PROSCAR® (finasteride 5 mg)

Supplemental New Drug Application

Prostate Cancer Prevention Trial

Oncologic Drugs Advisory Committee Briefing Document

Presented to ODAC on 01-December 2010

Available for Public Disclosure Without Redaction

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
5-ARI	5α-reductase Inhibitor
AN	Allocation Number
ASCO	American Society of Clinical Oncology
AUA	American Urological Association
AUC	Area Under the Curve
BPH	Benign Prostatic Hyperplasia
Bx	Biopsy
CARET	Carotene and Retinol Efficacy Trial
CBE	Change Being Effected
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
DHT	Dihydrotestosterone
DRE	Digital Rectal Examination
DSMC	Data and Safety Monitoring Committee
Dx	Diagnosis
EOS	End-of-Study
F/U	Follow-Up
FC	For-Cause
HGPIN	High-Grade Prostatic Intraepithelial Neoplasia
HR	Hazard Ratio
IPCW	Inverse Probability of Censoring Weighted
MITT	Modified Intention-to-Treat
MTOPS	Medical Therapy of Prostatic Symptoms
NCI	National Cancer Institute
NEJM	New England Journal of Medicine
NG	Not Graded
NNT	Number Needed to Treat
ODAC	Oncologic Drugs Advisory Committee
OR	Odds Ratio
PCL	Pathology Core Lab
PCPT	Prostate Cancer Prevention Trial
PLESS	Proscar Long-Term Efficacy and Safety Study
PSA	Prostate-Specific Antigen
REDUCE	Reduction by Dutasteride of Prostate Cancer Events
ROC	Receiver Operating Characteristic
RR	Relative Risk
SD	Standard Deviation
SWOG	Southwest Oncology Group
TRUS	Transrectal Ultrasonography
TURP	Transurethral Resection of the Prostate
U.S.	United States

THE PROSTATE CANCER PREVENTION TRIAL
KEY DATES

Event	Date
First participant randomized	January 5, 1994
Last participant randomized	May 16, 1997
Data and Safety Monitoring Committee recommendation to close study early	February 21, 2003
Data cutoff date for New England Journal of Medicine (NEJM) primary study publication	March 19, 2003
Trial unblinding (investigators notified)	June 23, 2003[†]
Online posting of NEJM primary study manuscript [1]	June 24, 2003
Print publication of NEJM primary study manuscript [1]	July 17, 2003
Last prostate biopsy performed	December 31, 2003
Last data cutoff date	January 15, 2004[†]

[†] Efficacy and safety analyses presented in Sections 3.7 and 3.8, respectively, primarily use the January 15, 2004 dataset. Many of the secondary analyses described in Section 3.9 use a dataset that included endpoints obtained up to the trial unblinding date of June 23, 2003.

Foreword

The Prostate Cancer Prevention Trial (PCPT) was a landmark study sponsored by the National Cancer Institute (NCI) and designed and conducted by the Southwest Oncology Group (SWOG). Merck provided study medication (the 5α-reductase inhibitor PROSCAR® [finasteride 5 mg] and matching placebo) but did not have a role in the study design, trial management, or data collection.

The original analysis of the results of the PCPT was published on June 24, 2003 in the online version of the New England Journal of Medicine (NEJM). Treatment with finasteride resulted in a significant relative risk reduction in the prevalence of prostate cancer over 7 years compared with placebo. Also reported was an increase in high-grade (Gleason score 7-10) disease observed in the finasteride group. A "Changes Being Effected" (CBE) labeling supplement was submitted to FDA in September 2003 and approved in April 2004. This supplement added text to the ADVERSE REACTIONS section of the label for PROSCAR describing the incidences of Gleason score 7-10 prostate cancer in each treatment group as reported in the NEJM. The clinical significance of these findings was unknown. This CBE text remains as the only reference to the study in the current label for PROSCAR in the U.S. (highlighted text in Appendix 1A).

In the years since the NEJM publication, numerous analyses of the PCPT data have been conducted and published by SWOG, Merck and others. These analyses lend support to the hypothesis that the high-grade findings observed in the results of the PCPT may be explained by detection biases. In early 2009, the American Society of Clinical Oncology (ASCO) and the American Urological Association (AUA) jointly issued a clinical practice guideline on the use of 5α-reductase inhibitors (5-ARIs) for prostate cancer chemoprevention in which these analyses are reviewed [2]. The guideline states:

> *"Asymptomatic men with a prostate-specific antigen (PSA) ≤3.0 ng/mL who are regularly screened with PSA or are anticipating undergoing annual PSA screening for early detection of prostate cancer may benefit from a discussion of both the benefits of 5-ARIs for 7 years for the prevention of prostate cancer and the potential risks (including the possibility of high-grade prostate cancer). Men who are taking 5-ARIs for benign conditions such as lower urinary tract [obstructive] symptoms (LUTS) may benefit from a similar discussion, understanding that the improvement of LUTS relief should be weighed with the potential risks of high-grade prostate cancer from 5-ARIs (although the majority of the Panel members judged the latter risk to be unlikely)."*

Subsequently, FDA requested that Merck submit a labeling supplement to trigger and support a meeting with the Oncologic Drugs Advisory Committee (ODAC) to discuss the findings from the PCPT. Merck filed this labeling supplement on October 1, 2009. The ODAC Briefing Document that follows was prepared by SWOG in collaboration with Merck. Results of the originally-planned analyses of the trial as well as results of the

subsequent analyses conducted and published since the completion of the PCPT are extensively discussed in the labeling supplement and in this Briefing Document. The results of these analyses are reassuring that PROSCAR does not induce high-grade prostate cancer. However, these analyses are by their nature *post-hoc* and exploratory and hence do not meet typical regulatory standards for substantial evidence to inform an indication for use. Therefore, Merck is not seeking a new indication for the use of PROSCAR in prostate cancer chemoprevention in this application.

The proposed changes to the PROSCAR label can be found in Appendix 1B. They include the addition of text to the ADVERSE REACTIONS section acknowledging that analyses conducted subsequent to the initial conclusions of the trial suggest that the increase in the prevalence of high-grade (Gleason scores 7-10) prostate cancer observed in the PROSCAR group in the results of the PCPT may be explained by a detection bias due to the effects of PROSCAR on prostate volume and PSA, both of which facilitated diagnosis. Additionally, a description of the PCPT, including the study population and primary results, is proposed for the CLINICAL STUDIES section of the PROSCAR label. In contrast to the current label for PROSCAR, which presents only the study's findings of an imbalance in high-grade prostate cancer, the proposed labeling provide a balanced description of the trial results for consideration by physicians when treating men, or evaluating men for treatment, with PROSCAR for symptomatic benign prostatic hyperplasia. To the extent that the full disclosure of the results of the PCPT are important to a physician treating a man with BPH, consideration should be given to their inclusion in the label for PROSCAR.

At the December 1st ODAC meeting, Professor Ian Thompson, Principal Investigator of the PCPT, will present and discuss the results of the study, including the results of data analyses that followed the study's completion. As the Sponsor of the pending regulatory application for PROSCAR, Merck looks forward to the upcoming discussion with the ODAC regarding the results of the PCPT and appropriate labeling of the results of the study in the PROSCAR physician's circular.

1. Summary

One in 6 men in the U.S. can expect to be diagnosed with prostate cancer during their lifetime [3]. Treatment of the disease, including surgery and radiation, carries with it a risk of significant sexual, urinary, and bowel complications; advanced disease is associated with the side effects of androgen ablation and progression that despite treatment is often fatal [4]. The development and progression of prostate cancer rely, in part, on androgens, including testosterone and its more potent metabolite, dihydrotestosterone (DHT) [5; 6; 7]. The conversion of testosterone to DHT is catalyzed by the enzyme 5α-reductase. 5α-reductase exists as 2 isoenzymes (type 1 and type 2), with type 2 the predominantly-expressed isoform in the human prostate [8]. Finasteride, a selective inhibitor of 5α-reductase type 2, significantly reduces circulating and intraprostatic DHT at a 5 mg daily dose (PROSCAR®) and has been shown to be well tolerated as a treatment for men with benign prostatic hyperplasia (BPH) [Appendix 1A]. It was hypothesized that through its mechanism of action, finasteride would reduce the risk of prostate cancer by reducing androgen stimulation of prostatic cells [8; 1].

The Prostate Cancer Prevention Trial (PCPT) initiated in 1993 and randomized (1:1) 18,882 men with a low to moderate risk of prostate cancer to finasteride 5 mg or matching placebo daily for 7 years [1]. Entrance criteria included a prostate-specific antigen (PSA) level ≤ 3.0 ng/mL and a normal digital rectal examination (DRE). The primary study objective was to compare the between-group period prevalence of histologically-proven prostate cancer over 7 years. Prostate cancer detection was primarily by prostate biopsy, which, mimicking clinical practice, was prompted during the study by an elevated PSA or abnormal DRE, or conducted at the end of the study in men who completed the study without a diagnosis of prostate cancer. In February, 2003, 15 months before the planned end of the study, the PCPT Data and Safety Monitoring Committee (DSMC) recommended early study closure as the primary study objective had been met: treatment with finasteride resulted in a significant relative risk reduction in the prevalence of prostate cancer over 7 years compared with placebo. Treatment with finasteride was also associated with reduction in the symptoms and complications of BPH. Side effects of finasteride treatment were primarily those related to sexual dysfunction, consistent with the established safety profile of finasteride when used in men with BPH [1].

Despite the significant risk reduction in prostate cancer prevalence overall, an increase in high-grade (Gleason score 7-10) disease was observed with finasteride [1]. Subsequent analyses of the data have supported the hypothesis of detection bias to explain the apparent paradox of significantly fewer prostate cancers overall coupled with an observed increase in high-grade disease. Several sources of bias due to the mechanism of action of finasteride have been demonstrated and will be discussed later in this document: (1) finasteride significantly improves the sensitivity of PSA to detect both prostate cancer overall and high-grade disease [9]; (2) finasteride significantly improves the sensitivity of DRE to detect prostate cancer [10]; and (3) finasteride improves the accuracy of tumor

grading in prostate biopsies [11]. Several studies that model and adjust for the impact of these biases suggest that finasteride is not associated with an increase in the risk of high-grade disease [12; 13; 14; 15; 16].

Taken together, these data suggest that administration of finasteride to men at risk of prostate cancer significantly reduces the risk of the disease, thereby reducing the side effects and complications that accompany diagnosis and treatment. Because prostate cancer is the most common cancer diagnosed in men, with annual rates expected to increase in the U.S. with the aging of the population and the continued use of cancer screening [3], the impact of reducing prostate cancer on public health and the quality of life of tens of thousands of men could be substantial.

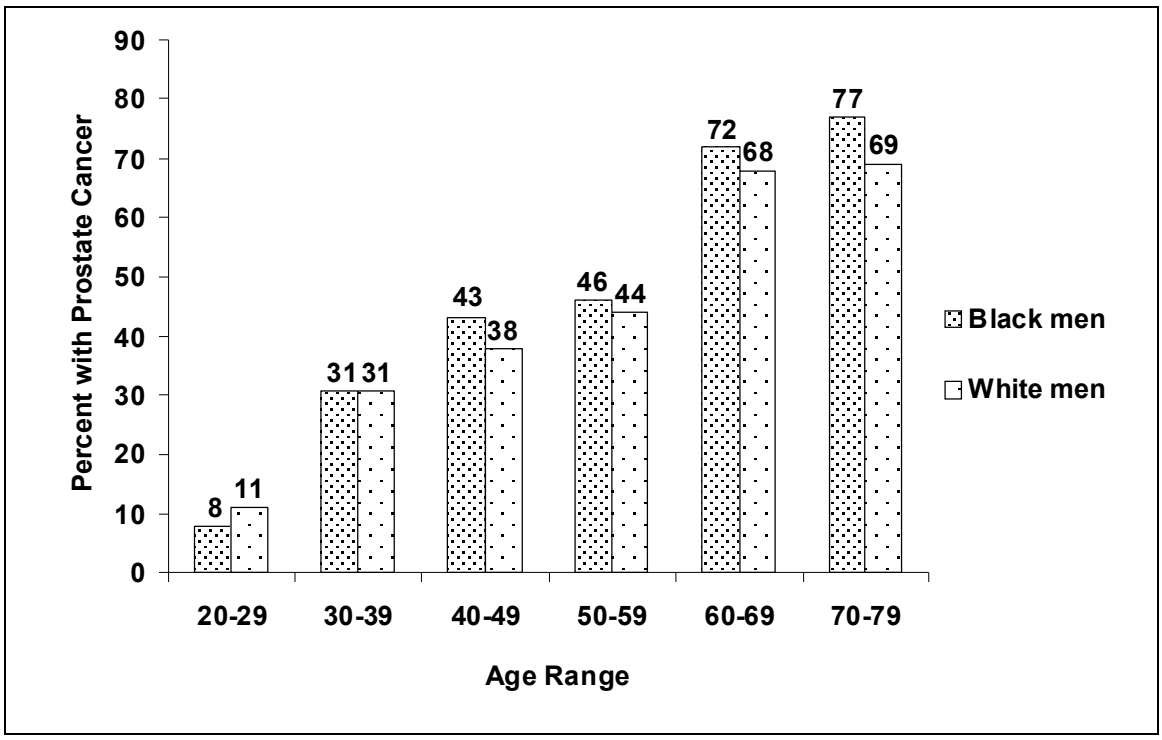
2. Background

2.1 Prostate Cancer Epidemiology

Prostate cancer is the most common non-dermatologic cancer of men. In 2010, prostate cancer will be diagnosed in 217,730 men and 32,050 deaths will be reported in the U.S. About 1 man in 6 (16%) in the U.S. can expect to be diagnosed with prostate cancer in his lifetime [3]. A recent study examined the prevalence of prostate cancer based on examination of the prostates of 1,056 men who died of causes other than prostate cancer (Figure 1, below) [17]. Given the high prevalence of prostate cancer, with about half of U.S. men currently undergoing PSA testing regularly, and with the population continuing to age, the lifetime risk of prostate cancer diagnosis is predicted to increase substantially beyond current rates. This is especially likely if a greater proportion of men opt for PSA testing [18; 19; 20].

Figure 1

Risk of Prostate Cancer by Age and Race



[17]

Several variables increase the risk of prostate cancer, including African-American ethnicity, family history of prostate cancer, and older age. The risk of prostate cancer is low in young men but increases dramatically with age. Compared with Caucasian men, African-American men of the same age have an approximately 60% greater incidence of the disease and more than twice the risk of a fatal outcome [21]. Twin studies suggest that 42-57% of the risk of prostate cancer is the result of heritable factors [22; 23; 24].

The natural history of prostate cancer is highly variable but is most commonly characterized by a slow rate of growth over many years. Nonetheless, over 90% of patients with localized disease and a large proportion of men with low levels of PSA undergo definitive, radical treatment with radiation or surgery [25]. These treatments are associated with high rates of impotence, risk of urinary complications including incontinence with surgery and obstruction with radiation, and the risk of bowel complications with radiation. In the case of radiation therapy, there is a small increased risk of secondary cancers, generally of the colon or bladder, with longer follow-up. With prolonged time in most tumors or shorter periods in more aggressive tumors, prostate cancer can metastasize beyond the prostatic capsule to regional lymph nodes and then

most commonly to bone. With widespread PSA testing, the majority of prostate cancers are now detected at early stages, prior to any detectable evidence of spread beyond the prostate. In 2009, about 91% of all prostate cancers were localized to the prostate at the time of detection [26]. Once prostate cancer is associated with bony metastases, it is generally treated with hormonal therapy followed by chemotherapy once hormonal resistance develops, with poor long-term survival.

