Scholar Commons
USF University of South Florida

University of South Florida
Scholar Commons

Graduate Theses and Dissertations | Graduate School

2006

Improving prostate cancer detection in veterans through the developement of a clinical decision rule for prostate biopsy

Owen T. Hill
University of South Florida

Follow this and additional works at: http://scholarcommons.usf.edu/etd

 Part of the American Studies Commons

Scholar Commons Citation
Hill, Owen T., "Improving prostate cancer detection in veterans through the developement of a clinical decision rule for prostate biopsy" (2006). *Graduate Theses and Dissertations.*
http://scholarcommons.usf.edu/etd/2559

This Dissertation is brought to you for free and open access by the Graduate School at Scholar Commons. It has been accepted for inclusion in Graduate Theses and Dissertations by an authorized administrator of Scholar Commons. For more information, please contact scholarcommons@usf.edu.

المنارة للاستشارات

www.manaraa.com

Improving Prostate Cancer Detection in Veterans through the Development of a Clinical Decision Rule for Prostate Biopsy

By

Captain Owen T. Hill, PA-C, MPAS

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
Department of Epidemiology and Biostatistics
College of Public Health
University of South Florida

Major Professor: Thomas J. Mason, Ph.D
Heather G. Stockwell, Sc.D
Skai Schwartz, Ph.D
Yougui Wu, Ph.D
Philip Foulis, M.D., MPH

Date of Approval:
April 10, 2006

Keywords: Prostate, Cancer, Screening, Biomarker, Biopsy

Copyright, 2006

www.manaraa.com

Table of Contents

www.manaraa.com

www.manaraa.com

www.manaraa.com

www.manaraa.com

www.manaraa.com

List of Tables

www.manaraa.com

www.manaraa.com

List of Figures

www.manaraa.com

List of Abbreviations

AUC	Area Under the Curve
BPH	Benign Prostatic Hypertrophy
CI	Confidence Interval
DRE	Digital Rectal Exam
ICD-9	International Classification of Disease: 9th Edition
JH	James Haley
ng/mL	Nanograms per Microliter
NPV	Negative Predictive Value
OR	Odds Ratio
PLCO	Prostate, Lung, Colorectal, and Ovarian
PC	Prostate Cancer
PPV	Positive Predictive Value
PSA	Prostate Specific Antigen
ROC	Receiver Operator Curve
SAS	Statistical Analysis Software
SEER	Surveillance, Epidemiology, and End Result Program
SES	Socioeconomic Status
TRUS	Transrectal Ultrasonography
VA	Veteran's Administration

www.manaraa.com

Improving Prostate Cancer Detection in Veterans through the Development of a Clinical Decision Rule for Prostate Biopsy

Captain Owen T. Hill, PA-C, MPAS

ABSTRACT

In the U.S., the number of prostate biopsies increases annually. This is partly due to elevated prostate specific antigen (PSA) values identified during PC screening.

This study's goal was improving prostate cancer (PC) detection through developing a clinical decision rule (CDR), based on an elevated PSA and laboratory biomarkers. This decision rule could be used after an elevated PSA, providing the patient and clinician information to consider prior to biopsy. This cross-sectional study evaluated men from the Tampa, Florida, James A. Haley (JH) VA (N=1,378), from January 1, 1998, through April 15, 2005.

The study hypothesized that specific lab biomarkers among JH VA PC cases would differ significantly from JH VA patients without PC. The following biomarkers were related to PC: hemoglobin (HGB) (OR=1.42 95%CI 1.27, 1.59); red blood cell count (RBC) (OR=2.52 95%CI 1.67, 3.78); PSA (OR=1.04 95%CI 1.03, 1.05); and, creatinine (OR=1.55 95%CI 1.12, 2.15).

This study attempted to determine whether including specific biomarkers (that are related to systemic diseases associated with advancing PC) could improve PC prediction (versus PSA alone). Comparing all PC stages versus non-cancerous conditions, the Receiver Operator Characteristic (ROC) curve area under the curve (AUC) expanded

www.manaraa.com

(increasing the probability of correctly classifying PC): PSA (alone) 0.59 (95% CI 0.55, 0.61); CDR model 0.68 (95%CI 0.65, 0.71), and the positive predictive value (PPV) increased: PSA 44.7%; CDR model 61.8%. Comparing PC (stages B, C, D) vs. other, the ROC AUC increased: PSA (alone) 0.63 (95% CI 0.58, 0.66); CDR model 0.68 (95% CI 0.68, 0.75), and the PPV increased: 20.6% (PSA); CDR model 55.3%.

These results suggest evaluating certain biomarkers might improve PC prediction prior to biopsy. Moreover, the biomarkers may be more helpful in detecting clinically relevant PC. Follow-up studies should begin with replicating the study on different U.S. VA data-sets involving multiple practices.

www.manaraa.com

Chapter I: Introduction

In the United States, the number of men who undergo prostate biopsies to rule out prostate cancer (PC) increases annually.[1] This is in large part a result of elevated serum prostate specific antigen (PSA) values identified during routine screening for prostate cancer. Debate over the appropriateness of prostate cancer screening is ongoing.[1, 8, 11] In addition; there is controversy over the proper course one should take upon detecting PSA elevations.[8] Moreover, deliberation continues over whether prostate cancer qualifies as a disease eligible for screening. Lastly, it is inconclusive whether early prostate cancer detection truly results in lower morbidity and mortality for the men identified. [1, 8, 11, 15]

Despite the wide spread use of the PSA screening test in the medical community, the U.S. Preventive Task Force (an agency that provides medical screening guidance) state the following, "routine screening for prostate cancer with digital rectal examination (DRE), serum tumor markers (PSA), or transrectal ultrasound (TRUS), is not recommended".[2] Additionally, the National Cancer Institute, World Health Organization, Canadian Cancer Society, and International Union against Cancer do not support the routine screening of men for prostate cancer. Conversely, the American Cancer Society, American College of Radiology, and the American Urological Association do recommend screening men above the age of 50 with a routine PSA serum draw and a DRE.[16]

The contrasts in the above recommendations demonstrate the diverse views that

www.manaraa.com

exist in the medical community on prostate cancer screening. Proponents' for routine prostate cancer screening argue that screening is a valuable early detection tool because it can identify PC in asymptomatic men prior to clinical presentation. Earlier identified PC should be at a less advanced stage, which implies a more treatable state. There is evidence that supports this claim, demonstrating longer survival in patients with earlier identified disease.[17] In a 1996 study looking at racial differences in prostate cancer screening, a statistically significant stage shift towards less invasive disease was discovered when evaluating men who were screened verses those not screened (or who had PC recognized by other methods than screening; i.e. clinical identification). Ninety percent of prostate cancer identified through screening were localized within the prostate, much more than that of clinical identification.[17] It is estimated that men who are diagnosed with non-palpable tumors (stage A-organ confined) have a survival rate of 87 percent, while metastatic PC (stage D) survival rates are approximately 30 percent.[4] Additionally, for the majority of cases, type A tumors have lower Grade status (determined by the Gleason score), lending themselves to be better candidates for curative treatments.[16] This data is controversial however, due in part to two major issues. The first revolves around the unknown path many of the stage A PC tumors (small and prostate confined) can take. Prostate cancer can be very slow growing, and in many cases never becoming clinically evident. In a study of PC identified on autopsy, 30 percent of men over the age of 50 had histological evidence of prostate cancer.[5] In an additional study of elderly men and prostate cancer, 57 percent of men over the age of 80 had prostate cancer identified by step section biopsy.[46] Secondly, categorizing all PC as 'prostate cancer' can be misleading. Not all prostate cancer act in the same fashion. Many

www.manaraa.com

prostate cancers are indolent, with a high likelihood of never becoming clinically relevant. Conversely, an aggressive PC may rapidly advance from a pre-clinical state to invading organs in a metastatic fashion.[16]

An essential goal of prostate cancer screening is to identify PC that would progress to clinically evident disease, the most deleterious form of prostate cancer. Unfortunately, as it stands today, prostate cancer screening has not been able to consistently delineate these tumors from the non-deleterious variety. As a result, a multitude of unnecessary, potentially life altering prostate procedures continue to occur.

A major concern with PC screening is proper classification of disease severity. Simply identifying 'prostate cancer' is not enough information to determine the appropriate course of treatment. A study performed in 1994 provided insight on the current ambiguity that surrounds prostate cancer. The study looked at the impact stage A PC had on men who elect for radical prostatectomy surgery. Twenty-six percent of the 157 men who had undergone radical prostatectomy were afflicted with insignificant disease.[5] In addition, researchers from a 1998 study demonstrated that 84 percent of men within their study population would not benefit from radical prostate surgery.[22] This data, coupled with prior research that demonstrates poor validity and reliability, makes using PSA alone a very suspect screening tool for prostate cancer detection.[7, 43, 116]

Prostate Cancer Epidemiology

Prostate cancer is the second leading cause of cancer death in men in the United States, accounting for 40,400 cases in 1995, and 8,500 in the United Kingdom.[6,10,15] It is the most common cancer detected in American men, with more than 230,000 cases detected each year.[6] It is also the most commonly diagnosed non-skin cancer in most

www.manaraa.com

developed countries.[10] Over a 10 year period (1985-1995), the reported incidence has increased from 85,000 to 244,000.[25] The annual incidence of PC does not match the prevalence identified on autopsy, where PC is present more than 40 percent of the time in men aged 60 years or older.[7] It is primarily a disease of elderly men, with PC mortality age distribution demonstrating this well. Eight-five percent of men who die from PC are above the age of 65.[6] Specifically, men aged 75-84 years of age account for the highest percent percentage of death (41.7 percent), men 55-64 account for 7.4 percent, 65-74 (28.4 percent), and 85 or greater (21.4 percent), respectively.[7] Younger men (less than 55) account for only 1.1 percent of the total prostate cancer mortality numbers.[18]

Screening Criteria

One function of a screening test is to identify the disease of interest in persons who are currently asymptomatic and would progress to a clinically evident case if not without early identification. For screening to be effective, it must be performed on a repetitive basis.[19] For screening to be cost-effective, it must be readably available, quick, and be of little risk.[19] In prostate cancer, if biopsies were performed on all men instead of utilizing surrogate markers (i.e. PSA and/or DRE); the assumed result would be better reliability and validity. This idea is impractical, given the number of potential problems seen with prostate biopsy. Known prostate biopsy morbidities include infection, bleeding, incontinence, acute and chronic pain.

Risk Factors of Prostate Cancer

The causes of prostate cancer are currently unknown. Known associated risk factors for prostate cancer include increasing age, family history, and ethnicity. Additional risk factors described with PC include environmental exposures, smoking,

www.manaraa.com

dairy products, red meat, animal fat, and biologically plausible fetal exposures (both environmental and genetic).[10]

Research Question/Study Design

The overall goal of this study is to improve the efficiency of PC detection through the development of a clinical decision rule that is based on an elevated PSA and set of laboratory biomarkers. This measure would be used as a secondary screening test (after an initial PSA test) that the patient and clinician can refer to for additional predictive information before undergoing a prostate biopsy. This is a cross-sectional study, evaluating men from a reference population within the VA healthcare network from January 1, 1998 through April 15, 2005. The men are between 40-90 years of age, prior military servicemen who utilize the Tampa Veterans Administration medical network for their healthcare needs. These men have undergone prostate biopsies as a result of an elevated PSA screening test (>4ng/dL) The subjects are classified into one of four 'histology' groups: biopsy confirmed prostate cancer (PC); biopsy confirmed Prostatic Interstitial Neoplasm (PIN); biopsy confirmed Benign Prostatic Hypertrophy (BPH); or biopsy confirmed PC negative/BPH negative/PIN negative, to accomplish three specific aims.

Aim 1 – The first aim is to identify biomarkers that are both related to prostate cancer and have the capability of improving the efficiency of PC screening. Within the prostate biopsied groups of men, evaluation of routinely ordered laboratory biomarkers (hematologic, serologic, and urologic) will be performed to assess for significant relationships between the biomarkers and histology groups.

www.manaraa.com

Hypothesis 1: **Among VA patients who have undergone prostate biopsies secondary to a PSA value of >4ng/dL, specified lab biomarkers* among cases of prostate cancer will differ significantly from those among VA patients without prostate cancer.**

Aim 2 - Upon completion of the above aim, statistical models (including biomarkers and known PC risk factors) will be developed to determine which can best predict the probability of prostate cancer. These potential screening models will be compared to the current screening tool (PSA only), to evaluate for improved overall effectiveness in prostate cancer detection and reduction in prostate biopsy. The inclusion of additional predictors offers potential for decreasing unnecessary prostate biopsies and false positive tests; resulting in increased specificity, predictive values, and better overall validity.

Hypothesis 2: **Among VA patients who have undergone prostate biopsies secondary to a PSA value of >4ng/dL, the addition of specified lab biomarkers* will improve the effectiveness of predicting the presence of prostate cancer when compared to PSA alone.**

Aim 3 - The third aim of this study is to assess for a dose-response relationship between specified lab biomarkers (surrogates for extra-prostatic disease development) and the progression of prostate cancer. If present, this parallel progression would demonstrate a gradient between PC and systemic disease. For example, as a patient afflicted with prostate cancer progresses through stage A to stage D, development of other systemic diseases (i.e. Iron Deficiency Anemia), would follow a similar progression of disease severity. Thus lab values associated with these systemic diseases should move further from there "normal" values. If this relationship can be demonstrated, it would be possible

www.manaraa.com

to classify PC patients in terms of likely benefit from invasive interventions verses employing an expectant observation approach.

Hypothesis 3: **Among VA cases of histologically confirmed prostate cancer, there exists a gradient between specified lab biomarkers* and increasing stage of prostate cancer.**

www.manaraa.com

Chapter II: Literature Review

The ideal prostate cancer screening tool would be one that identifies men with prostate cancer that is not yet clinically evident. The test characteristics would include a very high validity (demonstrated thorough high sensitivity and specificity), reliability, and predictability. It would be relatively inexpensive (when compared to follow-up diagnostic tool), minimally invasive, and readably available. Additionally, upon its implementation, mortality and morbidity rates secondary to prostate cancer would decrease with time. Unfortunately, we currently do not have such a screening tool. As a result, researchers are continuously looking at ways to improve prostate cancer screening.

Prostate Cancer Screening Tools

PSA

Prostate specific antigen is protein generated out of the epithelial tissue of the prostate. It is released primarily from the transitional zone of the prostate.[41] Multiple biological processes can elevate serum PSA. Cancer, BPH, acute bacterial prostatitis, chronic bacterial prostatitis, nonbacterial prostatitis, prostate stones, urinary tract infections, ejaculation, bicycle riding, and manual manipulation are all examples of potential sources of PSA elevation.[1]

PSA is a gene product from chromosome 19 and has a molecular weight of 34,000.[43] PSA is typically bound to protease inhibitors upon entry into systemic circulation.[68] The newly bound, 'complexed PSA' (cPSA), most often partners with the

www.manaraa.com

a1-antichymotrypsin (ACT).[68] Prior research has demonstrated that the ACT form of PSA occurs more often in men with prostate cancer.[69]

Prostate specific antigen was first identified in 1979, and not long after its discovery, researchers began to use it within prostate cancer screening. In 1986, the U.S. Food and Drug Administration approved the first commercial immunoassay for use in the treatment of prostate cancer patients.[7]

The serum levels of PSA correlates with the volume of both benign and cancerous cells. PSA was first used as a screening test for prostate cancer in 1986.[7] It was evaluated again in epidemiologic research in 1987 and 1988, where it was examined for its usefulness in clinic utilization as a predictor for final pathologic stage in patients with localized PC, and after radical prostatectomy.[7] In both cases, PSA was found to be a useful tool in monitoring PC patients for detection of recalcitrant or recurrent prostate cancer after radical prostatectomy.

PSA has been employed mostly as a tool for prostate cancer screening. False-positive results remain high with total PSA. It is estimated that 1 out of every 5 men who have pre-clinical localized prostate cancer have a PSA value of less than 4 ng/mL.[72] The estimated positive predictive value of PSA (4ng/dL) is 30 percent.[71] PSA is also used as a tool for staging and for monitoring of cancer reoccurrence post prostatectomy.[73] Prior studies have demonstrated post radical prostatectomy, elevations of PSA are a reliable and valid sign of recurrent cancer.[73]

Digital Rectal Exam

An additional prostate detection tool is the Digital Rectal Exam. Although the sensitivity and specificity of digital rectal exam (in prostate cancer detection) is

www.manaraa.com

considered poor, its relative convenience, lack of cost, and minimal side effects make DRE a frequent tool utilized by practitioners in prostate gland evaluation. The DRE is the most frequently performed prostate exam in clinical medicine today. Despite the lack of accuracy, it is recommended by the American Cancer Society, American College of Radiology, and the American Urological Association that all men above the age of 50 undergo routine annual DRE.[16] Although previous studies on DRE sensitivity and specificity vary widely due to the specific population under study, a study performed in 1988 estimated the sensitivity at .8 percent and specificity at .25 percent, respectively.[61] The positive predictive value is also mottled, with studies demonstrating PPV values from 6 to 50 percent.[30, 61, 62]

On physical exam, the posterior wall of the prostate gland can be palpated.[4] Prostate cancer arises primarily within the periphery of the gland, thus allowing for potential identification of large tumors by DRE. The characteristics of a prostate mass have been previously described as indurated, poorly differentiated, and hard.[63]

Prior studies have demonstrated many limitations of DRE. These limitations include poor identification of small, organ confined tumors, selection biases (on age and subjective history), and variability due to the skill level of the practitioner performing the exam.[63]

PSA Velocity

Over the last decade, the rate of PSA change has been gaining interest as a potential predictor of early prostate cancer. In a 2004 study recently published in JAMA, researchers found that the way PSA levels change over time (velocity) may be a more important factor than any specific level of PSA.[23] This prospective study included 1,095

www.manaraa.com

men who had undergone radical prostatectomy. The authors reported that the risk of death secondary to metastatic prostate cancer was directly related to the rate of velocity change in sequential PSA serum levels, which appeared to be more accurate than standard PSA testing alone. Comparing men whose PSA increased 2 ng/dL or greater to men without change in their PSA levels, the risk ratio (IDR) was found to be 2.8. This implies men with rising PSA values are nearly three times more likely to die within seven years of radical prostatectomy (than men without rising PSA values).[23]

PSA velocity is defined as the change of PSA value over a defined time period.[7] It is theorized that the PSA levels which increase more rapidly than expected over a specifically defined time period are more likely to be caused by prostate cancer than a benign, less aggressive prostate problem. PSA velocity is normally assessed by determining the percent change in serum PSA levels over a year basis. The 'acceptable' rate of change is still open to debate, although a change of greater than or equal to .75ng/dL per year is highly suspicious of prostate cancer.[26]

Carter et al. were the first to assess the functionality of PSA velocity change as a potential tool for prostate cancer detection. This retrospective study looked at 54 serum samples taken from men enrolled in the Baltimore Longitudinal Aging Study. The evaluated men were grouped as biopsy confirmed prostate cancer patients, BPH patients, or the control group. In men whose PSA levels were below the elevated 'positive' marker (4ng/dL), it was shown that an increase of .75 ng/dL or greater would identify PC in men with a test sensitivity and specificity of 80 percent and 66 percent, respectively.[26] PSA velocity identified prostate cancer cases from non-cancerous disease with a specificity of 90 and 100 percent when evaluating accrued PSA levels.[26] Their discussion centered on a

www.manaraa.com

potential biopsy reduction of upwards of 30 percent among men with a prior negative biopsy and persistently elevated PSA levels. Additionally, when compared to the standard total PSA serum evaluation, PSA velocity may be a more valid early identifier of prostate cancer.

A considerable drawback to the widespread use of PSA velocity is the intra-individual variation in men with regards to their PSA values. This variation is irrespective to the state of disease within the prostate. A change of .75ng/dL might be predictive of prostate cancer, but as described by Carter et al., three consecutive PSA measurements are needed over an 18 to 24 months time window to clearly distinguish the prostate cancer cases from that of the non-cases.[27] Given this key data, it is unlikely that PSA velocity (in its current form) will be incorporated in a national prostate cancer screening program as a substitute (or adjunctive) tool for total PSA.

Age specific cut-off points

Many researchers and clinicians have advocated the use of age specific cut-off ranges as a way to better to screen for prostate cancer.[86] Proponents for this screening method argue that using a higher cut-off point for older men will not result in increased PC morbidity and mortality events. It has been previously established that the prostate size increases with age. As the volume of prostate tissue increases with aging, so does the potential for elevated PSA values.[85] The hypothesized benefit of having a higher cut-off value for older men is an overall drop in the number of unnecessary biopsies that would occur each year.[84] Additionally, using a cut-off value that is under 4 ng/dL for younger men would increase the likelihood of detecting asymptomatic tumors. It is a given that younger men have a longer life expectancy than older men, and proponents

www.manaraa.com

believe it is more important to detect the disease in the young. This increased life expectancy places them at increased risk of prostate cancer development, progression, metastasis, and death.[27]

Over the last 12 years, published studies have produced conflicting data on this topic. Initially, it appeared that results from a 1993 study pointed towards potential improvement in disease detection with the utilization of age specific cut-off points.[27] The study by Oesterling et al., focused on developing the specific cut-off point values. The researchers found that by increasing the cut-off points as the age groups increased, the number of unnecessary biopsies could be reduced. Moreover, the large percentage of missed prostate cancers was classified as 'not clinically important'. For example, within the 60-69 age strata, nearly 20 percent of all biopsies would not have been performed, resulting in missing less than 5 percent of the total tumor amount (within the evaluated age strata). Additionally, 95 percent of the 'missed' cancers were deemed 'clinically irrelevant'.[27] In their follow-up study, the following age specific PSA levels were detailed and recommended:

40 to 49 years of age	**PSA value 2.5ng/dL or greater**
50 to 59 years of age	**PSA value 3.5ng/dL or greater**
60 to 69 years of age	**PSA value 4.5ng/dL or greater**
70 to 79 years of age	**PSA value 6.5ng/dL or greater**

Table 1. Age-Specific Reference Ranges: (Partin and Oesterling et al., 1996).

The authors stated by initiating the above cut-off values in place of the standard 4ng/mL, an additional 74 men (who had values below 4ng/dL) of the nearly 4,600 males sampled would have been identified as having prostate cancer.[27] Of these 74 men, 14 were

www.manaraa.com

identified as having 'unfavorable pathology', indicating increased likelihood that their tumor would cause significant morbidity or mortality if left untreated. The authors concluded that by incorporating the age specific reference ranges in conjunction with DRE, younger men at higher risk for prostate cancer development would be identified, and elderly men would be less likely to undergo unnecessary biopsies. They additionally stated that elderly men were more likely to present with less aggressive cancer when compared to their more youthful counterparts, providing more evidence to support changing the reference ranges.[27]

However, over the last decade numerous new studies have been published that seem to suggest age-specific cut off points are problematic. These studies demonstrate that many of the older men in the study in fact had aggressive tumors, often with Gleason score 7 or greater in grade type. A 1998 study reported that of the men who would not have been biopsied on the age-specific reference range algorithm, 1 out of 5 had 'aggressive cancer'.[84] Similar findings have been additionally published, demonstrating the potential for a total biopsy reduction of 8 to 15 percent, but with 15 to 30 percent of clinically important cancers being overlooked.[85, 86] As a result of the inconsistent findings between published research, incorporation of age-specific cut-off values has been met with skepticism and has not occurred on a national level.

PSA Density

PSA density is determined by dividing the total PSA by the prostate volume.[42] It has been suggested that the PSA density could control for total PSA increase related to the natural prostate enlargement correlated to age. PSA density was first reported to delineate between elevations related to prostate cancer and BPH in 1987.[39] The

www.manaraa.com

researchers concluded that after controlling for confounding factors, PC is ten times more likely to be the underlying etiology of total PSA elevations when compared to BPH. To further strengthen the PSA density role in delineating PC from BPH, researchers in a 1992 study of men referred to Urologic specialty center found that PSA density could better differentiate PC cancer patients from BPH patients.[40] The study looked at 595 patients who had an initial total PSA value of between 4-10 ng/dL. Evaluating men who had either prostate cancer or BPH, there was a statistically significant difference in the PSA density between the two groups ($p<0.001$), while the difference of the total PSA between the two groups was not.[40] Furthermore, additional studies found significant differences exist in the PSA density of men with PC compared to non-cancerous prostate conditions, although statistical significance could only be found in the 4 ng/dL groups.[41]

Recent PSA density research has looked more closely at the transitional zone volume as opposed to the volume of the entire prostate. The transitional zone is one of three distinctive histologic regions within the prostate.[41] The two additional regions include the peripheral and central zones. It is believed the transitional zone constitutes less than 5 percent of the total volume of the prostate.[41] Given that the majority of prostate tissue growth and PSA outflow occurs in the transitional zone, it has been hypothesized that focusing on this particular region as opposed to the entire gland might result in better prostate cancer prediction. A 1998 study looking at transitional zone PSA density and percent free PSA with and without total PSA demonstrated that at 0.22 ng/dL or above, transitional zone PSA density would have prevented almost 25 percent of all evaluated negative prostate biopsies would have been avoided.[42]

The limiting issue surrounding the widespread use of total prostate PSA density

www.manaraa.com

and transitional zone PSA density is that they both require ultrasound imaging of the prostate for the accurate determination of prostate volume. The most common ultrasound imagining available is the Transrectal ultrasound (TRUS), and it has previously reported that the volume calculations obtained from the TRUS are not always exact, further limiting its implementation. At this time the recommended usage of PSA density is for the recalcitrant PSA elevations with a previous negative biopsy for prostate cancer.[16]

Gleason Score

An important predictive characteristic of prostate cancer is the appearance of the glandular tumor cells (which assists in defining the aggressiveness of the cancer). The Gleason score was derived to describe the microscopic appearance of the glands that form prostatic cancer.[106] Prostate cancer of a low-grade is less likely to spread, while increasing grades are at higher risk of metastasis.[16] The Gleason score is based on the two most prominent areas of PC activity as identified by a pathologist on histologic examination.[4] Each prominent area is given a score of 1-5, with 1 being well differentiated, and 5 being poorly differentiated (implying a more aggressive appearance).[4] The two scores are added together, and this number is called the "Gleason score".[106]

A Gleason score of 2-4 is considered low grade (less aggressive); 5-7 is considered moderate grade (average aggression); and a Gleason score of 8-10 is considered high grade (most aggressive).[16] A man with a Gleason score above 7 is at increased risk of dying from PC than a man with a Gleason score of 7 or below.[106]

Transrectal Biopsy

In an attempt to heighten the understanding of prostate tumor location,

www.manaraa.com

aggressiveness, and increase accuracy in determining PC presence, ultrasound guided transrectal prostate biopsy has been incorporated into the standard of care for many PC patients. Originally, prostate biopsies were performed through a transperineal approach.[63] This technique was replaced due to the limited visibility it offered in terms of biopsy needle placement. The transrectal biopsy has been demonstrated to be a superior tool in providing information on appropriate needle placement in cases where prostate cancer is suspected.[62]

The biopsy is performed with an 18 gauge, spring loaded needle. The biopsies are performed in a systematic fashion, with an average of 6-10 sextant biopsies performed per biopsy procedure.[65] Controversy has increased recently over the amount and location of the TRUS biopsies. Many PC experts recommend increasing the number of biopsies performed per session, and increasing the area under evaluation. Typically the biopsies are performed within the periphery of the gland, given that the majority of PC arises within this prostate zone. However, many investigators have demonstrated that the rate of prostate detection from biopsies is inversely proportional to the size of the prostate.[63]

PSA Elevators

Prostate Cancer

Prostate cancer is comprised of an assorted set of tumor subtypes. Although the heterogeneity of prostate cancer is well documented, the natural history of the disease is poorly understood. All types of prostate cancer are androgen dependent. The androgen receptor is the prime regulator of both benign and cancerous prostate epithelial cell growth.[36] Upwards of 95 percent of all PC tumors are adenocarcinomas located along the edge of the prostate.[64] Greater than three quarters of prostate adenocarcinomas are

www.manaraa.com

multifocal in origin.[45] Transitional cell tumors account for 4 percent of all PC, and squamous cell tumors are very rare, making up the final 1 percent of the prostate cancer total.

