Use and knowledge of finasteride in the chemoprevention of prostate cancer:

Trends in prescriptions and a survey of VA primary care physicians and urologists

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Abstract:

Background:

Little is known about how physicians assimilate evidence regarding prostate cancer prevention. Finasteride, a drug studied as a chemopreventive agent for prostate cancer has produced controversial results. The purpose of this research design paper is to provide background and rationale for my proposed project to examine the current knowledge and use of finasteride among primary care physicians and urologists in the Veterans Health Administration (VHA).

Aims:

Specifically, I seek to a) identify trends in finasteride prescriptions in the VHA over time, and determine whether these trends correlate with publication of evidence or guidelines; b) identify trends in alpha-blocker prescriptions in the VHA over time to help determine that proportion of finasteride prescriptions attributable to combined treatment for benign prostatic hyperplasia (BPH); and c) determine the knowledge, and use of finasteride as well as the perceptions, characteristics and contextual factors of those physicians who are in a position to utilize finasteride.

Study Design:

A formal systematic review of the evidence pertaining to several aspects of finasteride use in the prevention of prostate cancer is presented. Thereafter, the first part of my proposed study will involve assessing time trends in prescriptions for finasteride and

alpha-blockers from October 1998 to December 2005 using the VHA Pharmacy Benefits Management (PBM) database. The second part will involve surveying VHA primary care physicians (PCPs) and urologists regarding their use and knowledge of finasteride.

Hypotheses:

I hypothesize that finasteride prescriptions will increase slowly during the late 1990s and early 2000s, but accelerate concomitant with the publication of the Prostate Cancer Prevention Trial (PCPT) and Medical Therapy of Prostate Symptoms (MTOPS) studies. However, prescriptions for alpha-blockers, in particular the selective alpha-blockers, will similarly increase. This would suggest that the overwhelming majority of increased finasteride use is for treatment of BPH rather than chemoprevention. I anticipate this finding will be confirmed in the survey when physicians indicate that they mostly use finasteride to treat BPH.

However, I also hypothesize that knowledge of finasteride main effects, side-effects and influence on prostate parameters will be surprisingly low. I anticipate, more urologists than primary care physicians will be comfortable prescribing finasteride in general, and more urologists will report using finasteride as a prostate cancer chemopreventive agent.

Impact:

Given the potential impact finasteride has on prostate cancer incidence, aggressiveness and screening, the insight gained regarding the current use of finasteride is important. Discovering that many men are currently taking finasteride, but that physicians are not

well informed regarding the influence of finasteride on parameters such as PSA, prostate volume and the potential increased risk of high grade tumors may indicate a need for directed educational interventions for both physicians and patients.

Understanding physician perceptions of the current evidence for finasteride as a chemopreventive agent will help guide future research and tailor guidelines to address the areas of greatest concern or uncertainty. I will gain insight into the different levels of knowledge and perception between PCPs and urologists. Such information could guide future recommendations for when PCPs should refer a patient to a urologist.

Summary:

The uncertainty surrounding use of finasteride to prevent prostate cancer is unlikely to be resolved for several years. This study will provide important information regarding how physicians in the VHA perceive the uncertainty and how these perceptions translate into use of finasteride. The VHA is uniquely positioned to study this problem and the results will influence future research and guideline creation.

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List of Abbreviations

VHA – Veterans Health Administration
PSA – Prostate Specific Antigen
DRE – Digital Rectal Examination
PLCO – Prostate Lung Colorectal and Ovarian Study
ERSPC – European Randomized Study of Screening for Prostate Cancer
NSAIDS – Non-steroidal anti-inflammatory drugs
PCPT – Prostate Cancer Prevention Trial
NPCT – Nutritional Prevention of Cancer Trial
RR – Risk Ratio
OR – Odds Ratio
CI – Confidence Interval
ATBC – Alpha-Tocopherol, Beta-Carotene, Cancer Prevention Trial
SELECT – Selenium and Vitamin E Cancer Prevention Trial
NCI – National Cancer Institute
RCT – Randomized controlled trial
AAM – African American men
REDUCE – Reduction of
COX-2 – Selective cyclooxygenase inhibitor
DHT – Dihydrotestosterone
USPSTF – United States Preventive Services Task Force
BMI – Body Mass Index
ITT – Intention to treat
NNT – Number needed to treat
NNH – Number needed to harm
DSMC – Data Safety Monitoring Committee
BPH – Benign prostatic hyperplasia
MTOPS – Medical Therapy of Prostate Symptoms Study
PLESS – Proscar Longterm Efficacy and Safety Study
TURP – Transurethral Resection of Prostate
ADT – Androgen deprivation therapy
TRUS – Transrectal ultrasound
SEER – Surveillance Epidemiology End Results
QALY – Quality adjusted life-year
WHI – Women's Health Initiative
HRT – Hormone replacement therapy
PBM – Pharmacy Benefits management
VERDICT – Veterans Evidence-Based Research Dissemination Implementation Center
PAID – Personnel and Accounting Integrate Data
FTE – Full-time equivalent

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Introduction

"In health care, invention is hard, but dissemination is even harder."[1] *(Donald Berwick)*

For every new piece of evidence pertaining to topics of public health importance much energy is spent dissecting the results, ascertaining internal and external validity and placing new proof in the context of existing evidence. This cycle of conjecture and refutation that plays out in the literature takes place among academic researchers and thought leaders. These opinions, distilled in editorials, meta-analyses, systematic reviews and clinical practice guidelines, are intended to convey consensus to the community of physicians facing these clinical dilemmas.

Yet little is known about the success of this dissemination. To what degree do physicians access the information, assimilate the information and incorporate the information into practice? Furthermore, many issues in public health do not have a clear-cut answer. Medical or biological uncertainty leads to variations in clinical practice,[2] but we are seldom aware of the specific issues or barriers causing physicians to hesitate in changing their practice.

These issues are particularly evident in the field of prostate cancer prevention. One in six men are destined to be diagnosed with prostate cancer in their lifetime with an estimated 234, 460 cases in the United States alone this year.[3] While the lifetime risk of death due to prostate cancer is much lower (1 in 33), the burden of suffering is considerable for those men diagnosed and facing treatment decisions in the context of uncertain prognosis.[3]

The objective of this project is to understand how physicians assimilate and use evidence regarding prostate cancer chemoprevention. Specifically, we seek to understand the use and knowledge of finasteride in the chemoprevention of prostate cancer among primary care physicians and urologists in the Veterans Health Administration (VHA).

Rationale

Prevention of Prostate Cancer

Fully understanding the dissemination of evidence for finasteride as a chemopreventive agent requires an understanding of the perspective of prostate cancer prevention and particularly chemoprevention.

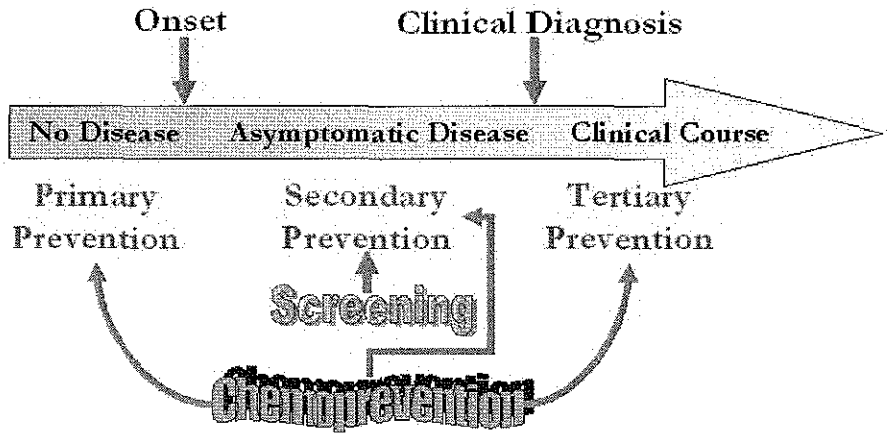
Prevention refers to any act which attempts to reduce the likelihood of bad health outcomes. Preventive behaviors are classified into primary prevention, secondary prevention and tertiary prevention. Primary prevention refers to all activities designed to reduce the incidence of an illness, while the goal of secondary prevention is to detect early disease when it is asymptomatic and when treatment is still effective. Tertiary prevention refers to activities that minimize further deterioration and complications of those who have the disease.

For prostate cancer, several factors, when taken together, suggest that prevention is the optimal strategy to reduce the burden of suffering: a) the high prostate cancer prevalence; b) the current inability of physicians to accurately distinguish those cancers destined for bad outcomes from those destined for an indolent course; c) the morbidity associated with currently available treatments; and d) the lack of sound evidence

demonstrating treatment prolongs quality and quantity of life in the U.S. setting. Every case of prostate cancer prevented is one fewer man who faces the uncertainty of treatment decisions, morbidity and prognosis.

In prostate cancer, preventive strategies refer to the use of screening and chemoprevention. Screening is a form of secondary prevention, while chemoprevention most commonly refers to primary prevention, though it can also act as a secondary or tertiary preventive strategy, as shown in Figure 1.

Figure 1: Prevention strategies to reduce burden of suffering



Screening

Screening is the testing for health problems in the absence of symptoms or signs that would indicate the presence of the disease. The goal is to detect disease early enough such that treatment can eradicate the disease before the quality or quantity of life is affected.

With respect to prostate cancer, screening principally refers to prostate specific antigen (PSA) testing and/or digital rectal examination (DRE). The U.S. Preventive Services Task Force, which periodically reviews the evidence regarding the benefits and

harms of screening, has concluded there is insufficient evidence to recommend for or against routine screening for prostate cancer using PSA or DRE.[4] There is good evidence that screening with PSA can detect cancers at an early stage.[5] However, the question remains whether such early detection translates into improved outcomes.

Screening is marred by several problems. First, the accuracy of the screening tests is suboptimal. The determination of a "normal" PSA value has come under scrutiny. Historically, PSA > 4.0 ng/ml was the chosen cut-off to recommend prostate biopsy. This has yielded sensitivities ranging from 56% to 91%, depending on the age of the patients and whether the study is examining aggressive cancers, low grade cancers, or all cancers.[6-9] PSA is more sensitive in detecting aggressive tumors. Arguments to reduce the cutoff to even as low as 2.5 ng/ml stem from evidence of prevalent cancer at PSA values much lower than 4.0 ng/ml.[10] The clinical importance of cancers detected at these lower PSA values is not known though. DRE is less accurate and has limited reproducibility as compared to PSA.[11] A meta-analysis found that DRE had a sensitivity of 59%.[12]

The second problem with screening is the reference standard, prostate biopsy. Unfortunately, prostate biopsy has a false-negative rate of between 10 to 30% for a first biopsy.[13-16] Thus, a significant proportion of men with a positive screening test will be falsely classified as being free of disease. Finally, once cancer is identified, the current parameters used to prognosticate cannot adequately distinguish those cancers destined to kill from those destined for an indolent course.[17-20]

The serial uncertainty in the process is multiplied and at each stage these uncertainties are anxiety provoking for the patient. Furthermore, screening introduces

physical pain and discomfort if a biopsy is warranted and subsequent treatment is undertaken. Thus, in the absence of clear evidence of benefit, screening cannot be recommended as a national strategy to reduce the burden of suffering from prostate cancer.

The urological community awaits the publication of two large randomized controlled trials examining the efficacy of screening. The Prostate Lung Colorectal and Ovarian (PLCO) cancer screening trial, which is set in the United States, and the European Randomized Study of Screening for Prostate Cancer (ERSPC) have closed to accrual and will likely publish before 2010.[21, 22] Until such time, it is doubtful that sufficient evidence will arise to significantly tip the balance in favor of, or against, screening for prostate cancer.

Chemoprevention of Prostate Cancer

Chemoprevention refers to the use of chemical agents, drugs, or food supplements to prevent disease. The term chemoprophylaxis has identical meaning and is used interchangeably in the literature but will not be used in this paper. As enthusiasm for prostate cancer screening wanes, hope for identifying a useful chemopreventive agent is peaking. Several promising agents exist.

I performed a formal systematic review addressing the evidence pertaining to the most promising chemopreventive agent, finasteride. However, it is important to realize that other agents have similar rationale for use in a primary chemopreventive setting. They include selenium, vitamin E, vitamin D, NSAIDS, soy, lycopene and green tea. A brief review of each of these is presented first.

Selenium

Selenium is an essential trace element found predominantly in grains, fish, meat, poultry, eggs and dairy products.[23] It enters the food chain through plant consumption but is also available in many over-the-counter supplements and multivitamins. Selenium is a constituent of many antioxidant enzymes called selenoproteins.[24] Several lines of evidence exist supporting selenium as having a protective effect against prostate cancer.

In vitro, selenium inhibits proliferation and induces apoptosis in prostate cancer cell lines.[25, 26] Early human case-control and cohort studies, also proved promising.[27, 28]

The strongest evidence in support for selenium comes from The Nutritional Prevention of Cancer Trial (NPCT). This was a randomized controlled trial of 1312 patients with non-melanoma skin cancer, 974 of which were male with a mean age of 64 years. Patients received either oral selenized yeast (200ug/day) or placebo and were interviewed every 6 months to determine the incidence of cancer.[29] All identified cancers were confirmed by review of medical records. No end-of-study prostate biopsy was performed, as prostate cancer was a secondary end-point and was added after the trial had commenced.

While there was no significant impact on the primary end-point, recurrence of basal cell carcinoma or squamous cell carcinoma, selenium reduced the incidence of several cancers which were secondary end-points. The secondary end-points were added to the trial protocol after preliminary data began to compile showing certain benefits in incidence of certain cancers. In the case of prostate cancer, only data after the declaration of prostate cancer incidence as a secondary end-point was reported. With a mean follow-up of 6.5 years, the incidence of prostate cancer was decreased by 63% in the selenium

group (RR 0.37; p=0.002).[30] Though not directly reported in the original study, baseline risk for prostate cancer after randomization was likely slightly higher for the selenium group given that patients had a higher mean age (64.4 vs 63.2) and had a higher percentage of men with baseline PSA > 4.0 ng/ml (10.4% vs 9.0%). This risk reduction held across all strata of baseline PSA levels with the exception of those patients with >10 ng/ml at baseline. However this sub-group likely had indolent cancer at the time of enrolment. A follow-up study to the NPCT reported mean follow-up to 7.45 years. The reduction in incidence of prostate cancer still held (RR 0.51; 0.29-0.87).[31]

With studies that have added secondary end-points mid-trial, caution must be applied to the results. By chance, certain associations will appear in the data. For a prostate cancer to become "incident" the patient needs to be symptomatic in such a way that he seeks urologic care which, in turn results in a biopsy, or he is screened and subsequently referred for biopsy. Given that these men were blinded to treatment and that selenium is not known to affect PSA levels, the only possible explanation is that selenium reduces lower urinary tract symptoms and thus reduces referrals for biopsy in that arm of the study. No such effect has been documented. Without an end-of-study biopsy, or data on the number of referrals for biopsy, it is impossible to know the true effect of selenium on prostate cancer incidence. However, the magnitude of risk reduction is large and cannot be entirely explained by chance or confounding.

Vitamin E

Vitamin E is one of the fat-soluble vitamins and functions as an antioxidant in cell membranes.[32] Alpha-tocopherol is the predominant form in human tissues and is known

to moderate prostate cell growth. In vitro studies have demonstrated that it can induce cell cycle arrest and exhibit antiandrogenic activity similar to bicalutamide, an androgen receptor antagonist.[33, 34]

In human studies, the largest trial to date examining the preventive role of Vitamin E in prostate cancer is the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial (ATBC).[35] This randomized controlled trial of 29,133 male smokers aged 50-69 given either vitamin E, beta-carotene, both or neither evaluated the incidence and mortality of lung cancer as the primary end-point.[36] Prostate cancer incidence and mortality was one of many planned secondary endpoint analyses. Those taking supplemental vitamin E had a significantly lower incidence of prostate cancer (RR 0.66; 95% CI, 0.44-0.94) and lower prostate cancer-specific mortality (RR 0.59; 95% CI 0.35-0.99). Given that this was one of many secondary analyses, there is a possibility that this finding could be due to chance. Furthermore, baseline prostate cancer risk data between groups was not complete, and since randomization was done by geographically defined blocks, there could be underlying risk differences between the groups in this study.

A more recent publication followed the ATBC cohort 6 years after termination of the trial. The apparent effect of alpha-tocopherol on prostate cancer incidence seen during the trial was considerably attenuated and no longer reached statistical significance with longer follow-up: RR 0.88 (95% CI 0.76-1.03).[37] It is possible that vitamin E exerts its anticancer effects at a late stage of carcinogenesis and in a transient fashion. Thus, shortly after stopping the drug, the late stage neoplastic changes progress to malignancies. It is clear that further information is needed to sort out the true effect, if any, of alpha-tocopherol on prostate cancer incidence.

SELECT TRIAL

The cumulative findings of the potential preventive role of both vitamin E and selenium formed the rationale for the large Selenium and Vitamin E Cancer Prevention Trial (SELECT).[38] In particular, in vitro studies demonstrating synergy between vitamin E and selenium in augmenting apoptosis prompted incorporating both nutrients into the study design.[39] This NCI sponsored phase III RCT tests the use of selenium and vitamin E alone, and in combination, in the prevention of prostate cancer. Men were eligible to participate in this two-by-two factorial design trial if they were older than 55 years of age (or 50 for African American men (AAM)), had a negative DRE and a PSA $\leq$4 ng/ml and normal blood pressure. The SELECT trial accrued more than 35,534 men from over 400 sites in the U.S., Canada, and Puerto Rico.[38, 40] Furthermore, it has enrolled 21% minorities, including 15% AAM, which is three fold more than other large prostate cancer prevention trials have accomplished (PCPT: 4% AAM;[41] REDUCE: 2% AAM[42]).