2.2 Prostate Cancer Grading

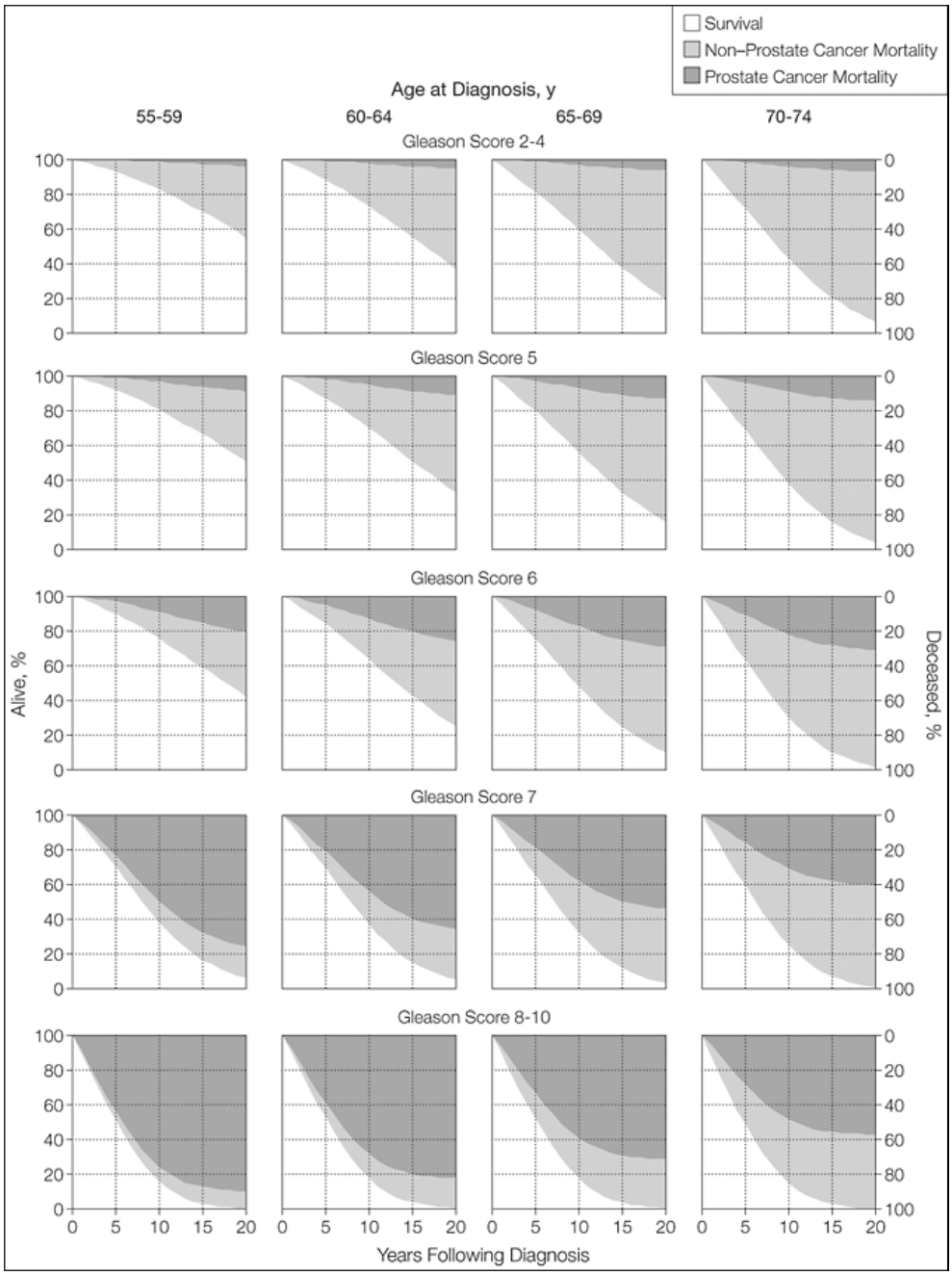
One of the most important variables that affect prognosis and response to treatment is tumor grade. Tumor grade is generally initially established on specimens obtained by a transrectal, ultrasound-guided prostate biopsy in which multiple cores are obtained to sample different regions of the gland. The *Gleason grading system* [27; 28; 29] is the most widely-used method of prostate tumor grading and is primarily based on architectural patterns of tumor growth. This system acknowledges that prostates often harbor multiple tumors with different grades and that both the grade and volume of the tumor play a role in the potential aggressiveness of the tumor. The Gleason grading system on a prostatectomy specimen assigns the primary grade (ranging from a low of 1 to a high of 5) to the preponderant tumor pattern observed and a secondary grade (again, ranging from 1 to 5) to the second most common tumor pattern. On a prostate biopsy, the recommended convention is to assign the most common pattern as the primary grade and the highest of the patterns remaining as the secondary grade. Gleason grade 1 and 2 tumors are uncommon and thus tumors generally range from grade 3 to 5. The primary and secondary grades are reported as a combined, or summed, *Gleason score*. Gleason grade 3 is generally the lowest grade reported; thus, a Gleason *score* of 3+3 (i.e., 6) is generally the lowest score reported; Gleason 5 is the highest grade, making a Gleason score of 5+5 (i.e., 10) the highest reported. If a Gleason grade 2 and Gleason grade 3 are reported, a Gleason score of 2+3 or 3+2 (i.e., 5) is reported. Gleason score is strongly predictive of many aspects of prostate cancer including risk of death if left untreated, risk of recurrence after radical prostatectomy, and risk of recurrence after radiotherapy, with lower Gleason scores generally associated with a better prognosis [30; 31; 32].

Although higher Gleason scores are related to greater risk of cancer progression and death, lower Gleason scores are also associated with a risk of cancer death without treatment. In a series of cancer deaths due to prostate cancer, about a third were Gleason score 6 at diagnosis [33]. Additionally, long-term follow-up studies by Albertsen et al. have demonstrated an inexorable increase in risk of cancer death with sufficient follow-up (Figure 2, below), including tumors that are Gleason score 6 at diagnosis [30]. Finally, among patients on active surveillance, most of whom were Gleason score 6 at diagnosis, who developed evidence of disease progression at a median of 29.5 months, 35% had extraprostatic extension, 6.2% had seminal vesicle invasion, and 15% had positive margins [34]. Likely due to such findings, most patients with Gleason 6 cancer do not opt for active surveillance or watchful waiting but instead select treatment with radiation therapy or radical prostatectomy [25].

In the PCPT, a planned analysis included an evaluation of prostate cancers by Gleason score. While there is a general step-wise increase in the aggressiveness of prostate cancer with each increase in the Gleason score, as illustrated in Figure 2, it is common practice to classify the higher Gleason scores as 'high-grade' disease, using either the grouping of Gleason scores from 7 to 10 or Gleason scores from 8 to 10. Gleason score 8-10 tumors, although less common, generally have worse clinical outcomes than the group of Gleason score 7-10 tumors. In this document, both groupings will generally be presented.

Figure 2

Survival and Cumulative Mortality From Prostate Cancer and From Other Causes Up to 20 Years After Diagnosis of Prostate Cancer Stratified by Age at Diagnosis and Gleason Score



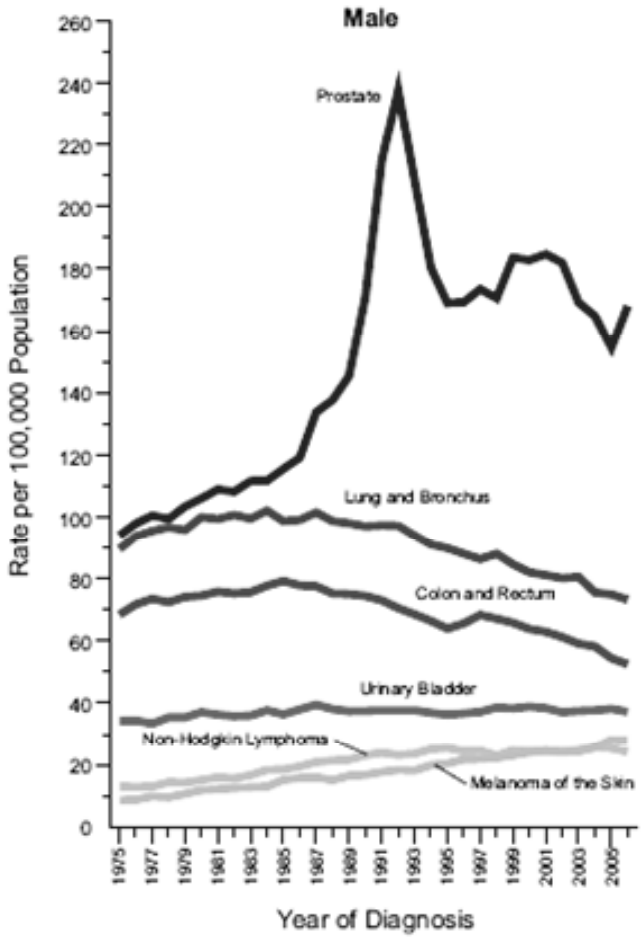
[30]

2.3 Prostate Cancer Detection

For the majority of the last century, prostate cancer detection was performed using DRE, with a nodule or area of firmness generally prompting a prostate biopsy. Unfortunately, tumors detected by DRE had often spread beyond the prostate at diagnosis, presumably due to the poor sensitivity of the test [35]. Beginning in the 1980s, with the clinical application of PSA testing to asymptomatic men and prostate biopsy conducted in men with a PSA > 4.0 ng/mL, a dramatic increase in prostate cancer detection was observed, as well as a greater likelihood of finding organ-confined disease at diagnosis (Figure 3, below) [3].

Figure 3

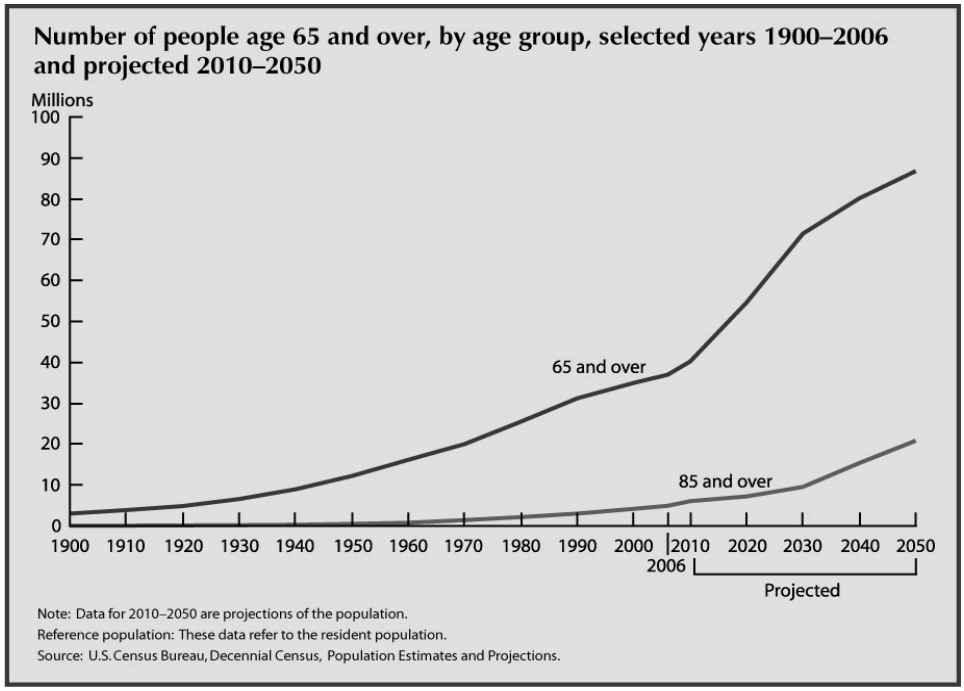
Prostate Cancer Detection Rates



Subsequently, it became apparent that the risk of prostate cancer could be substantial in men with PSA values ≤ 4.0 ng/mL [36]. With the growth of the population of men ≥65 in the U.S. (see Figure 4, below), the continued use of PSA screening, and the increasing use of lower PSA values to prompt prostate biopsy, the number of men diagnosed with prostate cancer can be expected to increase [37; 4].

Figure 4

Number of People Age 65 and Over by Age Group
Selected Years 1900-2006 and Projected 2010-2050



[38]

3. The Prostate Cancer Prevention Trial (PCPT)

3.1 Introduction

With the rapidly-increasing rate of prostate cancer detection associated with the use of PSA testing, demographic projections of continued expansion of the population at risk of prostate cancer, the possibility of preventing a cancer that not only metastasizes and causes death but whose treatment is associated with significant sexual, urinary, and bowel morbidities, consideration was given to a different approach to mitigate the public health impact of prostate cancer through chemoprevention of the disease. Because prostate cancer was known to be a hormonally-sensitive tumor, an option considered was use of a medication that interfered with androgen effects believed to promote the development of

prostate cancer and that had an acceptable safety profile for use in chemoprevention. Several lines of evidence at the time (1992) suggested that inhibition of the enzyme 5α-reductase, which catalyzes the metabolism of testosterone to dihydrotestosterone (DHT), might result in beneficial effects on the development of prostate cancer [39; 40; 41; 42; 43; 6; 44]. The first 5α-reductase inhibitor developed for human use was finasteride, a selective inhibitor of 5α-reductase type 2, the predominant isoenzyme expressed in human prostate. Finasteride was developed as a treatment for men with symptomatic BPH and was approved for use in 1992 (as PROSCAR®, Merck Sharp & Dohme Corp.). Due to its mechanism of action, finasteride reduces both prostate volume (approximately 20% in men with BPH [45; 46]) and PSA (approximately 50% in men with BPH [47; 48]), effects that could introduce bias in a trial that requires the use of the commonly-applied methods for prostate cancer detection (i.e., DRE, PSA and prostate biopsy).

Another consideration for any chemoprevention intervention is the safety of the agent, especially as treatment would be applied in a population of otherwise healthy subjects. At the time of the design of the PCPT, finasteride had been studied in large, placebo-controlled, Phase III trials in men with BPH, and the drug's demonstrated safety and tolerability profile supported its potential use as test agent in the PCPT [45; 46].

With the availability of an acceptably well-tolerated agent that held the promise of a potential preventative effect in prostate cancer, the PCPT was conceived. The trial was funded by the Division of Cancer Prevention of the National Cancer Institute and coordinated by the Southwest Oncology Group (SWOG), a cooperative clinical trials group with a history of implementing clinical trials. Merck provided study medication (finasteride and matching placebo) but did not have a role in the study design, trial management, or data collection.

3.2 Study Participants

Eligibility criteria included a general population of men at low to moderate risk of prostate cancer but without evidence of prostate cancer. A broad population of men was chosen because this would allow for conclusions to be drawn on a more general population; if the total patient sample was sufficiently large, the trial would also allow for conclusions to be made regarding the effects of study drug in higher-risk subgroups. Eligible subjects were men age 55 years or older, a PSA $\leq$ 3 ng/mL, a normal DRE, no clinically significant coexisting conditions, and no or only mild to moderate obstructive urinary symptoms based on an American Urological Association (AUA) Symptom score <20. Consideration had been given to enrolling a high-risk population (e.g., men with PSA > 4.0 ng/mL, family history (first-degree relative) of prostate cancer, and/or African-American descent). While selecting this cohort of men would be expected to yield a higher rate of prostate cancer, it would likely increase the probability that study participants would harbor undiagnosed prostate cancer at the time of randomization.

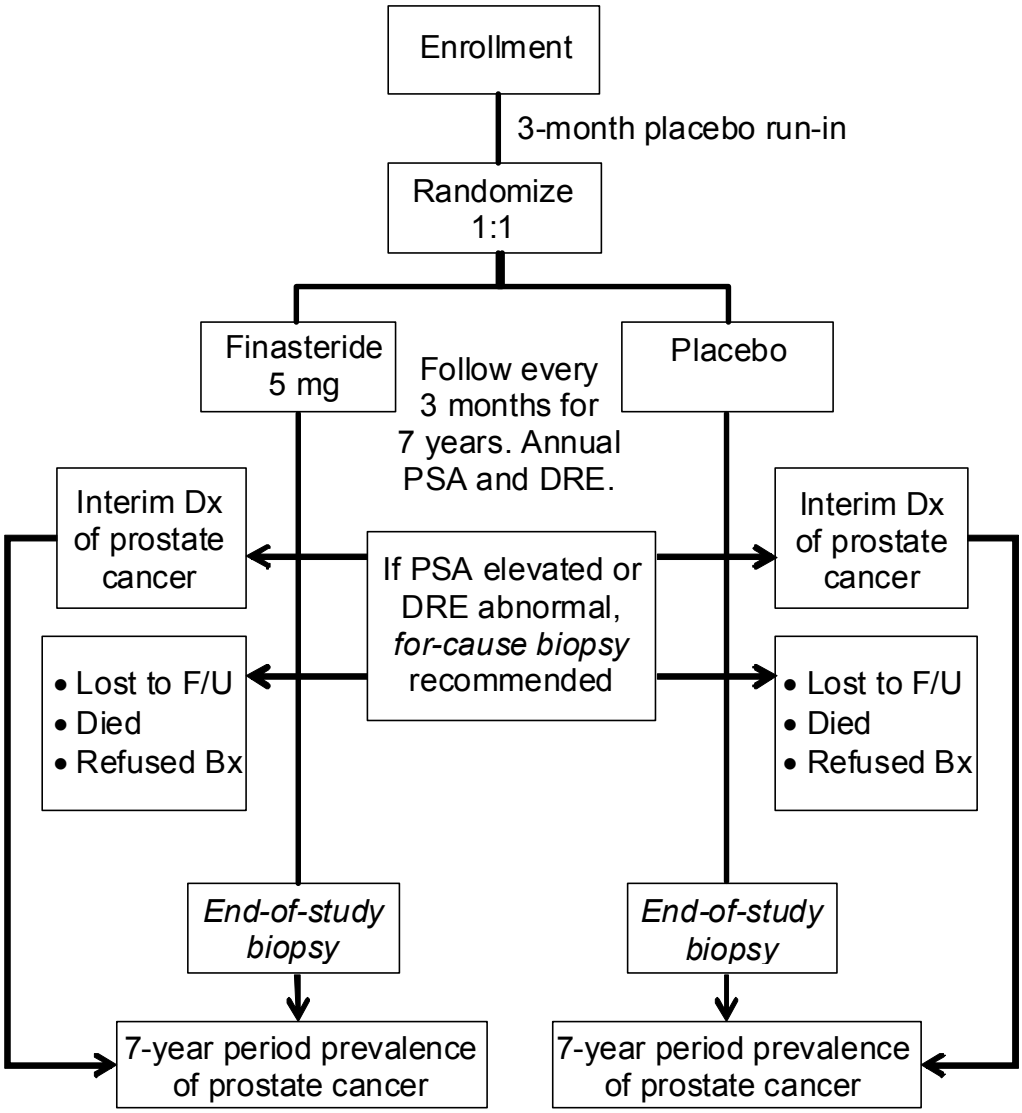
Further, conclusions generated from the trial could only be applied to the population studied.

3.3 Study Design

The PCPT was a randomized, double-blind comparison of treatment with finasteride 5 mg and placebo over 7 years of treatment. The primary endpoint was the period prevalence of prostate cancer over the duration of the trial, defined as the *histologically-proven presence or absence of prostate cancer at 7 years.* (For a description of other endpoint and study design options considered, see Appendix 2). The primary endpoint included prostate cancers diagnosed from a recommended prostate biopsy (e.g., conducted because of an elevated PSA or abnormal DRE, referred to as a *for-cause biopsy*) and prostate cancers diagnosed from a protocol-specified biopsy at the end of the study (referred to as an *end-of-study [EOS] biopsy),* which was to be conducted in all men who reached their 7-year milestone without a diagnosis of prostate cancer. Also included were prostate cancers diagnosed based on an interim procedure such as a transurethral resection of the prostate (TURP) or cystoprostatectomy. The use of the EOS biopsy was considered crucial to mitigate, at least in part, any bias in prostate cancer detection potentially associated with the effects of finasteride on PSA or DRE. A schema for the PCPT is shown in Figure 5, below.