Extraprostatic extension of prostate tumors typically occur posteriorly and posteriolaterally along a plane of least resistance into the perinueral space.[65] Local extraprostatic invasion commonly occurs in the seminal vesicle, urethra, bladder, and often continue to the local lymphatic chains.

The skeleton is the most frequent system of distant PC metastasis. It has been previously reported that upwards of 85 percent of patients dying of this cancer have bony metastasis present. Additional systems associated with distant PC metastasis include the lungs, brain, lymph nodes, and viscera.[67]

The tumor volume has been shown to correlate with its aggressiveness. Small tumors are unlikely to spread outside of the prostate. Conversely, tumors that achieve extraprostatic status and are greater than 4cc in volume are at increased risk for both seminal vesicle and lymphatic invasion.[66]

Staging and grade of prostate cancer is summarized below:

www.manaraa.com

Stage A	**Non-palpable confined to prostate**	**Gleason score 2-4**	**Well differentiated cells**	**Best prognosis**
Stage B	**Palpable confined to prostate**	**Gleason score 5-6**	**Moderately differentiated cells**	**Better prognosis**
Stage C	**Locally spread outside of prostate**	**Gleason score 7**	**Moderately poorly differentiated cells**	**Guarded prognosis**
Stage D	**Distant metastasis**	**Gleason score 8-10**	**Poorly differentiated cells**	**Poor prognosis**

Table 2. Prostate Cancer Stage and Grade

Prostatic Interstitial Neoplasm (PIN)

Prostatic Interstitial Neoplasm is thought to be a precursor for prostate cancer.[58] It has been previously described as a proliferative mass made up of prostatic acini epithelial cells that are dividing and multiplying at increased rates.[57] The cells are not cancerous in their morphology, although their presence on prostate biopsy suggests increased probability that prostate cancer development will occur in the patient under evaluation.[58]

Prostatic Interstitial Neoplasm is a dysplastic lesion; classified as low (grade I), medium (grade II), and high (grade III).[57] Low grade PIN does not have the same likelihood of progression to prostate cancer as medium and high grades.[59] The reported prevalence of medium grade PIN identified in benign prostates has been reported at 10-70 percent, respectively.[57] The prevalence of high grade PIN in cancer free prostates is estimated to be between 15-20 percent.[57] In specimens positive for prostate cancer, high grade PIN it is identified in approximately 33 percent of autopsied samples, and 70-100 percent in surgical samples status post radical prostatectomy.[59]

Currently, prostate cancer clinicians and researchers do not have a universally

www.manaraa.com

recommend treatment regimen for Prostatic Interstitial Neoplasm.[60] Chemoprevention, in which androgen deprivation techniques are employed to decrease the progression of PIN and possibly delay or arrest PC development, are currently under evaluation in clinical trials. Radiation therapy has been reported to decrease PIN.[60] Lycopene, soy, and certain vitamins (D, E) have been previously identified as potentially protective in prostate cancer development and therefore have been described as 'potentially helpful' in preventing PIN development.[56]

Prostatic Interstitial Neoplasm follow-up is not clearly defined. In general, it is recommended to have an additional trans-rectal biopsy within six months, and again possibly every 1-2 years thereafter. Routine PSA draws are additionally recommended.[60]

The correlation between PIN and PSA elevations and the effect PIN has on screening is poorly understood. In general, it is thought that prostatic interstitial neoplasm does not elevate PSA levels.[59] The screening for PIN is not recommended.[58] Numerous prospective studies on PIN are currently ongoing, but as of now the impact of PIN on prostate cancer screening is unknown.

Benign Prostatic Hypertrophy

Benign Prostatic Hypertrophy (BPH) is a frequent elevator of serum total PSA.[87] The underlying etiology of BPH is poorly understood. Hypothesized etiologies include endocrine activity, diet, activity, and familial genetic factors.[88] The incidence of BPH is related to increasing age.[4] The prevalence of BPH follows a linear trajectory with age, as BPH has been identified on autopsy in 22 percent of men aged 41-50 years old, with linear increasement to over 75 percent in men older than 80 years.[87] The genesis of Benign Prostatic Hypertrophy is typically in the periuretheral and transitional zones of

www.manaraa.com

the prostate.[89] Conversely, prostate cancer originates in the prostate's peripheral zone.[18]

Subjective symptoms of benign prostatic hypertrophy are comprised of both irritative and obstructive voiding complaints.[88] Irritative symptoms include urinary urgency, frequency, painful urination (dysuria), and increased urination at night (nocturia).[88] Obstructive symptoms include urinary hesitancy, weak urine stream, intermittent voiding, and weakened voiding force.[88]

Clinical objective evidence of benign prostatic hypertrophy includes localized or global enlargement of the prostate, as identified on digital rectal examination.[88] Additionally, supra-pubic abdomen distention may be palpable, indicating urinary retention secondary to the prostatic hypertrophy.[90]

Laboratory finding seen in conjunction with BPH include elevated PSA, blood urea nitrogen (BUN), creatinine, and less commonly hematuria, positive nitrates, and leukocytosis (if a urinary tract infection is concomitantly present).[88]
Imagining studies are frequently performed with benign prostatic hypertrophy. They include Intravenous Urography, Uroflometry, and Cystourethroscopy.[88] Uroflometry is considered the most useful urodynamic tool in assessing the degree of BPH, with a urine flow of less than 10mL per second indicating advanced obstruction secondary to the prostatic hyperplasia.[87]

Treatments for benign prostatic hypertrophy fall into one of three broad categories: medication, surgical, and minimally invasive treatments.[87]Medication treatments include a multitude of androgen deprivation medications, although these medications often result in decreased libido and sexual function.[90] The prostate contains $a_1$adrenoceptors, that if blocked have been shown to result in contraction of prostate

www.manaraa.com

tissue.[89] Therefore alpha$_1$blockade medication has been shown to improve the irritative and obstructive symptoms of BPH.[89] Surgical treatments involves removal of the enlarged prostatic tissue and can be performed through either the urethra or a traditional incision.[87] Transurethral resection of the prostate (TURP) has been identified as an effective treatment of decreasing the symptoms of BPH with relatively low morbidity and mortality statistics.[87] The reported mortality rate is estimated 0.1 percent, with a morbidity rate of less than 20 percent.[89] The most common side effect of TURP is retrograde ejaculation and bladder neck contracture.[88]

Additional minimally invasive techniques are currently under development and offer the potential for decreased morbidity and quicker post-operative recovery. Balloon dilation, ultrasound laser guided energy, and transrectal microwave hyperthermia are some of the techniques currently under study.[79] The use of these techniques is in the investigational stage, with ongoing clinical trials results pending.[79]

Prostatitis is an inflammatory process of the prostate.[80] It has been described previously as one of three conditions: acute bacterial, chronic bacterial, and nonbacterial prostatitis.[80]

Acute bacterial prostatitis

Acute bacterial prostatitis is characterized by complaints of fever; irritative voiding symptoms, perineal pain, and exquisite tenderness on DRE.[80] Urinalysis frequently demonstrate pyuria, bacteriuria, and hematuria.[79] Laboratory findings include an elevated leukocytosis and left shift.[79] Positive urine cultures are present, with the vast majority of cases caused by gram-negative rod organisms.[79] Specifically, Escheria coli, Pseuedomonas, and (less commonly) Enterococcus are the most frequent causal

www.manaraa.com

organisms identified.[78]

The hypothesized routes of infection include refluxed infected urine into the prostatic duct and an external infectious agent that ascents up the urethra.[80] Differential diagnosis for acute bacterial prostatitis include acute pylonephritis and acute epididymitis.[79] Treatments initially includes intravenous antibiotics and hospitalization. Upon reaching afebrile status for 48 hours, oral antibiotics can then be initiated. Oral antibiotics are commonly utilized for 4-6 weeks to ensure complete eradication of the offending organism is achieved.[80]

Complications of acute bacterial prostatitis include urinary retention, epididymitis, pylonephritis, and chronic prostatitis.[80] With aggressive effective treatment, complications are considered rare.[79]

Chronic bacterial prostatitis

Chronic bacterial prostatitis can arise secondary to an acute prostate infection, but often times afflicted men have no history of such an event.[80] Patients can be asymptomatic, but they often complain of mild irritative voiding with dull suprapubic and perineal pain.[79] Urinalysis are often normal, but expressed prostatic secretions display increased lipid-laden macrophage leukocytes (>10 per high powered field).[79]

The primary difference between acute and chronic prostatitis revolves around treatment. Antibiotics have difficulty reaching therapeutic intraprostatic levels without the acute inflammation seen with acute bacterial prostatitis.[78] Therefore, treatment for chronic bacterial prostatitis revolves around nonsteroidal anti-inflammatory medications.[78] Trimethoprim does penetrate the prostate, therefore it is often given for 3-4 months to complete the treatment regimen.[80]

www.manaraa.com

Nonbacterial Prostatitis

Nonbacterial prostatitis is the most common of prostatitis syndromes, and its etiology is unknown.[78] It is considered a diagnosis of exclusion, with some of the hypothesized causes including viruses, sexual transmitted diseases, and autoimmune disorders.[78] Physical exam with nonbacterial prostatitis is similar to the chronic bacterial condition, although prostatic secretion cultures are negative for organisms.[78]

Treatment for nonbacterial prostatitis include nonsteroidal anti-inflammatory medications, sitz baths, and possibly dietary modifications if the symptoms seem to correlated with food.[80] Trials of antibiotics are encouraged if the condition is believed to be secondary to a sexually transmitted disease.[80] Unfortunately for many patients, this condition is often recalcitrant to treatment and patients often experience recurrent bouts of pain. Although annoying, serious morbidity secondary to nonbacterial prostatitis has not been identified.[80]

In addition to the above known PSA elevators, it is believed that a recent digital rectal exam, urinary tract infection, sexually transmitted disease, ejaculation, or extended bicycle riding episode can all temporarily elevate PSA values as well.

Treatments for PC – confined to the prostate

Prostate cancer that is identified while confined to the borders of the prostate offer more treatment options than a tumor that has spread locally or systemically. Younger patients or patients with aggressive disease have many different options for their care, and because there is not one overt superior treatment, the specific treatment course is often determined by a patient's decision. The treatment options for confined prostate cancer can be grouped within two categories: radiation and surgery.

www.manaraa.com

Radiation treatments have two basic subcategories: internal and external radiation. Internal radiation (Brachytherapy) is usually provided through radioisotopes needle implants.[43] Brachytherapy utilizes radioactive 'seeds', that are usually smaller than 2 millimeters in size, 75 to 100 of which can be typically implanted into the prostate during the procedure.[44] One significant advantage of internal radiation is that it is a one time procedure, external radiation requires multiple treatments.[10] External radiation relies on imaging tools such as ultrasound, computed tomography (CT) scans, and pulse intensity beams to assist in delivering high-dose beams of radiation to the prostate while protecting the surrounding Genitourinary organs.[44] This type of radiation treatments lasts approximately two months, and usually includes over 40 treatment encounters.[46]

Radical Prostatectomy is the most common surgical approach in removing prostate cancer from a patient.[45] There are a multitude of surgical approaches with this surgery, but the two most common approaches are the retropubic approach and the perineal approach.[81] The former is used when there is a need for lymph node biopsy, while the latter is an acceptable approach for organ confined; low-risk disease is present.[81]

Over the last decade laparoscopic surgery has been used more frequently for radical prostatectomy surgery.[45] This type of procedure is gaining in acceptance because there is reportedly less blood loss during surgery, and less post-operative complications.[45] Access to the lymph nodes for sentinel and multiple node biopsy is maintained, and patients return to activities of daily living on average two weeks faster than the traditional surgery. The primary drawback to this technique is the highly technical nature of the procedure, which limits the number of surgeons qualified to perform the surgery.

www.manaraa.com

Cryosurgery is a technique in which the prostate is frozen by liquid nitrogen (or argon gas); killing the cancerous tumors while limiting the destruction of healthy tissues to a minimum.[45] This technique uses ultrasound and MRI to guide the cryoprobe as it distributes the liquid nitrogen. This surgery is a safe alternative for patients who are not candidates for traditional surgery or radiation, and the procedure can be repeated if deemed necessary. Disadvantages of cryotherapy include potential for incontinence, impotence, and urinary obstruction. Due to its relative newness, the long term outcomes of cryosurgery is unknown.[46]

For men afflicted with prostate cancer which is small, organ confined, and asymptomatic, expectant observation is often employed.[81] Additionally, men with a life expectancy of ten years or less, or patients with comorbidities that suggest they are likely to die from something other than their prostate cancer, often employ this strategy as opposed to more aggressive treatment options.[81] The focus for these patients usually centers around quality of life, healthy lifestyles, with bi-annual PSA evaluations to monitor their disease status. Benefits of watchful waiting include the avoidance of surgical and radiation side-effects, avoidance of prolonged recovery period, and the potential to maximize their quality of life. Disadvantages of expectant observation include the lost benefit from early treatment, metastatic spread of the tumor, and early than expected death.[81]

Local Spread treatments

Prostate cancer that has penetrated the external capsule of the prostate is treated differently than organ confined disease. Commonly, locally spread PC is described as having either ‘minimal capsular penetration’ (MCP), or ‘extensive capsular penetration’

www.manaraa.com

(ECP). The ECP subset includes PC that has invaded the seminal vesicle, bladder neck, or both.[77]

The treatment options for patients of both categories are quite extensive. Radical prostatectomy with inclusion of surrounding structures is the typical surgical treatment for the MCP subset. For men with ECP, the benefit of radical prostatectomy surgery is questionable. Prior research has demonstrated an increased risk of PC relapse for men in this subset.[82] In a retrospective study looking at ten year follow-up data, researchers found that 46 percent of post-radical prostatectomy patients with low grade, locally spread disease, had PC relapse within ten years. In addition, the same study determined that 58 percent of post-radical prostatectomy patients with high grade disease demonstrated clinical evidence of PC within the ten year time period.[95]

Many additional nonsurgical treatments are routinely employed for locally spread PC. These treatment options include irradiation, hormone therapy, cryosurgery, and combination therapies (androgen deprivation combined with medication, surgery or irradiation).

The application of nonsurgical treatment modalities for locally spread PC has increased significantly over the last ten years. Prior studies have shown survival rates of nonsurgical treatments to be similar with that of radical prostatectomies, without the associated morbidities that are often seen with major surgery.[77] The use of nonsurgical monotherapies is controversial in that relapse disease has been reported to be high (relative to combination therapy). Relapse of PC within ten years is estimated at 55-65 percent for patients receiving radiotherapy as a single treatment agent.[93]

www.manaraa.com

Distant Spread

Metastatic PC treatments focus on palliative and combination therapies. The typical first line treatments center on decreasing circulating androgen levels.[92] PC is hormone dependent, and the decrease of androgens will slow its spread. A primary therapy of metastatic PC is the gonadotrophin releasing hormone (GnRH) analogous. In survival analysis studies evaluating patients with metastatic prostate cancer treated with GnRH, estrogen, or orchiectomy, significant differences in survival time were not observed.[94] This data, coupled with the known cardiovascular risks of estrogen, and the general patient disdain for orchiectomy, has made GnRH compounds well liked by both PC clinicians and patients.

Anti-androgens are commonly used as a part of a combination treatment regimen for advanced PC. Prior clinical trials have shown Flutamide and Cyproterone (commonly used anti-androgens) to be correspondent to estrogen in their anti-androgen actions with decreased cardiovascular risk profiles.[93] They are not without side effects, however, as all medications within this class demonstrate varying degrees of gynocaemastia, gastro-intestinal derangement, and erectile dysfunction.[93]

Hormone therapy has been associated with improved PC survival time if used in combination with other treatment modalities.[93] Finesteride is a 5-alpha reductase inhibitor that acts by blocking the conversion of testosterone to dihydrotestosterone.[94] Clinical trials looking at Finesteride are currently underway, with early results demonstrating evidence of a synergistic interaction between it and traditional anti-androgen medications.

Chemotherapy is utilized as both a combination therapy option and as a single

www.manaraa.com

agent medication. Although palliative benefits have been realized (when used in combination with steroids), increased survival has not been demonstrated.[92]

Prostate Cancer Relapse

Relapse of PC (post primary treatment) does occur, with prevalence rates estimated at 11 percent for patients with a pre-operative PSA velocity of 2ng/dl/year or less.[11] When relapse occurs, the median time until early biochemical activity is 2 years; with the median time until clinical evidence at approximately 3 years.[93] Upon detection of relapse (increasing PSA values on three consecutive tests), a multitude of different treatments can be initiated. Castration, in combination with androgen blockers, corticosteroids, and radiotherapy, is often employed. Radiotherapy in particular is beneficial in patients with skeletal metastasis. Many advanced therapies for both metastatic and relapsed PC are limited secondary to high cost and geographical availability.

Hematologic Complications of Prostate Cancer

It is known that patients with prostate cancer routinely present with complications outside of the prostate. Patients with advanced prostate cancer often present with objective hematologic findings that are secondary to either the side effects of PC treatment, unrelated causes, or the cancer itself.[29] Despite this commonly known fact, (and fruitful advances in other areas of prostate cancer research), the relationship between serologic and urinary disorders and prostate cancer has been largely ignored.

It is also known that PSA values can be elevated due to a many prostate conditions, but it is unlikely that PSA elevations secondary to non-cancerous etiologies will cause changes to other body systems (represented by the lab biomarkers). In prior

www.manaraa.com

published research, advanced prostate cancer has been indisputably identified as a cause for such laboratory changes. In a study performed by *Strum SB, et al*, anemia in varying severity was found as a frequent complication of advanced prostate cancer. The two primary types of anemias found with prostate cancer are Iron Deficiency Anemia (a subset of microcytic anemia), and anemia of chronic disease (either normocytic/microcytic anemia).

The following is a description of hematologic conditions and laboratory biomarkers that have been associated (directly or indirectly) with prostate cancer.

Anemia

Anemia is a known frequent complication of prostate cancer.[32] Upon identification of anemia in a prostate cancer patient, it is important to correctly diagnosis the sub-category present, as the underlying etiology is then more easily identifiable. In the presence of prostate cancer, anemia is likely a result of the prostate tumor itself, the provided treatment, or secondary to an unrelated biological process.[29] Iron deficiency anemia (IDA) is the most common type of anemia found in medicine, and in prostate cancer as well. Iron deficiency anemia is a sub-type of the Microcytic anemia group.[30] Microcytic anemia is defined as an anemia with a mean corpuscular volume of under 80fL.[33] Thalassemia is another commonly found type of Microcytic anemia, although it correlation with prostate cancer is rare.[33] IDA in any type of cancer patient is frequently associated with chronic covert blood loss from either the genitourinary or gastrointestinal tract.[29] Anemia secondary to a local prostate tumor extension into the rectum and/or colon resulting in bright red rectal bleeding has been reported.[92]

www.manaraa.com

Hemoglobin

Hemoglobin is a protein that carries oxygen from the lungs to the tissues and organs of the body, and it also transports carbon dioxide to the lungs for exhalation. A hemoglobin test value measures the amount of hemoglobin in the blood sample. A value less than 13.8 gm/dL indicates a value out of the normal reference range and is an indicator of potential hematologic problems.

Hemoglobin has been studied as a predictive factor in recalcitrant prostate cancer.[34] Multiple published studies have reported that a low hemoglobin value is an independent risk factor for deleterious survival outcomes in patients with hormone refractory prostate cancer.[91] It has been hypothesized that prostate cancer cells can exert an effect on bone marrow that depresses normal erythropoieses synthesis, resulting in the decreased hemoglobin values. The effect of prostate cancer on hemoglobin as it relates to prostate cancer screening and disease aggression has not been thoroughly evaluated.

Hematuria

Blood may appear in the urine as a result of numerous medical conditions, including cancer of the prostate.[33] Additional known common risk factors for hematuria in men include: internal trauma, kidney stones, vigorous exercise, urinary tract infections, prostatitis, glomerulonephritis, and cancers of the bladder, ureters, or kidneys.[33]

Hematuria is a rare initial clinical presenting complaint with prostate cancer, but is a common finding in patients with prostate tumors that have spread outside of the prostate capsule, but has not yet spread to distant body regions.[33] Gross hematuria in an adult male should be considered secondary to malignancy until proven otherwise.[47] Terminal hematuria has been correlated in prior research as more likely related to bladder

www.manaraa.com

neck or a prostatic source then initial void hematuria. Terminal hematuria is defined as the presence of blood at the end of the urinary stream.[51]

Urea Nitrogen (BUN)

Amino acids from endogenous sources and exogenous proteins generate NH_3, which is then converted to urea by the hepatic cells. Patients with minimal varying degrees of urinary retention or with concealed ureteral obstruction secondary to prostate cancer may present with elevations in serum urea nitrogen.[17] Urea nitrogen may additionally be elevated due to many other factors, including renal failure, drug-induced renal failure (i.e. Nonsteroidal anti-inflammatory, Tetracycline drugs, Corticosteroids), stress, gastrointestinal bleeding, shock, and volume depletion.[21] Other known etiologies of elevated BUN include catabolic states and high-protein diets.

Serum Creatinine

Creatinine is produced by the breakdown of muscle creatinine. It is thought that creatinine clearance declines by 1mL/minute per year as a person ages. In an adult male, serum creatinine that is greater than 1.2 mL/dL is considered above the standard normal level.[21] Increasing serum creatinine has been correlated in previous studies with advancing renal failure due to obstruction and use of certain types of medications (Nonsteroidal anti-inflammatory, Aminoglycosides). Decreased serum creatinine has been linked to decreased muscle mass and severe liver disease (seen in patients with advancing prostate cancer).[35]

Proteinuria

Elevated levels of protein in the urine of a male patient should warrant a complete genitourinary workup. The condition has 12 known potential etiologies in the differential

www.manaraa.com

diagnosis, of which malignancy of the lower urinary tract (to include prostate cancer) is among them.[21] Elevated urine protein is most commonly seen in prostate cancer patients with systemic disease spread and has not been evaluated as it relates to preclinical, early prostate cancer.

Prothrombin (PT)/Partial thrombin time (aPTT)

Disseminated intravascular coagulation (DIC) disorder has been reported as a complication of prostate cancer for many decades.[74] Disseminated intravascular coagulation disorder is an activation of the coagulation cascade, which if untreated can lead to multiple blood clots in the bodies blood vessels, as well as severe bleeding and organ failure.[75] Originally, a succession of case series reported patients with advanced prostate cancer demonstrated lower levels of serum fibrinogen (when compared to patients without prostate cancer).[76] It was hypothesized that the prostate tumor expressed a fibrinlytic tissue factor that was the underlying etiology of the DIC disorder.[75] However, later epidemiologic studies pointed to systemic coagulation irregularities as the primary culprit.[76] The exact incidence of DIC in PC patients has been estimated at 10 to 15 percent, with more studies reporting rates closer to 5 percent .[75] Most published studies surrounding DIC and prostate cancer have evaluated DIC incidence in patients with localized disease, or in patients post transrectal prostate biopsy. The incidence and prevalence of DIC with advancing stage and grade has not been thoroughly evaluated. In addition, there is a lack of published research on changes (if any) of Prothrombin Time (PT) and Partial Thromboplastin Time (aPTT) values in the presence of prostate cancer. Both PT and aPTT are used to evaluate the coagulation system, with increasing levels of PTT an independent predictor of DIC.[75]

www.manaraa.com

Disseminated intravascular coagulation is a systemic disorder that is seen as a complication of prostate cancer. The exact rate of occurrence in PC is unknown, and the changes seen in hematologic tests as a result of DIC have not been evaluated as a predictive tool for advancing stage and grade of prostate cancer.