The primary endpoint in the SELECT study is clinical incidence of prostate cancer. No end-of-study biopsies will be performed. Unlike the use of finasteride in the PCPT, no PSA adjustment is needed in SELECT as vitamin E and selenium are not known to have a direct effect on PSA production. This reduces the biases inherent in using incident cancers rather than period prevalent cancers. Secondary endpoints include prostate cancer survival, all cause mortality and the incidence and mortality of other malignancies. Prostate cancer survival may be subject to differential lead time bias if use of selenium and vitamin E promoted the early detection of prostate cancer. However, there is no evidence to support such a bias. The study is powered to detect a 25%

reduction in the incidence of prostate cancer for either selenium or vitamin E. However, it has sufficient power to detect an additional 25% reduction attributable to the combination of selenium and vitamin E. The results of this trial are anticipated in 2013.

Vitamin D

Vitamin D has received interest as a chemopreventive agent for prostate cancer. It is hypothesized that 1,25-dihydroxycholecalciferol ($1,25(OH)_2D_3$), or the active form of vitamin D, plays an important role in inhibition of tumor growth and metastasis.[43] In vitro, exogenous administration of $1,25(OH)_2D_3$ to prostate cancer cells halts proliferation.[44] This hypothesis has been supported, though inconsistently, by several epidemiological studies. These observations were thoroughly reviewed recently,[45] and they include: a) men receiving less sun exposure, such as those living in northern latitudes, have lower levels of vitamin D and a higher mortality rate from prostate cancer; b) prostate cancer occurs more frequently in older men, in whom vitamin D deficiency is more common; c) AAM, whose increased levels of melanin in the skin blocks ultraviolet-induced production of vitamin D, have the highest incidence and mortality from prostate cancer in the world; d) native Japanese men, whose diet is rich in vitamin D, have a low incidence of prostate cancer; and e) dietary intake of calcium-rich products, which suppresses vitamin D levels, are associated with higher risk of prostate cancer.

This latter finding is supported by two large prospective cohort studies. The Cancer Prevention Study II Nutrition Cohort studied 65,321 elderly U.S. men with mean age ranging from 63 to 66 yrs (depending on the tertile of calcium intake) and gathered detailed questionnaire data on diet, medical history and lifestyle at enrolment.[46] Total

calcium intake was associated with a modest increase in prostate cancer risk (RR 1.2; 95% CI 1.0-1.6) adjusted for education, family history of prostate cancer and total energy intake. A dose-response relationship was noted between calcium intake and prostate cancer risk (p=0.02 for trend). The Health Professionals Follow-Up evaluated 47,781 men from 1986 to 1994 and found a stronger association.[47] The highest tertile of calcium consumption compared to the lowest was associated with increased total prostate cancer (RR 1.71; 95% CI 0.94-3.19), advanced prostate cancer (RR 2.97; 95% CI 1.61-5.50) and metastatic prostate cancer (RR 4.57; 95% CI 1.88-11.1).

Taken together, these studies provide some indirect evidence for a protective influence of vitamin D on prostate cancer. However, use of vitamin D anaologs has been limited by their hypercalcemic effects.[48,49] Newer analogs with more specificity are currently being tested and may provide another chemopreventive strategy for prostate cancer.[50]

Other chemopreventive possibilities

Several other chemopreventive strategies have emerged. Cyclooxygenase-2 (COX-2) inhibitors are currently being studied. It is known that prostate cancers express more COX-2 than benign tissue, and that this overexpression is associated with decreased apoptosis,[51] increased angiogenesis,[52] and immunosuppression.[53] Thus, rationale exists for a potential role for COX-2 inhibition in the prevention or inhibition of prostate cancer carcinogenesis. However, epidemiologic studies examining the association between prostate cancer incidence and use of NSAIDS are conflicting.[54]

The role of soy in prostate cancer stemmed from the observation that eastern countries, where soy plays an important role in traditional diets, have lower rates of prostate cancer, while western countries, where soy plays a minimal role in our diets, have higher rates of prostate cancer. A recent case-control study involving 133 prostate cancer cases and 265 age-matched controls from China demonstrated a protective effect associated with soy consumption (OR 0.51; 95% CI 0.28-0.95).[55] In vitro studies have shown that soy and its components and their metabolites inhibit benign and malignant prostatic epithelial cell growth, downregulate androgen-regulated genes, and reduce tumor growth.[56, 57]

Lycopene, found primarily in tomatoes and other red fruits and vegetables, possesses potent antioxidant activity. In vitro, lycopene inhibits growth of benign and malignant prostatic epithelial cells.[58] Yet, epidemiological evidence regarding the association of lycopene consumption and prostate cancer risk is mixed.[59-61]

Finally, green tea has been studied in vitro or in animal models only. Similarly based on the observation that men from Asian countries have lower incidence of prostate cancer and substantially higher consumption of green tea, the polyphenols contained in green tea have been scrutinized. The major constituent has been shown to induce apoptosis and inhibit cell-growth,[62] and in the mouse has been shown to inhibit tumor development and metastasis.[63]

Finasteride: a review of the evidence

Background

The most promising agent and the one that has received the most interest of late is finasteride. Finasteride inhibits the enzyme 5-α-reductase type 2, which is found in two locations in the body: the prostate and genital skin. Here, it catalyzes the conversion of testosterone to dihydrotestosterone (DHT). In serum, DHT concentrations are one-tenth that of testosterone; in prostatic tissue, DHT is several times higher in concentration.[64, 65] Furthermore, it is known that DHT is 8 to 10 times as potent as testosterone. The importance of DHT is seen in a large cohort living in Dominican Republic where the incidence of 5-α-reductase type 2 deficiency is high. The males in that population have only a rudimentary prostate without epithelium, an undetectable PSA and no development of either benign prostatic hyperplasia or prostate cancer.[66]

DHT is thought to be a promoter of the development of prostate cancer, thus reducing the concentrations of DHT within the prostate may reduce the genesis of neoplasia.[67] In vitro, finasteride has been shown to inhibit growth of prostate cells.[68, 69] In vivo, men treated with finasteride for BPH experienced a 50% reduction in PSA and a 20% decrease in gland volume.[70] Finally, physicians, both primary care and urologists, as well as patients have familiarity with finasteride from its role in treating BPH. The safety and side-effect profile is well accepted.[71, 72] Thus, there is good rationale to test whether finasteride may reduce the incidence of prostate cancer.

In this section, a systematic review was conducted to address the evidence pertaining to finasteride in preventing prostate cancer.

Methods

I developed 6 key questions that address the important issues surrounding the use of finasteride as a chemopreventive agent. The overarching question, or Key Question #1, asks: Does daily use of finasteride reduce the incidence of prostate cancer? The target population is average risk men >45 yrs of age with life expectancy > 10yrs.

Though preventive strategies, on the whole, focus on reducing the incidence of bad outcomes such as mortality, I chose this specific question for two reasons. First, as I argued above, the majority of the burden of prostate cancer stems not from mortality but from the psychological and physical side-effects of being diagnosed and treated. Thus, the first and most important step in reducing this burden would be to reduce the incidence of the disease. Second, a systematic review addressing the question of whether finasteride reduces prostate cancer mortality would require an indirect analytic approach and a very involved review that is outside the scope of this masters paper.

The six key questions used in the analysis are listed here:

Key questions:

1) What is the efficacy of finasteride in preventing the incidence of prostate cancer?

2) What harms are associated with using finasteride as a chemopreventive agent for prostate cancer?

3) What is the effect of finasteride on the performance of currently used screening tests (DRE, PSA) or prostate biopsy?

4) What costs are associated with using finasteride in every male patient within the defined population to prevent prostate cancer?

5) Have studies modeled the potential benefits of using finasteride to prevent prostate cancer?

6) What is the cost-effectiveness of using finasteride to prevent prostate cancer?

With the 6 key questions established, I systematically searched MEDLINE, EMBASE, CINAHL and Cochrane databases from January 1988 to September 15, 2002, using the Medical Subject Headings "prostate neoplasms" or "prostate" and combining these terms with predefined terms for each of the key questions to identify English language studies concerning the 6 key questions. Additionally hand searches of review bibliographies were conducted. The complete search strategy is defined below.

The start date was chosen for two reasons. First, the first published article mentioning finasteride use in humans was in 1988 and finasteride was not approved by the FDA until 1992. Second, the PSA era did not begin until this time. Thus, results from prostate cancer epidemiological studies before this era may not apply to cancers seen presently.

The following inclusion criteria were used in identifying appropriate articles: (1) randomized controlled trials (RCTs), secondary analyses of RCTs, case-control studies, and ecologic studies that examined links between using finasteride and reduced prostate cancer incidence; (2) studies that addressed changes in prostate cancer biology, presentation, behavior or the performance of screening tests secondary to finasteride exposure; (3) studies with patient reports about their experience (especially side effects) with taking finasteride; and (4) studies that examined or modeled the costs and benefits of using finasteride to prevent prostate cancer.

Papers pertaining to the following were excluded: papers at the basic science level with non-clinical outcomes, and papers involving men who have already been diagnosed with prostate cancer.

From the list of titles generated by searches of each database, I chose titles that may apply to the key questions. At this stage, I emphasized sensitivity rather than specificity. That is, if in doubt, I included a title. Next, I reviewed the abstracts for the chosen titles and selected all articles that met eligibility criteria. Data from the chosen articles were then abstracted using a standardized form (Appendix 1). In addition to abstracting the setting of the study, the patients involved, the intervention(s) used, measures of exposure and outcome, results and conclusions, I also graded the quality of all included articles according to criteria established by the USPSTF in their review series.[73]

The most sensitive search, which I have termed the *primary search*, combined the key words "prostate neoplasms", "prostate" and "finasteride". Limiting this search to "English language" and "humans" yielded 300 titles. From these 300, 56 were chosen as possibly pertaining to any of the 6 key questions. To ensure that no papers were missed within each key question, additional *secondary searches* were performed combining the terms "prostate neoplasms" and "prostate" in series with key words in table 1 below:

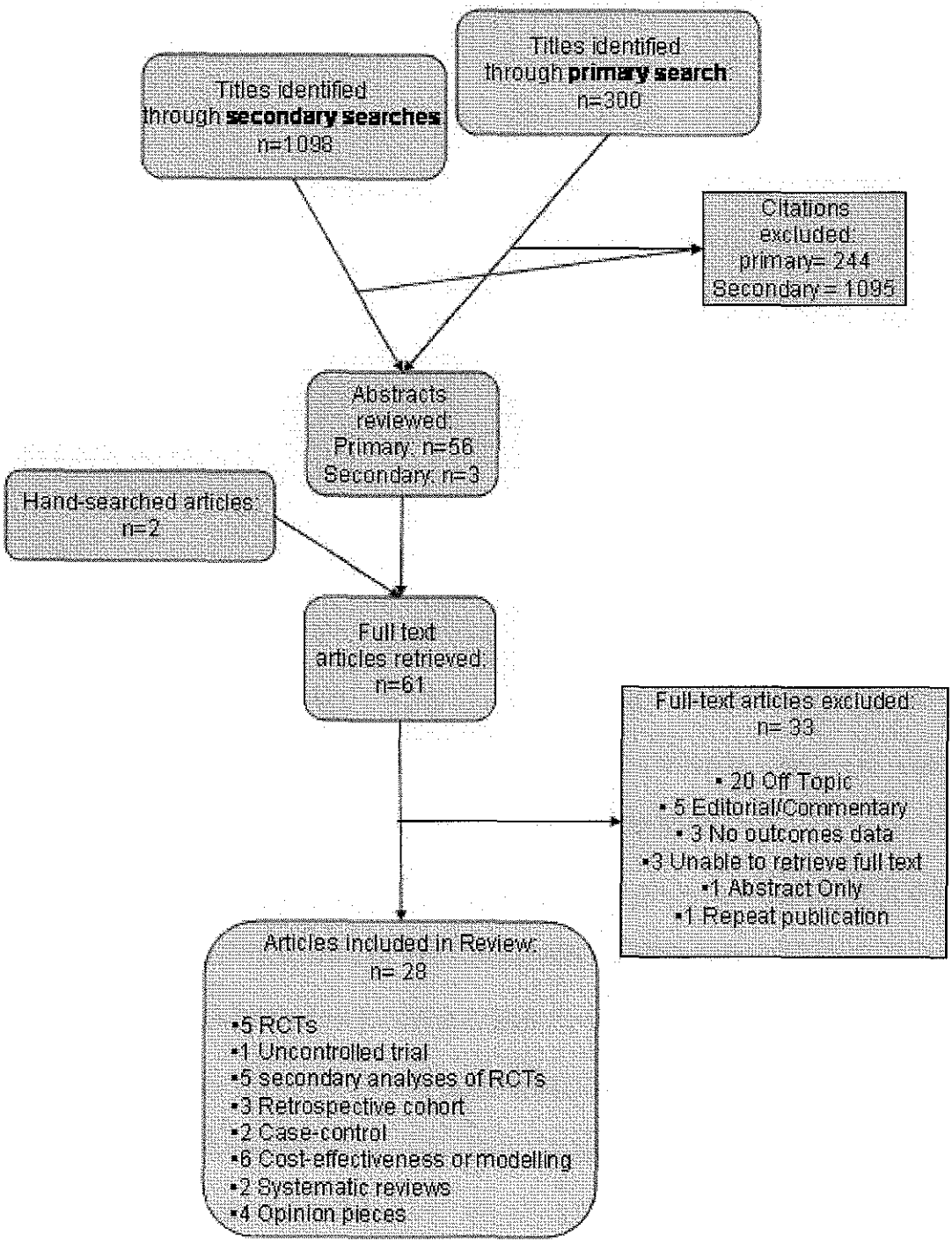
Table 1: MeSH headings used to search specific key questions

Finasteride/adverse effects/*therapeutic use	Cost and cost analysis
Humans	Cost-benefit
Male	Cost-effectiveness
Middle aged	Biopsy
Azasteriods/therapeutic use	Morbidity
Testosterone 5 alpha reductase/*antagonists and inhibitors	Neoplasms, hormone-dependent/prevention & control
Enzyme inhibitors/*therapeutic use	Prostate specific antigen/blood
Antineoplastic agents, hormonal/adverse effects	Prostate/pathology
*therapeutic use	Adenocarcinomoa/*prevention & control

From the secondary searches, 1098 titles were identified however, only 3 more unique titles were identified that met inclusion criteria. This low number is a result of the considerable overlap between the primary search and all of the secondary searches. This illustrates how inclusive the primary search was. Finally, hand-searches of review articles identified before the formal literature search yielded 2 additional unique titles and were included for review.

Figure 2 illustrates the selection procedure for the first and most inclusive search described above.

Figure 2: Results of literature searches



Articles identified as pertaining to any of the 6 key questions were then ear-marked to the appropriate key question. Some papers provided information on more than one key question. Table 2 illustrates the number of articles identified for each key question. Questions 4 to 6, because of their similarity, are grouped together in the table and also during data abstraction.

Table 2: Full-text articles reviewed for each key-question

Key Question	Articles reviewed
1) What is the efficacy of finasteride in preventing the incidence of prostate cancer?	7
2) What harms are associated with using finasteride as a chemopreventive agent for prostate cancer?	6
3) What is the effect of finasteride on the performance of currently used screening tests (DRE, PSA) or prostate biopsy?	11
4) What costs are associated with using finasteride in every male patient within the defined population to prevent prostate cancer? 5) Have studies modeled the potential benefits of using finasteride to prevent prostate cancer? 6) What is the cost-effectiveness of using finasteride to prevent prostate cancer?	6

Key Question #1: What is the efficacy of finasteride in preventing the incidence of prostate cancer?

Of all the chemopreventive agents studied in prostate cancer, finasteride has the largest volume and highest quality of evidence addressing the question of whether its use reduces the risk of prostate cancer. The Prostate Cancer Prevention Trial (PCPT) in particular, is a large, recent and good quality randomized controlled trial that has assessed this question directly.[41] Before discussing this trial in detail, evidence from other studies pre-dating the PCPT will be discussed.

Before publication of the PCPT, data were conflicting regarding the benefits of finasteride in preventing prostate cancer. However, all studies were of poor quality, as

outlined in Appendix 1, Key Question 1. A nested case-control study set in France examined 639 men with prostate cancer and compared them to 659 men without prostate cancer.[74] These men were chosen consecutively from patients referred to 12 French urological centers for prostate biopsy. Medication usage was assessed through patient self report. Comparing those who had ever used finasteride to those who had never used finasteride, the odds ratio for developing prostate cancer was 0.58 (95% CI 0.37-0.92) adjusted for age, ethnic origin, family history of prostate cancer, investigator center, use of NSAIDs, BMI, history of farming, red meat, poultry, fish and wine consumption. However, this study has several fatal flaws. The median time of exposure to finasteride was only 12 months, with some men reporting taking finasteride for only 1 month. Men categorized as having ever taken finasteride included men who reported taking it fewer than once per month. Both of these question the observed protective effect of finasteride in this study since such short and inconsistent exposure to finasteride would be unlikely to translate into reduced cancer risk. Finally, this population was not average risk; these were all men referred for biopsy. This is confirmed by their median PSA levels of 12.2 ng/ml among those with cancer and 7.9 ng/ml among those without cancer.

In contrast, a pooling of results of 1,645 men from 2 RCTs of finasteride in the treatment of BPH showed that there was no difference in the detection of prostate cancer among those taking finasteride (0.7% vs 0.7%, no statistics performed). However, no regimented pre-study biopsies were performed, and patients were only on finasteride for 12 months before their end-of-study biopsies. Thus, the cancers detected are more likely to represent cancers present before the study rather than effects of the study drug.

