Correlation of Hepatitis C and Prostate Cancer, Inverse Correlation of Basal Cell Hyperplasia or Prostatitis and Epidemic Syphilis of Unknown Duration

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ABSTRACT

Purpose: The accuracy of prostate specific antigen (PSA) to detect prostate cancer has not yet been determined. Autopsy evidence suggests one-third of men have evidence of prostate cancer. Correlation between prostate cancer and sexually transmitted infection is indeterminate.

Materials and Methods: A retrospective database was created of all men who underwent transrectal ultrasound guided prostate biopsy over 3 years. Men were 49% African or African Caribbean, and 51% Central or South American. Information about prostate specific antigen, cholesterol, hepatitis A, B and C, human immunodeficiency virus, syphilis, tuberculin skin testing and histology were collected.

Results: Hepatitis C antibody detection correlated with prostate cancer OR 11.2 (95% CI 3.0 to 72.4). The odds of prostate cancer increased annually (p = 0.0003). However, no correlation was found between prostate cancer and the following: PSA, biopsy date, repeat biopsy, more than 12 cores at biopsy, total cholesterol, high density lipoprotein, triglycerides, low density lipoprotein, risk measure reported with free and total PSA, hepatitis B surface antibody, high grade prostatic intraepithelial neoplasia or atypical small acinar proliferation. Histologic prostatitis and basal cell hyperplasia were inversely correlated with prostate cancer. Syphilis of unknown duration occurred in 17% of men with indeterminate correlation to prostate cancer.

Conclusion: In inner city men of African and African-Caribbean, or Central and South American descent, prostate specific antigen levels did not correlate with prostate cancer. Hepatitis C antibody detection correlates significantly with prostate cancer. One prostate biopsy is sufficient to diagnose statistically significant prostate cancer. Histologic prostatitis and basal cell hyperplasia decrease odds of prostate cancer. Atypical small acinar proliferation may not correlate to prostate cancer and is pending further investigation. Men should be screened for epidemic syphilis of unknown duration.

Key words: prostatic neoplasm; hepatitis c antibodies; biopsy; prostate; syphilis; prostate specific antigen
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INTRODUCTION

Background: The second leading cause of cancer death in men is prostate cancer (1). Prostate-specific antigen (PSA) testing, digital rectal examina-tion and family history are the mainstays of screening (2). The accuracy of PSA to detect prostate cancer has not been determined (2-9). Combining digital rectal examination with PSA testing has not been shown to increase survival (10). Autopsy evidence suggests

nearly one-third of men have evidence of prostate cancer of unknown clinical significance (11). There are indeterminate correlations between prostate cancer and sexually transmitted infections (12).

Objectives: A retrospective review was conducted on all men who underwent transrectal ultrasound guided prostate biopsy (TRPB) at an inner city hospital over 3 years to identify potential risk factors for prostate cancer and improve selection criteria for TRPB.

MATERIALS AND METHODS

A retrospective database was created of all men who underwent transrectal TRPB at Lincoln Medical and Mental Health Center from January 1, 2007, through December 31, 2009. The cross-sectional study "Risks, Benefits and Selection Criteria for Transrectal Ultrasound Guided Prostate Biopsy: A Study of Men in the Bronx Community", was approved by the Institutional Review Board. According to 2006 statistics, the patient population consisted of approximately 49% African or African Caribbean, and 51% Central or South American patients. Information about PSA, cholesterol, hepatitis A, B and C, human immunodeficiency virus (HIV), syphilis, tuberculin skin testing and histology were collected. Histology specimens suspicious for or containing adenocarcinoma underwent additional central pathology review at Memorial Sloan-Kettering Cancer Center. Completeness and accuracy of data entry into the database was ensured by double data entry and follow-up comparison with additional random checks. Receiver operating and skill curve analysis (ROC) were used to interpret PSA data. Skill curves were used to assess PSA for optimal diagnosis cut-off. Skill measure compared the diagnostic ability of PSA beyond random guessing. Skill-based cut-off was equivalent to the cut-off indicated by optimizing posterior odds in accordance with Bayesian decision theory. Confidence intervals for the cut-off point were constructed (13,14). Chi-squared analysis was used to interpret serologic data. Standard statistical methods were used to report confidence intervals. Logistic regression was used to analyze prostate cancer risk and age.