Figure 5

The PCPT Study Schema



Several critical assumptions were central to the design of the PCPT (see Appendix 3). These assumptions dealt with potential sources of bias, primarily those that might impact the detection of prostate cancer during the study. These assumptions were dynamically monitored by the DSMC and, if needed, mid-course adjustments to the study design could be made. For example, finasteride was known to reduce the level of laboratory-measured PSA by approximately 50% in men with BPH [49]. Annual PSA

testing in the PCPT was one of two common mechanisms (DRE being the other) by which a recommendation for prostate biopsy could be made to determine if prostate cancer were present. It was assumed that finasteride treatment would result in a simple downward shift in the PSA distribution and allow for a simple algorithm to be used in the PCPT (i.e., adjust the laboratory-measured PSA by multiplying the measured value by 2.0 for participants on finasteride). If, over the course of the trial, an adjustment factor that balanced biopsy recommendations better across the two study arms became apparent, the DSMC could make such a change in the PSA algorithm as the study was proceeding. This, in fact, did occur; the adjustment factor for PSA for men on finasteride was changed (increasing the PSA multiplier for men receiving finasteride from 2.0 to 2.3) at the beginning of each participant's fourth year in the study (see Appendix 3). Other critical assumptions included that treatment with finasteride would not affect the screening properties of PSA or DRE, or the diagnostic properties of the prostate needle biopsy, despite the known effect of finasteride to reduce prostate volume [45; 46]. Each of these assumptions proved to be incorrect (see Sections 3.9.4.1 and 3.9.4.2). Further details on the critical assumptions used in the design of the PCPT are in Appendix 3.

3.4 Sample Size

The PCPT planned for randomization (1:1) of 18,000 men to finasteride 5 mg or placebo. This sample size was based on a conservative estimate of 6% prevalence of diagnosed prostate cancer in the placebo group, based on data from Cooner and Corder [50; 51]. A relative risk reduction (finasteride vs. placebo) of 25% in the period prevalence of prostate cancer (primary endpoint) was determined to be of clinical and public health interest. The planned sample size of 18,000 yielded 92% power (type I error of 5%, 2-sided) to detect a relative risk reduction of 25%. If needed, adjustment to the sample size during the trial was possible based on monitoring of design assumptions by the DSMC. Additional details on the assumptions used in determining the sample size of the PCPT are presented in Appendix 4.

3.5 Trial Conduct

After providing informed consent, men had PSA determined by a central laboratory and were enrolled in a 3-month placebo run-in phase. Following this run-in phase, if PSA level was $\leq$3.0 ng/mL and adherence to placebo tablets was $\geq$80%, men were randomized to daily treatment with finasteride 5 mg or matching placebo. Men were seen in the clinic every 6 months for recording of clinically significant medical conditions and side effects; in the intervening 3-month periods, men were contacted by telephone for collection of interim medical events. PSA level was obtained and DRE was conducted annually. If either the PSA level was elevated or the DRE was abnormal, a for-cause prostate biopsy was recommended. At the end of 7 years of follow-up, all men without a diagnosis of prostate cancer were recommended to undergo an EOS prostate biopsy for determination of prostate cancer status.

Between January 1994 and May 1997, 18,882 men (9423 finasteride, 9459 placebo) were randomized at 219 clinical study sites (218 in the U.S. and 1 in Canada). Individual study sites randomized between 1 to 1444 men to the study. Accrual to the trial (Figure 6, below) was rapid, with 64% of the participants randomized in the first year. Baseline characteristics of study participants were balanced between the treatment groups (Table 1, below). Mean age was 63 years, baseline PSA was ≤ 1 ng/mL in 48% of participants, and 92% of participants were Caucasian.

Figure 6

Participant Accrual

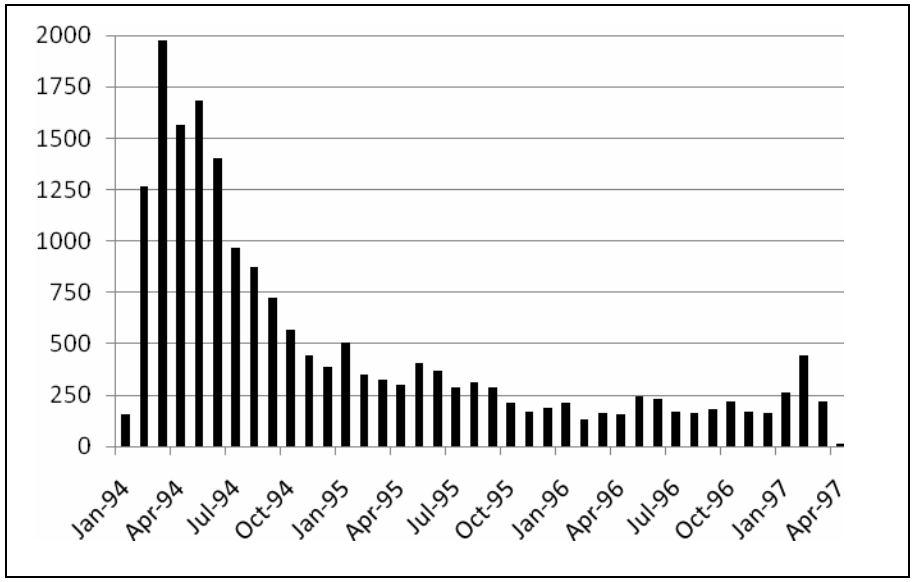


Table 1

Baseline Characteristics

	Finasteride (N=9423) N (%)	Placebo (N=9459) N (%)	Total (N=18,882) N (%)
Age (Years)			
<55	2 (0.0)	1 (0.0)	3 (0.0)
55-59	2953 (31.3)	2952 (31.2)	5905 (31.3)
60-64	2966 (31.5)	2824 (29.9)	5790 (30.7)
≥65	3502 (37.2)	3682 (38.9)	7184 (38.0)
Mean	63.2	63.3	63.2
S.D.	5.70	5.73	5.71
Median	62.0	63.0	63.0
Range	51 - 86	54 - 86	51 - 86
Race or Ethnic Group			
African-American	356 (3.8)	356 (3.8)	712 (3.8)
Caucasian	8672 (92.0)	8721 (92.2)	17,393 (92.1)
Asian	71 (0.8)	91 (1.0)	162 (0.9)
Other	324 (3.4)	291 (3.1)	615 (3.3)
AUA Symptom Score (mean)	6.3	6.4	6.4
Moderate symptoms of urinary obstruction (AUA Symptom Score of 8 to 19)	3010 (31.9)	3047 (32.2)	6057 (32.1)
Prostate Cancer in First-Degree Relative			
Yes	1458 (15.5)	1455 (15.4)	2913 (15.4)
No	7965 (84.5)	8004 (84.6)	15,969 (84.6)
PSA Level at Study Entry (ng/mL)			
0.0-1.0	4486 (47.6)	4635 (49.0)	9121 (48.3)
1.1-2.0	3400 (36.1)	3315 (35.0)	6715 (35.6)
>2.0	1537 (16.3)	1509 (16.0)	3046 (16.1)

3.6 Disposition of Study Participants, Analysis Populations and Approaches to Analysis

Because the rate of enrollment into the PCPT was 'front-loaded,' the vast majority of endpoint determinations to support the primary endpoint analysis accumulated well before the last randomized participant's 7-year EOS biopsy endpoint determination. On February 21, 2003, the DSMC determined that the primary objective of the study had been met, that further endpoint determinations (i.e., additional EOS biopsies) would be unlikely to affect this conclusion, and that the trial should be stopped. SWOG decided that the results would be best disseminated through publication of a peer-reviewed

manuscript with participant notification several days in advance. The results, based on a data cutoff of March 19, 2003, were published electronically in the *New England Journal of Medicine* (NEJM) on June 24, 2003 [1]. Participants were informed of the trial results and their treatment assignment, were advised to discontinue study drug, and those who had not yet undergone EOS biopsies were given the opportunity to have this conducted by December 31, 2003. The analyses of efficacy and safety presented in this document are based on the data collected up to January 15, 2004 unless otherwise noted. See Page 9 for a table of key dates related to the PCPT.

Two approaches to analysis are provided:

1) The prespecified primary analysis of the PCPT comprised data on *all eligible and evaluable men*, defined as the population of men with an endpoint determination, also referred to as *a known prostate cancer status* in this document. A man was considered to have a known prostate cancer status if either prostate cancer was diagnosed at any time from randomization to 7 years + 90 days since randomization or a negative EOS biopsy was obtained within the time window of 7 years ± 90 days since randomization. **This predefined primary population (n=9898) and analysis are termed the *SWOG population* and *SWOG analysis* in this document.** Note that not all men had a known prostate cancer status due to a variety of reasons, including death (not due to prostate cancer), loss to follow-up, medical circumstances that contraindicated a prostate biopsy, biopsy refusal, or an EOS biopsy performed earlier or later than the predefined 7-year ± 90 days time window.

2) An analysis based on the larger, modified intention-to-treat (MITT) population comprised data on all *eligible* randomized men. Of 18,882 men randomized, 2 men were considered ineligible due to prostate cancer diagnosed prior to randomization and were excluded from the MITT population and analysis. The MITT population of all eligible randomized men and the analysis of this population include all prostate cancers diagnosed up to the January 15, 2004 cutoff date. **This population (n=18,880) and analysis are termed the *MITT population* and *MITT analysis* in this document.**

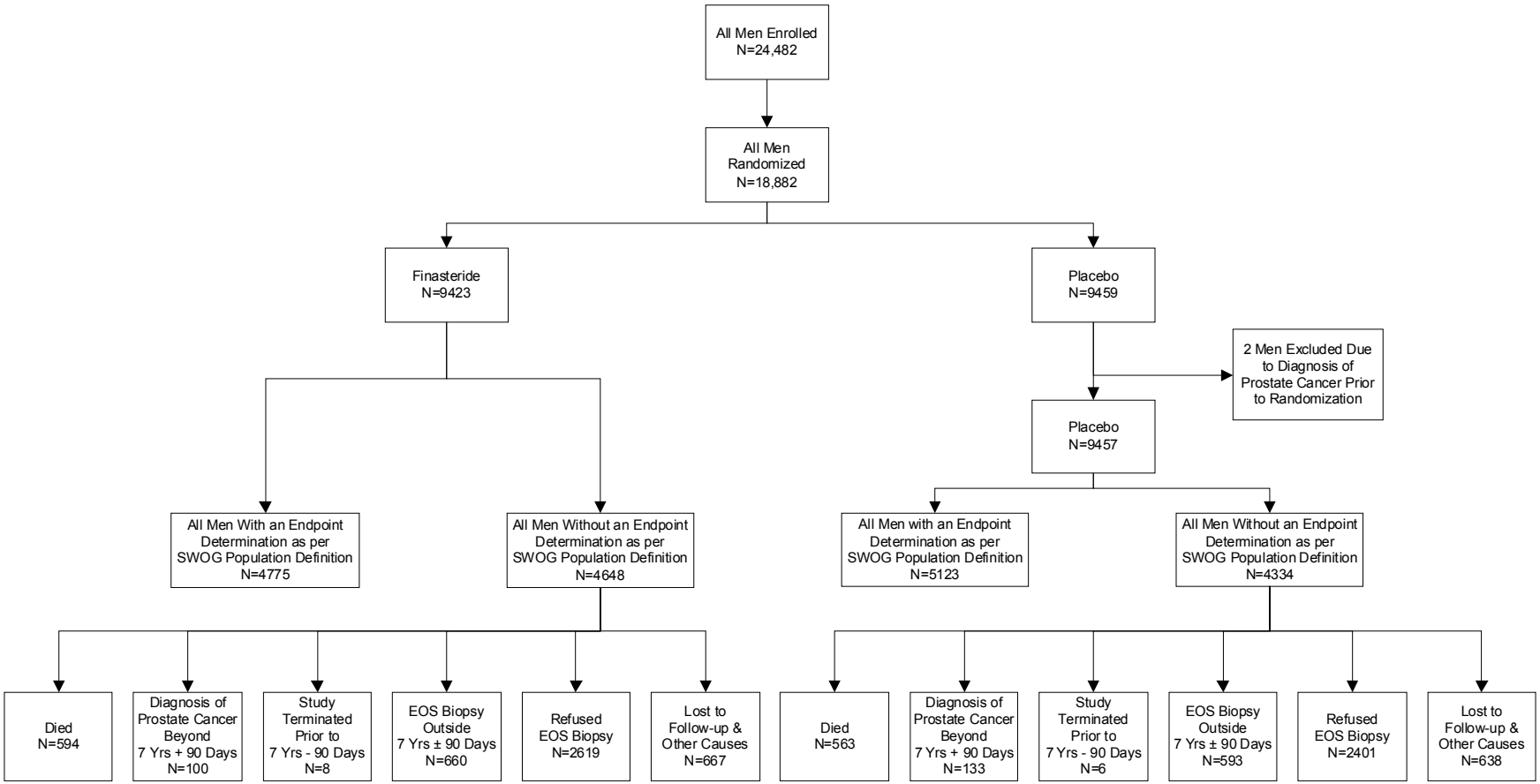
Each of these approaches to analysis has its strengths and potential drawbacks. The predefined SWOG analysis gives the most precise estimate of the true magnitude of the treatment effect of finasteride relative to placebo, but because the analysis only includes data on the population of evaluable men there is a potential bias regarding who was and was not evaluated for the primary endpoint. That is, the assumption that the prevalence of prostate cancer in the SWOG analysis is representative of the entire randomized population is not verifiable. In contrast, the MITT population includes all eligible randomized men and, thus, randomization is preserved for between-group comparisons in the MITT analysis. The MITT analysis includes 233 additional prostate cancer cases (100 on finasteride, 133 on placebo) that are excluded from the SWOG analysis because the diagnosis of prostate cancer was based on biopsies obtained later than 7 years + 90

days since randomization, and assumes that all men without a diagnosis of prostate cancer do not have prostate cancer, including men without an EOS biopsy. This assumption is made even though a man's prostate cancer status can not be known without a diagnosis of prostate cancer or a negative EOS biopsy. Based on a data analysis of the PCPT population subsequent to the publication of the primary results, men with a PSA value < 4.0 ng/mL and a normal DRE have an approximately 15% chance of having an EOS biopsy positive for prostate cancer at 7 years [36]. Thus, the MITT analysis will provide an underestimate of the actual period prevalence of prostate cancer in both treatment groups. Although these populations and analytic approaches differ, both analyses lead to similar conclusions regarding the relative risk of prostate cancer with finasteride compared with placebo.

A CONSORT-like diagram showing the disposition of participants in the PCPT, including the status of men excluded from the primary SWOG population, is in Figure 7, below.

Figure 7

Disposition and Status of Participants in the PCPT



3.7 Efficacy

3.7.1 Primary Efficacy Endpoint: 7-year Period Prevalence of Prostate Cancer

The primary endpoint of the PCPT was the total number of prostate cancers detected during subjects' 7-year study participation. The predefined primary analysis was based on data from the SWOG population (n=9898), which comprised men with a known prostate cancer status at 7 years. In this analysis (Table 2, below), prostate cancer was detected in 879 of 4775 men (18.4%) in the finasteride group and 1274 of 5123 men (24.9%) in the placebo group, resulting in a relative risk reduction (finasteride vs. placebo) of 26.0% (95% CI: 20.1%, 31.4%; p<0.0001) in the period prevalence of prostate cancer over 7 years. The absolute risk reduction was 6.5% (95% CI: 4.8%, 8.1%; p<0.0001).

Table 3, below, shows the analysis of the primary endpoint based on the MITT population. In the MITT analysis, prostate cancer was detected in 979 of 9423 men (10.4%) in the finasteride group and 1407 of 9457 men (14.9%) in the placebo group, for a relative risk reduction of 30.2% (24.6%, 35.3%; p<0.0001). The absolute risk reduction was 4.5% (95% CI: 3.5%, 5.4%; p<0.0001).

The relative risk reductions (finasteride vs. placebo) in the period prevalence of prostate cancer of 26.0% based on the SWOG analysis and 30.2% based on the MITT analysis are similar and consistent with the 25% relative risk reduction prespecified as of clinical and public health interest in the design of the PCPT.

Table 2

Primary Endpoint
SWOG Population

	Finasteride	Placebo	Total
Randomized population	9423	9459	18,882
SWOG population	4775	5123	9898
Diagnosis of prostate cancer (%)	879 (18.4)	1274 (24.9)	2153 (21.8)
Relative risk reduction [95% CI]	26.0% [20.1%, 31.4%], p<0.0001		
Absolute risk reduction [95% CI]	6.5% [4.8%, 8.1%]		

Table 3

Primary Endpoint
MITT Population

	Finasteride	Placebo	Total
Randomized population	9423	9459	18,882
MITT population	9423	9457	18,880
Diagnosis of prostate cancer (%)	979 (10.4)	1407 (14.9)	2386 (12.6)
Relative risk reduction [95% CI]	30.2% [24.6, 35.3], p<0.0001		
Absolute risk reduction [95% CI]	4.5% [3.5%, 5.4%]		

The robustness of the results of the predefined primary analysis based on the SWOG population are supported by the results of the MITT analysis, which is based on the broader population of all eligible randomized men (n=18,880). In the MITT analysis, the absolute prevalence of prostate cancer is lower in both treatment groups than in the SWOG analysis because men without an EOS biopsy are assumed not to have prostate cancer in the former analysis. Nonetheless, the relative risk reductions based on each analysis are similar, and in both analyses men on finasteride were significantly less likely than men on placebo to be diagnosed with prostate cancer.

Note 1: The diagnosis of prostate cancer was further categorized in both the SWOG and MITT analyses (as shown in Table 7, below, and Appendix 5, respectively) by Gleason score at biopsy and based on the reason for prostate biopsy (i.e., for-cause or EOS). For-cause cancers comprise those cancers diagnosed due to a biopsy performed for a PSA >4.0 ng/mL or an abnormal DRE. EOS cancers comprise those cancers diagnosed due to the protocol-specified biopsy at the end of a subject's 7-year participation. In addition, cancers diagnosed as a result of an interim surgical procedure (e.g., TURP), an 'early EOS biopsy' (i.e., an EOS biopsy obtained prior to the predefined time window of 7 years - 90 days since randomization), or a for-cause biopsy that coincided with the a participant's 7-year anniversary in the trial are included in the for-cause prostate cancer grouping.

Note 2: As noted above (Section 3.6), prostate cancers diagnosed from biopsies obtained later than the predefined time window of 7 years + 90 days since randomization are excluded from the SWOG analysis. These prostate cancers (n=233) are included in the MITT analysis.

