PROSTATE CANCER: THE SCREENING CONUNDRUM

by

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A Thesis/Practicum submitted to the Faculty of Graduate Studies of The University of Manitoba in partial fulfillment of the requirements of the degree of

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ABSTRACT

Prostate cancer is the most common cancer among men, but of even more importance, is the statistical fact that prostate cancer is second only to lung cancer as the cause of cancer mortality in men. The prevalence in society is causing a significant health care burden. It is an incorrect perception that prostate cancer is an indolent disease whereby men will die with the disease and not because of the disease which suggests that prostate cancer has an insignificant clinical impact. The reality is that prostate cancer kills. With the advent of detection methods, particularly prostate specific antigen serum testing (PSA), and the study of the disease history, how the disease progresses and significant advances in treatment modalities, it is no longer acceptable morally, ethically or medically to allow men to die of prostate cancer.

The purpose of this study is to present a systematic overview of the literature pertaining to prostate cancer screening and early detection rationale, the significance of prostate cancer and the impact on health care, particularly treatment modalities. Secondary data bases published by the Canadian Cancer Society and data from published articles are examined with a focus on the incidence and mortality rates of prostate cancer. The literature is synthesized to provide explanations to promote the feasibility of prostate screening and early detection,

including the value of PSA testing.

The outcome of the study demonstrates that earlier detection with PSA testing is a means of addressing the issue of prostate cancer and saving the lives of men. A health promotion prostate cancer algorithm included a critical reflection of the theory that early detection and treatment substantially lowers cause-specific mortality while contributing to health promotion, individual responsibility and well-being health behavior, components desirable and advocated by Government agencies across Canada. The amalgamation of the literature via a systematic overview and synthesis of published articles and data demonstrate that prostate cancer does constitute a major health problem and PSA based prostate screening is an effective tool.

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CHAPTER ONE

1. INTRODUCTION

Prostate cancer (CaP) is the most common cancer among men, but of even more importance, is the statistical fact that prostate cancer is second only to lung cancer as the cause of cancer mortality in men. The literature no longer supports the frequently recited belief that prostate cancer is an 'old man's disease' since the Canadian Cancer Statistics for 1998 estimate 4,400 new cases in men aged 60 to 69 years and 990 new cases in men aged 50 to 59 years.[1] Few men who live a normal life span of 75 years[2] will be spared prostate ailments (ranging from inflammation, benign enlargement to cancer) which is an inevitable part of aging.[3] Unfortunately, prostate cancer prevalence increases rapidly with age.[4] Prostate cancer accounts for one quarter of all Canadian male cancers.[5] It is estimated in 1998 that *every day* in Canada, fifteen men under the age of 70 years will be diagnosed with prostate cancer while prostate cancer will kill **one** Canadian man every two hours.[6] By comparison, the United States estimated 334,500 new cases of prostate cancer in 1997 with 41,800 deaths; prostate cancer accounts for 43% of all male cancers in that country.[7] It is expected in 1998 that one man will be diagnosed with prostate cancer every three minutes in the United States.[8] By virtue of the number of individuals affected, both men and their nuclear/extended families, the prevalence of prostate cancer is a significant health care burden. The number of prostate cancers in Canada have been increasing at a rate of 5.3% per

year[9] with the number of incidence cases forecast to triple by the year 2016;[10] American men have experienced an increase of 58% from 1973 to 1991.[11] It is an incorrect perception that prostate cancer is an indolent disease whereby men will die *with* the disease and not because of the disease which suggests that prostate cancer has an insignificant clinical impact. The reality is that prostate cancer kills since it is estimated that 4,300 Canadian men will succumb to the disease in 1998.[12] With the advent of detection methods, particularly prostate specific antigen (PSA) serum testing, study of the disease history, how the disease progresses and significant advances in treatment modalities, it is no longer acceptable either morally or ethically to allow patients to die *of* prostate cancer. Breast cancer screening of asymptomatic women is widely accepted and practiced in this country and is thought to reduce breast cancer mortality by estimates of 30% in some studies.[13] The Canadian Cancer Statistics indicate that breast cancer incidence among women has increased by 1.5% annually over the past decade, largely due to the rising number of mammographic examinations since the mid-1980's; whereas, the estimated age-standardized mortality rate declined by 3.8% since 1985 with the declining number of deaths attributed in part to increased survival rates.[14] Why is prostate cancer screening and early detection not being given the same consideration? The number of prostate cancers in Canada has been increasing at an accelerated annual rate of 7% since 1986,[15] largely due to earlier detection methods with PSA, while age-standardized mortality rates (refer to Appendix A - Definitions, p. 194) have increased by 2.8% during the same time

frame.[16] A desirable outcome of this study would be the ability to demonstrate that earlier detection through PSA testing, digital rectal examination (DRE) and transrectal ultrasound (TRUS) decreases mortality; thus, screening for prostate cancer, with the goal of prevention and early detection, saves lives.

The concept analysis utilized in this project focuses on the theory that early detection and treatment of prostate cancer substantially lowers cause-specific mortality. This is depicted in a health promotion algorithm specific to prostate cancer that was constructed as a critical reflection of the theory pertaining to this study. The reality is that a portion of men are being screened for prostate cancer through their family physicians or via referrals to urologists; therefore, health care dollars are being spent on screening. In 1995, a national survey by Health Canada, the National Cancer Institute of Canada and the Institute for Clinical Evaluative Sciences in Ontario revealed that 9% of Canadian men over the age of 40 years have had a PSA test performed for screening purposes.[17] But the question that begs an answer is why screening and early detection have not been adopted on a national scale?

The objective of this study is to explore the significance of prostate cancer, the impact on health care, the issue of screening and early detection and analysis of existing data. The intent is to generate explanations derived from a systematic overview of the literature which promote the feasibility of prostate screening and

early detection, in addition to examining secondary data bases, particularly the incidence and mortality rates of CaP. An extension of the study will be an attempt to examine the literature and statistical data related to PSA testing. Does prostate cancer constitute a major health problem?

2. PROBLEM STATEMENT

Screening for prostate cancer is under considerable debate in Canada, as it is elsewhere in the world. Although prostate cancer accounts for 13% of all cancer deaths in Canadian men,[18] it is a controversial subject faced by men as to whether they should be screened and if found to have prostate cancer, whether they should be treated aggressively.[19] Prostate cancer management presents a dilemma resulting from the unresolved current issues: 1) no available treatment has been proven capable of providing a cure for prostate cancer, 2) no available treatment for prostate cancer has been proven capable of providing an appreciable extension of life, 3) no available treatment has been proven capable of doing more good than harm, and, 4) the prostate cancer death rate has continued to rise for the past 30 years, although there has recently been a reduction in the death rate, it has not been established to be the result of either screening or treatment.[20] However, many researchers feel that preliminary, short term studies are addressing these issues.

Thompson, speaking at the 1997 Toronto National Forum on Prostate Cancer,

states that there is growing evidence that PSA screening in the United States, which saw a dramatic increase in the number of individuals both diagnosed and treated for prostate cancer, has decreased mortality rates by 6.2% in the five to six years after the onset of PSA screening.[21] Fradet, who was also speaking at the same forum, states that surgery does make a difference whereby he cited a Mayo Clinic study in which 84% of the clinically detected intermediate grade 2 prostate cancer (refer to Appendix B, p. 200) patients who had radical prostatectomies were metastasis free after ten years compared to only 58% of the 'watchful waiting'[1](footnote) patients.[22] In addition, he stated that there is good evidence that PSA screening can detect the 'bad' cancers with a four to five year time lag which may give a window of opportunity to cure these cancers.[23]

The National Cancer Institute recently reported data showing that prostate cancer death rates in the United States have declined from 26.5 deaths per 100,000 population in 1990 to 17.3 deaths per 100,000 in 1995.[24] This represented a decline in mortality rates of 11.7% in white men under the age of 75 years and 6.6% in black men under the age of 75 years. By comparison, the overall mortality rate in the United States for prostate cancer had been subjected to an increase of 13.2% from 1984 to 1989.[25] In contrast, the Canadian Cancer statistics reported the bad news that prostate cancer deaths are increasing in this country from 25 per 100,000

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[1] Watchful waiting, also referred to as conservative management, is a form of treatment for selected men that does not implement active treatment at the time of CaP diagnosis. Refer to treatment modalities, Chapter 4.

in 1969 to 32 per 100,000 estimated for 1997.[26] Could the widespread introduction of PSA screening in the late 1980's be responsible for the declining prostate cancer mortality rate in the United States and does this support the argument for increased efforts to identify men who have treatable prostate cancer and offer them the appropriate treatment choices?[27] Although many short term studies have been published, long term studies of fifteen years are required to provide definitive answers to the issues, but many of the studies in progress will not be concluded until after the turn of the century. Screening advocates maintain that these issues remain unanswered largely due to the lack of funding allotted to prostate cancer research and studies; in addition, an individual is impeded in his ability to make an informed decision regarding his own personal management of prostate cancer[28] and his ability to opt for screening.

Screening for prostate cancer is an examination or testing of asymptomatic men, whereas, diagnostic tests are performed when signs or symptoms are present.[29] In the early, curable stages, prostate cancer is a *silent* killer that does not present with symptoms. Unfortunately, when symptoms appear, the cancer has often spread beyond the prostate capsule and is considered to be no longer curable. Screening provides men with the opportunity to detect cancer while it is most curable.[30] Prostate cancer is usually a very slow growing cancer that has been developing for years, and therefore, has had time to micrometastatize or spread very small groups of prostate cancer cells outside the prostate.[31] The spectrum

varies from faster growing and aggressive prostrate cancers to indolent or clinically insignificant cancers. Many within the medical community believe that the cure rate has improved with the advent of new screening methods, most notably PSA testing.[32] There are four PSA groups which provide an approximation of localized disease. For example, a PSA of 0 to 4.0 ng/ml suggest that there is a 75% chance that the prostate cancer cells are located within the prostate gland.[33]

PSA GROUPS	
PSA Level	Chances of Prostate Cancer Cells Located Only Within the Prostate Gland
0.0 - 4.0 ng/ml	75% chance
4.1 - 10.0 ng/ml	50% chance
10.1 - 20.0 ng/ml	25% chance
over 20.0 ng/ml	Almost all men have cancer cells outside the prostate

Georgia Center for Prostate Cancer Research and Treatment: Information on Prostate Cancer[34]
Figure 1

For men with localized prostate cancers discovered at this stage, the five year survival rate is 99% and survival greater than ten years is 66%.[35] By comparison for non-organ confined cancer, the 5 year disease-free survival is only 37%.[36] Despite the abundance of published articles, mass screening presents a dilemma for physicians and patients since advocates contend that early detection, before the appearance of symptoms, affords the best chance for survival while those opposed to screening point to the lack of scientific data or controlled studies that

demonstrate mortality and morbidity are decreased with early detection. Regardless of the incongruity, American statistics indicate that one out of every five men will develop prostate cancer during their lifetimes[37] while Canadian statistics suggest one in nine men will develop prostate cancer in their lifetime.[38] As a result, guidelines recommending PSA testing have been established by the American Cancer Society, the American Urology Association and the American College of Radiology (refer Appendix C, p. 204). Unfortunately, there is disagreement and controversy among different organizations regarding the appropriateness of PSA testing for routine screening of the general population which creates even more frustration, confusion and anxiety for the men. Some groups feel that current evidence does not warrant use in the general male population primarily because of a relatively low specificity and the possibility of detecting indolent tumors that would not progress;[39] in addition, to a lack of prospective randomized studies that associate decreased CaP mortality with routine PSA screening.[40] Some opponents to screening suggest that the question is cost, both personal and societal.[41] Although not conclusive, there is some evidence emerging that prostate cancer screening has resulted in men being diagnosed at an earlier stage of disease and at younger ages, which could ultimately decrease mortality and improve the opportunity for successful treatment.[42] The most notable study was presented in May 1998 by Labrie of Laval University. His study over an 8 year period found that screening with PSA testing reduced prostate cancer deaths by 69% by detecting the cancers early and while treatable.[43] The Mayo Clinic has found in a study that

the advent of PSA testing has led to prostate cancers being caught at an earlier and more successfully treatable stage where the percentage of men whose cancer was confined to the prostate gland increased from 55% in 1987 (when PSA testing was first introduced) to 74% in 1995.[44] Researchers are speculating that early detection efforts will eventually translate into improved long-term survival [45] which is encouraging for a population that has been exposed to so much confusion regarding prostate cancer screening, early detection and treatment.

The etiology of prostate cancer, like other cancers, is not known; therefore, prevention is not a viable option at this time although the long term objective would be to prevent prostate cancer. However, prostate cancer has been linked to genetic factors, family history, age, race and environment (mostly this implies diet). Nearly 3% of American men over the age of 50 years will die of prostate cancer;[46] African-American men have an incidence rate 66% higher than Caucasian men and more than twice the mortality rate of Caucasians.[47]

To cure prostate cancer, the disease must be found and although PSA is not a perfect tumor marker, it is currently the single best test for the early detection of prostate cancer . Serum PSA compares favorably with screening tests for breast and cervical cancers, although PSA lacks specificity to be diagnostic of prostate cancer.[48] PSA is a protein produced by cancerous, non-cancerous and normal prostate cells. PSA levels may be elevated due to a number of factors other than

prostate cancer, such as: benign prostatic hypertrophy (BPH), distorted architecture, disruption of the basement membrane integrity that could occur with prostatic infarction, prostatitis, ejaculation, digital rectal manipulation or prostatic instrumentation.[49] The most common areas of metastasis are bone and pelvic lymph nodes where prostate cancer cells in these locations continue to produce PSA. When cancer grows in the prostate, more PSA is produced.[50] Although the PSA serum level is a simple blood test performed in almost any doctor's office, clinic or laboratory, the results must be interpreted by an experienced clinician with judgement in its application to individual patients.[51] A normal prostate gland produces 2.5 ng/ml or less of PSA, but may produce up to 4.0 ng/ml of PSA[52] although the level varies with age and extraneous variables, such as BPH. An enlarged or inflamed prostate gland can increase PSA levels whereas some aggressive prostate cancers will not produce much PSA.[53] Since 1979, PSA has been identified as the best marker for prostate cancer, the best overall tumor marker in biology and has revolutionized how prostatic disease is managed.[54] Along with PSA levels, digital rectal examinations, transrectal ultrasounds, biopsies, scanning/imaging and classification by Whitmore staging or the TNM system (refer to Appendix B, p. 200), a treatment course is determined for the individual with prostate cancer.

The treatment modalities are varied and present a conundrum for men with prostate cancer which has been precipitated by concerns that the impact of these

interventions on survival rates, morbidity and costs related to treatment is currently unknown. Prostate cancer has a length-time and/or a lead-time bias: 1) tumors undetected during a patient's lifetime, 2) tumors detected but pose no risk, 3) tumors detected and cured; otherwise patient's demise, or 4) tumors are virulent, and thus, incurable by the time detected.[55] Therefore, prostate cancer treatment depends on the extent of the disease when detected. Tumor size, grade, stage, PSA, and PSAD (PSA density) predict tumor behavior and extent which dictates the choice of treatment. In addition, the patient's age, medical status, life expectancy and preferences also influence the treatment choice. With improved treatment modalities, the prostate cancer survival rate in the United States for all stages has risen from 50% to 87% over the last 30 years.[56] It is generally accepted that complications from surgery may be highly dependent on the skills of the surgeon and the facility selected by the patient.[57] Reports from major academic centers in the United States indicate that 40 - 65% of radical prostatectomy patients recover sufficient potency for satisfactory sexual intercourse,[58] although other reports, including a Health Canada report from 1998 cite impotency rates of 20 - 40% and incontinence rates of 5 - 25% with both radiation and surgery for early stage disease.[59] The Hopkins Center (Dr. Walsh) reports that in men 50 - 59 years, 75% regain potency after surgery while less than 5% have a recurrence of cancer.[60] The important determinants in the return of sexual function include: age, stage of cancer, and the extent of nerve loss during surgery, although the level of sexual function prior to treatment is important to determine. For example, one study of

medicare patients in 1993 reported 60% of patients did not have any erections since surgery while in the same study, 90% reported that they had not had an erection sufficient for intercourse in the month prior to surgery.[61] Walsh reports that he has three goals: removing all the tumor, preserving urinary control and preserving sexual function, but sexual function is last because if it is lost there are many ways to restore it.[62]

Currently, only 60% of newly diagnosed CaP are clinically localized and curable by available gold standard treatments: radical prostatectomy or radiation therapy.[63] Various treatments exist for the management of CaP such as: 1) radical prostatectomy (radical retropubic or radical perineal prostatectomy) which may include a nerve sparing procedure, 2) radiation therapy - external beam and/or brachytherapy (seed implantation), 3) hormone therapy - surgical and/or chemical, 4) cryosurgery, 5) laparoscopic lymphadenectomy for establishing pelvic lymph node metastasis, 6) chemotherapy, or 7) drug therapy, such as suramin, proscar or others. (refer to Appendix F, p. 207).

The approaches to CaP consist of early detection and treatment, conservative management (also referred to as watchful waiting, expectant management, observation or surveillance), delayed intervention until disease progression or metastasis evident, and chemoprevention. Arguments exist supporting early intervention versus conservative management (surveillance), such as, early

intervention improves health status, despite side effects, compared to metastatic disease progress. In addition, advancements in early detection and intervention produce a greater understanding of CaP epidemiology. Because CaP may have an indolent behavior in some cases, controversy is generated over conservative management or active treatment. Since screening and treatment options remain controversial as to the quality of life or extended survival rates, further research is warranted to answer these questions.[64] However, a review of 59,876 men registered with the Surveillance, Epidemiology, End results program (SEER) registries between 1983 - 1992, revealed that men with poorly differentiated and moderately differentiated prostate cancer have an improved survival rate if treated rather than managed with observation[65] (refer to Appendix B, p. 200).

3. PURPOSE OF STUDY

Carcinoma of the prostate is a perplexing and common disease that has seen a 173% increase in incidence since 1973 (to 1996) in the United States[66] while Canada estimates a 137% increase from 1990 - 2010.[67] The dramatic increase in prostate cancer is coupled with an increase in elderly Canadian males as the baby-boom population move into the fifty plus age groups where prostate cancer is more prevalent as the disease increases with age. Prostate cancer is gaining recognition as a public health challenge[68] due to the increased numbers of individuals affected which compounds the escalating economic burden imposed by the illness. As the economic impact of the illness continues to skyrocket, public policies will be

essential. The financial burden of cancer is immense for both the individual affected with the disease and to society as a whole. The National Cancer Institute estimates overall annual costs for cancer at $107 billion in the United States in 1998.[69] In Canada, the total cost of illness in 1993 was estimated at $156.9 billion with cancer consuming $13.1 billion.[70]

The purpose of this study is a systematic overview of the literature pertaining to cancer of the prostate screening and early detection rationale, the significance of prostate cancer and the impact on health care, particularly, treatment modalities. In addition, secondary data bases published by Health Canada, National Cancer Institute of Canada and Statistics Canada are examined with a focus on the incidence and mortality rates of CaP in Canadian men. The intent is to synthesize published articles that provide explanations to establish the feasibility of prostate screening and early detection, including the value of PSA testing and other screening and diagnostic tools. A desirable outcome of the study would be the ability to demonstrate that the effectiveness of earlier detection, with PSA testing, DRE, and the diagnostic aide of TRUS, decreases mortality; thus, screening for CaP with the goal of early detection, saves lives. Prevention, although currently not a viable option since the etiology of prostate cancer is not known, is a long term goal toward saving lives. A health promotion prostate cancer algorithm includes a critical reflection of the theory that early detection and treatment substantially lowers cause-specific mortality while contributing to health promotion, individual

responsibility and well-being health behavior; components desirable and advocated by Government agencies across Canada. A systematic overview and synthesis of amalgamated published data from the Canadian cancer registries and published articles demonstrate that prostate cancer does constitute a major health problem.

4. RESEARCH QUESTIONS

1. Does early detection, in which the tumor is confined to the prostate gland, with appropriate treatment improve health outcomes compared to those men who are not screened, and thus, do not benefit from the diagnosis of early stage CaP? The dependent variable of decreased mortality and the independent variables of early detection and treatment form the hypothesis that guides the project: lower mortality is dependent on early detection and treatment of CaP. The published literature and secondary data are analyzed to capture the variables.

2. Does the existing literature support the concept that an increased incidence rate of CaP is indicative of improved screening methods which detect tumors at an earlier stage, but that the annual death rate has decreased largely due to the effective detection and more effectual treatment of early stage CaP?

It was hypothesized that current treatment modalities have improved with reduced complication rates; in addition, treatment for complications can be alleviated which improves quality of life for patients.

5. METHODOLOGY

i) Literature Review

Extensive literature is available regarding prostate cancer, history and progression of the disease, the screening dilemma and early detection. Unfortunately, very little literature is Canadian-based. The majority of the literature search has revealed authors and research from the United States. The American Cancer Society and the American Urological Society have endorsed annual PSA screening for men fifty years and older or age forty if African American and/or a family history of prostate cancer and if the man's life expectancy is greater than ten years. The literature search was confined to 1995 to 1998. The field is expanding so rapidly with new information that literature prior to 1995 is deemed to be dated. The challenge was to synthesize the vast amounts of published articles into a manageable format via a systematic overview of the disease entity, prostate cancer and the screening conundrum.

Published articles were identified using a computerized database search of the time frame 1995 to 1998. Many articles from 1995 and years prior to this date were considered to be outdated in comparison to findings depicted in later articles which had the advantage of recent research findings; thus, many articles prior to 1995 were discarded. Reference lists of retrieved articles were searched and direct communication with experts in the field of prostate cancer suggested relevant articles. Only published articles or articles accepted for publication were

considered. Data bases were searched using the 'net doc' system through the University of Manitoba and reference services at the library. The search history used the heading 'prostate cancer screening' and confined the search to English articles only. Specific terms such as early detection, cancer screening and prostate cancer were also used. The literature review confirmed that although prostate cancer is recognized as a significant disease, the published articles and data to support a declining mortality rate indicative of a successful approach to early detection of the disease is not readily apparent.

ii) Internet

The Internet was used extensively and yielded numerous web sites and home pages specific to prostate cancer. E-mail services were also established that provided weekly urology updates and the capability to communicate with various sites and experts in the field of prostate cancer. The Internet generated current and timely information with link sites to relevant information.

iii) Statistical Data

Initial review of secondary data sources such as cancer registries, provincial health agencies and Canadian Cancer Societies indicated that long term studies of ten to fifteen years follow up of prostate cancer patients who were treated because of early detection programs are not available to date.

iv) Research Design

The research design consisted of a systematic overview of published articles which guided the synthesis of literature and secondary data published by Health Canada and the National Cancer Institute of Canada. The major emphasis of the research design was exploratory research to gain ideas and insights into the conundrum of prostate cancer screening. The intent of the project was to generate possible explanations for the feasibility of prostate screening facilitated by secondary data based on the Canadian statistics of incidence rates and mortality rates of prostate cancer. Data from the United States was utilized as a parallel to provide a comparison for the Canadian experience and possible future directions; plus, there was a predominance of published articles originating in the United States. The exploratory research was accentuated by descriptive research which determined the frequency with which prostate cancer is occurring in specific age groups. An extension of the study attempted to examine statistical data related to PSA testing; unfortunately, exploratory research determined that provincial or national data regarding PSA volumes is limited and not readily accessible. The initial hypothesis suggested that a higher incidence of prostate cancer reveals that earlier detection (variable) elevates the frequency rates of prostate cancer, but decreases the mortality rates (variable). The intent of examining secondary data sources was to compare provincial statistics and age groups, with a focus on similar age groupings and age standardization.

The research design consisted of a literature search (1995 to 1998), systematic overview of published articles and data with synthesis of material based on five selection criteria suggested for the feasibility of CaP screening. The key characteristic of exploratory research is flexibility.[71]

v) Data Collection Methods

This project is a systematic overview of published articles and data. Subjects/participants were not part of the study. Questionnaires or observations of subjects were not used in any part of the study; therefore, ethical issues regarding primary data and subjects were negated. The standard ethical committee documentation was satisfied.

Accrued published data are available in the completed thesis project in visual presentation of graphic formats. Since this project utilized published data, no primary data were obtained for the study, and thus, access, confidentiality, instruments, notes or storage of primary data were not applicable.

As pertaining to the use of the amalgamated secondary data in the study, the data can be utilized for expansion of studies on prostate cancer or to identify areas of deficient essential data, especially PSA data and actual provincial incidence and mortality rates, that may be of interest to the cancer registry, the National Cancer Institute of Canada, public policy agencies, health care agencies and other parties

with an interest in prostate cancer and early detection.

vi) Data Analysis

The research problem used published secondary data, and therefore, subjects were not recruited for the project. The project analyzed data to determine the extent of the statistics available pertaining to the research problem. The main source and contacts initiated for the secondary data were cancer registries and the Canadian Cancer Statistics, verified for publication by the National Cancer Institute of Canada. Actual rates and frequencies up to the most recent year for which complete data are available are 1993 for incidence rates and 1995 for mortality rates. Estimate values are provided for 1996, 1997 and 1998. PSA was introduced in clinical practice at various times throughout the provinces, for example, Manitoba began utilizing PSA testing in 1989 while Saskatchewan introduced the testing in 1990.

Secondary data has many advantages, primarily the time and money saved by the researcher. It also offers the researcher the ability to better state the problem under investigation, suggest improved or further data that should be collected and provide comparative data by which primary data can be interpreted.[72] Since the cancer registry is a primary source for cancer statistics, it is feasible and prudent to analyze the secondary published data before proceeding with primary data.

6. SUMMARY

An exploratory and descriptive research design consisted of a systematic overview of published articles pertaining to the significance of prostate cancer, the impact on health care, and the issue of screening and early detection. The scope of prostate cancer is immense, and thus, the challenge was to synthesize the vast amounts of published articles and secondary data published by Health Canada and Canadian cancer registries, specifically the National Cancer Institute of Canada, into a manageable format. An overview of literature presented in a readable format is required by the male individual faced with health promotion, well-being and the conundrum surrounding screening and early detection of prostate cancer. Men are faced with confusing and frustrating information: screening and early detection, PSA testing and implications, prostate cancer treatment modalities and complications versus conservative management (watchful waiting). Men have not been vocal in their quest for equal treatment, that is, a screening program similar to breast screening programs and cervical pap tests for women. Prostate cancer is a significant health care burden which is evident by the projections that it will affect 16,100 Canadian men[73] in addition to their families and significant others in 1998.

CHAPTER TWO

1. CONCEPTUAL FRAMEWORK

Aggressive intervention dramatically improves survival among men diagnosed with early stage CaP disease compared with a more conservative approach which deals with the clinical manifestations of the natural progression of the disease.[74] In a study recently published by the Mayo Clinic, only 17% of prostate cancers detected were clinically insignificant while 83% were significant.[75] Other studies support the Mayo Clinic findings by maintaining that the pathological features of most prostatic cancers detected via PSA screening do not resemble indolent cancers, and thus, most prostatic cancers detected in screening programs are likely to be clinically important.[76] Localized prostate cancer is potentially curable in a very high proportion of men without recurrence of the cancer.[77] Prostate cancer is the second leading cause of cancer mortality in men, so there is no question that it kills.[78] This supports the theory that early detection and treatment of CaP substantially lowers cause-specific mortality.[79] Screening is a vehicle for early detection. Debate exists concerning the appropriate use of health care dollars and the pressure to control costs coupled with what is the appropriate cost of saving a life and is the expenditure justified by an improved health status?[80]

The controversy produces supporters and non supporters who see screening and the early detection of CaP as either appropriate and cost-effective or inappropriate and unethical because the health gains do not justify the significant health costs

and adverse health effects.[81] There are no easy answers; however, the benefits of screening are early detection, treatment and cure which research has shown does save lives. The key to early detection is the ability to discover the disease while confined to the prostate gland. Once prostate cancer has escaped the confines of the prostate, the chances of a *true* cure become very small given current available forms of treatment, although, it is everyone's goal to change this in the near future.[82] Therefore, based on current evidence, analysis of the concept confirms that prostate screening is a feasible and viable vehicle to diagnose, manage and treat CaP.

Igun defines well-being health behavior as "any activity undertaken by a person believing himself to be healthy, for the purpose of preventing disease or detecting it in an asymptomatic stage".[83] By virtue of the definition alone, detection in an asymptomatic stage implies the need to promote and practice regular screening guidelines. Whylie, Director of Cancer Control for the Canadian Cancer Society, comments that there have been significant gains largely due to research into more sophisticated techniques for detecting cancer at an earlier stage.[84] An analogy with breast cancer screening clinics demonstrate that although the incidence of breast cancer has increased, the annual death rate has decreased largely due to detection of tumors at an earlier stage and more effective treatment.[85] One criticism of routine prostate cancer screening is that there is an increased detection of latent cancer which could lead to over-treatment which results in increased morbidity,

mortality and health care costs.[86] Recent large-scale prostate cancer screening studies have reported a latent cancer detection rate of 2.9% to 8.0% which is virtually the same as that found by the traditional method of detection (DRE in men with voiding symptoms).[87] However, there appears to be little concern regarding the detection of latent cancer in established breast cancer screening programs which report a latent cancer detection rate of 8.1% to 15.6% which is three to five times the detection rate of latent breast cancer prior to mammography screening.[88] The lifetime cumulative risk of clinically significant breast cancer in women is approximately 11%, but autopsy studies demonstrate a 25% incidence of breast cancer in women with a mean age of 67 years.[89] The majority of tumors discovered at autopsy, but not diagnosed in life, were DCIS or ductal carcinoma in situ which is a noninvasive cancer that can progress to invasive carcinoma in some cases.[90] Estimates derived from the literature suggest that only one third to one half of all DCIS lesions will develop into invasive breast cancer.[91] By comparison, the lifetime cumulative risk of clinically significant prostate cancer in men is approximately 9%, but autopsy studies demonstrate a 30% incidence of microscopic prostate cancer in men over the age of 50 years.[92] Latent prostate cancer is a low-volume cancer that is not likely to reach a clinically significant size during a man's lifetime because of the slow doubling time of these cancers.[93] As a result, studies have suggested that prostate cancer screening does not increase the rate of latent cancer detection with screening and the risk of unnecessary or over-treatment would not be expected to increase with screening.[94] The study

results suggest that the rate of latent prostate cancer detection is similar to or less than the rate of latent breast cancer detection in screening programs; however, prostate cancer screening does not appear to increase the rate of latent cancer detection over traditional methods of detection, in contrast to breast cancer screening which does appear to increase the rate of latent cancer detection substantially when compared with traditional methods of detection.[95] The study demonstrates that successful breast cancer screening accepts a level of over-treatment given the decrease in mortality. Therefore, the study authors, Benoit and Naslund, conclude that prostate cancer screening should not be withheld due to concerns regarding insignificant cancers until definitive data regarding decreased mortality rates with screening are available.[96]

2. CRITICAL ATTRIBUTES AND EXAMPLE CASES

Critical attributes are characteristics of a concept that repeatedly appear in the literature review. Also known as provisional or defining criteria,[97] the following critical attributes are key characteristics:

- The attribute of early detection: identifying men with organ confined CaP that is potentially curable.
- The attribute of appropriate intervention: identifying men with asymptomatic CaP or early stage CaP by providing appropriate treatment options. Screening provides a vehicle for intervention demonstrated by literature discussing: i) screening tools - PSA, DRE, and diagnostic aides - TRUS, biopsy, ii) treatment options - surgery,

radiation, conservative management, and iii) an increased understanding of CaP epidemiology and the association of CaP with related prostatic disorders, including BPH.