Epidemiologic Risk Factors for Prostate Cancer

Ethnicity

Prostate cancer incidence and mortality rates are disproportionately higher in African-American males than white males in the United States.[44] African-American men have incidence rates that are two times higher than white males, and their mortality rates are 120 percent higher.[44] African-American men have a risk rate 1.12 times higher than white men for developing prostate cancer in their lifetime.[49] Many reasons have been hypothesized as to why this is so, with a preponderance of prior research pointing towards delay in diagnosis as a primary factor. Diagnoses of prostate cancer is made at later stages in African-American men than white men.[45] Data on prostate cancer incidence stratified on ethnicity from the National Cancer Institutes' SEER program (Surveillance, Epidemiology, and end results) demonstrates the disparities between ethnicities well. African-American men have the highest rates of prostate cancer incidence, mortality, and aggressive spread of all ethnic groups in the United States.[48] Age adjusted incidence rates for African–American men have risen faster than other ethnic groups. For example, from 1973 to 1993 African–American rates have risen from 62.8 per 100,000 to 270 per 100,000.[48] Conversely, white male incidence rates have increased from 62.5 per 100,000 to 164 per 100,000 in 1993.[48] The increased incidence of prostate cancer overall has been attributed to better screening techniques, as well as

www.manaraa.com

increased clinician and public awareness.[47] However, the improved screening techniques and increased awareness does not account for the difference between ethnic prostate cancer rates. African-American men have shown a significance difference in prostate cancer mortality rates as well. From 1973-1993, the SEER data demonstrates an increase in death secondary to PC for African-American men from 39.5 per 100,000 to 56 per 100,000.[48] In comparison, white males had an increase of 20.3 to 24.3 in the same time period.[48]

The underlying etiology of these differences has proven difficult to discern. It is believed that African-American in general have delayed medical care when compared to whites, but it is believed that this care deferment difference does not completely account for the ethnic differences that exist in prostate cancer incidence and mortality.[17]

No clear genetic link has been demonstrated to account for the differences in prostate cancer rates between white and African-American men. A study looking at changes of different chromosomal regions in prostatectomy samples noted changes in the 8p chromosome were seen more frequently in the samples from African-American patients than samples obtained from white patients.[52] The samples were matched on stage and grade and follow-up studies are currently ongoing.

Prostate cancer has been shown in previous studies to be a hormonally dependent condition.[4, 108, 110, 113, 115] Decreasing circulating testosterone in men with prostate cancer (orchiectomy vs. medication) has been shown to be an effective PC treatment. Researchers have hypothesized that there could be a link between increased levels of hormones and subsequent prostate cancer development. Various epidemiological studies have failed to demonstrate an association between androgen levels and PC.[56, 115]

www.manaraa.com

Furthermore, African American adult men have not shown any difference in their hormone levels when compared to other ethnicities. Studies looking at levels of circulating hormones in utero and adolescence have not been thoroughly evaluated, although one published study did demonstrate increased levels in utero for African-American men.[56] The relationship between increased hormones in utero and the latter development of PC has not been fully evaluated.

Foods and other environmental factors have been hypothesized as possible exposures than could explain the difference in prostate cancer rates between ethnicities. It has been previously demonstrated that consumption of dairy products, saturated fats, proteins, soy, and lycopene affects (both increasing or decreasing) the probability of developing cancer of many different systems, including the gastro-intestinal, urinary, and genital tract.[99] Although complex, diets high in animal saturated fat have been linked to increasing risks of prostate cancer.[53] In a study that evaluated diet, exercise, and body size with the development of prostate cancer demonstrated for all ethnicities (including Asian), the risk of PC increased as animal fat intake also increased.[54] In addition, prior studies on food consumption tendencies among different ethnicities points towards increased fat consumption among African Americans when compared to whites.[55] However, a clear causal pathway between increased animal fat consumption in African American men and increased rates of PC has not been demonstrated, and with the possibility of significant confounding and misclassification, the likelihood of uncovering such an association in the future is unlikely.

Age

The incidence and prevalence of prostate cancer increases as men become older.[10]

www.manaraa.com

The median age at diagnosis for PC is 71 years old.[105] The mortality rates associated with PC are not as high as incidence and prevalence rates because of the many competing causes of death seen with the elderly. The leading cause of death in men aged 55 years or higher is heart disease.[2] Prostate cancer is the fifth leading cause of death in men.[10] In 2001, 31 percent of male cancer deaths are secondary to lung cancer with only 11 percent due to prostate cancer.[105] Approximately 35 percent of men aged 60-69 years old have PC, compared to an autopsy prevalence of 70 percent in men aged 80-89 years old.[9] In developed countries, over 80 percent of PC cases occur in men 65 years old or older.[105] The lifetime risk of developing PC is over 3 times greater for a men living in developed countries compared to third-world countries. This discrepancy is attributed to greater life expectancy and diagnosis at earlier disease states.[102, 115]

Family History

A positive family history of prostate cancer is a strong risk factor for future prostate cancer development.[10] Over the last decade; genetic researchers have been working towards identifying the specific genes associated with hereditary PC. The goal is to create tests that can be used to identify men at high risk for future PC development. The exact gene that is responsible for hereditary PC has not been identified, but a positive family history does increase risk. This risk depends on certain factors, including the number of first degree relatives afflicted with PC and the age at diagnosis. [10, 106, 115]

In a 1999 prospective study at the John Hopkins Hospital, (which evaluated the value of screening individuals at known increased risk for prostate cancer development), the researchers evaluated over 10,000 participants and found that men in families with two or more cases of PC had 11 times the risk of developing prostate cancer at 60 years

www.manaraa.com

of age and 5 times the risk at 70 years of age when compared to a man without a family history.[106] In addition, this study used Cox regression techniques to control for other risk factors and found that men with brothers who had had PC increased their risk greater than that of having a father or uncle with the disease.[106]

Many studies have been performed to evaluate whether PC in a patient with a positive family history is different than PC in a patient without a family history of the condition. Factors including clinical stage at presentation, preoperative PSA level, prostate size, prostate weight, and number of cancer foci present were all evaluated. There were no significant differences between the two PC groups in any of the above factors.[107, 108, 109]

Geographic Location and Diet

Exogenous factors are believed to influence PC incidence. For example, prostate cancer rates differ based on geographic location. The United States and Western Europe have historically had the highest rates of PC incidence, prevalence, and mortality in the world. Conversely, the Asian continent has had the lowest known risk of prostate cancer.[97] In an ecologic study looking at cancer incidence rates between continents, the age standardized annual cumulative incidence rates (CIR) for Asian men were reported at 1 per 100,000. In comparison, U.S. African American men PC CIR were at 82 per 100,000, with Caucasian males at 62 per 100,000, respectively.[97]

Additionally evidence that supports exogenous factors influencing PC development is seen through migratory studies that have looked at PC trends in Asian men living in Asia, the United States, and Europe. The incidence of PC is higher in men who migrate from countries of low risk for PC development to countries of higher

www.manaraa.com

risk.[100, 101] Asian men living in the U.S. or Europe had higher rates of PC incidence than their ancestors still residing in Asia.[100, 101] When the study controlled for differences in the detection time between the different regions, statistically significant differences in PC incidence remained.[101]

Correlational data also suggests alteration of PC risk can be realized by modification of dietary practices. Where as some types of foods seem to increase PC risk (red meat, dairy products, and animal fat), others appear to offer protective benefits (lycopene, selenium, and Vitamin E).

Prior published ecological studies have demonstrated strong correlations between PC development and consumption of dairy products, red meat, and animal fat. The positive correlation appears strongest with dairy products, with one study demonstrating a correlation of .69.[102, 117, 118] Ecologic fallacy and confounding are possible explanations, but additional case-control and cohort studies seem to support this relationship, albeit not as strong.[107, 109, 119, 120] Two hypothesized explanations of the relationship between PC and dairy products centers on the fat content and the high bio-availability of calcium in milk. The calcium hypothesis has gained support from a 1997 prospective study that evaluated dietary fat intake and PC risk. This study demonstrated that consuming increased amounts of fat-free and skim milk carried an increased risk of PC development.[103]

The 'Western diet' has also been evaluated as a PC risk factor. It has been hypothesized that this diet (high intake of red meat, animal fat, dairy products, and protein) results in increased energy consumption, which can lead to increased levels of Testosterone, cell proliferation, and angiogenesis, with decreased cell differentiation and

www.manaraa.com

apoptosis.[104] This combination would lead to increased prostate growth, PIN, PC, and faster disease progression. However, epidemiologic studies have varied in their results. Where some studies have demonstrated increased PC risk, many others have reported no increased associated risk. [107, 109, 118, 119]

Although as a group, fruits and vegetables have not been associated with decreased PC risk profiles, certain vegetables have been supported as potentially protective. Lycopene has been studied since the 1980s for its affect on PC risk. Many of the studies demonstrated reduced risks associated with high intake of Lycopene; however they were not statistically significant. One 1995 U.S. study, which evaluated 773 subjects, demonstrated a statistically significant risk reduction (RR-0.65, 95 percent CI-0.44-0.95) when consuming greater than 10 dietary tomato-based products per week (compared to less than 1.5 servings). Although the data remains controversial, the increased consumption of tomato-based products (as well as fruits and vegetables) is recommended for cancer risk reduction and better overall general health.

Vasectomy

Prior epidemiologic studies looking at a possible link between PC and undergoing a vasectomy have failed to demonstrate consistent evidence of a causal association.[111, 112] This potential association has been under review for approximately twenty years. Although a number of studies have suggested there are increased risks of PC development associated with vasectomy surgery, many other studies have failed to demonstrate similar outcomes.[113, 114, 115]

In a 1992 retrospective cohort study looking at the incidence rates of cardiac arrest, testicular cancer, and prostate cancer in men who had underwent a vasectomy; no

www.manaraa.com

evidence of increased PC risk was identified. Over 13,000 men who had a vasectomy were compared to 26,000 men who were hospitalized for elective operations, appendicitis, or injuries. The study reported a relative risk of 1.0, but noted longer periods of follow-up may be needed to study vasectomy effects on PC definitively.[117]

An additional study from 1996 conducted in Puget Sound evaluated 175 men (who were status post vasectomy and recently diagnosed with histologically confirmed PC) with 258 controls. These controls were randomly selected from the general membership of the Puget Sound insurance group health plan. Conditional logistic regression analysis yielded an odds ratio for PC associated with vasectomy of 0.86 percent (95 % confidence interval 0.57-1.32).[112]

Skepticism remains over this suspected relationship, centering around two primary factors; biological plausibility and selection bias.[111] The biological basis that attempts to explain the link between vasectomy surgery and increased PC risk has been questioned and remains speculative.[113, 116] It has been shown that vasectomies result in a complete decrease of sperm, which in turn results in a decrease of total percent concentrations of prostate secretion and seminal vesicle hormones, while simultaneously increasing the level of sperm-antibodies.[116] It is unknown if (and how) any of these biological changes results in increased PC development.[116]

In addition, selection bias remains a potential explanation for the previously demonstrated increased risk. Most vasectomies are performed by urologists, and most PC are diagnosed by urologists, therefore men who have undergone vasectomies are more likely to have their PC diagnosed.[113]

Additional research is needed in this area, specifically prospective cohort studies

www.manaraa.com

and clinical trials. Moreover, previous studies have shown potentially increased risk in various sub-populations, therefore focus on those men at potentially increased risk prior to the vasectomy should deserve particular acute focus.

Alcohol

Alcohol consumption effect hormones by transiently depressing circulating testosterone levels (in men) and increasing estrogen levels (in women).[119] Alcoholic cirrhosis has also been shown to depress circulating testosterone levels.[120] There has been significant interest in a possible link between alcohol use and PC development.[121]

Alcohol consumption is a prevalent life-style activity and is modifiable, therefore the identification of a causal relationship with PC would have a significant impact on public health.[119] Prospective and retrospective reviews have been performed on the potential relationship between alcohol consumption and PC and has found limited evidence to support a causal association.[119] There has been greater than 30 studies investigating this potential link over the last 30 years.[119]

A 1996 study looking at PC risks in relation to alcohol intake in U.S. African-Americans and whites demonstrated a significant association (RR 1.8, 95% CI 1.1-3.0) with high grade PC and heavy alcohol intake (greater than 57 drinks per week). When the PC outcome was evaluated as a binary outcome, the relative risk was not significantly increased. Moreover, follow-up studies have not found similar results.[118]

A European study, looking at the influence alcohol plays on PC, found a gradient association between total grams of alcohol consumption and PC development in Swedish men. However, their results were not statistically significant, thus the apparent relationship could have occurred by chance.[125]

www.manaraa.com

In a review of all previously published literature that summarized issues of causation, no compelling evidence of a causal link between low-to-moderate alcohol use and PC was observed.[119] The authors recommended targeted research focused on select subsets of men including heavy alcohol consumers. In addition, they recommended population prospective studies, as well as increased attention on genetic markers of patients with familial risks.[119]

Vitamin A

Prior research on cancer incidence suggests increased consumption of vitamin A can be a protective dietary practice.[125] However research on the association between vitamin A and PC has hinted that a more complex relationship may exist. There have been published studies that have attributed both protective and causal effects associated with increased vitamin A intake on PC developement.[125-129]

The National Health and Nutritional Examination Survey I Epidemiologic Follow-up Study followed over 2,440 men (> 50 years old) for an average of 10 years and found mean levels of serum vitamin A were lower in men who developed PC when compared to men who did not develop PC.[126] These results were statistically significant and were evaluated as both a continuous and ordinal variable.[126] After adjusting for age and ethnicity, the researchers found that men in the lowest quartile of vitamin A intake had a RR of 2.2 (95% CI 1.1-4.3) when compared to men in the highest quartile. The increased risk of PC development did not weaken with increasing time between serum draw and diagnosis.[126] In addition; similar protective findings were also reported between vitamin A intake and PC in a case-control study published in 1988.[127]

In 1989, dietary and lifestyle characteristics of approximately 14,000 Seventh-day

www.manaraa.com

Adventist men were obtained for comparison with subsequent PC development.[128] Each study subject completed detailed questionnaires on a variety of lifestyle factors, including information on foods known to be high in vitamin A. Consumption information was obtained on the following specific foods: green salads, citrus fruits, and tomatoes.[128] The researchers utilized Cox proportional hazards regression models for statistical analysis and found men that consumed foods that are known to contain increased levels of vitamin A had a decreased risk of PC development (See Table 3 below).

Fruit and Vegetable Consumed	Relative Risk	95% CI
Green Salad (>= 1x/Day)	**0.68**	**(0.44-1.05)**
Fresh Citrus fruit (>= 5x/Week)	**0.53**	**(0.34-0.86)**
Tomatoes (>= 5x/Week)	**0.57**	**(0.35-0.93)**

Table 3. Age-Adjusted Relative Risk for PC by Fruit and Vegetable Consumption (Mills, Beeson, Phillips, and Fraser, 1989).

One study that demonstrated conflicting findings was a retrospective, case-control study, which was performed in Hawaii on 1,351 men (452 PC positive, 899 population controls). All men within the study provided detailed dietary histories between the years of 1977-1983. The men were stratified on age (< 70 or >= 70 years), and controlling for differences in ethnicity was performed.[126] The researchers found that men 70 years or older strata, who were in the highest quartile of vitamin A consumption group, had a statistically significant odds ratio of 2 when compared to the lowest consumption group.[126]

Two additional published studies demonstrated larger risks of PC development with increased consumption of vitamin A. A study by *Graham, et al.,* found the relative risk of PC increased in a gradient fashion as vitamin A increased. This trend was more

www.manaraa.com

apparent in men 70 years or older.[129] Hershmat, et al., described a similar relationship in a case-control study that was published in 1985, although the odds of PC development was strongest in younger men (less than 50 years of age).[130]

Many explanations have been hypothesized as to these conflicting results. The differences may be a result of inherent difficulties of capturing data on diet, as well as separating vitamin A from other carotenoid and retinoid compounds. Additionally, the majority of the retrospective analyses have lacked large case numbers and as a result the powers of these studies remain in question.

Other Micronutrients

The antioxidant, vitamin E, has been evaluated as a possible protective agent in cancer genesis due to its reported anti-cancer properties.[999] It is previously been suggested that vitamin E may impede the development of cancer by inducing apoptosis in cells with altered or damaged DNA.[105] There is limited epidemiologic studies on the possible relationship between vitamin E and PC, however.

A randomized prospective study published in 1998 demonstrated a protective effect with vitamin E use. In the study, men were either randomly assigned to receive either a placebo or vitamin E supplementation in their diets. The men that received the vitamin E had a reduction in their PC incidence of greater than 30 percent, and the mortality second to PC decreased by greater than 40 percent.[120] In a more recent evaluation of the potential protective effects of vitamin E, 1,896 physicians were tracked prospectively in the Health Professionals Follow-up study. Augmentation of diets with vitamin E did not result in a lowering of the risk of PC development. This particular study enhanced the accuracy of the vitamin E measurement by documenting intake twice

www.manaraa.com

per year, and also had increased power when compared to the previous (1998) study.[121]

However, a protective effect was seen after stratifying on smoking status and looking only at the aggressive PC cases. The ex-smokers had a relative risk of 0.51 (95% CI 0.26-0.98) when compared to never smokers. The authors recommended further study of vitamin E, in particular the potential effect modifying relationship seen with smokers. Prospective studies exploring this relationship are ongoing.

Vitamin D has been evaluated for over 10 years to discern the exact role it plays in prostate cancer genesis. Molecular studies have demonstrated that vitamin D receptors are present on prostate epithelial cells and PC cell lines.[131] These receptors are thought to increase the expression of androgen receptors and PSA androgen-regulated genes.

A 1990 study that evaluated vitamin D as a risk factor for PC development reported that patients with low serum vitamin D levels had a significant relationship with ethnicity, age, and geographic location, frequently cited PC risk factors. A second epidemiological study demonstrated that decreased serum vitamin D levels (Ca^2 less than 8mg/dl) was associated with increased risk of high-grade tumors and advanced stage disease.[132]

Clinical trials of vitamin D and its analogs are underway currently and although hypercalcemia was a frequent complication, it is believed that these compounds can reduce any PC prompting activity currently seen with varying vitamin D serum levels.

Obesity

Previously published case-control studies suggested that obesity increases the risk of PC development.[99, 107, 109, 110] Ecological studies have demonstrated strong correlations between obesity and increased risk of PC development.[99-, 107, 109] However, given certain

www.manaraa.com

methodological issues, this relationship has been questioned. In many studies, the utilization of only height and weight was utilized to assess body mass.[107] Moreover, consistency between retrospective and prospective studies have been lacking. As a result, it is unclear if obesity is a causal exposure for PC development.

The first study that published findings suggestive of a causal association between increasing body mass and PC was a hospital based case-control study out of Northern Italy.[110] The researchers reported that increased PC risks existed in obese men (when compared to men of the expected body mass). Limitations of this study included the utilization of hospital based controls, and determining body mass strictly on the basis of height and weight.[110]

To correct for this limitation, a prospective study published in 1988 evaluated the influence that body mass had on PC development with the utilization of several body measurements.[52] The authors initiated a more detailed assessment of the subjects to delineate increased body mass secondary to muscle verses adipose tissue. They calculated Incidence Density Ratios (IDR) on 7,820 men, comparing a multitude of different body measurements. The researchers reported that the risk of PC was not significantly related to BMI, skinfold thickness, height, or leg length.[52] They did note that the RR was significantly increased with girth in the upper arm and weight in kilograms, although this relationship did not demonstrate a linear trend.[52] The authors concluded that their results were preliminary and that it appears the risk of PC increases with increasing muscle mass and not necessarily with adipose tissue weight gain.[52]

In a study published in 1971, *Wynder et al.* retrospectively evaluated 1,050 patients to better determine the epidemiologic factors of prostate cancer and review

www.manaraa.com

certain factors believed to be associated with PC development.[51] The review looked at 300 subjects who were diagnosed with PC, 400 controls, and the charts of 350 additional patients who had PC.[51] Two factors that were evaluated closely included weight and height. The authors found no significant difference in the height and weight of the PC subjects when compared to the controls. In fact, a higher percentage of control patients were overweight than the PC patients.[51]

In addition, a 1984 prospective study noted increased PC risks for overweight men.[59] The study evaluated a cohort of 6,763 white male Seventh-day Adventists who had completed a dietary questionnaire in 1960.[107] They were followed-up to assess the effects obesity played on the risk of fatal PC development. They authors reported that men who were overweight had a significant RR of 2.4 (95% CI 1.3-4.5) for fatal PC development, when compared to men within the referent group.[107] Although this study provides compelling statistics, the study utilized basic measures of diet, as well as basic measures of body mass. In addition, since the studies endpoint was fatal PC, it is unclear whether the disparities in types of food intake resulted in increased death secondary to the PC or a competing cause of death. In addition, the issue of inaccurate cause of death determination on the death certificates cannot be discounted.

Although there appears to be some evidence of a causal relationship between obesity and PC, difficulties with methodological issues (and a lack of prospective studies) has hampered the understanding of this complex relationship. As a result, any assertion that obesity can increase a subject's risk of PC development is purely speculative.

Circulating Testosterone

Testosterone is an essential androgen hormone that is vital for the healthy, normal

www.manaraa.com

development of male reproductive organs. It is believed to be responsible for spermatogenesis and the regulation of gonadotropic secretion.[31] In addition; testosterone is a common treatment for hypogonadism, and is used as a palliative therapy for breast cancer.[31]

For decades, many researchers and clinicians have hypothesized that increased levels of circulating testosterone is a risk factor for PC development. However, the plausibility of this causal relationship has been questioned, given that PC is dependent on continued availability of androgens, and androgen levels decrease as a man ages.[109] The decreasement of circulating testosterone has been a PC treatment strategy for many years.[108] The complete understanding of this complex relationship has proven to achieve. Difficulties in evaluating testosterone levels and methodological limitations in previous studies designs has been cited as limiting factos.[109] For instance, many of the published studies have utilized blood samples that were taken after the diagnosis of PC, thus concerns over the temporality of the relationship exist. In addition, many of the previous studies have limited sample size, or non-representative control groups.[108]

However, a study out of Canada evaluated the relationship between Serum testosterone and dihydrotestosterone with PC on 75 (33 PC patients, 42 controls) otherwise healthy men. The noted the mean value of serum testosterone for the control group was 16.74 (95%CI 17.5, 15.98), while the PC patients was 20.94 (95%CI 22.42, 19.46). The results were statistically significant, however the researchers stated that the wide range in values seen in the PC patients limits the practical value of the biomarker, and further study by a prospective approach would be necessary.

In 1996 a prospective study was performed, investigating whether plasma

www.manaraa.com

testosterone and sex hormone-binding globulin levels in men were related to the subsequent development of PC.[107] The researchers utilized a prospective, nested case-control approach, looking at the participants of the Physicians' Health Study who provided blood samples for future evaluation. There were 222 participants who subsequently developed PC after the study began. Three hundred-ninety controls were matched on age, smoking status, and length of follow-up. Logistical regression modeling was used to determine the Odds Ratio specifying the risk associated with increasing hormone levels. High levels of circulating testosterone demonstrated a association with PC as levels of plasma testosterone increased.[107] For increasing quartiles of plasma testosterone, the OR were as follows: 1.00, 1.41, 1.98, and 2.60.[107] The confidence intervals were statistically significant, and the researchers concluded that high levels of circulating testosterone were likely associated with PC.

History of STD and Other Sexual/Reproductive Factors

Age at first sexual intercourse, intercourse frequency, history of Sexual Transmitted Diseases (STD), and the number of sexual partners have all be evaluated as potential risk factors for the subsequent development of PC. It has been hypothesized that PC may be caused by the transmission by an infectious agent through sexual activity.[112] However a cohort study of cancer mortality demonstrated an excess of PC deaths in Catholic priests, which points away from an STD etiology.[113] The results of the subsequent follow-up studies have failed to demonstrate a clear causal pathway.

The most thorough evaluation of these potential causal exposures was performed in California in the late 1970s. This population-based, case-control study was performed on 221 men who were identified by the Los Angeles county cancer surveillance program

www.manaraa.com

as having histologically diagnosed prostate adenocarcinoma. Cases were restricted to white, non-Spanish sir names, and each case was assigned a similar neighborhood control. Both the cases and control were interviewed over the phone using a structured format by a single trained interviewer. The researchers reported that the risk of PC development were higher in men with earlier age at first sexual intercourse (age <17 vs. 21+, RR = 2.3, 95% CI 1.3-4.0), but there was no association with the number of sexual partners or the frequency of sexual intercourse.[112] Moreover, there was not a significant relationship with STD history, although the small number of cases limits the interpretation of the results.

Socio Economic Status

The relationship between socio economic status (SES) and PC incidence has been evaluated since the 1950s. At that time, literature suggested that the increased PC incidence seen in African-American men could be related to lower SES.[107] However, follow-up studies that have evaluated education, income, and residence zip code (with PC development), failed to demonstrate consistent evidence to support this hypothesis. In a 1971 study of PC modifiable risk factors, the relationship between education attainment and PC development was analyzed separately for both Caucasian and African-American men.[108] For Caucasian men, there was no significant difference between rates of PC incidence and the different education categories (stratified as 'no school attendance'; 'grammar school'; 'high school'; and 'college'). African-American men who had attended grammar school or less had a 14 % increased risk of PC development. However, due to small sample size, the results were not statistically significant.

In 1972, a study in California again revisited socio economic status and its

www.manaraa.com

relationship to PC incidence and mortality. This case-control study compared PC incidence data from the Alameda county cancer registry and death certificates data with the average income for the Alameda residence zip codes. The researchers found that after stratifying on ethnicity, African-American men maintained their increased incidence rates (compared to Caucasian men), despite the increased education. However, the study did not report the statistical significance of their findings.

