
74. Dennis LK, Dawson DV. Meta-analysis of measures of sexual activity and prostate cancer. Epidemiology. 2002; 13(1):72–79. [PubMed: 11805589]
75. Taylor ML, Mainous AG III, Wells BJ. Prostate cancer and sexually transmitted diseases: A meta-analysis. Family Med. 2005; 37(7):506–512.
76. Sutcliffe S. Sexually transmitted infections and risk of prostate cancer: Review of historical and emerging hypotheses. Future Oncol. 2010; 6(8):1289–1311. [PubMed: 20799875]
77. Hrbacek J, Urban M, Hamsikova E, Tachezy R, Heracek J. Thirty years of research on infection and prostate cancer: No conclusive evidence for link. A systematic review. Urol Oncol. 2012; 31(7):951–965. [PubMed: 22459691]
78. Sfanos KS, Sauvageot J, Fedor HL, Dick JD, De Marzo AM, Isaacs WB. A molecular analysis of prokaryotic and viral DNA sequences in prostate tissue from patients with prostate cancer indicates the presence of multiple and diverse microorganisms. Prostate. 2008; 68(3):306–320. [PubMed: 18163428]
79. el-Demiry MI, Hargreave TB, Busuttil A, James K, Ritchie AW, Chisholm GD. Lymphocyte sub-populations in the male genital tract. Br J Urol. 1985; 57(6):769–774. Epub 1985/12/01. eng. [PubMed: 3910154]
80. Bostwick DG, de la Roza G, Dundore P, Corica FA, Iczkowski KA. Intraepithelial and stromal lymphocytes in the normal human prostate. Prostate. 2003; 55(3):187–193. Epub 2003/04/15. eng. [PubMed: 12692784]
81. McClinton S, Miller ID, Eremin O. An immunohistochemical characterisation of the inflammatory cell infiltrate in benign and malignant prostatic disease. Br J Cancer. 1990; 61(3):400–403. Epub 1990/03/01. eng. [PubMed: 1691655]
82. Bergh J, Marklund I, Gustavsson C, Wiklund F, Gronberg H, Allard A, Alexeyev O, Elgh F. No link between viral findings in the prostate and subsequent cancer development. Br J Cancer. 2007; 96(1):137–139. [PubMed: 17117176]
83. Wise GJ, Shteynshlyuger A. How to diagnose and treat fungal infections in chronic prostatitis. Curr Urol Rep. 2006; 7(4):320–328. [PubMed: 16930504]
84. De la Rosette J, Hubregtse M, Meuleman E, Stolk-Engelaar M, Debruyne F. Diagnosis and treatment of 409 patients with prostatitis syndromes. Urology. 1993; 41(4):301–307. [PubMed: 8470312]
85. Didier ES, Weiss LM. Microsporidiosis: Not just in AIDS patients. Curr Opin Infect Dis. 2011; 24(5):490. [PubMed: 21844802]
86. Weber R, Bryan RT, Schwartz DA, Owen RL. Human microsporidial infections. Clin Microbiol Rev. 1994; 7(4):426. [PubMed: 7834600]
87. Sak B, Kvá M, Kučerová Z, Květoňová D, Saková K. Latent microsporidial infection in immunocompetent individuals—A longitudinal study. PLoS Negl Trop Dis. 2011; 5(5):e1162. [PubMed: 21629721]
88. Birthistle K, Moore P. Microsporidia: A new sexually transmissable cause of urethritis *Microsporidia* are worldwide ubiquitous intra. Genitourin Med. 1996; 72:445–452. [PubMed: 9038646]
89. Ghosh K, Weiss LM. Molecular diagnostic tests for microsporidia. Interdiscip Perspect Infect Dis. 2009; 2009:926521. Epub 2009/ 08/07. eng. [PubMed: 19657457]
90. Strickler HD, Goedert JJ. Sexual behavior and evidence for an infectious cause of prostate cancer. Epidemiol Rev. 2001; 23(1):144–151. [PubMed: 11588840]
91. Ghannoum MA, Jurevic RJ, Mukherjee PK, Cui F, Sikaroodi M, Naqvi A, Gillevet PM. Characterization of the oral fungal microbiome (mycobiome) in healthy individuals. PLoS Pathog. 2010; 6(1):e1000713. [PubMed: 20072605]
92. Lipkin WI. Microbe hunting. Microbiol Mol Biol Rev. 2010; 74(3):363–377. [PubMed: 20805403]

93. Kostic AD, Ojesina AI, Pedamallu CS, Jung J, Verhaak RG, Getz G, Meyerson M. PathSeq: Software to identify or discover microbes by deep sequencing of human tissue. Nat Biotechnol. 2011; 29(5):393–396. Epub 2011/05/10. eng. [PubMed: 21552235]

94. Stott-Miller M, Wright JL, Stanford JL. MSMB gene variant alters the association between prostate cancer and number of sexual partners. Prostate. 2013; 73(16):1803–1809. [PubMed: 24037734]