RESULTS

Prostate Specific Antigen

There was no correlation between PSA levels and prostate cancer in 462 of 473 men with 2899 PSA results (range 38.8 to 91.7 years). Eleven men were excluded from PSA analysis due to prior prostate cancer diagnoses with treatment. The American Cancer Society recommendation for prostate biopsy in men with PSA level 4 ng/mL or more (2) served as a reference point for analysis (Figure 1A-C).

An estimate of the frequency of PSA values for men with and without cancer was made. Considerable overlap demonstrated PSA values were equivalent for men with and without cancer. Cancer was not more common than non-cancer until PSA values surpassed 150 ng/mL (Figure-1A). Standard receiver operating characteristic (ROC) plot confirmed PSA could not predict cancer (Figure-1B). The skill curve suggested the cut off value for PSA to diagnose prostate cancer was not appreciated until levels were above 400 ng/mL. Negative skill indicated PSA usefulness to detect prostate cancer below 400 ng/mL was worse than chance diagnoses (Figure-1C).

The latest free and total PSA values for 111 patients were used to assess the risk value reported with these tests. Risk measurement was not found to be predictive of cancer OR 1.01 (95% CI 0.98 to 1.06). The risk of prostate cancer increased annually with age (p = 0.0003, Table-1).

Cholesterol

There was no correlation observed between cholesterol and prostate cancer in 359 of 473 men with available test results: Total cholesterol OR 1.0 (95% CI 0.99 to 1.01); high density lipoprotein OR 1.0 (95% CI 0.99 to 1.02); triglycerides OR 1.0 (95% CI 0.99 to 1.01); low density lipoprotein OR 1.0 (95% CI 0.99 to 1.01).

Serology

Not all patients had serologic markers available for analysis. This limitation is acknowledged.
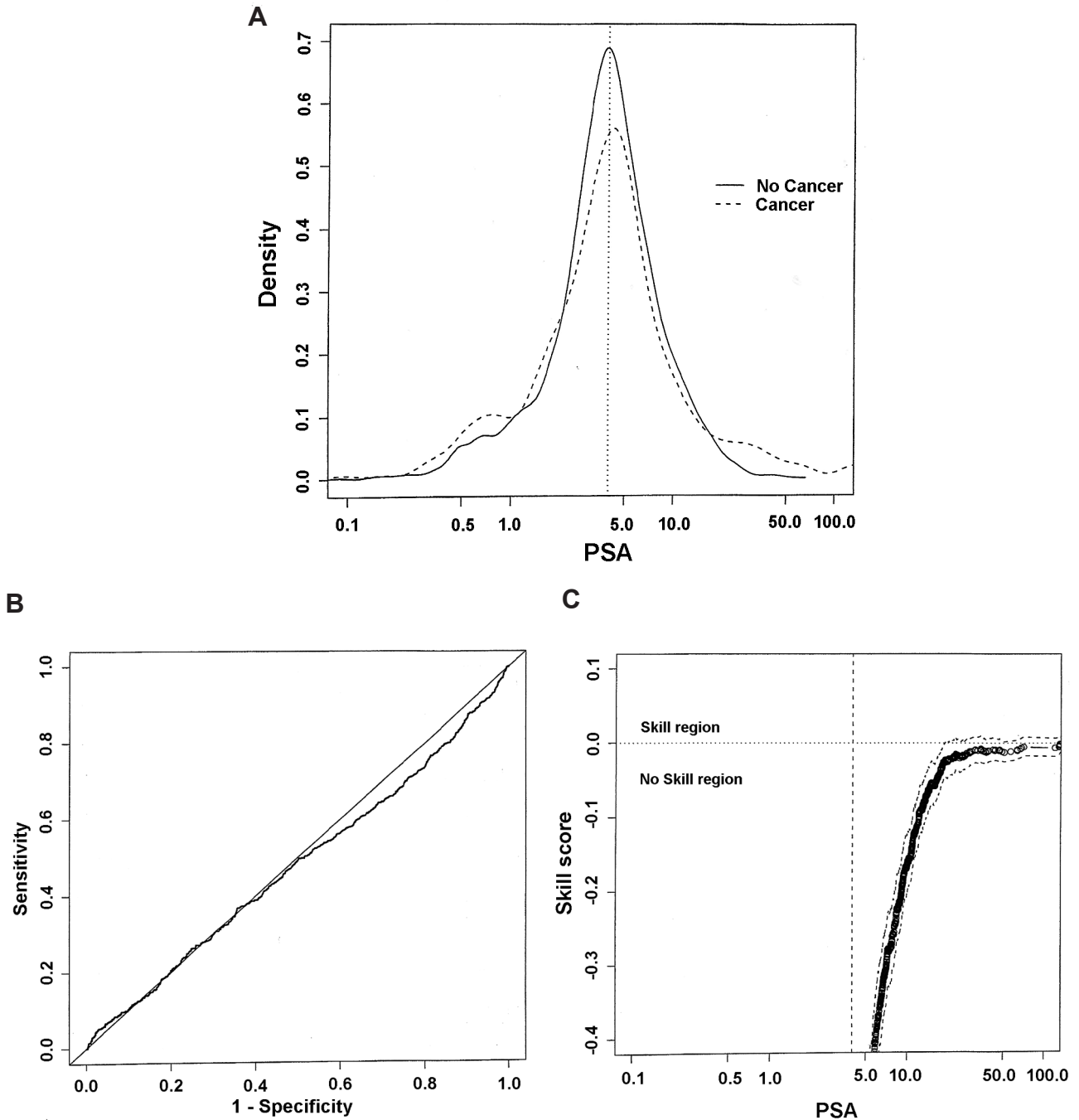
A