3.7.1.1 Logistic Regression Analyses of the Prevalence of Prostate Cancer

Logistic regression analyses of the prevalence of prostate cancer adjusting for factors known to be predictive of prostate cancer risk (age, African-American race and a history of prostate cancer in a first-degree relative) were conducted. The analysis populations included 9898 and 18,880 men for the SWOG (Table 4, below) and MITT (Table 5, below) populations, respectively. The estimated odds ratio (finasteride vs. placebo) of 0.68 ($p<0.0001$) for the period prevalence of prostate cancer based on the SWOG population is similar to that based on the same model for the MITT population (0.66, $p<0.0001$). As anticipated, in each population the known risk factors were strongly associated with prostate cancer period prevalence.

Table 4

Logistic Regression Analysis of the Prevalence of Prostate Cancer,
Adjusting for Prognostic Baseline Covariates
SWOG population

Summary by Treatment				
		Number of Events		95% CI[§] for Percentage
Treatment	N[†]	n[‡]	(%)	Of Events (%)
Finasteride	4775	879	(18.4%)	(17.3%, 19.5%)
Placebo	5123	1274	(24.9%)	(23.7%, 26.1%)

Logistic Regression Results	Odds Ratio	95% CI[§] for Odds Ratio	P-value
Finasteride vs. Placebo	0.68	(0.62, 0.75)	<0.0001
Other model covariates			
Age group 1 (55-59 vs. 65+)[‖]	0.62	(0.55, 0.70)	<0.0001
Age group 2 (60-64 vs. 65+)	0.78	(0.70, 0.88)	<0.0001
Race (African American vs. other)	1.80	(1.42, 2.29)	<0.0001
Prostate cancer in a first-degree relative (yes vs. no)	1.53	(1.35, 1.72)	<0.0001

Hosmer-Lemeshow goodness-of-fit test: p-value=0.6623.
[†] N = Number of SWOG participants in the treatment group.
[‡] n = Number of prostate cancer cases.
[§] CI = Confidence interval.
[‖] One participant in each treatment group (AN 17094 in the finasteride group and AN 3644 in the placebo group) was 54 years old and was included in the 55 to 59 year-old age group.

Table 5

Logistic Regression Analysis of the Prevalence of Prostate Cancer,
Adjusting for Prognostic Baseline Covariates
MITT population

Summary by Treatment				
		Number of Events		95% CI[§] for Percentage
Treatment	N[†]	n[‡]	(%)	Of Events (%)
Finasteride	9423	979	(10.4%)	(9.8%, 11.0%)
Placebo	9457	1407	(14.9%)	(14.2%, 15.6%)

Logistic Regression Results	Odds Ratio	95% CI[§] for Odds Ratio	P-value
Finasteride vs. Placebo	0.66	(0.61, 0.72)	<0.0001
Other model covariates			
Age group 1 (55-59 vs. 65+)[‖]	0.74	(0.67, 0.82)	<0.0001
Age group 2 (60-64 vs. 65+)	0.93	(0.84, 1.03)	0.1581
Race (African American vs. other)	1.36	(1.10, 1.67)	0.0041
Prostate cancer in a first-degree relative (yes vs. no)	1.63	(1.47, 1.82)	<0.0001

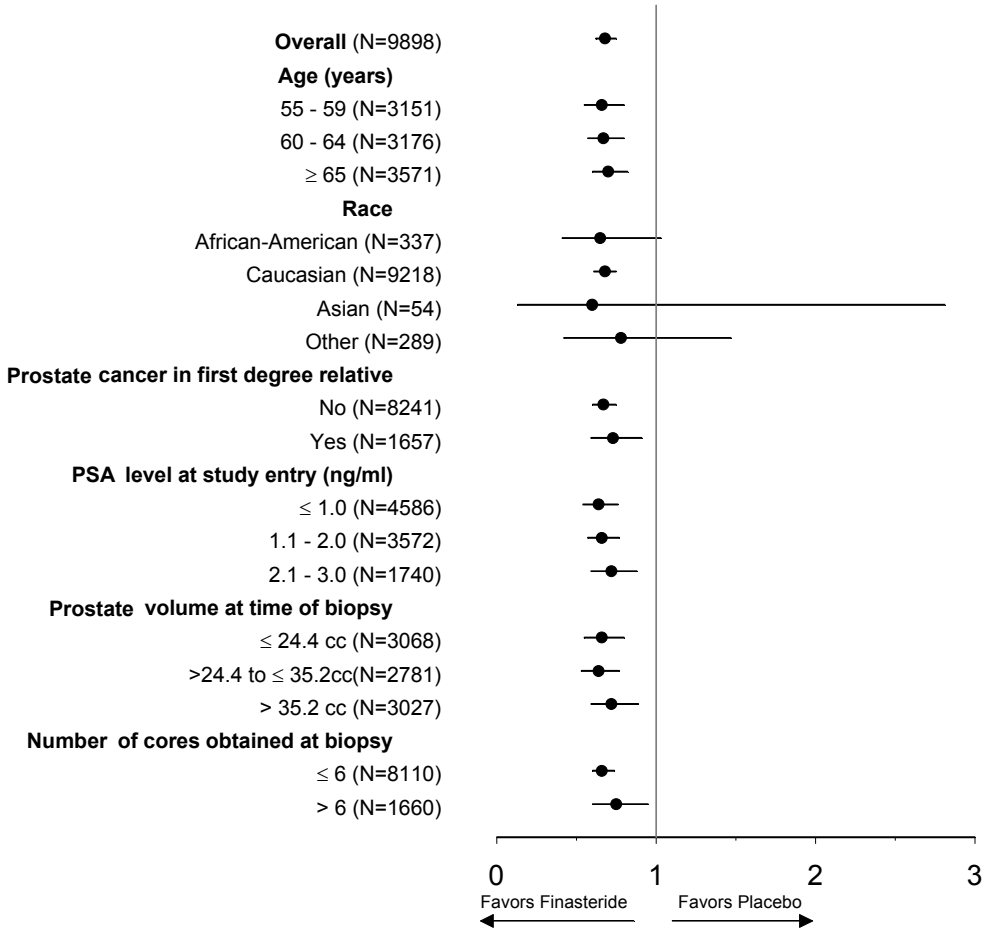
Hosmer-Lemeshow goodness-of-fit test: p-value=0.6748.
[†] N = Number of MITT participants in the treatment group.
[‡] n = Number of prostate cancer cases.
[§] CI = Confidence interval.
[‖] Two participants in the finasteride group (ANs 6295 and 17094) and 1 participant in the placebo group (AN 3644) were 51 to 54 years old and were included in the 55 to 59 year-old age group.

3.7.1.2 Odds Ratio for Diagnosis of Prostate Cancer by Subgroups Defined by Known Risk Factors

As PCPT enrolled a population of men with a low to moderate risk of prostate cancer, it was possible to examine how finasteride affected the risk of prostate cancer among different strata of risk using several variables known to be associated with risk of prostate cancer. Figure 8, below, displays estimates of the odds ratios from univariate logistic regression models of prostate cancer overall and by strata of risk for the variables of age, race-ethnic group, family history, and PSA at study entry. Risk reduction was comparable across strata.

Figure 8

Odds Ratio (Finasteride vs. Placebo) by Subgroups
SWOG Population



3.7.2 Time to Diagnosis of Prostate Cancer

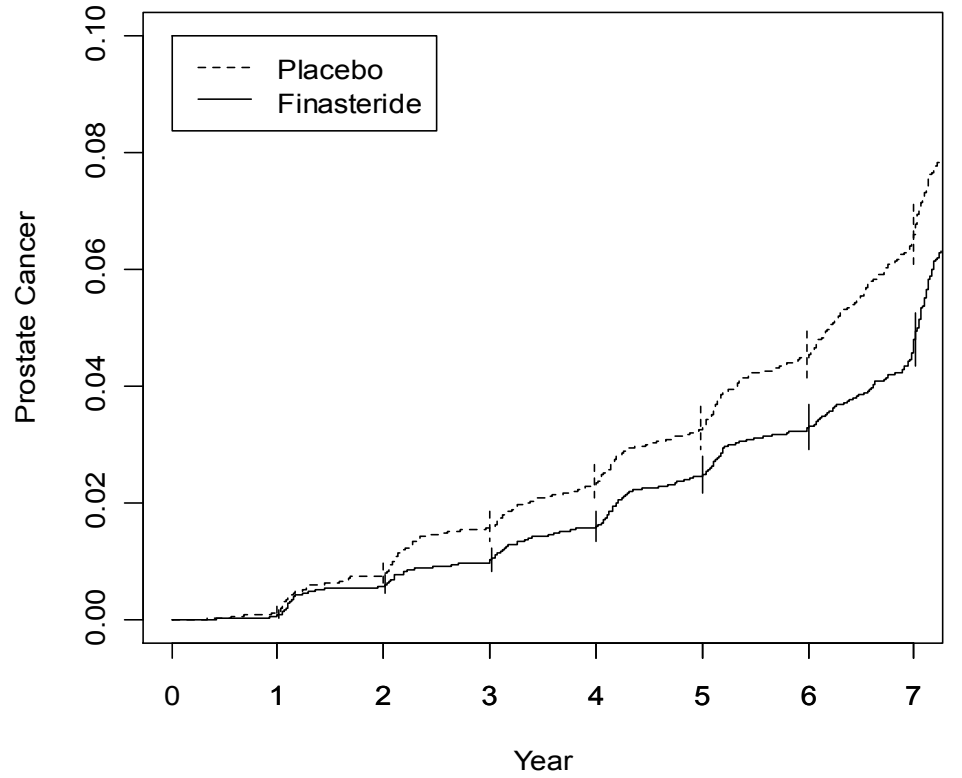
During the planning stage of the PCPT it was known that there was a potential for bias between treatment groups related to the detection of cancers based on for-cause biopsies. Accordingly, EOS biopsies were included in the study to mitigate this potential bias. An endpoint of 7-year period prevalence of prostate cancer was specified as the primary endpoint, which does not lend itself to a time-to-event statistical analysis. However, a supportive analysis of the prevalence of prostate cancer based on for-cause biopsies was performed that investigated the time to diagnosis of prostate cancer (Figure 9, below).

The cumulative prevalence of prostate cancer in the 2 study groups is displayed using the Kaplan-Meier method; the impact of the study-specified annual PSA and DRE testing can be seen as upticks in cancer detection as each anniversary is reached.

A multivariate Cox proportional hazards regression model was used to investigate the relationship between finasteride and time to diagnosis of prostate cancer based on for-cause biopsies, with adjustment for possible prognostic factors. All eligible randomized men (MITT population) were assumed to be at risk of being diagnosed with prostate cancer by a for-cause biopsy during the study and are used in this analysis.

Figure 9

Proportion of Participants with Prostate Cancer
Based on Biopsies Performed For Cause
(Kaplan-Meier Curves)
MITT Population



The results of the Cox regression analysis closely resemble the results of the logistic regression analysis of the period prevalence of prostate cancer. The hazard ratio (HR) (finasteride vs. placebo) for being diagnosed with prostate cancer (adjusted for age, race, and prostate cancer in a first-degree relative) is 0.76 (95% CI: 0.67, 0.85; p<0.0001), indicating a reduced risk of prostate cancer with finasteride compared to placebo. Analyses demonstrating that the sensitivity of the screening procedure to recommend a for-cause biopsy in a participant with cancer was greater in the finasteride group than in the placebo group are presented later in this document, and suggest that the observed benefit of finasteride vs. placebo (i.e., HR of 0.76) is likely to be a conservative estimate.

3.7.3 Recommended and Performed Prostate Biopsies

During the PCPT, prostate biopsies were recommended to a participant if there was an elevated PSA level or an abnormal DRE (for-cause biopsy). Among the eligible randomized population (N=18,880), at least one for-cause biopsy recommendation was given to 2153/9423 (22.8%) men in the finasteride group and 2378/9457 (25.1%) men in the placebo group (p<0.001) (Table 6, below). The proportion of men recommended for at least one for-cause prostate biopsy who subsequently underwent prostate needle biopsy was similar in the 2 treatment groups; 68.7% in the finasteride group and 69.8% in the placebo group; p=0.456).

Table 6 also displays the total number of for-cause biopsies recommended. This number is larger than the number of men in whom a prostate biopsy was recommended due to some men having > 1 biopsy recommendation during the study. The proportion of prostate biopsies performed based on these recommendations was 50.9% in the finasteride group and 52.7% in the placebo group (p=0.137). Sensitivity analyses accounting for any potential bias introduced by differential biopsy rates are presented later in this document (Sections 3.9.4.3 and 3.9.5).

Table 6

For-Cause Biopsy Recommendations and For-Cause Biopsies Performed
Up to Unblinding Date of June 23, 2003

	Finasteride	Placebo	P-value
Proportion of Men With Biopsy Recommendations	2137/9423 (22.7%)	2361/9457 (25.0%)	<0.0002
Proportion of Men Who Underwent Biopsy Among All Men With Biopsy Recommendations	1454/2137 (68.0%)	1637/2361 (69.3%)	0.35
Proportion of Biopsies Done Among All Biopsy Recommendations†	1690/3348 (50.5%)	1873/3570 (52.5%)	0.098
Proportion of Biopsies Done By Reason for Biopsy Recommendation			
Abnormal DRE	893/1753 (50.9%)	960/1991 (48.2%)	0.096
Elevated PSA	717/1480 (48.4%)	826/1463 (56.5%)	<0.0001
Abnormal DRE *and* Elevated PSA	77/112 (68.8%)	84/113 (74.3%)	0.35
Missing reason	3/3 (100.0%)	3/3 (100.0%)	N/A

† The number of biopsy recommendations exceeded the number of men with a biopsy recommendation because a man could have > 1 for-cause biopsy recommendation over the course of the 7-year study.
N/A=not applicable

3.7.4 Distribution of Gleason Scores at the Time of Diagnosis

A secondary objective in the PCPT was to evaluate tumor score at biopsy using the Gleason grading system (Table 7, below). Based on men in the SWOG population with a diagnosis of prostate cancer, the most common Gleason score at the time of prostate biopsy among tumors graded at biopsy was Gleason score 6, which was reported for 53% (443/836) and 64% (771/1201) of men in the finasteride and placebo groups, respectively.

In an analysis of the predefined SWOG population, a decrease in the period prevalence of low-grade (Gleason score 2-6) tumors was observed in the finasteride group relative to the placebo group (11.1% vs. 18.4%), while an increase in the period prevalence of high-grade (Gleason score 7-10) tumors was observed in the finasteride group relative to the placebo group (6.3% vs. 5.0% for Gleason score 7-10; 2.0% vs. 1.2% for Gleason score 8-10; see Table 7 and Figure 10, below). The relative risk [95% CI] (finasteride vs. placebo) for Gleason score 2-6 cancer was 0.60 [0.55, 0.67] ($p<0.001$), for Gleason

score 7-10 cancer was 1.26 [1.07, 1.48] (p=0.005), and for Gleason score 8-10 cancer was 1.70 [1.23, 2.34] (p=0.001).

In the MITT population, the evaluation of tumor score at biopsy using the Gleason grading system showed smaller between-group differences in the observed period prevalence of low-grade (Gleason score 2-6) tumors (6.2% vs. 11.0%) and high-grade (Gleason score 7-10) tumors (3.5% vs. 3.0% for Gleason score 7-10; 1.1% vs. 0.7% for Gleason score 8-10; see Appendix 5). In the MITT analysis, the relative risk [95% CI] (finasteride vs. placebo) for diagnosis of Gleason score 2-6 cancer was 0.57 [0.51, 0.62] (p<0.001), for Gleason score 7-10 cancer was 1.18 [1.01, 1.38] (p=0.039), and for Gleason score 8-10 was 1.59 [1.16, 2.18] (p=0.003).

Two important observations regarding the observed increase in high-grade cancer in the finasteride group relative to the placebo group are illustrated in Figure 10, below. Table 7, below, displays the differences in high-grade cancers observed in the SWOG population in two ways: by definition of high-grade disease (Gleason 7-10 vs. Gleason 8-10) and by type of biopsy (for-cause and EOS). It is first apparent that the number of high-grade tumors is increased substantially by the inclusion of Gleason score 7 tumors and that Gleason 8-10 tumors represent a smaller fraction of high-grade tumors. A second observation is that the majority of the increase in high-grade tumors can be attributed to those detected as a result of a biopsy that was prompted (for-cause). For example, the increase in Gleason score 7-10 and 8-10 tumors observed in the finasteride group relative to the placebo group based on for-cause biopsies was 41 and 25, respectively. Conversely, based on the EOS biopsies the observed increase in the finasteride group was considerably less, 4 and 10, respectively. The possible explanation for this observation will be discussed later in this document in the exploration of potential sources of bias related to the detection of prostate cancer in the PCPT (see Section 3.9.4, below).