❑ The attribute of survival: identifying treatment options that reduce morbidity and mortality associated with CaP.

❑ The attribute of cost-effective CaP screening: recommends that certain criteria are satisfied.

Although there is considerable debate on the cost-effectiveness of CaP screening, screening advocates recommend that five criteria are satisfied:[98] 1) CaP is a significant health burden, 2) screening can identify localized disease, 3) tests have acceptable performance, 4) the potential for cure is greater among patients with screen-detected disease, and 5) screen-detected patients have improved health outcomes compared with those who are not screened.

Cases are utilized as examples of the concept, concept analysis, uses of the concept and contain all or a portion of the critical attributes that are characteristics of the concept. Model, borderline, related, contrary and invented cases demonstrate the critical attributes of the concept.

Case 1 - Model Case

A 55 year old man is asymptomatic, fit and active. He has been encouraged by his

wife to request prostate screening during his next annual physical examination and he decides to request same on an annual basis. At the time of his next periodic visit, he has a DRE and PSA test with a resulting value of 5.8 ng/ml. A urological consultation leads to a TRUS and sextant prostate biopsy. Because the DRE and ultrasound were both normal, six cores biopsies were obtained from different areas of the prostate. The biopsy revealed a Gleason Score 6 adenocarcinoma in 50% of one core at the right apex.[99] The patient and his wife review the results with a urologist one week later for discussion of treatment options. Because the man has prostate cancer and a good chance of 20 years or more of life expectancy, his urologist recommends treatment. They are inclined toward surgery, but are confused about several issues. The urologist provides treatment option information and approaches, side effects and possible treatment of complications in relation to impotency and stress incontinence as a result of the surgery. Both the patient and his wife are given extensive educational sessions explaining the current treatment regimes available for impotency. As a result, both the patient and his wife make an informed decision based on the best treatment approach for the tumor and quality of life issues.

The model case contains all the critical attributes. The attribute of early detection is evident by an asymptomatic male presenting for prostate screening during his annual examination. The results reveal an organ confined CaP that is potentially curable. The attribute of intervention identified that he had a normal DRE and

TRUS but an elevated PSA. Treatment options were discussed and the couple made an informed decision on the course of treatment that will increase the patient's chance of survival and maintain quality of life. Because the man was identified in the early stages of the disease, he has cost the system less in economic terms since his hospitalization is vastly reduced, effects of metastatic disease progress are eliminated or vastly reduced, his years of productivity are maintained and he remains a contributing member of society. In addition, the man and his wife maintain a quality of life that is substantially higher than the progressive metastatic progress of the disease.

Case 2 [100]

A 82 year old man has diabetes, hypertension and considerable difficulty breathing. He continues to smoke ten or more cigarettes a day. He is restricted in his activity and many days he is unable to do much more than sit in a living room chair. During a recent visit to his family physician, the doctor detected a slight abnormality during the DRE and ordered a PSA which was 12.8 ng/ml. After discussion, the man and his doctor decide to monitor his prostate on a regular basis with DRE and PSA. The man has opted for conservative management or watchful waiting since he is in poor health, life expectancy is well below ten years and he is currently asymptomatic for prostate symptoms.

This case also illustrates all the critical attributes of a model case, including the

application of a treatment option based on the best treatment approach for the tumor and the man's quality of life.

Case 3 - Borderline Case

A 55 year old man presents in his physician's office for advice regarding urinary symptoms, particularly a slow stream and frequent urination during the night. During a routine examination, the family physician discovers an enlarged prostate gland consistent with moderate BPH. Because of the man's age, the family physician draws a serum PSA which reveals an elevated PSA level of 6.2 ng/ml. The man is referred to a urologist who orders a TRUS and biopsy that confirms an organ confined CaP.

A borderline case contains a portion of the critical attributes or the case may contain all of the criteria, but differ substantially in one of the criteria, such as length of time or intensity of occurrence.[101] In this case, the man has not had annual prostate screening, but he was examined by his family physician for symptoms of BPH. Although the attribute of early detection and intervention were met, there was a time delay in his treatment since he delayed seeking medical advice until he was symptomatic which required referral to a urologist for further diagnosis and treatment. The attributes of survival were met since the man was identified in the early stages of disease and treatment instituted. The attributes of cost-effective screening were only partially met since the man did not have the benefit of annual

examinations for prostate screening or the availability of a prostate screening clinic, but he did have the benefit of screening through his family physician.

Case 4 - Related Case

A 60 year old man presents in his urologist's office for advice regarding urinary symptoms. The symptoms have been slowly progressive over five years, and his American Urology Association symptom score is 15 (refer to Appendix D, p. 205). DRE results are consistent with moderate BPH. After failed medical therapy, the patient underwent a combined TURP. Of the chips removed, several fragments had prostate cancer and prostatic intraepithelial neoplasia (PIN).[102]

Related cases are similar or connected to the concept being studied, but the critical attributes are absent.[103] In this case, the patient did not have regular prostate screening examinations or have access to a prostate screening clinic. His cancer was detected merely by chance in the treatment of BPH. He did not focus on early detection since he was being treated for BPH and had not considered CaP. His survival will now depend on the treatment options associated with CaP. The symptomatic features of BPH are secondary to the progression of his cancer.

Case 5 - Contrary Case

A 35 year old man presents in his urologist's office with severe right flank pain. A DRE reveals a normal prostate. He is diagnosed with cystinuria. A preoperative

KUB reveals right ureteral calculi whereby a laser lithotripsy procedure reduces the calculi to fragments which are passed in the urine over the next several days. A ureteral stent is placed and removed in 48 hours. There are no complications and the patient is discharged home asymptomatic.

A contrary case describes what the concept is not; it clearly excludes the critical attributes,[104] including the absence of CaP.

Case 6 - Invented Case

Doctor G. is a 60 year old practicing urologist who is a consultant for a newly established local prostate screening clinic. He routinely works at the clinic two days per week and is a strong advocate for annual screening for the male population between 50 - 80 years of age. His speciality is prostate surgery and he is an expert in the field; thus, he frequently lectures globally. As a matter of principle, he routinely has an annual examination at the local clinic which consists of DRE and PSA testing. During his last scheduled examination, he was asymptomatic, but his PSA level was 2.8 ng/ml. The accompanying TRUS and biopsy revealed minimal BPH, but there were no traces of CaP in six core biopsies. Doctor G. will continue to monitor his PSA and have annual examinations at the prostate screening clinic. His diligence in attending the screening clinic recognizes early detection, intervention, survival and cost-effective screening if a malignant disease of the prostate is detected.

An invented case is constructed by utilizing ideas outside our own experience which gives a true picture of the critical attributes.[105] In this case, prostate screening clinics are established and available to men who choose to be screened.

3. ANTECEDENTS and CONSEQUENCES

Antecedents and consequences assist with refining critical attributes and may define the social contexts in which the concept is used. Antecedents are events or incidents which must precede the occurrence of the concept; consequences are events or incidents that occur as a result of the concept.[106]

For a man to consent to regular prostate screening or attend a prostate screening clinic, there must be a stimulus or trigger event to propel him to submit to an examination. Education, informational sessions, referral by a family physician, encouragement by his partner or word of mouth may have alerted him to the importance of annual screening. He may have a symptomatic BPH, a family history of CaP or a friend who has succumbed to the disease.

A consequence of ensuring regular prostate screening or attending a prostate screening clinic may be the assurance of normal results that did not detect any evidence of CaP. Anxiety levels may be reduced that result in an improved quality of life. As a result of the education received through screening, the male recipient has a greater knowledge base that heightens his awareness of early detection of

prostate disease. His chances of survival are increased. For the man who was asymptomatic, he has a greater chance of survival with the early detection of CaP. Denial, ignorance or procrastination contribute to men not submitting to annual examinations with appropriate testing and follow-up. For others, detection reveals a disease beyond the prostate capsule and the realization that a 99% cure rate is no longer feasible. Survival has an inverse relationship with the stage of cancer at the time of detection and 11% of prostate cancers are diagnosed at a distant stage or when the cancer has metastasized; unfortunately, the five year survival rate is only 30.9% when diagnosed at this stage.[107]

4. EMPIRICAL REFERENTS

Empirical referents, which may be identical to the critical attributes or categories of actual phenomena that demonstrate the occurrence of the concept, are useful in instrument development and can be used to measure the concept. They also provide observable phenomena to diagnose the existence of the concept in patients.[108]

Empirical referents for early detection, intervention and treatment of CaP include research and statistics which demonstrate increased survival rates and quality of life for those individuals diagnosed with early stage CaP. Regular screening or access to screening clinics provide a vehicle for early detection, epidemiology of the disease, treatment results and statistics for improved quality of life issues.

Experts agree that screen detected patients do have improved health outcomes compared to those not screened.

5. CRITICAL REFLECTION OF THEORY

Critical reflection of a theory is a process that asks how well a theory serves some purpose.[109] The nature of the theory is basic in choosing a guide to research, practice and education.[110] The theory states that early detection and treatment of cancer of the prostate substantially lowers cause-specific mortality. Semantic clarity defines the major concepts of the theory which are: 1) early detection which identifies men with organ confined CaP that is potentially curable, 2) treatment of cancer or intervention which identifies men with asymptomatic or early stage CaP by providing appropriate treatment options, and 3) a lowering of cause-specific mortality or survival which identifies treatment options that reduce morbidity and mortality associated with CaP.

The major concepts of the theory have semantic consistency or definitions applicable to all disciplines. The purpose of the theory is early detection, which confines the cancer to the prostate gland. Assumptions of the theory imply that appropriate treatment increases survival and the quality of life; however, the interventions should be cost-effective with beneficial health gains, such as possible cure and improved health outcomes. Prostate screening with expansion into prostate screening clinics would ensure that certain criteria are satisfied and as

such are a feasible and viable vehicle to: 1) diagnose in the early stages of CaP, 2) manage the disease, 3) study the epidemiology of CaP, 4) reduce side effects and treat complications, 5) treat CaP and, 6) provide statistics for improved quality of life issues. Because screened men have a four or five year potential difference in longevity with earlier detection of their cancer,[111] it appears justified to assume that screen detected men do have improved health outcomes compared to those who are not screened. In addition, research has shown that early detection does save lives. The relationships between the concepts are consistent with the assumptions that prostate screening enables early detection, management and appropriate treatment of CaP. Therefore, the theory could be expanded to include the attribute of cost effective CaP screening; thus, the concepts are interconnected and organized into a coherent whole for structural clarity. The empirical referents of research and statistics provide structural consistency. The theory is relatively simple in that it consists of three related concepts: health promotion, individual responsibility and well-being health behavior. The scope is narrow with one disease entity, cancer of the prostate, although it has a broad population base which encompasses the male population, their partners and nuclear/ extended families. Therefore, the theory is parsimonious with a high degree of universal application for well-being health behavior. The theory links the empirical referents of research and statistics with the concepts since research has already proven that there is increased survival rates and quality of life for those individuals diagnosed with early stage CaP. In addition, the referents of early detection and treatment of

CaP provides credibility to the theory and valuable operational tools congruent with empirical data.

The inclusion of prostate screening in the theory completes the conceptual network in a diagrammatic representation as follows:

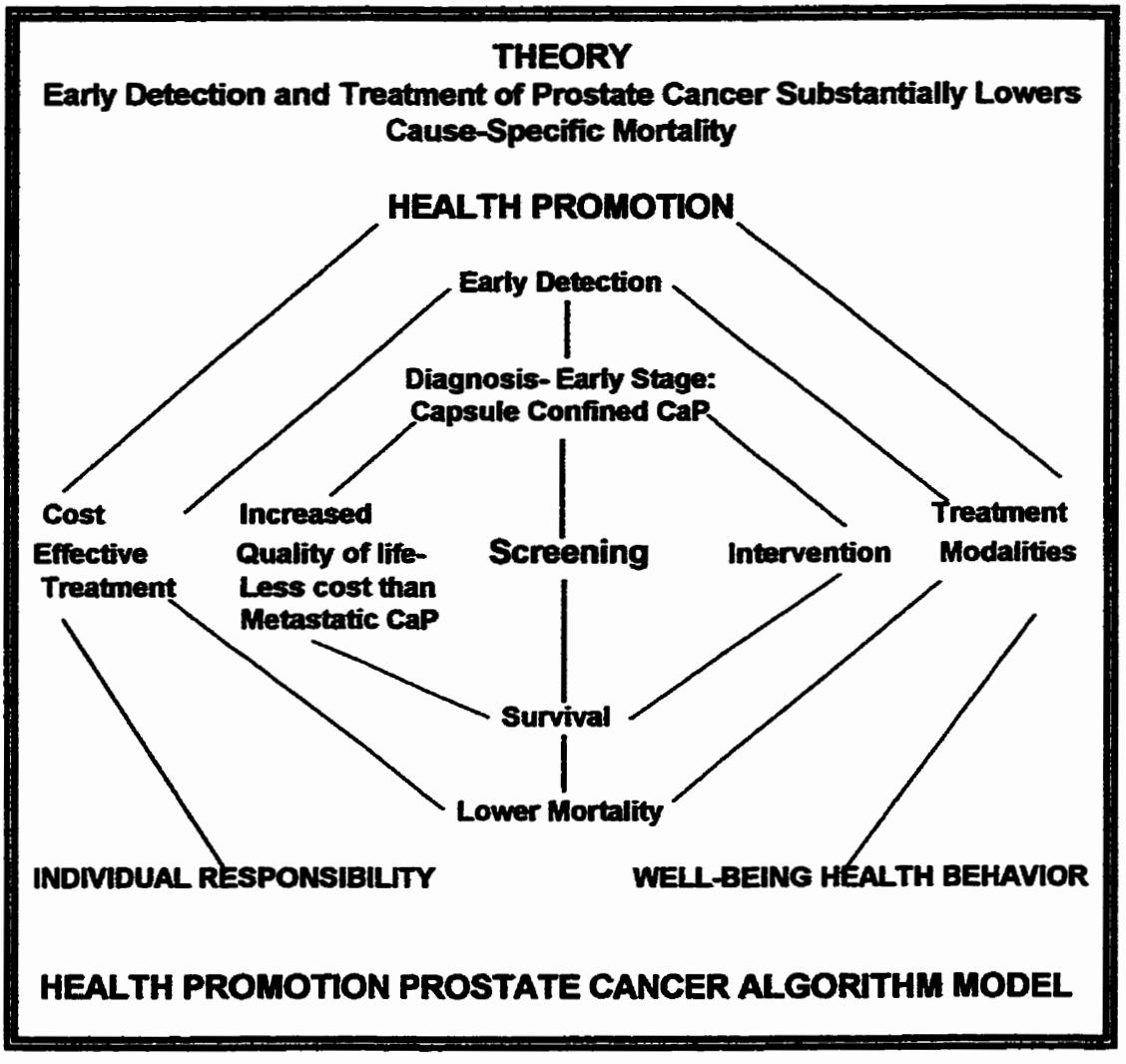

Figure 2: Health Promotion Algorithm

The inclusion of cost-effective screening in the expanded form of the deduction theory includes the potential for positive clinical outcomes which are grounded in practice. Research has shown that early detection of CaP does save lives. The dependent variable of decreased mortality (C) and the independent variables of early detection (A) and treatment for CaP (B) form the hypothesis that guides research: lower mortality is dependent on early detection and treatment of CaP. The variables are logically consistent in the mathematical representation of: A + B = C. However, A and B do not have to be equal.

Prostate screening clinics will have the ability to provide statistics for improved quality of life issues, treatment evaluation and results, health promotion and well-being health behavior that encourages individual responsibility for a disease that has a significant health burden.

6. SUMMARY

A research design is the framework for the project or study.[112] The utilization of a theory and conceptual framework organize the phenomena or explanations into an organized and coherent pattern.[113] Theories are sets of concepts which express a relationship. The process of concept analysis provides an understanding of the critical attributes of early detection, intervention, survival and cost effective treatment for CaP. The formation of a health promotion prostate cancer algorithm provides visual representation of the phenomena and depicts the relationship

between the concepts, critical attributes and theory. Prostate screening provides health promotion and well-being health behavior that encourages individual responsibility for a disease that has a significant health burden. Health promotion is a driving force in current public policies and advocated by government agencies. If the key to survival is early detection, prostate screening and the implementation of screening clinics will provide research and statistics to evaluate treatment, survival, quality of life issues and cost effectiveness on a long term basis.

CHAPTER THREE

1. THE PROSTATE GLAND

i) Anatomy and Physiology

The prostate gland, part of the male reproductive system, is a solid organ that surrounds the urethra and lies immediately below the bladder (refer to Figure 3, page 40). At birth, the prostate is about the size of an almond and weighs only a few grams, but during puberty, the gland enlarges and continues to grow to double the size or about the size of a walnut (20 grams)[114] in a young male adult.[115] The prostate contributes fluid to the semen which assists with transport of sperm. After 40 years of age, the prostate begins to grow again which is thought to be influenced by hormonal changes.[116] This age-related increase in size is referred to as benign prostatic hypertrophy (BPH) which is a common cause of urinary symptoms such as: outflow obstruction, difficulty starting a stream, poor flow and increased frequency.[117] The prostate as part of the male urogenital system has two important functions: 1) to help in the control of urination; that is, the prostate has a passive role by controlling the rate at which urine flows out of the bladder and into the urethra by the muscle fibers in the prostate that surround the urethra, and, 2) an active role in sexual functioning.[118] The prostate gland produces a whitish glandular secretion which collects in the prostate and is fed into the urethra during ejaculation.[119] The glandular secretion helps sperm motility in the urethra and comprises approximately one third of the seminal fluid which gives the seminal fluid its whitish appearance.[120] The growth of the prostate and control over functions are

based on the levels of testosterone, a male sex hormone produced by the testes. The production of testosterone is controlled by another complex set of hormonal interactions.[121] The prostate gland can be felt by inserting a gloved finger into the rectum and is referred to as a digital rectal examination (DRE). A DRE procedure is an important screening tool in the detection of prostate cancer and other prostatic diseases.

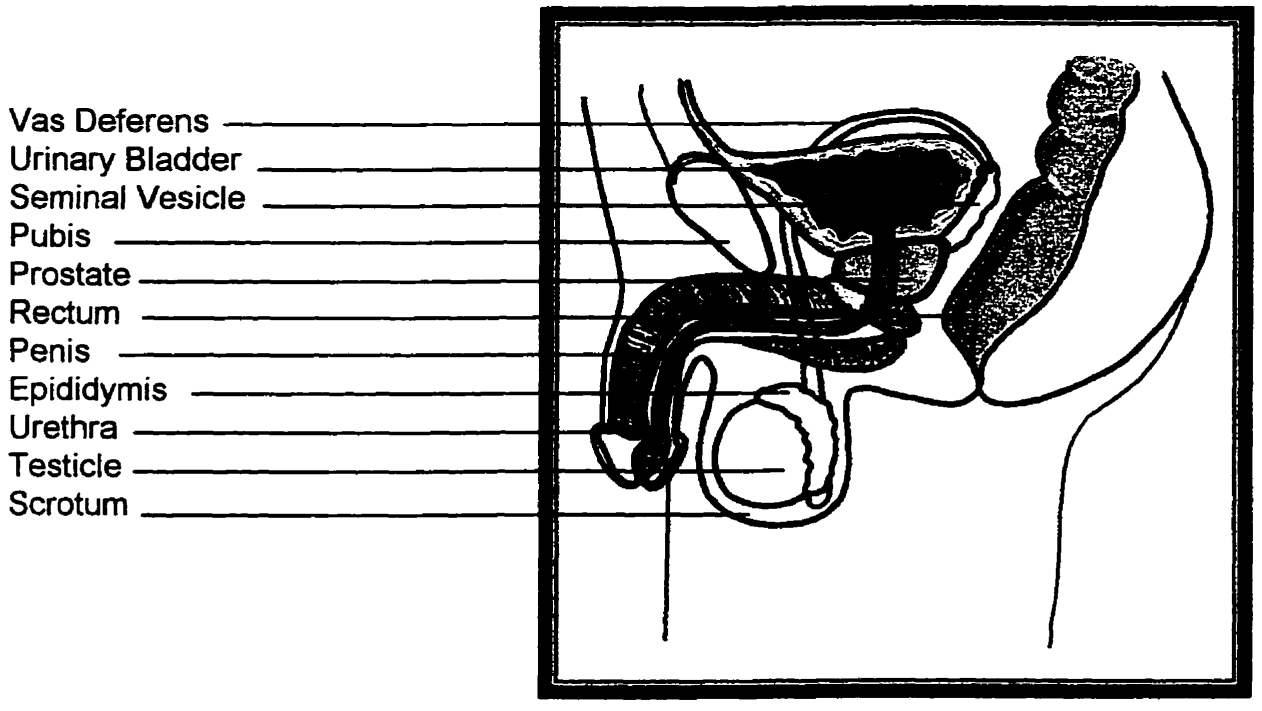

Figure 3: The Male Urogenital System depicting the prostate immediately below the bladder and surrounding the urethra.

ii) Prostate Symptoms

Prostate cancer in the initial stages is devoid of symptoms, and thus, the disease is considered a silent killer. When symptoms develop because of significant disease process, they frequently are indistinguishable from the symptoms of

BPH[122] and other normal consequences of an aging prostate gland. Another problem in the identification of prostate cancer is that signs or symptoms often do not appear until many years after the disease has started to develop.[123] There are no definitive symptoms that a male can easily identify in the initial stages of prostate cancer; unfortunately, metastatic disease causes pain, especially bone pain.[124] The National Cancer Institute has identified clinical indicators of prostate cancer, although, they could also be caused by a number of disorders other than prostate cancer:[125]

- ➢Frequent urination - especially at night.
- ➢Inability to urinate.
- ➢Trouble initiating a stream or trouble holding back urination.
- ➢Pain during ejaculation.
- ➢A weak or interrupted urine flow.
- ➢Pain or burning feeling during urination.
- ➢Blood in the semen or in the urine.
- ➢Frequent pain or stiffness in the lower back, hips or upper thighs.
- ➢Loss of appetite and weight.[126]

iii) Etiology and Risk Factors of Prostate Cancer

There are two potential precursors of prostate cancer that have been recognized: atypical adenomatous hyperplasia (AAH) and prostatic intraepithelial neoplasia (PIN).[127] There is some question as to the premalignant potential of AAH; however,

PIN, which may be detected on needle biopsy, has been identified as a precursor to prostate cancer and may precede the disease by several years.[128] PIN, which is a proliferation of epithelial cells with marked cytologic abnormalities, is a microscopic finding that arises within pre-existing ducts and acini .[129] PIN is known by a variety of terms including: dysplasia, intraductal dysplasia, large acinar atypical hyperplasia, atypical primary hyperplasia, hyperplasia with malignant change, marked atypia or duct-acinar dysplasia.[130] PIN has been described as the most likely precursor of prostatic adenocarcinoma with a twenty to thirty year lag time.[131] PIN is divided into low or high grades and has comparable cellular structures to an early form of breast cancer known as intraductal carcinoma of the breast.[132] Currently, there is no relationship between PSA levels and the occurrence of PIN, but it should also be noted, that there is no relationship between the occurrence of PIN and the presence of prostate cancer.[133] A Mayo Clinic study found that 88% of CaP patients had high-grade PIN compared to previous studies which found that 33% to 100% of CaP had high-grade PIN.[134] The same study reported that high-grade PIN does not significantly contribute to serum PSA concentrations, and therefore, PIN should not be attributed to elevated PSA levels.[135] It is generally agreed that if a patient has a high grade PIN, then the patient is at risk for prostate cancer; a diagnosis of low-grade PIN is considered insignificant.[136] If high-grade PIN is found in a biopsy specimen, it is recommended that a careful examination should be completed to rule out the presence of CaP, repeat a PSA test with biopsy guided TRUS, and if no cancer is found, repeat

biopsies and PSA testing every six months for two years.[137] High-grade PIN in the presence of an elevated PSA is a predictor for small foci of localized CaP.[138] Currently, there is no evidence that PIN can be successfully treated, although, researchers have initiated studies with androgen deprivation therapy, finasteride or finasteride combined with nonsteroidal antiandrogens.[139]

The cause of prostate cancer is not known; however, several risk factors in addition to PIN have been identified: 1) genetic predisposition, such as family history and ethnic race, 2) age and, 3) environment, especially diet. CaP has recently been linked to a gene (HPC-1) on chromosome 1 and proves that CaP can be inherited like other cancers.[140] Studies have suggested the gene is autosomal-dominant.[141] Only about 10% of all CaP cases are thought to be hereditary; however, many scientists believe that the defective gene or mechanisms involved in hereditary cancer are the same ones that go askew in sporadic cancer, the disease that develops over the course of a lifetime.[142] Prostate cancer has been found to have a stronger familial aggregation than either breast or colon cancer.[143] If a close relative (father or brother) has CaP, there is a risk two times greater than the average American male or about 13% of developing CaP.[144] The risk increases with the number of affected relatives and the closer genetically to the affected relative.[145] For example, if at least three close relatives or if two relatives both were younger than 55 years of age with a diagnosis of CaP, or if a family has CaP in three generations, then, the risk could be as high as 50%.[146] Men with three

affected relatives are at an eleven fold risk.[147] A Canadian study, which utilized the Alberta Cancer Registry to identify 382 prostate cancer cases, reported that a patient was three times more likely to develop CaP if they had a first-degree relative with CaP.[148] Because hereditary CaP appears to occur at a younger age, age 40 is recommended for screening guidelines.

African American men have the highest rate of developing CaP in the world, and thus, race is a risk factor.[149] Some studies suggest that African American men, who are about two times more likely to develop CaP than Caucasian men, have a slight variation in androgen receptors through which the prostate is controlled by hormones; therefore, these men are at a higher risk of developing CaP.[150] This phenomenon, which makes testosterone more efficient in prostate cells, is also common in Caucasian men with clinically localized CaP who are found after surgery to have micrometastasis.[151] Another study used data collected between 1988 and 1992 and reported that African Americans had a 35% higher incidence rate and a 223% higher mortality rate compared with Caucasian men.[152] African Americans present at a younger age, with a higher grade and stage of CaP and with a greater delay in diagnosis.[153] By comparison, Japanese men living in Japan have an extremely low incidence of CaP, but men of Japanese origin living in America have a similar risk of developing CaP as any other average American man living in the same area.[154] Other studies suggest Chinese-Americans have an intermediate rate, which means they have a greater risk of developing CaP than Chinese men

living in China, but a lesser rate than Caucasian American men. This phenomenon suggests an environmental link.[155] Various attempts to explain the differences between races of being affected with CaP has not produced definitive answers. Are African Americans more susceptible to CaP through promoting events or are they exposed to different promoting agents?[156] Socioeconomic status and education do not appear to be factors in studies that controlled for these variables.[157] Other studies suggest factors such as: a higher dietary fat intake, higher circulating testosterone levels, decreased ability to produce vitamin D, larger volumes of latent prostate cancer, lack of screening, different genetics and different environmental exposures.[158]

Age is a dominant factor in developing CaP with the risk increasing with age. Since men have a longer life expectancy today, the incidence of CaP will rise, coupled with the swelling age groups as the baby-boom generation reach fifty plus years. The average age of men diagnosed with CaP in America is still over 60 years, although it is more common in younger men than in the past.[159] Prostate cancer appears to exist in two forms: 1) a latent form that can be identified in about 30% of males over the age of 50 years and 60% - 70% of males over the age of 80 years, and 2) a clinically significant form that will affect approximately one in five American men.[160] The probability of developing clinically significant CaP in men:

- Less than 39 year of age - 1 in 10,000.
- 40 - 59 years of age - 1 in 78.

➢ 60 - 79 years of age - 1 in 6.[161]

Some believe that the latent form is a precursor to the clinically significant form, separated by time and/or promotional events, although, this concept is unproven.[162] Other genetic alterations appear to be acquired with age, such as: increased mutation susceptibility of prostate cells, loss of tumor-suppressor genes, and mutations in the androgen receptor that may give prostate cancer cells selective growth advantage after androgen ablation.[163] Prostate cancer is rarely seen in men younger than 50 years; although, the Canadian Cancer Statistics estimate 70 Canadian men under 50 years of age will be affected with CaP in 1998.[164]

Environmental links with prostate cancer, especially diet, have received considerable attention over the years. Many studies have reported a positive correlation with fat intake, particularly polyunsaturated fat, and prostate cancer.[165] Unsaturated fatty acids may have a role in androgen action or alter the risk for CaP;[166] however, the suggestions are circumstantial at best. Other studies have clearly linked prostate cancer risk with saturated fat intake, which is further exemplified by Japanese men who experienced an increased incidence of CaP when they adapted their diet toward westernized levels of increased fat content.[167] Fat from fish, vegetables and dairy sources (except for butter) were not found to be relevant.[168] Evidence is very weak, but there are suggestions that fat may increase the level of sex hormones which has implications for fat soluble vitamin A, D, E and trace minerals such as zinc[169] (the prostate gland contains the highest

concentration of zinc of any organ in the body).[170] Intake of tomatoes and related products has been linked to a lower risk of CaP while other studies have reported no effect of Vitamin C on CaP.[171] Therefore, at present there is little evidence to support that CaP risk varies with consumption of dietary antioxidant and Vitamin D.[172] There is no known diet that will prevent CaP,[173] but the American Cancer Society recommends a life style that includes low fat and high fibre based on the latest scientific research.[174]

Extraneous lifestyle factors, such as alcohol, smoking, occupation and physical activity, have always been contentious issues. Initially, alcohol was thought to enhance the metabolic clearance of testosterone, but virtually all studies have failed to demonstrate a relationship.[175] Smoking introduces pollutants into the lungs and other organs. Studies have produced mixed results; however, an Iowa study observed that 20 or more cigarettes per day resulted in nearly a threefold increase in CaP risk compared to non-smokers.[176] Although such studies are provocative, there is not enough consistent or duplicated evidence to introduce public health policies.