B

C

Figure 1 – A) Logarithmic PSA comparison. B) PSA ROC curve. C) PSA Skill curve.

Hepatitis C antibody testing in 172 men correlated with prostate cancer OR 11.2 (95% CI 3.0 to 72.4).

Inconclusive correlation was observed as follows: Syphilis IgG testing with reflex microhemag-glutination Treponema pallidum test (MHATP) in 404 men OR 1.8 (95% CI 1.1 to 3.0); rapid plasma reagin test in 243 men OR 1.8 (95% CI 0.9 to 3.7); HIV antibody testing in 222 men OR 1.6 (95% CI 0.3 to 8.2).

Table 1 – Patient demographics.

Age (years)	42.3 - 49.9	50.0 - 59.9	60.0 - 69.9	70.0-79.9	80.0-91.9
Few glands			1		1
Gleason 4			1	2	
Gleason 5	1		3	1	2
Gleason 6	2	20	27	19	1
Gleason 7	4	16	30	18	4
Gleason 8		3	3	5	1
Gleason 9		1	5	4	
Total cancer	7	40	70	48	9
No cancer	15	79	120	63	11
% Cancer	31.8	33.6	36.8	43.2	45

The risk of prostate cancer increased with age odds ratio 1.03 (95% CI = 1.02 to 1.05, p=0.0003). The odds ratio is multiplicative and applies to each year of age. Prostate cancer specimens received central pathology review at Memorial Sloan-Kettering Cancer Center.

Hepatitis B surface antibody testing in 176 men and tuberculin skin testing with purified protein derivate in 223 men did not correlate with prostate cancer OR 0.9 (95% CI 0.5 to 1.8) and OR 1.2 (95% CI 0.7 to 2.1), respectively. Hepatitis B surface antibody measurements after documentation of vaccination were excluded from analysis in 3 patients.

There was not enough data to perform statistical correlation for hepatitis B surface antigen, hepatitis B e antigen or antibody, hepatitis B core antibody or antigen, hepatitis B polymerase chain reaction or hepatitis A antibodies.

Histology

During the 3 year study period 473 men had 537 TRPBs. All TRPB histology reports at our institution for 7 years prior to the study period were examined for a total of 717 TRPBs in 473 men. There was no correlation between the date of TRPB and prostate cancer diagnosis OR 0.64 (95% CI 0.49 to 0.81).

There was no correlation between prostate cancer and atypical small acinar proliferation (ASAP) OR 0.88 (95% CI 0.48 to 1.55) or high grade prostatic intraepithelial neoplasia (HGPIN) OR 0.99 (95% CI 0.33 to 2.72) on initial or repeat TRPB. With initial or repeat biopsy there was an inverse correlation between prostate cancer and prostatitis OR 0.35 (95% CI 0.21 to 0.56) with a similar result between prostate cancer and basal cell hyperplasia (BCH) OR 0.30 (95% CI 0.09 to 0.80).