Occupational Studies

There is mounting evidence that suggests there exists an inverse relationship between certain types of cancers and occupational activity.[123] In particular, diverse populations have been studied in relation to job-related activity and their risk of colon cancer, and there is a consistent association between occupational physical activity level, recreational physical activity level, and colon cancer risk.[123] The specific relative risks has varied between the studies, with one study demonstrating no apparent association, while other epidemiological studies report risks between 20-100 percent, respectively.[122]

In a 1991 Missouri case-control study, the odds of white men being diagnosed with prostate cancer were increased if they had low or moderate activity levels at work.[122] This study was initiated to evaluate cancers in relation to occupational activities. The OR of a white male worker developing PC was 1.1 (95% CI 1.0-1.3) for men with moderate activity, and 1.5 (95% CI 1.2-1.8) for men with low activity levels (compared to the reference group; high activity).[122] The odds ratio for low activity level was statistically significant, and the researchers controlled for age and smoking status. The authors concluded that their results should be considered preliminary and require confirmation with other studies.[122]

www.manaraa.com

In a study published in 1987, which looked at the relationship between occupational activity and the incidence of cancer (including PC), it was reported that longshoreman with decreased occupational activity levels had increased odds of PC development (when compared to longshoremen with increased activity levels).[124] This study was performed in San Francisco, California, and did have certain limitations. These limitations included a lack of controlling for Social Economic Status (SES), and had a vague surrogate marker for physical activity.[124]

The biological mechanism that links physical activity levels and PC development remains unclear. Researchers and clinicians have hypothesized that the relationship may be bound by a decrease in the cancer growth promotion factors as a result of the physical exertion.[122] This may be so, but it has been proven difficult to discern exactly how much physical activity is required, and for what duration, for the protective effects to be realized. A better measure of job related activity, randomized clinical trials, and prospective studies are required to answer this question with more clarity.

Tobacco

The use of tobacco products (specifically cigarette smoking) has been evaluated as an exposure that increases the risk of developing prostate cancer. However, the results of previous studies evaluating this relationship have been unclear. A slightly increased risk has been identified; however it has not been consistently demonstrated and researchers are unsure if this relationship was actually due to the biological effect of the tobacco smoking, or secondary to delayed diagnosis and treatment.[94]

Different pathways have been hypothesized on how tobacco could induce PC. One revolves around the tobacco use prompting a more ‘aggressive’ phenotype that

www.manaraa.com

progressives more quickly and is more fatal. A second hypothesized pathway centers on the concept of 'hormone alteration', either resulting in the hormones prompting cancer growth, or turning off the tumor impeding genes.[95]

Conclusion/Assessment of the Literature

There exists a gap in the literature addressing PSA as a prostate cancer screening tool. Earlier PSA research by Catalona, the U.S. Preventive Task Force, (and more recent work by Thompson, Carter, the PLCO, and others) have been critical in improving our ability to identify prostate cancer at earlier disease stages. However, there is continued debate on whether (or not) PSA remains the best currently available tool for the detection of pre-clinical PC. This debate is likely to continue until the results of the PLCO trial are released (tentatively scheduled for 2014). There seems to be little debate over the limitations PSA possesses as a PC screening tool. Undoubtedly, a strength to prior peer-reviewed published literature has been the consistent demonstration that, since the inception of PC screening on a national level, the utilization of a single PSA draw (with or without DRE) as the prompting factor for prostate biopsy referral has resulted in millions of unnecessary (non-risk free) prostate biopsies.[5, 22] An overt weakness of the prior published studies has been the lack of easy to implement solutions to this complex problem.

How can PC screening be improved upon? Despite a wealth of published literature that has evaluated PSA and argued against its use as a PC screening tool, PSA remains the mainstay for clinicians for PC screening. Thus, the focus must be on augmenting PSA, not replacing it all together. Prior attempts at improving PC screening have focused on replacing PSA with a new test. Tools such as PSA velocity, PSA

www.manaraa.com

density, Free/Total PSA ratio, and newer assays have all shown promise in studies for improving PC screening results, but difficult implementation and a lack of universal acceptance among clinicians have hindered their incorporation into daily clinical practice.[7, 23, 26, 27, 40, 41, 41, 86]

Has researchers and clinicians made the most of all available information when evaluating a patient for prostate cancer? Routinely ordered lab panels (complete blood counts (CBC), basic metabolic panels (BMP), and urinalysis (UA)); all contain biomarkers that change in value when diseases associated with prostate cancer are present. Yet these biomarkers have been in essence 'ignored' when evaluating a patient for PC.

Many previous studies have accurately described PSA elevations as 'specific to a condition of the prostate'. However, in what must be considered a weakness of the literature, there has been a lack of clarity in describing that the aforementioned PSA elevations are not specific to prostate cancer. In what may hold the key to improving the overall yield of PC screening, evaluating changes in certain laboratory biomarkers values that (in the presence of an elevated PSA) are associated with diseases that are a product (directly or indirectly) of PC spread may provide a wealth of important information that can improve of ability to accurately predict PC presence in patients undergoing PC screening.

www.manaraa.com

Chapter III -Methods

The overall goal of this study is to improve the efficiency of prostate cancer screening through the development of a clinical decision rule that is based on an elevated PSA and a predictive set of clinical biomarkers. The study is a cross-sectional study, evaluating men from the James A. Haley VA hospital from January 1, 1998 through April 15, 2005. The men are between 40-90 years of age, prior military servicemen, who utilize the Tampa VA medical network for at least some of their health care needs. All men have all undergone prostate biopsy. The subjects are classified into one of four 'histology' groups. The cases consist of biopsy confirmed prostate cancer. There are 3 control groups: (1) biopsy confirmed Prostatic Interstitial Neoplasm (PIN), (2) biopsy confirmed Benign Prostatic Hypertrophy (BPH), or (3) biopsy confirmed prostatitis, to answer three primary questions of interest (see below).

1 - Aims/Hypothesis

Aim 1: The first aim is to identify biomarkers that are both related to prostate cancer and have the capability of improving the efficiency of PC screening. Within the biopsied groups of men, evaluation of routinely ordered laboratory biomarkers (hematologic, serologic, and urologic) will be performed to assess for statistically significant relationships between the biomarkers and disease status. It is known that PSA values can be elevated due to many prostate conditions, however it is believed to be unlikely that the non-cancerous conditions that elevate PSA would also cause changes to

www.manaraa.com

other body systems (represented by the lab biomarkers). In prior published research, advanced prostate cancer has been indisputably identified as a cause for such laboratory changes.[34] In a 1997 study; anemia was a frequent complication of advanced prostate cancer. The two primary types of anemias identified with PC are Iron Deficiency Anemia (a subset of microcytic anemia), and anemia of chronic disease (either normocytic/microcytic anemia). The etiology of anemia in prostate cancer patients is due to the cancer itself, the therapy for the cancer, or unrelated conditions.[34] Currently; there is a paucity of documented research assessing the impact of cancer related anemias on cancer screening.[32]

Hypothesis 1: **Among VA patients who have undergone prostate biopsies secondary to a PSA value of >4ng/dL, specified lab biomarkers* among cases of prostate cancer will differ significantly from those among VA patients without prostate cancer.**

Aim 2: Upon completion of the above aim, sets of orthogonal biomarkers will be developed to determine which can best predict the presence of prostate cancer. These potential screening sets will be compared to the current screening tool (PSA only), to evaluate for improved effectiveness in prostate cancer detection. The inclusion of additional predictors offers potential for decreasing false positive tests, resulting in increased specificity, predictive values, and better overall validity.

Hypothesis 2: **Among VA patients who have undergone prostate biopsies secondary to a PSA value of >4ng/dL, the addition of specified lab biomarkers* will improve the effectiveness of predicting the presence of prostate cancer when compared to PSA alone.**

www.manaraa.com

An essential goal of this study is to increase the identification of PC that has the potential to threaten life. This PC has not yet afflicted serious morbidity and mortality, but will if untreated. Therefore, perhaps the most important cases of prostate cancer to identify through screening are stage A and B which have aggressive grade scores.

Many stage A (low grade), indolent prostate cancers are unlikely to become clinically evident, and their identification through PC screening is not of paramount importance.[10, 16] Prostate cancers that contain aggressive properties would (theoretically) demonstrate evidence of both prostate activity (verified through elevated PSA), and systemic evidence of cancer (verified through lab biomarker changes). It has been previously established that PSA values can be elevated due to a multitude of prostate conditions.[41, 87] However, it is considered unlikely that non-cancerous prostate conditions will cause changes to other body systems (represented by the lab biomarkers). Moreover, indolent cancers are believed to be unlikely to cause an identifiable biological change, and the PC that has overtly traversed the prostates borders will typically demonstrate clinical symptoms (urinary obstruction, bone pain, weight loss, etc.), thus more likely to be diagnosed in the clinical setting.

Aim 3: The third aim of this study is to assess for a dose-response relationship between specified lab biomarkers (surrogates for extra-prostatic disease development) and the progression of prostate cancer. If present, this parallel progression will demonstrate the presence of a gradient between prostate cancer and systemic disease.

Hypothesis 3: **Among VA cases of histologically confirmed prostate cancer, there exists a gradient between specified lab biomarkers* and increasing stage of prostate cancer.**

www.manaraa.com

2 - Participant Description

Participants are men who have undergone prostate biopsy within the VA Healthcare networks located in Tampa, Florida. The demographic characteristics of the population under study are as follows: The James A. Haley VA group are primarily Caucasian middle-aged veterans (mean=68 y/o, SD=12) with an education attainment level of at least four years of high school, or some college attendance.[37] When the education of veterans is compared to that of non-veterans on a national level, significant differences exist. For instance, 12 percent of veterans had not graduated from high school, compared to 18 percent of non-veterans. Moreover, 65 percent of veterans have completed high school or have attended 1 to 3 years of college, compared to 56 percent of non-veterans. Lastly, when comparing the rates of completing 4 or more years of college, non-veterans are more likely to have accomplished this feat (26 percent compared to 23 percent).

Data suggest that upwards of 2.5 million individuals receive all or part of their healthcare needs from the VA medical system.[37] The Florida VA healthcare network handles on average a total of 1,718,528 male patient encounters each year.[37] This total represents approximately 6 percent of all the male visits within the National VA system. The following table (Table 4) stratifies these numbers by age specific groups:

State	**Age 50-54**	**Age 55-59**	**Age 60-64**	**Age 65-69**
Florida	**155, 611**	**198, 258**	**147, 565**	**164,481**

Table 4. Summary of age distributions: male patient visits (Florida VA, 2001). Data Source: VA Department, National Survey of Veterans.

The VA and census data estimate that as of 30 September, 2004, approximately

www.manaraa.com

93,500 men in Hillsborough County (Tampa, Florida) are eligible to receive healthcare services at the James Haley VA hospital. Additional demographic data reveal veterans compare closely to their non-veteran counterparts on several measures of socioeconomic status; including personal income, and health insurance coverage.[38] However, users of VA inpatient and outpatient care have less health insurance coverage than veterans in general.[38] Approximately 9 percent of all veterans were uninsured in 1993, compared to 21 percent of veterans who used their VA medical benefits. This holds true for veterans under the age of 65, as 13 percent did not have health insurance, compared to 29 percent of those veterans that used the VA healthcare system.[38]

Inclusion criteria:

1. All patients with a PSA value of 4ng/dL (or higher) with a history of prostate biopsy (TURP and/or core biopsies and/or prostatectomy) dated between January 1, 1998 until April 15, 2005.

2. Additional laboratory data (obtained at the time of PSA sample):

Hematology:	**Chemistry:**	**Urinalysis:**
Red Blood Count (RBC)	Albumin	Hematuria
Hemoglobin	Urea Nitrogen (BUN)	Proteinuria
Mean Corpuscular Volume (MCV)	Creatinine	
Platelet count	Bilirubin-Direct/Indirect	
White blood count (WBC)	Lactate Dehydrogenase	
PT/aPTT	Total Protein	

Table 5. Laboratory Biomarkers

3. Males age 40 to 95 at time of initial diagnosis of PC, PIN, BPH, or prostatitis.

Exclusion criteria:

1. History of prior genital urinary malignancy.

2. Individuals for whom pathology report states that the biopsy specimen is

www.manaraa.com

inadequate.

3 - Design

The design for this investigation is a cross-sectional study. The subjects are classified into one of four 'histology' groups. The cases consist of biopsy confirmed prostate cancer. The controls consist of 3 groups; biopsy confirmed PIN, BPH, or prostatitis.

4 - Case Identification

A diagnosis of PC is based upon a set of standard procedures for both the clinical decision making process and the biopsy of the prostate. Upon identification of an elevated PSA lab test (with or without the identification of a prostate nodule during physical examination or transrectal ultrasound), the patient undergoes a prostate biopsy that is then sent to the pathology department for histological determination. For quality control purposes, random case review is performed monthly by local VA pathologists, and external quality control is assured by 10 percent random case review by pathologists assigned to the Armed Forces Institute of Pathology, located in Washington, DC.

5 – Data Collection Methods

A case of prostate cancer is defined by prostate tissue that demonstrates cells of adenocarcinoma on histologic evaluation.[4] With that, identification of potential study subjects was accomplished through utilizing the search option in the Anatomic Pathology portion of VISTA (SNOMED finalized accession logs) to find all cases coded as 'prostate disease' (SNOMED codes: 77220, 77103, 77102, 77101, 77110, 77105, 77350, 77230, 77210, 77300, 77200, 77240, 77104, 77100, 77000, 77900, 77250). The patient's identification number, date of the specimen, diagnosis text code, and accompanying

www.manaraa.com

narrative text description were captured through this VISTA search. The SNOMED system (Systematized Nomenclature of Medicine) is a division of the College of American Pathologists, and is the standard tool used by pathologists to create, share, and retrieve pathology information.[125] The SNOMED system is used by the James Haley VA hospital for aggregating all pathology data. The collection of both the diagnosis text code and accompanying text description was performed intentionally as a way to validate the histologic diagnosis. For instance, if the diagnosis code was 'adenocarcinoma of the prostate' (SNOMED code 77220); the corresponding narrative text description would provide the same diagnosis. The goal of this initial search was to capture all prostate related cases; hence the abundant amount of SNOMED codes used. At this point there were 2,575 unique patient identifiers that could be potentially associated with prostate cancer.

The James Haley VA electronic medical records (EMR) were then accessed for all of the identified potential PC cases to validate the diagnosis (by identifying PC ICD-9 codes or 'PC' stated as the assessment in the narrative dictation) and capture additional data relevant to this study. Demographic data (age, ethnicity), laboratory biomarkers, and any previous pathology results were captured through the review of surgical operative reports, progress notes, medication logs, admitting summaries, and discharge dictation summaries. This data was still grouped within the Vista system, and to development a relational database, it was exported to the Microsoft Access system for further dataset development. (A relational database is required to match data from different datasets for each individual).

Upon satisfactory export of the above data, a relational database was created to

www.manaraa.com

link the different data sources. Multiple Access tables, queries, and forms were created. In particular, the following 7 different tables were created in Access: histologic diagnosis codes, narrative histologic dictation notes, inpatient diagnosis codes, demographics (gender, age at biopsy, race, and ethnicity), laboratory biomarkers of interest, date of biopsy (with age at biopsy), and ICD-9 codes for all previous diagnosis (within the JH VA) recorded for each patient.

Access forms were then created as a tool to create new diagnosis categories. In particular, new data elements were created that categorized each prostate biopsy as PC, PIN, BPH, or prostatitis. Each biopsy diagnosis text code and accompanying text descriptions were reviewed closely to reduce the probability of misclassification of the study outcome (histologic evaluation of adequate prostate tissue).

A second Access form was created for capturing both the PC stage and Gleason score for each patient with a histologic diagnosis of PC. The stage was categorized as follows: stage A for non-palpable, prostate contained cancer; stage B for palpable, prostate contained cancer; stage C for locally spread PC; and stage D for metastatic PC. To determine the Gleason score, the two most prominent areas of PC activity (as identified by the evaluating pathologist on histologic examination) were identified. Each prominent area was given a score of 1-5, with 1 being well differentiated, and 5 being poorly differentiated (implying a more aggressive appearance). The two scores are added together, and this number was the recorded Gleason score for all subsequent analysis.

Upon establishing each subject's new diagnosis category (which is to be used as the primary outcome variable of this study) and Gleason score, these variables (as well as laboratory and demographic data) were exported into Microsoft Excel for continued

www.manaraa.com

dataset development. After successful export of the above mentioned data into Microsoft Excel, attention was given to determining the accurate ethnicity of each potential study subject. Initially, both the race and ethnicity fields (within the histology text description reports) were screened for ethnicity key words (e.g. Caucasian, African American, white, black, etc.). However, more than 60 percent of these fields were left blank; therefore addition capture techniques were employed.

For the 40 percent of the potential study population that did not have race or ethnicity captured within the prostate biopsy histology text description reports, evaluation of (EMR accessible) previous surgical operative reports, outpatient progress notes, emergency room notes, admitting hospital summaries, and discharge dictation summaries were reviewed, looking for any mention of race and or ethnicity. Screening for commonly used medical short-hand information (e.g. 67 y/o aam; “67 year old African American male”) was also performed, which ultimately left only 6.6 % (170/2575) of the potential subjects with “unknown/refused” as their ethnicity designation.

For accurate determination of each subject’s age, the age was calculated by subtracting the birth date from the date of prostate disease determination. The age of non-cancer subjects was established by subtracting birth date from the date of histologic evaluation.

To aggregate the specific laboratory biomarkers of interest in this study, an MS Excel table was created that contained all laboratory samples obtained from each potential study subject within the studies time frame. After successful creation of the table, lab values that were not of interest in this study were then deleted. The below tables details the laboratory biomarkers of interest:

www.manaraa.com

Hematology:	**Chemistry:**	**Urinalysis:**
Red Blood Count (RBC)	Albumin	Hematuria
Hemoglobin	Urea Nitrogen (BUN)	Proteinuria
Mean Corpuscular Volume (MCV)	Creatinine	
Platelet count	Bilirubin-Direct/Indirect	
White blood count (WBC)	Lactate Dehydrogenase	
PT/aPTT	Total Protein	

Table 6. Laboratory Biomarkers

Subsequent to deleting the extraneous lab biomarkers, attention was given to the specific date of the lab biomarker sample. Inclusion criteria for this study state that the lab biomarker sample was to be obtained at the time of PSA sample; therefore PSA and biomarker sample dates were compared to ensure time consistency. If the lab biomarkers were not obtained at the same time as the PSA draw, they were deleted from the table (Inclusion criteria).

After performing the above mentioned activities, an aggregate table was created in MS Excel that contained the following information on each of the 2,575 potential study subjects: patient ID number, age, histology category (PC, PIN. BPH, prostatitis), PC stage (A, B, C, D), Gleason score (if PC positive), ethnicity (Caucasian, African-American, Hispanic, Other), and the above lab biomarkers. This table was then utilized as the base dataset for all subsequent data analysis, to include the below data reduction strategies.

Data Reduction Strategies

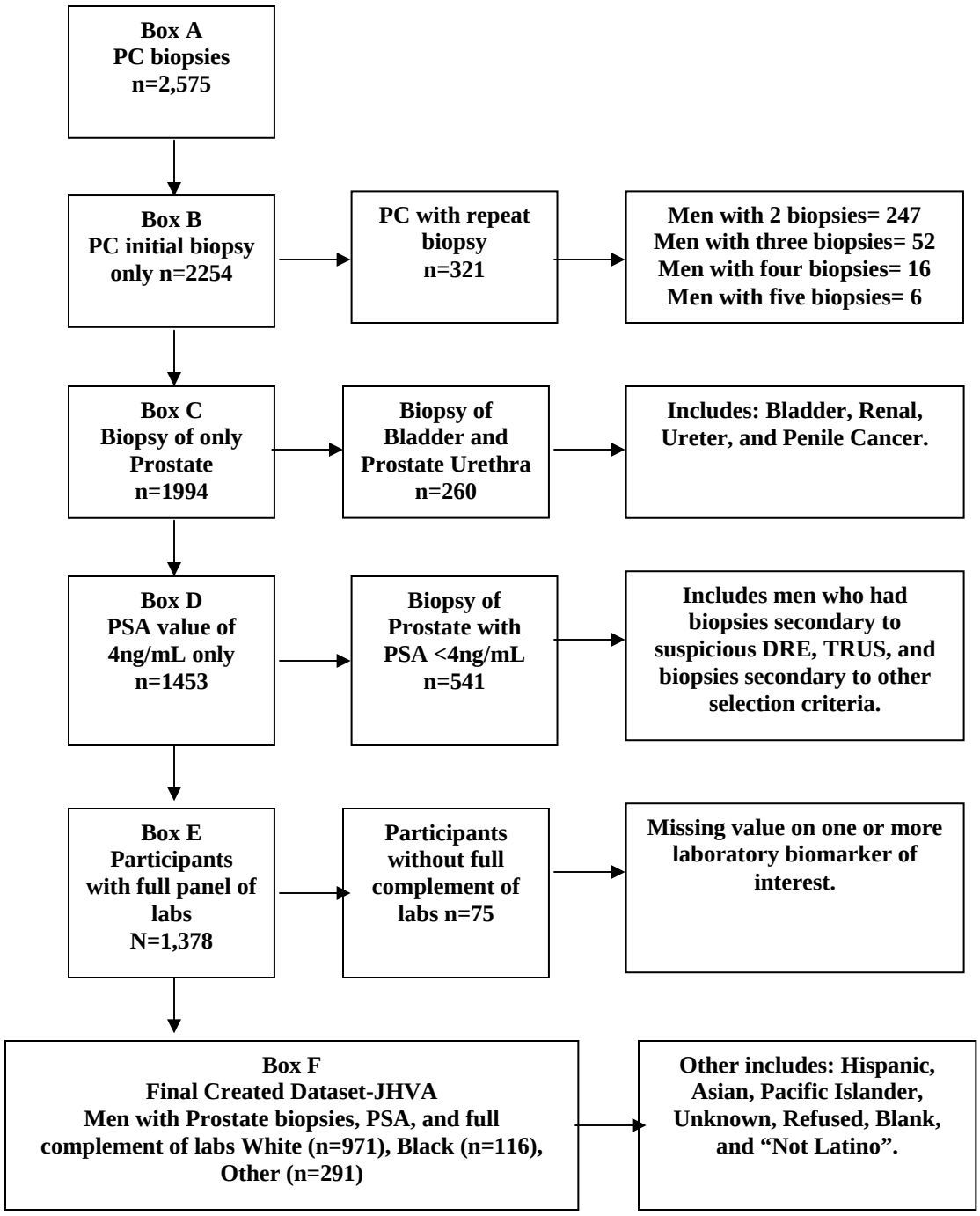
Upon developing the base dataset for the data analysis portion of this study, data reduction strategies were employed which ultimately left 1,378 participants available (form 2,575 potential subjects) for statistical analysis. Over 500 prostate biopsies (541) did not meet inclusion criteria because they where performed on men who did not have a

www.manaraa.com

PSA test value of 4.0 ng/dl or greater. Typical situations that would result in this scenario includes men who had biopsies secondary to a suspicious DRE or TRUS, or biopsies secondary to other reasons (e.g. patient request due to family history). There were 321 biopsies identified as "repeat biopsies", which were then dropped from the study. Next, prostate biopsies that were performed as a result of other genital urinary malignancies (i.e. bladder, renal, ureter, and penile cancer) (N=260) were excluded. It is important to note that the specific prompting for all prostate biopsies was confirmed through a detailed record review of each prostate biopsy report within the VISTA system. These notes were in narrative form and were validated by confirming the ICD-9 code for that event. Lastly, participants without a full complement of laboratory biomarkers were excluded from the study (N=75). At the completion of the above mentioned data reduction strategies, 1,378 participants were analyzed in this study. Figure 1 below is a schematic of the studies data reduction process.

www.manaraa.com

Figure 1. – Data reduction strategy.



www.manaraa.com

6 - Statistical Procedures

Univariate, bivariate, logistical regression, linear regression, and receiver operator characteristic curves were utilized to address the primary and secondary questions of interest. All models were risk adjusted for ethnicity and age.

All data was abstracted from the VA hospital medical and laboratory records computer system (VISTA). It was then entered into MS EXCEL for data verification and review (See above for detailed explanation). Data was then imported into the SAS statistical software program and univariate analysis was initiated. The use of this descriptive analysis process allowed for careful review of data frequencies, measures of central tendency, and distribution shapes. Additionally, identification of out of range data, determination of the quantity of missing data, and accurate description of the study population was achieved by utilizing this process.

Upon completion of the descriptive analysis, bivariate analysis was performed. Bivariate analysis allows for testing of hypothesis 1 (see above), to determine the statistical significance and degree of correlation between the independent variables under review and the presence of prostate cancer.

Multivariate logistical regression was utilized to evaluate hypotheses 1 and 2. Regression techniques were used to identify linear mathematical equations which best described the relationship between the presence of PC and the independent predictor variables. Regression diagnostic techniques were employed to increase the likelihood of obtaining statistically sound and reliable analysis results. Binomial logistic regression was also utilized, given the outcome variable (prostate disease status) was coded as a two category outcome (PC yes= 1, PC no = 0).

www.manaraa.com

A complete model (including age, ethnicity, biomarkers, and any interaction terms) was established initially. Exclusion of each covariate, one by one, was performed, looking for a change in the overall – 2 Log Likelihood Ratio. A potential covariate was permanently removed from the model development process if there was no effect on the overall – 2 Log Likelihood value. This lack of change indicates the specific variable is not contributing to the prediction of the outcome, and conversely, if there was a change of statistical significance, the variable was included in the final model. Additionally, interaction between covariates was assessed by creating combination variables, which assessed for additive and multiplicative effects. To test the significant difference between the full model and the final model, evaluation of the likelihood ratio p-value was performed, in which a value greater than 0.05 indicated a satisfactory fit of the smaller model.

Receiver operating characteristic (ROC) curves were employed to address the second hypothesis. ROC curves are graphical tools which plots the sensitivity vs. 1- the specificity for a binary classification system (as a function of changes in the cut-off value threshold).[39] This analysis technique was utilized to demonstrate the difference that exists between the existing prostate cancer screening test (PSA alone) and the addition of a secondary test (biomarker clinical decision rule) to assess at what degree we could expect to improve PC screening by including the clinical decision rule into the PC screening process.