Occupations have focused on exposures to cadmium, rubber production and farming. In a 1991 review, farming was associated with an increased risk of CaP in seventeen of twenty-four studies.[177] One study identified herbicide spraying as the causative agent; however, the National Academy of Sciences's committee

concluded that there is limited evidence liking herbicide exposure to CaP in Vietnam veterans.[178] A review of studies regarding cadmium and rubber concluded there may be a weak increase in risk.[179]

Physical activity has been proposed to lower body fat and testosterone levels, however, studies have been inconclusive.[180] Sex hormones, particularly androgens, may play a role in development of CaP since growth rates of prostate cancer can be manipulated through hormonal therapy.[181] The prediagnostic levels of serum testosterone and dihydrotestosterone have not been associated with an increased risk of CaP; however, studies are exploring the activity of 5-alpha-reductase, the enzyme in the prostate that converts testosterone to dihydrotestosterone.[182] It has been demonstrated that African Americans have a 15% higher testosterone level than Caucasian, while Japanese men have a different level of testosterone-metabolizing enzymes than Americans.[183] A low fat, high fibre diet has been shown to decrease the circulating levels of testosterone.[184] Although the exact role of hormones is unknown, they obviously play an important role.[185]

Although studied extensively, the role of sexual activity in the development of CaP has been inconclusive. Some studies suggest that early first intercourse, a large number of sexual partners and a history of sexually transmitted diseases increase the risk of CaP; however, it also has been reported that celibate men develop CaP at the same rate as the general population.[186] Similarly, study results have been

inconclusive regarding vasectomies.[187] A major concern is bias since men with vasectomies have possibly been screened with prostate examinations earlier by urologists; also, there are an estimated 500,000 men who have vasectomies each year in the United States.[188] There is no evidence of a cause effect relationship between vasectomies and CaP[189] and it is unlikely that there is a biological mechanism.[190]

iv) Prostate Cancer Prevention

Prostate cancer, as other cancers, has an unknown etiology. There are identified risk factors that are explained by the interaction of a combination of genetic and environmental variables. Studies continue to find a cause and effect relationship that will enable interventions to be designed to prevent prostate cancer. The increasing incidence of CaP has suggested that preventive measures should be initiated to reverse the trend.[191] In 1993, the National Cancer Institute organized the Prostate Cancer Prevention Trial involving 18,000 men that is designed to test whether finasteride (proscar) will prevent CaP from developing in men.[192] Proscar is known to reduce dihydrotestosterone levels in the prostate and has a low level of side effects.[193] The trial has a seven year time frame.

2. SCREENING TOOLS FOR PROSTATE CANCER

The purpose of early detection modalities, PSA, DRE, TRUS and biopsy is to identify, diagnose, treat and eradicate cancer of the prostate with a resulting

decrease in morbidity and mortality. The goal of any screening program is to reduce the burden of suffering by application of a test that detects a disease at a stage when an intervention can significantly modify the natural history of the disease process. [194] Lead-time bias occurs when the clinically recognizable stage is lengthened and the preclinical stage is shortened without affecting overall survival.[195] This bias occurs only because the diagnosis is established for a longer period of time.[196] Length bias refers to the tendency of fast-growing tumors to become clinically evident between screening intervals while slow-growing tumors are likely to be discovered during screening; therefore, bias is introduced in favor of better survival for those individuals who had a better prognosis from the start.[197] The sensitivity of a test is the proportion of patients with the disease who test positive for the disease while specificity of a test is the proportion of patients who do not have the disease who test negative for the disease. An ideal test would be a combination of high sensitivity and specificity. The positive predictive value (PPV) is the proportion of people with a positive test who actually have the disease.[198] The average, normal, healthy male will probably have a PSA of less than 4.0 nanograms per millilitre of blood (ng/ml), but there are many reasons for a variation and why a variety of detection modalities are needed to identify CaP.

i) Prostate Specific Antigen Test

Prostate specific antigen (PSA) was initially identified in human seminal plasma as gamma seminoprotein and utilized as a semen marker in rape victims.[199] In 1979,

Wang et al. isolated and purified a protein produced only in prostate epithelial cells that was later called PSA.[200] The gene for PSA is located on chromosome 19 and is under androgen regulation.[201] PSA, which is synthesized in the ductal epithelium and prostatic acini is located within the cell and secreted into the lumina of the prostatic ducts via exocytosis to become a component of seminal plasma. It reaches the serum after diffusion from luminal cells through the epithelial basement membrane and prostatic stroma where it passes through the capillary basement membrane and epithelial cell or into the lymphatics.[202] It was originally assumed that PSA was tissue-specific to the prostate, and thus, gender-specific; however, PSA has been detected via immunohistochemical and immunoassay methods in female and male periurethral glands, anal glands, apocrine sweat glands, apocrine breast cancers, salivary gland neoplasms and human breast milk.[203] "Based on the discovery of androgen-response elements in the PSA gene promoter regions and glandular tissues where PSA has been found, PSA in nonprostatic tissues may reflect end-organ responses to circulating steroids".[204] PSA is secreted from the lumen of the prostate and enters the seminal fluid as it passes through the prostate. PSA functions to release the sperm by liquefying the coagulum in seminal fluid which have trapped the spermatozoa.[205] PSA, which is found in normal, hyperplastic, primary and metastatic prostate tissue, is a member of the human tissue kallikrein gene family.[206] It is a serine protease which is immunoreactive, and thus, detectable by immunoassays.[207] Since 1987, PSA has been used in all aspects of prostate cancer management: screening, diagnosis, staging, response

to treatment and identifying treatment failure.[208] Despite the shortcomings of PSA, most notably a sensitivity of 68% to 80% and a specificity of 49% to 90%,[209] the ability of PSA to diagnose, predict tumor volume and stage, and predict prognosis of men with CaP has revolutionized the care of men affected with the disease.

In 1986, the Food and Drug Administration approved the first commercial immunoassay for PSA as an aid in the clinical management of patients with CaP.[210] PSA is measured by both monoclonal (Hybritech, San Diego, CA, and Abbott) and polyclonal (Yang, Bellevue, WA) assays.[211] The polyclonal assay, which is less commonly used than monoclonal, yields values approximately 1.6 times higher than the monoclonal assays resulting in a upper normal limit of 7.0 ng/ml.[212] Therefore, it is important to check which assay is used in testing to ensure accurate results and interpretation of the values. PSA testing is derived from the use of total serum measurements, although, the PSA transformations of density, slope or velocity, age-specific references and free or unbound serum levels have increased the clinical use of PSA to make it a more valuable tool in the diagnosis of early-stage CaP.[213] It has been estimated that 8% to 15% of men older than 50 years of age have a PSA level greater than 4.1 ng/ml, and 11% to 34% of the men who agree to a biopsy are diagnosed with CaP.[214] The false positive PSA elevations are primarily due to BPH, especially in men older than 50 years.[215] By the age of 60 years, 50% of men have microscopic evidence of BPH with an increase to 100% by age 90 years.[216] In the aging male, BPH is the most common benign neoplasm and

CaP is the most common malignant neoplasm, often both present in the same patient. At age 50 years, 25% of males will have either clinical BPH and/or reduced urinary flow which affects their quality of life.[217] Over 80% of CaP is associated with BPH; therefore, the strategy is to distinguish the patients with clinically significant and potentially curable CaP from those with BPH alone.[218] Approximately 25% of BPH patients will have a PSA greater than 4.0 ng/ml [219] while 48% of men with clinically significant, but organ confined CaP will have a normal PSA.[220] There is significant overlap in serum PSA values between men with BPH and organ-confined CaP[221] which creates some of the controversy in utilizing PSA as a tumor marker or for utilization in screening programs. As a result, PSA is not the perfect cancer marker. The contribution of BPH to PSA levels is not clearly understood, although the assumption is that as epithelial prostate cells are produced, more PSA is produced.

The lack of accuracy in PSA testing is most notable in the 4.1 to 10.0 ng/ml range which is considered a grey area, but where many men have organ-confined disease and require TRUS and biopsy to determine the cause of the PSA elevation.[222] Some studies suggest that the prevalence of CaP is only 1.4% for a PSA less than 4.1 ng/ml, whereas, there is a 53.3% prevalence of CaP when the PSA is greater than 10.0 ng/ml.[223] The question of economics is raised since it is estimated that patients with a PSA level of 4.1 to 10.0 ng/ml comprise 20% of the referral volume for further evaluation and of these one-fifth are diagnosed with CaP which required

TRUS and biopsies, a cost requirement.[224] Thus, there are continuous efforts to improve the sensitivity and specificity of PSA testing which will enable CaP patients to be distinguished from other prostatic conditions. There are many factors which affect the serum PSA level including: acute and chronic prostatic inflammation, urinary retention, prostatic massage, prostate needle biopsy, cystoscopy, TURP, TRUS and possibly ejaculation.[225/226] Study results regarding the effect of ejaculation on PSA levels are mixed, but it appears that ejaculation causes a significant increase in the serum PSA concentration of men aged 49 to 79 years that may persist for up to 48 hours[227] with one study finding that both the total and free PSA were elevated after ejaculation.[228] It is thereby recommended that a waiting period of 48 hour abstinence prior to PSA measurements is required to prevent skewing clinical results affecting PSA levels which would allow PSA velocity to be a more reliable parameter and potentially avoid unnecessary prostate biopsies.[229] PSA levels are increased with prostatic manipulation, stimulation or injury with one report by Stamey citing that a cystoscopy causes a fourfold increase in PSA levels; however, other reports suggest that cystoscopy, whether rigid or flexible, cause only a small and transient elevation in serum PSA that return to baseline within 24 hours.[230] Various studies have concluded that DRE does not affect PSA dramatically enough to alter treatment decisions, although there is a minor increase in serum PSA levels after DRE, it is not clinically significant.[231] However, vigorous prostate massage can be significant and it is prudent to wait at least three days before PSA levels return to baseline levels.[232] In comparison,

serum PSA levels rise significantly after needle biopsy with reports indicating an elevation of 1.3 to 57 fold depending on the technique, type of needle used, number of core samples, and type of assay.[233] Therefore, it is recommended to wait at least six weeks before repeat PSA determinations.[234] All studies show a significant rise in PSA levels after TURP procedures due to the release of acini rich PSA into the circulation, but long-term follow-up will show a decreased PSA level correlating directly with the number of grams of tissue removed.[235] Stamey et al concluded that each gram of resected tissue accounted for 0.3 ng/ml of PSA.[236] PSA levels are reduced by 70% after three months and after a complete TURP, the PSA level should fall to less than 4 ng/ml.[237] It is suggested to wait at least six weeks before obtaining repeat PSA determinations.[238] Similarly, TRUS elevated the PSA levels and it is recommended that PSA determination should be done prior to the TRUS examination or after seven days.[239] Prostatitis can cause a PSA leak that will elevate PSA levels, but levels should return to a normal range after antimicrobial therapy.[240] The effects of exercise on PSA levels have produced conflicting reports, but it appears that exercise and bicycling, which puts direct pressure on the perineum and prostate, does not change serum PSA levels.[241] Similarly, studies of biological variations of PSA have concluded that PSA does not have a significant diurnal rhythm and serum can be drawn at any time of the day.[242] Other studies report that men who are on medications such as finasteride have a 50% decrease in PSA levels and terazosin reduced levels by 25%.[243] Because PSA plays such a crucial role in the management of prostate cancer, any intervention that may skew

the PSA results should be identified.

Determining a so-called *normal* level of PSA, which is not cancer-specific, has been the source of extensive study and controversy since the level is prostate-specific and influenced by many other factors besides CaP. The bench mark figure of a serum PSA concentration of 0 to 4.0 ng/ml [244] has been utilized as a normal level although not all men with CaP have an elevated PSA. Various studies have reported that 18% to 32% of the men in study populations had a positive biopsy with PSA levels less than 4.1 ng/ml.[245] Most of the men had a suspicious DRE, but other studies have reported risks of prostate cancer with a normal PSA and a nonsuspicious DRE. A study by Vallancien et al found no CaP in 34 men with a normal DRE and PSA level of 0.6 to 2.5 ng/ml.[246] Another study demonstrated that men with a baseline serum PSA between 2 and 4 ng/ml were twelve times more likely to be diagnosed with CaP during the next ten years than men with a level less than 1 ng/ml.[247] The results of these new studies have influenced some to recommend further evaluation for any man with a serum PSA greater than 2.5 ng/ml.[248] In addition, studies have reported that PSA screening detected pathologically organ-confined CaP in 63% to 71% of the men tested; other studies have revealed that PSA determination correctly identified 87% of all aggressive cancers of the prostate occurring during the first four years of follow-up with 75% mortality from CaP.[249] A PSA test result of less than 4 ng/ml rarely exhibits cancer that extends beyond prostate margins,[250] and thus, PSA is instrumental in detecting

localized CaP that has the potential for cure. Several studies have confirmed that biologically significant cancer is discovered by serum PSA elevation, and that only a small minority of PSA detected cancers are latent or indolent[251] with estimates that only 8% to 26% of cases diagnosed with PSA are probably latent with little potential for further invasion.[252] Potential overtreatment of these cases has been an argument against PSA screening; however, similar figures have been established regarding the latent cases of breast cancer diagnosed by mammography in screening programs.[253] Using baseline PSA determinations, a mean lead time in the diagnosis of CaP of 5.5 years was established which suggests that more than half of the fatal cancers could have been detected at least three years earlier if PSA testing had been available in 1982.[254] These studies confirm that PSA has a relatively high sensitivity, and specificity for detection of aggressive CaP arising within a four year period of a single PSA measurement.[255] PSA sensitivity is the ability to detect cancer in a high number of men who actually have the disease, while PSA specificity is the ability to determine that an abnormality in the PSA test is due to the presence of CaP.[256] It is also noteworthy that the SEER Utah Tumor Registry reported a 35% drop in CaP detection rates from a peak in 1992 which supports the suggestion that repetitive PSA based screening does not result in the detection of a larger number of insignificant cancers.[257] The largest increase in CaP incidence rates occurs in the initial years of screening when many undiagnosed cases present; however, the overall incidence rate decreases while the percentage of patients with organ-confined and

potentially curable CaP increases.[258]

Study results from screening trials estimate that 70% of cases are organ confined, whereas, only 30% are organ confined in unscreened populations.[259] There are studies that suggest screening is beneficial such as a study by Gilliland et al who examined the temporal trends in CaP survival in New Mexico from 1983 to 1992 and reported improved prognosis of CaP for those cases diagnosed in the post-PSA screening era.[260] Boring et al in a similar study reported that the overall five year survival rates for localized CaP increased from 77% (pre-PSA: 1974 to 1979) to 92% (post-PSA: 1983 to 1988).[261] Although the argument could be proposed that the studies are skewed by lead time bias because of earlier diagnosis, screening does appear to provide a survival benefit to those who participate.[262]

Recent evidence suggests that the specificity of PSA may be improved by the use of certain PSA transformations, one of which is age-specific reference ranges. Some studies related to age-specific PSA reference ranges continue to recommend that men aged 60 to 79 years with a negative DRE should be biopsied if their PSA is greater than 4.0 ng/ml, because of the higher number of missed cancers.[263] One report by Borer et al [264] reported that although the higher levels avoided 5.7% of the biopsies in a study sample of 1,280 men, 60% of the missed cancers exhibited an unfavorable histology. Other studies suggest that the number of missed clinically significant prostate cancers in older men using reference ranges higher than 4.0

ng/ml would be lower than the Borer study and the specificity in men older than 60 years would increase since the number of negative biopsies would be reduced. [265] However, the real question involves determining what percent of the undetected significant prostate cancers will impact the older male in terms of morbidity and mortality rates. Interpretation of results often requires the expertise of a skilled urologist. Other studies suggest decreasing the level in younger men (under 60 years of age) to improve the sensitivity of PSA and increase the diagnosis of early, organ-confined CaP.[266] Further attempts to improve the diagnostic performance of PSA reported that serum PSA increases 26% per decade of age and 32% for each 10 ml increase in prostate gland volume; thus, prostate volume increased with age and that age and prostate volume influence the serum PSA concentration independently.[267] Oesterling et al were the first researchers to explore the relationship between age, prostate volume and PSA levels[268] In 1993, they established that age is independently associated with increased PSA levels of 0.09 ng/ml in men with BPH, in addition to serum PSA being more strongly associated with prostate volume rather than age.[269] Multiple regression analysis demonstrated that 30% of PSA variance was due to prostate volume and 5% was due to age.[270] Of additional significance is the determination of differing age-specific reference ranges in Caucasians, Asians, and African Americans; therefore, it is not only essential to know the age of the patient, but also the race of the patient to interpret the serum PSA. As a result, utilizing age-specific reference ranges will continue to improve the clinical utility of the PSA test such as depicted in the following table:

Age Range	Reference Range (ng/ml)		
	Asians	African Americans	Caucasians
40 - 49	0 - 2	0 - 2	0 - 2.5
50 - 59	0 - 3	0 - 4	0 - 3.5
60 - 69	0 - 4	0 - 4.5	0 - 4.5
70 - 79	0 - 5	0 - 5.5	0 - 6.5

Figure 4: Adapted from Richardson, T. and Oesterling, J. 1997.[271]

PSA velocity (PSAV) or slope is the rate of longitudinal change in PSA levels over time. Change in PSA and the time between measurements are two factors to be extrapolated. PSAV has been shown to be a specific marker since most men with a rate of PSA change less than 0.75 ng/ml per year do not have cancer. In fact, as a marker for the presence of CaP, PSAV has a high specificity since less than 5% of men without CaP will have a PSAV indicating the presence of CaP.[272] Men with a non-organ confined CaP had a mean PSA velocity of 1.88 ng/ml/yr compared with 1.12ng/ml/yr for men with organ-confined CaP.[273] The rate of rise in PSA prior to a diagnosis of CaP would not appear to reflect disease extent and remains a challenging dilemma.[274] Using a cut-off point of 0.75 ng/ml/yr, the data suggest that to maintain sensitivity and specificity at least 1.5 to 2 years is necessary for PSAV evaluation;[275] however, there is a 90% specificity for diagnosing CaP when the PSAV is greater than 0.75 ng/ml in one year.[276] PSAV is one method to assess the risk of CaP in men with a rising PSA level. It can help distinguish between the expected rise in PSA that occurs with age and the rise in PSA that suggests the presence of cancer and the need for prostate biopsies.[277] In addition, PSAV is an

important tool in monitoring the reoccurrence of disease in treated patients since a persistently rising PSA suggests progression of prostate cancer.

PSA density (PSAD), which is the value of total serum PSA in ng/ml divided by the volume of the prostate gland in cc's, is based on the premise that cancer, on a gram for gram basis, will increase serum PSA levels to a greater degree than will BPH or normal prostate tissue.[278] PSAD is the concentration of PSA in the prostate gland. However, prostate volume is dependent on accurate TRUS volume determinations of the prostate gland which are largely subjective depending on the operator. Malignant tissues display an anarchic structure and behavior which results in a progressive elevation of the serum PSA levels at an estimated rate of 3.5ng/ml/g of tumor compared with BPH that respects normal cell behavior and grows strictly by local expansion which results in a constant increase in serum PSA levels at an estimated rate of 0.3 ng/ml/g of hyperplastic tissue.[279] A PSAD cut-off value of less than 0.15 can safely reduce the number of biopsies performed in patients with a negative DRE and TRUS results, but with a serum PSA level between 4.1 and 10.0 ng/ml.[280] However, the cut-off value of 0.15 has not been safely established in patients on medications such as finasteride and has not shown superior staging or prognostic abilities in predicting outcomes in patients who have had surgical treatment for CaP compared with Gleason score and total serum levels[281] Other studies demonstrate that a low PSAD (< 0.15) can predict with 90% accuracy the operative success in patients with clinically localized CaP who

were treated with radical prostatectomy.[282] It can be concluded from the studies that PSAD is a valuable secondary tool in assisting the urologist obtain information regarding the need for biopsy and the likelihood of CaP in men with an intermediate PSA serum level of 4.1 to 10.0 ng/ml. A study by Presti et al have recently suggested that PSAD may miss a significant number of CaP in men with intermediate PSA levels, and a normal DRE and TRUS.[283] Therefore, the percentage of free PSA may provide useful information in this subset of men.[284]

Two different molecular forms of PSA that can be measured in commercial assays are free and complexed.[285] Complexed PSA is predominantly bound to ∝-antichymotrypsin (ACT) and measurable, but the less dominant form is not measurable by the current assays; free PSA is unbound and present in lower concentrations.[286] It has been shown that the proportion of free PSA (FPSA) is significantly lower in men with CaP than in men with BPH.[287] The challenge is especially significant for men with a PSA in the intermediate area of 4.1 to 10.0 ng/ml; however, men with a PSA level less than 4.0 ng/ml and a normal DRE are very susceptible to missed cancers. Approximately 28% of all men with BPH have a PSA level greater than 4.0 ng/ml,[288] while another study found that 35% of the men who presented with localized CaP had a PSA level less than 4.0 ng/ml.[289] Other studies reveal that 20% of men with a PSA greater than 4.0 ng/ml, but with initial negative biopsies, are diagnosed with cancer on subsequent biopsies performed within a one year period.[290] The clinical utility of free to total PSA

(FTPSA) is dependant on the man's age and total PSA level; however, a FTPSA of less than 7% has a high probability (98% in men with a PSA of 10.1 to 20.0 ng/ml and older than 70 years) of cancer whereas a FTPSA of greater than 25% has a low probability of cancer (2% in men with a total PSA of 10 ng/ml or less and younger than 60 years). [291] The current practice is to routinely biopsy men with a PSA level greater than 10.0 ng/ml, but for men who have a initial negative biopsy and a FTPSA less than 7%, they should have a repeat biopsy to exclude CaP.[292] Hause et al found in a study that the ratio of FTPSA is influenced by prostatic volume in men with CaP; therefore, the information is useful in differentiating BPH from CaP in men with small prostates (60 ml or less), but is less useful in men with larger prostates because of the proportion of hypertrophic tissue which produces less free PSA.[293] A significant prostate tumor can be expected if the cancer volume is 0.5 ml or larger.[294] Selection of cutoff values of free PSA is complicated and dependent on the man's age, prostate volume, and total PSA level. In a previous study by Catalona et al, a free PSA cut-off value of 25% yielded a 95% sensitivity in detecting CaP and avoided 20% of negative biopsies; however, a more recent study by the same researchers found a cut-off value of 30% to yield a 95% sensitivity and avoided 12% biopsies.[295] They attributed the higher cut-off value to the larger prostates, which also have a higher false-negative biopsies.[296] Catalona et al concluded that the measurement of free PSA percent and PSAD provide predictive information regarding the presence of CaP in men who have had prior negative biopsies, but continue to have serum PSA levels between 4.1 to 10.0 ng/ml and

negative DRE's.[297] The free PSA measurement offers the advantage of avoiding repeat TRUS.[298] Studies have concluded that the specificity of differentiating between patients with CaP and BPH can be potentiated with TPSA and FTPSA; however, caution is recommended in using the cutoff values in clinical practice and further studies are required.

Some estimates suggest that PSA testing has an associated 20% to 40% false negative and overall false positive rate of 20%.[299] Enhancing the positive predictive value of PSA has been possible with the addition of age-specific reference ranges, PSAV, PSAD, and FTPSA. There are estimates that between 20% to 40% of men who consent to radical prostatectomies have a PSA level of less than 4.0 ng/ml; therefore, recent studies have indicated the need to develop assays to increase the sensitivity and specificity of testing.[300] One such new assay is ProstAsure Index which is serum based and determined using several input variables (age, TPSA, creatinine phosphokinase isoenzymes and prostatic acid phosphatase).[301] It is being compared against free PSA testing which to date has not had an optimal cutoff value determined.[302] Another recent introduction, transition zone volume-adjusted PSA (PSAT) is an evolution of PSAD.[303] It is based on the rationale that BPH is almost exclusively the result of hyperplasia of the transition zone of the prostate.[304] Numerous cross sectional studies have been published that confirm PSA as the best tumor marker for CaP. Although PSA lacks specificity, it stratifies men into a high risk of having CaP that requires additional testing such as biopsy

and men who have a low risk of CaP who can be reassured and followed without additional testing. By combining DRE, TRUS with PSA, the detection of CaP can be increased:

n = 1,807		
PSA Level	PPV	DRE
4 - 10 ng / ml	20%	normal
4 - 10 ng / ml	45%	abnormal
> 10.0 ng / ml	31%	normal
> 10.0 ng / ml	77%	abnormal
Overall CaP detection rate = 14.6%		

Figure 5: Value of combined detection modalities
Cooner et al [305]

The PPV of a serum PSA greater than 10.0 ng/ml is 50% to 77% with an overall rate of 8% to 12% of screened men over the age of 50 years who have a serum PSA greater than 4 ng/ml.[306] The detection rate of CaP using PSA testing in a community based population is 2% to 3% which is approximately double that of DRE used alone, but two or three times the detection rate of breast cancer utilizing mammography based screening programs.[307] When applied together, PSA and DRE detect 27% more CaP than PSA alone and 34% more than DRE alone.[308] Catalona et al confirmed that a positive biopsy rate for men with a PSA greater than 4 ng/ml was 32% which was substantially greater than the positive biopsy rate for men with a suspicious DRE which was only 21%.[309]

ii) Digital Rectal Examination

Digital rectal examination (DRE), the traditional method for detection of CaP, is a procedure whereby the physician inserts his/her finger into the rectum to feel the size, shape and texture of the prostate gland and tissue that is in close proximity to the prostate. DRE is a subjective technique that lacks sufficient sensitivity to detect early-stage disease; usually, a more advanced stage is detected. Only 30% to 40% of CaP detected by DRE can be expected to be organ confined.[310] In one study sample of 31,953 men, 7.6% of the men had a DRE that was normal or non-suspicious, but a PSA level greater that 4.0 ng/ml that resulted in a PPV of 23.2%.[311] If DRE had been used in isolation, 115 cancers would have been missed.[312]

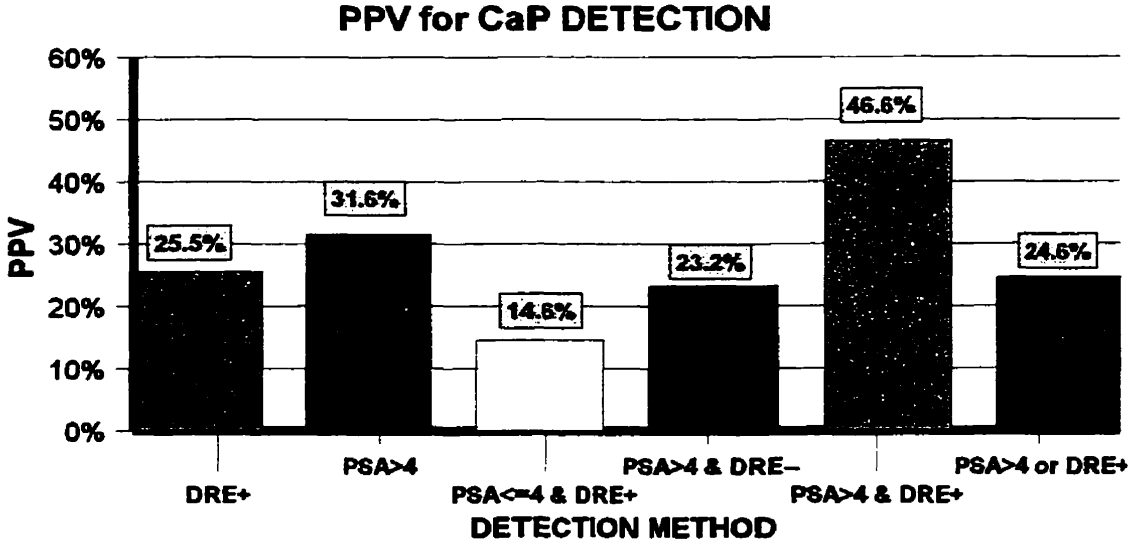

Figure 6: Positive Predictive Value for Prostate Cancer Detection (Crawford et al[313])

The PPV results confirm that DRE is not as effective or efficient as PSA plus DRE in the detection of CaP. The study confirmed that screening for CaP in asymptomatic men should include both DRE and PSA testings.[314]

Prostate cancer screening begins with a DRE that should be done at the initial visit. Results are obtained immediately, cost is only the time of the examiner and there is minimal discomfort. The entire surface of the posterior aspect of the prostate gland is examined noting the consistency and symmetry of the gland and the presence of any nodules.[315] In addition, the lateral sulci, midline furrow and the seminal vesicles are assessed with the overall size of the prostate gland.[316] DRE assists with the detection of rectal malignancy, estimates the sphincter tone and may detect advanced CaP that causes urethral obstruction. Cancers detected by DRE tend to be of significant size in which one study (n = 185 men) detected CaP with 90% having volumes greater than 0.5 cc in the radical prostatectomy specimens.[317] Earlier studies had estimated that only 50% of CaP detected by abnormal DRE was organ-confined CaP; however, some studies are finding more optimistic results and are citing that 68% of pathologically staged CaP in men with abnormal DRE were found to be organ confined.[318] The same population were also screened via biopsies (17.6%) and PSA. It has been estimated that 28% to 35% of CaP are detected by DRE that would have been missed if PSA alone had been utilized to screen.[319]

DRE by itself is a very weak tool. It is variable and subjective to the skill of the examiner.[320] One study (n = 116) of men examined by two different urologists found agreement in only 18% of the suspicious cases; this has immense consequences considering that approximately 15% of men over the age of 50 screened with DRE are considered to have an abnormal DRE.[321] One study cited two literature reviews which concluded the PPV of DRE to be 3% to 34%; however, most commonly it is cited as 20% to 25%.[322] Therefore, at best, only one in four patient who have a suspicious DRE will be diagnosed with CaP via biopsy.[323] Only one half of CaP detected is found in a palpable area of the prostate.[324] The Prostate Cancer Prevention Trial (PCPT) is expected to yield more conclusive results where all men will undergo a needle biopsy as part of the trial.[325]

The DRE, which has been the gold standard in past practice, is now viewed as an adjunct to other tools. It has been shown to miss 44% of organ-confined CaP [326] and obviously does not benefit men screened with DRE alone. Therefore, agencies including the American Urological Association (AUA) and the American Cancer Society (ACS) recommend that DRE should continue to be included in a total prostate screening program, which includes PSA.[327]

iii) Transrectal Ultrasound

Transrectal ultrasound (TRUS) uses sound wave echoes to create an image of the prostate gland enabling visual inspection for abnormal conditions such as

enlargement, nodules, penetration of tumor through the capsule and /or invasion of the seminal vesicles.[328] TRUS is commonly used to guide the physician during a biopsy of the prostate gland and to establish the volume and size of the prostate gland which is utilized in PSAD.[329] TRUS of the prostate revolutionized the prostate needle biopsy procedure since it allowed accurate, systematic and lesion-directed biopsies of the prostate.[330] It decreases the rate of morbidity since bladder, prostatic urethra, and large vessel puncture is avoided.[331] TRUS-guided sextant prostate biopsies identified more CaP than either digitally directed biopsies or TRUS-guided biopsies of hypoechoic areas only.[332] TRUS usually describes CaP lesions on the prostate as being hypoechoic, but in reality, 24% to 39% of CaP are actually isoechoic.[333] Therefore, the addition of TRUS, without the benefit of a needle biopsy, is of little benefit. In a large screening study by the ACS, TRUS was used as a primary screening test and only 14% of the men had visually abnormal lesions.[334] Only 15% had CaP when biopsies were preformed.[335] The PPV of TRUS is less than DRE, but in comparison, TRUS is a more expensive and uncomfortable procedure; therefore, TRUS is generally accepted as an adjunct to needle biopsy and not as a primary screening tool.[336] About 23% of all second biopsies and 9% of all third biopsies detect CaP.[337] The rate varied with the PSA level as follows (refer to Figure 7, p. 70):