Prostate cancer was found in 37.8% (175/463) of undiagnosed men as follows: First TRPB 31.7% (147/463), second TRPB diagnosed an additional 4.75% (22/144), third 0.6% (3/60) and fourth 0.6% (3/22). No prostate cancers were detected on fifth, sixth, seventh or eighth biopsy. There was no correlation between repeat TRPB and finding statistically significant prostate cancer OR 0.64 (95% CI 0.49 to 0.81). Our institution used a protocol of 12 cores as the minimum standard number of specimens during the study period. There was no correlation between increased number of prostate specimens over 12 and finding statistically significant prostate cancer on initial TRPB OR 0.93 (95% CI 0.89 to 0.97) or repeat TRPB OR 0.95 (95% CI 0.89 to 0.99).

Men were staged according to the current American Joint Committee on Cancer staging system. Staging information was available for 167 men:

Stage I 1.2% (2/167, average age 78.4 years); stage II 85.6% (143/167, age range 42.3 to 86.7, average age 66.0 years); stage III 6.0% (10/167, age range 54.0 to 70.3, average age 63.1 years); and stage IV 7.8% (13/167, age range 56.6 to 86.5, average age 65.7 years). Two of the men included as stage II had suspicious findings for metastatic lesions. One of the patients had diffuse spinal uptake on bone scan without evidence of lesions on MRI. Another man had a lytic lesion on the iliac crest, which had a non-diagnostic biopsy, and was thought to be a bone island by radiographic interpretation. He also had a sacral mass thought to represent a schwannoma. Of note, 28 men classified as stage II had prostatectomy, with 39.3% (11/28) reclassified after surgery: 10 stage III and 1 stage IV.

COMMENTS

The population studied was considered vulnerable secondary to educational and economic disparities and consisted of approximately 49% African or African Caribbean, and 51% Central or South American men. This cross-sectional study was instituted as a quality control measure. One objective was to identify PSA selection criteria for improved screening. All men had PSA testing. The utility of PSA to predict prostate cancer was worse than chance diagnosis (Figure 1A-C). A recent longitudinal study also supports this observation (15).

PSA testing has not achieved positive and negative likelihood ratios typically required to meet statistical standards for population based screening tests (15). However, American Cancer Society guidelines consider PSA of 4.0 ng/mL a reasonable threshold for further evaluation and suggests that providers consider individualized decision making when PSA levels fall in the indeterminate range of 2.5 to 4.0 ng/mL (2). Evidence-based medicine has proven that prostate cancers, including high grade cancers are not rare in men with PSA levels below 4.0 ng/mL (16). Autopsy observation suggests nearly one-third of men under the age of 80 have prostate cancer of unknown significance (11). These findings suggest prostate cancer occurs ubiquitously.

The hypothesis that prostate cancer is caused by an ubiquitous or communicable factor is not novel. A total of 37.8% of men were diagnosed with prostate cancer. Syphilis of unknown duration occurred in 17% (69/404) of men tested suggesting an epidemic. Indeterminate correlation to prostate cancer was congruent with previously published data (17). Increased rates of both syphilis (18) and prostate cancer (19) in Jamaica suggested a circumstantial correlation, although sexually transmitted infections have been extensively studied without an identified causative agent (12). Hepatitis C is communicable by sexual contact and has not been established as a risk factor for prostate cancer, although there are no studies which have investigated hepatitis C antibody in a prospective trial. This observational study suggests the odds ratio for hepatitis C antibody is 11.2 (95% CI 3.0 to 72.4). This finding suggests a common molecular modulation may exist between hepatitis C and prostate cancer. This correlation is novel and would be best investigated by prospective trials and experiments focusing on immune modulation. Not all men had hepatitis C testing since this was an observational trial. It is possible that some men would have had more serologic testing if their physician suspected cancer and this limitation is acknowledged.

The risk of prostate cancer increased with age OR 1.03 (95% CI = 1.02 to 1.05, p = 0.0003). The odds ratio is multiplicative and applies to each year of age. For instance, a man 20 years old has odds of 20*1.03 (minus a constant) and a man 60 years old has odds 60*1.03 (minus a constant). Overall, a man 60 years old will have three times the odds of a man 20 years old (Table-1).

One 12 core biopsy was sufficient to detect prostate cancer. Additional cores or repeat TRPBs were unlikely to find statistically significant cancers. Although not statistically significant, 15% (22/144) of second biopsies diagnosed prostate cancer, a finding of clinical significance. Recent evidence which suggests 48 men with prostate cancer need to be treated to prevent 1 prostate cancer associated death (20) implies 461 repeat TRPBs would be needed to prevent 1 death.