Table 7

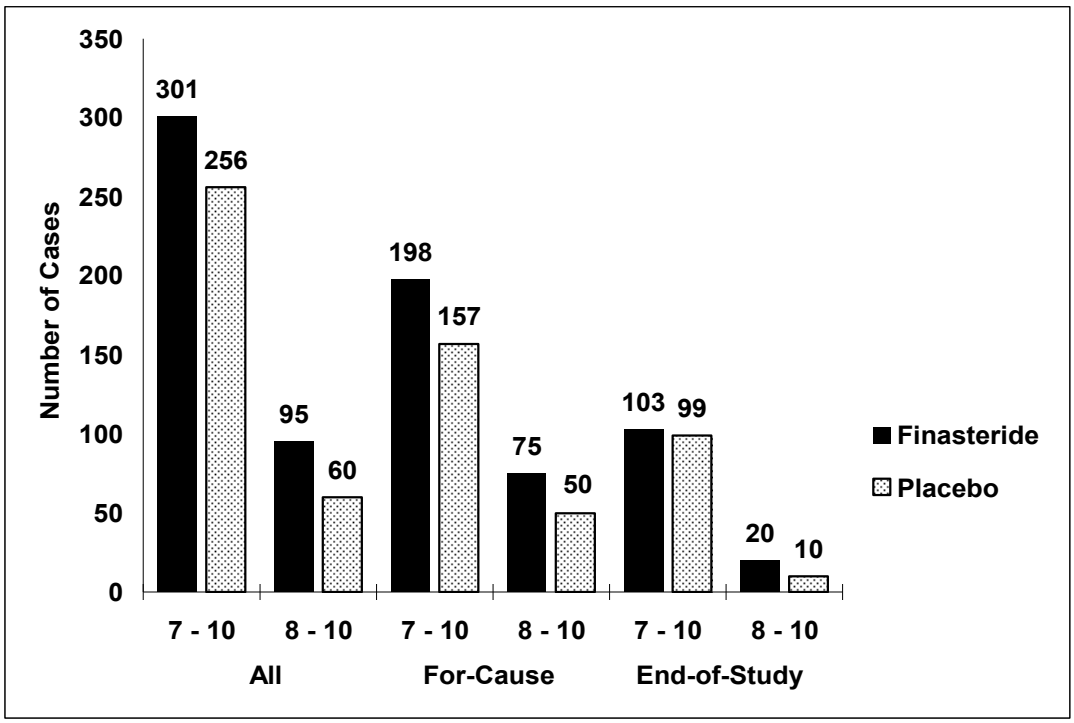
Distribution of Gleason Scores at Time of Diagnosis
SWOG Population

Gleason Score	All Cancers		Cancers Diagnosed in For-Cause Biopsies[†]		Cancers Diagnosed in End-of-Study Biopsies[‡]	
	Finasteride Group ($N^{§}$ = 4775) $n^{‖}$ (%)	Placebo Group ($N^{§}$ = 5123) $n^{‖}$ (%)	Finasteride Group ($N^{§}$ = 4775) $n^{‖}$ (%)	Placebo Group ($N^{§}$ = 5123) $n^{‖}$ (%)	Finasteride Group ($N^{§}$ = 4775) $n^{‖}$ (%)	Placebo Group ($N^{§}$ = 5123) $n^{‖}$ (%)
2	4 (0.1)	8 (0.2)	3 (0.1)	7 (0.1)	1 (0.0)	1 (0.0)
3	1 (0.0)	8 (0.2)	0 (0.0)	7 (0.1)	1 (0.0)	1 (0.0)
4	15 (0.3)	35 (0.7)	7 (0.1)	21 (0.4)	8 (0.2)	14 (0.3)
5	69 (1.4)	123 (2.4)	38 (0.8)	60 (1.2)	31 (0.6)	63 (1.2)
6	443 (9.3)	771 (15.0)	181 (3.8)	311 (6.1)	262 (5.5)	460 (9.0)
7	206 (4.3)	196 (3.8)	123 (2.6)	107 (2.1)	83 (1.7)	89 (1.7)
8	48 (1.0)	27 (0.5)	35 (0.7)	21 (0.4)	13 (0.3)	6 (0.1)
9	38 (0.8)	28 (0.5)	31 (0.6)	24 (0.5)	7 (0.1)	4 (0.1)
10	9 (0.2)	5 (0.1)	9 (0.2)	5 (0.1)	0 (0.0)	0 (0.0)
2 to 6	532 (11.1)	945 (18.4)	229 (4.8)	406 (7.9)	303 (6.3)	539 (10.5)
7,8,9 or 10	301 (6.3)	256 (5.0)	198 (4.1)	157 (3.1)	103 (2.2)	99 (1.9)
8,9 or 10	95 (2.0)	60 (1.2)	75 (1.6)	50 (1.0)	20 (0.4)	10 (0.2)
Not graded	46 (1.0)	73 (1.4)	41 (0.9)	59 (1.2)	5 (0.1)	14 (0.3)
All cancers	879 (18.4)	1274 (24.9)	468 (9.8)	622 (12.1)	411 (8.6)	652 (12.7)

[†] Includes cancers diagnosed in biopsies performed for cause either during the study or at the end of the study and those diagnosed after interim procedures.
[‡] Excludes cancers diagnosed in biopsies performed for cause at the end of the study.
[§] N = Number of SWOG participants in the treatment group.
[‖] n = Number of participants with the corresponding Gleason score.

Figure 10

Distribution of Gleason Scores At Time of Diagnosis by Treatment Group
SWOG Population



*46 cancers in the finasteride arm and 73 in the placebo arm were not graded

Note: The observed increase in the proportion of men with high-grade disease in the finasteride group relative to the placebo group is larger when expressed as a percentage of all men with prostate cancer than when expressed as a percentage of all men in the analysis due to the use of a smaller denominator (men with prostate cancer vs. men included in the analysis). This effect is further amplified by the significantly smaller number of men with prostate cancer in the finasteride group than in the placebo group. For example, if the rate of high-grade cancers is compared between finasteride and placebo groups using the total number of cancers in each group as denominator, the incidences of high-grade disease are 301/879 (34.2%) for finasteride and 256/1274 (20.1%) for placebo (relative risk=1.70; risk difference=14.1%). Table 8, below, displays the increased number of high-grade cancers in relation to the number of men at risk, using either the predefined primary population of men with an endpoint determination (SWOG population) or all eligible randomized men (MITT population).

Table 8

Incidence of High-Grade Prostate Cancer in the SWOG and MITT Populations

	Finasteride	Placebo	Summary Measure
Number of cancers	879	1274	395 more on placebo
Number of high-grade cancers	301	256	45 more on finasteride
Period prevalence of high-grade prostate cancer:			
SWOG population	301/4775 (6.3%)	256/5123 (5.0%)	Risk difference=1.3% Relative risk=1.26
MITT population	328/9423 (3.5%)	279/9457 (3.0%)	Risk difference=0.5% Relative risk=1.18

Further discussion and detailed analyses of the observed high-grade tumor findings are in Section 3.9, below.

3.8 Safety

An assessment of symptoms and/or side effects was conducted at randomization, at each 6-month visit, and at the Year 7 end-of-study visit, with PSA measured and DRE conducted at each annual visit. These data were either spontaneously reported events, information that was solicited from questionnaires, or information solicited from participants when they came in for their 6 monthly visits.

At each annual study visit, participants completed questionnaires that assessed their urinary symptoms and sexual function. Symptoms reported on the questionnaires were not automatically recorded as adverse experiences; however, there were no specific directions as to whether participants should complete the questionnaire prior to or after the assessment of adverse experiences and, thus, prompting of adverse experience reporting may have occurred.

In the PCPT, an adverse experience was defined by the National Cancer Institute (NCI) as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure. An adverse experience consisted of:

1. Any new event that was not pre-existing at initial study drug administration;

2. A pre-existing event that recurs with increased intensity or increased frequency subsequent to initial study drug administration; or

3. An event that is present at the time of study drug administration that exacerbates following initial study drug administration.

In the analysis of safety data that follows, *serious adverse experiences* have been defined as all adverse experiences that were designated as either death, resulting in death, or life-threatening. Prostate cancers were not reported as adverse experiences in the PCPT but, instead, as endpoint data. Accordingly, prostate cancers are not counted as adverse experiences or serious adverse experiences.

The finding of a greater prevalence of high-grade prostate cancer (Gleason scores 7-10) among finasteride participants in the study was unanticipated. Consequently, the interpretation of this finding has fostered discussion in the medical community and in the literature debating whether it reflects a 'true' (i.e., treatment-induced) increase in high-grade cancer or is an artifact due to confounding factors such as detection bias. Several analyses conducted subsequent to the publication of the initial results of the PCPT that provide useful insight into the high-grade tumor findings observed in PCPT are reviewed in Section 3.9.

3.8.1 Extent of Exposure

Of the 18,882 men randomized to treatment, 18,880 received at least 1 dose of study medication (2 men, 1 in each treatment group, are recorded as not having receiving at least 1 dose of study medication). Table 9, below, shows the number of participants on study drug by dose and cumulative period of time study medication was taken up through 7 years. Study medication (200 tablets) was dispensed every 6 months for the following 6-month time period. SWOG did not ask study staff to record study medication start or stop dates on the study case report forms. Accordingly, treatment duration was derived from a hierarchy of multiple data fields, and the data in Table 9 should, therefore, be considered a best estimate.

Table 9

Cumulative Period Study Medication Was Taken
All Participants Randomized

	Days								Total Number of Participants	Day Range	Average Number of Days
	1-365 † (Year 1)	366-730 (Year 2)	731-1095 (Year 3)	1096-1460 (Year 4)	1461-1825 (Year 5)	1826-2190 (Year 6)	2191-2555 (Year 7)	>2556 (>Year 7)			
Finasteride	1121	836	582	465	394	364	3014	2647	9423	1-3382	1849.0
Placebo	742	621	548	479	407	387	3291	2984	9459	1-3275	1994.9
† Randomized participants who did not take study drug are assigned 1 day of therapy by default.											

Based on the data in Table 9, above, the average number of days of treatment for study participants was 1849 days (5.1 years) in the finasteride group and 1995 days (5.5 years) in the placebo group, with 2647 and 2984 men in the finasteride and placebo groups, respectively, having taken study medication for > 7 years. Follow-up of participants who discontinued study drug early was encouraged for collection of adverse experiences and endpoint determination.

3.8.2 Adverse Experience Summary

Table 10, below, summarizes the adverse experience profile for all participants who took at least 1 dose of study medication. The rates of overall adverse experiences in the 2 treatment groups were similar, with any adverse experiences reported in 96.1% and 95.9% of men randomized to finasteride or placebo, respectively. Serious adverse experiences, defined as those adverse experiences designated as either Grade 4 (life-threatening) or Grade 5 (death or resulting in death) according to SWOG Toxicity Criteria were reported in 18.9% and 20.0% of subjects treated with finasteride and placebo, respectively, with a similar proportion of deaths reported (7.3% and 7.1% in the finasteride and placebo groups, respectively, excluding deaths due to prostate cancer [n=5 and 6, respectively]). Discontinuation of treatment due to an adverse experience was more common in the finasteride group (20.4% vs. 12.9%), primarily due to more participants in the finasteride group discontinuing study drug due to sexual side effects. Specifically, 12.0% of finasteride participants and 5.7% of placebo participants ($p<0.001$) discontinued due to a sexual adverse experience.

Table 10

Number (%) of Participants With Adverse Experience Categories
All Participants Who Took at Least One Dose of Study Medication

	Finasteride (N=9422) n (%)	Placebo (N=9458) n (%)	Difference in Proportions (%)	95% CI for Difference (%)
With one or more adverse experiences	9050 (96.1)	9072 (95.9)	0.1	(-0.4, 0.7)
With serious adverse experiences	1777 (18.9)	1896 (20.0)	-1.2	(-2.3, -0.1)
Who died[†]	684 (7.3)	668 (7.1)	0.2	(-0.5, 0.9)
Discontinued due to an adverse experience	1921 (20.4)	1221 (12.9)	7.5	(6.4, 8.5)
Discontinued due to a sexual adverse experience	1128 (12.0)	542 (5.7)	6.2	(5.4, 7.0)

N= number who took at least one dose of study medication
n = number with adverse experience.
CI = confidence interval computed using the Wilson score method.
p-value based on Fisher's Exact Test.
[†] Excludes deaths due to prostate cancer (5 in the finasteride group and 6 in the placebo group)

3.8.3 Specific Adverse Experiences

Adverse experiences reported in ≥ 5% of participants in either treatment group are presented in Table 11. The most common adverse experiences, and their corresponding cumulative incidences over 7 years in the finasteride and placebo groups, were erectile dysfunction (68.9% and 63.1%, respectively), loss of libido (67.0% and 61.5%, respectively), and semen volume abnormal (decreased) (61.5% and 48.8%, respectively). These sexual adverse experiences are known to be associated with the use of finasteride, and are included in the product labeling.

Table 11

Common Adverse Experiences
Number (%) of Participants With Adverse Experiences
Incidence ≥5% in One or More Treatment Groups By System Organ Class
All Participants Randomized

	Finasteride (N = 9423)		Placebo (N = 9459)	
	n	(%)	n	(%)
Participants With One Or More Adverse Experiences	9050	(96.0)	9072	(95.9)
Cardiac Disorders	**2503**	**(26.6)**	**2718**	**(28.7)**
Arrhythmia	939	(10.0)	1064	(11.2)
Cardiovascular Disorder	988	(10.5)	1101	(11.6)
Myocardial Ischaemia	1092	(11.6)	1217	(12.9)
Eye Disorders	**698**	**(7.4)**	**888**	**(9.4)**
Gastrointestinal Disorders	**1616**	**(17.1)**	**2049**	**(21.7)**
Gastrointestinal Discomfort	378	(4.0)	586	(6.2)
General Disorders And Administration Site Conditions	**2073**	**(22.0)**	**2508**	**(26.5)**
Pain	1406	(14.9)	1746	(18.5)
Infections And Infestations	**982**	**(10.4)**	**1555**	**(16.4)**
Infection	491	(5.2)	789	(8.3)
Respiratory Tract Infection	323	(3.4)	549	(5.8)
Injury, Poisoning And Procedural Complications	**535**	**(5.7)**	**734**	**(7.8)**
Accident	478	(5.1)	657	(6.9)
Investigations	**6189**	**(65.7)**	**5357**	**(56.6)**
Investigation Abnormal	1039	(11.0)	1401	(14.8)
Semen Volume Abnormal	5796	(61.5)	4616	(48.8)
Metabolism And Nutrition Disorders	**893**	**(9.5)**	**1102**	**(11.7)**
Diabetes Mellitus	550	(5.8)	554	(5.9)
Musculoskeletal And Connective Tissue Disorders	**1360**	**(14.4)**	**1686**	**(17.8)**
Arthritis	886	(9.4)	1082	(11.4)
Musculoskeletal Disorder	523	(5.6)	636	(6.7)

Common Adverse Experiences
Number (%) of Participants With Adverse Experiences
Incidence ≥5% in One or More Treatment Groups By System Organ Class
All Participants Randomized (Cont.)

	Finasteride (N = 9423)		Placebo (N = 9459)	
	n	(%)	n	(%)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**666**	**(7.1)**	**634**	**(6.7)**
Nervous System Disorders	**3314**	**(35.2)**	**3590**	**(38.0)**
Dizziness	1697	(18.0)	1841	(19.5)
Headache	1608	(17.1)	1674	(17.7)
Psychiatric Disorders	**6395**	**(67.9)**	**5938**	**(62.8)**
Loss Of Libido	6315	(67.0)	5814	(61.5)
Renal And Urinary Disorders	**2373**	**(25.2)**	**2991**	**(31.6)**
Dysuria	832	(8.8)	1111	(11.7)
Pollakiuria	1242	(13.2)	1539	(16.3)
Urinary Retention	409	(4.3)	648	(6.9)
Reproductive System And Breast Disorders	**7088**	**(75.2)**	**6680**	**(70.6)**
Benign Prostatic Hyperplasia	645	(6.8)	968	(10.2)
Breast Pain	829	(8.8)	591	(6.2)
Erectile Dysfunction	6491	(68.9)	5967	(63.1)
Prostatitis	437	(4.6)	606	(6.4)
Respiratory, Thoracic And Mediastinal Disorders	**867**	**(9.2)**	**1025**	**(10.8)**
Skin And Subcutaneous Tissue Disorders	**2756**	**(29.2)**	**2953**	**(31.2)**
Urticaria	2262	(24.0)	2408	(25.5)
Vascular Disorders	**1877**	**(19.9)**	**2015**	**(21.3)**
Hypertension	1667	(17.7)	1763	(18.6)

Although a participant may have had two or more adverse experiences, he is counted only once within a category. The same participant may appear in different categories.

The incidences of BPH-related adverse experiences (urinary retention, urinary tract infection and incontinence) and adverse experiences in the sexual, breast-related and cardiovascular categories are presented in Table 12, below. The categorical cardiovascular adverse experience group included reports of cardiac ischemia, cardiac failure congestive, cardiac disorder, cardiovascular disorder, chest pain, cardiac dysrhythmia, cardiac valve disease, hypertension, hypotension, and pericardial disease.

Compared with placebo, treatment with finasteride was associated with a higher incidence of sexual and breast-related adverse experiences and a lower incidence of BPH-related adverse experiences. In addition, fewer men in the finasteride group underwent TURP than men in the placebo group: 1% (97/9423) vs. 1.9% (182/9459), respectively. No increase in the incidence of cardiovascular adverse experiences was

observed with finasteride compared with placebo. The specific adverse experience of congestive heart failure was reported for 1.8% (166/9423) of participants in the finasteride group and 2.0% (187/9459) of participants in the placebo group.

Table 12

Number (%) of Participants With Specific Adverse Experiences
All Participants who Took at Least One Dose of Study Medication

	Finasteride (N=9422) n (%)	Placebo (N=9458) n (%)	Difference in Proportions (%)	95% CI for Difference (%)
Urinary retention	409 (4.3)	648 (6.9)	-2.5	(-3.2, -1.9)
Urinary tract infection	113 (1.2)	235 (2.5)	-1.3	(-1.7, -0.9)
Incontinence	187 (2.0)	224 (2.4)	-0.4	(-0.8, 0.0)
With sexual adverse experiences	7762 (82.4)	7132 (75.4)	7.0	(5.8, 8.1)
With breast-related adverse experiences	1086 (11.5)	768 (8.1)	3.4	(2.6, 4.3)
With cardiovascular events	3641 (38.6)	3903 (41.3)	-2.6	(-4.0, -1.2)

N= number who took at least one dose of study medication
n = Number with adverse experience.
CI = Confidence Interval computed using the Wilson score method.
p-value based on Fisher's Exact Test.

3.8.3.1 Sexual Adverse Experiences

The most commonly-reported adverse experiences were sexual adverse experiences and were reported by 7% more men in the finasteride group than in the placebo group ($p<0.001$). Specific sexual adverse experiences reported are shown in Table 13, below.