The Prostate Cancer Prevention Trial (PCPT)

Amidst the established biological plausibility but absent good quality evidence, in 1992, the large randomized controlled PCPT opened to accrual to test whether taking finasteride daily for seven years would reduce the incidence of prostate cancer. This good quality trial directly addresses key question #1 and as such, is discussed in detail.

The objective of the PCPT was to determine whether finasteride can reduce the period prevalence of prostate cancer among initially healthy men during a seven-year period. The term "period prevalence" was used in the trial rather than "incidence" as it more accurately depicts that many cancers were identified by end-of-study biopsy in men who would not have otherwise been biopsied during the 7 year period. Men, aged 55 years or older with a normal digital rectal examination (DRE), no clinically significant coexisting conditions, and an American Urological Association symptom score of less than 20 were recruited.[75] A 3-month placebo run-in was performed. At the conclusion of the run-in, a PSA was drawn. If the PSA was less than 3.0 ng/ml and adherence during the run-in period was satisfactory, then men were randomized to receive either 5mg of finasteride daily or placebo. Men underwent yearly PSA measurements and digital rectal examination. Every six months, men were seen for prescription renewal, pill counts, and evaluation of clinically significant medical conditions and side effects. Every 3 months the men were contacted by telephone to identify any interim medical events. At the end of the study, all men who had not received a diagnosis of prostate cancer were offered an end-of-study prostate biopsy. PSA levels were determined by a central laboratory and reported back to the clinicians caring for the patients. Because finasteride is known to cause a decrease in PSA,[76] the actual PSA values reported back to the clinicians was

adjusted such that the biopsy rate in the finasteride arm would approximate those in the placebo arm. For years 1-3, the PSA was doubled. As men entered their fourth year in the study, their PSA values were multiplied by a factor of 2.3. Triggers for biopsy included a PSA level (or adjusted PSA level for the finasteride group) > 4.0ng ml or an abnormal digital rectal examination. Biopsies were performed transrectally with the assistance of transrectal ultrasound (TRUS).

In total, 24,482 eligible men were enrolled, and 18,882 underwent randomization. The majority of men (71%) were excluded because their PSA values were above 3.0 ng/ml. Information regarding why others were excluded is not given. The study was stopped early by the Data Safety and Monitoring Committee (DSMC) because it was felt that additional data were highly unlikely to change the study outcome. At the time of publication, 86.3% of men had completed the full 7 year protocol. Only men with complete follow-up information were included. Thus, those who died before undergoing a for-cause or end-of-study biopsy (1123), those lost to follow-up before undergoing a for-cause or end-of-study biopsy (1256), and those refusing an end-of-study biopsy (3927) were not included in the analysis.

With the primary end-point of prostate cancer period prevalence, men in whom prostate cancer status was not known could not be included in any analyses. If the end-point was incidence rate then these men could contribute person-time. Thus, only 9,060 men, or 48% of the initial 18,882 men randomized were included in the final analysis. The study states that an intention to treat (ITT) analysis was performed on these 9,060 men. While calling this an ITT analysis would be inappropriate if the outcome were

incidence rate, it is fair to consider this an ITT analysis among men with known prostate cancer status.

The main finding of the study was that prostate cancer was detected in 18.4% of the finasteride group and 24.4% of the placebo group (RRR 24.8%; 95% CI 18.6-30.6; $p<0.001$). This translates into a number needed to treat (NNT) of 17. In other words, 17 patients would need to be treated with finasteride 5mg for 7 years in order to prevent one case of prostate cancer. The risk reduction was similar across risk groups as defined by age, race, family history and strata of PSA at baseline.

For cause biopsy was recommended to 22.5% of the finasteride group and 24.8% of the placebo group ($p<0.001$) after adjusting the PSA results for the finasteride group. The DSMC adjusted the PSA levels such that the rate of biopsy recommendations would be equal between the two groups. The degree to which recommendations for biopsies were followed by patients was found to be related to PSA level in the placebo group, but not in the finasteride group.

Adherence was fair, with 10.8% of days of treatment missed in the placebo group and 14.7% of days missed in the finasteride group. Additionally, serum DHT levels were measured in a random sample of 5% of patients to ascertain adherence in the finasteride group and a measure of drop-in rate in the placebo group. The percent with DHT levels above 16 ng/ml (suggesting non-adherence) in the finasteride group was 14.5%, the percent with DHT levels below 16 ng/ml (suggesting drop-ins) in the placebo group was 6.5%.

In summary, despite the early conflicting evidence from poor quality studies, the large, good quality randomized controlled PCPT answers the first key question directly.

Finasteride can be used to reduce the period prevalence of prostate cancer. Whether it should be used requires answering key questions 2 through 6.

Key Question #2: what harms are associated with using finasteride as a chemopreventive agent for prostate cancer?

Side-effects and adverse events warrant particular consideration in evaluating a chemopreventive agent since the drug will be given to healthy, or average risk men. Information on the side-effects of long term finasteride use can be gleaned directly from the PCPT or indirectly from trials of finasteride in the treatment of BPH.

Side-effects:

The Medical Therapy of Prostate Symptoms (MTOPS) trial and the Proscar Long-term Efficacy and Safety Study (PLESS) were randomized controlled trials involving finasteride in the treatment of BPH.[71, 77] The MTOPS study compared 3047 men over the age of 50 with BPH symptoms ranging from mild to severe. Men were randomized to receive the alpha-blocker doxazosin, finasteride 5mg, the combination, or placebo for 4 years. In PLESS, 3040 men were randomized to receive 5mg of finasteride or placebo for 4 years.

While the primary outcomes related to clinical progression of BPH (MTOPS) and changes in symptom scores (PLESS), side-effect data were collected through physician interview repeatedly during the study period. Side-effect data were similarly collected by physician interview in the PCPT. As such, for these three trials, reported side-effect rates may be underestimates as physician-reported symptoms often underestimate the

incidence relative to patient reported. However, such bias should be present across the treatment and control groups given adequate masking and thus should not affect risk estimates.

Direct comparisons of incidence of side-effects are difficult given the varying side-effects recorded, the units of measure (incidence density versus cumulative incidence) and differences in the duration of study. Table 3 summarizes the observed incidences and rates for the four most common side-effects observed in those on finasteride.

Table 3: Summary of incidence and incidence density of the most common side-effects associated with finasteride use

Symptom	MTOPS[Θ]		PLESS[€]		PCPT[ß]		Overall RR[δ]
	Placebo	Finasteride	Placebo	Finasteride	Placebo	Finasteride	
Decreased libido	1.42	2.36*	3.4%	6.4%*	59.6%	65.4%*	1.09 – 1.88
Erectile dysfunction	3.32	4.53*	3.7%	8.1%*	61.5%	67.4%*	1.09 – 2.19
Ejaculate abnormalities[Δ]	0.83	1.78*	0.8%	3.7%*	47.3%	60.4%*	1.28 – 4.62
Breast Tenderness or enlargement	N/A	N/A	0.1%	0.4-0.5%*	2.8%	4.5%*	1.61 – 5.00

Θ = measured as rates per 100 person-years of follow-up (incidence density)
€ = data reported after year 1 of the study, reported as % of patients
ß = data reported as cumulative incidence at 7 years, reported as % of patients
Δ = includes decreased ejaculate and abnormal ejaculate
δ = shown as a range of the smallest to the largest risk (or rate) ratio calculated from each trial
* = $p<0.05$ for comparison between finasteride and placebo group

The overall risk ratio reported in the table was obtained by calculating the risk ratio (or rate ratio in the case of MTOPS) for each individual study. The highest and lowest individual risk ratio is reported as a range. Overall, finasteride is associated with statistically significant decreases in libido and erectile function as well as ejaculate abnormalities and breast tenderness or enlargement.

Additionally, the PCPT found that despite the increase in sexual side-effects listed above, those treated with finasteride had less urinary urgency and frequency (12.9% finasteride vs 15.6% placebo), prostatitis (4.4 vs 6.1%), urinary tract infections (1.0 vs 1.3%) urinary retention (4.2 vs 6.3%), diagnoses of BPH (5.2 vs 8.7%) and transurethral resections of the prostate (1.0 vs 1.9%); $p<0.001$ for all comparisons. This is in keeping with the understanding that finasteride reduces prostate volume. The PCPT found that prostate sizes, as evaluated at biopsy, were 24% smaller in the finasteride group (mean volume: 25.5 cm^3 in the finasteride group vs 33.6 cm^3 in the placebo group). MTOPS found that those receiving finasteride, either alone or in combination with an alpha blocker, had a median 19% decrease in prostate size, while those on placebo or alpha blockers alone had a median 24% increase in prostate size over the 7 year study ($p<0.001$). Similarly, in PLESS, men treated with finasteride experienced a mean 18% decrease in prostate volume, while the placebo group had a 14% increase ($p<0.001$)

Two other studies were identified that addressed the question of side-effects of finasteride treatment in the average risk population. However, these were deemed only fair quality and as such were not included in table 3 above. One study which pooled data from 2 RCTs that continued in open extension format for 6 years revealed identical side-effect patterns described above.[78] However, less than 50% of the originally randomized cohort was used in this analysis. It was not made clear who these men were, or how their baseline risks compared. Thus, the potential for selection bias was large. Despite arriving at similar results, unlike PCPT, MTOPS and PLESS, their instruments for measuring side-effects and symptoms were not validated. The final study was small in

number (n=297) and short in duration (12-months).[79] However, it revealed a similar side-effect profile as above.

Adverse Events

In all studies, no deaths were attributed to the use of finasteride. Thus, the two main categories of adverse events include a) incident breast tumors; and b) incidence of high grade prostate cancers.

There is biologic plausibility that finasteride may increase the risk of breast cancers in men by altering the ratio of dihydrotestosterone to estrogen in serum.[80] Concern was raised after MTOPS showed that 4 of the 1554 men receiving finasteride, either alone or in combination with doxazosin, developed breast cancer. Though this number is small, this rate is nearly 64 times that of the general population.[81] However, in examining PLESS data, no men taking finasteride were diagnosed with breast cancer, while 2 men on placebo were. Similarly, the PCPT which had over 9,000 men on finasteride for 7 years only had 1 man diagnosed with breast cancer. Thus, it appears the balance of evidence does not support an association between finasteride and breast cancer.

The key secondary endpoint of the PCPT was the proportion of high grade, or aggressive tumors found in each arm of the trial. There was a higher proportion of tumors with Gleason grades 7 or higher in the finasteride group than in the placebo group (37.0% vs 22.2%; $p<0.001$; RR 1.67 95% CI 1.44-1.93).[41] Thus, the number needed to harm (NNH) is 7. That is, 7 men need to be treated with finasteride for 7 years to have 1 case of high grade cancer diagnosed. Examining men who only underwent for-cause

biopsies, which approximates cancers diagnosed in North America more closely than end-of-study biopsies, the disparity in rate of high-grade disease was greater: 47.8% had Gleason 7 or higher cancer in the finasteride group versus 29.4% in the placebo group ($p<0.001$; RR 1.63, 95% CI 1.37-1.93). The NNH in this case is 6. This issue will be addressed specifically in a later section entitled, "Issues raised by the PCPT".

In summary, good quality evidence exists showing that finasteride use is associated with an increased incidence of sexual side-effects, but a lower incidence of lower urinary tract symptoms. Of greatest concern is that finasteride appears to be associated with high grade prostate cancer.

Key Question #3: what is the effect of finasteride on the performance of currently used screening tests (DRE, PSA) or prostate biopsy?

PSA

As discussed previously, the merits of screening for prostate cancer are debated. The USPSTF has concluded there is insufficient evidence to recommend for or against screening. However, screening remains prevalent.[82] Thus, it is imperative to know how finasteride influences PSA and DRE, tests currently used to screen for prostate cancer. Secondarily, understanding how finasteride affects these tests will provide insight into potential biases present in the PCPT.

Several good quality studies, including the large RCTs, PCPT and MTOPS, have shown finasteride reduces PSA by approximately 50%.[41, 77, 83, 84] The time course for this reduction is less well known. A study which pooled data from 2 RCTs involving

finasteride in men with either BPH or BPH and prostate cancer, drew PSA tests on days 1, 2, 7, 14 and months 1, 2, 3, 4, and 6. They found, on average, PSA nadir was reached around the 12th week after starting finasteride treatment.[85] This was not a main outcome of the study and by diluting the study population with men with prostate cancer, the accuracy of this estimate is not clear. It has been shown that the reduction in PSA among men with prostate cancer treated with finasteride is less. Kaplan et al., in a trial of 38 high-risk men with 2 prior negative biopsies challenged with finasteride for 1 year showed that the mean decrease in PSA among those who went on to be diagnosed with cancer at the 1 year end-of-study biopsy was less than those who remained cancer free (28.8% decrease vs 41.0%; p=0.03).[86] Though this study was conducted in a high-risk population that may not apply to our population of interest, this raises the possibility that there may be effect measure modification in the influence of finasteride on PSA among men harbouring cancer. Such interaction could preserve the screening or diagnostic utility of PSA in the setting of long-term finasteride treatment.

Andriole et al., performed a secondary analysis of the PLESS data analyzing the performance of PSA in predicting prostate cancer while under the influence of finasteride. Details of the PLESS trial were discussed above. For the first 4 years, investigators were not made aware of PSA test results, but were informed if patients surpassed *a priori* defined thresholds (PSA increased >0.5 from baseline for finasteride treated patients, or 2.0 from baseline for patients on placebo). After four years, investigators received the adjusted PSA results only, similar to the PCPT algorithm. Prostate biopsies were offered to men with PSA > 4.0 ng/ml. Those with PSA values >4.0 ng/ml with a negative biopsy during the study, were offered an end-of-study biopsy

as well. Cancers detected at biopsies triggered by elevations in PSA accounted for the same percentage of total prostate cancer cases in the finasteride group as in the placebo group (35% finasteride vs 34% placebo; p value not given). Area under the receiver operator curves for PSA (placebo) and PSA x 2 (finasteride) showed no significant differences (0.84 placebo vs 0.79; 95%CI difference: -0.005, +0.118; p=0.07).[76] Using a PSA cut-off of 4.0 ng/ml (accounting for multiplying by two in the finasteride group) applied to the final PSA before diagnosis, similar sensitivities were found (66% finasteride vs 70% placebo, p=0.6) but higher specificity for the finasteride group was shown (82% vs 74%, p<0.001). The performance characteristics of PSA in the setting of finasteride may even be more desirable than in the placebo setting. A slight decrease in sensitivity with an increase in specificity may mean fewer unnecessary biopsies and fewer cancers detected that would have remained indolent.

Most studies conclude multiplying PSA by a factor of two for anyone on finasteride longer than 6 months is appropriate. A recent study by Etzioni et al., showed that this multiplicative factor actually needs to increase gradually with duration of time on finasteride.[83] This secondary analysis of the PCPT data showed that to make the median PSA of men not destined to have cancer during the 7 year trial be equal in the finasteride and placebo arms, the multiplier needed to increase gradually from 2 to 2.5 over 7 years. This study also showed that even without this multiplicative factor, the velocity of PSA among men taking finasteride but destined to be diagnosed with cancer was significantly higher than in men not destined to be diagnosed with cancer. This suggests that PSA velocity may remain an important predictor of cancer in the setting of finasteride.

In summary, it appears appropriate to multiply the PSA by 2 in men treated with finasteride for longer than 3 to 6 months. It may even be appropriate to increase this multiplier up to 2.5 with longer durations of finasteride consumption. Most importantly, it appears that finasteride does not hinder the performance characteristics PSA as a screening test.

DRE

To date, no study has addressed the effect of finasteride on the sensitivity and specificity of DRE. Argument could be made for finasteride either improving or hindering the utility of DRE. By reducing the overall volume of the prostate by 25% on average, finasteride may dampen the ability to detect nodules. Alternatively, by shrinking the non-malignant portion of the gland, the neoplastic nodule could become more discernible. Data on the performance of DRE is available in the PCPT database and likely would be able to answer this question.

Biopsy

Prostate biopsy provides information on the presence or absence of cancer, as well as the grade. Finasteride may affect both of these: a) it may increase the detection of cancer; b) it may distort the Gleason grade assigned to the cancer.

No study has quantified the impact of finasteride on the sensitivity of prostate biopsy. Intuitively, by decreasing the non-malignant volume of the gland on average 25%, this would increase the likelihood of sampling a cancer, if present. With respect to cancer grade, a retrospective cohort of 48 men who were taking finasteride for > 6

months, had biopsy proven prostate cancer and went on to have RP attempted to address this question. Freedom from recurrence was predicted using validated nomograms which incorporate Gleason grade. When the biopsy Gleason grade was used in estimating 5 year progression-free survival, the estimated survival was not significantly different from the actual survival observed.[87] This suggests the predictive ability of biopsy Gleason score is not altered by finasteride. However, this result should be interpreted with caution. The 5 year progression-free survival is a surrogate marker only for longer term outcomes. Furthermore, their mean follow-up was only 33.5 months, suggesting that few men contributed to this 5 year progression-free survival statistic. Finally, given the retrospective and uncontrolled nature of the study, the potential for selection and confounding bias renders the internal validity of this study low.

There may also be interaction between detection of cancer, gland size and grade. The details of this will be discussed in the next section on issues raised by the PCPT.

In summary, there is insufficient evidence to assess the influence of finasteride on the performance of prostate biopsy in the diagnosis of prostate cancer.

Key Question #4: what costs are associated with using finasteride in every male patient within the defined population to prevent prostate cancer?

Key Question #5: have studies modeled the potential benefits of using finasteride to prevent prostate cancer?

Key Question #6: what is the cost-effectiveness of using finasteride to prevent prostate cancer?