PSA LEVEL	% POSITIVE SECOND BIOPSY
PSA < 4.0 ng/ml	19%
PSA = 4.0 to 10.0 ng/ml	15%
PSA = 10.0 to 20 ng/ml	32%
PSA > 20.0 ng/ml	44%

Figure 7: Percentage of Positive Biopsies Based on Second Biopsy.[338]

In the critical area of the intermediate PSA level, the positive biopsy rate of 15% was the same regardless of DRE results, whereas men with a PSA > 10.0 ng/ml, had a 38% positive biopsy when the DRE was positive compared with only 33% when the DRE was negative.[339] Therefore, it was concluded from the study results that a repeat TRUS-guided biopsy rate of 23% warrants the performance of a second or even third set of sextant biopsies if the diagnosis of CaP would be of clinical significance; that is, the man's age and comorbidities make him a candidate for possible curative treatment.[340] TRUS should only be performed in men with abnormal PSA or DRE. PSA and DRE are considered to be both inexpensive and easy to perform and their acceptance rate among the population at risk is high.[341] There has been an overwhelming voluntary participation of American men in prostate screening programs in the last several years; similarly, in an European study which included PSA, DRE and TRUS, 35% to 42% of a group with access agreed to participate in the screening with 87% of the participants agreeing to future reexamination.[342] This is superior to only 20% participation in breast and cervical cancer trials in the same geographic area.[343]

iv) Prostate Biopsy

Prostate biopsy, which is the main method used to diagnose prostate cancer, is a surgical procedure that removes a small sample of prostate tissue for examination under a microscope.[344] The procedure causes little discomfort and is typically done in the physician's office.[345] The physicians's finger or a TRUS guides the needle to the area of the prostate to be biopsied.[346] Men who have an elevated serum PSA are generally advised to have a TRUS guided biopsy; however, the optimal biopsy technique for detecting CaP has not been validated.[347] Cancer greater than 3mm on one core biopsy or more than one core with cancer is highly predictive of cancer volumes greater than 0.5 cm^3.[348] Tumor volumes less than 0.5 cm^3 are considered insignificant,[349] although recent studies suggest a lower volume of 0.25 cc or less or less than 0.25 cc and a Gleason sum less than 7. Other indications for prostate biopsy may include: significant change in PSAV, PSA level between 2.5 and 10.0 ng/ml, a low FPSA/TPSA ratio, or a suspicious feeling prostate on DRE.[350] Keetch et al reported that one repeat set of biopsies of the prostate in men who continue to meet the indication for biopsy was supported by their observation that the detection rate of CaP in the second biopsy procedure was 19%.[351] A portion of men in their prospective study underwent up to five sets of biopsies, but 96% of the CaP was detected in the first two sets.[352] A study by Levine et al concluded that two consecutive sets of TRUS guided sextant biopsies of the prostate performed in a single office visit represent a cost-effective biopsy strategy for men with an abnormal DRE or PSA.[353] The benefits include increasing the detection of CaP and

providing the recommended second set of biopsies for high grade PIN without increasing cost or morbidity.[354] The cost of a prostate biopsy include urologist procedure fee ($440 American for 2 consecutive sets of sextant biopsies) and pathology professional and technical processing fees ($210 American).[355] Assuming 15% of men will require a second biopsy owing to high grade PIN, and an additional 10% will have a second biopsy due to the urologist's concern of a false-negative biopsy, the strategy of doing two consecutive sets of sextant biopsies will save an estimated $160 per patient which is justified as a means of saving costs, increasing diagnostic yield and no increase in morbidity.[356]

The most common complications associated with prostate needle biopsy include urinary tract infection, urosepsis, hemorrhage and urinary retention.[357] The reported rates of urosepsis and infection have been reduced from 48% infections to a range of 0% to 3% with routine use of prophylactic antibiotics and TRUS guidance in conjunction with spring loaded devices.[358] In a study of 137 men by Levine et al who presented with an abnormal DRE or elevated PSA based on age-specific reference ranges, only 0.8% had bacteremia, which resolved with antibiotics and only 1.6% experienced urinary retention which resolved with simple catheterization and irrigation.[359] No patient had significant rectal bleeding or hematoma formation. Preliminary evidence from the study suggested that there is a greater tendency to identify pathologically organ confined tumors.[360]

Improved detection methods, particularly PSA and TRUS guided biopsies are largely responsible for the remarkable increase in the incidence of clinically localized CaP.[361] Ten years ago, the majority of men who presented with CaP had metastatic disease, whereas in 1997, at least 60% to 75% are diagnosed with localized disease.[362] The issue of clinically insignificant CaP, which has historically been defined by cancer volume and grade (and to a lesser extent on doubling time and life expectancy), is of immediate concern in the context of screening and early detection initiatives.[363] Various studies have reported that only 9% to 16% of detected CaP were insignificant.[364] In a computer modeling simulation study of 59 autopsy prostates, Crawford et al concluded that as many as 20% of CaP detected by six random sextant core biopsy may be histologically insignificant and detected strictly by chance (primarily in the posterior peripheral zone); however, only about half of the clinically significant tumors are being detected by random biopsy method because the volumes make them hard to miss implying that there is a positive correlation between volume and detection rate for carcinomas in the posterior peripheral zone.[365] Crawford et al also recognized that to their knowledge no validated criteria exist for the definition of significant versus insignificant CaP.[366] They concluded that despite the significant shortcomings of the standard prostate biopsy methods, particularly that the six random sextant core biopsy too easily detects insignificant CaP that are indistinguishable from clinically important CaP, they recommended that clinical significance be defined as a tumor volume of 0.25 cc or greater or less than 0.25 cc and a Gleason sum 7 or greater.[367] This differs

from the more conservative view of using 0.5 cc as the lowest threshold for significance.[368] In another study by Chen et al utilizing a computer model, they concluded that CaP of significant volume can be present in areas not sampled by standard sextant biopsies.[369] Biopsies of the transition zone, midline peripheral zone and inferior portion of the anterior horn of the peripheral zone should be considered for re-biopsy after negative sextant biopsies.[370] They suggest incorporating in an initial biopsy scheme these areas to increase overall initial rate of prostate cancer detection.[371]

It would appear that the issue of significant and insignificant CaP is subject to determining an appropriate cut-off value for prostate volume; however, prostate biopsies play an important role in diagnosing CaP and detecting early stage cancers. Extraprostatic spread of CaP carries a poor patient prognosis; therefore, it is important that sensitive and specific tests are devised to detect significant prostate cancer in its earliest localized stage.[372] Elevated PSA values, abnormal TRUS and DRE are all tests that can lead to clinical suspicion of CaP.[373] The definitive diagnosis of cancer is made only with a positive prostate biopsy.[374] While systematic TRUS guided sextant biopsies have been shown to be more sensitive than directed biopsies,[375] additional areas to biopsy the prostate have been under review as a means of increasing the overall initial rates of detection of CaP.

v) Imaging and Scanning to Diagnose Prostate Cancer [376]

Various other procedures in the field of imaging and scanning are available to assist the urologist in diagnosing CaP or determining the extent of the disease. A radionuclide bone scan is a radioactive injection to determine whether the cancer has spread from the prostate gland to the bones. Diseased bone is referred to as 'hot spots' and will be seen as dense, gray areas; however, these areas may suggest cancer is present, but are also indicative of arthritis or other bone conditions. Bone biopsies or magnetic resonance imaging (MRI) may be used to distinguish the conditions. MRI uses magnetic fields in place of x-rays to create images of selected areas of the body. MRI can find abnormal nodules in bones or lymph nodes that might be metastatic cancer from the prostate. Computerized tomography (CAT scan) uses a rotating x-ray beam to create a series of pictures from various angles. Dye injections may be used to enhance particular body structures. CT scans have the ability to reveal abnormal lymph nodes which may indicate metastatic spread of the prostate cancer to the lymph nodes.

3. SUMMARY

Although the widespread acceptance of prostate cancer screening in the United States has led to a dramatic increase in the number of men diagnosed with prostate cancer, the urological community agrees that early detection and subsequent treatment of clinically localized prostate cancer in men with a probability of ten years life expectancy is beneficial.[377] Recent statistics from the ACS indicate that

the death rate from CaP is declining in the United States despite the aging of the male population, presumably due to PSA based screening.[378]

Although the etiology of prostate cancer is unknown and prevention of CaP is a long term goal, there are several identified risk factors: PIN, family history, race or ethnic background, age, and environmental factors, especially diet. Several studies have explored the link with extraneous lifestyle factors and occupations, sexual activity and vasectomies. The known risk factors of age, family history and race would appear to be explained by a combination of genetic predisposition and acquired genetic events influenced by the environmental milieu.

PSA is currently the best available tumor marker for any human malignancy,[379] and thus, PSA determinations are an important part of urological examinations. DRE, TRUS, cystoscopy and ejaculation have minimal effects on serum PSA levels; however, prostatic massage, needle biopsy, TURP, and prostatitis can cause significant elevations of PSA.[380] Diurnal variation and exercise have no known effect on PSA levels.

The combination of DRE, serum PSA, and TRUS has increased the rate of cancer detection by 70% and doubled the detection rate of organ-confined CaP, many of which are non-palpable.[381] The aim of early detection or screening is to identify localized or organ-confined CaP that is potentially curable. The challenge is to

distinguish patients with BPH from clinically significant CaP. DRE assesses the size and shape of the prostate gland. All men with an abnormal DRE should have a prostate biopsy. PSA results of 4.0 ng/ml or greater is clinically important. Currently, 20 - 40% of men diagnosed with CaP have a normal PSA[382] or results of less than 4.0 ng/ml; therefore, recent studies have suggested 2.5ng/ml as the cut-off level for men of a specified age range. For men older than 65 years, levels above 4.0 ng/ml should be considered abnormal. All men with an abnormal PSA level should have a prostate biopsy. CaP detected by PSA is more likely confined to the prostate gland than cancers detected by DRE.[383] As tumor volume increases, the PSA levels increase. Over half the patients with a PSA greater than 10 ng/ml have pathologically advanced CaP.[384] There is considerable overlap in serum PSA levels between men with BPH and CaP which has prompted several studies and new methods to improve the clinical usefulness of PSA: PSA density, PSA velocity, age-specific PSA reference ranges, and molecular forms of PSA [385] - free and complex.

TRUS with biopsies are utilized if the PSA or DRE results are abnormal. TRUS with biopsy is beneficial for detecting non-palpable CaP with detection rates as high as 80% of organ-confined CaP.[386] It is the only reliable method to determine prostate volume; however, it is subject to examiner variability.

There have been several extensive studies related to prostate cancer and serum

based PSA for the early detection of CaP. Men with a persistent serum PSA elevation and a negative biopsy should have a repeat biopsy at least once.[387] A PSA velocity of greater than 0.75 per year, a PSAD greater than 0.10 and a FPSA less than 20% should be evaluated with a prostate biopsy,[388] although caution is recommended in using the cutoff values in clinical practice because more studies are needed to establish parameters.

Nearly twenty years have passed since PSA was definitively identified; the clinical application as a tumor marker has expanded significantly. PSA monitors CaP treatment therapies and is used extensively in mass screening programs for the early detection of CaP and has become the most important tumor marker in urologic oncology.[389] PSA based screening has been established as substantially increasing the detection rate and percentage of organ confined CaP.[390] PSA represents the most effective and valuable tool to detect early CaP and should be used to improve early diagnosis of CaP.[391]

CHAPTER FOUR

1. PROSTATE CANCER STAGING AND GRADING

Another step in the diagnostic process of prostate cancer is measuring or grading the cancer cells; the most common method is called the Gleason system after the physician who first described the method.[392] Grading describes the appearance of thin slices of tissue under the microscope and determines how aggressive the cancer is by the shape and arrangement of the cells which are taken from the prostate gland during biopsy. The cancer cells are measured by how closely they resemble normal cells. The ability of a tumor to mimic normal gland architecture is referred to as differentiation.[393]

There are five grades, with grade one or well differentiated to grade five or poorly differentiated: [394]

- Gleason Grade 1 and 2: Closely resembles a normal prostate. Both grades are composed of very pale glands which grow closely together. The cells form a compact mass in grade 1, whereas, in grade 2 they are loosely aggregated with some glands invading into the surrounding muscle (stroma). The wandering glands of grade 2 are very prominent and is the main defining feature.
- Gleason Grade 3: This is the most common grade and is considered well differentiated. Grades 1, 2 and 3 have a normal gland unit like a normal prostate which means that every cell is part of a circular row which forms the lining of the lumen or central space. The lumen contains prostatic secretions like normal

prostates and each gland unit is surrounded by prostate muscle which keeps the gland units apart. The cells of Gleason grade 3 are dark rather than pale and the glands often have more variable shapes.

- Gleason Grade 4: If a considerable amount is present, the patient prognosis has usually deteriorated by an appreciable degree. There is disruption and loss of the normal gland unit. Grade 4 is identified by the loss of ability to form individual, separate gland units. Experience is required for this diagnosis since not all patterns are easily distinguished from grade 3.
- Gleason Grade 5: Predicts a poor prognosis and is seldom seen in the early development of CaP. There is no evidence of gland units and the grade is referred to as undifferentiated.

The pathologist identifies the two most common patterns of cells (primary and secondary patterns) and assigns a grade to each pattern.[395] The addition of the two grades determine the Gleason score. There may often be a single pure grade[396] which is added together to give the total score. For example, grade 3 may denote both the primary and secondary patterns; thus, 3 + 3 denotes a Gleason score of 6. The number range is from 2 to 10 with the lower number representing the lower grade as follows:

- Gleason Grades less than 4 (low-grade): cancer cells similar to normal cells and likely to be less aggressive and slow-growing. The cells are well differentiated (nearly normal) and clearly defined under the microscope.

- Grades 5 to 7 (intermediate): cancer cells do not resemble normal cells and are likely to be more aggressive and grow at a faster rate.
- Grades 8 to 10 (high-grade): cancer cells are very aggressive in growth. The cells are shapeless in mass.

The Gleason score is considered in context with other factors including the PSA level and tumor stage. The grade of a CaP specimen is valuable in assisting the urologist determine a treatment regime and prognosis for the patient.

Staging, or extent of the disease, refers to the process of determining if cancer cells have spread from the prostate to surrounding tissues or other parts of the body. There are several staging systems, but the most common and recent is the TNM Staging system that refers to the primary **T**umor within the prostate, extent of spread to lymph **N**odes and **M**etastasis or extent of spread to other parts of the body. The tumor size has four stages, the extent of spread to lymph nodes has two indicators and the extent of metastasis to other parts of the body has two indicators as follows: [397]

Tumor Size:

1.) T1 is a tumor that cannot be felt during DRE or seen through imaging, but is verified by a biopsy.

2.) T2 is a tumor that is confined to the prostate gland and can be felt during a DRE.

3.) T3 is a tumor that extends through the prostate capsule.

4.) T4 is a tumor that has spread to other parts of the body close to the prostate or to more distant parts.

Nodal Status:

1.) NO implies that the tumor has not spread.

2.) N+ is a tumor that has spread to one or more lymph nodes.

Metastasis Status:

1.) MO means that the tumor has not spread to other parts of the body.

2.) M+ is a tumor that has spread to other parts of the body.

Another common staging method refers to four stages plus a recurrent stage. The Jewett-Whitmore system may still be referred to and uses an ABCD designation which is denoted in parenthesis as follows: [398]

- Stage I (A): CaP cannot be felt and is asymptomatic. CaP is usually found accidentally during surgery, such as BPH or during a needle biopsy for an elevated PSA level.
- Stage II (B): Cancer cells are contained within the prostate gland. The tumor may be found by a needle biopsy (elevated PSA) or felt during a DRE.
- Stage III (C): Cancer cells have spread outside the prostate capsule. The seminal vesicles may contain cancer.
- Stage IV (D): Cancer cells have metastasized to the lymph nodes either near or far from the prostate or to other parts of the body.
- 'Recurrent' means that the cancer has recurred after it has been treated,

either in the prostate or in another part of the body. The stages are further subdivided into a,b,c and 1,2,3 classifications (Refer to Appendix B, p. 200).

The grade and stage of CaP predict the current stage and potential for future growth and spread. By combining the Gleason score, PSA level and clinical stage, the physician can use the Partin coefficient tables to estimate whether the prostate cancer is localized or advanced (refer to Appendix B, p. 200). All the information is used by the physician to assist the patient with the treatment options and estimate prognosis.

2. TREATMENT MODALITIES

The treatment regime is based on the established diagnosis of CaP as a result of DRE, PSA, Gleason score and stage; also, anticipated survival, age, comorbid conditions, tolerance of side effects, and Partin tables are utilized by physician and patient to decide on a treatment course. Because of the extensive number of factors that must be evaluated, the principles that guide the treatment of prostate cancer requires the skill and expertise of physicians who are able to weigh the benefits of treatment against the possible side effects and risks. The male patient diagnosed with prostate cancer, works in concert with his physician to determine the best course of treatment in conjunction with the patient's own personal preferences. There is general agreement that prostate cancer is a progressive disease that is likely to grow and spread over time.[399] The issue of treatment

modalities is an extensive topic that requires the input and assessment of expert physicians familiar with the many aspects of each treatment modality and which are subsequently tailored to each individual situation. Therefore, only an overview of the options and associated complications will be provided since the area of CaP treatment options is a topic within itself and beyond the scope of this paper.

The issue of prostate screening is impacted by the treatment modalities which influence men to accept screening and early detection as a means of addressing prostate cancer; however, a portion of the screening debate centers on the treatment options and the associated morbidity that men diagnosed with prostate cancer must evaluate. For men who enter into screening programs, the issue of a positive diagnosis carries with it the implications of assessing the treatment options; therefore, if a man chooses to have a PSA test, he must consider the consequences and what he is prepared to do if the PSA is elevated.[400] The male patient diagnosed with CaP and his urologist are faced with the dilemma of which treatment approach is best suited for the tumor and quality of life.

Some stages of CaP, especially localized cancer, are potentially curative. Locally advanced CaP is less likely to be cured and metastatic disease is not curable at this time. However, that does not preclude the advances made in the treatment of CaP and the increased survival rates being recognized and documented in the United States. Currently, the most common treatment options are: 1) conservative

management (watchful waiting), 2) surgery, 3) radiation therapy, 4) cryotherapy, 5) hormone therapy, and 6) chemotherapy.[401] (refer to Appendix E, p. 206).

1. Conservative Management (Watchful Waiting)

It is estimated that four out of five men with histological CaP do not require therapy;[402] however, other studies suggest that the distinction between significant and insignificant CaP is based only on the size of the neoplasm[403] in which the cutoff value for the volume is under debate. The frequency of how often microscopic foci progress to larger tumors is not known; also, the length of time tumors need to progress from a localized stage to the patient's death is being continuously challenged.[404] It is not clear how many cancers are insignificant;[405] therefore, the belief that there is an epidemic of CaP caused by overdetection could be factual or fiction. The reality is that CaP is the number one diagnosed malignancy in men in the USA and Canada and men are dying from the disease.

Watchful waiting is a form of treatment for selected men that does not implement active treatment at the time. It is generally practiced on men who for some reason would be better served to avoid potentially curative treatments such as surgery or radiation.[406] Age is an important consideration where the physician may recommend no immediate treatment for a man of advanced age with localized CaP that is slow-growing and causing no symptoms.[407] The concept is that the age and/or comorbidities of the man with prostate cancer will result in the man outliving

the risk of clinically active cancer occurring,[408] or the man will succumb to another concomitant health problem before he would have died from CaP. The man may choose conservative management as the treatment of choice because he would prefer the risk of disease progression rather than one of the other treatment options with the associated risks of side effects. The physician will monitor the indicators of tumor progression, including regular PSA and DRE testing and possibly TRUS, and treat the symptoms as they appear or if there is a significant increase in the PSA level (PSAV), active treatment may be initiated. The decision to observe the patient is largely examiner dependent since the tumor is considered slow growing or indolent and confined to the prostate gland. The perceived benefit of watchful waiting is that the man avoids active treatment which implies he is spared the side effects of surgery or radiation and the system avoids the expense of immediate treatment. However, the man with prostate cancer who chooses watchful waiting as a treatment course does risk disease progression with treatment of symptoms required as they appear. The tumor could progress more rapidly than anticipated and unexpected problems are encountered including metastasis beyond the prostate capsule. Many urologists support the clinical impression that saving a patient from a prostate cancer death, even an older aged man, is worthwhile to avoid the suffering that most men experience from advanced prostate cancer, because it does not seem that radical treatment results in a lower quality of life compared with watchful waiting.[409] Even though patients scheduled for conservative management may live several years, many experience urological

complications that require treatment.[410] Some men also find it too stressful living with the knowledge that they have CaP and opt for active treatment.[411] For a man diagnosed with CaP in his late 70's or 80's, a small, low-grade cancer is not likely to be the cause of his death.[412] Therefore, treatment guidelines suggest that for an asymptomatic man with less than five years life expectancy, observation is prudent and appropriate initial therapy.[413] Treatment with surgery or radiation is likely to extend the life of a man in his 50's or 60's with a high-grade tumor; in addition, improvements in surgery and radiation have reduced the risk of undesirable side effects.[414]

The British Columbia Cancer Agency (BCCA) reported high rates of clinical tumor progression within a watchful waiting population of 113 referred patients with early localized CaP.[415] Preliminary studies focus on PSA doubling time as an indicator of disease activity.[416] Another study by Hugosson et al in Sweden concluded that comparative data on results after conservative (watchful waiting) and curative treatment point convincingly to a beneficial effect of curative treatment, particularly radical prostatectomy.[417] Conservative management does not seem to be the best option because of the high costs of suffering associated with death from progressive cancer, even in men of advanced ages.[418] Another study by Palmer and Chodak indicate that watchful waiting is a treatment option that has its own set of risks and benefits; however, if a patient wishes to maximize his survival and minimize the chances of prostate cancer causing him pain and suffering, then

aggressive therapy should be selected.[419] Significant morbidity results from disease progression and can be expected to occur in nearly half of the men followed with this form of management for five years.[420] The study concluded that watchful waiting is equivalent to a 'throw of the dice' with the degree of risk dependent on the rate of tumor growth and the patient's expected life span, neither of which can be reliably predicted.[421] It is generally recognized that the treatment of CaP has improved, and that, the complication rates are less today than published complication rates.[422]

2. Surgery

Statistics from a 1995 published article reveal a 65% ten year survival rate for localized CaP, while 17% die of CaP and another 17% succumb to other causes.[423] Surgery is the most common treatment available, especially for younger, healthy men whose tumor is believed to be confined to the prostate gland (stages T1 or T2).[424] Surgical removal of the prostate is the standard therapy for localized prostate cancer.[425] Radical prostatectomy, which is surgical removal of the entire prostate gland, is the most common treatment for localized cancer. The goal of a radical prostatectomy is complete eradication of the tumor, [426] since removal of part of the prostate is not recommended and technically not feasible.[427] Of the more than 3,000 men who had prostatectomies at the Mayo Clinic since 1966, approximately 90% survived ten years or more.[428] In selected cases, a laparoscopic lymphadenectomy, is done prior to a radical prostatectomy to

determine if there is pelvic lymph node metastasis.[429] If there is suspected lymph node involvement, a more informed decision about the possible risk-benefit equation can be discussed before proceeding with the actual removal of the prostate.[430] If a pelvic lymphadenectomy (PSA>10 ng/ml; Gleason score>3) reveals nodal involvement, then a radical prostatectomy has questionable value [431] since metastasis has already occurred. If cancer has spread beyond the prostate, most physicians will consider it incurable and suggest treatment to slow the growth[432] since it is no longer localized CaP, but is locally advanced or possibly advanced CaP.

There are two basic forms of radical surgery for removal of the prostate: radical retropubic prostatectomy (access to the prostate via an incision in the lower abdomen) and radical perineal prostatectomy (incision between the scrotum and anus).[433] Each technique has specific advantages and disadvantages such as a higher incidence of rectal injury with the perineal approach.[434] The initial cost to the health care system consists of hospital stays of 2-3 days,[435] an indwelling catheter, and 2-3 months for patients to regain their stamina.[436] The complications associated with a radical prostatectomy include: urinary incontinence (about 5%),[437] urethral stricture (about 8%),[438] impotence and the normal risks associated with anesthesia and surgical procedures.[439] Lower complication rates are associated with surgeons proficient in prostatectomies.[440] In the Mayo Clinic study of the assessment of 3,000 prostatectomy patients, it was noted that in the last 1,000 men

treated, less than 1% experienced total incontinence[441] while other studies suggest that 2% to 4% of men will have permanent problems with urinary control that require some form of protection such as pads.[442] Incontinence is generally predicted in 5% of the cases,[443] although in those rare cases, surgical appliances can be implanted to control incontinence if it remains a problem [444] The current treatments for incontinence are: 1) collagen injections into the sphincter zone, 2) artificial urinary sphincter implants, 3) penile urethral compressive devices, 4) pharmacological blockade of detrusor instability, and 5) biofeedback techniques in the form of exercises. The chances of impotency are greater (estimated 25% with nerve sparing surgery), but the risk of impotency varies with the quality of the man's erections prior to surgery, psychological factors, refinements in the surgical procedure including preservation of the sphincter, nerve-sparing techniques that preserve erection capability and urinary continence.[445] Some reports suggest that a success rate of between 40% to 70% can be achieved with nerve sparing surgery which is dependent on the extent of the disease.[446] Most urologists advise that a wide dissection without nerve sparing because of the extent of cancer, will result in some degree of impotency. There is no guarantee prior to surgery that neurovascular bundles can be spared.[447] Problems with an erection prior to surgery lead to a higher than average risk of impotence after surgery.[448] If sexual difficulties occur, assistive devices (vacuum pumps), injection therapy (intracavernous), surgery (penile prosthetic implants), medication and counseling may be effective.[449] The introduction of the drug 'Viagra' is being promoted as the

answer to the problem of impotency and is expected to relieve much of the anxiety associated with surgical and radiation eradication of CaP and the resulting side effect of impotency. Despite all the shortcomings of radical prostatectomy surgery, it is still the gold standard surgical intervention for CaP with notable improvements in technique such as nerve sparing and bladder neck preservation, that reduce postoperative impotence and incontinence rates in properly selected patients.[450] One study (n = 2,758) reported a ten year survival of 94% for grade 1, 80% for grade 2 and 77% for grade 3 CaP men.[451]

Blood transfusions are not the norm for radical prostatectomy surgery. However, the average blood loss is usually more than one unit and many patients store their own blood to have available if required during surgery. Less than 1% of patients die intraoperatively,[452] while less than one in a hundred die during or as a direct consequence of their surgery.[453] Surgical complications include: pain, infection, anesthetic problems, pneumonia, blood clots and heart problems with other complications, although rare, including rectal injury, major bleeding and pulmonary emboli.

Other surgical interventions are a transurethral resection which cuts cancer from the prostate by utilizing a tool through the urethra. This operation is usually done to relieve the symptoms caused by CaP or in men who cannot have a radical prostatectomy due to comorbidities or advanced age.[454]

3. Radiation Therapy

External beam radiation therapy, the simplest of therapies, consists of 15 minutes of daily treatment, 5 days per week for a six to seven week period.[455] A published 1995 article indicated a ten year survival rate of 60%;[456] however, patient selection is essential, since nodal involvement usually implies metastasis has occurred and the results are poor. The radiation is aimed at the prostate from may different angles to reduce the dosage to surrounding tissues while maximizing the dosage to the prostate.[457] During the last two to three weeks of treatment, diarrhea and urinary frequency and urgency are common; however, it is seldom that treatments need to be halted.[458] Complications consist of injury to the bladder or rectum (10% to 15% [459]) which causes pain or bleeding;[460] in addition, cystitis, proctitis and urethral strictures are possible side effects. Urinary incontinence rates are low, usually less than 5%.[461] Erectile dysfunction occurs in approximately 30% to 40% of patients;[462] other studies report varying rates such that radiotherapy patients have been associated with some subsequent urinary and sexual dysfunction.[463] The advantages of external radiation therapy is the ease of administration, but the disadvantage is that the cancer is left in place.[464] The aim is that enough radiation and the correct location has been determined such that the cancer can be eradicated or the growth has been slowed. Currently, there is not definitive proof that radiation therapy can cure localized CaP;[465] therefore, the question of whether radiation offers benefits or equal survival rates compared with surgery remain unanswered. Some studies have concluded that in properly selected patients,

fifteen year survival rates of external beam radiation are similar to those observed with radical prostatectomy; other studies have reached vastly different conclusions.[466] Several studies demonstrated that surgical management appears to have a long-term survival benefits over either external beam radiation or conservation management independent of cancer grade.[467] A smaller randomized prospective study by Paulson et al concluded that 58% of external beam radiation patients had evidence of disease progression compared to only 12% of radical prostatectomy men. [468]

The Radiotherapy Clinics of Georgia maintain that only a small portion of the current radiotherapy literature is properly analyzed, whether describing results of accelerator radiation (external), conformal radiation (accurate delivery of radiation to the prostate without excess to surrounding tissues), seed implant or accelerator radiation followed by seed implant.[469] After a patient is diagnosed with Stage A or B prostate cancer, most urologists trained in the United States recommend radical prostatectomy as the method to cure CaP which is truly confined to the prostate gland.[470] Radiation survival rates have received mixed results with suggestions that radical prostatectomy produces substantially better cancer free results than either implants or external radiation alone; however, 68% of PSA-monitored patients who had radiation prostatectomies by simultaneous radiation (seed implants followed by accelerator) were disease free after ten years.[471] It appears by the study results from the Georgia Radiotherapy Clinics that the various types

of irradiation produce varying survival rates; therefore, they no longer use accelerator radiation (external) radiation as the sole modality for curative treatment of the prostate.