There was no correlation on initial or repeat TRPB between prostate cancer and high grade pros-

tatic intraepithelial neoplasia supporting recommendations for repeat biopsy on these men is not indicated (21). However, lack of correlation between atypical small acinar proliferation and prostate cancer in these men on initial or repeat biopsy was incongruent with current recommendations (21). Specimens suspicious for adenocarcinoma receive a central pathology review at Memorial Sloan-Kettering Cancer Center. Specimens containing ASAP are not reviewed by an external institution. On first biopsy ASAP was seen in 25.5% of men (118/463). Cancer and ASAP were seen on first biopsy in 7.6% of men (35/463). In men with ASAP on first biopsy, cancer was seen on second biopsy in 17.3% of men (9/52) which was not statistically different from the overall cancer rate on second biopsy of 15.2% (22/144). We will continue to investigate this discrepancy by obtaining external histology review and continuing data collection to generate a larger number of patients.

Inverse correlation of microscopic inflammation or prostatitis with prostate cancer confirmed previous observations (22). Statistically, prostatitis showed some protection against prostate cancer as 21% of men in this study with prostatitis had prostate cancer, which was lower than the overall rate of 37.8% of men diagnosed. This finding while statistically significant is not clinically satisfactory given a rate of cancer of 21% in men with this finding. A similar relationship between basal cell hyperplasia (BCH) and prostate cancer was observed. Statistically, BCH had an inverse correlation to prostate cancer, however, 16% of men with BCH had prostate cancer, which again was much lower than the overall rate of 37.8% in this population. Basal cell hyperplasia has been linked to a rare form of prostate cancer (23) and the clinical importance of this finding is not understood. Overall, lower rates of prostate cancer were seen in men with prostatitis and BCH, suggesting there is some protective effect conferred.

CONCLUSION

In inner city men of African, African-Caribbean, South or Central American descent, PSA levels do not correlate with prostate cancer. One 12 core prostate biopsy can diagnose statistically significant cases of prostate cancer. Repeat prostate biopsy was positive in 15% of cases, a finding clinically, but not statistically significant. High grade prostatic intraepithelial neoplasia on initial or repeat prostate biopsy does not correlate statistically to prostate cancer. On going investigation is pending concerning lack of correlation concerning prostate cancer and atypical small acinar proliferation. Prostatitis and basal cell hyperplasia have an inverse correlation with prostate cancer. Men should be screened for epidemic syphilis of unknown duration. The presence of prostate cancer is increased with hepatitis C antibody detection. Prospective trials and experiments focusing on hepatitis C antibody detection and immune modulation are needed to investigate this association.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

In this manuscript by Krystyna et al., the authors conducted a retrospective review of all men who underwent a transrectal ultrasound guided prostatic biopsy at a community hospital in New York over a 3 year period. The study population consisted predominantly of American men of African/African-Caribbean or South/Central American descent. The authors concluded that among inner city men of such ethnic background, prostate specific antigen (PSA) levels did not correlate with prostate cancer. Hepatitis C antibody detection correlated significantly with the detection of prostate cancer. Furthermore, the authors concluded that one prostate biopsy is sufficient to diagnose significant prostate cancers in the majority of their study population. Atypical small acinar proliferation (ASAP) did not correlate with prostate cancer. The authors as well propose that men should be screened for epidemic syphilis of unknown duration. The pathophysiology underlying prostate cancer remains poorly understood particularly in such minority groups. In this regard, I applaud the efforts of the authors in addressing this important clinical question. This intriguing possible association between hepatitis C and prostate cancer will require validation in subsequent prospective studies and a causal relationship between hepatitis C and prostate cancer must be demonstrated for this hypothesized association to have clinical merit. However, several conclusions made by the authors namely the adequacy of a single prostate biopsy to diagnose prostate cancer in the majority of patients, lack of correlation between PSA and prostate cancer, and the inability to demonstrate an association between ASAP and prostate cancer may all reflect their retrospective study design, study population characteristics, and limited statistical power in view of their relatively small sample size.

As we strive to advance the field of cancer research, one must always critically evaluate the results and conclusions of such studies which must be contrasted to those of prior peer reviewed scientific papers on the subject matter and in reference to our fundamental understanding of cancer biology. Failure to do so may result in confounding clinical messages and conclusions.

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