Issues raised by the PCPT

Much of the evidence for key questions 4 through 6 attempts to address many controversial issues and areas of potential bias raised by the PCPT. These issues are discussed here prior to reviewing the evidence for key questions 4 through 6.

The main finding of a 25% reduction in the period prevalence coupled with a 67% increase in gleason 7 or higher tumors raised several issues.

Differences between the finasteride and placebo arms in incidence of prostate cancer suggest finasteride may have treated subclinical microscopic disease. The fact that the difference persisted and even increased suggests that it also prevents or delays the onset of cancer. Though the overall cancer status ascertainment was less in the finasteride group (59.6% vs 63% in the placebo group), this difference unlikely contributed to the difference seen between the two groups in terms of prostate cancer. This discrepant ascertainment stems from three trends observed in the trial: a) fewer abnormal DREs were detected in the finasteride group leading to fewer recommendations for biopsy; b) due to the effects of finasteride on prostate volume, fewer transurethral resections of the prostate were performed; c) more end-of-study biopsies were refused in the finasteride group which could also be attributed to fewer lower urinary tract symptoms among the finasteride group.

Cancer was detected in 24.4% of patients in the placebo group. This figure is approximately 4 times the rate typically seen in other screening trials,[88, 89] and more closely approaches the 25 to 30 percent rate of prostate cancer seen in autopsy specimens of men older than 50 years.[90-93] Of men who had a biopsy driven only by elevated PSA or abnormal DRE, the rate of cancer detection approximated that seen in other screening

trials (6%). This calls into question the clinical significance of the cancers detected in this study. The study promotes early detection of potentially insignificant tumors through two mechanisms: a) through an intense screening mechanism of yearly PSA values and DREs; and b) by offering a biopsy to everyone at the end of study in the absence of PSA or DRE abnormality.

The use of period prevalence as an end-point and end-of-study biopsies to accurately obtain this end-point was a calculated decision by the PCPT investigators. The risk of identifying asymptomatic tumors of unknown clinical significance was deemed a necessary side-effect to eliminating the multiple detection biases introduced by finasteride.[94] In defense of their end-point, PCPT investigators caution conclusions based only on for-cause biopsies because of the large number of known and potential biases that worked for and against finasteride. Among these biases, the reduced PSA levels, potential altered DRE sensitivity, oversampling of smaller glands, nonadherence to treatment, and differing transurethral resection of prostate (TURP) prevalence are most likely to be operational.

Increased Grade: fact or fiction

One of the most controversial aspects of the PCPT was the finding of increased prevalence of high-grade tumors among those taking finasteride. The authors of the PCPT suggested two possible explanations. First, finasteride may induce high-grade tumors by inhibiting intraprostatic conversion of testosterone to dihydrotestosterone (DHT). Decreased levels of intraprostatic DHT are analogous to men with low serum testosterone levels. Prostate cancers arising in these men have been shown to be of

higher Gleason grade and are associated with worse outcomes.[95] Second, it is also biologically plausible that finasteride selects for high-grade tumors by inhibiting or treating low-grade tumors. At present, no evidence supports this hypothesis.

In examining the ratio of excess high-grade tumors as broken down by year in the PCPT it can be seen that the largest discrepancy occurred in the first and second year of the study (see Figure 3).[96]

Figure 3: Proportion of excess high-grade cancers in each year of the PCPT (adapted from Roehrborn, 2003)

Table 1. Proportion of Cases of Prostate Cancer Diagnosed That Had a Gleason Grade of 7, 8, 9, or 10.

Variable	Year						
	1	2	3	4	5	6	7
Proportion of cancers diagnosed that were grade 7–10 (%)							
Placebo group	10.4	8.5	25.0	43.8	26.1	25.0	30.6
Finasteride group	26.2	31.4	43.6	45.6	35.9	51.0	52.5
Ratio of proportion in finasteride group to proportion in placebo group	2.5	3.7	1.7	1.0	1.4	2.0	1.7

In particular, to have 2.5 times as many high-grade cancers detected in the first year of the study violates one of the causal criteria of Hill: temporality.[97] It is highly unlikely that finasteride could either induce or create a selective environment so rapidly to observe that many excess high-grade tumors. Similarly, if this were a case of induction, then the ratio should increase over time as more tumors have been exposed to the inducing factor. This violates another causal criterion of Hill: consistency.

Based on this observation, several theories have been put forth in attempt to explain how the false increase in high-grade cancers arose. One possibility is histological artifact. It has been shown that by reducing intraprostatic DHT, finasteride causes similar architectural changes as androgen deprivation therapy.[98] Specifically finasteride has been shown to cause atrophy and involution, smaller nuclei and nucleoli, increased apoptosis, decreased vessel density and decreased cellular proliferation.[99-102] In the case of androgen deprivation therapy (ADT), a consensus panel has concluded that Gleason grading of tumors post-ADT is of no value.[103] No formal recommendation has been made for 5-alpha reductase inhibitors, however, two systematic reviews have recommended that chemoprevention trials using these agents should avoid using Gleason grade as a secondary end-point because of this grading bias.[98, 104]

A recent study examined 369 TRUS guided biopsy specimens in men with PSA <10 ng/ml that subsequently went to radical prostatectomy. They found that prostate volume, as determined by TRUS, was a significant predictor of finding a Gleason pattern 4 or more in the biopsy specimen. However, prostate volume is not a significant predictor of high-grade disease in the RP specimen. Stated another way, the sensitivity of TRUS biopsy to identify high-grade disease was highest (81%) in glands <30.7 cm^3, but decreased to 62.5% in glands greater than 53.4cm^3.[105] This disparity in sensitivity dependent on gland volume amounts to an overdetection bias and could explain why those on finasteride had a higher prevalence of high grade tumors: their prostates were, on average, 25% smaller in volume.

In further support of this histological artifact, a post-hoc analysis of 159 of men in the PCPT diagnosed with a Gleason 8 or higher tumor that went on to RP was completed.

Though presented only in abstract form to date, it showed that those on finasteride had significantly fewer bilateral tumors (26.5% vs 44.3%, RRR 40.2; p=0.002).[106] Until this publication appears in the peer-reviewed literature in its entirety it is difficult to comment on the validity of the results. They have obviously included incident cancers since the termination of the PCPT because at the study close date, only 143 such cancers had been identified. Regardless, if the finding holds, this further supports that the excess high-grade tumors seen were histological artifact.

Finally, additional analyses have been completed on over 500 radical prostatectomy specimens from participants in the PCPT. These were reviewed by a blinded uropathologist. It was found that there was no longer a significant difference in the proportion of Gleason 7-10 cancers between the two groups.[107] This finding has yet to reach even abstract form and so should be interpreted with caution.

In summary, despite biological plausibility that finasteride induces or selects for high-grade cancers, further analysis of the PCPT data corroborated by other studies suggests that the excess high-grade cancers seen are a product of overdetection bias and histological artifact.

Key Question #4: what costs are associated with using finasteride in every male patient within the defined population to prevent prostate cancer?

Key Question #5: have studies modeled the potential benefits of using finasteride to prevent prostate cancer?

Key Question #6: what is the cost-effectiveness of using finasteride to prevent prostate cancer?

In choosing the primary end-point of prostate cancer period prevalence, the PCPT limited its ability to address whether finasteride use reduces overall mortality. The PCPT also did not assess any cost or utility parameters associated with the observed outcomes. This information is necessary before recommending mass implementation of a prevention strategy. As identified through the systematic literature search, the PCPT has spawned 5 studies that attempt to answer these questions through modelling. No other literature was found that can address key questions 4 through 6, thus these three questions are discussed together in this section.

All five studies are of fair or good quality. However, each one uses the PCPT data to answer a slightly different question using different methods and reporting different outcomes. Thus, pooling of these data is not feasible. By way of summary they are presented in table 4. Data shown represent the net benefit of treating a group of men with finasteride for 7 to 10 years. The unit of analysis ranges from a single man to the entire U.S. population of men. Men considered are over the age of 55 and have not already received a diagnosis of prostate cancer when they begin finasteride treatment.

Table 4: Summary of studies modelling benefit-risk, survival and cost outcomes based on PCPT findings

	Klein et al.[108]	Unger et al.[109]	Lotan et al.[110] *	Grover et al.[111]	Zeliadt et al.[112]
Outcome	Benefit:Risk ratio (Ca prevented : excess HG tumor)	Person-years saved (PYS) in US pop.	15 year cancer-specific survival (months/person)	Overall survival (yrs/person)	Cost per life-year Cost per QALY For 1000 men
Overall estimate	4.6:1	262,567 over 10 yrs	RP: 1.7 m/p WW: <1 m/p	+0.14 y/p	6 life-years @ $1.7 million/yr 46 QALYs @ $200,000/QALY
If assume Grade artifact	5.1:1 – 9.2:1	316,760 over 10 yrs	RP: 3 m/p WW: 3 m/p	+0.2 y/p	40 life-years @$233,000/yr
If assume detection bias[θ]	8.2:1 – 16.3:1[θa]	N/A	RP: 0.35 m/p [θb] WW: 55-65: -0.2 m/p >65: +0.04 m/p	+0.02 y/p [θb]	N/A
Change with age	N/A	N/A	> benefit with age	<benefit with age	Only men who live beyond 80 benefit
Sensitivity Analysis	N/A	Rate of high-grade in finasteride arm needs to triple before PYS=0	N/A	N/A	Grade difference is most influential parameter If RR of high grade in finasteride increases to 1.8: no benefit

* = RP → assume treatment with radical prostatectomy; WW → assume treatment with watchful waiting
HG = high-grade tumors (Gleason 7-10)
Θ = Refers to either a) over-detection of cancers in finasteride arm because of reduced gland size; or b) over detection of cancers in both arms because of end-of-study biopsy protocol

The most simplistic of the studies was by Klein et al., a subset of authors from the PCPT.[108] They calculated an absolute benefit-risk ratio based on PCPT data. This ratio was the absolute reduction in prostate cancer risk over the absolute excess risk of high grade cancers (Gleason7-10) when treated with finasteride. This ratio was computed to be 4.6:1, meaning that for every 4.6 prostate cancer cases prevented, 1 excess high grade cancer is diagnosed.

Altering the assumed percentage of excess high-grade cancers due to artifact between 10 to 50% yielded increased ratios as shown in Table 4. Similarly altering the number of cancers detected in the finasteride arm based on the assumption that the

smaller glands in finasteride treated patients led to sampling bias and over-detection revealed increased ratios ranging from 8.2:1 to 16.3:1.

Such positive results would favor large scale implementation of finasteride. However, this study is only of fair quality and warrants caution. First, the ratios they presented are based on the prevalent cancers in PCPT, meaning those from both for-cause and end-of-study biopsies. Such cancers may not represent those that are commonly diagnosed in North America with current practice. Using data only from cancers detected by for-cause biopsies in the PCPT may be more representative. Doing so lowers the overall benefit-risk ratio to 1.9:1 and even in the most favorable setting of assumptions regarding grade artifact and overdetection, the ratio is only 8:1.

Second, the relative value assigned to one cancer prevented and one excess high grade cancer is not discussed. As evident from their analysis, they are assuming that the relative value of both outcomes is equal, but this may not necessarily be true. A more in-depth analysis would project the survival of the high grade cancers relative to the low grade cancers and compare this value to preventing predominantly lower grade cancers.

Unger et al., expanded on the idea of absolute benefit-risk ratios and estimated person-years saved by using finasteride as a chemopreventive agent.[109] Using SEER survival data for men with prostate cancer of differing grades and National Center for Health Statistics actuarial data for men without prostate cancer, the number of years of life saved by using finasteride was calculated. They calculated that 262,567 person-years would be saved if the entire U.S. population of men over age 55 were treated with finasteride for 10 years. Of note, according to their models, the excess high-grade tumors

in the finasteride arm would have to triple relative to those not taking finasteride before the survival benefits of finasteride were cancelled out.

This study is of better quality than that of Klein et al. A particular strength is that they did not model cancer incidence based on PCPT period prevalence. Rather they used SEER incidence rates, which are much lower and more in keeping with current population rates. However, one weakness is they did not attach a quality value to these life-years saved nor a cost.

Two studies, one by Lotan et al., and the other by Grover et al., modelled similar outcomes: 15-year cancer-specific survival and overall survival.[110, 111] Grover et al., used a validated Markov model, while Lotan et al., developed their own decision analysis model. The Lotan et al., study was unique in that they stratified their projected outcomes based on whether men were treated with watchful waiting or radical prostatectomy. Based on recent data from an RCT from Scandinavia showing an overall survival benefit in men with localized prostate cancer treated with radical prostatectomy over watchful waiting, this stratification seems appropriate.[113]

Lotan et al., showed men with the same inclusion criteria as the PCPT, given finasteride for 15 years and treated with radical prostatectomy if they had cancer were estimated to have 1.7 months longer cancer specific survival as compared to if they had not been treated with finasteride. This survival advantage dropped to less than 1 month in men treated with watchful waiting. Grover et al., while not stratifying based ultimate treatment, found a similar 1.7 month overall survival advantage in men treated with finasteride for 15 years. Comparing this to other primary prevention modalities, childhood vaccines, such as measles, rubella and pertussis increase life expectancy by

about 0.1 month each.[114] Screening for cervical cancer will increase a woman's life expectancy by 3 months[115] and tamoxifen in breast cancer prevention will increase life span by 0.9 to 2.3 months depending on the age at which it is initiated.[116]

In assuming that the grade difference was artifactual, a near doubling of cancer-specific and overall survival was noted. By changing model probabilities based on for-cause biopsy data only (see θb in Table 4) where the overall incidence of prostate cancer was markedly less, survival estimates drop considerably. So much so that in younger men, those on finasteride have a decrease in cancer-specific survival by 0.2 months. This point was illustrated in both studies that as the incidence of prostate cancer in the population being modelled increases, the benefit of finasteride increases. From this finding, it has been postulated that if we can identify a subgroup of men who are at higher risk for prostate cancer, that finasteride may be more beneficial. The REDUCE trial, mentioned earlier, will be able to address this issue, as the source and study population are inherently higher risk. To be eligible for the trial, men had to have been biopsied for-cause at least once.[117]

Both the Lotan et al., and Grover et al., studies were of good quality. However, the survival benefits attributed to finasteride should be cautioned as the use of PCPT data to model cancer incidence rates may artificially inflate the benefits. Furthermore, they did not attempt to assign relative values, either economical or psychological, to cancers prevented, low grade cancers or high grade cancers.

The most complex of the 5 studies, by Zeliadt et al., modelled cost per life year saved and cost per quality adjusted life year (QALY) and addressed several weaknesses identified in the four prior studies.[112] They used SEER data to model the incidence of

prostate cancer, high grade disease and the outcomes of those with cancer in the general population. Cost of finasteride was estimated based on men starting at age 55 and continuing finasteride daily until age 85 or their first diagnosis of prostate cancer. Unique to this study, they also modelled the benefits of finasteride relative to BPH symptoms and surgery. In assigning utility to each health state, they accounted for the psychological burdens and quality of life changes.

It was estimated that their base cohort of 1000 men treated with finasteride would gain 6 life-years survival and 46 QALYs relative to men not taking finasteride. Each life year came at a cost of $1,660,000 while each QALY cost $200,000. Only men living beyond age 80 derived any benefit from preventing low grade tumors. Assuming the excess high grade tumors were due to artifact increases the life-years and QALYs gained and reduces the cost for each year respectively (see Table 4). In a sensitivity analysis, grade proved to be the most influential parameter. It was found that the true relative risk of high grade tumors in the finasteride arm relative to the placebo arm would have to be 1.8 before the benefits of finasteride were eliminated.

Even using the most favorable assumptions, Zeliadt et al., concluded that the cost per QALY is substantially higher than the $100,000 willingess-to-pay threshold per QALY that is often used as a benchmark.[118] It was estimated that the cost of finasteride must be reduced by 50% from its current average wholesale price and finasteride must prevent high-grade disease equally well as low-grade disease before the cost-benefit will be justifiable.

In summary, five studies have attempted to use the PCPT data and answer practical questions regarding harms relative to benefits, survival, and costs. With the

variance introduced by unknown grade artifact and over-detection biases, it is difficult to precisely estimate the benefit relative to the risk. However, it appears, those at highest risk of prostate cancer and those most likely to live beyond 80 will benefit the most from finasteride. Even if it is proven that the excess high-grade tumors seen are explained by artifact and that substantial over-detection occurred in the finasteride arm, the benefits of finasteride are modest. At present, the costs to achieve these benefits appear steep.

Summary of systematic review

Overall, there is good quality evidence to show that finasteride is efficacious in reducing the period prevalence of prostate cancer. While side-effects are minimal, the potential increased risk in high-grade tumors is worrisome. Though not conclusive at present, evidence is suggestive that the excess high-grade tumors observed in the PCPT may be fallacious. There is insufficient evidence to assess the influence of finasteride on the performance of current screening modalities. There is good quality evidence the cost-effectiveness of treating men over the age of 55 with finasteride to prevent prostate cancer is modest at best. Thus, presently, there is insufficient evidence to recommend finasteride use in every man of average risk for prostate cancer.

If the grade issue is cleared definitively or a subset of higher risk patients is identified in which finasteride is most effective, then in future, there may be sufficient ground to recommend its use.

Guideline consensus

To compare the findings of my systematic review with current guideline recommendations, a guideline search was conducted using the National Guidelines Clearing House and the search engine Google™. Only one guideline was identified that dealt directly or indirectly with the issue of finasteride as a prostate cancer chemopreventive agent. The National Cancer Institute produced a guideline which assessed whether finasteride can reduce the mortality attributable to prostate cancer. They concluded that, "based on solid evidence, chemoprevention with finasteride reduces the incidence of prostate cancer, but the evidence is insufficient to determine whether chemoprevention with finasteride reduces mortality from prostate cancer."[119] This is in line with the results of my systematic review.