Mean and medium values of all significant biomarkers was determined for each PC stage subset to determine if there exists a gradient between advancing prostate cancer severity and increasing systemic disease severity (hypothesis 3).

www.manaraa.com

Study Power

A power calculation was performed prior to the start of the study. The exposure estimation was based on the mean number of JHVA male individual patients with abnormal laboratory values noted during 1998 through 2004. The denominator was the total number of male patients who underwent laboratory testing during the same time period. The calculation allowed us to conclude that the study has sufficient power (>0.80) to accurately detect an odds ratio of 2 with 95 percent confidence in the case population of 1,378 subjects is present. In addition, this calculation indicated that our study is designed and equipped to deal with larger than expected censured data loss, thus if a number of participants would have been lost, adequate study power will remain. An alpha value of 0.05 was the significant cutoff level throughout the analysis.

7 - Variables

Dependent

Hypothesis I & Hypothesis II - The outcome variable, prostate disease status; was defined as 1, for histological identification of PC and 0, for histological identification of BPH, PIN, and other non cancerous pathologies (i.e. prostatitis).

Hypothesis III – The outcome variable, prostate cancer severity, was defined as 3, (PC positive, organ confined, low grade); 2, (PC positive, palpable, moderate grade); 1, (PC positive, palpable, locally spread disease, moderate grade); 0, (PC positive, distant spread, high grade).

Independent

The independent variables were treated as continuous, categorized, and binomial in the analysis. There were 14 independent variables available for inclusion as predictor

www.manaraa.com

variables in the logistical regression models. Four variables that were initially scheduled for analysis were dropped due to excessive participants with missing data (Pro-thrombin time/Partial pro-thrombin time (PT/aPTT), Folate, Lactate Dehydrogenase, and Total Protein). The 14 independent variables are outlined in Table 7 below.

ID		
Age	**Continuous**	**Age for subjects and was be calculated by subtracting the birth date from the date of disease determination.**
Histology	**Categorical**	**Disease status will be coded as 1-'prostate cancer', 2-'PIN', 3-'BPH', 4-'control group'.**
Stage	**Categorical**	**1-Stage A, 2-Stage B, 3-Stage C, 4-Stage D**
Gleason	**cat/continuous**	**1-10**
Ethnicity	**Categorical**	**Obtained directly from the VA EMR. Coded as 'White", 'Black', 'Hispanic', and 'Other'.**
ALB	**Continuous**	
TBILI	**Continuous**	
CREAT	**Continuous**	
FLT	**Continuous**	
HGB	**Continuous**	
LDH	**Continuous**	
MCV	**Continuous**	
PLT	**Continuous**	
PSA	**Continuous**	
RBC	**Continuous**	
UREAN	**Continuous**	
HMTU	**Recoded**	**Original data: 1 + H, LG, lg, MOD, NEG, neg., SM and TR.**
PRTU	**Recoded**	**Original data: 1+ H, 100.0 H, 2+ H, 3+H, 30.0 H, >300 H, NEG, neg., TR**
WBC	**Continuous**	
PCYes	**Binary flag**	**PC Yes=1, PC No = 0**
Black	**Binary flag**	
Hispanic	**Binary flag**	
Other/Unknown	**Binary flag**	
HMTU2 (Hematuria)	**Categorical**	**Recoded- NEG, neg.=0 (negative), 1+H and TR=1 (trace), SM=2 (small), MOD=3 (moderate), lg and LG=4 (large)**
PRTU2	**Categorical**	**Recode of PRTU. NEG and neg.=0 (negative), TR=1 (trace), 1+H=2 (moderate), 2+ H=3, 3+ H and 100.0 H and >300 H and 30.0 H=4**

Table 7. Coding of the criterion and independent variables

www.manaraa.com

8 - Summary

The overall aim of this study is to improve the efficiency of prostate cancer screening through the development of a clinical decision rule that is based on an elevated PSA and a predictive set of clinical biomarkers. This is a cross-sectional study evaluating men from the James Haley VA healthcare network from January 1, 1998 through April 15, 2005. These men have undergone prostate biopsies as a result of an elevated PSA screening test (>4ng/dL). The target population is all men who utilize the VA healthcare system throughout the U.S. There are three hypotheses under evaluation:

H1: Specific lab biomarkers among cases of prostate cancer will differ significantly from those patients without prostate cancer.

H2: In men with elevated PSA values, the addition of specific lab biomarkers will improve the effectiveness of predicting prostate cancer when compared to PSA alone.

H3: There exists a gradient between specified lab biomarkers and increasing levels of prostate cancer.

www.manaraa.com

Chapter IV Results

4.1 – Population Characteristics

Demographics

Demographic data is outlined below in table 8. After study exclusions (see chapter III), there were 1,378 men available for analysis. The age range of the subjects was 40-95 (mean=68, SD=12). Most of the men had either prostatitis, BPH, or stage A PC. Prostate cancer (stage B, C, D) accounted for 20.6% of all diagnosis. The study population was largely Caucasian men (study total=70.75%, PC=69.4%, PIN=71.73%, BPH=74.82%, prostatitis=69.29%). Age at diagnosis (PC stage A group=68.37, PC stage B group=69.73, PC stage C group=67.73, stage D group 67.88, PIN group=67.75, BPH group=67.83, prostatitis group=68.17) was comparable across all diagnosis groups.

	Prostatitis	BPH	PIN	PC Stage A	PC Stage B	PC Stage C	PC Stage D
No. Subjects	**342**	**282**	**138**	**332**	**220**	**48**	**16**
Ethnicity*							
Caucasian	**237 (69%)**	**211(75%)**	**99 (72%)**	**238 (72%)**	**149 (68%)**	**31(65%)**	**10 (63%)**
African American	**18 (5%)**	**19 (7%)**	**13 (9%)**	**34 (10%)**	**22 (10%)**	**7 (15%)**	**4 (25%)**
Hispanic	**22 (6%)**	**14 (5%)**	**7 (5%)**	**15 (5%)**	**11 (5%)**	**1 (2%)**	**1 (6%)**
Other	**65 (20%)**	**38 (14%)**	**19 (14%)**	**45 (13%)**	**38 (17%)**	**9 (18%)**	**1 (6%)**
Mean Age***	**68.17**	**67.83**	**67.75**	**68.37**	**69.73**	**67.73**	**67.88**
SD Age	**8.54**	**8.19**	**8.49**	**8.99**	**9.36**	**9.39**	**10.6**

Table 8. Demographics of Study Participants by Prostate biopsy results
*** P-value < 0.05**
**** P-value <0.01**
***** Not statistically significant**

www.manaraa.com

Table 9 (below) outlines the mean value and standard deviation of all continuous laboratory biomarkers by the prostate biopsy results. The mean values of albumin, hemoglobin (HGB), RBC count, creatinine, and folate all decreased as the stage of PC increased. Conversely, the mean value of PSA increased as the stage of PC increased. For the laboratory biomarkers MCV, BUN, platlet count, WBC, LDH, and bilirubin, their mean values fluctuated without demonstrating any particular trend.

A test for trend significance was additionally performed on table 8. As the prostate biopsy result increased from prostatitis to stage D PC, significant trends (p-value <.05) were noted for the mean value of HGB, creatinine, PSA, and BUN. Conversely, the lab biomarkers RBC, MCV, albumin, WBC, bilirubin, and platlet count did not demonstrate statistically significant trend changes.

	Prostatitis N=342	**BPH N=282**	**PIN N=138**	**PC Stage A N=332**	**PC Stage B N=220**	**PC Stage C N=48**	**PC Stage D N=16**
Albumin							
Mean	**4.00**	**3.98**	**4.09**	**4.04**	**4.00**	**3.95**	**3.90**
SD	**0.38**	**0.37**	**0.37**	**0.38**	**0.42**	**0.39**	**0.42**
HGB *							
Mean	**14.27**	**14.24**	**14.30**	**14.17**	**13.70**	**12.59**	**12.84**
SD	**1.54**	**1.76**	**1.68**	**1.66**	**1.87**	**2.20**	**14.08**
RBC							
Mean	**4.67**	**4.65**	**4.76**	**4.69**	**4.63**	**4.58**	**4.50**
SD	**0.46**	**0.52**	**0.52**	**0.50**	**0.57**	**0.44**	**0.67**
Creatinine*							
Mean	**1.25**	**1.16**	**1.20**	**1.16**	**1.15**	**1.14**	**1.13**
SD	**0.70**	**0.32**	**0.35**	**0.56**	**0.34**	**0.39**	**0.20**
PSA*	**8.06**	**7.99**	**7.67**	**9.70**	**14.12**	**21.85**	**44.03**
Mean	**6.74**	**11.20**	**4.58**	**11.66**	**29.27**	**30.21**	**48.71**
SD							

www.manaraa.com

	Prostatitis N=342	BPH N=282	PIN N=138	PC Stage A N=332	PC Stage B N=220	PC Stage C N=48	PC Stage D N=16
MCV							
Mean	**90.78**	**91.13**	**90.09**	**91.17**	**90.98**	**90.23**	**92.24**
SD	**4.65**	**5.35**	**5.79**	**5.05**	**6.11**	**4.18**	**4.99**
Bilirubin							
Mean	**0.66**	**0.65**	**0.60**	**0.66**	**0.67**	**0.65**	**0.60**
SD	**0.40**	**0.30**	**0.25**	**0.35**	**0.35**	**0.34**	**0.30**
BUN*							
Mean	**17.98**	**17.60**	**17.23**	**16.53**	**17.40**	**16.00**	**15.97**
SD	**6.93**	**7.90**	**6.50**	**6.56**	**6.73**	**6.74**	**4.54**
Platlet							
Mean	**230.45**	**227.63**	**240.81**	**226.54**	**232.50**	**234.30**	**235.44**
SD	**59.16**	**61.56**	**84.31**	**62.26**	**69.25**	**68.07**	**50.76**
WBC							
Mean	**7.24**	**7.11**	**7.42**	**7.19**	**7.13**	**10.41**	**7.37**
SD	**2.11**	**2.17**	**3.24**	**2.42**	**2.08**	**17.78**	**1.84**
Folate							
Mean	**12.93**	**12.56**	**12.31**	**13.37**	**11.92**	**10.71**	**10.03**
SD	**5.44**	**5.78**	**5.29**	**5.25**	**5.43**	**5.44**	**4.99**
LDH							
Mean	**426.91**	**424.78**	**371.84**	**404.60**	**406.41**	**392.11**	**393.33**
SD	**375.09**	**144.84**	**185.54**	**155.38**	**158.19**	**170.98**	**73.76**

Table 9. Mean value and SD of Lab biomarkers by Prostate biopsy results
*** - Trend significance (P-value <.05)**

Testing the Hypothesis

***4.2 - Hypothesis 1*: Among VA patients who have undergone prostate biopsies secondary to a PSA value of >4ng/dL, specified lab biomarkers* among cases of prostate cancer will differ significantly from those among VA patients without prostate cancer.**

www.manaraa.com

Crude Odds Ratios (with 95 % CI) for the association of each laboratory biomarker with prostate cancer is presented in three ways:

- **Method 1** - all stages of PC vs. non-cancerous prostate conditions
- **Method 2** - PC stages (B, C, D) vs. other (stage A PC, PIN, BPH, and prostatitis)
- **Method 3** - PC stages (B, C, D) vs. non-cancerous conditions (PIN, BPH, prostatitis). Stage A PC is excluded in this analysis method. This data is outlined in Table 10-12, respectively.

Method 1

There were 3 independent variables in this analysis that were statistically significantly related to the PC positive cases when compared to the control group (PC negative: PIN, BPH, and prostatitis) (Table 10). Initial crude analysis revealed hemoglobin, PSA, and serum BUN were significantly related; while age, hematuria, albumin, creatinine, MCV, platlet count, RBC count, bilirubin, and WBC were not statistically significant.

www.manaraa.com

Covariates Included	Odds Ratio	OR 95% Confidence Interval
HGB *	0.87	(0.82-0.93)
AGE	1.01	(0.99-1.02)
PSA*	1.04	(1.02-1.06)
Hematuria	0.95	(0.86-1.06)
Proteinuria	0.94	(0.83-1.07)
Albumin	1.03	(0.78-1.36)
Creatinine	0.76	(0.76-1.01)
MCV	1.01	(0.99-1.03)
PLT	1.00	(0.99-1.00)
RBC	0.92	(0.75-1.13)
Total Bilirubin	1.14	(0.84-1.55)
BUN*	0.98	(0.96-0.99)
WBC	1.01	(0.98-1.05)

Table 10. Odds Ratio and 95% CI for Method 1: PC (all stages) vs. non-cancerous conditions, per laboratory unit
*** P-value significance at 0.05**
**** P-value <0.01**
***** P-value <.001**

Method 2

When the stage A PC subjects were placed in the comparison group (leaving stage B, C, and D PC subjects as the 'cases'), there were 5 independent variables that demonstrated statistically significant relationships with the PC positive cases (when compared to the control group: stage A PC, PIN, BPH, and prostatitis). Initial bivariate analysis revealed hemoglobin, age, PSA, hematuria, and RBC count were the significant biomarkers, while albumin, creatinine, MCV, platlet count, bilirubin, BUN, and WBC were not.

www.manaraa.com

Covariates Included	Odds Ratio	OR 95% Confidence Interval
HGB *	0.79	(0.74-0.85)
AGE*	1.02	(1.01-1.03)
PSA*	1.04	(1.03-1.05)
Hematuria*	1.23	(1.10-1.38)
Proteinuria	1.16	(1.00-1.34)
Albumin	0.77	(0.55-1.08)
Creatinine	0.76	(0.52-1.12)
MCV	1.00	(0.97-1.03)
PLT	1.00	(0.99-1.00)
RBC*	0.76	(0.59-0.98)
Total Bilirubin	1.15	(0.80-1.66)
BUN	0.99	(0.98-1.01)
WBC	1.03	(0.99-1.06)

Table 11. Odds Ratio and 95% CI for Method 2: PC (stage B, C, D) vs. other (PC stage A, PIN, BPH, prostatitis), per laboratory unit
*** P-value < 0.05**
**** P-value <0.01**
***** P-value <0.001**

Method 3

When the stage A PC subjects were dropped from the analysis process (leaving stage B, C, and D PC subjects as the 'cases', and PIN, BPH, and prostatitis subjects as the 'controls'), there were 3 independent variables that were significantly related to the PC positive cases. Initial bivariate analysis revealed hemoglobin, PSA, and hematuria were significantly related to PC, while age, proteinuria, albumin, creatinine, MCV, platlet count, bilirubin, BUN, and WBC were not (See table 12 below).

www.manaraa.com

Covariates Included	Odds Ratio	OR 95% Confidence Interval
HGB *	0.79	(0.73-0.85)
AGE	1.02	(1.00-1.03)
PSA*	1.06	(1.04-1.08)
Hematuria*	1.15	(1.02-1.29)
Proteinuria	1.09	(0.94-1.27)
Albumin	0.83	(0.58-1.18)
Creatinine	0.68	(0.46-1.02)
MCV	1.00	(0.98-1.03)
PLT	1.00	(0.99-1.00)
RBC	0.77	(0.59-1.01)
Total Bilirubin	1.19	(0.81-1.75)
BUN	0.99	(0.97-1.01)
WBC	1.02	(0.99-1.06)

Table 12. Odds Ratio and 95% CI for Method 3: PC (stage B, C, D) vs. non-cancerous conditions (PIN, BPH, prostatitis), per laboratory unit (stage A PC not in analysis)
*** P-value significance at 0.05**

Table 13 below summarizes the laboratory biomarkers which demonstrated a statistically significant relationship with PC. The lab biomarkers proteinuria, albumin, creatinine, platlet count, bilirubin, and WBC were not significantly related to PC in the crude analysis.

Independent Variable	Method 1	Method 2	Method 3
Hemoglobin (HGB)	***	***	***
RBC count		*	
BUN	*		
Hematuria		*	*
PSA	***	***	***
Age		*	*

Table 13. Summary table of independent variables that demonstrate statistically significant relations with PC (by analysis methods 1-3)
*** P-value <0.05**
**** P-value <0.01**
*****P-value <0.001**

www.manaraa.com

4.3 - Hypothesis 2: **Among VA patients who have undergone prostate biopsies secondary to a PSA value of >4ng/dl, the addition of specified lab biomarkers* will improve the effectiveness of predicting the presence of prostate cancer when compared to PSA alone.**

Comparison Groups	Method 1	Method 2	Method 3
PC Cases/Total biopsies	616/1,378	284/1,378	284/1,046
Positive Predictive Value	44.7%	20.6%	27.2%

Table 14. Positive Predictive Value of PSA > 4ng/dL
Method 1: PC (all stages) vs. non-cancerous conditions (PIN, BPH, prostatitis)
Method 2: PC (stage B, C, D) vs. other (stage A PC, PIN, BPH, prostatitis)
Method 3: PC stage (B, C, D) vs. non-cancerous conditions (PIN, BPH, prostatitis)

Table 14 outlines the PPV of PSA (4ng/dL) alone for detecting prostate cancer. This PPV was evaluated 3 different ways:

- ***Method 1*** - all stages of PC vs. non-cancerous prostate conditions
- ***Method 2*** - PC stages (B, C, D) vs. other (stage A PC, PIN, BPH, and prostatitis)
- ***Method 3*** (stage A PC excluded) - PC stages (B, C, D) vs. non-cancerous conditions (PIN, BPH, prostatitis), respectively.

The positive predictive value was decreased significantly when stage A PC was not considered as a case. In particular, the PPV decreased by 24.1% when the stage A PC group was considered as in the comparison group (non-diseased).

To begin the regression process, a full model was assimilated, including all laboratory biomarkers, age, and ethnicity. Multiple models were then run, excluding each covariate, one by one, to assess the change of the -2 Log Likelihood value and the C-statistic. The evaluation process continued until the most parsimonious model with the

www.manaraa.com

lowest -2 Log Likelihood value and highest C-statistic was determined for each of the 3 analysis methods (tables 15-17 below).

Interaction terms were evaluated for each of the 3 analysis methods. While the overall change to the of the -2 Log Likelihood value and the C-statistic were minimal and not statistically significant, the interaction between age and HGB and age and PSA were significant (p-value <.05). For a 50 year old man, the OR for HGB and PSA would be (1.02, 95%CI 1.01-1.04, respectively. For a 70 year old man, the comparable OR would be (1.03, 95%CI 1.01-1.04), respectively. This interaction was noted to be of quantitative rather than qualitative significance.

Parameter	ML Est.	SE	OR	95% CI	C stat	-2 LL
Intercept	**-7.9494**	**1.88**	**xx**	**xx**	**0.68**	**1777.339**
HGB**	**-0.3519**	**0.06**	**0.70**	**(0.63-0.79)**		
RBC**	**0.9227**	**0.21**	**2.52**	**(1.67-3.78)**		
Hematuria**	**-0.2874**	**0.15**	**0.75**	**(0.56-1.01)**		
Creatinine**	**-0.4393**	**0.17**	**0.65**	**(0.47-0.89)**		
Black**	**0.6336**	**0.21**	**1.89**	**(1.25-2.90)**		
PSA**	**0.0408**	**0.08**	**1.04**	**(1.03-1.06)**		
AGE**	**0.0196**	**0.01**	**1.02**	**(1.01-1.03)**		
MCV**	**0.0663**	**0.02**	**1.07**	**(1.04-1.10)**		
Albumin***	**0.2871**	**0.16**	**1.33**	**(0.98-1.82)**		

Table 15. Best fit Logistical Regression for Method 1: Risk of PC with Lab biomarkers and 95% CI, per laboratory unit
Method 1: PC (all stages) vs. non-cancerous conditions (PIN, BPH, prostatitis)
**** p-value <.05, *** Not significant**

www.manaraa.com

Parameter	ML Est.	SE	OR	95% CI	C Stat	-2 LL
Intercept	-5.1041	xx	xx	xx	0.713	1276.366
HGB**	-0.3784	0.05	0.69	(0.62, 0.76)		
RBC**	0.7641	0.21	2.15	(1.43, 3.23)		
Creatinine**	-0.6069	0.23	0.55	(0.35, 0.85)		
PSA **	0.0325	0.01	1.03	(1.02, 1.05)		
Age**	0.0183	0.01	1.02	(1.01, 1.04)		
MCV**	0.0488	0.02	1.05	(1.02, 1.08)		
Black***	0.3612	0.24	1.44	(0.90, 2.31)		

Table 16. Best fit logistical regression model for Method 2: Risk and 95% CI for PC with lab biomarkers, per laboratory unit
*** P-value <0.05, ** P-value <0.001, *** Not significant**

Parameter	ML Est.	SE	OR	95% CI	C stat	-2 LL
Intercept**	-6.8083	2.2821	xx	xx	0.742	1077.58
HGB***	-0.4720	0.0658	0.62	(0.55, 0.71)		
RBC**	1.1051	0.2516	3.02	(1.84, 4.94)		
Creatinine**	-0.8150	0.2543	0.44	(0.27, 0.73)		
Black*	0.6092	0.2664	1.84	(1.09, 3.10)		
PSA***	0.0540	0.0090	1.06	(1.04, 1.08)		
AGE*	0.0238	0.0010	1.02	(1.01, 1.04)		
MCV**	0.0658	0.0181	1.07	(1.03, 1.11)		

Table 17. Best fit logistical regression model for Model 3: Risk and 95% CI for PC with Lab biomarkers, per laboratory unit
Method 3: PC stage (B, C, D) vs. non-cancerous conditions (PIN, BPH, prostatitis)
PC stage A excluded from analysis
*** P-value <.05**
**** P-value <.01**
***** P-value <.001**

The ROC curves below demonstrate the validity that was yielded for analysis method 1-3, respectively. These ROC curves demonstrates the difference that exists between the existing prostate cancer screening test (PSA alone) and the secondary screening test to assess at what degree can we expect to improve PC screening by including this secondary rule into the PC screening process (see figures 2-7 below). Confidence intervals between PSA alone and the clinical decision rule models (PSA + lab

www.manaraa.com

biomarkers) did not overlap and were statistically significantly different. The ROC AUC: **Method 1** PSA alone 0.59, (95% CI 0.55, 0.61) to CDR (PSA+ significant lab biomarkers) 0.68 (95% CI 0.65, 0.71); **Method 2** PSA alone 0.63, (95% CI 0.58, 0.66) to CDR (PSA+ significant lab biomarkers) 0.72 (95% CI 0.68, 0.75); **Method 3** PSA alone 0.64 (95% CI 0.59, 0.68) to 0.74 CDR (PSA+ significant lab biomarkers) (95% CI 0.71, 0.78).

www.manaraa.com

ROC Curves: Figures 2-7.