Table 13

Number (%) of Participants With Sexual Adverse Experiences
All Participants Randomized

	Finasteride 5 mg (N=9423)		Placebo (N=9459)	
	n	(%)	N	(%)
Participants With One Or More Sexual Adverse Experiences	7762	(82.4)	7132	(75.4)
Semen Volume Abnormal	5796	(61.5)	4616	(48.8)
Penis Carcinoma	1	(0.0)	1	(0.0)
Testis Cancer	2	(0.0)	0	(0.0)
Loss Of Libido	6315	(67.0)	5814	(61.5)
Male Orgasmic Disorder	58	(0.6)	28	(0.3)
Dyspareunia	4	(0.0)	4	(0.0)
Ejaculation Disorder	120	(1.3)	79	(0.8)
Erectile Dysfunction	6491	(68.9)	5967	(63.1)
Infertility	1	(0.0)	0	(0.0)
Painful Erection	24	(0.3)	6	(0.1)
Pelvic Pain	25	(0.3)	16	(0.2)
Penile Pain	7	(0.1)	6	(0.1)
Penis Disorder	85	(0.9)	54	(0.6)
Sexual Dysfunction	188	(2.0)	193	(2.0)
Testicular Pain	137	(1.5)	111	(1.2)

Although a participant may have had two or more clinical adverse experiences, he is counted only once within a category. The same participant may appear in different categories.

3.8.3.2 Breast-related Adverse Experiences

Breast-related adverse experiences (predominately breast pain/tenderness and gynecomastia) were reported by 3.4% more men in the finasteride group than in the placebo group ($p<0.001$). Specific adverse experiences in the category of breast-related adverse experiences are shown in Table 14, below. Reports of breast cancer were balanced between groups, with 1 case of breast cancer reported in each treatment group.

Table 14

Number (%) of Participants With Breast-Related Adverse Experiences
All Participants Randomized

	Finasteride (N=9423)		Placebo (N=9459)		Difference in Proportions
	n	(%)	n	(%)	
Breast Mass or Breast Lump	41	(0.4)	15	(0.2)	0.2
Breast Pain/Tenderness	829	(8.8)	591	(6.2)	2.6
Gynecomastia	429	(4.6)	263	(2.8)	1.9
Breast Cancer	1	(<0.1)	1	(<0.1)	0.0

3.8.3.3 Drug-related Adverse Experiences

In the PCPT, the dataset for drug-related adverse experiences comprised a subset of all adverse experiences considered by the investigator to be associated with the use of the drug during the trial. Only adverse experiences that met SWOG Toxicity Criteria for severity (Grade 3-5 for unlabeled adverse experiences; Grade 4-5 for labeled adverse experiences) were reported to the SWOG Operations Office for assessment and confirmation and reported into the PCPT database. This included a total of 750 adverse experience reports from 648 participants (319 finasteride, 329 placebo), or 3.4% of the randomized population. For these reported adverse experiences, a SWOG nurse consultant and physician assigned a final relationship of the adverse experience to the study drug, and only these drug relationships assigned by the SWOG Operations Office were entered into the database. This resulted in a total of 588 participants (282 finasteride, 306 placebo) reported with adverse experiences meeting SWOG Toxicity Criteria and determined to be drug-related by the SWOG Operations Office (Appendix 6). The most common drug-related adverse experiences meeting these criteria were in the cardiac disorders system organ class (1.2% finasteride, 1.2% placebo), with myocardial ischemia being the most common specific adverse experience reported (0.9% and 1.0%, respectively).

3.8.4 Quality-of-Life Analysis

In a longitudinal analysis of sexual function, the effect of finasteride on sexual dysfunction in participants over the 7 years of the trial was quantified using the Sexual Activity Scale. The magnitude of its effect was compared to that of naturally occurring influences, relevant covariates associated with male sexual dysfunction, and with individual variation both within and between treatment arms.

The 4-item Sexual Activity Scale was developed for the PCPT based on items used previously in BPH research: ability to have an erection when desired (5 response levels);

degree of participant's satisfaction with his sexual activities (4 response levels); change in sexual performance (7 response levels); and frequency of sexual activities (7 response levels). Each item was transformed to a 0–100 scale, and the overall Sexual Activity Scale score was computed as the mean score for the four items. Scores range from 0 to 100, with higher scores reflecting more sexual dysfunction (less positive sexual activity). The psychometric properties of the scale are presented in [52].

To be included in this analysis, participants were required to have completed the Sexual Activity Scale and all covariates at the time of randomization and the Sexual Activity Scale at least 2 times after randomization. A total of 17,313 (8550 on finasteride, 8763 on placebo) out of 18,880 eligible randomized men were included in this analysis. By the end of the study at 7 years, the sample size decreased to 56% of the men at study entry in the placebo arm (n=5169) and 52% of the men at study entry in the finasteride arm (n=4777).

Participants who received finasteride reported increased sexual dysfunction relative to placebo, an increase in the Sexual Activity Scale score of 3.21 points (95% CI = 2.83 to 3.59 points; p <0.001) at the first assessment that decreased to 2.11 points (95% CI = 1.44 to 2.81 points; p <0.001) at the end of study. These Sexual Activity score values were small on a scale of 0 – 100, the range observed in the study, and in comparison with the expected individual variation between two 'similar' men of 15.34 points. The effect of aging on sexual dysfunction in this study was on average 1.26 points (95% CI = 1.16 to 1.36 points; p <0.001) per year corresponding to a cumulative increase of 8.22 points (95% CI = 7.52 to 8.92 points; p <0.001) over the study period [52].

3.8.5 Safety Summary

Treatment with finasteride was generally well tolerated. The increase in sexual and breast-related adverse experiences and the reduction in BPH-related adverse experiences and TURPs were consistent with the established profile of finasteride in the treatment of men with BPH.

3.9 Examination of the High-Grade Prostate Cancer Data in PCPT

While the efficacy analyses presented earlier in this document demonstrated a significant improvement in the prevalence of prostate cancer with finasteride, an increase in the percentage of men diagnosed with high-grade prostate cancer (Gleason score 7-10 or 8-10) was observed with finasteride in the PCPT. Table 15, below, shows the data on the detection of high-grade prostate cancer based on the prespecified analysis of the SWOG population. Table 16, below, shows these data based on the MITT population.

Table 15

High-Grade Prostate Cancers
SWOG Population

	Finasteride		Placebo	
All men in analysis	4775		5123	
All prostate cancers (%)	879 (18.4%)		1274 (24.9%)	
	Gleason Score 7-10	Gleason Score 8-10	Gleason Score 7-10	Gleason Score 8-10
All high-grade cancers[†]	301 (6.3%)	95 (2.0%)	256 (5.0%)	60 (1.2%)
For-cause	*198 (4.1%)*	*75 (1.6%)*	*157 (3.1%)*	*50 (1.0%)*
End-of-study	*103 (2.2%)*	*20 (0.4%)*	*99 (1.9%)*	*10 (0.2%)*
[†] 46 and 73 cancers in the finasteride and placebo groups, respectively, were not graded				

Table 16

High-Grade Prostate Cancers
MITT Population

	Finasteride		Placebo	
All men in analysis	9423		9457	
All prostate cancers (%)	979 (10.4%)		1407 (14.9%)	
	Gleason Score 7-10	Gleason Score 8-10	Gleason Score 7-10	Gleason Score 8-10
All high-grade cancers[†]	328 (3.5%)	100 (1.1%)	279 (3.0%)	63 (0.7%)
For-cause	*203 (2.2%)*	*75 (0.8%)*	*163 (1.7%)*	*51 (0.5%)*
End-of-study	*125 (1.3%)*	*25 (0.3%)*	*116 (1.2%)*	*12 (0.1%)*
[†] 46 and 73 cancers in the finasteride and placebo groups, respectively, were not graded				

In order to better understand the cause for the observed high-grade disease findings with finasteride, several additional *(post-hoc)* analyses were conducted. These included additional histopathological analyses conducted by the PCPT Pathology Core Lab (PCL) and statistical analyses of the data by SWOG and by others. To test the hypothesis of whether finasteride treatment induced high-grade prostate cancer, examination of the time course of the hazard ratio (HR) for diagnosis of high-grade prostate cancer was conducted; if finasteride induced high-grade disease, it would be anticipated that the HR for diagnosis would increase with longer duration of treatment. To further test this hypothesis, a centralized histopathological evaluation of biopsy slides of high-grade cases was conducted by the PCL to examine for evidence of measures of tumor aggressiveness using surrogates of tumor volume and multifocality; if finasteride induced high-grade

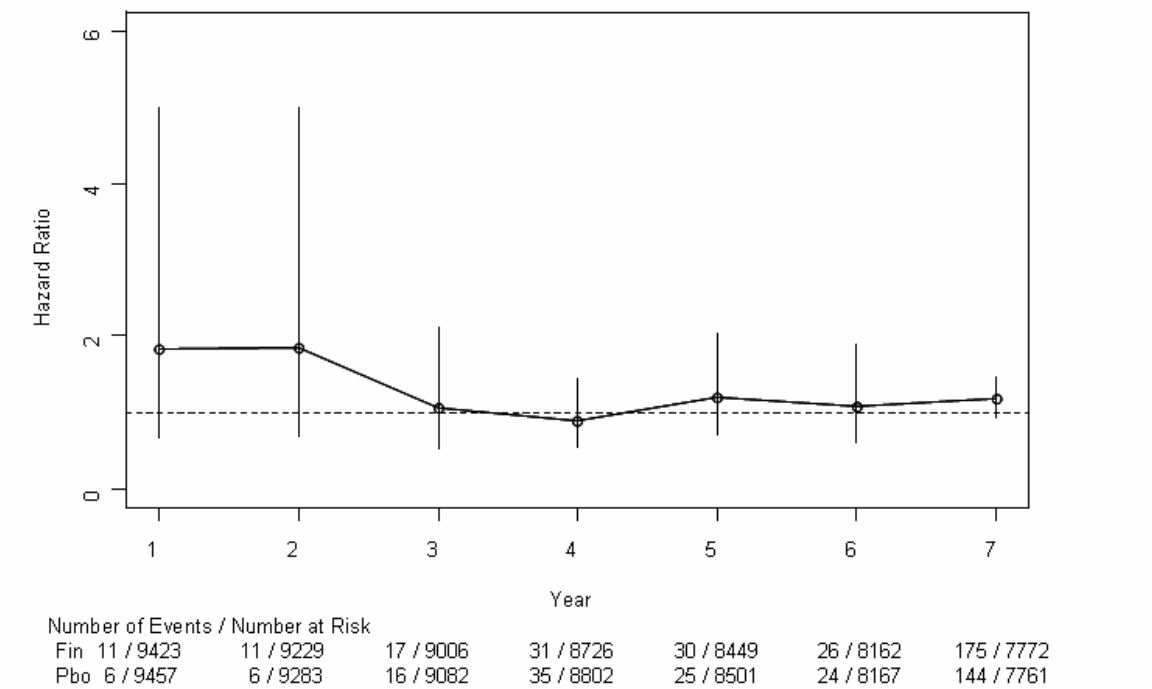
disease, these measures would be anticipated to be increased. Other analyses included covariate-adjusted logistic regression modeling, adjusting for factors related to the size of the prostate gland, and analyses examining the potential for detection bias due to differential sensitivities between finasteride and placebo with respect to tests (PSA, DRE, and prostate needle biopsy) used in the PCPT to detect and diagnose prostate cancer, including high-grade prostate cancer.

3.9.1 Time Course of High-Grade Prostate Cancers

The hazard ratio (HR) for detecting high-grade prostate cancer for the SWOG population was fit for each year of follow-up in PCPT (Figure 11, below). Vertical lines represent 95% confidence intervals. While there is a numerical imbalance in favor of placebo in most years, there is no suggestion of an increasing effect with time as would be expected if finasteride treatment were inducing the development of high-grade prostate cancer. However, these data would be consistent with a between-group bias impacting the detection of high-grade prostate cancer that was present early and persisted throughout the study. See Section 3.9.4 for discussion and analysis of potential sources of bias.

Figure 11

Hazard Ratio For High-Grade (Gleason 7-10) Prostate Cancer
SWOG Population



3.9.2 Tumor Extent Among Gleason Score 7-10 Cancers Diagnosed by Biopsy

Hallmarks of aggressive, generally high-grade prostate cancer are higher tumor volume and multifocality; these measures on prostate biopsy are most often manifested by larger amounts of cancer in individual cores, more cores involved with cancer, and tumors located in both prostate lobes (i.e., bilateral disease). If treatment with finasteride induced high-grade disease, it was hypothesized there would be evidence of more extensive and multifocal disease in prostate biopsies of men on finasteride. To explore this question, the PCL conducted pathologic assessments to characterize these measures in cases with Gleason scores of 7-10. All available Gleason score 7-10 prostate cancer needle biopsies from the PCPT were assessed for pathologic and biochemical measures of tumor aggressiveness, including: (1) percentage of needle biopsy cores positive for prostate cancer, (2) greatest linear extent of disease in millimeters (measured in the core with the greatest amount of tumor), (3) aggregate linear extent of disease in millimeters (adding the extent of all cores with cancer), and (4) bilaterality (cancer present in both the right and left lobes of the prostate). The pathologist who conducted the assessment was blinded to treatment assignment. Because the results of the PCPT were unblinded on June 23, 2003, the following analysis includes data up to the trial unblinding date rather than up to January 15, 2004.

Table 17, below, displays summary statistics for measures of tumor extent and multifocality for Gleason score 7-10 cancers diagnosed by prostate biopsy [13]. All measures assessed showed numerically less extensive disease in the finasteride group compared with placebo. This finding was observed despite a higher sampling density upon prostate biopsy in men on finasteride due to an equivalent number of biopsy cores in both groups and a reduced prostate volume (~25% decrease relative to placebo) in the finasteride group.

Table 17

Biopsy Characteristics of Tumors
With Gleason Scores 7–10 in the PCPT
Up To Unblinding Date of June 23, 2003

	Gleason 7		Gleason 8-10	
Measures of tumor extent and volume	Finasteride N=191	Placebo N=187	Finasteride N=91	Placebo N=57
N of cores positive (median)	2	2	2	3
% of positive cores (median)	33.3%	33.3%	33.3%	45.0%
Total linear extent (mm)	4.5	5.5	6.2	7.25
% bilateral prostate cancer	20.0	26.3	28.6	44.6

[13]

3.9.3 Assessment of the Effect of Finasteride on High-Grade Prostatic Intraepithelial Neoplasia (HGPIN)

To further explore for a relationship between finasteride and the potential to induce high-grade disease, the effect of finasteride on the development of high-grade prostatic intraepithelial neoplasia (HGPIN) in the PCPT was assessed [53]. Many observations suggest that HGPIN is a premalignant lesion [54; 55], as it is frequently associated with, or may precede a diagnosis of, prostate cancer; HGPIN also shares molecular features with, and is morphologically similar to, prostate cancer. If finasteride were found to increase the prevalence of HGPIN, a potential precursor to prostate cancer, it would provide evidence that finasteride treatment has a deleterious impact on the carcinogenic pathway, potentially providing an explanation for the observed increase in high-grade prostate cancer in the PCPT.

The pathologist conducting this analysis was blinded to treatment assignment. As with the previous analysis, the following analysis includes data up to the trial unblinding date of June 23, 2003 rather than up to January 15, 2004. Men were considered evaluable for HGPIN in this analysis if they 1) were diagnosed with HGPIN or prostate cancer on a for-cause or EOS biopsy, or 2) had a negative EOS biopsy at 7 years in the study. Of the 18,880 eligible randomized men (9423 finasteride, 9457 placebo), 4568 (48%) and 4886 (52%) were evaluable for HGPIN diagnosis. Of evaluable men in the finasteride group, 3500/4568 (76.6%) compared to 3409/4886 (69.8%) in the placebo group had a negative EOS biopsy and were not diagnosed with either HGPIN or prostate cancer during the study (RR = 0.77; 95% CI = 0.72-0.83, p<0.0001). The analysis of the prevalence of HGPIN is shown in Table 18, below.

Table 18

Analysis of High-Grade Prostatic Intraepithelial Neoplasia (HGPIN)
Up To Unblinding Date of June 23, 2003

	Finasteride (N=4568)	Placebo (N=4886)	Relative Risk 95% CI	p-Value
HGPIN alone	276 (6.0%)	347 (7.1%)	0.85 (0.73-0.99)	0.04
HGPIN and prostate cancer	144 (3.2%)	223 (4.6%)	0.69 (0.56, 0.85)	< 0.001
Any HGPIN	420 (9.2%)	570 (11.7%)	0.79 (0.70, 0.89)	< 0.001

[53]

Based on the analysis of evaluable men, treatment with finasteride was associated with a significantly reduced risk of HGPIN, either diagnosed alone or diagnosed concurrently with prostate cancer. The analysis demonstrates that treatment with finasteride reduced the risk of HGPIN by 21% overall (alone or with prostate cancer), which is similar to the relative risk reduction observed in the PCPT for prostate cancer overall. If additional data confirm the hypothesis of HGPIN as a precursor lesion that leads to prostate cancer, the significant reduction in the risk of HGPIN observed with finasteride treatment may provide additional insight into the effect of finasteride on the development of prostate cancer. In addition, because a diagnosis of HGPIN often leads to a repeat prostate biopsy, with the attendant morbidity of the procedure and risk of a diagnosis of prostate cancer, a reduction in the risk of HGPIN with finasteride would be of medical and public health interest.

3.9.4 Potential Sources of Bias

In light of the above analyses and their findings, none of which identified an etiology for, or was consistent with, the observed increase in high-grade disease with finasteride, another potential explanation for the high-grade disease findings was considered. Androgen deprivation therapy in men with prostate cancer is known to be associated with degenerative changes in prostate cancer cellular morphology and architecture that artifactually make tumors appear to be of a higher Gleason grade, leading to a higher Gleason score, than they actually are. Therefore, it had been hypothesized that finasteride may similarly cause degenerative changes that could cause prostate cancer to appear to have a higher Gleason score (*diagnostic bias*). To further evaluate this hormonal-effect hypothesis, a blinded re-grading of Gleason 8-10 tumors in PCPT was conducted by a panel of expert pathologists. The panel concluded that finasteride does not cause distinctive histopathologic changes to prostate cancer tissue that can be distinguished from untreated prostate cancer tissue, and thus this potential for bias does not appear to explain the high-grade disease findings in the PCPT [11].