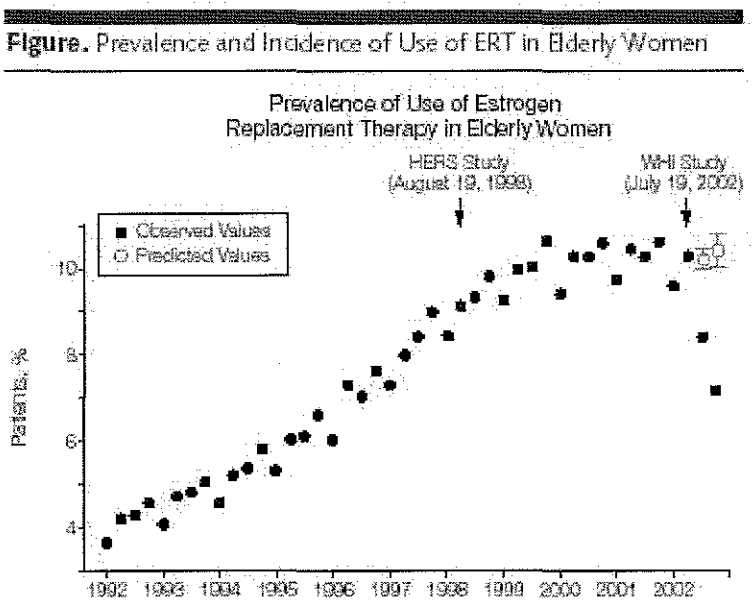
Dissemination of the evidence

Dissemination is defined as, "a scattering or spreading abroad, as of ideas, beliefs, etc.; diffusion for propagation and permanence."[120] This term has been applied to describe how evidenced-based medicine propagates from scientific discovery to regular practice. As identified in the systematic review above, evidence for a chemopreventive agent for prostate cancer was scarce before the publication of the PCPT. Thus, the National Cancer Institute (NCI), which funded the PCPT, had the task of beginning the process by disseminating the results of the PCPT to the public and physicians. They outlined 5 main messages to communicate with these results: 1) to accurately convey the scientific excitement that prostate cancer risk was shown to be reduced with a drug intervention; 2) to appropriately explain the side effects, both well-documented and potential; 3) to discuss the risk-benefit trade-off associated with any drug intervention;

and 4) to impress upon the public that prevention interventions such as finasteride are not acute medical decisions but should be made after careful consideration.[121] From these goals, it can be seen that the NCI was careful not to appear clearly in favor or against using finasteride as a chemopreventive agent for prostate cancer. Rather, they focussed on ensuring that accurate information regarding the trial was delivered, while letting the individual physicians and thought leaders sort through the uncertainty. Releasing this information was complicated by the fact that millions of men were already taking finasteride for treatment of BPH or, at a lower dose, for male pattern baldness. Thus, the effects on overall use of finasteride, regardless of indication are difficult to predict.

It may be possible to estimate the rate and magnitude of influence the PCPT results would have on prescribing patterns by examining other large impact RCTs. The Women's Health Initiative (WHI) trial showed that overall risks exceeded benefits in using combined estrogen and progestin in postmenopausal women.[122] After its publication in July 2002, prescriptions for hormone replacement therapy dropped dramatically. In Ontario, Canada, prevalence of hormone replacement therapy (HRT) prescriptions was 32% lower in the last quarter of 2002 in comparison to the first quarter of 2002 (Figure 4).[123]

Figure 4: Prevalence and incidence of use of HRT in elderly women



From Austin et al., 2003

The rapid decline may be, in part, due to the concomitant decline in promotional spending by pharmaceutical companies regarding hormone replacement therapy.[124] Similarly, a 400% increase in prescriptions for ramipril in Ontario was seen within a year of publication of the Heart Outcomes Prevention Evaluation (HOPE) which showed ramipril is effective in secondary prevention of cardiovascular disease (Figure 5).[125, 126]

Figure 5: Numbers of new prescriptions for angiotensin-converting-enzyme inhibitors filled by elderly (aged 65 and over) Ontario residents.

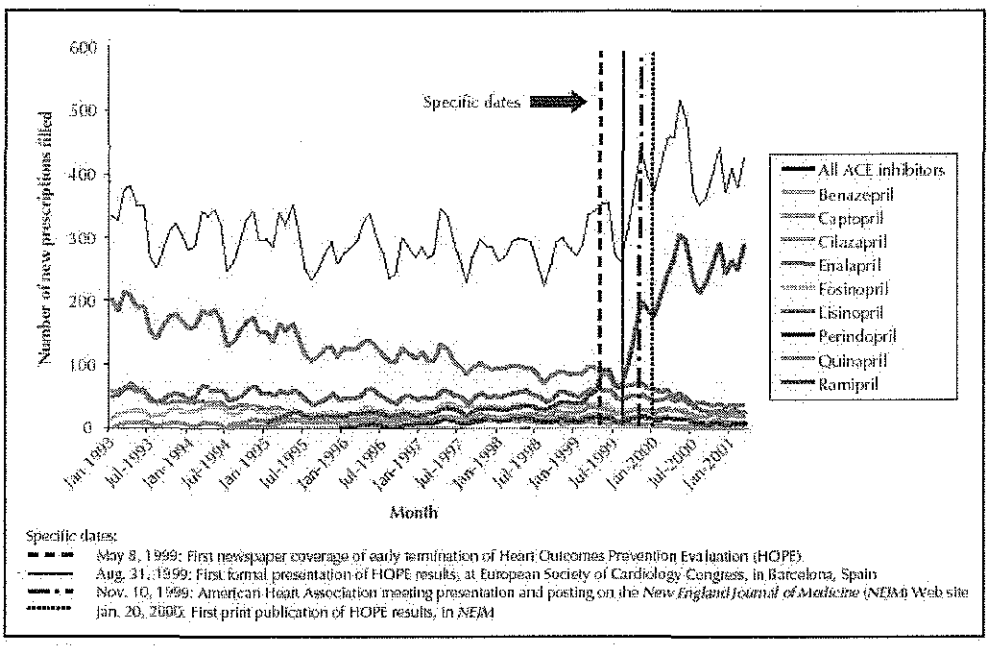


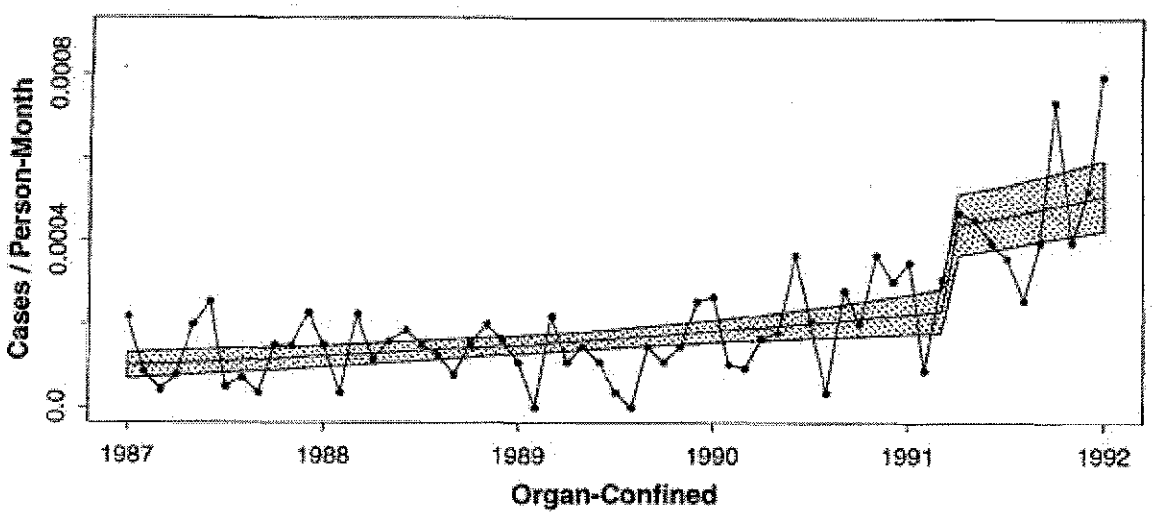
Fig. 1: Numbers of new prescriptions for angiotensin-converting-enzyme (ACE) inhibitors filled by elderly (aged 65 and over) Ontario residents.

From Tu et al., 2003

Similar trends have been observed in prescriptions of diuretics and angiotensin converting enzyme inhibitors after the publication of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[127] The ALLHAT trial also affected prescriptions for doxazosin. The doxazosin arm of ALLHAT was terminated early because of a 2-fold increased risk of congestive heart failure attributed to the alpha-blocker. Before publication of ALLHAT, use of alpha-blockers was gradually increasing. Within 2 years of this publication, physician-reported alpha-blocker prescribing decreased by 54%.[124] This reduction was not explained by changes in pharmaceutical promotion, cost of doxazosin or introduction of generic drugs. Finally, statins have also seen similar fluctuations after the publication of major RCTs.[128]

Using an example more specific to prostate cancer, in April 1991, Catalona et al., published an article in the New England Journal of Medicine endorsing the use of prostate cancer screening with a PSA cut-off of 4.0 ng/ml.[129] A large health maintenance organization in Washington reported a 3-fold increase in the ordering of PSA tests immediately after the publication of this paper.[130] No doubt as a result of the rapid increase in PSA testing, in the month after the publication of the Catalona et al., article, prostate cancer diagnoses arose by 87% in men in the Health Professionals Follow-Up study(Figure 6).[131] This rapid dissemination is somewhat surprising given the quality of the original Catalona et al., article. The article was very controversial in that they did not have an unscreened asymptomatic control group for comparison.

Figure 6: Rate of prostate cancer diagnoses over time in the Health Professionals Follow-Up Study.



From Giovannucci et al., 1998

It is not known to what degree finasteride use has increased or decreased after the publication of the PCPT. It is also difficult to estimate given that no studies have examined the determinants of dissemination of primary prevention innovations relative to cancer. Pentz reviewed the elements of diffusion of drug abuse prevention research and categorized 4 stages of diffusion: adoption of a new program, implementation of the new program with fidelity, dissemination of the program within a system and sustainability of the program once disseminated.[132] Pentz further summarized barriers to adoption, implementation and dissemination phases. Among the common themes was inadequate funding or infrastructure, lack of program teaching materials, lack of positive communication or lack of network structures to diffuse positive communication. Comparing such descriptions to the use of finasteride for prostate cancer chemoprevention is difficult. After the results of the PCPT, no formal program was established to disseminate the innovation. Infrastructure has been established to spread the results of the PCPT but, similar to the neutral message from the NCI, teaching materials and communication networks do not promote the use of finasteride as a chemopreventive agent.

Donald Berwick identified three clusters of influence that correlate with the rate of diffusion of innovations: perceptions of the innovation, characteristics of the people who adopt the innovation (or fail to do so), and contextual factors involving communication, incentives, leadership and management.[1]

It has been shown that perceptions of a new innovation account for up to 90% of the variance in the rate of spread of the innovation.[133] Within these perceptions, the most powerful is the perceived benefit of adopting the new innovation relative to harm. In a

situation of uncertainty regarding this perceived risk-benefit ratio, the more knowledge individuals can gain about the expected consequences of the innovation, the more likely they are to adopt it. In the case of finasteride as a chemopreventive agent, it is likely that perceptions are mixed and uncertainty looms. Despite the few studies modelling results based on the PCPT data, little new data has emerged to assuage the perception of uncertainty. Thus, it is largely unknown how finasteride is perceived in the United States. In addition to the perceived risk-benefit, perceptions of new innovations are determined by how compatible the new innovation is with values and beliefs of the physicians as well as the complexity of the innovations. Generally, physicians are loath to subject healthy men to the potential adverse effects of drugs unnecessarily. As such, finasteride may not be compatible with most physicians' values and beliefs. However, finasteride chemoprevention is a relatively simple concept at face value, one pill per day for every man. This simplicity would be expected to facilitate dissemination.

Research Project:

Use and knowledge of finasteride in the primary prevention of prostate cancer -

Trends in prescriptions and a survey of VA primary care physicians and urologists

Rationale

Given the burden of suffering attributable to prostate cancer, the potential impact a chemopreventive agent like finasteride could have is considerable. As identified by the systematic review however, the issue of the benefits relative to harms of using finasteride as a chemopreventive agent is not clear. Moreover, how physicians respond to this uncertainty is not known.

To better understand the dissemination of finasteride in the primary prevention of prostate cancer, the proposed project has two elements. First, we seek to quantify the change in finasteride use over time and whether this use changed with the publication of the PCPT. Second, we seek to understand the key elements of dissemination outlined by Berwick, specifically the perceptions, characteristics and contextual factors of those physicians who are in a position to utilize finasteride.

A better understanding of the current state of dissemination of finasteride chemoprevention information, specifically finasteride use and knowledge, could allow directed educational interventions and guide future research to target areas of physician uncertainty.

PROCEDURES/METHODS

Design

This study is divided into two parts. Part A involves the collecting and analyzing prescription data for finasteride and alpha-blockers using the VA pharmacy benefits management (PBM) database system. Part B involves surveying VA primary care physicians and urologists regarding their use, knowledge and perceptions of finasteride as a chemopreventive agent.

Study population

The source population includes VA primary care physicians and urologists in the United States. Eligibility criteria include physicians registered as a full-time equivalent (FTE) at a VA institution in the fields of urology, family or general practice, general internal medicine, or geriatrics. Resident physicians, physician assistants and nurse practitioners will be excluded. A list of all such eligible physicians will be generated by the from the Personnel and Accounting Integrate Data (PAID) payroll system by the Veterans Evidence-Based Research Dissemination Implementation Center (VERDICT). All FTE urologists (325) will be invited and a random sample of 1000 primary care physicians from the 4557 FTE PCPs will be selected. Those chosen will be sent email invitations. Sampling will not be stratified for geographic area, but our hope is that our study population will represent practice patterns across the United States. Thus, the final study population will be comprised of those physicians who meet the eligibility criteria, do not meet the exclusion criteria, have the ability to receive email, and respond to the survey invitation.

Sample size

For an estimated target population size of 5,000 VA primary care physicians and urologists, with a 95% confidence level, a 4% confidence interval (or margin of error) and a 50% prevalence for each response, the required sample size is 536. This was computed using the formula:[134]

$$Ns = \frac{(Np)\,(p)\,(1-p)}{(Np-1)\,(B/C)^2 + (p)(1-p)}$$

Where Ns = the number of completed surveys needed for the desired level of precision; Np = size of the source population; p = proportion of the population expected to choose one of the two response categories (estimated conservatively at 0.50); B= acceptable amount of sampling error (set to 0.04); C = z-statistic associated with 95% confidence level (1.96). The confidence interval or margin of error refers to how accurately the proportion revealed from the survey population represents the actual proportion in the source population. For example, if 68.5% of respondents reported they use finasteride as a chemopreventive agent, and the confidence interval was set a priori to 4%, then the true proportion lies within 68.5 ± 4%. The confidence level refers to the precision of the survey sample. That is, the probability that, if the population were sampled and surveyed in a similar fashion repeatedly, the resulting values would fall within the specified margin of error. Using the same example, if 68.5% of respondents reported they use finasteride, and the confidence interval was set to 4% and the confidence level was set to 95%, then if the survey were repeated 100 times, 95/100 times the observed proportion would fall within 4% of 68.5%.

We estimate a 45% response rate, thus 1191 email invitations will be sent. Enrolment is accomplished by respondents accessing the online survey and completing

the survey. Though IRB approval is still pending, we have requested a waiver of formal informed consent. Thus, no formal signed informed consent process will take place. Consent is implied when the physician completes the online survey.

Variables/Interventions

Part A:

The primary data to be collected for Part A are all prescriptions for finasteride written between October 1, 1998 and December 31, 2005. Additionally all prescriptions for alpha-blockers will similarly be obtained. Capturing alpha-blocker prescription trends will serve as a pseudo-control for finasteride prescriptions. MTOPS confirmed the combination of finasteride and alpha-blockers was superior to treatment with either finasteride or alpha-blockers alone. This trial was published shortly after PCPT in 2003. Thus, rises in finasteride prescriptions after 2003 may not be attributable solely to use in a chemopreventive role, rather in combination treatment for BPH. By ascertaining rises in alpha-blocker therapy, it may be possible to determine what proportion of rise in finasteride prescriptions is attributable to use in BPH. October 1, 1998 is the date of first entry for the PBM database.

Part B:

For Part B survey domain variables include: current practice patterns regarding diagnosis and treatment of BPH, frequency and indication for finasteride use, what the physician discusses with the patient, knowledge of issues surrounding finasteride use in both benign prostatic hyperplasia and for prevention of prostate cancer, and where the

physician finds such information (guidelines, journals). The survey was designed de novo and is not based on prior surveys. After careful critique from the study team, the survey was administered to 15 physicians (approximately 50% primary care providers and 50% urologists). Final changes were made to the survey and the final survey is attached as Appendix 2. The survey tool Zoomerang™ will be used to conduct the web survey.