Seed implants (brachytherapy) are the placement of radioactive seeds in the prostate to produce high doses of irradiation inside the gland.[472] Currently, ten year follow-up results with seed implant alone is not available, although data from selected centers suggest that brachytherapy is potentially as effective as either radical prostatectomy or external beam radiation therapy for 'some' patients by physicians with appropriate levels of experience.[473] The combination of simultaneous internal and external irradiation is designed for stage C disease, although the Georgia Radiotherapy Clinics believe it applicable for Stage A, B, and C[474] and maintain that preliminary results indicate a man can achieve an undetectable PSA nadir directly related to his PSA group.[475] One group of radiation oncologists has given the name prostRcision to the technique of brachytherapy and external beam radiation therapy used in combination in appropriate patients.[476] Radiation therapy is also utilized in men who are poor surgical candidates, men who do not want the risks of surgery and men who have a cancer recurrence after radical prostatectomy.

Whether surgery or radiotherapy is the better choice for localized prostate cancer is dependent on every patient as an individual case and the fact that surgical

techniques and equipment improve continuously.[477] However, there is sufficient information to offer guidance such as:[478]

- External beam is not recommended for patients with a PSA> 15 ng/ml.
- External beam is not capable of substituting for nerve-sparing radical prostatectomy. External beam is associate with significant impotency in the long term.
- The earlier and lower the stage/grade, the more likely surgery is superior.
- The later and higher the stage/grade suggests a greater risk of non-localized CaP in which radiotherapy *might* work as a curative therapy.

4. Cryotherapy [479]

Cryosurgery (cryotherapy) is the application of extreme cold to freeze the prostate. Metallic probes, which circulate liquid nitrogen, apply a 'ice-ball' around the prostate and associated tissues under the monitoring of a TRUS. Cryosurgery is still considered experimental. Currently available data appears to indicate that about 20% of patients have a positive biopsy for CaP two years after treatment and a high percentage of patients have an elevated PSA level. In order to preserve urinary continence, the surgeon places a special catheter in the urethra which warms the urethral tissue and prevents it from freezing during cryosurgery. If there are prostate cancer cells in the tissue immediately surrounding the urethra, then the cancer cells are unlikely to be destroyed and every prostate cancer cell will not be eradicated. A small amount of living prostate tissue that was in contact with the

warmed urethra will be left behind after cryosurgery; thus, PSA will still be produced by prostate tissue and it will be difficult to assess if the cryosurgery has been effective. To date there is very limited information, but preliminary results indicate that 80% of patients are impotent. Temporary urethra and bladder irritation is experienced by the majority of patients. Less common complications include fistulas and permanent difficulty urinating which requires catheterization. Many questions regarding the potential and long term success of cryosurgery in the management prostate cancer are unanswered.

5. Hormone Therapy

Neoadjuvant hormonal therapy is hormone therapy given prior to, but in association with another form of therapy, such as a radical prostatectomy.[480] Adjuvant hormonal therapy is hormone therapy given at the time of or following another form of therapy; thus, some patients may receive both neoadjuvant and adjuvant hormonal therapies.[481] Many uses of hormonal therapy is still investigational.[482] One trial of randomized patients with clinical stage T2b received three months therapy with neoadjuvant maximal androgen deprivation (goserelin acetate and flutamide) prior to radical prostatectomies (refer to Appendix F, p. 207). The results showed that patients receiving the neoadjuvant therapy were less likely to have positive surgical margins; however, the surgeons believed the surgery was more difficult and took longer in the neoadjuvant therapy patients.[483]

Another unpublished trial by the Radiation Therapy Oncology Group randomized patients with clinical stage T2b, T3, T4 to receive neoadjuvant and adjuvant maximal androgen deprivation (goserelin acetate and flutamide) followed by external beam radiation therapy. The results suggested a clinical benefit in the use of neoadjuvant and adjuvant therapy patients of increased median survival (4.4 years vs 2.6 years), lower rate of local failure (16% vs 33% at four years) and significantly increased median disease-free survival using PSA criterion (2.7 vs 1.5 years).[484] A number of trials are currently in progress, but some interesting preliminary information suggests that there are benefits to the use neoadjuvant / adjuvant hormonal therapy in the treatment of localized prostate cancer.[485]

Testosterone is the predominant male hormone largely produced in the testicles (90 - 95%) and involved in the development and function of the prostate gland.[486] The adrenal gland produces a variety of other male hormones which can be converted into testosterone (5-10%).[487] In prostate cells and prostate cancer cells, testosterone is converted to dihydrotestosterone (DHT) which has profound effects on the growth of prostate cells and prostate cancer cells.[488] The aim of removing a man's testosterone-producing ability, is to remove the source of DHT and remove the ability to stimulate the growth of prostate cells or prostate cancer cells which results in slowing down the development of prostate cancer.[489] Physicians stop the body's ability to synthesize testosterone by surgical removal of the testicles (orchiectomy, also referred to as surgical castration) and by pharmaceuticals (refer

to Appendix F, p. 207).

All therapies for advanced CaP are palliative methods which slow the progression of the disease and relieve symptoms.[490] Although no form of advanced CaP is curable, there have been major advances in the management of the disease such that it is relatively common for some men to live ten years or more with advanced CaP.[491]

6. Chemotherapy

Chemotherapy is used for metastatic CaP as palliative management. Suramin and Emcyt are examples of chemotherapeutic agents.[492] Today, with prostate cancer being diagnosed earlier, patients become eligible for chemotherapy before they have reached a severe degree of debility that was evident in the past; thus, some forms of chemotherapy have started to show potential in some patients who fail hormonal therapy.[493]

3. PROSTATE SCREENING GUIDELINES: CANADA and USA

At present there is disagreement as to the appropriateness of the PSA test for routine screening of asymptomatic men in the general population; thus the guidelines by specific organizations are different. Evidence-based groups such as the Canadian Task Force on the Periodic Health Examination and the US Preventive Services Task Force do not support CaP screening using PSA in the

general population because they feel that current evidence suggests that PSA as a screening tool has a relatively low specificity and the possibility of detecting indolent tumors that would not progress.[494] The National Cancer Institute, the US Preventive Services Task Force, the Canadian Task Force on the Periodic Health Examination and the International Union Against Cancer are among organizations opposed to screening on the basis that insufficient data exist to promote PSA or TRUS screening.[495] Other organizations such as the American Cancer Society and the American Urological Association, two recognized organizations,[496] are strong supporters and advocate annual screening with PSA. The Canadian Urological Association 1992 Guidelines supported annual PSA testing; however, the 1994 guidelines took a softer approach presumably due to the controversy raging within the country, including the varying provincial guidelines regarding the use of PSA as a screening tool (refer to Appendix C, p. 204). Studies from as early as 1995 by Guilliland et al concluded that the earlier stage of diagnosis and the documented improved survival rates during the period of increased PSA screening are consistent with changes expected from an effective screening test and treatment modality.[497] As recent as June, 1998, the American Cancer Society reaffirmed their guidelines of annual PSA and DRE at age 50 years.[498] Such differences of opinion obviously result in anxiety and confusion for both physicians and the male population. For certain cancers, such as breast cancer, mass screening of asymptomatic women has improved overall survival rates, as such, CaP is also a disease for which screening is likely to be beneficial because it is both serious and

common enough to warrant screening.[499] While not yet demonstrated conclusively with long-term randomized studies, it is widely believed that early-stage detection of CaP improves the opportunity for successful treatment.[500] Freeman of Columbia University, estimates 25 million American men over the age of 50 years have CaP of which most of them do not know they have the disease and will never know they have it in the course of their lifetimes. However, the fact remains that because many men are dying with CaP, but not of CaP, raises a very fundamental research question. He points out that a recent survey by the American College of Surgeons reported that the positive outcomes associated with surgical treatment may not be the same as outcomes at local hospitals, which further complicates the issue of treatment options for the CaP patient.[501] The American Cancer Society further states that screening for prostate cancer in asymptomatic men can detect tumors at a more favorable stage; plus, there has been a reduction in mortality from prostate cancer, but it has not been established that this is a direct result of screening.[502] However, the American Cancer Society also claims that early detection of CaP improves the chances that it can be treated successfully; in addition, most cases of early CaP cause no symptoms and are detected by a screening examination and that is why screening with PSA and DRE is so important.[503] It is therefore the responsibility of the individual man to absorb all this information and make an informed decision regarding which screening guidelines are most applicable to him. The following table illustrates the various guidelines

as outlined by Health Canada 1998:

CaP GUIDELINES - CANADA and USA	
ORGANIZATION	**RECOMMENDATION**
Canadian Task Force on the Periodic Health Examination, 1994	Does not recommend the routine use of PSA or DRE as part of a periodic health examination.
Canadian Workshop on Screening for CaP, 1994	No PSA screening unless for a screening trial or patient request after pre-test counseling and informed consent.
Canadian Urological Society, 1996	DRE and PSA measurements increase the early detection of clinically significant CaP. Men should be made aware of the potential benefits and risks of early detection so that they can make an informed decision as to whether to have this test performed.
Canadian Urological Association, 1992	Recommends men between 50 - 70 years have annual PSA and DRE performed. In men with a family history of CaP, age 40 years may be appropriate.
US Preventive Services Task Force, 1996	Not recommended, routine screening for CaP with DRE or TRUS.
US National Cancer Institute, 1997	There is insufficient evidence to establish whether a decrease in mortality from CaP occurs with screening by DRE, TRUS or PSA.
American Cancer Society, 1992, 1998	Annual PSA for men > 50 years Annual DRE for men > 40 years Comment: Annual PSA if younger than 50 in high risk group until life expectancy is less than 10 years.
American Academy of Family Physicians, 1996	Men aged 50 - 65 should be counseled about the known risks and uncertain benefits of screening for CaP
American College of Radiology, 1995	Every man 40 and older should have an annual DRE and at age 50, an annual PSA.
American Urological Association, 1995	Annual DRE and PSA measurement substantially increase the early detection of CaP. There tests are most appropriate for men 50 and older and for those 40 and older who are at high risk. PSA testing should continue in a healthy male who has life expectancy of 10 years or more.

Figure 8: Prostate Cancer Guidelines adapted from Health Canada, 1998.[504]

4. SUMMARY

When properly staged via such tools such as the TNM system or Jewett-Whitmore system and graded by the Gleason score, a man diagnosed with CaP has the responsibility to consider the many treatment options available. The treatment is based on the individual's general health, age, expected life span, personal preferences, anticipated effects of treatment, aggressiveness of disease, review of stage, grade and Partin tables. Because CaP is a progressive disease that is likely to grow and spread over time, the individual must carefully evaluate his treatment regime with a skilled urologist familiar with the latest literature on CaP. The Canadian and American recommended screening guidelines for CaP add confusion, frustration and anxiety for the average male faced with health promotion, individual responsibility and the aim of detecting a potentially fatal disease at the earliest opportunity.

CHAPTER FIVE

1. CANADIAN CANCER STATISTICS [505]

The National Cancer Institute of Canada (NCIC) in collaboration with Statistics Canada, Provincial/Territorial Cancer Registries, Health Canada and university based researchers publish an annual monograph that is part of a series that began in 1987.[506] The purpose of the publication is to provide health professionals, researchers and policy makers with information regarding the incidence and mortality of the most common types of cancer, by age, sex, time period and province.[507] It is hoped that the data will assist decision-making and priority-setting processes at individual, community, provincial and national levels.[508] Therefore, it would be prudent to analyze data as published by the National Cancer Institute of Canada related to incidence and mortality rates of prostate cancer, the leading cancer currently being diagnosed in the male population of Canada. If data is published to assist policy makers, what is the data saying that may influence CaP policy?

According to NCIC, caution must be exercised in interpreting the data. Differences continue to exist in reporting procedures that vary between provinces and may account for error, especially in interprovincial comparisons. There is a lack of uniformity inevitable in cancer death statistics and reporting of data. Because of the reporting process and the prevalence of non-melanoma skin cancer, the disease is excluded in all data information. In addition, the accessibility to

diagnostic procedures is subject to variability between provinces; thus, not all male patients have access to the same diagnostic aides, procedures or treatment options. The availability of screening programs, including breast screening, is variable between provinces. Incidence rates, particularly the sharp increases noted in CaP may be partially attributed to risk factors; however, the correlation between risk factors and area of residence are not known and can not be considered in provincial variations. Reporting procedures for cancer deaths have been standardized both nationally and internationally; however, some lack of uniformity is inevitable. The estimation of prostate cancer has presented a special challenge because of the dramatic rise in incidence rates due to early detection; plus, comparisons with the United States suggest that the trend in increasing incidence will not continue. Some provinces were able to provide actual CaP incidence data up to 1995 which now depicts a rapid decline after reaching a peak in 1993 that can be attributed to the advent of PSA testing. The United States experienced a decline in incidence rates once the early detection with active PSA screening programs exhausted the pool of prevalent cancer in the population. A similar phenomena is shaping the projected estimates for Canada.

The process of collecting completed information from each province results in a considerable delay in publishing reliable data for a particular year; thus, actual data is only available to 1993 for incidence rates and 1995 for mortality rates.[509] Therefore, data for later years up to 1998 are based on estimates.[510] The statistical

methodology from 1995 to 1998 utilized uniform methods; however, years prior to 1995 differed.[511] In addition, the age-standardized rates were categorized to the 1991 Canadian population; therefore, rates prior to 1995 can not be compared to rates from 1995 to 1998. Only the data from 1995 to 1998 will be used in this study from the National Institute of Canada and Health Canada, which meets the needs of this study. Occasional reference will be made to years prior to 1995 to provide a historical perspective. PSA was not introduced into clinical practice in Canada until 1989 and at varying rates of adoption within the provinces. As result, PSA as a screening and early detection tool is not being applied consistently within the provinces.

2. INCIDENCE and MORTALITY RATES OF PROSTATE CANCER in CANADA[512]

Since 1986, CaP has surpassed lung cancer to become the most commonly diagnosed cancer in Canadian men and ranks second only to lung cancer in deaths. Incidence rates refer to the number of new cases of CaP per year. Mortality rates refer to the number of deaths attributed to CaP each year. The incidence rate in CaP has experienced a 7% average annual increase from 1986 to 1993 with an estimated decline from 137 per 100,000 in 1997 to 112 in 1998. The increased incidence in CaP prior to 1990 has been partially ascribed to an increase in detection following TURP procedures for BPH; however, the increase after 1990 has been predominantly the result of early detection with PSA . Despite the sharp increase in incidence rates, the increase in mortality has been more

subtle with only a 0.4% average annual increase from 1986 to 1995. While the estimated number of new cases of CaP is expected to decline in 1998, the mortality rate is expected to remain almost status quo with only a minor increase anticipated (Figure 9). The gap between incidence and mortality rates prior to 1998 has been increasing over time, which suggests that despite the sharp increase in the volume of new CaP cases diagnosed, the disease is being detected earlier and being treated more effectively. The literature has revealed many studies that relate to the improved and earlier detection of CaP with continued progress in improved treatment options with less complications.

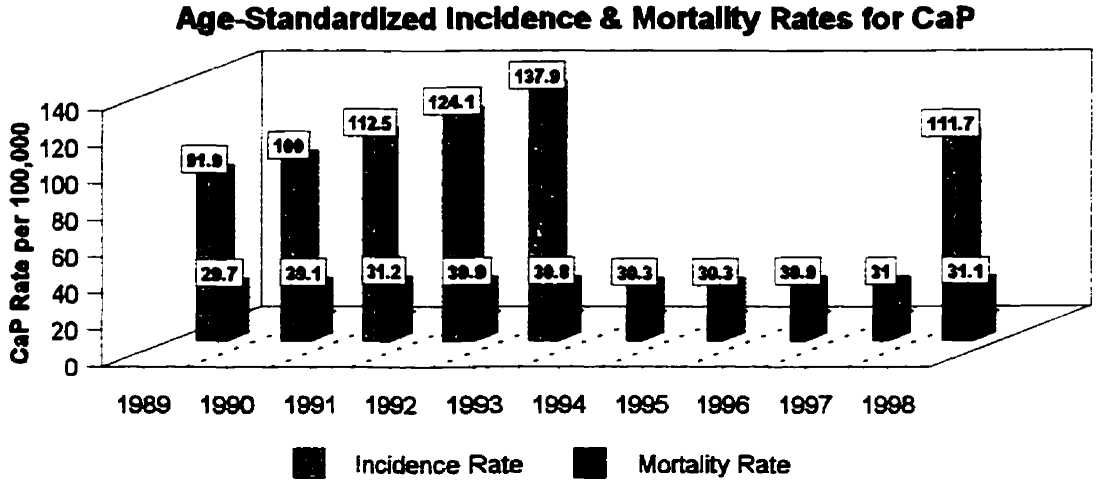

Figure 9: Incidence Rate for 1994, 1995, 1996, 1997 not available. Data obtained from Canadian Cancer Statistics 1998, pp. 32.

The number of new cases of CaP each year reveal that in comparison to other cancers it is a significant health burden accounting for about one quarter of all cancers in men compared with 13% of all male cancer deaths in 1998. In relation to breast cancer which has breast screening programs across the country, the data

are very similar. However, men do not have the advantage of screening clinics (Figure 10).

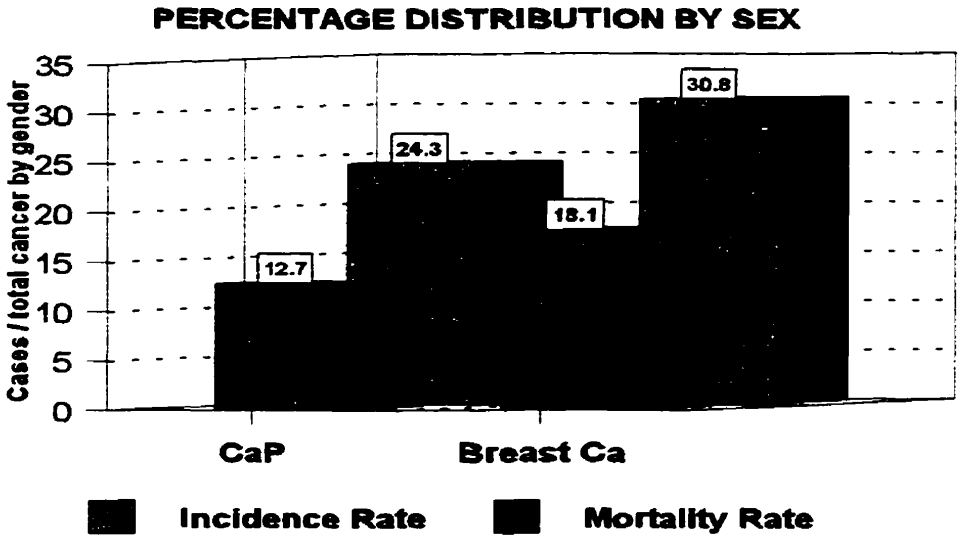

Figure 10: CaP cases per total number of male cancer cases in 1998. Breast cancer cases per total number of female cancer cases - 1998

In comparison to CaP, breast cancer in women is also the leading cause of cancer in the female population and the second cause of cancer deaths after lung cancer. Breast cancer, which is also a hormone-related disease, has a mortality rate that is 59% of the incidence rate. The statistics for CaP in men are very similar with a mortality rate that is 52% of the incidence rate (Figure 10).

The incidence and mortality rates in breast cancer have been decreasing and can be attributed to the success of breast screening clinics across the country. By comparison, CaP does not have the benefit of screening clinics which is compounded by the problem that provincial health registries and the Canadian

Cancer Statistics data bases either do not document the true picture of PSA usage or the usage is not readily available. CaP incidence has been increasing dramatically, but increases in mortality rates have only been very subtle (Figure 11 - incidence rates; Figure 12 - mortality rates).

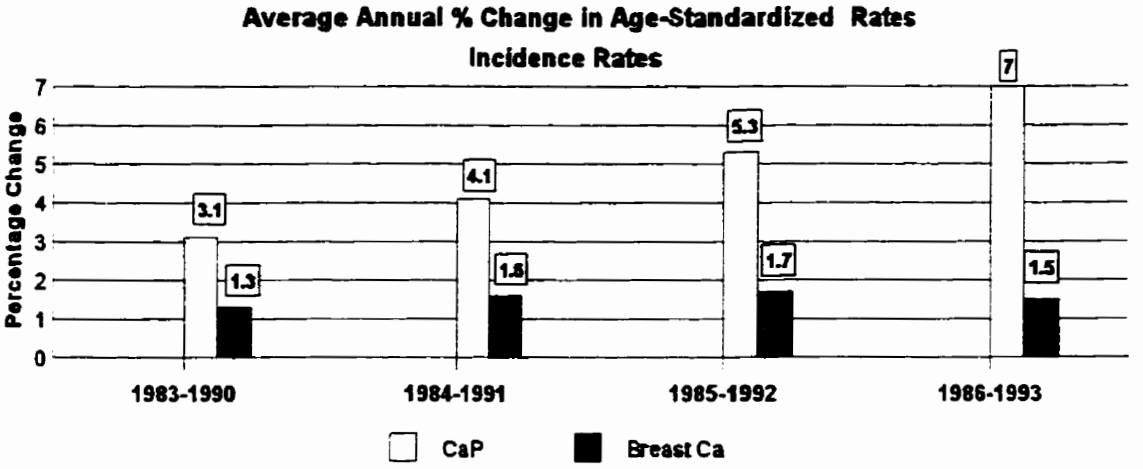

Figure 11: Comparison CaP and Breast Cancer Incidence Rates For 1983 to 1993.

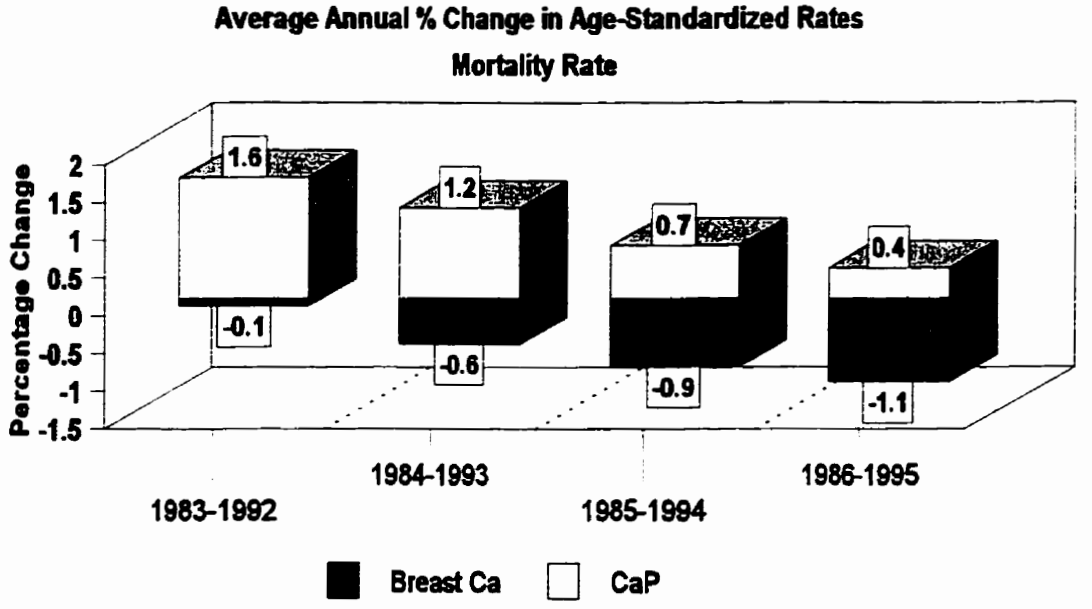

Figure 12: Comparision CaP and Breast Cancer Mortality Rates for 1983 to 1995.

Total volume data of PSA testing is not readily available and impossible to attain in many provinces. However, the total volume of PSA is of little value because of the inability to distinguish why the PSA test was ordered: screening of asymptomatic men, investigation of symptomatic men, follow-up for men with a previously diagnosed CaP, monitoring of men who have had CaP treatments and the number of PSA tests ordered per individual. The volume of PSA testing and the break-down of ordering practices is poorly documented within the provinces and is currently unavailable in published format.

3. RATES OF PROSTATE CANCER

Canadian Cancer Statistics 1998 defines the age-standardized rate as the number of new cases of cancer or cancer deaths per 100,000 that would have occurred in the standard population (1991 Canadian population) if the actual age-specific rates observed in a given population had prevailed in the standard population; thus, age-standardized rates account for differences in provincial age distributions thereby facilitating interprovincial comparisons. The age-specific rate is defined as the number of new cases of cancer or cancer deaths during the year, expressed as a rate per 100,000 persons in a given age group. The age-specific incidence rates for CaP between 1974 and 1993 show an increase with advancing age and have increased over time in most age groups (Figure 13, page 110). The average annual incidence rate reveals at least a five fold increase for ages 45 to 69 years and a doubling of rates from ages 65 to over 85 years of age.[513] While CaP is rare among males under

age 45 years, incidence rises faster with age than for any other major cancer.[514]

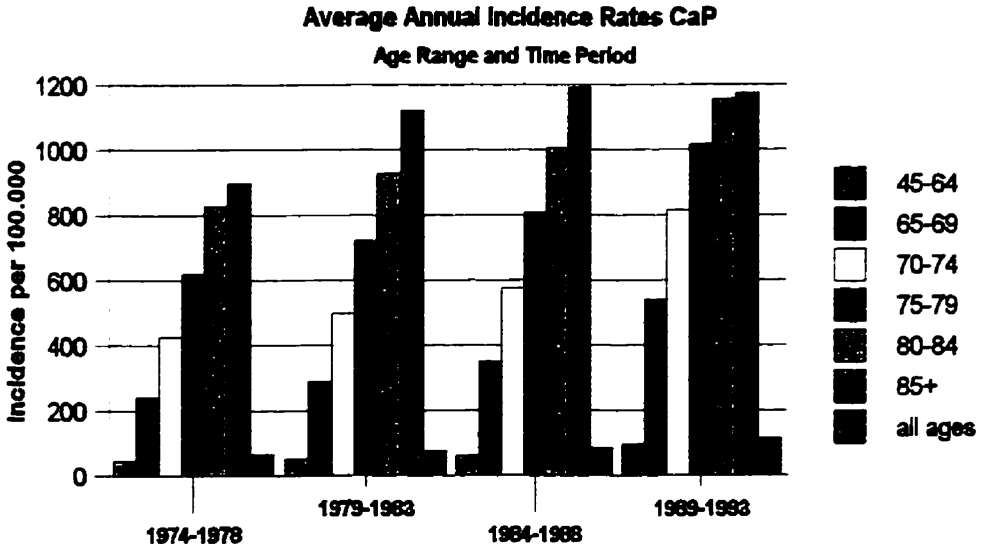

Figure 13: Average Annual Incidence rate CaP from 1974 to 1993.

The estimated new cases of CaP in Canada by age group for the time period 1995 to 1997 exhibit dramatic increases in all age groups, especially as age increases. However, estimates for 1998 anticipate a decline in the incidence rate of CaP which will correspond to the trend experienced in the United States (Figure 14).

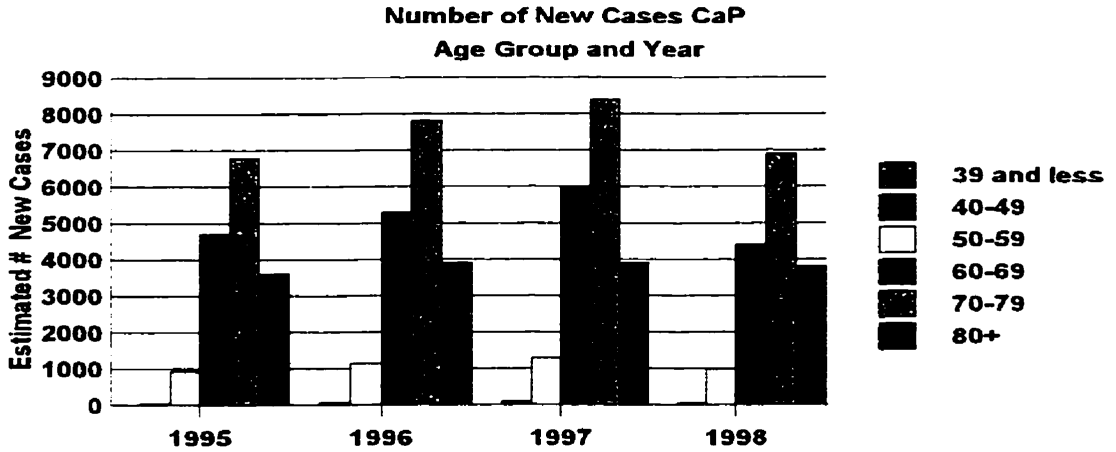

Figure 14: New Cases CaP by Age Group from 1995 to 1998.
Incidence rate for under age 39: 5 in 1995 and 10 in 1996.

CaP is the second leading cause of cancer deaths in Canadian men. Health Canada estimates that 1 in 27 men will succumb to the disease. In 1998, it is estimated that 4,300 men will die of the disease, but by the year 2016, the number is expected to reach 7,800 deaths. It is a significant health burden. The mortality rates for CaP increased with age from 25.5 per 100,000 males in 1976-1980 to 30.7 in 1991-1995. The number of deaths attributed to CaP increased with age for all the time periods with a sixfold increase in rates from ages 45 to 69 years and a tenfold increase from ages 65 to 85 years and over (Figure 15)[515].

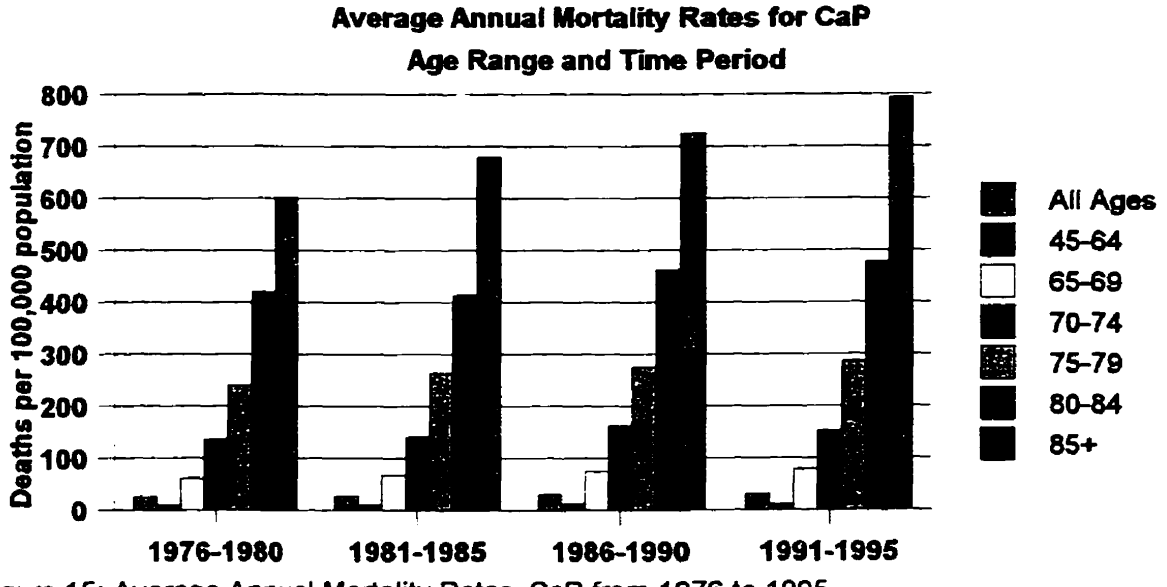

Figure 15: Average Annual Mortality Rates CaP from 1976 to 1995.