Several observations from the PCPT results suggested that the observed increase in high-grade disease may have been an artifact due to *detection bias* rather than to a change in the biology of the disease. As was demonstrated in the initial report of PCPT results as published in the NEJM, more men in the finasteride group who underwent a for-cause biopsy had high-grade (Gleason 7-10) tumors than men in the placebo group, while for men in whom prostate cancer was diagnosed based on an EOS biopsy, no meaningful between-group difference was observed for those with Gleason 7-10 tumors (although an imbalance remained among a smaller number of men with Gleason 8-10 tumors; see Figure 10, above). In addition, the analysis of the hazard ratio over time for a diagnosis of high-grade disease demonstrated an increase with finasteride during a study participant's first few years of study participation that did not increase with time, as noted in Figure 11, above. These and other observations raised the possibility that the increase in high-grade disease with finasteride was due to enhanced *detection* of high-grade disease that was due to an increased sensitivity of the methods used to screen for prostate

cancer (PSA testing and DRE) and/or in the method used to diagnose prostate cancer (prostate biopsy), including high-grade prostate cancer. Many of these potential sources of bias were suspected during the design of the PCPT and mechanisms were put in place to mitigate them during the trial (see Appendix 3). However, what follows are several analyses that examined these potential phenomena and demonstrate that detection of high-grade prostate cancer, and likely prostate cancer overall, was enhanced in the finasteride group relative to the placebo group due to bias.

In order to more accurately quantify the effect of finasteride on potential detection biases in the PCPT, many of the secondary analyses that follow use a dataset that included prostate cancer endpoints that were obtained up to the reporting of the PCPT results and trial unblinding (i.e., up to June 23, 2003), rather than the dataset up to January 15, 2004. If participants stopped taking study drug after trial unblinding, the effect of finasteride on PSA, DRE and prostate volume would be reduced and so including these factors in analysis after the study was stopped could dilute the ability to detect differences between treatment groups. In the following sections, each analysis summary describes the specific inclusion and exclusion criteria used for the respective analysis.

3.9.4.1 Analysis of a Potential PSA Detection Bias

One potential source of bias in the endpoint screening procedure was the effect of finasteride on PSA. As described in Section 3.3 (Study Design), it was known that treatment with finasteride would lower PSA in treated men. Accordingly, the laboratory-measured PSA in men on the finasteride arm in the PCPT was adjusted using *PSA indexing*. The indexing procedure corrected for the effect of finasteride on PSA and was adjusted to target an equal number of biopsies in the 2 treatment arms (details as to how this was implemented during the PCPT are in Appendix 3.) However, even with this indexing procedure, it was possible that the screening properties of PSA would differ for men on finasteride vs. placebo due to possible differential effects of finasteride on PSA in prostate cancer cases vs. non-cases. If this were the case, the probability of an elevated PSA level to detect prostate cancer, including high-grade cancer, would be different in the 2 treatment arms.

3.9.4.1.1 Finasteride Increases the Sensitivity of PSA for Detection of Prostate Cancer and High-Grade Cancer

Over the 7 years of a man's participation in the PCPT, a PSA was obtained annually and, if elevated (> 4.0 ng/mL in the placebo group; > an adjusted value in the finasteride group that was modified to seek a similar number of biopsies in both groups), a biopsy was recommended. Although it was assumed that the sensitivity of PSA for detection of prostate cancer in men receiving finasteride would be similar to that in men receiving placebo, it was nonetheless possible that treatment with finasteride could alter the PSA sensitivity and thereby affect cancer detection. This could occur due to finasteride's effect on the prostate gland.

For example, for a man in the placebo group, PSA could increase over time not due to cancer but due to an enlarging prostate secondary to BPH; an elevated PSA could then occur due to more adenomatous prostate tissue and, in such a man, the elevated PSA would prompt a biopsy yet find no cancer. Conversely, if this man were in the finasteride group, it would be expected that with finasteride treatment the PSA would fall due to the drug's effect on the enlarged prostate; even with the use of an adjustment factor to correct for the fall in PSA with finasteride, such a man may have a lower likelihood of developing an elevated PSA over time and precipitating a biopsy, as continued enlargement of adenomatous prostate tissue would be slowed by treatment. Alternatively, if this man had BPH and developed prostate cancer, he might not be expected to have the same degree of PSA reduction with finasteride as a man with BPH but without prostate cancer [56]. Assuming that finasteride has no effect on prostate cancer prevalence, if a similar number of biopsies were recommended in both the finasteride and placebo arms by adjusting the PSA cutoff for men on finasteride, the end result of the phenomena described above would be *fewer biopsies in the finasteride group in men who were cancer-free and more biopsies in the finasteride group in men who actually were found to have cancer.* If instead finasteride reduces prostate cancer prevalence, as was observed in the PCPT, this phenomenon would be expressed as an improved *sensitivity* of the PSA test for cancer detection in the finasteride group. Due to the large number of subjects undergoing annual PSA testing and subsequent biopsies in the 2 study arms in the PCPT (particularly the end-of-study biopsies recommended for all participants), this possibility could be evaluated.

One common approach to evaluating the sensitivity and specificity of a diagnostic procedure is to construct a Receiver Operating Characteristics (ROC) curve. The ROC curve displays the function of a test by comparing its sensitivity and specificity, often expressed graphically as sensitivity vs. 1-specificity (i.e., sensitivity vs. the false-positive rate). An ROC curve at the 45-degree angle is non-discriminatory, performing no better in predicting presence of disease than the toss of a coin. The AUC of such a curve is 0.5. The greater the value of the AUC for an ROC curve above 0.5, the more likely the test will correctly (1) identify a patient with disease (sensitivity) and (2) indicate a normal value in a patient without disease (specificity). In the case of PSA and prostate cancer, the performance of PSA between the finasteride and placebo groups can be assessed by comparing the Area Under the ROC Curve (AUC) for each group. If the PSA test had a greater AUC in men receiving finasteride, it would more likely prompt a biopsy in a man with cancer and would be less likely to prompt a biopsy in a man without cancer. As will be shown, this was indeed the case.

To examine whether finasteride affected the ability of PSA to detect cancer, an analysis included all men randomized to finasteride or placebo who underwent a prostate biopsy (either for-cause or EOS) during the 7-year study period, were on treatment at the time of the PSA measurement, and had a PSA measurement and DRE within 1 year prior to the biopsy [9]. Biopsies included in this analysis were conducted up to the reporting of the primary results of the PCPT and trial unblinding (i.e., up to June 23, 2003). For

participants with multiple biopsies, the most recent biopsy was used. The ROC of PSA for detection of prostate cancer by biopsy in the placebo and finasteride groups were summarized in terms of the sensitivity and specificity of a series of cutoff values of PSA; ROC curves were calculated for prostate cancer vs. no prostate cancer, for Gleason score 7 or higher prostate cancer vs. Gleason score less than 7 or no prostate cancer, and for Gleason score 8 or higher prostate cancer vs. Gleason score less than 8 or no prostate cancer. Sensitivity was defined as the proportion of men with prostate cancer whose PSA value exceeded each cutoff value and specificity as the proportion of men without prostate cancer whose PSA value was equal to or less than each cutoff value [9].

As mentioned previously, finasteride reduces PSA by approximately 50% in men with BPH, but in men who developed prostate cancer the effect of finasteride on PSA may differ from 50% [56], so comparisons of sensitivity between the finasteride and placebo groups were made for PSA cutoffs that achieved the same specificity in each group. PSA cutoffs for the finasteride group were defined as those that yielded the same specificity as the corresponding PSA cutoffs for the placebo group. The ROC curve was plotted as sensitivity vs. 1-specificity for all cutoff values in the range of PSA values observed.

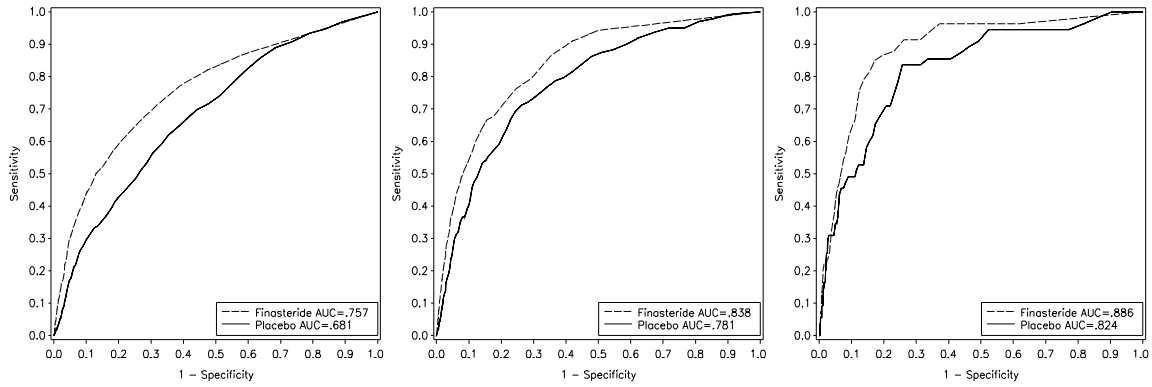
Of the 18,882 participants in the PCPT, 9423 were randomly assigned to finasteride and 9459 to placebo. As of the date when the study was reported and unblinded, a total of 4579 men in the finasteride group and 5112 men in the placebo group had at least 1 biopsy during the study period, either for cause or per protocol at the end of the study, had a PSA and DRE within 1 year prior to the biopsy, and were taking study drug when their PSA was measured; these men were included in this analysis [9].

Of the 5112 men in the placebo group, 1111 (21.7%) were diagnosed with prostate cancer. Information on tumor grade was available for 1100 of these men, of whom 240 had a Gleason score of 7 or higher (21.8% of evaluable cancers) and 55 had a Gleason score of 8 or higher (5% of evaluable cancers). Of the 4579 men who received finasteride, 695 (15.2%) were diagnosed with prostate cancer. Information on tumor grade was available for 686 of these men, of whom 264 had a Gleason score of 7 or higher (38.5% of evaluable cancers) and 81 had a Gleason score of 8 or higher (11.8% of evaluable cancers) [9].

Figure 12

Receiver Operating Characteristic (ROC) Curves
For PSA Detection of All Prostate Cancer and
High-Grade Prostate Cancer
Up to Unblinding Date of June 23, 2003

All Prostate Cancer | Gleason Score ≥7 Prostate Cancer | Gleason Score ≥8 Prostate Cancer



Solid line = placebo group; dashed line = finasteride group.
P-values for difference between groups [from test of DeLong et al.] are <0.001 for all prostate cancer, 0.003 for Gleason score ≥7 prostate cancer, and 0.071 for Gleason score ≥8 prostate cancer [9].

Comparisons between the finasteride and placebo groups for the ROC curves of PSA for detection of prostate cancer vs. no prostate cancer, of Gleason score 7 or higher vs. Gleason score 6 or less or no cancer, and of Gleason score 8 or higher vs. Gleason score 7 or less or no cancer (Figure 12, above) showed that, in each case, the area under the curve (AUC) of PSA was greater for the finasteride group than for the placebo group. For detection of prostate cancer overall, the AUCs were 0.757 in the finasteride group and 0.681 in the placebo group ($p<0.001$); for detection of Gleason score 7 or higher disease, the AUCs were 0.838 and 0.781, respectively ($p=0.003$); and for detection of Gleason score 8 or higher disease, the AUCs were 0.886 and 0.824, respectively ($p=0.071$) [9].

Table 19

Sensitivity of PSA For Detection of Prostate Cancer,
Gleason Score ≥ 7 Cancer, and Gleason Score ≥ 8 Cancer
For Standard Cutoffs of PSA and Cutoffs for Finasteride
Chosen to Match PSA Specificities for Placebo
Up to Unblinding Date of June 23, 2003

PSA Placebo Cutoff (ng/mL)	PSA Finasteride (unadjusted)	Specificity† Placebo and Finasteride	Sensitivity Placebo (95% CI)	Sensitivity Finasteride (95% CI)
Prostate cancer vs. no prostate cancer				
4.0	1.6	92.7	24.0 (21.5, 26.5)	37.8 (34.2, 41.4)
Gleason ≥ 7 cancer vs. Gleason ≤ 6 or no prostate cancer				
4.0	1.6	90.5	39.2 (33.0, 45.4)	53.0 (47.0, 59.0)
Gleason score ≥ 8 cancer vs. Gleason score ≤ 7 or no prostate cancer				
4.0	1.7	89.5	49.1 (35.9, 62.3)	64.2 (53.8, 74.6)

† Confidence intervals for specificities were on average within ± 0.9% (largest 1.5%) from the estimates reported in the table for both finasteride and placebo [9].

While ROC curves mathematically explain differences in the performance of clinical tests, they are often difficult to put into clinical context. Table 19, above (an abbreviated version of the table included in [9]; an expanded table is available in Appendix 7), shows how this improved PSA performance affects prostate cancer detection with finasteride. The upper row of the table explores how, with a PSA threshold of 4.0 ng/mL to prompt a biopsy recommendation, the ability to detect prostate cancer is significantly improved if a man is receiving finasteride. As can be seen, with specificity maintained at 92.7% the sensitivity for cancer detection increases from 24.0% in the placebo group to 37.8% in the finasteride group. Similarly, for detection of high-grade, Gleason score 7-10 cancer, sensitivity increases from 39.2% to 53.0% if a man is receiving finasteride. Similarly, for detection of high-grade, Gleason score 8-10 cancer, sensitivity increases from 49.1% to 64.2% if a man is receiving finasteride. The hypothesis that *if cancer, including high-grade cancer, is actually present, PSA is more likely to indicate this if a man is taking finasteride, thus improving cancer detection* is confirmed with this analysis. This effect of finasteride on the improved sensitivity of PSA may have been, at least in part, responsible for the increased detection of high-grade disease in the finasteride arm of the PCPT. This effect also likely caused an underestimation of the actual reduction in the risk of prostate cancer overall with finasteride relative to placebo.

3.9.4.2 Analysis of a Potential Detection Bias Due to Prostate Volume

Another potential source of bias is the effect of finasteride on the prostate and the shrinkage of the prostate gland. These effects have 2 potential bias components – the effect of finasteride on the DRE endpoint screening procedure and the effect of the change in volume on the prostate biopsy diagnostic procedure.

3.9.4.2.1 Finasteride Increases the Sensitivity of DRE for Detection of Prostate Cancer

At the time of the design of the trial, the direction of this DRE bias was not known and it could be hypothesized to go in either direction. With a smaller gland, it could be that there was a smoother-feeling examination with less nodularity, resulting in fewer biopsy recommendations in the finasteride group compared to the placebo group. With fewer recommendations, there would be a decreased chance to detect prostate cancer and the resultant bias would be in favor of finasteride. However, it could also be that with a finasteride-treated smaller prostate, there would be enhanced subtle palpable abnormalities resulting in an increased number of biopsy recommendations compared to men on placebo. More biopsy recommendations, resulting in an increased chance to detect prostate cancer, would result in a bias against finasteride [57]. However, unlike the PSA bias where an indexing procedure was used to adjust for differences, it was not possible to control for this possible bias in the performance of the DRE. In the analysis that follows, DRE detection bias with finasteride was examined to determine if there was a bias and in what direction the bias went [57].

Table 20, below, presents the total number of DREs done while the participants were on treatment. The percent of DREs leading to a biopsy recommendation was higher in the placebo arm than in the finasteride arm (4.0% vs. 3.7% p=0.01), and the percent of men with at least 1 DRE resulting in a biopsy recommendation was higher in the placebo arm than in the finasteride arm (13.7% vs. 11.4%, $p < 0.001$).

Table 20

Digital Rectal Examination (DRE)
Up to Unblinding Date of June 23, 2003

	Finasteride (N=9423)		Placebo (N=9459)	
Total number of DREs performed	45,008		48,746	
Number (%) of DREs resulting in a biopsy recommendation	1661	3.7%	1946	4.0%
Average number of DREs per participant	4.78		5.15	
Number (%) of participants with at least 1 DRE resulting in biopsy recommendation	1071	11.4%	1296	13.7%

[57]

This increase in abnormal DREs on the placebo arm could be due to bias but could also have been due to the preventive effect of finasteride. As mentioned previously, participants underwent annual DRE and PSA assessment and were recommended to undergo prostate biopsy if either the DRE was abnormal or if the PSA was > 4.0 ng/mL (actual value) in the placebo group or > an equivalent adjusted value in the finasteride group.

Similar to the PSA detection bias analysis, a DRE sensitivity analysis was also conducted [10]. Men included in this DRE sensitivity analysis must have (1) undergone a prostate biopsy at any time during the 7 years they were on study, (2) had a PSA and DRE measurement within 1 year prior to biopsy, and (3) been on treatment at the time of the biopsy. The biopsy had to be ascertained no later than the reporting of the primary results and trial unblinding (i.e., up to June 23, 2003). If a participant had multiple biopsies, the most recent biopsy was analyzed. Sensitivity and specificity of DRE for both prostate cancer and high-grade disease were calculated for each treatment group. Sensitivity was defined as the proportion of men with an abnormal DRE among those who had prostate cancer and specificity was defined as the proportion of men with a normal DRE who did not have prostate cancer. Differences in sensitivity and specificity were evaluated using the Fisher exact test.

A total of 4579 men in the finasteride group and 5112 in the placebo group were available for this analysis. Biopsies prompted by PSA or DRE were generally for one or the other and rarely for both (7% of the men on finasteride and 5% of the men on placebo who had a for-cause prompt). Of the 4579 men in the finasteride group, 695 (15.2%) were diagnosed with prostate cancer and, of these, tumor grade information was available in 686. Of these 686 men, Gleason score 7 or higher disease was diagnosed in 264 men

and Gleason score 8 or higher disease was diagnosed in 81. Of the 5112 men in the placebo group, 1111 (21.7%) were diagnosed with prostate cancer and, of these, tumor grade was available in 1100. Of these men, Gleason score 7 or higher disease was diagnosed in 240 and Gleason score 8 or higher in 55 [10].