Data Collection:

For Part A, data from the PBM database will be queried through the Department of Pharmacoepidemiologic Outcomes Research at the VA. This de-identified data will be downloaded to the VA National Center for Health Promotion and Disease Prevention and stored there. For Part B, those selected to be invited will receive an email inviting them to participate in the online survey. The invitation email is attached as Appendix 3. The email will include a link to a secured website provided by Zoomerang™ should they agree to participate. Zoomerang will collect all survey data in real-time as the survey is being completed. Upon completion, the results will initially be mapped to the email address of the person completing the survey. This is only for the purpose of eliminating that person's name from the list of people who have not completed the survey. When the survey is terminated, the results will be downloaded en bloc and all identifying data will be removed by one of the study personell. Results will be downloaded into an Excel spreadsheet at the VA National Center for Health Promotion and Disease Prevention. Once downloaded, all data (Part A and Part B) will be stored in de-identifed form and

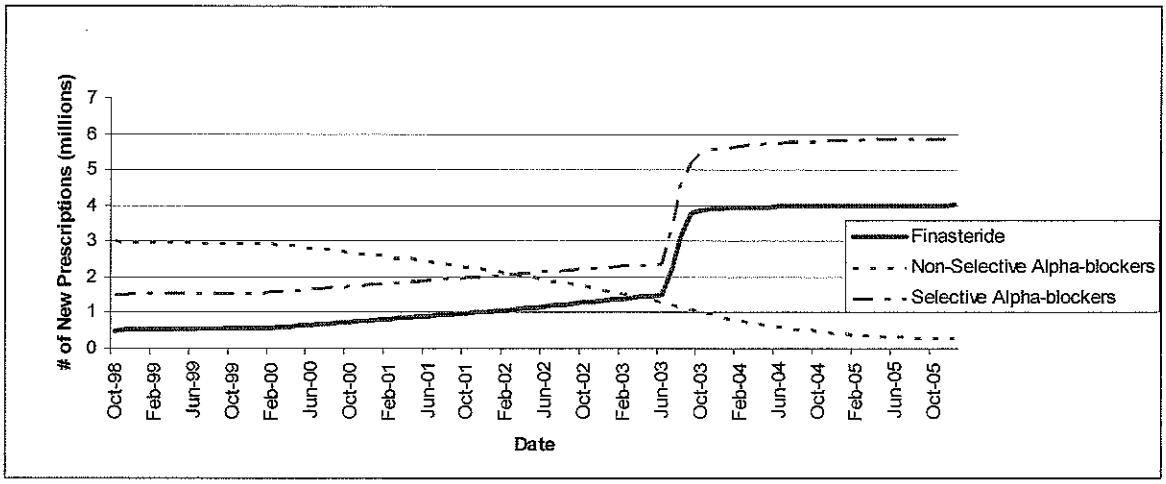
will not be shared or made accessible to anyone outside of the Center. Analysis will done using the statistical software package Stata™(Version 9.0).

Data analysis and sample results

Part A – PBM prescription data:

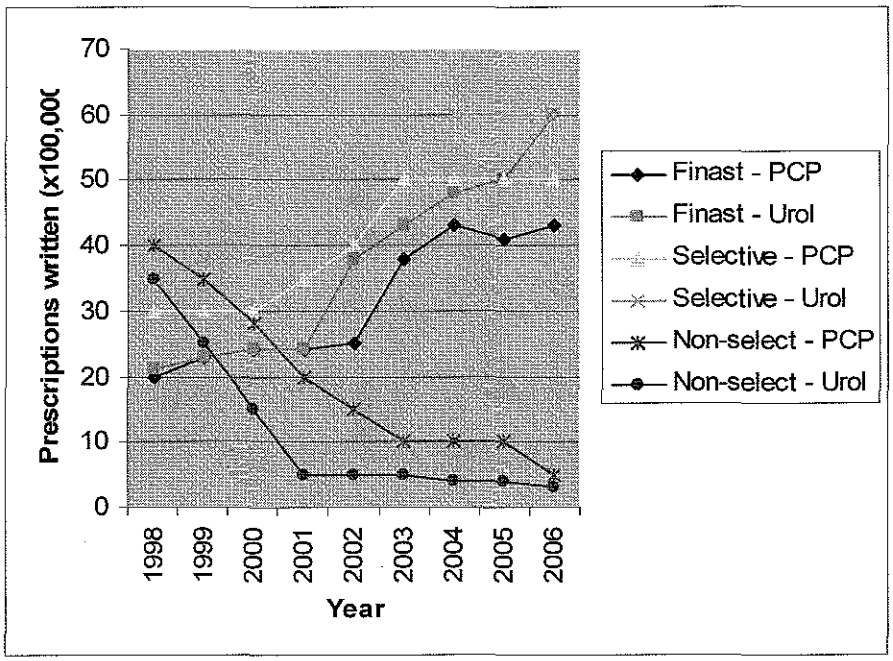
Prescription data for finasteride and alpha blockers will be analyzed. First, the total number of prescriptions written for finasteride and alpha-blockers will be plotted over time on a month-by-month basis. Example data are displayed in Figure 7 below. Alpha-blocker data will be subclassified into selective and non-selective. The specific time point of interest is July 2003, when the PCPT was published and December 2003, when MTOPS was published. It is hypothesized that finasteride prescriptions will significantly increase thereafter. A two-sided Cox and Stuart test for trend will be used to determine if there is a statistically significant trend in finasteride or alpha-blocker prescriptions. Then exponential smoothing models will be applied to model finasteride and alpha-blocker prescriptions, and finally, using multivariate time-series techniques, confounding variables, such as geographic location and physician (PCP vs urologist), will be controlled for. Mean finasteride prescriptions from January 2004 to 2006 will be compared with mean finasteride prescriptions from Oct 1998 to June 2003 using a t-test. A similar analysis will be done with all alpha-blockers, and then stratified based on selective and non-selective alpha-blockers.

Figure 7: New finasteride and alpha-blocker prescriptions over time



Then, the prescription data will be classified according to primary care physician or urologist prescription. Within these categories, prescriptions will be plotted over time. Sample data are shown in Figure 8 below. These data will be analyzed using longitudinal models to detect significant differences between primary care physicians and urologists within each category of pharmaceutical.

Figure 8: Prescriptions for finasteride and alpha-blockers written by primary care physicians and urologists over time



Part B – Physician Survey:

Within each domain of the survey, all closed-ended questions will produce categorical data and will be analyzed with the chi-squared statistic. Comparisons will be made between urologists and other primary care physicians, academic versus community physicians, physicians serving different proportions of African American patients and age of physicians. Table 5 illustrates a sample categorical table and chi-squared statistic generated from the survey results.

Table 5: Assessment of knowledge: "What effect does finasteride have on PSA LEVELS? (Choose 1)" n=583

Variable	PCP	Urologist	Total
No effect on PSA levels	70	15	85
Decreases PSA only slightly	15	60	75
Decreases PSA by approximately half	95	140	235
Increases PSA only slightly	70	10	80
Increases PSA by approximately double	50	3	53
I don't know	50	5	55
Total	350	233	583

P=0.007 – Chi-squared test

Bias and Limitations:

In Part A, with the PBM system nearly all outpatient prescriptions written by VA physicians will be registered in the PBM database. Given the low copayments for prescriptions in VA pharmacies, there is strong incentive for patients to obtain all their medications from VA pharmacies. Nonetheless, it is possible for patients to receive finasteride from pharmacies outside the VHA. Such activity would cause an underestimate of the total number of prescriptions written, but would be unlikely to influence the relative trend in prescriptions over time.

As mentioned above, changes in finasteride use may represent use in treating BPH or use in prostate cancer chemoprevention. Given that finasteride is not FDA approved to use in a chemopreventive setting and there is no ICD-9 code to identify a person who is being treated for chemoprevention, it is impossible to capture this data on this scale. However, we have attempted to minimize this bias by ascertaining alpha-blocker prescriptions. It may be possible to estimate the proportion of the increase in use

of finasteride due to BPH treatment by measuring the increase in alpha-blockers at the same points in time.

However, alpha-blockers, particularly the non-selective ones, may be used for treating hypertension as well as BPH. This may cause an overestimate of the use of alpha-blockers. This bias is susceptible to changes over time, as publication of evidence pertaining to alpha-blockers in treatment of hypertension has been shown to change prescribing habits.[135]

In Part B, there is potential for selection bias given that those physicians most likely to respond may over-represent physicians who are up to date on the literature. Since it is an online survey, respondents may also over-represent younger, more computer savvy physicians who work at larger academic centers with readily available internet access. As such, one of the largest potential limitations of this study pertains to response rate. Physician enrolment in survey studies is highly variable ranging from 45% to 74%.[136-139] For our sample size calculation above, we used the most conservative response rate estimate of 45% to minimize the influence of poor response rate on our results.

Overall Conclusions

The burden of suffering attributable to prostate cancer is large. However, much of this burden is not caused by prostate cancer deaths, but rather by the psychological and physical burdens of receiving a diagnosis and undergoing treatment. Thus, preventing prostate cancer appears the best strategy to reduce this burden. With insufficient

evidence supporting screening, attention has turned to chemoprevention. Finasteride has shown the most promise and has the best quality of evidence supporting it.

It is clear that finasteride reduces the period prevalence of prostate cancer. However, it is not clear that the tumors prevented would have ultimately been diagnosed or warranted treatment. It is also not clear whether finasteride may increase the risk of high grade tumors. With the intimidating costs of treating every man of average risk with finasteride for life, the cost-effectiveness is modest at best. Thus, the decision to place men on finasteride is marred with uncertainty.

The uncertainty surrounding use of finasteride to prevent prostate cancer is unlikely to be resolved for several years. Yet finasteride is still available for long-term use in treating BPH, and may well be used by some physicians to prevent prostate cancer despite the controversy. Given the potential impact finasteride has on prostate cancer incidence, aggressiveness and PSA levels, the insight gained regarding the current use of finasteride is important. Discovering that many men are currently taking finasteride, but that physicians are not well informed regarding the influence of finasteride on parameters such as PSA, prostate volume and the potential increased risk of high grade tumors may indicate a need for directed educational interventions for both physicians and patients.

Understanding physician perceptions of the current evidence for finasteride as a chemopreventive agent will help guide future research and tailor guidelines to address the areas of greatest concern or uncertainty. I hope to gain insight into the different levels of knowledge and perception between PCPs and urologists. Such information could guide future recommendations for when PCPs should refer a patient to a urologist.

Until new evidence is presented clearing the picture for finasteride or identifying a new promising chemopreventive agent, men are best served through a better understanding of how current evidence is interpreted and assimilated.

Appendix

Table Short-forms:

Bx – biopsy
PEP – primary end-point
SEP -
CaP – prostate cancer
BCR – biochemical recurrence
PIN – prostate intraepithelial neoplasia
LUTS – lower urinary tract symptoms
AUA SxS – AUA symptom score
Qmax – maximum urinary flow rate (ml/sec)
SWOG – Southwestern Oncology Group
PFS – Progression free survival
CSS – Cancer-specific survival
MFS – metastasis-free survival
PSAD – PSA density

Key Question #1 – Abstraction Table

Citation/Design	Participants	Inter-ventions	Measurements	Results	Conclusions	Quality Comments	Overall Comments
Thompson et al; 2003 RCT	18,882 men ≥ 55 Norm DRE PSA ≤ 3	Finast 5mg od Placebo	PEP – CaP period prevalence PSA/DRE drive bx End of study biopsy	PEP - CaP in finest group compared to plaebo (18.4% vs 24.4%; RRR 24.8%; 95% CI 18.6-30.6, p<0.001) ; NNT=17 SEP- % gleason grade 7-10 (6.4% vs 5.1%; p=0.005); NNH = 77	Finasteride prevents prostate cancer. But concerns regarding high-grade tumors	Well done Quality - Good	Best case scenario: Cancer risk reduction is real Increased high grade is artifact Worst case scenario: Cancers prevented are indolent Grade inflation is real
Rubin et al; 2005 Case-control	56 men with CaP taking finast for BPH for min 6 months (mean 2.9yrs) 56 matched controls from database of CaP 44 unmatched men consecutively chosen from database on 3 months LHRH course Matching: age, DRE, PSA, Gleason	None	Pathology review looking for "hormonal effects" Specimens graded 1-3	PEP – mean hormonal treatment score 0.4 for control, 0.5 finasteride and 1.6 for LHRH SEP – BCR. 85.4% vs 72.6% finasteride, p=0.85).	Finasteride does not appear to have the same morphological changes as LHRH therapy.	Mixture of RP, TURP and biopsy specimens Comparison group (LHRH) was not matched and was just a consecutive sample. No attempt to control for confounding SEP – BCR: grossly underpowered, no control for confounding Quality – Poor	Poor quality study. Conclusion, even if true, does NOT answer the question of whether finasteride may artifactually increase the grade
Irani et al; 2002 Case-control	Consecutive patients undergoing Bx at 12 different sites in France 639 CaP	None -min 6 core bx -	Medication use: self questionnaire Other diet and lifestyle risks also assessed	Never vs Ever users: Univariate -NSAIDs: OR 0.80 (95%CI 0.64-0.99) -Finast: 0.71 (0.47-1.06)	Finasteride has chemopreventive effect NSAIDS do not, but warrant further investigation	Median PSA high, esp in control group: suggests more BPH (therefore more likely taking	Poor quality study Short duration of exposure Weak definition of exposure adherence High risk population (mean PSA high)

	659 no Cap		Use categorized as user if : >15/month, >1/month, < 1/month Non user if never	Multivariate: -NSAIDS: OR 0.84 (0.66-1.07) -Finast: 0.58 (0.37-0.92)		finasteride) High risk: Hospital referral pop: not avg risk popn No adjustments for PSA in finest rx Innappropriate classification of exposure Quality - poor	Not avg Risk population
Andriole et al; 2004 Pooled 3 RCTs	3 RCTs pooled 4325 men with BPH PSA 1.5 – 10	Dutast 0.5 Vs Placebo X 24 months Then open label ext	Cum Incid by non-protocol mandated biopsy	CI at 24.4 months 1.1 % dutast 1.9% placebo P=0.025 HR 0.61 (0.37-1.02) CI at 27 months 1.2% dutast 2.5% placebo p=0.002 HR 0.49 (0.31-0.77) Path data only available in 27 subjects (no sig dif)	Cumulative Incidence lower in dutast group	At 27 months, open label may have lead to increased biopsies in placebo group Quality- poor Fatal flaws introducing bias Do not have a good sense of these men. Inappropriate pooling	Cancer status before trial not known; indications for biopsy or biopsy cores not specified. Path specimens not centralized
Cote et al; 1998 RCT	52 men "several institutions"?? PSA > 4.0 previous neg Bx	Finest 5mg (27) Placebo (25) x 12 months	Biopsied at 12 months: PEP: % hyperplastic tissue SEP: Cancer +/- PIN +/- Pathologist blinded	PEP - % change in hyperplastic epithelium -8.3 finast vs -2.9 placebo; p=0.11 SEP – Finast 30% cancer vs 4% placebo (p=0.025)	"provides little evidence that finasteride is an effective chemotherapeutic agent" in high risk men	Not clear who these men are Unclear source popn Very Short Quality - Poor	With only 9 cancers detected, high chance of spurious findings Likely many of these men already had cancer…therefore can't conclude that finast does not prevent cancer Finast shrinks gland size: detection bias Operational? Control group issue
Guess et al; 1997	125,000 men from		Serum marker			Quality: good	Not directly applicable to

Nested case-control	Kaiser Permanente 1964-1971 106 cases selected Controls: matched age, date of serum and clinic location		levels: Total T, Free T Andosterone			Asking the wrong question	KQ#1
Stoner et al; 1994 Pooled results 2 RCT's "North American Study" "International Study"	1645 age 40-83 BPH PSA >40: excluded N. America: 25 US, 5 Canadian centers International: 45 centers in 17 countries	Finast 1 or 5mg Vs Placebo 12 months total	Unspecified biopsy criteria DRE and PSA at 6, 9, 12, 18, 24 months	12 cases of Cap during 12 month study (4 placebo, 3 on 1mg, 5 on 5mg) 20 cases of CaP in the open extension		Unable to discern differences between groups at baseline Follow-up too short	Again, CaP likely present before the case began

Key Question #2 – Abstraction Table

Citation/Design	Participants	Inter-ventions	Measurements	Results	Conclusions	Quality Comments	Overall Comments
Thompson et al; 2003 "PCPT" RCT	18,882 men ≥ 55 Norm DRE PSA ≤ 3	Finast 5mg od Placebo	**PEP** – CaP period prevalence PSA/DRE drive bx End of study biopsy HARMS (using validated SWOG classification)	PEP and SEP in other table HARMS: See table 4 for exact Decr ejaculate, erectile dysfxn, loss libido, gynecomastia: all more in finast (p<0.001) BPH, urgency, frequency, retention, TURP, prostatitis, UTI: all less in finast (p<0.001) Breast Ca (1 case finast; 1 case placebo), Incont: NS	Finasteride causes more sexual side-effects relative to placebo, but improves LUTS and BPH. Concerns regarding high-grade tumors also applicable (see prior table)	Well done Quality - Good	Best documentation of side-effects and harms. Most applicable to the population of interest.
McConnell et al; 2003 "MTOPS" RCT	3047 men 17 clinical centers in U.S. >50 yrs AUA SxS=8-30 Qmax: 4-15 ml/sec Enrolled 1993-1998 Excl: prior meds or surg for BPH BP <90/70 PSA >10 ng/ml	Placebo Vs Doxazosin (1mg →8mg) Finast 5mg Combo	**PEP:** "overall clinical progression" – AUASxs incr 4 pts over baseline; urinary retention, renal insuff, UTI, incont **SEP:** AUA SxS (← validated) Qmax Compliance DRE PSA U/A TRUS	Mean F/U: 4.5 yrs Risk of progression reduced relative to placebo by: Dox (39% ARR, p<0.001) Finast (34% ARR, p=0.002) Combo (66% ARR, p<0.001) NNT combo: 2 Many SEPs reduced as well (see table in paper) Harms finasteride (see table 4): -ED, decr libido, abnormal ejac	Long term combo Rx was safe and reduced overall clinical progression of BPH more than placebo, or either drug alone	Well done Quality – good	2nd best documentation of side-effects and harms. Though no cancer outcomes even addressed. Population in this study may be slightly different since men with known BPH (Mean serum PSA still <3..so still avg risk)