The estimated mortality rate for CaP in Canada for the time period 1995 to 1998 reveals status quo rates, but a decrease in rates for males aged 69 years and under. However, for men 70 years or older, the overall mortality rate continues to increase, but at a slow and steady rise (Figure 16, page 112). As mentioned

previously, the gap between incidence and mortality rates suggests earlier detection and improved treatments have prevented the number of prostate cancer deaths from keeping pace with the same increase in new cases.

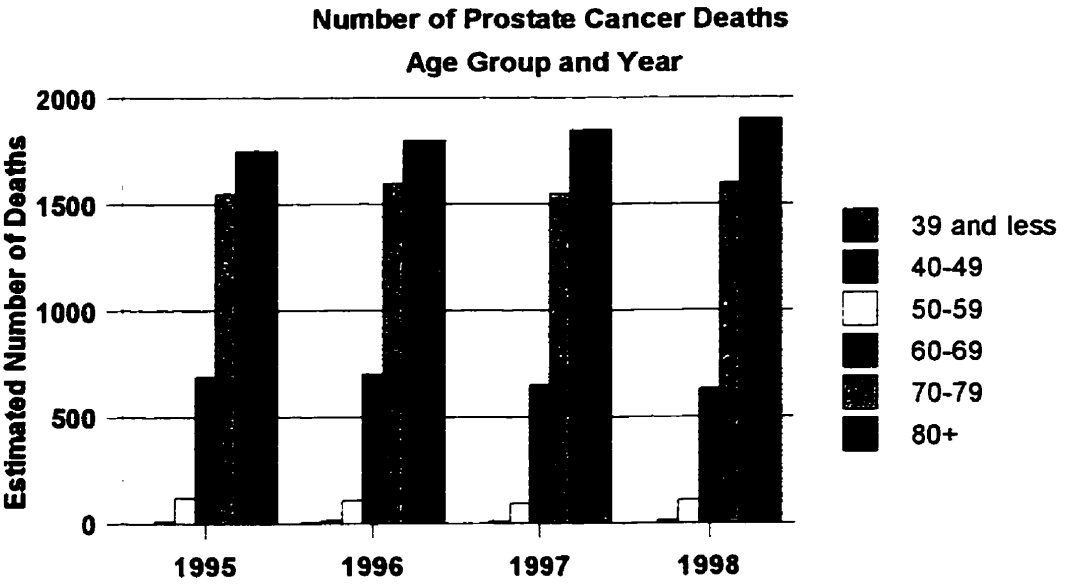

Figure 16: Estimated CaP Deaths by Age Group from 1995 to 1998.
Mortality Rate for under 39 years is estimated at 5 cases in 1996.

4. PROVINCIAL COMPARISONS OF PROSTATE CANCER RATES

A comparison of age-standardized prostate cancer incidence rates by province in 1991 indicated that British Columbia had the highest rate, followed by Manitoba and New Brunswick. However, British Columbia had the distinction of the lowest mortality rate from 1991-1995. The highest mortality rates occurred consistently in Prince Edward Island from 1976 to 1995. All the provinces had an increase in death rates from 1976 to 1995, except for Quebec, Manitoba and British Columbia. By 1993, incidence rates for CaP in Canada were lower than the United States (and

especially African Americans who have the highest rate in the world); however, the United States had adopted PSA screening at an accelerated rate.

For the purposes of this study, only British Columbia, Alberta, Saskatchewan, Manitoba and Ontario will be compared. A comparison of all the Canadian provinces is beyond the scope of this paper; in addition, the intent of the provincial analysis was to present the spectra of information provided by the Canadian Cancer Statistics.

In 1993, British Columbia released a document by the Center for Health Services and Policy Research indicating that in 1992, PSA did not appear on the fee-schedule of the Medical Services Plan.[516] The BC Cancer Agency was the only source of PSA testing for diagnostic and monitoring purposes; however, some reimbursements may have occurred under other categories. At this time, the report recognized an increasing trend, but also recognized that the Medical Services Plan had no mechanism for identifying PSA used as a screening tool, and thereby, selectively reimbursing only tests ordered for diagnostic or monitoring purposes. The volume of PSA testing suggested that practitioners were using PSA for screening. The report recommended that PSA screening was not cost-effective by suggesting that many more nonprogressive cancers would be detected rather than progressive cancers which would result in over treatment and increased costs. In addition, costs would be incurred with associated biopsies and treatment as a result

of false-positive PSA tests.

In Alberta in 1998, PSA for screening is not a billable service. In addition, there is no easy method to distinguish between PSA tests to investigate or for CaP follow-up which suggests the possibility of PSA being utilized in screening, but billed as investigative. Provincial data indicating the volume of PSA and break-down according to ordering practices is not available.

Saskatchewan currently reimburses all physicians, including family practitioners, for all PSA tests; however, a 1995 report released by the Health Services Utilization and Research Commission[517] did not support PSA screening. The report determined that 80% of PSA tests were requested by family physicians, 63% of whom indicated that they used PSA for screening purposes.[518] In addition, Saskatchewan reported a forty fold increase in total PSA testing between 1990 and 1994.[519] The report concluded that:

1.) asymptomatic men should not be PSA screened.

-PSA test has a high rate of false positives.

- Other common conditions such as BPH cause an elevated PSA.

- There is no evidence based on randomized clinical trials that early detection of CaP improves survival.

2.) PSA test should be used selectively on men who have symptoms of prostatism and/or positive DRE and for whom treatment would be

appropriate.

- PPV of PSA increases with DRE.

- PSA test should not be used on men for whom treatment is inappropriate because of age, comorbities or life expectancy less than 10 years.

3.) PSA test used to monitor treatment in CaP men, including those being observed with watchful waiting strategy.

- PSA is effective in monitoring treatment in CaP men.

- Periodic PSA provides information in men who have chosen watchful waiting as a treatment strategy.

- Increased cooperation between oncologists, urologists and family physicians will reduce the number of needless repeat tests.

4.) Physicians should discuss with patients the reliability of the PSA test and potential risks of follow-up surgery or treatment.

- Good communication enables patients to make informed decisions about treatment based on their values and experiences.

- Counseling may encourage patient acceptance of more moderate management of prostate problems, where this strategy is appropriate.

As a result of the report the provincial guidelines do not support PSA screening; however, physicians are currently reimbursed for all PSA tests. The province does not distinguish between PSA for screening, investigative or diagnostic purposes. The first PSA tests were in 1990 in which PSA volumes have fluctuated in the

following years. Recent data are not available regarding the volume of PSA screening in the province, especially since the guidelines discourage the practice.

In Manitoba in 1998, physicians are reimbursed for all PSA tests as part of the health examination; patients do not incur the costs of PSA tests. The physician does not distinguish on the requisition between PSA for screening, investigative or diagnostic purposes when ordering the test. PSA testing began in Manitoba in 1989. The province does not have a centralized record of PSA data, nor is there any means of distinguishing which PSA tests are ordered for screening. There is no record that the province has released a report similar to British Columbia or Saskatchewan regarding the use of PSA testing.

In Ontario, PSA testing for screening is not an insured service and there are no centralized records of PSA data. Asymptomatic men who request a PSA test must pay between $15 and $30 per test depending on the facility supplying the service. Dr. Peter Bunting, Sunnybrook Health Science Center, is currently publishing articles pertaining to PSA utilization in Ontario.[520] Dr. Bunting's objective is to ascertain the extent of PSA testing in Ontario in patients with CaP, other cancers, and no cancer, in two clinical laboratory databases. Dr. Bunting estimates that half of the PSA tests in the no cancer group of patients is for screening purposes; in addition, PSA testing in this group of patients continues to increase rapidly. Dr. Bunting states in his report that there is little information on the extent of PSA

testing on patients with or without CaP in Canada.

Exploratory research exposed the lack of available data within the provinces pertaining to the use of PSA as a screening tool. Without the ability to compare the volume of PSA screening with the trend in mortality rates, the study can not compare provinces or possibly link PSA screening with earlier detection of prostate cancer and the accompanying decline in mortality rates. However, provincial incidence rates and mortality rates within the provinces are compared with each other and against the Canadian rates. All the provinces were estimated to continue experiencing an increased rate of new cases for 1995, 1996 and 1997; however, a projected decline in 1998 is estimated for all provinces (Figure 17).

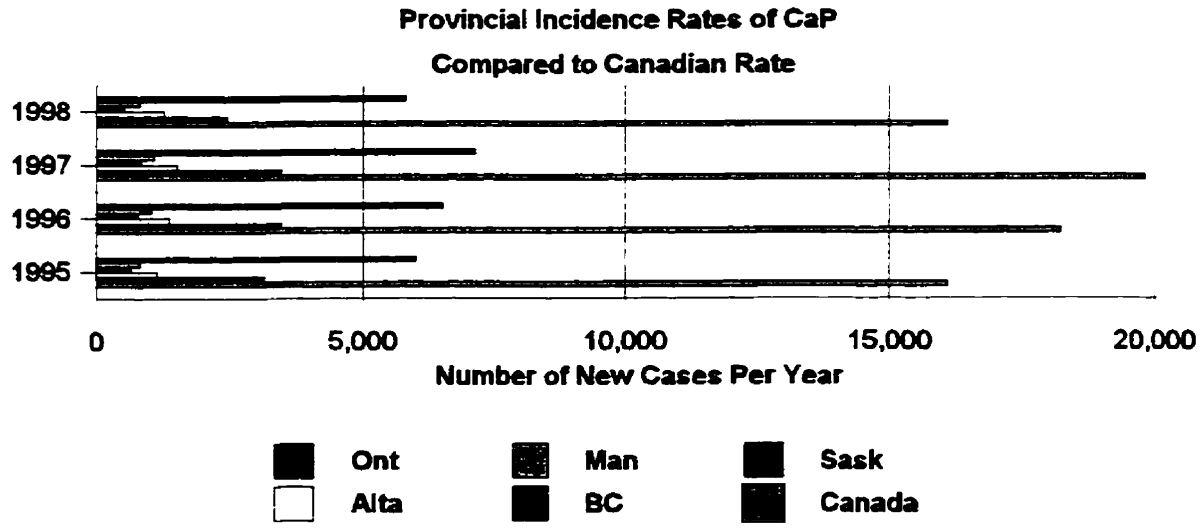

Figure 17: Provincial Comparisons of Number of New Cases of CaP per year

Saskatchewan is projected to have the largest decline of 39% in new cases while Alberta is estimated to have the least at 16%. Canada is expected to observe an

overall 19% decline in the number of new cases of prostate cancer in 1998. Unfortunately, without the data pertaining to PSA screening the decline can not be attributed to prior screening practices that have exhausted the pool of prevalent CaP in the population, nor can the decline be attributed to the lack of PSA screening or the provincial change in policy that may be restricting PSA screening that results in missing early cases of CaP.

The mortality rate for the same five provinces is compared with the National projections. All the provinces, except for Manitoba, are estimated to continue with the same subtle increase in mortality rates for 1998 (Figure 18). Manitoba is projecting a decline.

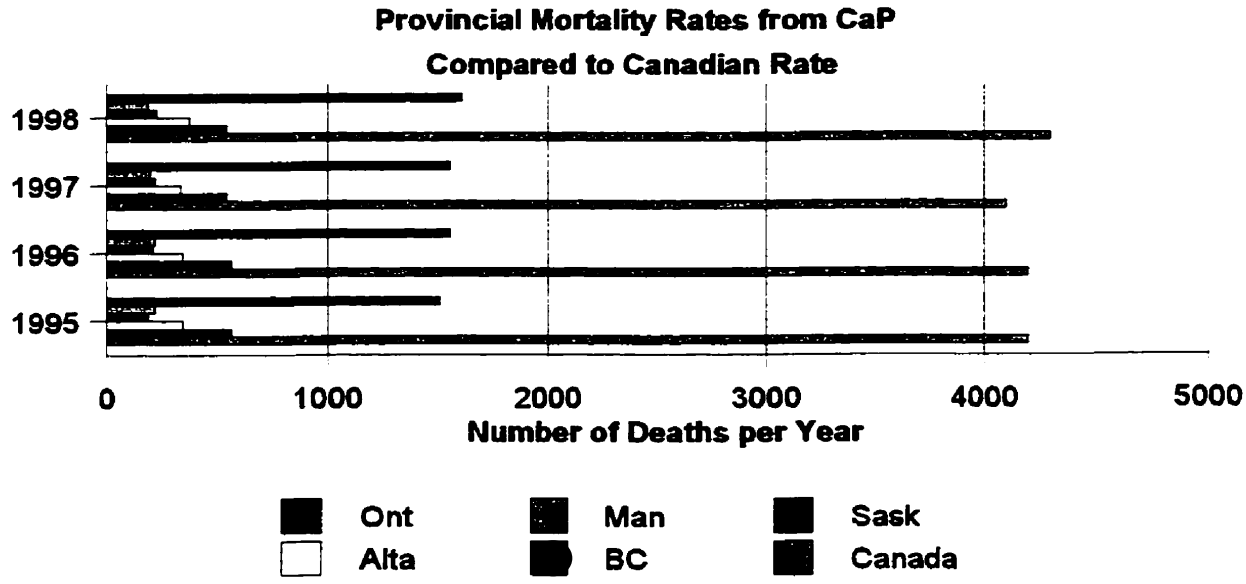

Figure 18: Provincial Comparisons of Number of Prostate Cancer Deaths per Year

Manitoba is projected to have a 5% decline in mortality rate in 1998; however,

without the provincial volume of PSA screening tests performed, the assumption can only be alluded to that possibly the ability to promote PSA screening in a province that has insured services for all PSA testing may be rewarded with a declining mortality rate.

Disease severity, which is the ratio of number of deaths to number of new cases, is a crude indicator of the gravity of CaP as a disease entity. The closer to 1.0 (100%) the value, the poorer the prognosis. CaP and breast cancer are considered to have a fairly good prognosis with a disease severity ratio of less than 30% (Figure 19).

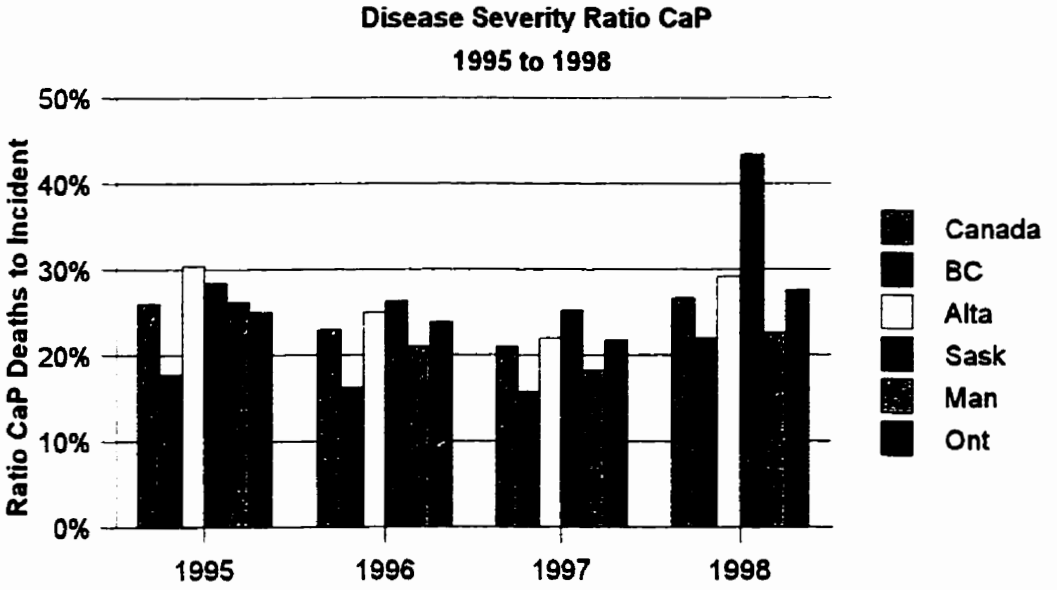

Figure 19: Provincial Comparisons of Prostate Cancer Disease Severity

All of the provinces have a disease severity ratio for prostate cancer of less than 30%, except for Saskatchewan which is prominent with 43.4%. By comparison,

Manitoba and British Columbia have the lowest ratio at 22.6% and 22% respectively for 1998. The question raised, can the usage of PSA screening and the earlier detection of prostate cancer be cause for the estimated discrepancies in the provincial disease severity ratios?

A comparison of the age-standardized incidence rates of prostate cancer over the four year time frame indicated that British Columbia is expected to have the highest rate per 100,000 population, but Manitoba follows closely (Figure 20). Alberta and Ontario have the lowest rate per 100,000 population, but Saskatchewan is expected to have the lowest rate in 1998.

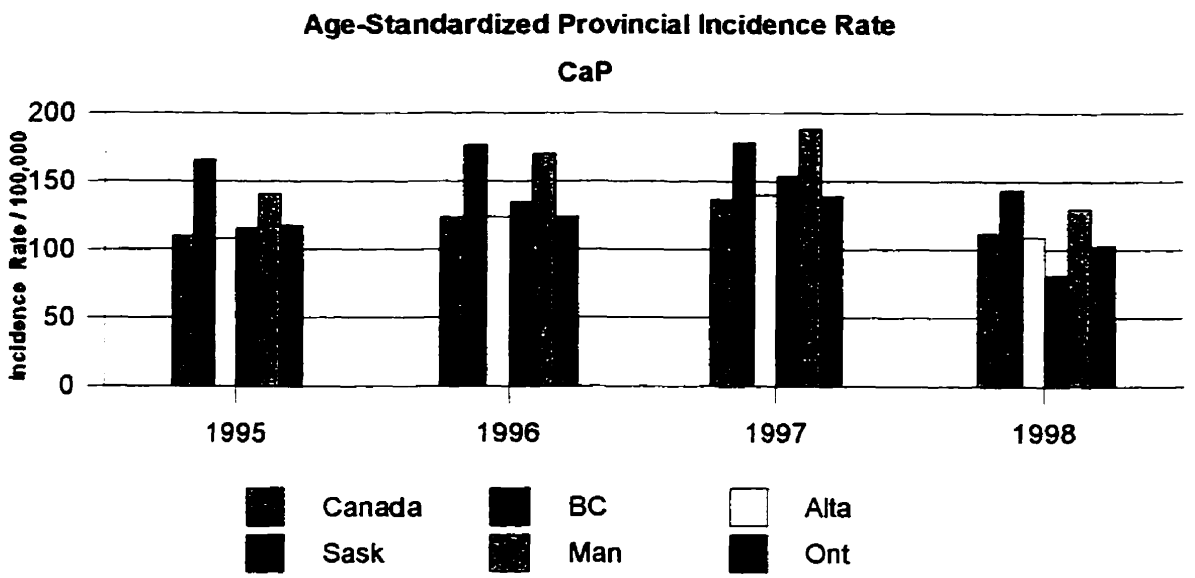

Figure 20: Age-Standardized Incidence Rates CaP - Provincial Comparison

In an effort to refine the analysis of provincial comparisons and to examine the data other than by age-standardization rates, the number of new prostate cancer cases

for each province was divided by the total male population in that province which would compensate for the variation in provincial population bases. The higher ratios would indicate that a larger portion of men are having prostate cancers diagnosed and possibly less cancer cases are being missed. Manitoba had the highest ratio followed closely by British Columbia (Figure 21). Alberta had the lowest ratio which indicates that the number of diagnosed prostate cancer is low. Does this imply that Alberta is missing prostate cancer cases in comparison to Manitoba or is there another reason such as more cases being diagnosed outside the province, such as men on winter vacations and PSA testing being done elsewhere?

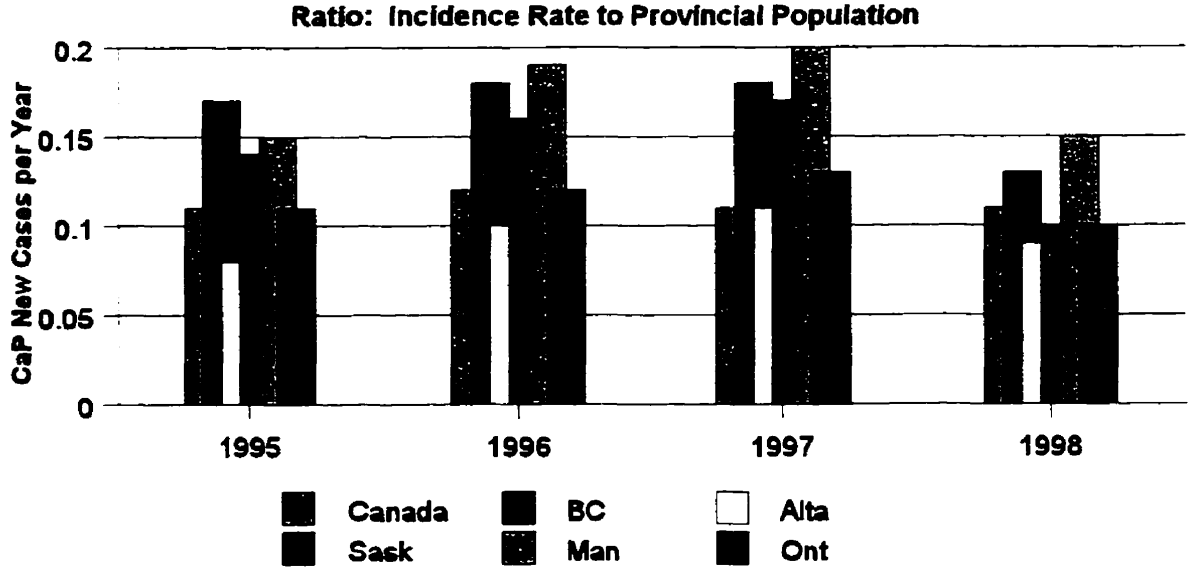

Figure 21: Ratio: New Cases of CaP Divided by the Provincial Male Population

A comparison of age-standardized mortality rates indicate that Manitoba had the

highest number of prostate cancer deaths per 100,000 population in 1995 and 1996, but Saskatchewan is expected to have the highest number of deaths in 1997 and 1998 (Figure 22). British Columbia had the lowest ratio for all four years.

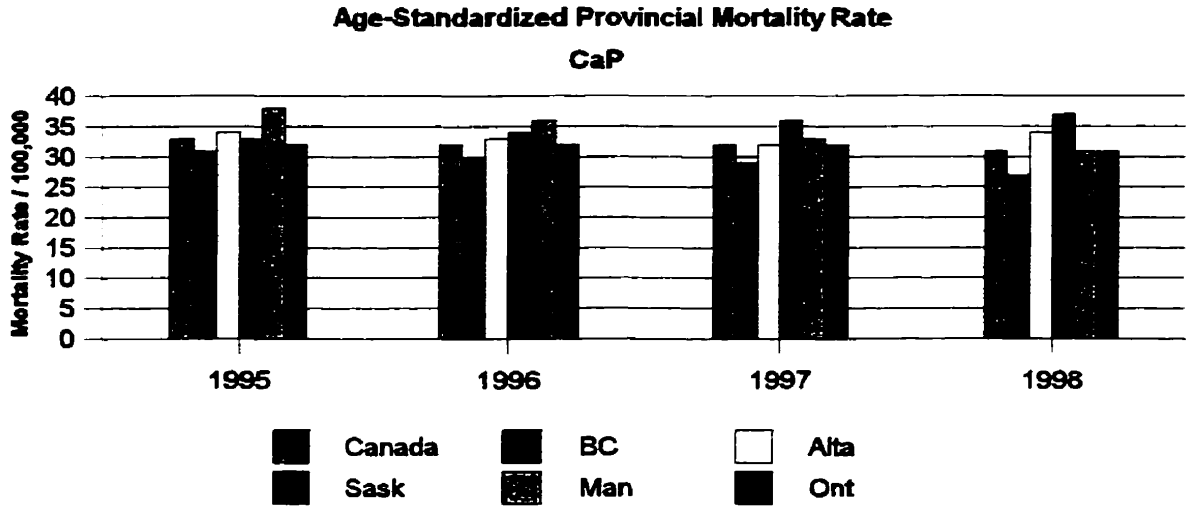

Figure 22: Age-Standardized Mortality Rates CaP - Provincial Comparisons

The number of prostate cancer deaths for each province was divided by the total male population in each province to produce a percentage value. The analysis compensates for the variations in provincial populations and the intent is to provide a comparison with age-standardized provincial mortality rates. The lower ratios indicate that a lower number of men are dying of prostate cancer. Alberta has the lowest ratios while Saskatchewan has the highest (Figure 23, page 123). In analyzing the data, Manitoba may have had the highest ratio in incidence rates suggesting a possibility that prostate cancer is being detected and less prostate cancer is being missed; however, the detection rate appears to be reflected in an improved mortality rate over the 1995 to 1998 time frame. Caution should be

exercised since the data are only estimations. In addition, it will take a period of time before the earlier detection methods and treatment regimes will be reflected in lower mortality rates. The literature overview suggests a 15 year time frame of actual data to observe trends. Saskatchewan had one of the lower ratios of incidence rates per population over the time frame 1995 to 1998, but the province had the highest mortality rate in 1998 and is predicted to have the highest disease severity ratio for 1998. Could this reflect the provincial PSA screening guidelines that discourages PSA testing of asymptomatic men?

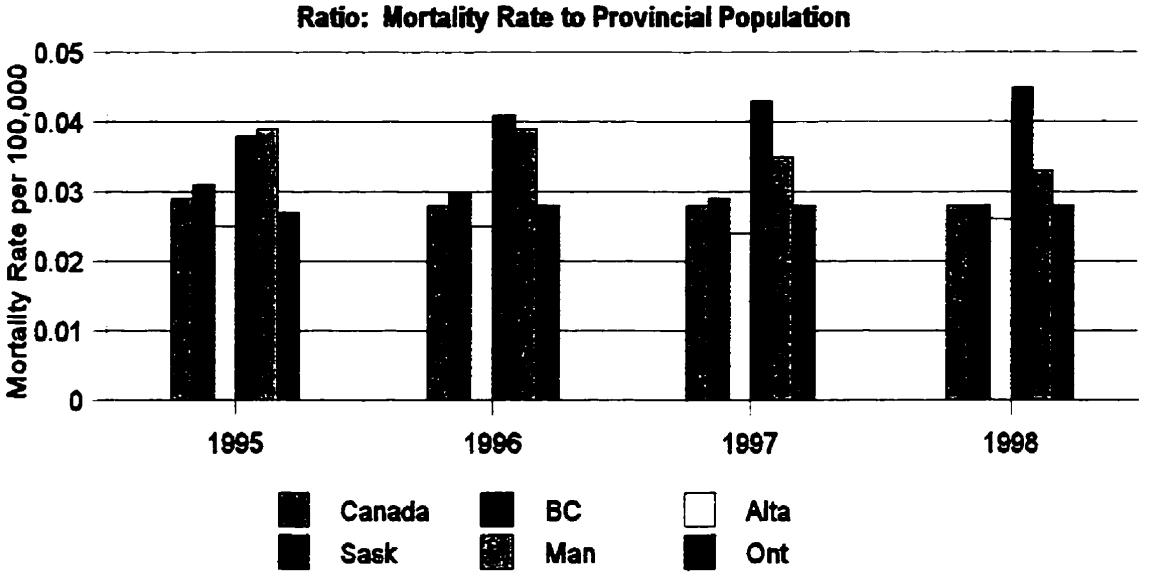

Figure 23: Ratio CaP Deaths Divided by Provincial Male Population

Disease severity for age-standardized rates accounts for differences in provincial age distributions while providing a crude indicator of the gravity of prostate cancer as a disease entity. The mortality rate per 100,000 population is divided by the incidence rate per 100,000 to give a percentage value (Figure 24, page 124).

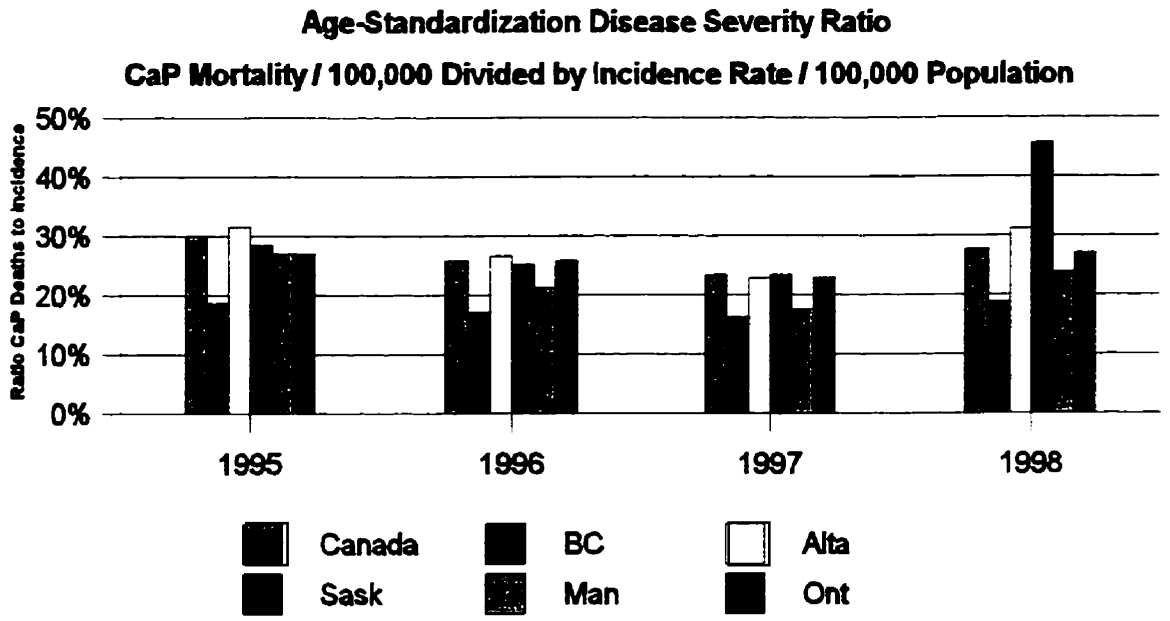

Figure 24: Disease Severity CaP Age-standardized

All the provinces had disease severity ratios of 30% or less for 1995, 1996 and 1997 with the exception of Alberta recording 31.5% for 1995. In 1998, Saskatchewan is projected to have a ratio of 45.7% indicating a greater level of prostate cancer disease severity than the other provinces. The lowest ratio was British Columbia. The results of the age-standardized disease severity ratio was comparable to the disease severity ratio results when the population was not age-standardized (Figure 19 and Figure 24).