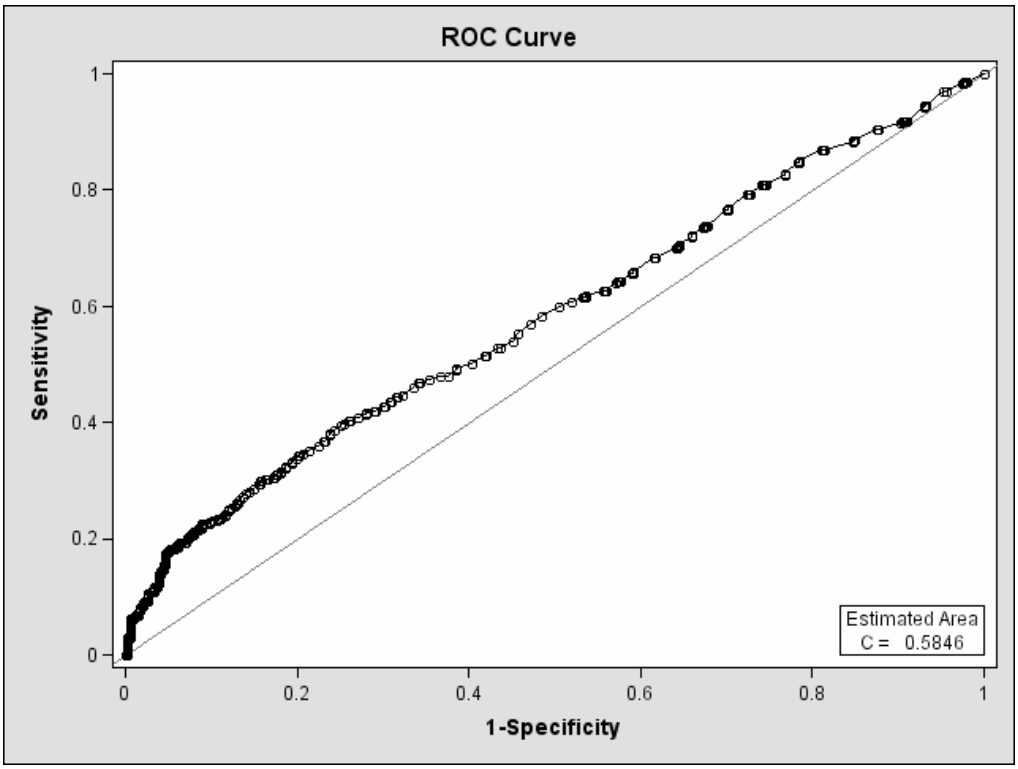


Figure 2. Diagnostic statistics = ROC curve of PSA Alone - Method 1

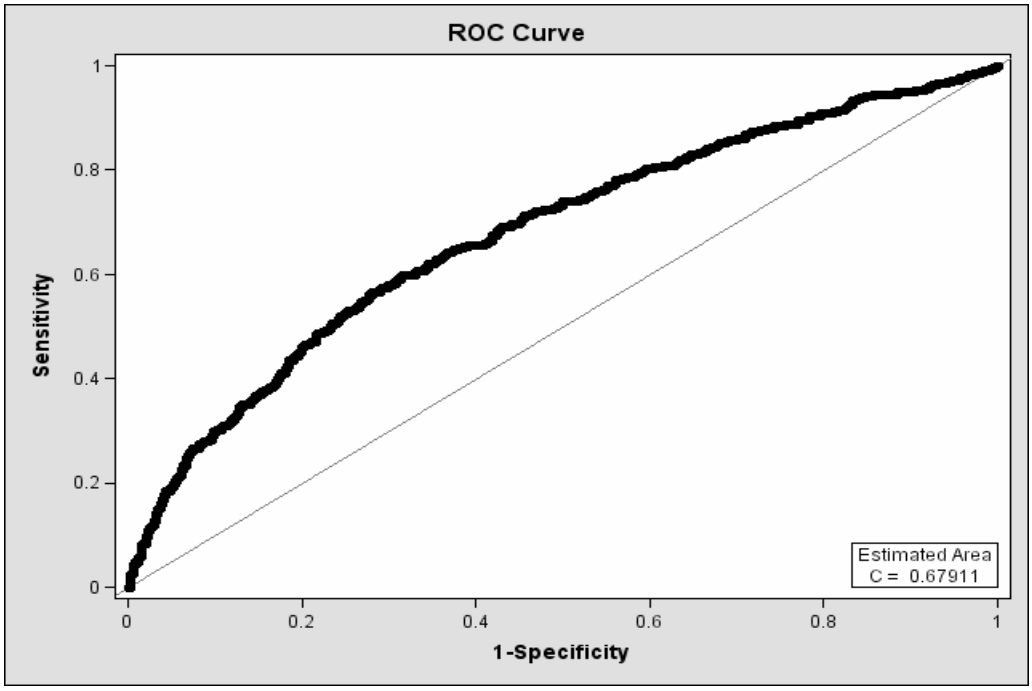


Figure 3. Diagnostic statistics = ROC curve of PSA + lab biomarkers - Method 1

www.manaraa.com

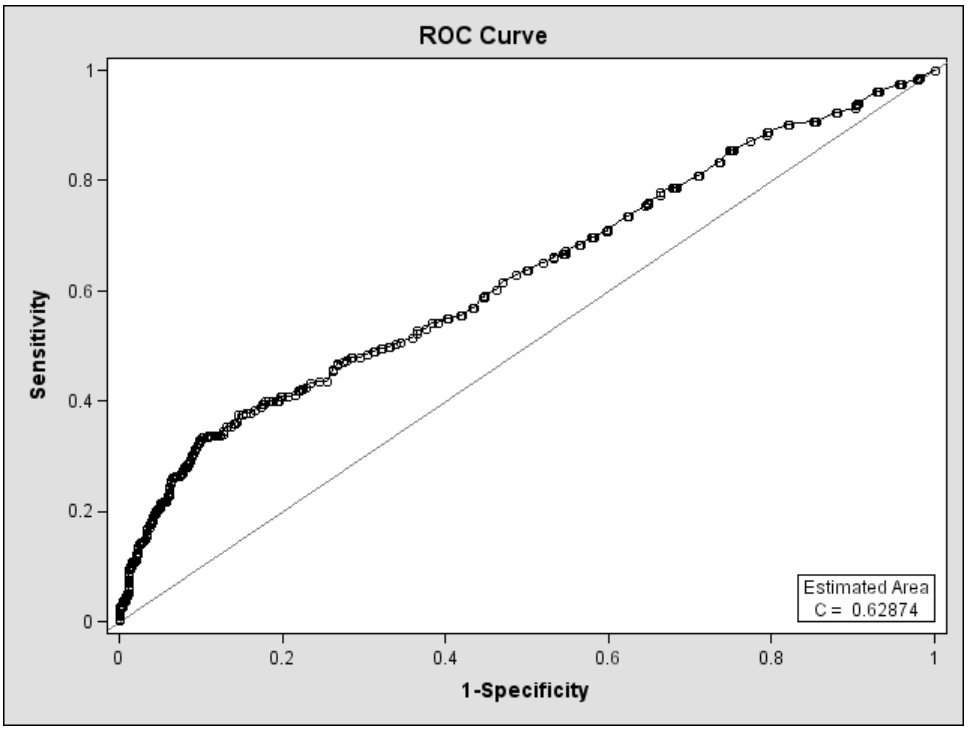


Figure 4.Diagnostic statistics = ROC curve of PSA Alone - Method 2

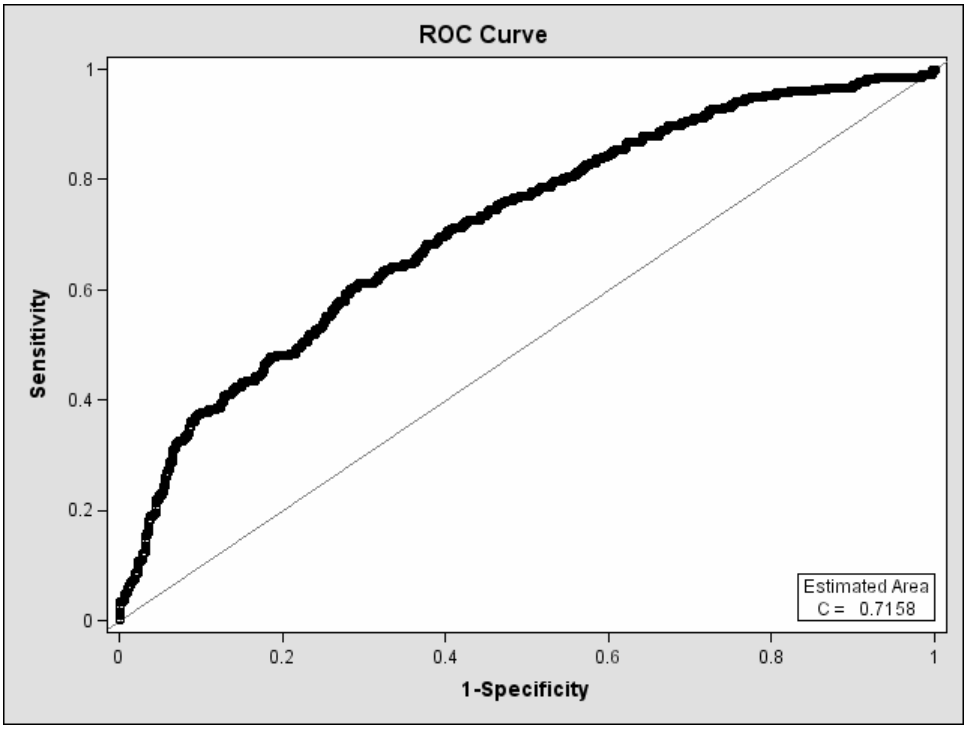


Figure 5. Diagnostic statistics = ROC curve of PSA + lab biomarkers - Method 2

www.manaraa.com

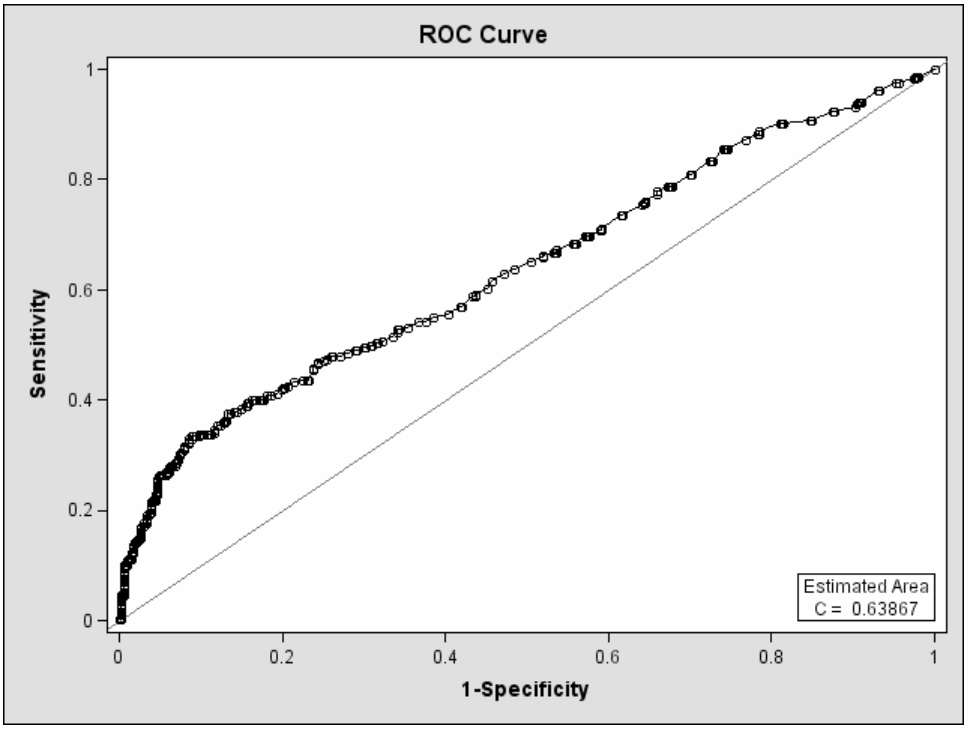


Figure 6. Diagnostic statistics = ROC curve of PSA Alone - Method 3

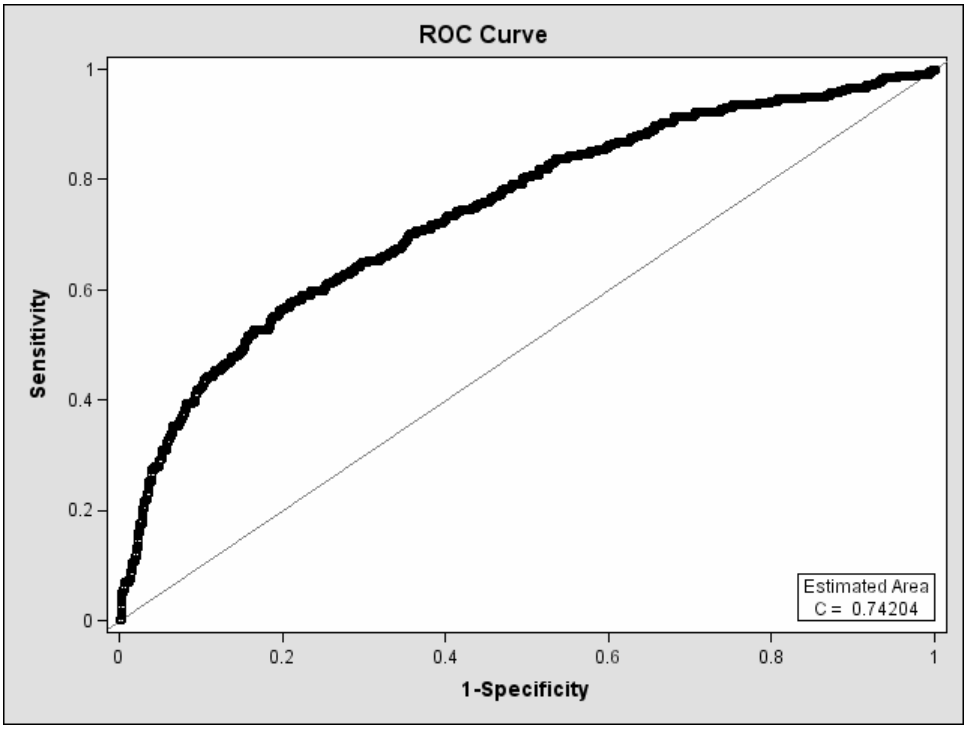


Figure 7. Diagnostic statistics = ROC curve of PSA + lab biomarkers - Method 2

www.manaraa.com

For determining the ideal cut-points for recommending prostate biopsy, 4 different cut-points where chosen, each providing either increased sensitivity or specificity. The cut-points are presented in four ways:

- ***Cut-point 1*** – The maximum likelihood ratio. This was determined by dividing the sensitivity by 1- the specificity (SEN/1-SPC), thus maximizing the quotient.
- ***Cut point 2*** – The probability that yielded a sensitivity of approximately 90% with the highest corresponding specificity.
- ***Cut point 3*** - The probability that yielded a sensitivity of approximately 80% with the highest corresponding specificity.
- ***Cut point 4*** **-** The probability that yielded a specificity of approximately 80% with the highest corresponding sensitivity. This data is outlined in Table 18- 19, respectively.

www.manaraa.com

	Method 1	Method 2	Method 3
Cut-point 1 (MLE)	**Probability .45**	**Probability .41**	**Probability .42**
Sensitivity	**52.1 %**	**18.3 %**	**33.5 %**
Specificity	**74.0 %**	**96.2 %**	**93.4 %**
PPV	**61.8 %**	**55.3 %**	**65.5 %**
NPV	**65.7%**	**81.9 %**	**79.0 %**
Cut-point 2 (Sen. 90%)	**Probability .33**	**Probability .13**	**Probability .17**
Sensitivity	**90.9 %**	**89.8 %**	**90.1 %**
Specificity	**17.6 %**	**28.0 %**	**31.1 %**
PPV	**47.1 %**	**20.6 %**	**32.8 %**
NPV	**70.5 %**	**91.3 %**	**89.4 %**
Cut-point 3 (Sen. 80%)	**Probability .37**	**Probability .15**	**Probability .20**
Sensitivity	**80.5 %**	**78.2 %**	**78.9 %**
Specificity	**37.1 %**	**45.0 %**	**49.9 %**
PPV	**50.9 %**	**28.7 %**	**37.0 %**
NPV	**70.2 %**	**88.8 %**	**86.4 %**
Cut-point 4 (Spc. 80%)	**Probability .48**	**Probability .23**	**Probability .29**
Sensitivity	**39.9 %**	**45.8 %**	**52.1 %**
Specificity	**81.4 %**	**79.5 %**	**81.8 %**
PPV	**63.4 %**	**36.7 %**	**51.6 %**
NPV	**62.6 %**	**85.0 %**	**82.1 %**

Table 18. Sensitivity, Specificity, PPV, and NPV for probability cut-off points

	Method 1	Method 2	Method 3
Crude PPV	**44.7 %**	**20.6 %**	**27.2 %**
Cut-point 1	**61.8 %**	**55.3 %**	**65.5 %**
Cut-point 2	**47.1 %**	**20.6%**	**32.8 %**
Cut-point 3	**50.9 %**	**28.7%**	**37.0 %**
Cut-point 4	**63.4 %**	**36.7%**	**51.6 %**

Table 19. Comparison of PPV between PSA (>4ng/dL) and cut-points 1-4 by analysis method

www.manaraa.com

***4.4 - Hypothesis 3*: Among VA cases of histologically confirmed prostate cancer, there exists a gradient between specified lab biomarkers* and increasing stage of prostate cancer.**

To evaluate hypothesis III, the mean values of each specified lab parameter (with accompanying 95 % CI) was determined for each PC stage. If there exists a gradient between the lab biomarkers and increasing stage of PC severity, one would expect to see a change in the mean value of the biomarker (away from the normal expected level) as the PC stage increases. This set of circumstances is seen in mean change of the lab biomarkers HGB, RBC, Albumin, and PSA (Table 20, below).

www.manaraa.com

	PC Stage A N=332	PC Stage B N=220	PC Stage C N=48	PC Stage D N=16
Albumin				
Mean	**4.04**	**4.00**	**3.95**	**3.90**
SD	**0.38**	**0.42**	**0.39**	**0.42**
95%CI	**(4.00, 4.08)**	**(3.96, 4.05)**	**(3.84, 4.06)**	**(3.69, 4.11)**
HGB				
Mean	**14.17**	**13.70**	**12.59**	**12.84**
SD	**1.66**	**1.87**	**2.20**	**14.08**
95%CI	**(14.00, 14.35)**	**(13.45, 13.95)**	**(11.97, 13.21)**	**(5.94, 19.74)**
RBC				
Mean	**4.69**	**4.63**	**4.58**	**4.50**
SD	**0.50**	**0.57**	**0.44**	**0.67**
95%CI	**(4.64, 4.74)**	**(4.55, 4.71)**	**(4.46, 4.70)**	**(4.17, 4.83)**
Creatinine				
Mean	**1.16**	**1.15**	**1.14**	**1.13**
SD	**0.56**	**0.34**	**0.39**	**0.20**
95%CI	**(1.10, 1.22)**	**(1.11, 1.20)**	**(1.03, 1.25)**	**(1.03, 1.23)**
PSA				
Mean				
SD	**9.70**	**14.12**	**21.85**	**44.03**
95%CI	**11.66**	**29.27**	**30.21**	**48.71**
	(8.45, 10.95)	**(10.25, 17.99)**	**(13.31, 30.39)**	**(20.16, 67.90)**
MCV				
Mean	**91.17**	**90.98**	**90.23**	**92.24**
SD	**5.05**	**6.11**	**4.18**	**4.99**
95%CI	**(90.63, 91.71)**	**(90.17, 91.79)**	**(89.05, 91.41)**	**(89.79, 94.69)**
Bilirubin				
Mean	**0.66**	**0.67**	**0.65**	**0.60**
SD	**0.35**	**0.35**	**0.34**	**0.30**
95%CI	**(0.28, 1.04)**	**(0.62, 0.72)**	**(0.60, 0.70)**	**(0.45, 0.75)**
BUN				
Mean	**16.53**	**17.40**	**16.00**	**15.97**
SD	**6.56**	**6.73**	**6.74**	**4.54**
95%CI	**(15.82, 17.24)**	**(16.51, 18.29)**	**(17.91, 14.09)**	**(13.74, 18.20)**
Platlet				
Mean	**226.54**	**232.50**	**234.30**	**235.44**
SD	**62.26**	**69.25**	**68.07**	**50.76**
95%CI	**(219.8, 233.2)**	**(223.4, 241.7)**	**(215.1, 253.6)**	**(210.6, 260.3)**
WBC				
Mean	**7.19**	**7.13**	**10.41**	**7.37**
SD	**2.42**	**2.08**	**1.78**	**1.84**
95%CI	**(6.93, 7.45)**	**(6.86, 7.40)**	**(9.91, 10.91)**	**(6.47, 8.27)**

Table 20. Mean value, SD, and 95% CI of Lab biomarkers by PC stage

www.manaraa.com

A trend analysis was performed to determine whether or not the change seen with lab biomarkers HGB, RBC, Albumin, and PSA was statistically significant. This trend analysis was performed through linear regression modeling. These linear models were analyzed by first coding each continuous laboratory biomarkers as the criterion variable, with the PC stage coded as the predictor variable. The model results suggest that PC stage is a significant statistical predictor for gradient changes in the laboratory biomarkers HGB, RBC count, albumin, and PSA (table 21, below). The four subsequent graphs further demonstrate the change in mean value by PC stage for each significant lab biomarker.

Criterion Parameters	Parameter Estimate	SE	T value	R square	Adjusted R square	F value	Biomarker change
HGB*	-0.58752	0.099	-5.96	0.0547	0.0532	35.54	0.555
RBC*	-0.06291	0.028	-2.22	0.0079	0.063	4.91	0.939
MCV- NS	-0.11639	0.292	-0.4	0.0003	-0.00014	0.16	XX
Creat. - NS	-0.009	0.026	-0.37	0.0002	-0.0014	0.14	XX
Albumin*	-0.0483	0.021	-2.26	0.0083	0.0067	5.12	0.953
PSA*	7.458	1.227	6.08	0.0568	0.0552	36.95	1733.6

Table 21. Results of Linear Regression modeling of lab biomarker by PC stage
*** P-value <.05**
**** P-value <.001**
***** P-value <.001**
NS-Not statistically significant

www.manaraa.com

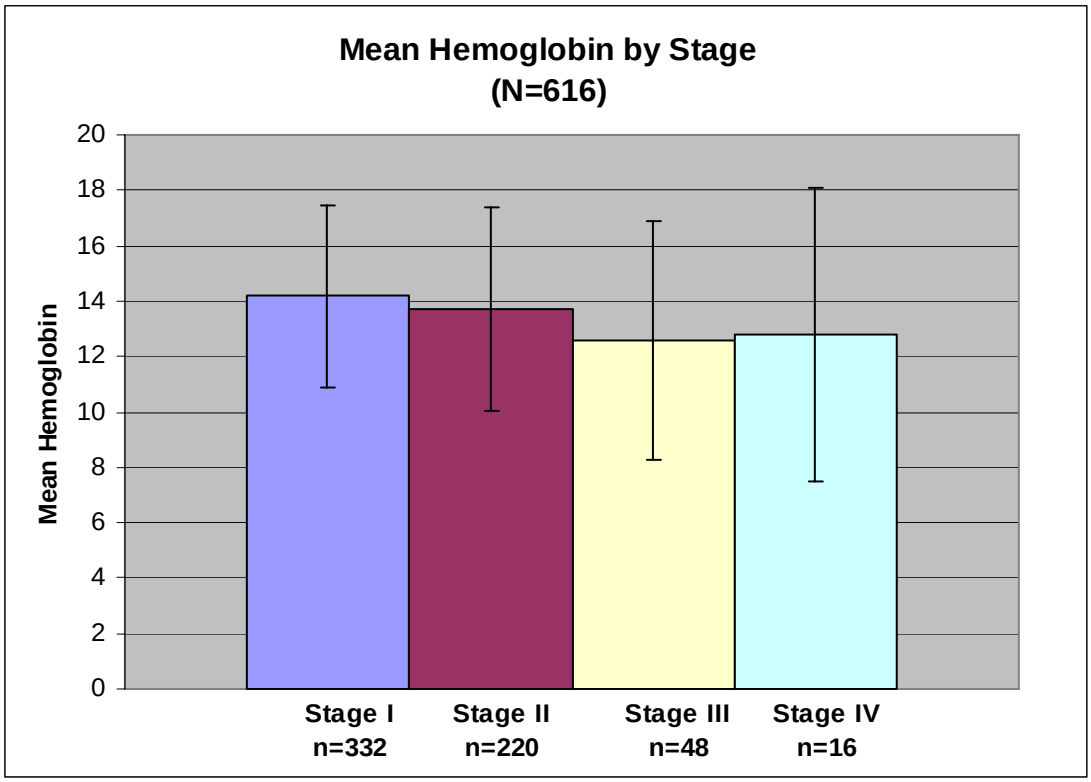


Figure 8. Mean Hemoglobin value by PC stage

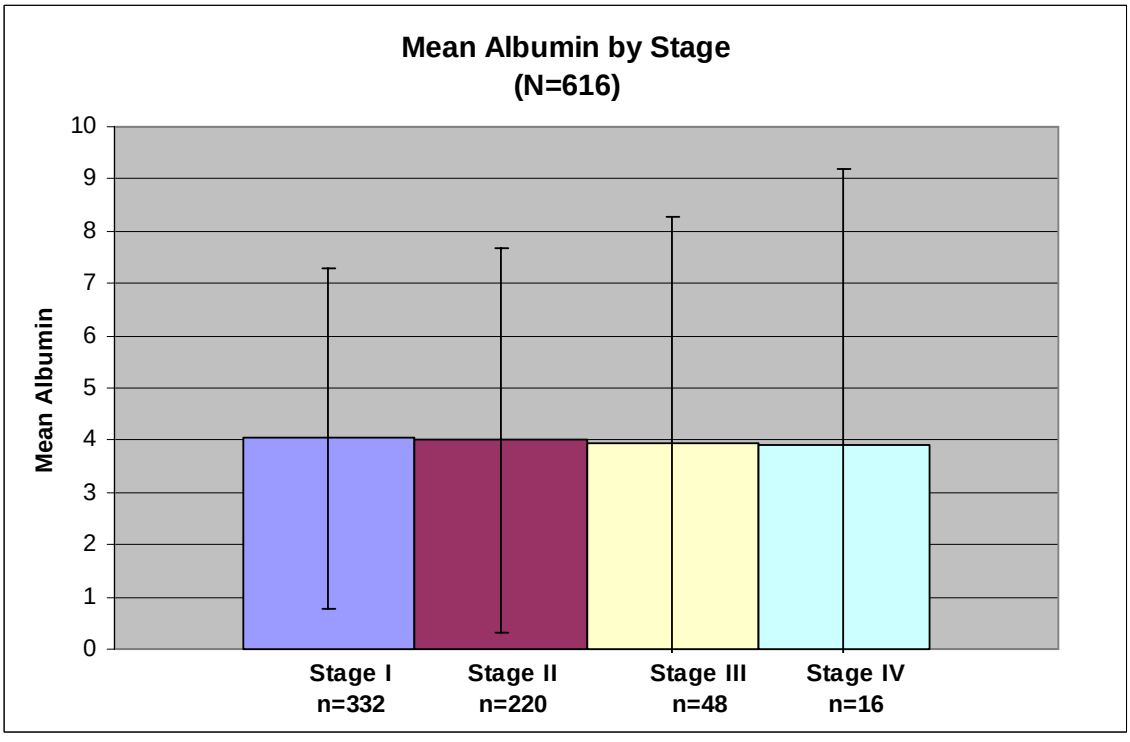


Figure 9. Mean Albumin value by PC stage

www.manaraa.com

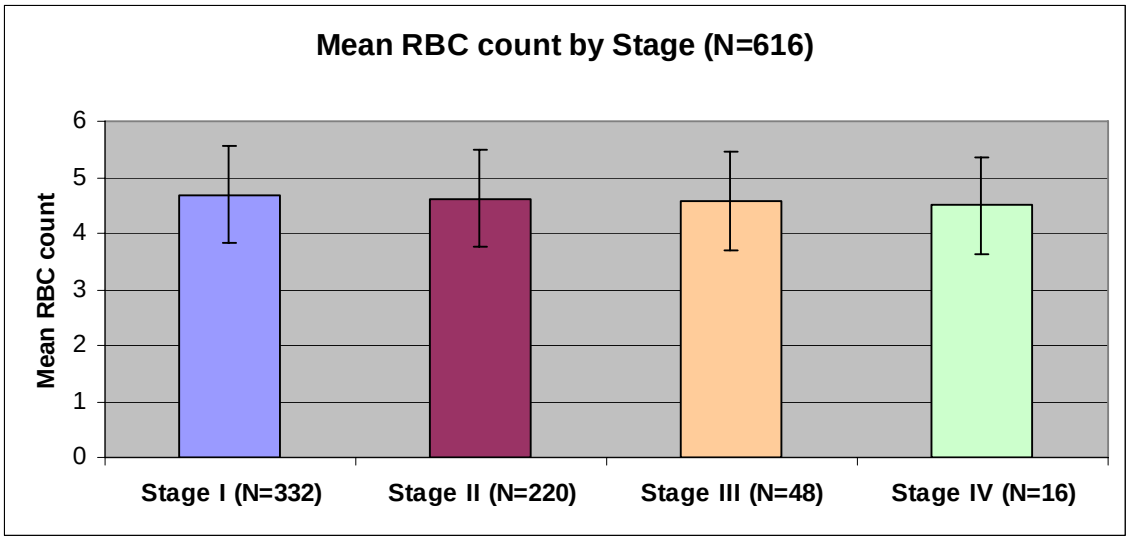


Figure 10. Mean RBC count by PC stage

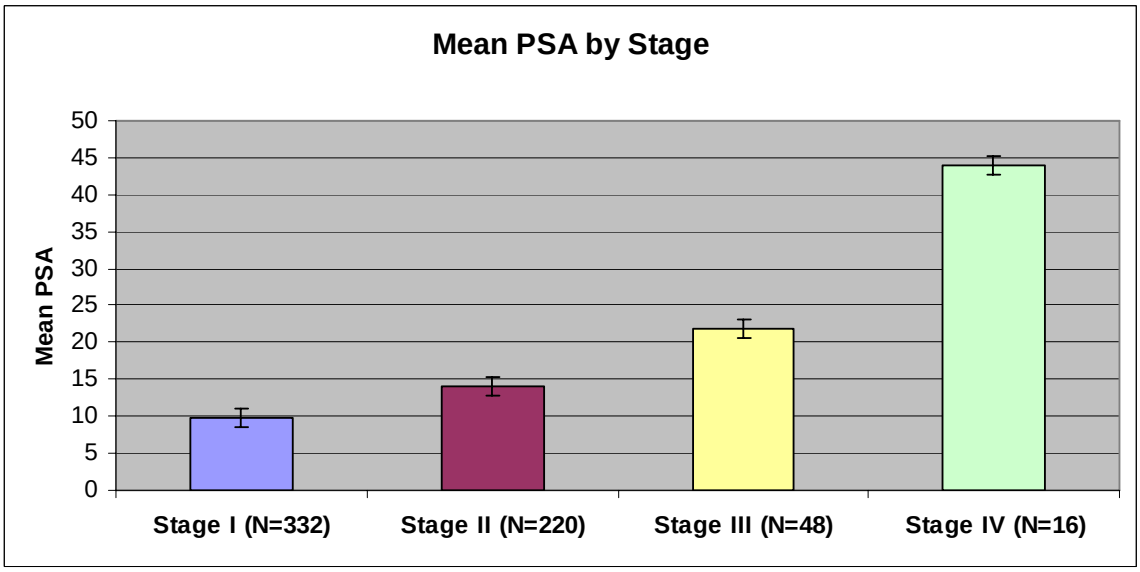


Figure 11. Mean PSA value by PC stage

www.manaraa.com

Chapter V: Discussion

5.1 - Introduction (Chapter I-III Review)