			Adverse events	-27% d/c'd finast Rx 18% d/c'd combo Breast Ca: 4 pts on finast; 0 on dox or plac			
Lowe et al; 2003 Pooled 6 year data from patients enrolled in BPH RCT's	1657 men from Phase II N.America and international trials After 1 yr double blind placebo controlled: asked to participate in 5 yr open extension on 5mg Finast DRE: enlarged prostate Symptoms of obstructive uropathy Max flow <15 cc/s	Finast 5mg	Monitored q6mo Prostate vol Qmax Safety eval Non –validated instruments	6 year data only for 487 Finast men; 238 placebo men Adverse events: see table II in paper: Finast had higher rates of decr libidio, ejac, impotence, breast complaints. Rates declined with time. 6yr rates were lower than 1yr placebo. Attrition large	Finasteride: durable improvement in LUTS; prevealence of adverse events does not increase over time.	Quality – fair Only 50% of original randomized cohort included; not clear how this sub-cohort compares to one another (?selection bias: motivated patients) -caution declining rates with time: as people drop out due to adverse events, people left in study less likely to have side-effects	Results in agreement with better quality studies. Doctor reported vs patient reported Instruments not standardized
McConnell et al; 1998 "PLESS" RCT	3040 Moderate to severe LUTS (using a "validated" symptom score but not AUA or IPSS) Qmax <15 DRE: enlarged Exc: any antiandrogen rx, hx of prostatitis, prostate or bladder cancer or surgery, PSA <10	Finast 5mg Placebo X 4yrs	Evaluated q4mon Sx and Side Fx using previously validated instrumen Qmax PSA DRE	See table 3 Finasteride treated arm had more decr libido, impotence, decr ejaculate, breast enlargement, breast tenderness, rash ($p<0.05$) The sexual symptoms lessened with longer treatment Prostate cancer: 5% in each group.	Treatment with finast for 4 years reduces symptoms and prostate volume, increases urinary flow rate, reduces probability of surgery and AUR. More sexual side-effects in finasteride: lessen with time	Quality – good Validated instruments used	Results in agreement with more recent studies. Still doctor reported symptoms but no bias between groups.
Gormley et al;	25 US centers	297:	Evaluated	See table 4 in paper for	5mg finasteride	Quality –fair	Results in agreement with

1992 RCT Double blind, placebo controlled	5 Canada centers 895 men Age 40-83 Sx of obst DRE: enlarged prostate Qmax <15 ml/s	Finast 5mg 298: finast 1mg 300: placebo 12 months	qmonth Prostate volume Symptoms Side-effects	adverse events Finast had higher rates of: decreased libido, ejaculatory disorder ($p<0.05$) Had NS higher rates of abdo pain, flautulence, breast pain, dysuria, impotence, orgasmic dysfunction,	decrease obstructive symptoms and increases flow: but slightly increasd risk of sexual dysfunction	Short follow-up Instruments not standardized Doctor reported vs patient reported	more recent studies with longer follow-up

Key Question #3 – Abstraction Table

Citation/Design	Participants	Inter-ventions	Measurements	Results	Conclusions	Quality Comments	Overall Comments
Etzioni et al; 2005 2ndary Data analysis	From PCPT Data EOS Biopsies: 928 with Cancer 8620 with no Interim Biopsies: 671 with cancer	None	Estimated long-term effects of finast on PSA	PSA growth associated with disease status and treatment group assignment Placebo: PSA median increase 3%/yr noncase, 6%/yr cases, 11%/yr for cause ($p<0.001$) Time x High-grade significant Placebo arm: HG cases had PSA increase of 18% annually vs LG 8% Finast arm: Noncance: PSA -5%/yr Cancer: PSA +15% /yr EOS: 5% vs 7%	Confirms need for PSA adjustment of >2. Multiplicative factor would increase with time (by their calc increase from 2 to 2.5 over 7 years) Increase in PSA due to disease progression apparently dominates any decrease associated with finasteride PSA increases by grade on finast were comparable to those not on finast	Quality – Good Sound statistics Good use of 2ndary data analysis	2ndary data analysis of PCPT data PSA still sensitive even on finasteride in terms of velocity, but not absolute number. Must multiply by 2-2.5
Carver et al; 2005 Retrospective cohort	1996-2003 45 men had RP and on finast >6 months -blinded pathological review -	None	Recurrence free survival Predictive ability of gleason score at biopsy as measured by comparing the predicted 5 year PFS from nomograms using biopsy gleason score with actual 5 yr	Mean duration of finasteride Rx 23.6 months 5 yr estimate PFS 85% actual 86% Mean follow-up only 33.5 months	Finast does not compromise assignment of gleason grade for using prediction tools Gleason grade remains an important prognostic predictor	Quality - poor Retrospective cohort Uncontrolled Outcome not validated Can't draw the conclusion they did from the outcome they chose Too small n Not enough followup	Poor internal validity renders this study useless

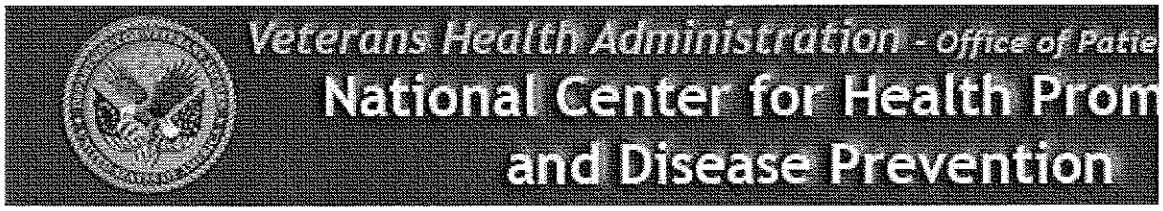
			PFS				
Kaplan et al; 2002 Uncontrolled trial	38 men: baseline serum PSA >4 normal DRE >2 previous negative biopsies	5 mg finas od	PSA measured 6 and 12 months after Repeat Bx at 1 yr Changes in Vol, PSA measured	Mean baseline PSA 6.32 Mean volume 37.3 cm3 1yr psa: 3.73 (-41%) 1yr vol: 30.4 (-18.5%) 29% CaP+: PSA 7.3-5.2 (-28.8%) Vol 37.3-32.3 (-13.4%) PSA decrease: >50%: 0% cancers 33-50%: 32% cancers <33%: 56% cancers	Response to finasteride challenge among those with prior negative biopsy could be prognostic	Quality – fair No control group Small N No a priori definition of cut-points for PSA decrease	Outcome measured does not address key question specifically: further example though of what finasteride does to PSA and Vol even after 1 year -men in this study are high-risk: not applicable to our popn of interest
Yang et al; 1999 2ndary data analysis: PLESS	53 cases: (35 finasteride, 18 placebo) 50 control: (25 finast, 25 placebo)	none	Blinded path review looking for several pathological characteristics	No significant histological changes were noted with finasteride	Finasteide does not alter histological appearance of cancer	Quality – fair Only one pathologist opinion	2ndary data analysis from PLESS
Andriole et al; 1998 RCT – PLESS 2ndary analysis	3040 men age 4-78 PSA <10 No hx of Ca If pre-study PSA >4: negative prestudy bx req'd	Placebo (1516) Finast(1524) X 4 years	PSA q4-8 months DRE annually 1st 4 yrs: investigators unaware of actual PSA values. Just told if it met threshold (>0.5 change/yr on finast, >2/yr on placebo) After 4 years: told adjusted values like PCPT	21% had biosy 6.6% had turp CaP 4.7% finast vs 5.1% placebo Elevated PSA prompted Dx in 35% of finast cases and 34% placebo AUC PSA: Finast 0.84 Placebo 0.79 p=0.07 Use of cut off of PSA 2.0 for finast and 4.0 for placebo: similar sensitivity 66% vs 70%, but higher specificity (82% vs 74%)	Men tx with finast: Multiplying PSA by 2 and using normal ranges for untreated men preserves the usefulness of PSA for CaP detection	Quality – Good No selection bias b/c PLESS selection was clean. Magnitude of these results enough not to question whether Bias would drive result below significance	Directly addresses the key question(best paper so far on this) Essentially validated current practice of multiplying by 2
Oesterling et al;	72 with BPH from	Finast	PSA doen at	Similar results between	Finasteride decreases	Quality – Fair	But does it cause

1997 Pooled data from 2 RCTS	BPH study 77 with BPH and CaP from BPH/CaP study 50 of 77 had TURP already which led to Dx 8 US centers 14 european centers age 44-80 PSA 1-10	5mg vs placebo X 6 months	days 1,2,7,14 and months 1,2,3,4,6 Blinded to PSA Placed into strata based on baseline PSA PEP: % change in PSA from baseline PSA doubled for finast after 3 months tx	2 studies PSA nadir around 12 weeks of tx At 3 months: PSA drop 56% in BPH, 46% in BPH and CaP for low strata vs 44% and 53% for highstrata	PSA by 50% Doubling of PSA in finast groups does not mask detection	Mixing of distinctly different patient populations (Cancer and not) is not appropriate. However, short follow-up and endpoint choosen: may be able to get away with it.	overdetection of indolent cancers: we cannot tell this without a study examining mortality
Gormley et al; 1994 2ndary analysis of 12 month RCT	895 men 30 centeres in N.America age 40-83 All: enlarged DRE LUTS Excl: PSA >40, UTI, chronic prostatitis, neurogenic bladder	Finast 1mg (to 50%) and 5mg (to 50%) vs placebo X 12 months	Volume: MRI PSA: central lab -at baseline 3, 6, 12 months PSAD = PSA/vol Sn=% cancers with PSAD >0.1 Sp=% no cancer with PSA <0.1 PPV % with PSAD>0.1 and dx with cancer	Analysis combined 1 and 5mg finasteride Finast increased the PPV of PSAD from 14 to 30% Using PSA alone with cutoff of 10ng/ml at baseline and 5 ng/ml after 12 months of finasteride tx produces similar Sn and Sp	PSAD may provide additional reassurance without requiring adjustment for finasteride tx	Quality – fair Not clear who these men are, nor their baseline risk Also not clear criterion for when biopsy; no end of study biopsy to minimize bias	Adjunctive evidence showing that PSAD may have fair Sn and Sp

Key Question 4-6: Abstraction Table

Citation/Design	Methods	Results	Conclusions	Quality Comments	Overall Comments
Unger et al; 2004 Person-years saved modelling	Outcome: person-years saved (PYS) Weighted outcomes to evaluate risk-benefit Weights assigned based on survival (easy & accurate) Used SEER survival data for men >55 with low/int grade and high grade tumors Also: survival for gen population from National Center for Health Statistics Assumed: if cancer prevented, followed normal life-span Area under survival curves = avg survival time Weight of HG = (AUCprev-AUChg)/(AUCprev – AUClg) Total person years lived (PYL) = cohort size x AUC -sum of weights for each outcome N= all men with CaP between 1993-1997	"Control" SEER data: 1000 men aged 63 (mean PCPT age) - 6% (or 60) would get CaP over 7 yrs; and 20% get Gleason 8-10 PCPT – only 45 get cancer over 7 yrs, but If no change in rate of high-grade: 316,760 PYS over 10 yrs Assume from PCPT 6.9% increase relative to normal cohort 262,567 PYS over 10 yrs Assume 8.9% diff (graded only) 246,859 PYS over 10 yrs Final: rate of HG would have to be 40% higher than normal for risks to = benefits (PYS=0)	Using finast: net positive impact on population mortality weven with an increase in the rate of HG tumors	Quality – fair Simplistic view Assumed that the relative change in HG tumors seen in PCPT would apply to overall popn. But gen pop has higher rate of high grade tumors than that seen in PCPT control group. ?is this an under estimate?	Need QALY and economic impact measures One strength: did not use PCPT incidence rates to model the system: used SEER – more accurate to population incidence rates
Lotan et al; 2005 Decision-analysis model of survial outcomes	Outcome: PFS, CSS, MFS Assumes men meet PCPT entry criteria (age and low risk of CaP) Probability of cancer detection taken from PCPT Assumed that patients with no cancer survived entire 15 years (overestimates) Survival estimates based on published cohort data with 10yr or more survival after RP or WW…NOT XRT Studies included did not have overall survival data: had PFS, mets-free survival etc. Modelled variability: by using LCI and UCI of 95% CI around RRR from PCPT (24.8%)	Cause-specific survival Benefit for finast tx popn with WW: <1 month (-0.4 months in 55-59, +0.8 in 65-69) Benefit for finast tx popn with RP 1.7 month (0.7 RFS) Assume no gleason effect: 3 month CSS – regardless of WW/RP For-cause subset tx RP: 0.35 month survival in 15yr CSS 0.09 month survival in 15yr RFS For-cause subset tx WW: 0.2 month decrease in younger 0.04 month increase in older If gleason scores equiv: 0.7 month advantage	Finasteride can impart survival benefits: especially in higher risk patients and if assume no grade effect	Quality – good Overestimates probability of cancer detection b/c uses PCPT control of 18%...way too high (autopsy like-rates) – ah but they did subset analysis using for-cause only. Didn't account for competing risks	Given that advantage to finast increases with incidence, then using the PCPT to estimate incidence will overestimate finast benefits. Note: assumes finast has equal efficacy in higher risk popn

		Benefit of finast increases with increasing incidence of CaP in gen popn		XRT or brachy outcomes not modelled. Estimates based on PFS and MFS Only 15 yrs	
Unger et al; 2005 Person-years saved modelling ?Repeat	Identical model as presented above – essentially a repeat publication.				
Klein et al; 2005 Benefit: risk ratios	Absolute benefit/absolute risk ratio calculated Used: ratio of absolute risk reduction: absolute excess risk of excess high-grade cancers Altered assumptions: 10,25, 50% of excess was artefact Altered assumptions: 25% overdetection in finasteride arm Repeated analysis for-cause biopsies	Overall: 4.6:1 -meaning 4.6 cancers prevented for every 1 excess case of high-grade disease -Delta % artefact: 10% = 5.1:1 25% = 6.2:1 50% = 9.2:1 -assuming 25% over detection: 0% = 8.2:1 10% = 9.1:1 25% = 10.9:1 50% = 16.3:1 -For-cause: only ranges from 1.9:1 – 8.0:1	Finasteride ranges from being beneficial to more beneficial depending on degree of grade bias and overdetection	Quality –fair - Weights not assigned to each outcome -biased reporting and modelling by not using for-cause biopsy -all assumptions positively shed light on finast -conflicts of interest: Merk++	Absolute risk increase for grade: they used only graded tumors rather than the ARR for all men in the study: therefore underestimates?
Grover et al; 2006 Markov c Life Years	Montreal prostate cancer model: a markov model Used to forecast survival Estimates expected age at Dx, probability of progression, and overall survival, MFS, DSS Base case: cohort 1000, 62 yr old men tx c finast Modelled primary tx, salvage tx options based on data from medicare patients Progression rates from published data Rates based on PCPT for-cause and EOS biopsies	Base cohort tx with finast: Increased survival 140 life years (0.14 years/person) Benefit of finasteride decreases with increasing age Assume grade diff is artefact: 200 life years (0.2 years /person) Model only for-cause biopsy: 20 life years (0.02 yrs/person)	PCPT results look promising in terms of benefit, but caution grade and over-detection issue	Quality – good But didn't weight value to cancers not detected vs cancers detected and treatment	No costs incorporated (wasn't the goal though…decisio n analysis model)
Zeliadt et al;	Models cost per life-year and cost per QALY	Base-case analysis:	Cost burden	Quality – good	Most elegant of



Prostate Diseases Survey

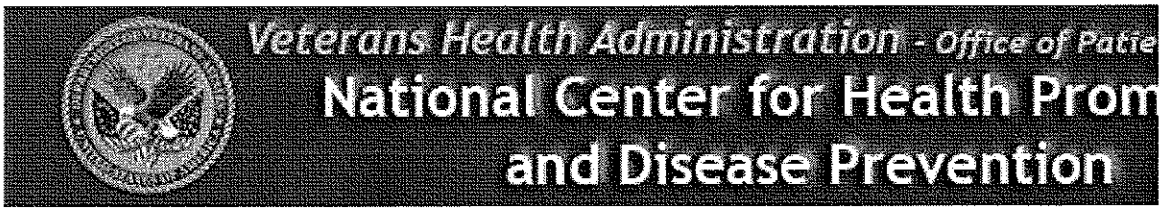
1

To help tailor this survey, please indicate which of the following best describes your practice?(Choose 1)

- Family Practice
- General Internal Medicine
- Geriatrics
- Urology
- Other, Please Specify

SUBMIT

Survey Page 1



Prostate Diseases Survey

Survey Progress

We are interested in how you diagnose and treat a common prostatic disease like Benign Prostatic Hyperplasia (BPH).

2

How frequently do you diagnose benign prostatic hyperplasia (BPH) in your male patients? (Choose 1)

- I've never diagnosed it
- Only a few times in my career
- About once a year
- Two or three times a year
- About once a month
- Two to three times a month
- About once a week
- More than once a week

3

How frequently do you ask about lower urinary tract symptoms (e.g., hesitancy, nocturia, weak stream) in your male patients? (Choose 1)

- Never
- Occasionally
- Most of the time
- Always
- Only after they have brought it up first

4

How frequently do you calculate American Urological Association (AUA) symptom scores or International Prostate Symptom Scores (IPSS) on your patients who complain about lower urinary tract symptoms?