5. INTERPRETATION OF DATA ANALYSIS

Since the implementation of PSA as a urological tool in clinical application in Canada, the provinces have adopted PSA screening at various rates. To date, the

use of PSA as a screening tool in the provinces is confusing and poorly documented. It would appear from preliminary investigation that PSA data is not readily available, nor has it the ability to distinguish ordering practices which would identify the use of PSA testing: 1) as a diagnostic tool for symptomatic men, 2) repeat or follow-up testing of CaP who have already received treatment, 3) follow-up testing of men who are being monitored in conservative management of their CaP, 4) PSA as a screening tool in asymptomatic men, or 5) the number of PSA tests each man has in a year. The majority of the five provinces reviewed only have PSA volumes available; however, none of the provinces had the data readily accessible, nor could there be an assurance that the data were accurate and reflective of the total provincial volume. Thus, the true volume of PSA as a screening tool in Canada is unknown.

The province of British Columbia has had an overall increase in new cases diagnosed with an accompanying decline in mortality and disease specificity for 1995, 1996 and 1997, suggesting progress has been made in addressing prostate cancer. However, 1998 projects that disease severity will increase to 1995 levels which could be skewed by the projected 29% decline in new cases expected in 1998. Age-standardized disease severity will remain less than 20%, but it will be interesting to note if the age-standardized mortality rate will continue to decline.

Alberta, which does not insure PSA testing of asymptomatic men, has estimated

continual increases in new cases for 1995, 1996 and 1997 with a very subtle decline in mortality rates for the same time frame. Projections for 1998 expect a 16% decline in the diagnosis of new cases, but an increase in mortality rates. The mortality rate had remained fairly status quo with subtle declines; however, a 12% increase is estimated for 1998. Disease severity ratios had declined to the low 20% levels, but are expected to increase to over 30% in 1998. There does appear to be a need for exploratory research into the declining incidence rate in 1998, along with the projected rise in mortality rates and disease severity ratio for the province. An assumption could be alluded to that prostate cancer is not being addressed with the suggestion that non-insured PSA testing of asymptomatic men has affected the number of men opting for PSA screening as a preventive health measure. It also raises the question that non-insured PSA testing restricts physicians from offering the test to asymptomatic men who must pay for the service.

Saskatchewan projected an increasing incidence rate in prostate cancer for 1995, 1996 and 1997, but also expected a continual rise in mortality rates. Disease severity ratios for the same time frame were projected to remain less than 30%; in fact, the estimates expected the disease severity ratio to decline. Projections for 1998 predict a dramatic 40% decline in the diagnosis of new cases; unfortunately, mortality rates are expected to continue to rise which may suggest that past practices have missed prostate cancers that are continuing to kill. Saskatchewan is predicting the highest mortality rate per population of all five provinces, plus a

substantial increase over the national projections for Canada as whole. The projected disease severity of 46% is cause for concern as the disease is now predicted to have a poorer prognosis in the province of Saskatchewan compared to the other provinces and the national average of less than 30%. The 1998 projections for Saskatchewan appear to suggest that the province has a problem with prostate cancer that is increasing in severity for the men of the province.

Manitoba had projected an increase in diagnosing new cases for 1995 to 1997 with a declining mortality rate. There has been a notable decline in disease severity to less than 20% with projected levels for 1998 below the 1995 level. Projections for 1998 are very encouraging suggesting that the incidence rate will decline by 24%, but Manitoba is the only province of the five to predict a decline in mortality rates for 1998. Disease severity is expected to remain well below the national rate. Manitoba is expected to experience the greatest drop in mortality per population over the four year time frame; in addition, Manitoba is the only province among the five provinces with a age-standardized disease severity level notably lower than the 1995 level. With a historic pattern of no increase in mortality rates for 1976 - 1995, it could be suggested that prostate cancer diagnosis and treatments are effective in Manitoba.

Ontario also predicted increased levels in diagnosing prostate cancer for 1995 to 1997; however, the province has only predicted a 18% decline in 1998. Mortality

rates have remained fairly status quo, but the disease severity ratio is expected to increase to levels approaching 30% which is higher than the 1995 level and greater than the national ratio of Canada as a whole. It would appear that the impact of prostate cancer on the province is not decreasing.

6. PROSTATE CANCER AND THE IMPLICATION OF COSTS

Policy implementation carries a financial burden weighed against the perceived improvement in health status or quality of life issues. In the face of burgeoning health care costs, the historic paradigm that the public encouraged all available efforts to fight disease has begun to shift in favor of resource utilization that maximizes the health of the population served.[521] Screening clinics recognize quality of life issues which are integral components of the CaP patient's health. Recognizing anxiety associated with PSA levels, providing informed choices for treatment, providing counseling in sexual rehabilitation and treating the complications of CaP surgery such as incontinence and related complications, asserts health promotion. Public education is essential and the success of Prostate Awareness week in the United States and Canada, prostate support groups and public forums and workshops are an example of the positive effects of public education.

The cost of using PSA as an early detection tool in Canada is unknown. It would appear that some provinces pay for the test through provincial medical services,

while other provinces directly charge the patient who requests the test. However, the paying system is not so simple. A province such as Saskatchewan pays for all PSA testing that is submitted by physicians, including family practitioners; however, the confusion follows with the provincial guidelines released from a provincial study stating that PSA as a screening tool should not be used. Therefore, family practitioners are encouraged not to screen asymptomatic men for CaP. British Columbia, Alberta and Ontario do not pay for PSA screening; thus, the male patient must incur the cost of the test, usually between $15 to $30 which is dependent on the agency or clinic doing the test. National Agencies, such as the Canadian Cancer Statistics and National Prostate Group, recognize that PSA statistics are not available on a provincial basis to give a national perspective of the situation.

The National Cancer Institute spent an estimated $59 million on prostate cancer research in 1995[522] Other researchers estimate that the actual amount is much less, such as Coffey of John Hopkins, who states that the total amount of money going to study the prostate and all the diseases it causes in the USA is only about $14 million which would not buy one fighter plane (a stripped down fighter plane costs about $39 million).[523] The National Cancer Institute estimates overall annual costs for cancer at $107 billion with $37 billion for direct medical costs, $11 billion for morbidity costs (lost productivity) and $59 billion for mortality costs.[524] Treatment of breast, lung and prostate cancers account for over half of the direct medical costs.

The cost of illness in Canada in 1993 was estimated at $156.9 billion with $71.7 in direct costs and $85.1 billion in indirect costs.[525] Cancer was estimated to cost a total of $13.1 billion.[526]

There have been major concerns expressed over testing for the early detection of CaP with significant financial cost projected for diagnostic follow-up testing and aggressive treatment. American statistics indicate a first-year cost of $25.7 million to screen all men for prostate cancer between 50 - 70 years of age utilizing DRE and PSA tools.[527] Other estimates suggest that one time screening for the American male population over 50 years of age would cost $12 - $28 billion.[528] Detection of CaP has increased over the last ten years partially due to an increased public awareness and partially due to the advent of serum PSA testing. On an individual basis, each PSA serum test costs $15-$20 with very low risk.[529] Based on existing research that the potential for cure is greatest in the earlier stages of disease, it has been estimated that 1% - 9% of cancer deaths associated with CaP would be averted with regular screening.[530] A 1995 report prepared for Quebec by the health ministry, suggested that the CaP fatality rate among non-screened men under 85 years of age is approximately 22% compared with approximately 15% for patients who had CaP surgery.[531] The report concluded that the costs of screening and treatment would be approximately $214,000 (Canadian) per year of life saved.[532] However, PSA testing and radical prostatectomy surgery should be compared to the health costs associated with bone metastasis, palliative care and

the human costs of dying with metastatic cancer.

Influenced by mortality rates, screening programs are essential to detect the best clinical course and the clinical significance of non-palpable CaP disease. As a result, the public has assigned a high priority to early detection whereby screening can confine the disease to the prostate gland. Other cancer screening programs, such as breast and cervical cancer were implemented without knowledge of the effect of screening on mortality rates.[533] In fact, proof of the efficacy of these programs was based on their widespread use in the community and not on controlled, randomized trials.[534] The impact for prostate cancer is that screening has become available at a time when cost control is a dominant concern in the health care system.[535] The rising cost of health care has made governments less willing to approve new benefits for the population. Various cost projections have been suggested in the literature regarding PSA screening in the first and subsequent years; however, the cost of terminal cancer for the patient with advanced stage prostate cancer also needs to be evaluated to give a true picture of the societal cost of this disease. The scope of presenting a cost-benefit analysis of prostate cancer screening, the impact of the disease and the cost in terms of health dollars currently being spent on the disease and future costs are beyond the scope of this paper.

7. SUMMARY

The National Cancer Institute of Canada in collaboration with Statistics Canada publish an annual monograph citing the estimated incidence rate and mortality rate for prostate cancer, along with other cancers. The information is used by various end-users to assist in decision-making and public policy formation. As a source of secondary data, the published statistics are available to the public; however, the process of collecting completed data cause a considerable delay. Actual data is only available to 1993 for incidence rates and 1995 for mortality rates. Estimates are provided for ensuing years.

The secondary published data from Health Canada, the National Cancer Institute of Canada and Statistics Canada were analyzed pertaining to prostate cancer as a disease entity. The years 1995, 1996, 1997 and 1998 were analyzed with graphic presentation to facilitate visual convenience in relation to: mortality rates, incidence rates, age-groups, disease severity, ratio of population and mortality/incidence rates, age-standardized groupings and interprovincial comparisons of British Columbia, Alberta, Saskatchewan, Manitoba and Ontario. Provincial Health Registries currently do not have the capability to provide PSA volumes with the ability to distinguish the ordering practices of the PSA test. Thus, it is impossible to analyze the incidence and mortality rates to determine if PSA screening is having an impact on reducing the mortality rates and which provinces are experiencing success. However, analysis of the secondary published data demonstrates certain

trends emerging in the five provinces analyzed. British Columbia appears to be continuing with subtle declines in mortality rates with disease severity remaining less than 20%. The data presented raises the question that if the disease is on the decline in the population, is the decline due to PSA early detection? Alberta is expected to have an increase in mortality rates in 1998 despite three years of slightly declining rates. Disease severity is projected to rise to more than 30% suggesting the possibility that the disease is increasing in severity in the population. Has the policy of de-insuring PSA screening had a cause and effect relationship on mortality rates? Saskatchewan expects mortality rates to continue to rise with a predicted disease severity of 46%. The projected estimates are cause for concern and the possibility that the disease is not being treated effectively. Manitoba is the only province to forecast a decline in mortality rates for 1998 with a decrease in disease severity ratio to less than the 1995 level. Ontario is predicting stable mortality rates; however, the disease severity in 1998 is expected to reach 30%. The impact of prostate cancer on the population is not projected to decline.

The data for 1995 and successive years is only an estimation; however, it is prudent to analyze data that assists in policy formation. The exploratory and descriptive research has demonstrated the lack of pertinent and essential data, especially PSA testing volumes and categorizations of ordering practices which are essential components to throughly analyze the issue of prostate cancer screening. The importance of the disease as the most commonly diagnosed cancer in the male

population suggests that a greater emphasis should be directed toward accessibility of data to explore the issue. An in depth cost-benefit analysis is necessary to complete the picture, but PSA data is mandatory. Otherwise, prostate cancer screening programs may have to forgo controlled, randomized clinical trials and follow the example of breast and cervical screening programs which began through public demand and widespread use in the communities.

CHAPTER SIX

1. PROSTATE CANCER SCREENING

Numerous studies have been completed and others are currently in progress since the inception of PSA in 1987 as a screening tool in clinical application and to monitor response to cancer therapy.[536] PSA is currently the best available tumor marker for any human malignancy.[537] Searching for CaP in asymptomatic men constitutes screening while evaluating men with clinical signs and symptoms that results in a diagnosis of CaP is known as detection.[538] Recent evidence suggests that only a small percentage of PSA diagnosed cases are probably latent cancers (8 - 26%). In screening trials, approximately 70% of cases are organ confined,[539] and thus, potentially curable. PSA based screening substantially increases the prostate cancer detection rate and the percentage of organ-confined tumors.[540] It appears that there is a benefit from screening for CaP because of the increased amount of potentially curable disease discovered, and the fact that 96% of the pathologically staged tumors detected have histological features associated with aggressive cancer.[541] Additional evidence that nearly all tumors detected on the basis of initial PSA screening are apt to be clinically significant may be derived from the information that PSA based screening decreases the incidence of incidental A1 Grade 3 and A2 tumors, but does not increase the detection of clinically insignificant A1 Grade 1 and 2 tumors.[542] It would also appear that since PSA has come into widespread use, CaP is being diagnosed earlier, and recent studies have reported a lower incidence of unsuspected lymph node metastasis.[543] At this time,

PSA represents the most effective and valuable tool to detect early CaP; therefore, PSA should be used to improve early diagnosis of CaP.[544] An algorithm for screening and early detection of CaP is illustrated as follows:

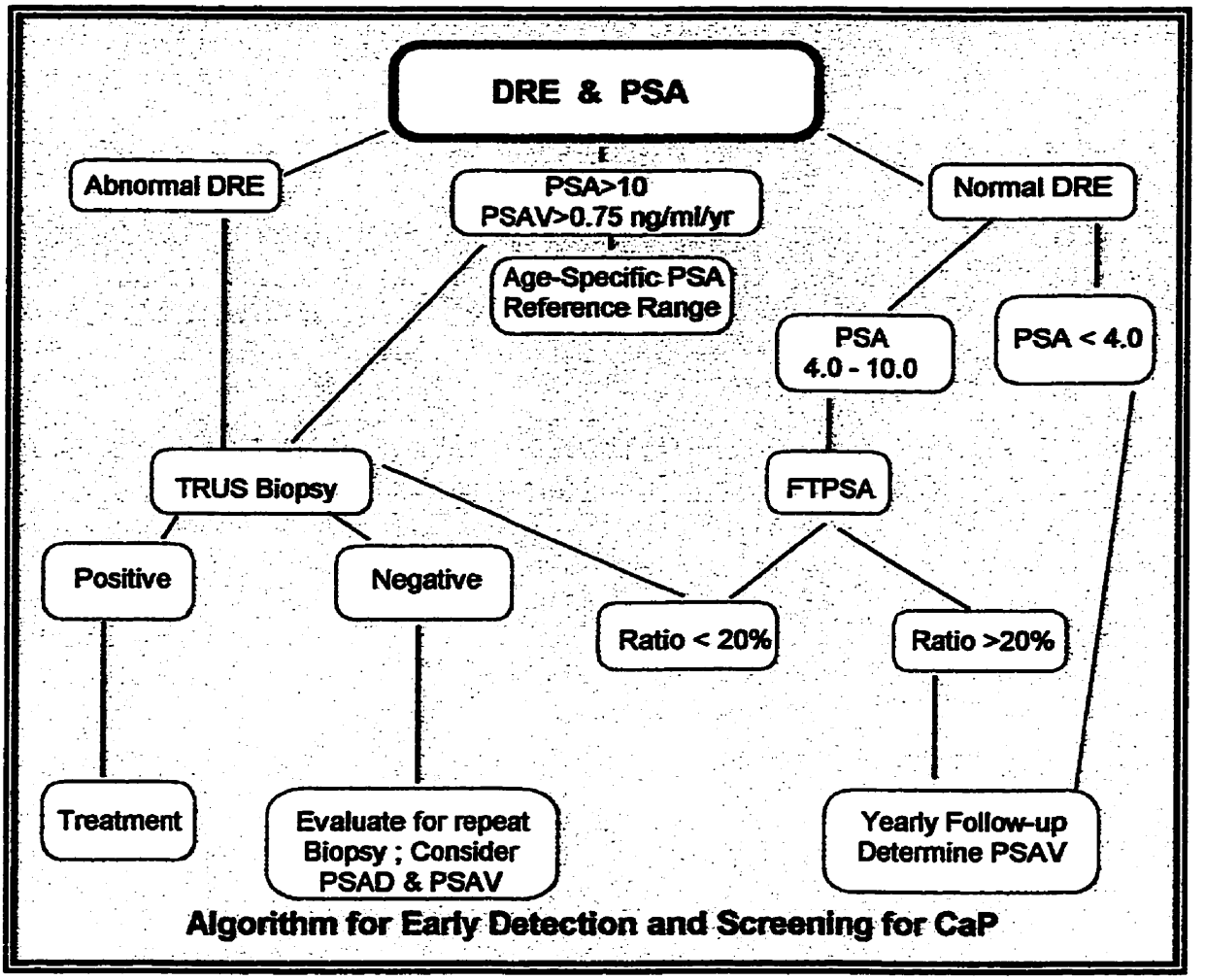

Figure 25: Screening Algorithm Adapted from R. Freid, et al[545] ; FTPSA cutoff value subjective - ACS and AUA have not presented policy on use of FPSA.

Some advances have been made with the introduction of PSA transformations to improve the usefulness of PSA as a marker for adenocarcinoma of the prostate. [546] In a recent review of 826 favorably selected cases managed with conservative

therapy, metastatic disease had developed in 19% with grade 1 tumors, 42% with grade 2 and 74% with grade 3 at ten years; therefore, if less than 20% of men present with grade 1 disease, then it is recognized that most prostate cancers are a threat to the life of a man who is going to live longer than ten years.[547] Because of improvements in evaluating the clinical stage, grade, PSA and reduction in the morbidity of radical prostatectomy, some men with even the most aggressive tumors can be treated by surgery if their pelvic lymph nodes are negative.[548] One such study demonstrated that men with a Gleason score of 8 to 10 on needle biopsies and clinically localized disease of T1c, T2a, T2b, T2c, and T3a, had radical prostatectomies with 43% of a selected subset of men with negative lymph nodes having an undetectable PSA at five years and 45% with organ confined disease having an undetectable five year PSA. Therefore, the study concluded that with proper evaluation, some men with even the most aggressive tumors can be 'cured' by surgery if their pelvic lymph nodes are negative.[549] Even proponents of a conservative approach to CaP agree that high grade disease will metastasize and kill.[550] However, it has been shown that high-grade disease is not necessarily high-volume disease as demonstrated in current screening programs which are identifying patients with smaller volume disease.[551] It is therefore possible to identify subsets of aggressive carcinomas that may be curable.[552] PSA screening programs are making it possible to identify men with lower-grade disease who may be on the threshold of progression. The usage of the word 'cure' is tentative at best; however, the overall summary of the studies suggests that prostate cancer is

a very complicated disease, but advances in the management of the disease have produced exciting results that are reducing mortality. The pivotal point is the use of PSA screening which identifies the disease at the earliest possible stage that gives a man the best chance of cure or increased survival that has improved morbidity over the metastatic progress of undetected CaP.

The goal of prostate screening is to detect CaP in asymptomatic men where the cancer is in the earliest stage possible to ensure a cure. The question of insignificant and significant is controversial. Studies confirm that the majority of non-palpable prostate cancers (stage T1c) are biologically significant.[553] It has been suggested that a Gleason score of 4 or greater predicts T1c stage tumor, but a Gleason score of less than 4 can not be safely eliminated; therefore, T1c tumors warrant therapeutic consideration.[554] The parameters of core length, Gleason grade, PSA and PSAD used together have contributed to fewer significant CaP being missed. There are four categories of non-palpable tumors (Epstein et al[555]):

1. Insignificant: Low grade, small volume less than 0.2 cm^3.
2. Minimal: Volume of 0.2 - 0.5 cm^3.
3. Moderate: Greater than 0.5 cm^3 volume but a low risk of progression.
4. Advanced: High probability of not being cured by radical prostatectomy.

A study of 257 patients treated by radical prostatectomies reported that impalpable tumors should not be regarded as insignificant based on pathological analysis.[556] A five year survival rate of 84% in the T1c stage was similar to the clinical stages T1a to T2a groups, but significantly better than that in the T2b/c group.[557] Another

article by Brendler reviewed the clinical and pathologic characteristics of non-palpable CaP (stage T1c) reported in five studies which revealed that T1c tumors more closely resemble palpable stage T2 cancers than incidental prostate cancers detected in cystoprostatectomy specimens removed because of bladder cancer.[558] The mean tumor volume of the T1c tumors (2.0 ml) is about 50 times greater than incidental cystoprostatectomy specimens (0.04 ml).[559] The studies indicated that 30% to 50% of T1c tumors had penetrated the prostatic capsule, 20% to 30% demonstrated positive surgical margins and 5% to 10% had seminal vesicle invasion and/or positive pelvic lymph nodes.[560] The studies further indicated that only 20 -25% of T1c tumors have a volume less than 0.5 ml which is considered by some to be insignificant;[561] although, more recent studies as described earlier suggest the cutoff value should be lowered to 0.25 ml. Some researchers postulate that CaP can be considered insignificant with a tumor volume less than 0.5 cc and no foci more undifferentiated than Gleason's grade 2.[562] Possible explanations for the non-palpability of T1c tumors include tumor location in the central and/or anterior zones of the prostate and increased gland volume due to BPH.[563] The data indicate that most T1c tumors are significant cancers with a volume greater than 0.5 ml that warrant aggressive treatment in accordance with the age and comorbities of the individual patient.[564] It is evident that T1c represents a wide spectrum of disease; however, studies reveal that most PSA detected cancers are clinically important and do not resemble the so called 'autopsy' cancers.[565] In men with stage T1c disease and a PSA of 10.0 ng/ml or less preoperatively, there was a greater chance of organ confined disease than in patients with a higher PSA.[566] Cases of T1c detected in a PSA based screening program had a lower median PSA

of 5.8 ng/ml compared to case detection of 10.0 ng/ml, a 59% organ-confined disease compared to 51% and a lower mean tumor volume of 1.9 cc compared to 4.0 cc.[567] Treatment of T1c tumors while they are small and organ-confined intuitively appears to be an effective strategy in CaP management.[568] Appropriate screening would appear to identify those who have a life expectancy of at least ten years or more as likely to have a surgically curable tumor.[569]

The high incidence of CaP makes the disease an important target for cancer control measures. In a study reviewing the conformity among urologists and primary care physicians, there were some differences noted.[570] The urologists believed that PSA was the single best tool which reflects the opinion expressed in current literature; therefore, the urologists used PSA as a screening tool significantly more often than the primary care physicians.[571] The urologists ceased screening more often than primary care physicians, usually for patients aged 75 to 80 years or if their life expectancy was less than ten years; again, reflecting the support of the literature.[572] According to a study by Aprikian et al published in 1994, males under 50 years of age account for 1% of all patients with CaP, but they present with similar symptomatology, histologic grade and disease stage as the older population.[573] He further concludes that patients with disease confined to the prostate have a relatively good disease-specific survival, but remain at risk for death even fifteen years after diagnosis.[574]

Although there is considerable debate regarding CaP screening, advocates

recommend that five criteria must be satisfied [575] to justify the validity of a screening program. The following brief summary confirms that the five criteria have been satisfied, thereby, justifying the validity of prostate screening programs.

1) Prostate Cancer Is A Significant Health Burden

Prostate cancer is the most frequently diagnosed cancer in men and the second leading cause of cancer deaths, which by volume alone, the disease is a significant health care burden. In addition, CaP can be aggressive, strike men in their 50's, cause prolonged suffering and disability associated with metastatic spread and will eventually kill, especially when detected at advanced stages.[576] Mortality rates have increased over time.[577] A 1995 published article by DeAntoni indicated that since 1986 there has been a 24% increase in the incidence of CaP despite a declining rate of TURP, but the increase had been attributed to improved diagnostic tools, PSA, TRUS and biopsy.[578] In 1984 in the United States, an analysis of PSA was included in the diagnostic work-up of only 6% of newly diagnosed prostate cancer patients compared with 68% in 1990.[579] PSA can be linked to the marked increase in early detection since 1989 whereby this trend was well established before the American Cancer Society, the American College of Radiology and the American Urology Association recognized the efficacy of PSA.[580] The value of PSA as a screening tool that fulfilled nearly all the criteria of screening programs was recognized as early as 1994 by Littrup as an investigator for the American Cancer Society National Prostate Cancer Detection Project.[581] He concluded that the

concerns about incomplete natural history, progression rates and the need for improved prognostic factors to identify patients for either observation or aggressive therapy were valid, but probably overstated compared with the implications of other social and public health issues caused by prostate cancer. In 1995 in the United States, 110 men were estimated to die of CaP every day;[582] however, as the American Cancer Society had plotted a continuing rise in CaP mortality, the five year survival rates were also improving. In 1998, one in five American men and one in nine Canadian men are expected to be affected by prostate cancer. The decrease in the number of new cases of metastatic CaP has been shown in the Utah Cancer registry and other local registries that are part of the SEER program.[583] As a result, the USA is currently seeing a decline in the prostate cancer mortality rates;[584] thus, in the United States relatively aggressive screening for CaP is a common and widespread practice.[585] Because the ratio of mortality to incidence is not decreasing in Canada, the increased incidence is not a result of frequent diagnosis of incidental stages of CaP. The increasing incidence and mortality rates are reality. Furthermore, once CaP reaches an advanced stage, there is no effective therapy,[586] and most prostate cancers metastasize and become incurable before they are found without screening.[587] Therefore, it can be safely concluded that CaP is a significant health burden causing a considerable number of new cases, deaths and premature loss of life each year. The cost of metastatic disease is enormous in terms of human suffering and the debilitating death that ensues for both the male patient and the associated impact on his nuclear/extended family.

2) Screening Can Identify Localized Prostate Cancer

Prostate cancer has an asymptomatic, non-metastatic period that is detectable to a certain degree by screening.[588] There is growing evidence that PSA when used in combination with DRE and other diagnostic aids can detect clinically significant disease during the asymptomatic stage and that these modalities are available at a reasonable cost and with little inconvenience or discomfort to the male patient. Asymptomatic men who are screened with DRE and PSA are diagnosed at an earlier stage; in addition, survival is increased for men who are diagnosed in early-stage over symptomatic men who are diagnosed.[589] Because lead-time bias and length-bias are a reality, randomized clinical trials are needed. However, it is recognized that even small tumors will progress to metastatic disease if the man lives long enough and it has been established that most PSA detected cancers can be expected to progress by their volume and histological grade.[590] Methods for detection of CaP have improved, especially with the advent of PSA transformations that improve the sensitivity of total PSA. Prostate cancer can only be cured if diagnosed in a localized confined state. Early diagnosis and treatment is the only available approach that might be certain to decrease CaP mortality.[591] PSA is an effective screening tool since biopsies reveal cancer in about a third of the men with elevated PSA levels; plus, PSA screening detects many tumors that would be missed by DRE.[592] Therefore, both PSA and DRE are recommended in screening programs. Prostate cancers detected by PSA screening are almost always larger and more aggressive than the indolent or insignificant tumors found incidentally or

at autopsy. PSA frequently detects CaP at an early, localized stage whereby there is a 99% cure rate. Before PSA testing was introduced, two thirds of diagnosed prostate cancer had already spread beyond the prostate, and thus, the cancer was essentially incurable.[593] Many men were faced with hormone therapy or surgical removal of the testis which rendered them impotent and plagued with side effects. A 1995 article by Denis stated that metastatic CaP is incurable with a median time to progression of 18 months and median survival of only 24 to 36 months depending on the prognostic factors.[594] Recent advances in palliative care are improving the length of survival; however, the goal is always to prevent metastatic spread. Detecting CaP in the localized stage is the only hope of cure such that radical prostatectomy and radiotherapy in the treatment of men with localized CaP has been accepted as state of the art treatment by the National Cancer Institute consensus development conference.[595] Both methods have continued to improve and in 1995, median survival of men with T2 disease is greater than 15 years.[596] Since CaP can be detected at a localized stage and treated surgically, nearly two thirds of CaP detected in screening programs can be eradicated.[597] In 1993 with the use of PSA screening, 58% of all newly diagnosed CaP cases were localized in comparison to only 10% prior to PSA screening.[598]

3) Prostate Screening Tests Have Acceptable Performance

The articles cited have identified that PSA has an acceptable performance that is potentiated with the use of DRE, PSA transformations and TRUS guided biopsies.

The PPV of digital rectal examinations used in isolation is estimated to be only 20% to 25%; therefore, the best case scenario is that only one in four men with a suspicious DRE will be diagnosed with prostate cancer via biopsy. PSA is estimated to have a sensitivity of 68% to 80% and a specificity of 49% to 90%;[599] therefore, when used in combination with DRE, PSA has a relatively high sensitivity and specificity for detection of prostate cancers. Studies have reported that PSA screening detected pathologically organ-confined CaP in 63% to 71% of the men tested; other studies have stated that PSA correctly identified 87% of all aggressive cancer. Studies confirm that PSA has a relatively high sensitivity and specificity for detection of aggressive prostate cancers arising within a four year period of a single PSA measurement. Using PSA transformations, such as PSAD, PSAV, FTPSA and age-specific reference range PSA, has increased the sensitivity of PSA to levels exceeding 90%. Although PSA lacks specificity, it does stratify men into a high risk group of having prostate cancer that requires additional diagnostic testing. Further studies are required, but randomized treatment studies in prostate cancer are difficult to conduct.[600] The reason is that it is ethically and morally wrong to deny men effective treatment to obtain statistics, and thus, the results of such studies are not available. In screening trials, approximately 70% of prostate cancers are organ-confined, whereas in unscreened populations, only 30% are organ confined. With an anticipated 'cure' rate of 99% for organ confined cancers, it is evident that the tests have acceptable performance and should be available to men as a method of promoting individual responsibility for health promotion and well-being health

behavior. The improved detection of prostate cancer through diagnostic tools and heightened public awareness are changing the dynamics of the disease.[601] The prevalence of advanced disease is falling and more knowledge is accumulating on the identification of clinically significant disease.[602] PSA is currently the best available tumor marker for any human malignancy,[603] and therefore, serum PSA determinations should be a mandatory part of the urological examination for prostate cancer. Prostate cancer is important to society and metastatic prostate cancer is a devastating disease that extracts a substantial toll and accounts for substantial costs in the medical system.[604] PSA is currently the best available tool for prostate cancer screening.