A search of peer reviewed published literature failed to identify any studies that evaluate whether (or not) combinations of laboratory biomarkers, used in concurrence with an elevated PSA, increase the detection of screened identified PC. However, previous research has demonstrated that specific systems are altered as PC increases in stage and severity.[29, 30, 32, 92] In particular, anemia (either iron defiency or anemia of chronic disease) is a frequent complication of PC, and hematuria is a common finding in patients with prostate tumors that have spread outside of the prostate capsule, but have not yet spread to distant body regions.[33] In multiple published studies, decreased hemoglobin has been reported as an independent risk factor for decreased survival outcomes in patients with hormone refractory prostate cancer.[91] Moreover, previous research has demonstrated that PSA has limitations (e.g. poor validity and reliability) and there is room for improvement. [1, 8, 11]

A primary goal of PC screening is to detect the cancers before they are too advanced for treatment, and to bypass the tumors that are not destined to become deleterious in the patient's lifetime.[106] With that stated, delineation between the different types of PC is difficult, but of paramount importance. Earlier PSA research by Catalona, the U.S. Preventive Task Force and more recent work by Thompson, Carter, the PLCO (and others), has been critical in improving our ability to identify PC at earlier disease

www.manaraa.com

stages.[11, 25, 106] However, there is continued debate over the utility of PSA as a screening tool for prostate cancer.[8] Is it the best currently available tool for the detection of pre-clinical PC? This debate is likely to continue until the results of the PLCO trial are released (tentatively scheduled for 2014).

How can PC screening be improved? Despite a wealth of published literature that has evaluated PSA and argued against its use as a PC screening tool, PSA remains the mainstay for clinicians for PC screening. Thus, the focus must be on augmenting PSA, not replacing it altogether. Prior attempts at improving PC screening have focused on replacing PSA with a new test. Tools such as PSA velocity, PSA density, Free/Total PSA ratio have all shown promise in studies for improving PC screening results, but difficult implementation and a lack of universal acceptance among clinicians have hindered their incorporation into daily clinical practice.[7, 23, 26, 27, 40, 41, 41, 86]

Have researchers and clinicians made the most of all available information when evaluating a patient for prostate cancer? Routinely ordered lab panels (complete blood count, basic metabolic panels, and urinalyses) all contain biomarkers that change in value when diseases associated with prostate cancer are present. Yet these biomarkers have not been utilized when evaluating a patient for PC. Many previous studies have accurately described PSA elevations as 'specific to a condition of the prostate'.[8, 18] However, these PSA elevations are not specific to prostate cancer. In what may hold the key to improving the overall yield of PC screening; evaluating changes in certain laboratory biomarkers values (in the presence of an elevated PSA) that are associated with diseases that are a product (either directly or indirectly) of PC spread may provide a wealth of important information that can improve the validity and reliability of PC screening.

www.manaraa.com

5.2 – Review of Main Findings (Chapter IV)

A primary goal of PC screening is to detect the cancers before they are too advanced for treatment, and to overlook the tumors that are not destined to become deleterious in the patient's lifetime.[106] With that stated, 2 questions arose during the course of this study. Given that stage A (non-palpable, organ confined) PC often is undetectable and offers little biological evidence of its presence, does its inclusion in this analysis mitigate the difference between the clinically important PC and non-cancerous prostate disease? Are the laboratory biomarkers under evaluation related more to more advanced (or aggressive) PC stages? To answer these questions, the statistical analysis procedures were performed utilizing 3 different methods. For method 1, stage A PC was included as a 'case', for method 2, stage A PC was included as a 'control', and in method 3, stage A PC was excluded from the analysis altogether. The intent in evaluating the data by multiple methods is to develop a clinical decision rule that can provide clinicians and patients information on the probability of the presence/absence of PC, and if it is PC, the likely stage of the cancer, prior to prostate biopsy.

This study hypothesized that specific lab biomarkers among cases of PC would differ significantly from those patients without PC. The countering null hypothesis states the specific laboratory biomarkers do not differ between the PC patients and non-cancerous patients. This hypothesis was evaluated by both bivariate (e.g. one outcome variable, one independent variable) and multivariate analysis techniques. Initially, analysis method 1 demonstrated that HGB, PSA, and serum BUN were significant variables (see chapter IV table 10). The relationships were then re-evaluated with multiple logistic regression, and a more precise picture began to develop. Additional

www.manaraa.com

significant predictor variables emerged, and serum BUN was not significant in the multivariate model. Throughout the method 1 modeling process, HGB (OR=1.42 95%CI 1.27-1.59), RBC count (OR=2.52 95%CI 1.67-3.78), PSA (OR=1.04 95%CI 1.03-1.05), serum creatinine (OR=1.55 95%CI 1.12-2.15), and the ethnicity variable 'Black' (OR=1.88 95%CI 1.25-2.85) were significantly related to the PC group. Under conditions where all other predictor variables are held constant; both HGB (point estimate -.3519 p-value <.0001) and creatinine (point estimate -.4393 p-value .008) demonstrated increased PC risk with a 1 unit negative change in their value; while RBC count (point estimate .9227 p-value <.0001), age (point estimate .0196 p-value <.005), PSA value (point estimate .0408 p-value <.005), MCV level (point estimate .066 p-value <.0001), and serum albumin (point estimate .2871 p-value .071) demonstrated increased PC risk of 1 unit positive increase in their respected values.

Analysis method 2 (stage A included in the comparison group) crude analysis demonstrated HGB, PSA, RBC count, hematuria, and age were significant variables (see chapter IV, table 11). Multiple regression modeling demonstrated HGB (OR 0.68 95%CI 0.62, 0.76), RBC (OR 2.15 95% CI 1.43, 3.23), serum creatinine (OR 0.545 95%CI 0.35, 0.85), PSA (OR 1.033 95%CI 1.02, 1.05), MCV (OR 1.05 95%CI 1.02, 1.08), and age (OR 1.018 95%CI 1.01, 1.04) were all significant after all other predictor variables were held constant.

Analysis method 3 (stage A excluded from the analysis); the crude analysis revealed HGB, PSA, and hematuria were significant variables (see chapter IV, table 12). Multiple regression modeling demonstrated HGB (OR 0.62 95%CI 0.55, 0.71), RBC (OR 3.02 95% CI 1.84, 4.94), serum creatinine (OR 0.44 95%CI 0.27, 0.73), PSA (OR 1.06

www.manaraa.com

95%CI 1.04, 1.08), MCV (OR 1.07 95%CI 1.03, 1.11), and age (OR 1.02 95%CI 1.01, 1.04) were all significant after all other predictor variables were held constant.

The second hypothesis stated 'the addition of specific lab biomarkers will improve the effectiveness of predicting prostate cancer when compared to PSA alone'. The countering null hypothesis is, 'there is no difference between the two models'. To address this question, ROC curves were employed. ROC curves measure the probability of correct diagnostic classification, i.e. the test accuracy.[114] I compared the ROC curve of the best fit model for analysis methods 1-3 to the ROC curves of PSA (4ng/dL) to determine if the area under the curve (AUC) between the models and the PSA model are significantly different. In addition, the 95 % CI was determined for all models. The AUC increased from: **Method 1** PSA alone 0.59, (95% CI 0.55, 0.61) to CDR best fit model 0.68, (95%CI 0.65, 0.71); **Method2** PSA alone 0.63, (95% CI 0.58, 0.66), to CDR best fit model 0.68, (95% CI 0.68, 0.75); **Method 3** PSA alone 0.64, (95%CI 0.59, 0.68), to CDR best fit model 0.74 (95% CI 0.71, 0.78). This indicates that the difference between the models is significant, thus the null hypothesis of no difference is rejected. In addition to the ROC curve, the validity (sensitivity/specificity) and predictive values (positive predictive value/negative predictive value) were determined for the best fit model. For the PSA only model, one can only determine the positive predictive value, given patients with a PSA less than 4ng/dL are not routinely forwarded for prostate biopsy. The PPV of PSA (>= 4ng/dL) decreased from 44.7% (method 1) to 20.6% (method 2). This indicates PSA is less effective as a tool for identifying the more clinically relevant PC (stage B, C, and D). Conversely, looking at method 2, cut-point 1 (see chapter IV, table 18) the sensitivity of this model was 18.3%, specificity was 96.2%, NPV 81.9%, and a PPV at

www.manaraa.com

55.3% These values are increased over the validity and predictive values that have been published in previous studies that attempted to clarify the ambiguity surrounding PSA sensitivity and specificity. This indicates that this model could improve our ability to detect clinically important PC. Moreover, depending on the cut-off point, the study offers hope that the number of unnecessary biopsies performed within the JH VA could be reduced.

The third hypothesis under evaluation was whether there exists a gradient of change between the significant lab biomarkers and increasing levels of PC. Four of the laboratory biomarkers did demonstrate a gradient with increasing stage of PC (hemoglobin, RBC, PSA, and albumin). For the stage IV PC, the small number of cases led to unstable point estimates, large confidence intervals, and it is suspected that if the numbers in this group increased, a similar gradient trend would materialize.

To evaluate the statistical significance of the gradient, linear regression analysis was performed. Each continuous laboratory biomarker was modeled as the outcome variable, with PC stage (A-D) modeled as the predictor variable. In addition to PSA, the variables hemoglobin, RBC count, and albumin demonstrated a significant difference between each PC stage (see chapter IV, table 21). These results indicate that the degree of change between the reference 'normal' value and the observed lab value could provide valuable insight for detecting PC, and improve our ability to differentiate between indolent PC and clinically relevant PC.

These results suggest that evaluation of additional laboratory biomarkers (in conjunction with an elevated PSA) might improve our ability to detect prostate cancer; while also decreasing the number of non-diagnostic prostate biopsies. Moreover, the

www.manaraa.com

results seem to indicate that the evaluated biomarkers may be more helpful in detecting clinically relevant cancer. After evaluating stage A PC in the comparison group, the PPV of PSA alone was 20.6% (284/1378). The CDR 'parsimonious' model (Method 2, cut-point 1), yielded a positive predictive value of 55.3% (52/94). With a specificity of 96.2% and a sensitivity of 18.3%, this model can reduce the number of unnecessary biopsies from 1,092 to 92. With a specificity of 96.2%, this clinical decision rule model will correctly identify more than 9 out of every 10 men who have do not have PC. In 1998, the JH VA performed 1,610 biopsies. If one were to apply this clinical decision rule (comparing PC stage B, C, D vs. stage A PC, PIN, BPH, and prostatitis) to the 1,378 subjects within this study, 52 of the 92 total biopsies (PPV= 55.3%) would have been positive for PC (stage B,C,D) (PSA alone=PPV 44.7%). In addition, if this clinical decision rule would have been employed, approximately 1,052 negative biopsies would not have been performed. This would have resulted in decreased cost for the VA hospital network, reduced anxiety and stress for patient, and a reduced risk of biopsy morbidity (given the biopsies would have never been performed).

5.3 - Consistency with Literature

There were many areas of this study that were consistent with prior published, peer reviewed studies. In particular, the proportion of PC that was localized to the prostate is consistent with the stage shift phenomenon (increased amounts of pre-clinical disease detected when compared to ways other than screening) seen with PC screening. Stage A comprised 53.9 % of all the PC cases; Stage B 35.7 %; Stage C 7.8 %; and Stage D 2.59 % (appendix: table 22). A stage shift towards less invasive disease at presentation has been attributed to PC screening and this scenario was seen in this study.

www.manaraa.com

Secondly, all laboratory biomarkers demonstrated 'movement' in the direction away from the 'normal' value that is consistent with previous literature and is biologically plausible.[101] For instance, PSA has been known to be elevated in both cancerous and non-cancerous prostate conditions.[1] This was seen in this study, as the range of the mean PSA value increased from 7.67 (prostatitis) to 44.03 (stage D PC). Multiple published studies have reported that a low hemoglobin value is an independent risk factor for deleterious survival outcomes in patients with hormone refractory prostate cancer.[91] In addition; the correlation between PC and hematologic disorders has been long recognized for its clinical significance, with anemia a frequent clinical manifestation of advancing PC.[101] In this study, the laboratory parameters HGB, RBC count, and MCV (all indicators of hematologic state) demonstrated values below their normal reference range (in patients with clinically relevant PC). When comparing the subjects with histologically confirmed prostatitis to patients with histologically confirmed stage C PC, the difference becomes evident. HGB decreased from 14.27 to 12.59, RBC count decreased from 4.67 to 4.58, and MCV decreased 90.78 to 90.23 (HGB and RBC count were statistically significant trends), respectively. In addition, it has been previously described that decreased creatinine has been linked to decreased muscle mass and severe liver disease (seen in patients with advancing PC).[35] In this study, creatinine demonstrated a decreasing trend as PC stage increased (1.16 to 1.13), although it was not statistically significant.

African-American ethnicity increased the risk of PC in men undergoing biopsy. There was an 83% increase in the risk of PC for African-American men when compared to Caucasian men. This is consistent with previous literature which describes PC

www.manaraa.com

incidence and mortality rates as disproportionately higher in African-American males than white males in the United States (up to two times higher).[44]

Advancing age is one of three non-modifiable risk factors for PC.[10] The incidence and prevalence of prostate cancer increases as men become older.[10] In this study, the mean age of subjects in this study was not significantly different. However, a one year increase in age did increase the odds of PC development by 2% (which was statistically significant).

5.4 - Internal Validity

There were specific study limitations that were identified during the performance of this study. Concerns with selection bias, incomplete data, misclassification of the outcome, and uncontrolled confounding were acknowledged and are outlined below. In addition, the perceived study strengths are outlined as well.

5.4.1- Selection Bias

One concern of this study was the potential for selection bias on obtaining prostate biopsies. It was believed that clinicians within the VA network follow an algorithm for sending patients for prostate biopsy. If a patient had an elevated PSA test, they would be referred onward for prostate biopsy. However, in the JH VA, do all men with an elevated PSA actually undergo prostate biopsy? As a check for internal validity (and to ensure selection bias is not present), further evaluation of this question was warranted. A search through the VISTA system was initiated to capture all PSA lab tests performed for the years 1998, 2000, and 2002. They were then sub-categorized for PSA values greater than 4ng/dL. This list was then crossed referenced against the list of patients that had a recorded prostate biopsy during the study period (1998-2004)

www.manaraa.com

(SNOMED codes: 77220, 77103, 77102, 77101, 77110, 77105, 77350, 77230, 77210, 77300, 77200, 77240, 77104, 77100, 77000, 77900, and 77250). During this period, there were 442,000 PSA tests performed at the JH VA, of which 3,425 patients had a value of greater than 4ng/dL. Of the 3,425 patients with elevated PSA values, 1,610 had undergone a prostate biopsy, and 1,810 had not (52.9%). Further investigation was needed to explain why over half of the patients with elevated PSA values did not undergo a biopsy. After much investigation and discussion with both JH VA Urology and Pathology physicians, it was determined that approximately 75% of the 1,810 elevated PSA values were of patients status post PC treatment (prostatectomy, radiation, cryotherapy, etc.), and had actually undergone a prostate biopsy before the timeline of this study, thus their biopsy results were not captured during the original VISTA search. It is important to note that PSA is used more frequently as a tool for post PC treatment follow-up than for screening.[106] It is considered the standard of care for all post-treatment PC patients to have an annual PSA draw to monitor for refractory prostate cancer. In addition, it was estimated that 12.5% of all patients that are found to have elevated PSA values through the VA medical network choose to have their care outside the VA network. Therefore, their specific treatment information is not available for analysis. It is estimated that 88-90 % of all participants in this study found to have an elevated PSA through screening were referred for evaluation via prostate biopsy.

5.4.2 - Incomplete data

Certain laboratory biomarkers had incomplete data which lead to the exclusion of these variables for analysis and interpretation. Although clinicians often obtain a complete blood count (CBC), basic metabolic panel (BMP), and urinalysis (UA) at the

www.manaraa.com

time of the screening PSA test, certain laboratory assays (e.g. PT/aPTT, and Folate) are not routinely included in these panels, thus they are not requested. Both PT and aPTT are used to evaluate the coagulation system, with increasing levels of both being an independent predictor of DIC (a systemic condition seen occasionally with metastatic PC).[75] High plasma levels of Folate has been previously reported as both protective and as a risk factor for PC development.[125] Given the plausible links to PC, they were of particular interest for this study. There are no current guidelines that recommended additional laboratory tests for PC screening; therefore clinicians do not make the request for such additional tests. This lack of data limits the strength of the analysis and interpretation of the results.

5.4.3 - Misclassification of outcome

Although each prostate biopsy was evaluated by two or more trained pathologists, the possibility that misclassification of disease status (i.e. patients who have PC were classified as 'no PC') does exist. Given that the outcome variable (PC yes or no) is determined by the results of a prostate biopsy, and that the biopsies themselves are a sampling of the entire prostate, there is a chance that the biopsy did not contain cancerous cells, yet the prostate itself does. If this scenario occurred, the patient would be categorized as 'no PC', when in fact they do have PC. When there are two outcome categories being compared (in this case, "PC yes/no"), this misclassification can bias the association either away or towards the null hypothesis. However, it is unlikely that an individual would be categorized as having PC if the carcinoma was not present on histological sample. Therefore if misclassification is present, it is more likely that a patient with PC is misclassified as not having prostate cancer, than a patient without PC

www.manaraa.com

being classified as having the disease.

5.4.4 - Uncontrolled confounding

Certain variables that were initially recommended for collection were not available for analysis; therefore this study's results may be a result of confounding. Specifically, information on family history of PC was found to be lacking in both the urological and general clinic patient encounter notes; and family history on any medical condition was available in less than 50 % of the study participants. In addition, social history (tobacco and alcohol use) and socio-economic status (which have been previously described as potential modifiable risk factors for PC) were initially scheduled for evaluation. Unfortunately, this information was also missing on a large percentage of the study participants (75%) and therefore unavailable for analysis.

5.4.5 – Study Strengths

The strengths of this study include the data quality, study population size, biologic plausibility, and the type of analysis performed.

The quality of the data was increased in that the diagnosis of prostate disease status was discerned from histologic evaluation of biological materials obtained from invasive prostate biopsy by at least two highly trained clinical pathologists. In addition, the use of laboratory data eliminates the chance of recall and interviewer bias entering the study. The ethnicity of each study participant was obtained from two different data sets to increase reliability of the variable.

The study population was 1,378 subjects, of which 616 were prostate cancer patients. This high proportion of cases increases overall study power and statistical efficiency (more likely to have stable parameter estimates and identify effect

www.manaraa.com

modification between independent variables). This increased study power allowed for stratification on key parameters, such as PC stage and ethnicity.

The results are biologically plausible. The results of this study are consistent with what existing knowledge. It is accepted within the medical community that there is a relationship between PC and systemic diseases that occur in presence of both local and metastatic spread of PC.[101] Moreover, it has been demonstrated that the specified laboratory biomarkers evaluated in this study are highly correlated with the systemic diseases related to PC spread.[21]

The types of analysis performed in this study included both logistical and linear regression modeling. These modeling strategies allow for controlling of known PC risk factors and other independent variables, thereby providing a linear combination of optimally weighted independent variables that best explain the outcome variable.

5.5 - External Validity

The study's subjects were men treated within the VA Healthcare networks located in Tampa, Florida. The demographic characteristics of the population under study are similar to that of the national VA system. The group are primarily Caucasian middle-aged veterans (mean=68 y/o, SD=12) with an education attainment level of at least four years of high school, or some college attendance.[36]

Approximately 2.5 million individuals receive all or part of their healthcare needs from the VA medical system, and the Tampa Florida VA healthcare network handles on average a total of 1,718,528 male patient encounters each year.[36] Given the above, this study's subjects are believed to be representative of the national male VA population.

www.manaraa.com

5.6 - Public Health Importance and Future Directions

Men with PC have been described as falling in to one of four groups, and screening can only benefit one of the groups. The first group consists of men with normally progressing disease that is identified clinically; the second group includes men with PC that advances very rapidly. For the above two groups, screening is of no benefit. The third groups contains men with screen-detected PC that would have never advanced to clinically relevant disease, therefore they are exposed to unnecessary procedures and treatments. Lastly, group four contains asymptomatic men who have PC identified through screening and receive beneficial outcomes that otherwise would have been deprived if not for the screening.[10] One difficulty in PC screening is identifying group 4 relative to group 3. This study results suggest evaluating four laboratory biomarkers (HGB, RBC count, MCV, creatinine) in conjunction to a PSA value of >4ng/dL might increase the validity of the PC screening process. This has important implications, especially if PSA is used as a cost effective PC screening program. The overlap of PSA values in men with PC and non-cancerous prostate conditions has been well documented. This study provides a glimpse of the potential benefit that these additional lab parameters can provide.

Future directions should first begin with repeating this study on multiple VA data sets collected from different VA clinics around the U.S. Are the findings similar in data sets that originate from a different geographic location? Do they vary in VA data sets that are from communities with different age distributions, or in areas with higher proportions of African American men? Individuals considered at high risk for PC include men with a positive family history; advancing age, and African-Americans.[10, 106] Does this clinical

www.manaraa.com

decision rule perform better for these high risk subsets? Can it address previous descriptive epidemiology that describes PC as affecting African-American men in more aggressive nature, and at an earlier age? Moreover, capturing information on PC family history is of paramount importance. Would the employment of this clinical decision rule result in a significant decrease of prostate biopsy numbers without increasing the false negatives? Does the duration of disease affect the degree of change for each biomarker, and by how much?

Stratification analysis techniques can provide additional insight on high risk patients and exposures, and although this study contained large numbers of patients with PC and non-cancerous prostate conditions (N=1,378), future studies should include a larger sample size, given that it will facilitate further stratification. Only after replicating this study on different data sets (and demonstrating consistency of findings), should a randomized prospective study be considered.

Perhaps the most important question yet to be answered is this: Given an elevated PSA value and values of the specified laboratory biomarkers that yield a probability value above the cut-off point, would a clinician confidently recommend a prostate biopsy for his/her patient? Moreover, if there is a lack of change in the biomarkers, would a clinician confidently recommend a more conservative, expectant observation (watchful waiting) approach?

www.manaraa.com

References

1. Dorr VJ WS, Stephens RL. An evaluation of prostate-specific antigen as a screening test for prostate cancer. A Internal Medicine: 2529-2537, 1993.

2. Clark RA RD. Principles of Cancer Screening. 1-20, 1994.

3. Marcos GL CD, Catalona WJ. Detection of Prostate Cancer by digital rectal examination (DRE), prostatic specific antigen (PSA), and transrectal ultrasonography (TRUS). Journal of Urology: 313A, 1990.