(Choose 1)

- Never
- Occasionally
- Most of the time
- Always

5

If you calculate AUA or IPSS scores, do you use a pre-printed score sheet to help you? (Choose 1)

- I never calculate AUA or IPSS scores
- Yes
- No
- Sometimes

6

How frequently do you obtain PSA levels in patients you suspect have BPH? (Choose 1)

- Never
- Occasionally
- Most of the time
- Always

7

How frequently do you TREAT men with BPH? (Choose 1)

- I've never treated it
- Only a few times
- About once a year

- Two or three times a year
- About once a month
- Two to three times a month
- About once a week
- More than once a week

8

How would you describe your comfort level in treating men with BPH? (Choose 1)

- Very comfortable
- Somewhat comfortable
- Somewhat uncomfortable
- Very uncomfortable

9

How frequently do you refer your male patients with BPH to a specialist? (Choose 1)

- Never
- Occasionally
- Most of the time
- Always

10

If you refer patients with BPH, which specific patients are you most likely to refer? (Choose all that apply)

- I never refer patients with BPH
- Men with BPH and large prostate glands (>40 ml or golf-ball size)

- Men with BPH and high PSA levels
- Men with BPH that haven't responded to initial medical therapy
- Men with BPH and concerns about prostate cancer
- Other, Please Specify

11

Which of the following are effective in treating BPH? (Choose all that apply)

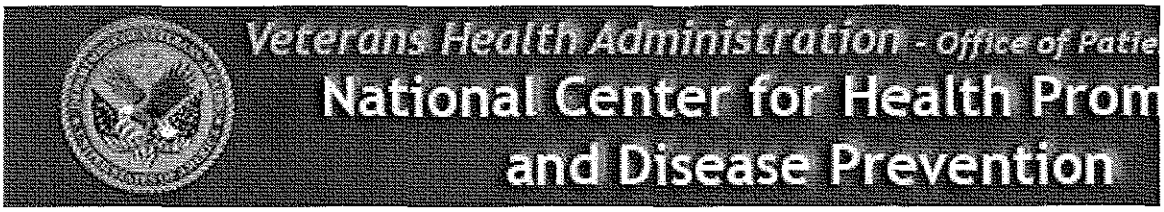
- Non-selective alpha blockers (e.g., doxazosin (Cardura))
- Selective alpha blockers (e.g., tamsulosin (Flomax))
- 5-alpha-reductase inhibitors (e.g., finasteride (Proscar))
- NSAIDs (e.g., Ibuprofen)
- Other, Please Specify

12

Is BPH a risk factor for prostate cancer? (Choose 1)

- Yes, BPH is a strong risk factor
- Yes, BPH is a weak risk factor
- BPH is not a risk factor
- BPH protects against prostate cancer

SUBMIT



Prostate Diseases Survey

Survey Progress

In this section, we are interested in how you treat a common prostate disease like Benign Prostatic Hyperplasia (BPH).

13

How frequently do you prescribe an alpha-blocker to treat BPH? (Choose 1)

- I've never prescribed it
- Only a few times in my career
- About once a year
- Two or three times a year
- About once a month
- Two to three times a month
- About once a week
- More than once a week

14

If you use alpha-blockers to treat BPH, which do you favor?

- Non-selective: doxazosin (Cardura); terazosin (Hytrin); prazosin (Minipress)

- Selective: tamsulosin (Flomax); alfuzosin (Uroxatral)
- Depends on the patient
- I never use alpha-blockers to treat BPH

15

Compared to 5 years ago, how frequently do you prescribe alpha-blockers? (Choose 1)

- More frequently than 5 years ago
- Less frequently than 5 years ago
- About the same
- I never use alpha-blockers to treat BPH
- Other, Please Specify

16

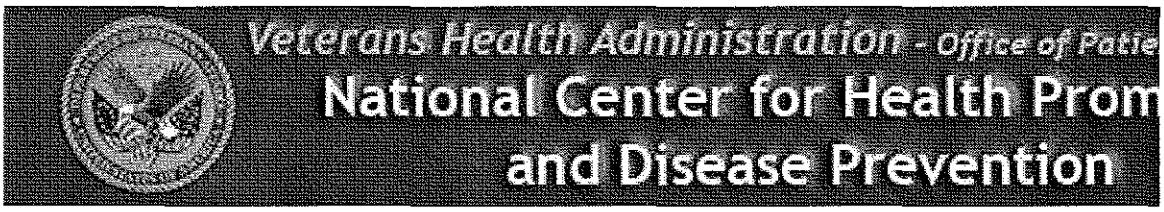
If your prescribing patterns have changed what has influenced you? (Check all that apply)

- My prescribing patterns have not changed
- Results of the Prostate Cancer Prevention trial (PCPT) - Finasteride vs Placebo in preventing prostate cancer
- Results of the Medical Therapy of Prostate Symptoms trial (MTOPS) - Doxazosin vs Finasteride vs Doxazosin & Finasteride vs Placebo in treating BPH symptoms
- The VA Pharmacy Benefits Management Guideline for Combination Alpha-Blocker and Finasteride Therapy for BPH
- American Urological Association guidelines for treating BPH
- My colleagues' opinions
- Information presented at continuing medical education conferences

- [ ] Interactions with pharmaceutical representatives
- [ ] Other, Please Specify

SUBMIT

Survey Page 3



Prostate Diseases Survey

Survey Progress

In this section we are interested in how you use the 5-alpha reductase inhibitors finasteride (Proscar) or dutasteride (Avodart) with your patients.

17

Currently, how frequently do you prescribe finasteride or dutasteride? (Choose 1)

- [ ] I've never prescribed it
- [ ] I've prescribed it only a few times in my career
- [ ] About once a year
- [ ] Two or three times a year
- [ ] About once a month

- Two to three times a month
- About once a week
- More than once a week

18

Compared to 5 years ago, how frequently do you prescribe finasteride or dutasteride? (Choose 1)

- More frequently than 5 years ago
- Less frequently than 5 years ago
- About the same
- I've never prescribed finasteride

19

If your prescribing patterns have changed, what has influenced you? (Check all that apply)

- My prescribing patterns have not changed
- Results of the Prostate Cancer Prevention trial (PCPT) - finasteride vs Placebo in preventing prostate cancer
- Results of the Medical Therapy of Prostate Symptoms trial (MTOPS) - doxazosin vs finasteride vs doxazosin & finasteride vs placebo in treating BPH symptoms
- The VA Pharmacy Benefits Management Guideline for Combination Alpha-Blocker and Finasteride Therapy for BPH
- American Urological Association guidelines for treating BPH
- My colleagues' opinions
- Information presented at continuing medical education conferences
- Interactions with pharmaceutical representatives
- Other, Please Specify

20

For each indication, please choose how frequently you prescribe finasteride or dutasteride?

1 Never	2 Only a few times	3 About once a year	4 Two or three times a year	5 About once a month	6 Two or three times a month	7 About once a week	8 More than once a week

Men with BPH regardless of prostate size

1 2 3 4 5 6 7 8

Men with BPH AND small to medium sized prostates

1 2 3 4 5 6 7 8

Men with BPH AND large sized prostates (>40ml or a golf-ball size)

1 2 3 4 5 6 7 8

Men WITHOUT BPH but with concerns regarding prostate cancer prevention

1 2 3 4 5 6 7 8

Men with BOTH BPH and concerns regarding prostate cancer prevention

1 2 3 4 5 6 7 8

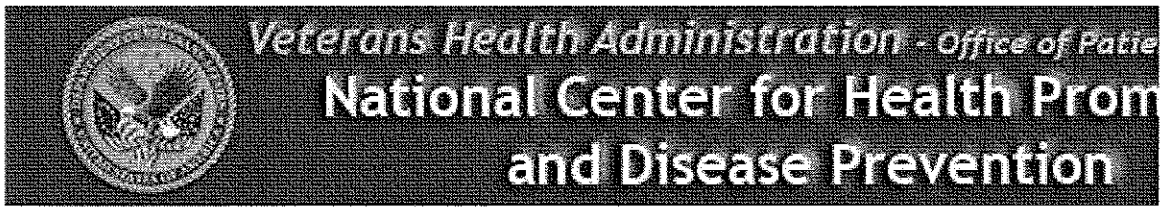
21

When you use finasteride or dutasteride to treat BPH, how frequently do you pair it with an alpha-blocker? (Choose 1)

- I ALWAYS use finasteride or dutasteride in combination with an alpha-blocker
- I SOMETIMES use finasteride or dutasteride in combination with an alpha-blocker
- I RARELY use finasteride or dutasteride in combination with an alpha-blocker
- I use finasteride or dutasteride only as monotherapy
- I never prescribe finasteride or dutasteride

SUBMIT

Survey Page 4



Prostate Diseases Survey

Survey Progress

Next we are interested in your awareness of the effects of finasteride.

22

Which of the following THERAPEUTIC EFFECTS are most frequently associated with men taking finasteride? (Choose all that apply)

- [ ] Finasteride has no discernible therapeutic effects
- [ ] Delaying/preventing progression of BPH
- [ ] Improving urinary flow rates
- [ ] Reducing acute urinary retention events
- [ ] Reducing urinary incontinence
- [ ] Reducing urinary tract infections
- [ ] Reducing the need for BPH surgery (e.g., TURP)

- [ ] I don't know
- [ ] Other, Please Specify

23

Which of the following SIDE-EFFECTS are most frequently associated with finasteride? (Choose all that apply)

- [ ] Dizziness
- [ ] Erectile dysfunction
- [ ] Decreased libido
- [ ] Abnormal ejaculation
- [ ] Postural hypotension
- [ ] Peripheral edema
- [ ] Dyspnea
- [ ] Fatigue/Weakness
- [ ] I don't know

24

What effect does finasteride have on PSA LEVELS? (Choose 1)

- [ ] No effect on PSA levels
- [ ] Decreases PSA only slightly
- [ ] Decreases PSA by approximately half
- [ ] Increases PSA only slightly
- [ ] Increases PSA by approximately double
- [ ] I don't know

25

What effect does finasteride have on PROSTATE CANCER RISK?

- No effect on prostate cancer risk
- Decreases prostate cancer risk, but only slightly
- Decreases prostate cancer risk, by 25%
- Increases prostate cancer risk, but only slightly
- Increases prostate cancer risk by 25%
- I don't know

26

Over what TIME-COURSE does finasteride influence these parameters (PSA, prostate volume, symptoms)? (Choose 1)

- Finasteride does NOT influence these parameters
- Days
- Less than 1 month
- Greater than 1 month, but less than 1 year
- Over 1 year
- I don't know

27

Does finasteride influence the GLEASON GRADE of prostate cancer? (Choose 1)

- NO, the grade of cancers seen in men taking finasteride is the same as those who are not taking it.
- YES, the grade of cancers seen is HIGHER
- YES, the grade of cancers seen is LOWER
- I don't know

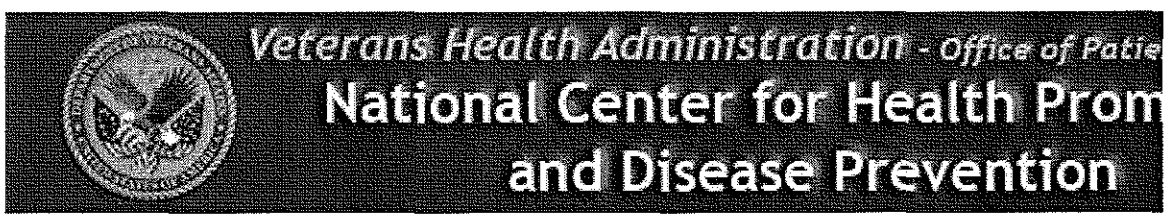
- [ ] Other, Please Specify

28

To whom do you look for recommendations regarding chemoprevention for prostate cancer? (Choose all that apply)

- [ ] I do not actively search for recommendations
- [ ] Colleagues in my local area (i.e., hospital/practice group)
- [ ] American Urological Association (AUA)
- [ ] American Cancer Society (ACS)
- [ ] National Cancer Institute (NCI)
- [ ] National Comprehensive Cancer Network (NCCN)
- [ ] National Institute of Health (NIH)
- [ ] U.S. Preventive Services Task Force (USPSTF)
- [ ] Other, Please Specify

SUBMIT



Prostate Diseases Survey

Survey Progress

In this section, we are asking about your use of finasteride as a prostate cancer chemopreventive agent.

29

How frequently do your male patients ask you about chemoprevention for prostate cancer? (Choose 1)

- Never
- Only happened a few times
- About once a year
- Two to three times a year
- About once a month
- Two to three times a month
- About once a week
- More than once a week

30

Do you raise the issue of using finasteride as a prostate cancer chemopreventive agent with your patients? (Choose 1)

- Never
- Occasionally
- Most of the time
- Always

31

If a patient comes to you asking about finasteride for chemoprevention what issues do you discuss with them? (Choose all that apply)

- [ ] I don't discuss the issue with my patients
- [ ] I don't discuss the issue, but I refer them to another physician for this discussion
- [ ] Potential to prevent prostate cancer
- [ ] Potential to cause side-effects
- [ ] Potential to improve urinary symptoms (if present)
- [ ] Potential to alter PSA level
- [ ] Potential to induce/select increased grade tumors
- [ ] Other, Please Specify

32

If you offer finasteride as a prostate cancer chemopreventive agent, IN WHICH PATIENTS do you choose to do this? (Choose all that apply)

- [ ] I don't offer finasteride as a chemopreventive agent
- [ ] I offer it to all male patients
- [ ] Men with a family history of prostate cancer
- [ ] African American men
- [ ] Men with elevated PSA
- [ ] Men with moderate to severe urinary symptoms from BPH
- [ ] Men with a previous negative prostate biopsy
- [ ] Other, Please Specify

33

If you DO NOT prescribe finasteride for prostate cancer prevention, please rank your reasons in order of importance: (1= most important, 5=least important)

NOTE: You may skip this question if you DO prescribe finasteride as a chemopreventive agent.

	1	2	3	4	5
I did not know it could be used for chemoprevention	■	■	■	■	■
Side effects of finasteride	■	■	■	■	■
Lack of comfort/familiarity with finasteride	■	■	■	■	■
Risk of increased Gleason grade cancers among those taking finasteride	■	■	■	■	■
Effects of finasteride on PSA levels	■	■	■	■	■

34

How do you change your screening practices for prostate cancer among your patients who are taking finasteride? (Check all that apply)

- ■ I don't. I screen men on finasteride the same as those who are not taking it
- ■ I check their PSA more frequently
- ■ I use a HIGHER PSA threshold to determine the need for further evaluation in men taking finasteride as compared to those who are not taking it
- ■ I use a LOWER PSA threshold to determine the need for further evaluation in men taking finasteride as compared to those who are not taking it

- I don't routinely screen for prostate cancer
- Other, Please Specify

35

What is your overall assessment of the BALANCE BETWEEN BENEFITS AND RISKS of using finasteride as a chemopreventive agent for prostate cancer? (Choose 1)

- Mostly positive - benefits outweigh the risks
- Neutral - benefits equal risks
- Mostly negative - risks outweigh the benefits
- I do not have an opinion
- Other, Please Specify

SUBMIT

Survey Page 6

Veterans Health Administration - Office of Patie
National Center for Health Prom
and Disease Prevention

Prostate Diseases Survey

Survey Progress

Finally, please tell us about yourself.

36

What is your age?

- Less than 30
- 30-40
- 41-50
- 51-65
- Over 65

37

Gender:

- Female
- Male

38

In what STATE do you practice? (Choose 1 from the drop-down menu)

39

How much time do you spend seeing patients in a VA facility? (Choose 1)

- 20% or less
- 21 - 40%
- 41 - 60%
- 61 - 80%
- >80%

40

Where do you see patients other than in a VA facility? (Choose 1)

- An academic practice setting
- A community (non-academic) practice setting
- Both
- I see patients only in a VA facillity

41

In what setting is the majority of your practice conducted? (Choose 1)

- Large city (pop >100,000)
- Suburb of large city
- Town or city (pop 50,000-100,000)
- Town or city (pop 10,000-50,000)
- Town (pop <10,000)
- Rural
- Other, Please Specify

42

Which of the following do you consider your main practice setting?

- Office or clinic – NOT at a hospital
- Office or clinic – AT a hospital
- Hosptial – in-patient

43

Approximately what percent of your male patients are African

American?

- <20%
- 20-40%
- 41-60%
- >60%

44

Approximately what percent of your male patients are over the age of 50? (Choose 1)

- < 20%
- 20-40%
- 41-60%
- >60%

SUBMIT

Survey Page 7

2005 Markov c QALY	Models 55 year old men: being finast or no tx 5 states: cancer-free, low-grade, high grade, death due to CaP, and death due to other causes For cancer free state: risk of progressing to LG CaP or HG CaP based on incidence in gen popn Those treated: grade distribution modified by PCPT ratio of HG to LG No Tx: modelled after SEER data Drug costs modelled from 55->85 or first Dx of CaP Also modelled benefit of reduced BPH with finast Accounted for psych value of diagnosis and treatment	Tx finast = 6 life-years and 46 QALYs gain per 1000 men -$1,660,000 per life-year -$200,000 per QALY -only men who live beyond 80 benefit from having low-grade tumors prevented -Assume grade diff is artefact -40 life years gained per 1000 men at $233,000 per life-year -Sn Analysis: if RR of high grade tumors increases to 1.8 (9% to 12% in finast arm): benefit is eliminated -Grade is most influential parameter -For QALY: most influential is effect of finast on BPH, disutility of BPH "willingness to pay threshold: 100,000 per QALY: finast not cost effective -Cost of finast would have to drop 50% to get 100,000 per QALY and 80% to get 100,000 per life-year	substantial Benefit small Releaized yrs after treatment Surival data beyond 10 yrs are based on pre-PSA data: ?not accurate QALY analysis: limited data based on utility in prostate-related conditions	But did not model the side-effects of finasteride (erectile dysfunction etc)	the 5 studies, addresses weakness in the other studies.

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