4) The Potential for 'Cure' is Greater Among Men with Screen-Detected Prostate Cancer

As indicated, there is a 99% cure rate for localized prostate cancer that is truly confined to the prostate. Therefore, prostate cancer must be detected and diagnosed before it extends beyond the prostate gland. Studies from 1995 reveal a 65% ten year survival rate for localized prostate cancer, while more recent studies from the Mayo clinic demonstrated 90% of patients survived ten years or more. There is growing evidence in the United States that PSA screening has decreased mortality rates by 6.2% in the five to six years period since PSA screening was implemented. Further studies from the Mayo Clinic suggest that 84% of radical prostatectomy patients with grade 2 prostate cancer were metastasis free after ten years compared

to only 58% of the conservative management patients. CaP is diagnosed four to five years earlier with PSA screening which provides a window of opportunity to cure these cancers. Survival has an inverse relationship with the stage of cancer at the time of detection; therefore, the earlier the detection, the greater the chance of diagnosing localized cancers. Men with prostate cancers detected at a distant stage or when the cancer has metastasized only have a five year survival rate of 30%. The combination of DRE, serum PSA, and TRUS has increased the rate of cancer detection by 70% and doubled the detection rate of organ-confined CaP, many of which are non-palpable. Recent statistics from the ACS indicate that the death rate from CaP is declining in the United States despite the aging of the male population, presumably due to PSA based screening. In addition, PSA screening is reducing the number of men diagnosed with CaP who already have metastatic disease. PSA represents the most effective and valuable tool to detect early CaP and has been established as substantially increasing the detection rate and percentage of organ confined CaP. PSA is revolutionizing the management of prostate diseases.

5) Men with Screen-Detected Prostate Cancer Have Improved Health Outcomes Compared with Men Who Are Not Screened

The systematic overview of the current literature as presented advocates PSA screening as a means of addressing prostate cancer. Prostate cancer does kill and the only chance of survival and prevention of metastatic disease is the detection of clinically significant prostate cancer confined to the gland. Mortality rates from

prostate cancer are declining in the United States by almost 12% in Caucasian men and less than 7% in African Americans. By comparison, the Canadian rates continue to escalate while the overall mortality rate in the United States for prostate cancer is declining. The Mayo Clinic has reported that PSA testing has increased the detection of localized cancers from 55% in 1987 to 74% in 1995. Researchers are speculating that this will translate into improved long-term survival. The survival rate of men with prostate cancer in the United States has risen from 50% to 87% over the last thirty years. Other studies have reported that the overall five year survival rates for localized CaP has increased from 77% prior to PSA screening to 92% since the inception of PSA. Because early stage CaP is a silent killer that causes no symptoms, PSA screening is so important as a means of early detection. Based on the encouraging results, the American Urological Association and American Cancer Society have recommended PSA screening. Dr. Labrie, Laval University, presented exciting results in May 1998, that PSA testing could prevent 27,000 of the 39,000 prostate cancer deaths in the United States each year.[605] Dr. Labrie found over an eight year period that PSA testing reduced deaths from CaP by 69% because of early detection; in addition, Labrie predicted that if men started PSA screening at age 50 years, PSA could eliminate the development of CaP that reaches the deadly metastatic stage.[606] It is essential that what has been learned from trials and studies should be applied to asymptomatic men and health promotion programs. The evidence from the literature strongly supports that men with screen-detected prostate cancer have an improved health outcome compared to men who are not screened.

The success in the United States with declining mortality rates and the release of Labrie's Canadian study strongly suggest that PSA screening is an effective vehicle to address prostate cancer. The systematic overview of published articles satisfies the five criteria that are essential components of screening programs. A cost-effective analysis is beyond the scope of this paper, but it is a reasonable assumption that metastatic disease is more expensive than 'curable' localized prostate cancer. Therefore, PSA screening for prostate cancer is feasible and viable.

2. ASSUMPTIONS and LIMITATIONS

The abundance of literature and the broad scope of the debate surrounding the concept of prostate cancer screening necessitated boundaries be established to clarify and condense the purpose of the research study into a manageable format. The assumption is that early detection of cancer decreases the annual death rate. This is substantiated by a 30% increase in cancer cases in the last decade due to better screening and earlier detection, but fewer Canadians are dying of the disease.[607] By comparison, the projected volume of prostate cancer cases have more than doubled in the last decade (1987 actual cases = 9,263; 1997 estimated cases = 19,800), while the projected volume of deaths attributed to prostate cancer has also increased by 50% (1987 actual deaths = 2,847 ; 1997 estimated deaths = 4,100).[608]

The assumption is that the concepts of the theory, that early detection and

treatment of CaP substantially lowers cause-specific mortality, are concrete: 1) that early detection identifies men with organ confined CaP that is potentially curable, 2) intervention or treatment of cancer identifies men with asymptomatic or early stage CaP by providing appropriate treatment options, and 3) survival or lower cause-specific mortality identifies treatment options that reduce morbidity and mortality associated with CaP.

Limitations of the study have been the inability to access pertinent PSA data essential to fulfill the extension of the research project which was to demonstrate a direct correlation between PSA screening and lower mortality rates through analysis of Canadian cancer statistics. However, the lack of essential data or incomplete data bases, which is beyond the control of the researcher, can be identified as an outcome of the study and a suggestion for future research or justification for the collection of primary data. The reader is also reminded that literature reviews are subject to publication bias with only positive or palpable studies allowed publication.

3. RECOMMENDATION FOR FUTURE STUDIES

The immense scope of prostate cancer and the conundrum surrounding PSA screening necessitated a systematic overview of the existing literature. Synthesis of the material and exploratory and descriptive research allowed flexibility, but fulfilled the purpose of the study. However, the following are suggestions for

further research studies:

➢ Cost-Benefit analysis of PSA based screening where the direct and indirect costing compares PSA based screening, detection of treatable localized prostate cancer, locally advanced prostate cancers and metastatic prostate cancers.

➢ A quantitative study of PSA data bases on a provincial level with the intent to conduct interprovincial comparisons that correlates PSA based screening with mortality rates. Design should focus on a cause and effect relationship.

➢ Draft a business proposal for government on the feasibility and viability of PSA based screening programs. Inclusion of qualitative research identifying interventions essential to alleviate symptoms and pain control measures of advanced metastatic prostate cancer patients.

➢ Systematic overview, synthesis and quantitative study of prostate cancer treatment modalities with interprovincial comparisons of survival rates.

4. STUDY CONCLUSIONS

The objective of this study was fulfilled:

1) the significance of prostate cancer was extensively explored and concluded that prostate cancer has both an individual and societal impact.

2) prostate cancer is a significant health care burden with considerable economic implications, in addition, to immeasurable human suffering.

3) the issue of PSA based screening and early detection of prostate cancer

was explored extensively and covered screening tools, in depth coverage of the prostate gland including anatomy and physiology, etiology, symptoms, cancer of the prostate prevention, treatment modalities and screening overview. The study concluded that PSA based screening is viable and feasible.

➢ Secondary data published by Health Canada and the National Cancer Institute of Canada were analyzed with a focus on the incidence rates and mortality rates of prostate cancer with particular attention to interprovincial comparisons of five provinces. It is prudent and efficient to analyze secondary data before generating primary data, especially since Health Canada publishes the data to assist in policy formation. The results of the data analysis were only assumptions and possible suggestions since the data was estimated; plus, the pertinent PSA data bases essential to construct a cause and effect relationship were lacking.

The intent of the project was fulfilled which was to generate explanations derived from a systematic overview of the literature which promoted the feasibility of prostate screening and early detection of prostate cancer. Numerous studies were cited that substantiated prostate screening and confirmed that early detection produced longer survival and decreased the morbidity of metastatic disease.

The purpose of the study was satisfied which was a systematic overview of the literature pertaining to cancer of the prostate screening, early detection rationale and the significance of prostate cancer. The research design provided the

researcher with the opportunity to refine critiquing skills, amalgamate and synthesize an abundance of material and present a logically constructed format with visual convenience of graphic presentations to facilitate the ease of reading the study. Extension of computer skills were required to complete an in depth computerized search; plus, the ability to access information on the Internet and link sites. Computer skills were expanded as a result of the project which was viewed by the researcher to be an important benefit of the project.

The theory and conceptual framework were successful in providing a format that maintained control of the large amount of material and provided focus directed at an overview of literature to give the reader an understanding of prostate cancer screening and why a conundrum continues to exist despite a decade of clinical accessibility to PSA testing.

The research questions maintained focus directed at retaining a manageable format for the abundance of literature. The literature provided ample studies that confirmed that early detection of prostate cancer with appropriate treatment does indeed improve health outcomes compared to men who are not screened. Unfortunately, the lack of PSA volume data and the inability to access ordering practices surrounding PSA testing within the provinces prevented the fulfillment of the second research question. However, analysis of the secondary data published by Health Canada and data presented in the literature did draw preliminary

conclusions that there is reason to strongly suspect that early detection with PSA screening does reduce mortality rates while increased incidence rates in the initial phases are indicative of improved screening methods. The current literature certainly supported that treatment modalities have improved with reduced complication rates and reduced patient morbidity.

The outcome of the study did demonstrate that the effectiveness of earlier detection, with PSA testing, DRE and the diagnostic aide of TRUS is being attributed to decreasing prostate cancer mortality rates in the United States. The literature synthesis strongly supports the notion that early detection of prostate cancer does save lives which is congruent with the theory that early detection and treatment of prostate cancer substantially lowers cause-specific mortality. Although clinical studies of long term results of fifteen years will not be available until after the turn of the century, studies of less than ten years, such as Labrie's eight year Canadian study are both encouraging and promising that earlier detection with PSA is reducing prostate cancer deaths.

5. SUMMARY

Metastatic prostate cancer can not be cured. The goal of prostate cancer management is to detect the disease in the localized confined state that has the potential to be cured with appropriate treatment. A systematic overview of the literature explored the significance of prostate cancer and concluded that prostate

cancer is a significant health burden. Secondary data published by Health Canada was analyzed with a focus on mortality rates and incidence rates of prostate cancer with interprovincial comparisons of five selected provinces. The analysis suggested assumptions based on projected figures.

One of the current issues in health care is the conundrum surrounding PSA based prostate screening. Because of the abundance of literature, this study identified published articles which confirmed that prostate cancer screening satisfies screening criteria and supports early detection rationale. The literature provided ample studies that confirmed that early detection of prostate cancer with appropriate treatment does improve health outcomes compared to men who are not screened. Further studies are suggested to provide an expansion of issues and generate primary data pertinent to PSA based prostate cancer screening.

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APPENDIX A

DEFINITIONS

Ablation: Hormonal ablation means the use of hormonal techniques to reduce the spread of CaP cells.

Adenocarcinoma: A form of cancer that develops from a malignant abnormality in the cells lining a glandular organ such as the prostate; almost all CaP is adenocarcinomas.

Adjuvant: An additional treatment used to increase the effectiveness of the primary therapy; radiation therapy and hormonal therapy are often used as adjuvant treatment following a radical prostatectomy.

Age- Standardization: Modified to take account of the age of a group of individuals; for example, CaP survival data and average normal PSA values can be adjusted according to the ages of groups of men.

Analog: A synthetic chemical or pharmaceutical that behaves like a normal chemical in the body, eg. LHRH.

Androgen: A hormone which is responsible for male characteristics and the development and function of male sexual organs eg. Testosterone, produced mainly by the testicles but also in the cortex of the adrenal glands.

Anterior: The front or anterior of the prostate is the part that faces forward.

Antiandrogen: A compound which blocks or otherwise interferes with the normal action of androgens at cellular receptor sites (usually synthetic pharmaceutical).

Apex: The tip or bottom of the prostate, the part farthest away from the bladder.

Asymptomatic: Having no recognizable symptoms.

Base: The base of the prostate is the wide part at the top of the prostate closest to the bladder.

BPH: Benign Prostatic Hypertrophy - increase in the size of cells rather than growth of more cells.

Biopsy: sampling of tissue in order to check for abnormalities such as cancer. Usually carried out under ultrasound guidance using a biopsy gun.

Bone Scan: Uses radiolabeled agent to identify abnormal growths within or attached to bone. In CaP, identify bony metastasis which are definitive for cancer which has escaped the prostate, appear as ' hot spots' on film.

Brachytherapy; A form of radiation therapy in which radioactive seeds which emit radiation are implanted in order to kill surrounding tissue.

Capsule: The fibrous tissue which acts as an outer lining of the prostate.

Castration: The surgical of chemical techniques to eliminate testosterone produced by the testes.

Chemoprevention: The use of a pharmaceutical or other substance to prevent the development of cancer.

Chemotherapy; The use of pharmaceutical or other chemical to kill cancer cells, usually kills not only cancer cells but also other cells in the body,

Combined Hormonal Therapy: The use of more than one hormone in therapy, especially the use of LHRH analogs to block the production of testosterone by the

testes, plus antiandrogens, to compete with DHT for cell sites thereby depriving cancer cells of DHT needed for growth.

Conformational Therapy: The use of careful planning and delivery techniques designed to focus radiation on the areas of the prostate and surrounding tissue which need treatment and protect areas which do not need treatment; three-dimensional conformational therapy is a more sophisticated form of this method.

Cryosurgery: The use of liquid nitrogen probes to freeze the prostate tissue and kill the tissue. Guided by ultrasound.

Dihydrotestosterone (DHT): 5 alpha-dihydrotestosterone - male hormone which is most active in the prostate made when an enzyme (5 alpha reductase) in the prostate stimulates the transformation of testosterone to DHT.

Differentiation: the use of the differences between prostate cancer cells when seen under the microscope as a method to grade the severity of disease.

Doubling Time: The time it takes a particular focus of cancer to double in size.

Ejaculatory Ducts: The tubular passages through which semen reaches the prostatic urethra during orgasm.

External Radiation Therapy (External Beam): A form of radiation in which the radiation is delivered by a machine pointed at the area to be radiated.

False Negative: Erroneous negative test result.

False Positive: A positive test mistakenly identifying a cancer that does not exist.

Finasteride: (Proscar): An inhibitor of the enzyme 5 alpha-reductase that stimulates the conversion of testosterone to DHT, used to treat BPH.

Gleason: Name of the physician who developed the Gleason grading system commonly used to grade CaP. Classifies the cellular differentiation of cancerous tissues.

Grade: A means of describing the potential degree of severity of a cancer based on the appearance of cancer cells under a microscope.

Hormone Therapy: The use of hormones, and analogs to treat advanced CaP either on their won or in combination with other hormones. Because CaP is dependent on male hormones to grow hormonal therapy can be an effective means of alleviating symptoms and retarding the development of the disease.

Imaging: A technique allowing a physician to see something which would not normally be visible.

Impotence: The inability to have or to maintain an erection.

Incidental: Insignificant or irrelevant; also known as latent as a form of CaP which is of no clinical significance to the patient.

Localized: Restricted to a well defined area.

MRI: Magnetic Resonance Imaging: The use of magnetic resonance with atoms in body tissue to produce distinct cross-sectional and even three-dimensional images of internal organs. Primarily used in staging biopsy-proven CaP.

Metastasis: secondary tumor formed as a result of a cancer cell or cells from the primary tumor site traveling through the body to a new site and then growing there.

Morbidity: Unhealthy consequences and complications resulting from treatment.

Nadir: The lowest point of a series of PSA values.

Neoadjuvant: Added before - hormonal therapy given prior to another form of treatment such as a radical prostatectomy.

Nerve Sparing: Term use to describe a type of prostatectomy in which the surgeon saves the nerves that affect sexual and related functions.

Overstaging: The assignment of an overly high clinical stage at initial diagnosis because of the difficulty of assessing the available information with accuracy.

Palliative: Designed to relieve a particular problem without necessarily solving it.

Posterior: The rear or posterior of the prostate is the part of the prostate that faces a man's back.

Partin Tables: Tables that use PSA, Gleason score, and clinical stage to predict the likelihood of organ-confinement, and capsule, seminal vesicle, and lymph node CaP involvement.

PIN: Believed to be precursor of CaP, pathologically identifiable condition.

Randomized: The process of assigning patients to different forms of treatment in a research study in a random manner.

Sensitivity: The probability that a diagnostic test can correctly identify the presence of CaP.

Sextant: A biopsy that takes six samples.

Specificity: The probability that a diagnostic test can correctly identify the absence of CaP assuming the proper test had been conducted.

Stage: A term used to define the size and physical extent of a cancer.

Stent: Tube used to drain fluids.

Transition: The transition zone of the prostate is the area of the prostate closest to the urethra and has features which distinguish it from the much larger peripheral zone.

TURP: Transurethral resection of the prostate - a surgical procedure to remove tissue obstructing the urethra.

Understaging: the assignment of an overly low clinical stage at initial diagnosis because of the difficulty of assessing the available information with accuracy.

Zone: Part or area of an organ.

NOTE: Glossary of CaP related terms taken from the Internet

http://ratt;er.cameron.edu/prostate/ed-pip/glossary.html

APPENDIX B

STAGING, GRADING , PARTIN COEFFICIENT TABLES

STAGING: The process of assigning a stage to a particular cancer. It is used to help determine appropriate therapy. There are two staging methods; Jewett-Whitmore staging classification(1956) and the more detailed TNM classification (1992).

STAGE	TNM	JEWETT-WHITMORE
T	Primary tumor	
TX	Primary tumor can not be assessed	
TO	No evidence of primary tumor	
T1	Clinically inapparent tumor- not palpable or visible by imaging	A
T1a	incidental histologic finding in 5% or less of resected tissue	
T1b	Incidental histologic finding in more than 5% of tissue resected.	
T1c	Tumor identified by needle biopsy because of elevated PSA	
T2	Tumor confined within the prostate	B
T2a	Tumor involves half of a lobe or less	
T2b	tumor involves more than half a lobe, but not both lobes.	
T2c	Tumor involves both lobes; extends through prostate capsule.	
T3a	Unilateral extracapsular extension	C
T3b	Bilateral extracapsular extension	

STAGE	TNM	JEWETT-WHITMORE
T3c	Tumor invades the seminal vesicle(s)	
T4	Tumor fixed or invades adjacent structures other than the seminal vesicles.	D
T4a	Tumor invades any of bladder neck, external sphincter or rectum	
T4b	Tumor invades levator muscles and/or is fixed to the pelvic wall.	
NX	regional lymph nodes cannot be assessed	
NO	No metastasis regional lymph nodes	
N1	Metastasis in single node, 2 cm or less	
N2	Metastasis in single node, more than 2 cm but not more than 5 cm or multiple lymph node metastasis none more than 5 cm	
N3	Metastasis in lymph node more than 5 cm in greatest dimension	
MX	Distant metastasis cannot be assessed	
MO	No distant metastasis	
M1	Distant metastasis	
M1a	Non regional lymph nodes	
M1b	Bone	
M1c	Other sites	

GRADE	
GX	Grade cannot be assessed
G1	Well differentiated (slight anaplasia)
G2	Moderately well differentiated (moderate anaplasia)
G3-G4	Poorly differentiated or undifferentiated (marked anaplasia)

Four Partin Tables: Prediction of Probability of Organ-Confined CaP: on the basis of Gleason score, PSA value and clinical stage.

PSA = 0 - 4.0 ng /ml							
Gleason Score	**Stage T1a**	**Stage T1b**	**Stage T1c**	**Stage T2a**	**Stage T2b**	**Stage T2c**	**Stage T3a**
2-4	90	80	89	81	72	77	-
5	82	66	81	68	57	62	40
6	78	61	78	64	52	57	35
7	-	43	63	47	34	38	19
8-10	-	31	52	36	24	27	-

PSA = 4.1 - 10.0 ng/ml							
Gleason Score	**Stage T1a**	**Stage T1b**	**Stage T1c**	**Stage T2a**	**Stage T2b**	**Stage T2c**	**Stage T3a**
2-4	84	70	83	71	61	66	43
5	72	53	71	55	43	49	27
6	67	47	67	51	38	43	23
7	49	29	49	33	22	25	11
8-10	35	18	37	23	14	15	6

PSA = 10.1 - 20.0 ng/ml							
Gleason Score	**Stage T1a**	**Stage T1b**	**Stage T1c**	**Stage T2a**	**Stage T2b**	**Stage T2c**	**Stage T3a**
2-4	76	58	75	60	48	53	-
5	61	40	60	43	32	36	18
6	-	33	55	38	26	31	14
7	33	17	35	22	13	15	6
8-10	-	9	23	14	7	8	3

PSA = > 20 ng/ml							
Gleason Grade	**Stage T1a**	**Stage T1b**	**Stage T1c**	**Stage T2a**	**Stage T2b**	**Stage T2c**	**Stage T3a**
2-4	-	38	58	41	29	-	-
5	-	23	40	26	17	19	8
6	-	17	35	22	13	15	6
7	-	-	18	10	5	6	2
8-10	-	3	10	5	3	3	1

NOTE: Tables extracted from Internet: the Prostate Cancer InfoLink http://comed.com/Prostate/partin/organ-confined.html

APPENDIX C

GUIDELINES

CANADIAN UROLOGICAL ASSOCIATION	AMERICAN UROLOGICAL ASSOCIATION
JUNE 1992	**1995**
CaP is the second most commonly diagnosed cancer in Canadian men and the second most common cause of cancer deaths. The majority of cases present at an advanced stage, thus precluding a chance for cure. Earlier diagnosis will hopefully lead to decreased mortality and morbidity.	Annual DRE and PSA substantially increase the early detection of CaP. These tests are most appropriate for male patients 50 years of age and older and for those 40 or older who are at high risk, including those of African-American descent and those with a family history of CaP. Patients in these age/risk groups should be given the option to participate in screening or early detection programs.
PSA is currently the best single test available for the detection of early CaP. The addition of DRE will further increase the early detection rate.	PSA and DRE are used for the early detection of CaP. The use of prostate ultrasound is best reserved to evaluate those patients who have an abnormal digital rectal examination and/or abnormal PSA levels.
The CUA supports the recommendation that men between the ages of 50 -70 years have an annual PSA and DRE performed. It is in this age group that early CaP will have time to progress and be a cause of death. In men with a family history of CaP beginning at age 40 would be more appropriate.	TRUS can be used as an adjunctive procedure for the diagnosis of prostatic cancer. Prostate ultrasonography serves as a method of determining prostate volume and can enhance the accuracy of prostatic biopsy, particularly in small lesions.
In those with elevated PSA and DRE suspicious for cancer, further investigation should be considered.	
Whether early detection will be beneficial can only be determined by long term eg. 10 year, studies of screened populations. Until such information is available, the current guidelines are based upon data which suggest that benefit will occur.	

APPENDIX D

INTERNATIONAL PROSTATE SYMPTOM SCORE

Score:

0 = not at all
1 = less than 1 time in 5
2= less than half the time
3= About half the time
4= More than half the time
5= Almost always

1. Incomplete emptying: over the past month how often have you had a sensation of not completely emptying your bladder after urinating?

2. Frequency: over the past month how often have you had to urinate more than once in a 2 hour period?

3. Intermittency: over the past month how often have you found you stopped and started again several times when urinating?

4. Urgency: over the past month how often have you found it difficult to postpone urination?

5. Weak Stream: over the past month how often have you had a weak urinary stream?

6. Straining: over the past month how often have you had to push or strain to begin urination?

7. Nighttime urination: over the past month how many times have you usually had to get out of bed in the middle of the night to urinate?

Add responses for total symptom score.
Score:
Mild = 7 or less.
Moderate to Severe = greater than 7

- Minimal to moderate urine retention.
- Moderate to significant urine retention.

Quality of life Due to Urinary Symptoms:
If your urinary condition were to continue for the rest of your life as it is now, how would it make you feel?

0 = delighted
1= pleased
2= mostly satisfied
3=mixed - equally satisfied and dissatisfied
4= Mostly dissatisfied
5= Unhappy
6= Terrible

NOTE: Provided by Manitoba Prostate Cancer Support Group.

APPENDIX E

PROSTATE CANCER PRACTICE GUIDELINES

Stage T1A:

- conservative management.
- life expectancy > 20years; prostatectomy.
- Gleason score> 7: discuss prostatectomy.
- TUR for BPH: PSA > 10 ng/ml persistent: prostatectomy offered.

Primary Definitive Therapy Stage T1b - T2c:

- Radical prostatectomy.
- External Beam Radiation,
- Gleason score > 7: lymph node dissection considered standard.
- Gleason score 6 or <: routine pelvic lymph node dissection not routine.
- Gleason score = 7; Lymph node dissection optional.

High- probability of Organ-confined Disease:

- high probability -
  - life expectancy < 10 years: observation or radiation therapy.
  - Life expectancy 10 - 20 years- observe until symptoms or radiotherapy or prostatectomy.
  - Life expectancy > 20 years: retropubic prostatectomy. Can recommend radiation also.

Moderate Probability of Organ-confined Disease;

-survival < 10years: observation, radiation.

- survival > 10 years: radiation or radical prostatectomy.

Low Probability of Organ-confined Disease:

- survival < 10 years; observation or radiation.
- survival > 10 years: radiation or prostatectomy.

Stage T3a Disease:

-androgen ablation or radiation or combination.

- low-volume disease and a Gleason score < 7 - radical prostatectomy alternative approach.

Stage T3b- 3c or T4, NO Disease:

- androgen ablation or radiation or combination.

Node-positive and Metastatic Disease:

-androgen ablation with or without radiation or observation.

Note: NCCN Guidelines for Practice. This only includes initial diagnosis. Guidelines are also available for recurrent and metastatic CaP. Extracted from the Internet http://www.cancer.med.umich.edu/prostcan/articles/guide.html,

APPENDIX F

PHARMACEUTICALS

Following is a brief list of pharmaceuticals used to treat CaP. The drugs may be used alone or in combined hormonal therapy:

1. **LHRH (luteinizing hormone releasing hormone) agonists**: An initial rise in testosterone levels is rapidly followed by a fall in testosterone concentration to castrate levels.

- Leuprolide acetate (Lupron)

- Goserelin acetate (Zoladex)

2. **Antiandrogens (maximal androgen deprivation)** : Can be used as single agents, but commonly used in conjunction with some form of castration (orchiectomy or LHRH agonist) to provide complete androgen deprivation.

- Bicalutamide (Casodex)

- Nitlutamide (Nilandron)

- Flutamide (Eulexin).

3.**Miscellaneous hormonally active agents**:

- Aminoglutethimide (Cytadren)- used for selected advanced CaP and patients who fail initial hormone therapy. Suppresses synthesis of adrenal androgens.

- Diethylstilbestrol (DES): synthetic analog of estrogen. Lowers testosterone levels.

- Finasteride (Proscar): Used for treatment BPH. Used in clinical trials

to investigate value in CaP and prevention of CaP.

- Ketaconazole (Nizoral): Antifungal treatment; however, blocks androgen synthesis.

- Megestrol acetate (Megace): Late stage CaP treatment; suppresses androgens, antineoplastic agent.

Chemotherapy drugs:

suramin and emcyt

NOTE: Information extracted from: Pharmaceuticals used to Treat Prostate Cancer. (1996). The Prostate Cancer InfoLink. Http://www.comed.com/Prostate/Pharmaceuticals.html , pp. 1 - 9.

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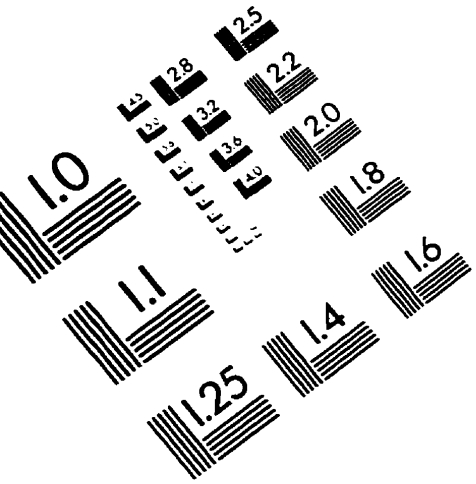

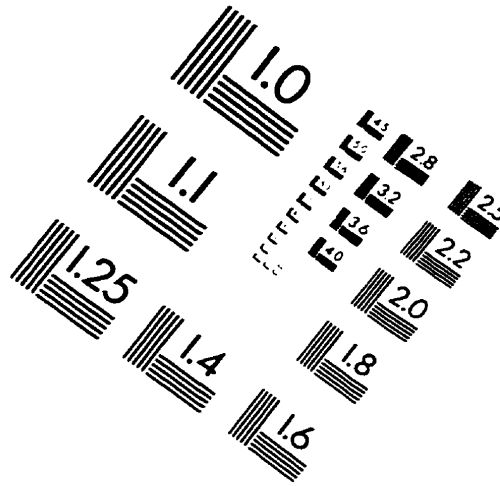

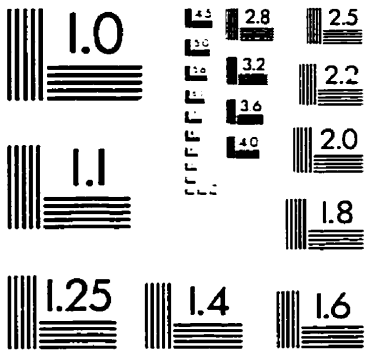

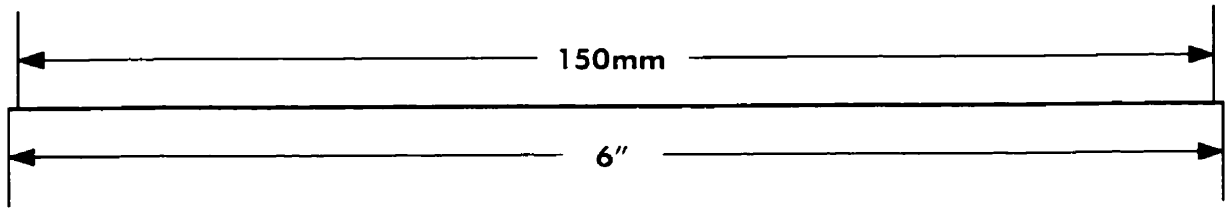

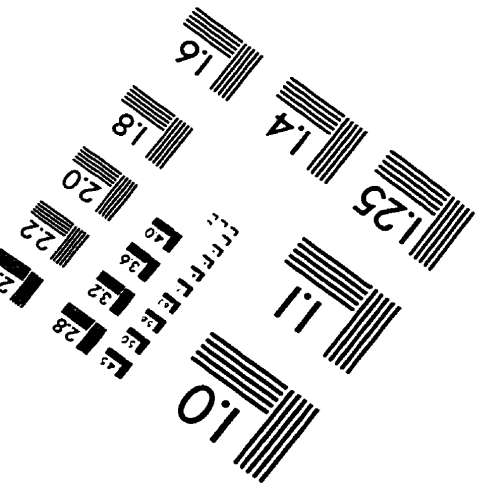

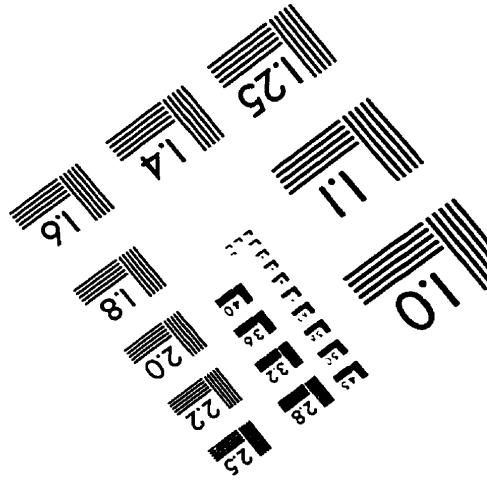

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