4. Ferri. Clinical Advisor. Prostate Cancer, 2001.

5. Fincham HG, Hanson J, Woayasinghe C. Epidemiology of prostatic cancer: a case control study. Prostate: 189-206, 1988.

6. Grimm PD, Sylvester JE, Meier RM, Cavanagh W. 10-year Biochemical (Prostate-Specific Antigen) Control of Prostate Cancer with 125I Brachytherapy. Int J Rad Radiat Oncol Biol Phys: 31-40, 2001.

7. Catalona WJ, Ratliff TL, Dodds RN, Coplen DE, Yuan JJ. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. New England Journal of Medicine: 1156-1161, 1991.

8. Cole P, Morrison, A. Basic Issues in Population Screening for Cancer. JNCL: 1263-1273, 1980.

9. Society: AC. Prostate Cancer Information.

10. Frankel S, Smith GD, Donovan J., Neal D. Screening for Prostate Cancer. Lancet 1122-1128., 2003.

11. Thompson I. Prevalence of Prostate Cancer among Men with a Prostate-Specific Antigen Level less than/equal 4 ng per Mililiter. JAMA 350(22): 2239-2246, 2004.

12. DeAntoni EP CE, Oesterling, JE, et al. Age and race-specific reference ranges for prostate specific antigen from a large community based study. Urology 48: 234-239, 1996.

13. Chan JM SM, Giovannucci, Gann PH, Ma J, et al. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. Science: 563-566, 1997.

www.manaraa.com

14. Reissigl A. KH, Pointner J., Fink K., Horninger W., Ennemoser O., et al. Usefulness of the ratio of free/total prostate-specific antigen in addition to total PSA levels in prostate cancer screening. Urology 48: 62-66, 1996.

15. Virtanen A GM, Kranse R, Stenman U. Estimation of Prostate Cancer Probability by Logistic Regression: Free and Total Prostate-specific Antigen, Digital Rectal Exam, and Heredity are Significant Variables. Clinical Chemistry: 987-994, 1999.

16. Lefebvre ML. Prostate Cancer Screening: More Harm Than Good? American Family Physician 58: 432-438, 1998.

17. Smith DS, Bullock A.D., Catalona, W.J. Racial differences in a prostate cancer screening study. Journal of Urology: 1366-1369, 1996.

18. National Cancer Institute D, Surveillance Program, Cancer Statistics Branch. Surveillance, Epidemiology, and End Results (SEER) Public use CD-ROM., May 1997.

19. Book. The Feasibility of screening programs, 2000.

20. Szklo M, Nieto F.J. Epidemiology: beyond the basics. Gaithersburg, Maryland: Aspen Publishers, INC., 2000.

21. Gomella LG. Clinician's Pocket Reference, 2000.

22. Wilson JM, Jungner G. Principles and practices of screening for disease. In: Paper # 34. Geneva, Switerland: World Health Organization, 1968.

23. Institute D-FC. PSA velocity more important than the specific PSA level. New England Journal of Medicine: 125-135, 2004.

24. Report TL. 1997.

25. Carter HB. PJ, Metter EJ., Brant LJ. Longitudinal evaluation of prostate specific antigen in men with and without prostate disease. JAMA 267(16): 2215-2220, 1992.

26. Oesterling JE. J, SJ, Chute CG. The establishment of age-specific reference ranges for prostate-specific antigen. Journal of Urology 149, 1993.

27. Crawford ED. DE, Stone NN. Prostate cancer awareness week demonstrates continued value to early detection strategies. Journal of Urology 153, 1995.

28. Spivak J. Cancer related anemia: its causes and characteristics. Seminal Oncology 21: 3-8., 1994.

www.manaraa.com

29. Cupp GW. OJ. Prostate-specific antigen, digital rectal examination, and transrectal ultrasonography: Their roles in diagnosing early prostate cancer. Mayo Clinical Protocol 68: 297, 1993.

30. Strum SB. MJ, Scholz MC., et al. Anemia associated with androgen deprivation in parients with prostate cancer receiving combined hormonal blockade. British Journal of Urology 79: 933-941, 1997.

31. Group. Taber's Medical Dictionary. Philadelphia: F.A. Davis, 2001.

32. Spivak J. Cancer-related Anemias: its causes and characteristics. Seminal Oncology 21: 3-8., 1994.

33. Jooston E. GB. American Journal of Medicine. 107: 24-29, 1999.

34. Oh WK KP. Management of hormone refractory prostate cancer: current standards and future prospects. Journal of Urology 160: 1220-1229, 1998.

35. Klein RE, Stockford, D. Data on the Socioeconomic Status of Veterans and on VA Program Usage, 2001.

36. Department VA. National Survey of Veterans, 1993.

37. Stamey T YN, Hay AR, et al. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. New England Journal of Medicine 317: 909-916, 1987.

38. Benson M WI, Olsson C, et al. The use of prostate-specific antigen density to enhance the predictive value of intermediate levels of serum prostate-specific antigen. Journal of Urology 147: 815-816, 1992.

39. McNeal J. The prostate gland: morphology and pathobiology. Monograph Urology 9: 36-54, 1988.

40. Horninger W RA, et al. Improvement of specificity in PSA-based screening by using PSA-transition zone density and percent free PSA in addiiton to total PSA levels. Prostate 37: 133-137, 1998.

41. Lundwall A. LH. Molecular cloning of human prostate specific antigen cDNA. FEBS Letters 214: 317, 1987.

42. Bullock AD MR. Prostate cancer in African-Americans. Advances in Urology 8: 131-156, 1995.

43. Catalona WJ SD, Ratliff TL. Detection of organ-confined prostate cancer is increased through prostate-specific antigen-based screening. 270: 948-954, 1993.

www.manaraa.com

44. Scott R MD, Laskowski T, et al. Carcinoma of the prostate in elderly men; incidence, growth charactreistics, and clinical significance. Journal of Urology 101: 602-607, 1969.

45. Miller BA KL, Berstein L, et al. Racial/ethnic patterns of cancer in the United States 1988-1992. Bethesda, Maryland: National Cancer Institue, 1996, p. 96-4101.

46. Ries LA KC, et al. SEER cancer statitics review. Bethesda, Maryland: National Cancer Institute, 1999.

47. Merrill R WD, Feuer EJ. The lifetime risk of developing prostate cancer in white and black men. Cancer Epidemiological Biomarkers Preview 6: 763-768, 1997.

48. Hiatt RA OJ. Dipstick urinalysis screening, asymptomatic microhematuria, and subsequent urological cancers in a population-based sample. Cancer Epidemiological Biomarkers Preview 3: 439, 1994.

49. Macoska J TT, et al. Evidence for three tumor suppressor gene loci on chromosome 8p in human prostate cancer. Cancer Registry 55: 5390-5395, 1995.

50. Correa P. Epidemiological correlations between diet and cancer frequency. Cancer Registry 41: 3685-3690, 1981.

51. Whittmore AS KL, WU A, et al. Prostate cancer in relation to diet, physiacl activity, and body size in blacks, whites, and Asians in the United States and Canada. Journal of National Cancer Institute 9: 652-661, 1995.

52. Patterson B HL, Block G, et al. Food choices of whites, blacks, and Hispanics: data from the 1987 National Health Interview Survey. Nutritional Cancer 2: 105-119, 1995.

53. Giovannucci E AA, Rimm E. Intake of carotenoids and retinol in relation to risk of prostate cancer. Journal of National Cancer Institute 87: 1767-1776, 1995.

54. McNeal J, Boswick DG. Intraductal Dysplasia: a pre-malignant lesion of the prostate. Human Pathology 17: 64-71, 1986.

55. Haagman M, Macoska JA, Wojno KJ, et al. The relationship between prostatic interstitial neoplasm and prostate cancer: critical issues. Journal of Urology 158: 12-22, 1997.

56. McNeal JE VA, Redwine EA. Microcarcinoma in the prostate: its association with duct-acinar dysplasia. Human Pathology 22: 644-652, 1991.

57. McNeal J. Signifcance of duct-acinar dysplasia in prostatic pathogenesis. Urology 34 (Supplemental): 9-15, 1989.

www.manaraa.com

58. Lee F. LP, Torp-Pederson ST., et al. Prostate cancer comparison of transrectal US and digital rectal examination. Radiology 168: 389-394., 1988.

59. Hodge K. M, J., et al. Random systematic versus directed ultrasound guided transrectal core biopsy of the prostate. Journal of Urology 142: 71-75, 1989.

60. Hodge K. M, J., Stamey T. Ultrasound guided transrectal core biopsies of the palpable abnormal prostate. Journal of Urology 142: 66-70, 1989.

61. Byar DP MF, and the VA Cooperative Urologic Research Groups. Carcinoma of the prostate: prognostic evaluation of certain pathologic features in 208 radical prostatectomy's. Journal of Cancer 150: 5-13, 1972.

62. Villers AA MJ, Redwine EA, et al. The role of perinueral space invasion in the staging and treatment of prostatic carcinoma. Journal of Urology 142: 763-768, 1989.

63. McNeal J. Cancer volume and site of origin of adenocarcinoma of the prostate: relationship to local and distant spread. Human Pathology 23: 258-266, 1992.

64. Whitmore WJ. Natural history and staging of prostate cancer. Urology 11: 209-220, 1984.

65. Fowler JJ, Bigler SA, Kilambi NK, et al. Results of transitional zone biopsy in black and white men with suspected prostate cancer. Urology 53: 346-350, 1999.

66. Hu JC PG. The association of selected pathological features with prostate cancer in a single needle biopsy assecion. Human Pathology 1998: 1536-1538, 1998.

67. Epstein JI GD, Humphrey PA, et al. Interobserver reproducibility in the diagnosis of prostatic intraepithelial neoplasia. American Journal of Surgical Pathology 19: 873-886, 1995.

68. Catalona WJ SD, Ratliff TL. Detection of organ-confined prostate cancer is increased through PSA-based screening. JAMA 270: 948, 1993.

69. Stamey T. Second Stanford conference on international standardization of PSA immunoassays. Urology 45: 173, 1995.

70. Pound CR PA, Epstein JL, et al. PSA following anatomical radical retropubic prostatectomy: patterns of recurrence and cancer control. Urological Clinician North America 1997: 395, 1997.

71. Pergament ML SW, Blackard CE. Disseminated intravascular coagultion in the urologic patient. Journal of Urology 116: 1-7, 1976.

www.manaraa.com

72. Levi M T-CH. Current Concepts: Dissiminated intravascular coagulation. New England Journal of Medicine 341: 586-592, 1999.

73. PW. S. Clinical intravascular coagulation. Clinical spectrum and diagnostoc criteria. Acta Med Scand (Suppl) 526: 1-95, 1971.

74. Lu-Yao GL YS. Population based study of long-term survival in patients with clinically localized prostate cancer. Lancet 349: 906-918, 1997.
75. Berger R. Case-control study of men with suspected chronic idiopathic prostatitis. Journal of Urology 141: 328, 1989.

76. Meares. Prostatitis. Medical Clinician of North America 75: 405, 1991.

77. Moul J. Prostatitis: Sorting out the different causes. Post-grad Medicine 94, 1993.

78. Walsh P. Radical Prostetectomy, preservation of sexual function, cancer control: the controversy. Urological Clinician North America 14: 663-673, 1987.

79. Perez Cea. Localized carcinoma of the prostate. Review of mangement with external beam radiation therapy. Cancer 72: 3156, 1993.

80. Hatcher L. S, E.J. A Step-by-Step Approach to Using the SAS System for Univariate and Multivariate Statistics. Cary, North Carolina: SAS Institute Inc., 1994.

81. Boer JG SJ, Soloman MC, et al. Age specific antigen referance ranges: population specifics. Journal of Urology 159: 444-448, 1998.

82. Andeson JR SD, Corbin D, et al. Age specific reference ranges for serum prostate-specfic antigen. Journal of Urology 46: 54-57, 1995.

83. Oesterling JE. J, SJ, Chute CG. Serum prostate-specific antigen in a community-based population of healthy men: establishment of age-specific referance ranges . JAMA 270: 860-864, 1993.

84. Moul J. Beneign Prostatic Hypertrophy: New concepts for the 1990s. Postgrad Medication 93: 141-145, 1993.

85. Grayback J. Beneign Prostatic Hypertrophy: The scope of the problem. Cancer 70: 1-275, 1993.

86. McConnell ea. Beneign prostatic hyperplasia: Diagnosis and treatment. Clinical Practice Guidlines 8, 1994.

87. Berges Rea. Results of randomized clinical trial of beta-sitosteral. Lancet: 1529, 1995.

www.manaraa.com

88. Ornstein P, Beiser, JA, Andriole, GL. Anaemia in men receiving combined finasteride and flutamide therapy for advanced prostate cancer. British Journal of Urology International 83: 43-46, 1999.

89. Wang J. Chemotherapy for prostate cancer. Urological Oncology 5: 93-96, 2000.

90. Mazhar D, Waxman, J. Prostate Cancer. Post graduate Medical Journal 78: 590-595, 2002.
91. Parmar H. Orchiectomy verses long-acting D-trip-6-LHRH in advanced prostatic cancer. British Journal of Urology 59: 248-254, 1987.

92. Duncan W. WP, Catton C, et al. Carcinoma of the prostate: results of radical radioththerapy (1975-1985). International Journal Radial Radiation Oncology Biol Phys 26: 203-210, 1993.

93. Parkin D, Muir CS, Whelen SL, et al. Cancer Incidence in five continents.: Lyon International Agency for Research on Cancer, 1992, p. 45-173.

94. Rodriquez C, Tathrum LM, Thun MJ. Smoking and fatal prostate cancer in a large cohort of adult men. American Journal of Epidemiology 145: 466-475, 1997.

95. Daniell HW. A worse prognosis for smokers with prostate cancer. Journal of Urology 154: 153-157, 1995.

96. Shimizu H, Ross R.K., et al. Cancers of the prostate and breast among Japanese and white immigrants in Los Angles county. British Journal of Cancer 63: 963-966, 1991.

97. Shimizu H, Ross R.K., Bernstein, L. Possible underestimation of the incidence rates of prostate cancer in Japan. Journal of Cancer 82: 483-485, 1991.

98. Rose D. BA, Wynder E. International comparisons of mortality rates for cancer of the breast, ovary, prostate, and colon, per capita food consumption. Cancer 58: 2363-2371, 1986.

99. Veierod M, Laake P., Thelle D. Dietary fat intake and risk of prostate cancer: a prospective study of 25,708 Norwegian men. International Journal of Cancer 73: 634-638, 1997.

100. Giovannucci E P, E. Nutritional and Environmental Epidemiology of Prostate Cancer. In: Prostate Cancer: Principles and Practices, edited by Bersin J. Philadelphia, PA: Lippincott Williams & Wilkins, 2002.

101. Albertsen P. Clinical Epidemiololgy: Incidence Rates, Ahe, Co-morbidities. In: Prostate Cancer: Principles & Practice, edited by Isaacs JT. Philadelphia, PA.: Lippincott

www.manaraa.com

Williams & Wilkins, 2002.

102. Steinberg G, Carter, B., et al. Family history and the risk of prostate cancer. Prostate 17: 337-347, 1990.

103. Keetch D, Humphrey P., Smith D., et al. Clinical and pathological features of hereditary prostate cancer. Journal of Urology 155: 1841-1843, 1996.

104. Carter BS. BG, Beaty, et al. Hereditary prostate cancer: epidemiologic and clinical features. Journal of Urology 150: 797-802, 1993.

105. Bastacky SI. WK, et al. Pathological features of hereditary prostate cancer. Journal of Urology 153: 987-992, 1995.

106. Goldenberg S.L., Thompson I.M. Prostate Cancer: All you need to know to take an active part in your treatment, edited by Carol Glegg. Vancouver, BC: Intelligent Patient Guide, 2001.

107. Snowdon, D., Phillips R., Choi W. Diet, Obesity, and Risk of Fatal Prostate Cancer. American Journal of Epidemiology 120: 244-250, 1984.

108. Gann P.H., Hennekens C.H., Jing M., Longscope C. Prospective Study of Sex Hormone Levels and Risk of Prostate Cancer. Journal of the National Cancer Institute 88: 1118-1125, 1996.

109. Le Marchand L., Kolonel, L., Wilkens L., Myers B., Hirohata T. Animal Fat Consumption and Prostate Cancer: A Prospective Study in Hawaii. Epidemiology 5: 276-282, 1993.

110. Field A., Graham A.C., Willett, W., Longcope C., McKinlay J. The Relation of Smoking, Age, Relative Weight, and Dietary Intake to Serum Adrenal Steroids, Sex Hormones, and Sex Hormone-Binding Globulin in Middle-Aged Men. Journal of Clinical Endocrinology and Metabolism 79: 1310-1316, 1994.

111. Honda G., Bernstein L., Ross R., Greenland S., Gerkins V., Henderson B. Vasectomy, cigarette smoking, and age at first intercourse as risk factors for prostate cancer in middle-aged men. Epidemiology 2: 233-248, 1988.

112. Platz, E., Giovannucci E., Rimm E., Curhan G., Spiegelman D., Colditz G., Willett W. Retrospective Analysis of Birth Weight and Prostate Cancer in the Health Professionals Follow-up Study. American Journal of Epidemiology 147: 1140-1144, 1998.

113. Ahluwalia B., Jackson M., Jones G., Williams A., Mamidanna S., Rajguru M. Blood Hormone Profiles in Prostate Cancer Patients in High-Risk and Low-Risk Populations.

www.manaraa.com

Cancer 48:2267-2273, 1981.

114. Henderson, R. Assessing test accuracy and its clinical consequences: a primer for receiver operating characteristic curve analysis. Annuals of Clinical Biochemistry 30: 521-539, 1993.

115. Ross R., Schottenfeld D., Prostate Cancer. Cancer Epidemiology and Prevention: edited by Schottenfeld, Fraumeni. Second Edition, Oxford University Press, 1996.

116. Optenberg SA, Thompson I. Economics of screening for carcinoma of the Prostate. Urol Clin North Am 17: 719-737, 1990.

117. Armstrong B., Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. International Journal of Cancer 15: 617-631, 1975.

118. Kolonel LN., Nomura A., Hinds MW. Role of diet in cancer incidence in Hawaii. Cancer Registry 43: 2397-2402, 1983.

119. Mettlin C. Milk drinking, other beverage habits and cancer risk. International Journal of Cancer 43: 608-612, 1989.

120. Talamini R., Francheschi S., La Vecchia C., et al. Diet and prostate cancer: a case-control study in northern Italy. Nutrition and Cancer 18: 277-286, 1992.

121. Giovannucci E., Rimm E., Wolk A., et al. Calcium and fructose intake in relation to risk of prostate cancer. Cancer Registry 58: 442-447, 1998.

122. Schuman L., Mandel J., Radke A., et al. Some selected features of the epidemiology of prostatic cancer: Minneapolis-St. Paul, Minnesota case-control study, 1976-1979. In: Magnus K, ed. *Trends in cancer incidence: causes and practical implications.* Washington, DC: Hemisphere Publishing Corp: 345-354, 1982.

123. Le Marchand L., Hankin H., Kolonel L., et al. Vegetable and fruit consumption in relation to prostate cancer risk in Hawaii: a reevaluation of the effect of dietary beta-carotene. American Journal of Epidemiology 133: 215-219, 1991.

124. Key T., Silcocks P., Davey G., et al. A case-control study of diet and prostate cancer. British Journal of Cancer 76: 678-687, 1997.

125. Pelucchi C., Galeone C., Talamini R., et al. Dietary Folate and Risk of Prostate Cancer in Italy. Cancer Epidemiology Biomarkers and Prevention 14:944-948, 2005.

www.manaraa.com

Appendix:

The following case examples provide a glimpse of the real world application of the proposed clinical decision rule outlined in this study.

Case example 1: (For this example, method 1, cut-point 1 will be utilized)

The probability of this cut-point is .45, therefore the Log OR p/1 – p = .45/1-.45, thus the cut-point is -0.08. (If the number yielded from equation is above this value, the patient should be referred for prostate biopsy). The patient is a 67 year old, African American male with a recent PSA test value of 5.2 (ng/dL). Additional lab work: HGB 10.5, RBC count 4.45, MCV 94.1, Albumin 4.0, Creatinine 1.12, and a positive test for Hematuria (at least 1 RBC per high powered field)

Prob..45/.55= -0.08 (cut-point)	**Patients value**	**Parameter estimate**	**Pt. value *Parameter estimate**	**Intercept**
HGB	**10.5**	**-0.3519**	**-3.69**	**-7.95**
RBC	**4.45**	**0.9227**	**3.65**	
Black	**(Yes=1) 1**	**0.6336**	**0.63**	
Hematuria	**(Yes=1) 1**	**-0.2874**	**-0.29**	
Age	**67**	**0.0196**	**1.31**	
Albumin	**4**	**0.2871**	**1.15**	
PSA	**5.2**	**0.0408**	**0.21**	
Creatinine	**1.12**	**-0.4393**	**-0.49**	
MCV	**94.10**	**0.0663**	**6.05**	
		sum of B*value	**8.53**	
		plus intercept= Total Score	**.58**	

Patients CDR Total Score 0.58 > -0.08. Recommendation? Send for Biopsy

Figure 12. Case Example 1 using Method 1, cut-point 1

www.manaraa.com

Case example 2: (For this example, method 2, cut-point 1 will be utilized)

The probability of this cut-point is .41 therefore the Log OR p/1 – p = .41/.59, thus the cut-point is -0.16 (If the number yielded from equation is above this value, the patient should be referred for prostate biopsy). The patient is a 75 year old, Caucasian male with a recent PSA test value of 4.3 (ng/dL). In addition, he had additional lab work to include a HGB, RBC count, MCV, and Creatinine:

Prob..41/1-.41 = -0.16	Patients value	Parameter estimate	Pt. value *Parameter estimate	Intercept
HGB	15.2	-0.378	-5.74	-5.10
RBC	4.50	0.764	3.44	
Black	(Yes=1) 0	0.361	0.00	
Age	75	0.018	1.35	
PSA	4.3	0.033	0.129	
Creatinine	1.65	-0.601	-0.99	
MCV	90.00	0.050	4.5	
		sum of B*value	2.69	
		plus intercept= Total Score	-2.41	

Patients CDR Total Score -2.41< -0.16. Recommendation? No Biopsy

Figure 13. Case Example 2 using Method 2, cut-point 1

www.manaraa.com

Case example 3: (For this example, method 3, cut-point 1 will be utilized)

The probability of this cut-point is .45, therefore the Log OR p/1 – p = .45/1-.45, thus the cut-point is 123456. (If the number yielded from equation is above this value, the patient should be referred for prostate biopsy). The patient is a 87 year old, African American male with a recent PSA test value of 14.7 (ng/dL). In addition, he had additional lab work to include a HGB, RBC count, MCV, and Creatinine.

Prob..42/1-.42 = -0.14	**Patients value**	**Parameter estimate**	**Pt. value *Parameter estimate**	**Intercept**
HGB	**11.2**	**-0.472**	**-5.29**	**-6.80**
RBC	**4.12**	**1.105**	**4.55**	
Black	**(Yes=1) 1**	**0.609**	**0.61**	
Age	**87**	**0.024**	**2.09**	
PSA	**14.7**	**0.054**	**0.79**	
Creatinine	**0.98**	**-0.815**	**-0.80**	
MCV	**89.51**	**0.066**	**5.91**	
		sum of B*value	**7.86**	
		plus intercept= Total Score	**1.06**	

Patients CDR Total Score 1.06 > -0.14. Recommendation? Send for Biopsy

Figure 14. Case Example 3 using Method 3, cut-point 1

www.manaraa.com

	All Ethnicity	White	African-American	Hispanic	Other	Unknown/Refused	Totals
Prostate Cancer	616 44.7%	428 43.9%	67 57.3%	28 39.4%	15 33.3%	78 45.9%	616
Stage A	*(332)* *53.9%*	*(238)* *55.6%*	*(34)* *50.7%*	*(15)* *53.6%*	*(11)* *73.3%*	*(34)* *43.6%*	332
Stage B	*(220)* *35.7%*	*(149)* *34.81%*	*(22)* *32.8%*	*(11)* *39.3%*	*(3)* *20.0%*	*(35)* *44.9%*	220
Stage C	*(48)* *7.80%*	*(31)* *7.24%*	*(7)* *10.4%*	*(1)* *3.5%*	*(1)* *6.66%*	*(8)* *10.2%*	48
Stage D	*(16)* *2.59%*	*(10)* *2.34%*	*(4)* *6.00%*	*(1)* *3.5%*	*(0)* *0.00%*	*(1)* *1.3%*	16
PIN	138 10.0%	99 10.15%	13 11.1%	7 9.86%	6 13.3%	13 7.65%	138
BPH	282 20.5%	211 21.6%	19 16.24%	14 19.7%	10 22.2%	28 16.5%	282
Prostatitis	342 25.0%	237 24.3%	18 15.4%	22 31.0%	14 31.1%	51 30.0%	342
Total prostate biopsies	1,378	975	117	71	45	170	N=1,378

Table 22: Baseline data by Ethnicity/Histologic biopsy.

www.manaraa.com

About the Author

Captain Owen T. Hill received a Bachelor's Degree in Science and a Master's degree in Physician Assistant Studies (Family Medicine) from the College of Medicine, University of Nebraska in 1998 and 1999, respectively. He entered the Ph.D. program (Epidemiology and Biostatistics) at the College of Public Health, University of South Florida in 2002.He is an active duty Army officer, currently assigned to the United States Army Research Institute of Environmental Medicine, located in Natick, Massachusetts.

Captain Hill's prior military assignments include: Fitzsimmons Army Medical Center (Aurora, Colorado), the Multinational Forces and Observers (Sinai, Egypt), Brooke Army Medical Center (Fort Sam Houston, Texas), 1st Special Forces (Okinawa, Japan), Evans Army Community Hospital (Fort Carson, Colorado), 4th Infantry Division (Fort Carson, Colorado), and the 3rd Armor Calvary Division (Fort Carson, Colorado). He has numerous military awards and citations, including the Army Parachute badge, Meritorious Service Medal, Joint Service Commendation Medal, four Army Commendation medals, and five Army Achievement Medals.

www.manaraa.com