The sensitivity of DRE was significantly greater for the detection of prostate cancer among men receiving finasteride: 21.3% for finasteride compared to 16.7% for placebo (p=0.015), see Table 21, below. The sensitivity of DRE for the detection of high-grade disease (Gleason score ≥ 7) was also greater in men receiving finasteride compared to placebo (26.1% vs. 21.7%). While the absolute difference in proportions was similar for both prostate cancer overall (21.3% vs. 16.7%) and high-grade, Gleason 7-10 disease (26.1% vs. 21.7%), the difference for high-grade disease did not achieve statistical significance due to the smaller numbers. Sensitivity for Gleason score ≥ 8 was also greater in men receiving finasteride compared to placebo (38.3% vs. 36.4%) but was not statistically significant. The specificity of DRE exceeded 90% for both treatment groups and was not significantly different between the 2 treatment groups. Although details are not shown here, in this publication it was demonstrated that the improved sensitivity of DRE with finasteride held up regardless of whether PSA was low, moderate or elevated [10].

Table 21

Sensitivity and Specificity of
Digital Rectal Examination
Up to Unblinding Date of June 23, 2003

	Sensitivity Finasteride	Sensitivity Placebo	P-value	Specificity Finasteride	Specificity Placebo	P-value
Prostate Cancer	21.3% (148/695)	16.7% (185/1111)	0.015	91.7% (3563/3884)	92.1% (3683/4001)	0.62
Gleason score ≥7	26.1% (69/264)	21.7% (52/240)	0.25	90.8% (3909/4306)	90.8% (4412/4861)	1.00
Gleason score ≥8	38.3% (31/81)	36.4% (20/55)	0.86	90.3% (4054/4489)	90.5% (4565/5046)	0.81

[10]

Results of DRE sensitivity by treatment arm stratified by PSA status (> 4.0 ng/mL vs. ≤ 4.0 ng/mL) can be found in [10] and Appendix 8. Since few DRE- and PSA-prompted biopsies were performed in men with both an abnormal DRE and elevated PSA, these independent improvements in both DRE and PSA sensitivity suggest that the magnitude of risk reduction with finasteride is likely greater than the observed 26% relative risk reduction in the period prevalence based on the primary analysis of the SWOG population in the PCPT (see Section 3.7.1).

3.9.4.2.2 Finasteride Increases the Sensitivity of Prostate Biopsy for Detection of High-Grade Prostate Cancer

Finasteride has a known effect on prostate volume. In the PCPT, prostate volumes were available for the majority of cases with biopsies. Median prostate volume was 25% lower in the finasteride group (25.1 cm^3) than in the placebo group (33.5 cm^3). Because the number of biopsy cores was balanced between treatment arms but the prostate gland volume was reduced by finasteride, a biopsy performed on a gland from a finasteride-treated participant would more thoroughly sample the gland (i.e., increased sampling density due to a relatively smaller gland) than a biopsy performed on the (relatively larger) gland from a placebo-treated participant. This would potentially result in a detection bias for cancer against finasteride. To account for this effect in the logistic regression model, in addition to covariates related to baseline risk factors, post-randomization covariates that indicated the number of biopsy cores obtained and the size of the prostate gland were also included. The outcome modeled high-grade disease (Gleason score ≥7 vs. Gleason score < 7 or no cancer). The model that only included baseline risk factors provided an odds ratio of finasteride vs. placebo of 1.27 (p=0.0155), indicating that the odds of being diagnosed with high-grade disease were higher in the finasteride arm. When the number of biopsy cores and prostate volume were also included in the model, the odds ratio for finasteride was reduced to 1.03 (p=0.8004) suggesting that the association between high-grade disease and finasteride was accounted for by the number of cores and volume of the prostate (Table 22 below) [14].

Adjustment for post-randomization variables (cores and volume) that are affected by treatment can introduce confounding bias and complicate causal interpretation. Additional analyses presented in this document will also address the prostate volume bias but with different assumptions. As will be seen, the conclusions from those pathologic examinations and statistical modeling exercises support the same conclusion as was found with this logistic regression modeling: accounting for prostate volume, the imbalance of high-grade disease detection between treatment arms is no longer observed [14].

Table 22

Analysis of the Prevalence of Gleason Score 7-10
Prostate Cancer Including Post-Randomization Covariates
Predictive of Biopsy Sensitivity
SWOG Population

Summary by Treatment		Number of Events		95% CI for Percentage of Events (%)
Treatment	N	N	(%)	
All subjects				
Finasteride	4775	301	(6.3%)	(5.6%, 7.0%)
Placebo	5123	256	(5.0%)	(4.4%, 5.6%)
Subjects with covariate data				
Finasteride	4251	243	(5.7%)	(5.0%, 6.5%)
Placebo	4576	209	(4.6%)	(4.0%, 5.2%)

Logistic Regression Results	Odds Ratio†	95% CI for Odds Ratio	P-value
Finasteride vs. Placebo, adjusted for baseline covariates only (age†, race, family history, PSA)	1.27	(1.05, 1.54)	0.016
Multivariate logistic model including # of biopsy cores and prostate volume			
Finasteride vs. Placebo	1.03	(0.84, 1.26)	0.80
Age†	1.47	(1.24, 1.75)	<0.0001
Race (African American vs. other)	2.35	(1.57, 3.51)	<0.0001
Prostate cancer in a first-degree relative (yes vs. no)	1.30	(1.02, 1.66)	0.036
Baseline PSA	2.41	(2.12, 2.74)	<0.0001
Prostate Volume at Biopsy†	0.82	(0.76, 0.88)	<0.0001
Number of Cores Obtained at Biopsy†	1.69	(1.25, 2.29)	0.0007

N = Number of participants in the treatment group, n = Number of high-grade prostate cancer cases.
CI = Confidence interval.
† Odds ratio for age is per 10 years increment of age, for volume is per 10 cc and for number of cores is per 6 cores.

[14]

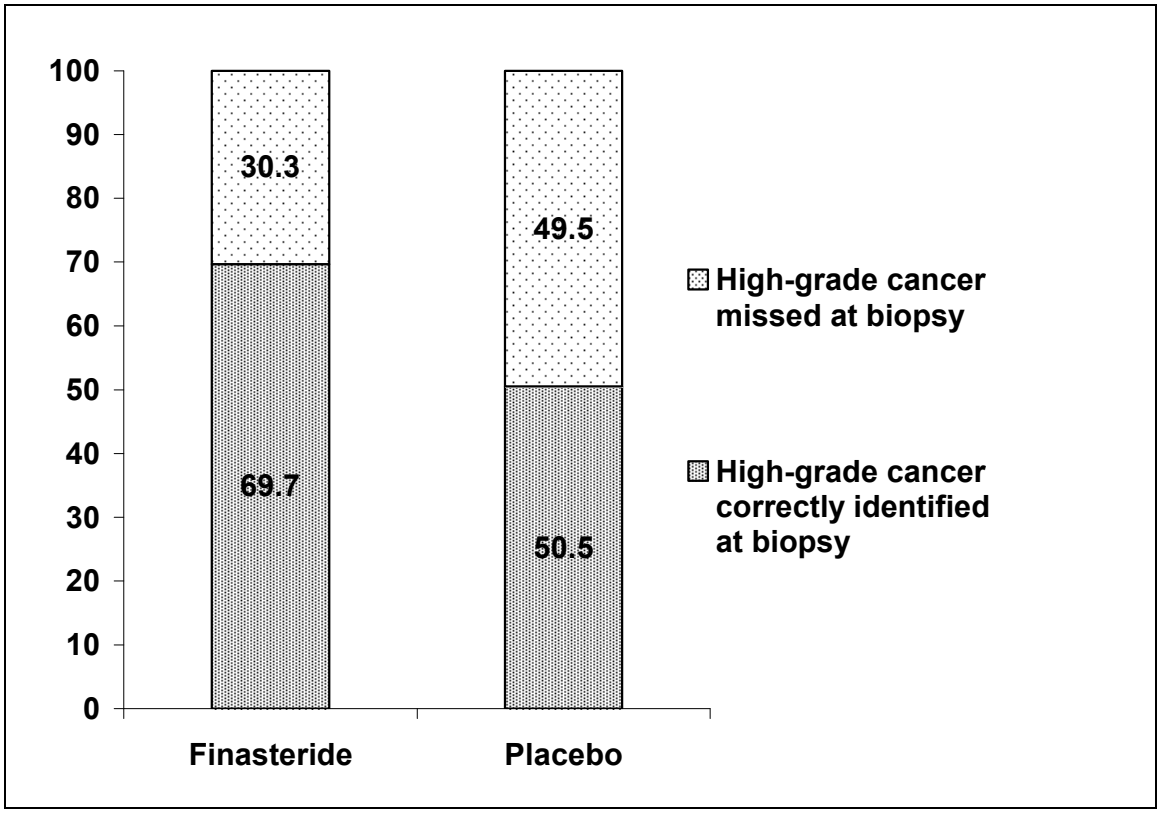
Two features of prostate cancer and the manner in which it is diagnosed make this analysis important. The first is that prostate cancer is usually heterogeneous in grade: individual tumor foci (there can be > 1 focus of cancer in an affected gland) often contain both high-grade and low-grade areas. The second is that prostate biopsy is a random process, the success of which is dependent on the size of the tumor relative to the size of the prostate. A small tumor in a large prostate may be completely missed, while a large tumor in a relatively small prostate may be sampled by more than 1 needle core in a sextant biopsy technique. This factor may also affect the accuracy of Gleason grading since the relative volume of *each individual grade pattern* will ultimately govern its likelihood of being sampled by the biopsy. These issues play an important role in the results of the PCPT as those subjects receiving finasteride had a significant reduction in

prostate gland volume; under these circumstances, it would be *expected* that improved grading of the tumor on needle biopsy would be noted. Initial evidence of this phenomenon was reported by others in a series of patients undergoing radical prostatectomy. The authors demonstrated that sextant needle biopsy procedure most accurately graded prostate cancer when gland volume was small and that, as gland volume increased, there was an increase in cancer undergrading [58].

To evaluate this potential effect in the PCPT, the Gleason score on biopsy was compared with that of the corresponding prostatectomy in 489 participants in whom Gleason scores for both biopsy and prostatectomy were available (see Appendix 9 for details of the characteristics of those who did and did not undergo prostatectomy and Appendix 10 for a table of prostate cancer Gleason score at biopsy vs. prostatectomy) [11]. This direct comparison of Gleason score based on prostate needle biopsy and prostatectomy for individual participants allowed for an assessment of whether there was a difference between treatment groups in the likelihood of missing high-grade disease at the time of needle biopsy. As seen in Figure 13, below, if high-grade prostate cancer was truly present, which can only be determined when the entire prostate is available to examine at prostatectomy, it was missed 49.5% of the time (correctly identified 50.5% of the time) among men in the placebo group, with a lower Gleason score reported at needle biopsy. By comparison, among men in the finasteride group, high-grade prostate cancer was missed 30.3% of the time (correctly identified 69.7% of the time). This increase in the sensitivity of needle biopsy to detect high-grade cancer is clinically and statistically significant (19% absolute higher sensitivity, p=0.01). This finding implies that: (1) many men in the placebo group with prostate cancer considered as low-grade (Gleason score ≤6) on needle biopsy were, in fact, undergraded, and (2) if high-grade disease truly existed, it was more likely to be identified at needle biopsy in men on finasteride.

Figure 13

Sensitivity of Prostate Biopsy to Detect High-Grade Cancer
Prostatectomy Cohort



This analysis demonstrates that the performance of needle biopsy for detecting high-grade foci is enhanced by finasteride, most likely due to reduction in prostate gland volume relative to tumor volume. If finasteride had a greater effect on reducing or inhibiting growth of low-grade cancer areas relative to high-grade areas, then the likelihood that a needle biopsy would sample the high-grade focus in a smaller prostate would be further augmented [11].

3.9.4.3 Analysis of a Potential Bias Due to Unequal Number of Biopsies

It has been suggested that a cause for the observed reduction in the period prevalence of prostate cancer with finasteride in the PCPT was related to fewer biopsies conducted in this group [59]. Later in this document (Section 3.9.5, below), a comprehensive analysis incorporating multiple detection biases provides for estimates of the actual rates of

prostate cancer. However, in order to evaluate how this single bias affected the primary outcome (total prostate cancer period prevalence), a simple calculation is presented based on the SWOG dataset.

If the same percentage of men in the finasteride and placebo groups had undergone biopsy, an additional 330 biopsies would have occurred in the finasteride group. Based on the rate of prostate cancer from for-cause procedures in the finasteride group from the trial's primary publication (435/1639, or 26.5%) [1], those additional biopsies would lead to 87 more prostate cancer cases in the finasteride group (Table 23). The analysis in Table 24, below, shows that having the same rate of biopsy in the 2 treatment groups would decrease the relative risk reduction for prostate cancer with finasteride relative to placebo from 26.0% to 23.9% (a relative risk reduction that remains highly significant). This analysis did not take into account the complex characteristics of those men who did and did not undergo prostate biopsy. A more detailed modeling analysis that took these other factors into account is discussed in Section 3.9.5, below.

Table 23

Imputation of Number of Cancers If Equal Percentages of Men in Each Treatment Group Had Biopsies

	Finasteride	Placebo
All eligible randomized men	9423	9457
All men with known prostate cancer status (biopsy conducted and reviewed)	4775 (50.7%)	5123 (54.2%)
Prostate cancers detected	879	1274
If finasteride group had same percentage of men with biopsies conducted and reviewed as placebo	5105 (54.2%) (330 more biopsies)	5123 (54.2%)
Prostate cancers that would have potentially been detected	966 (87 more prostate cancers)	1274

Table 24

Imputation of the Relative Risk Reduction If Equal Percentages of Men in Each Treatment Group Had Biopsies

	Finasteride	Placebo	Relative Risk Reduction (Finasteride vs. Placebo)
Initial prostate cancer detection	18.4%	24.9%	26.0%
Adjusted prostate cancer detection	18.9%	24.9%	23.9%

3.9.4.4 Summary of Potential Sources of Bias

PCPT was a highly complex trial to design because of the confounding of finasteride's mechanism of action and detection of the disease under study. There were a large number of known and potential biases that worked both for and against finasteride, as summarized in Table 25, below. In addition to sources of bias discussed above, other sources included non-adherence to study medication, contamination (use of finasteride outside of the study), and imbalance in the number of BPH-related surgical procedures (e.g., TURP) that can lead to a diagnosis of prostate cancer. See Appendix 3 (Critical Assumptions in the Design of the Prostate Cancer Prevention Trial) and Appendix 4 (Assumptions Used in Determining the Sample Size of the Prostate Cancer Prevention Trial) for further details.

Table 25

Known Sources of Bias in the PCPT

Source of bias	Direction	Summary
PSA	Against finasteride	Finasteride increases sensitivity of PSA for detecting all prostate cancer and high-grade disease.
DRE	Against finasteride	Finasteride increases sensitivity of DRE for detecting prostate cancer (and trend for increased sensitivity for detecting high-grade disease).
Prostate needle biopsy	Against finasteride	Needle biopsy is more sensitive for detecting high-grade disease in the finasteride group due to smaller volume of the gland.
Number of men with endpoint determined	Favors finasteride	Fewer biopsies done on the finasteride arm. However, imputing for the imbalance has little change on the relative risk reduction estimate (from 26.0% to 23.9%).
Non-adherence	Against finasteride	Known non-adherence rate was slightly less than projected in the study design and unlikely to have affected study results significantly.
Contamination	Against finasteride	Known contamination rate was slightly less than projected in the study design and unlikely to have affected study results significantly.
TURP	Favors finasteride	Because finasteride treats BPH, more TURPs were performed in the placebo group than in the finasteride group (182 vs. 97, respectively). However, this led to only 3 more cancers due to TURP detected in the placebo group than in the finasteride group (18 vs. 15, respectively).

3.9.5 Combinatorial (Modeling) Studies

In February 2003, the independent DSMC provided their recommendations to stop the PCPT based on the following observations: (1) the primary endpoint of the study had been met, i.e., finasteride significantly reduced the risk of prostate cancer over the 7 years of the study relative to placebo; and (2) additional prostate biopsies, which at that time were ongoing, would be statistically unlikely to affect this result, based on a futility analysis. SWOG was faced with 2 issues: (1) a positive study, vis-à-vis the primary

endpoint, associated with the unexpected finding of a higher number of men with high-grade disease in the finasteride arm; and (2) the responsibility to take steps to end the study as all subsequent prostate biopsies were unnecessary with respect to the primary study purpose and each biopsy posed a set of risks to the participant (e.g., bleeding or infection). As a result, steps were taken to expeditiously terminate the study through an attentively-planned agenda to publish the results quickly, provide information to study sites and to participants immediately prior to publication, and provision of an approximately 6-month period during which participants could undergo an EOS biopsy.

From the data described above, it is clear that there were biases that affected prostate cancer detection in very different manners in men taking finasteride and placebo in the study. Many of these differences would not have been understood if not for the study's EOS, 7-year prostate biopsy. It was only with careful examination of these effects, including (1) the improved performance characteristics of PSA in men receiving finasteride, (2) the improved performance of DRE in men receiving finasteride, (3) the improved assignment of correct tumor grade in men receiving finasteride, as well as (4) the decreased biopsy rate in men receiving finasteride, that a clearer understanding of the impact of finasteride on prostate cancer was possible. As some of these effects, including the performance of PSA and prostate biopsy, had the potential to have profound impact on detection of prostate cancer overall and detection of high-grade disease, after these studies were completed, SWOG posed the question: *what would the results have been had there been equal opportunity for detection of prostate cancer and high-grade disease in the 2 treatment groups*? It was the consensus of SWOG that the only way to answer this critical question was by statistically modeling the results of all of these biases.

This question was not only addressed by SWOG but, over time, by other investigators and groups. These groups used different methods to adjust for the various detection biases in the 2 study groups. Of interest, the conclusions of these groups using very different methods were quite similar; their results will be shown at the end of this section. What follows are the results from modeling of the biases conducted by SWOG.

3.9.5.1 Results of Combinatorial Studies Designed to Determine 'True' Rates of High-Grade Cancer

Quantifying the combined effect of multiple functional biases of the PCPT: PSA, DRE, proportion of recommended biopsies performed, and needle biopsy sensitivity (Redman et al. [13])

To better understand the combined effect of all of the known biases on detection of prostate cancer in the PCPT, a set of analyses exploring the impact of finasteride on both prostate cancer overall and high-grade disease had all study participants had a known prostate cancer status at 7 years (i.e., had an endpoint determination) was conducted. As a second analysis, the prevalence of high-grade prostate cancer among men with prostate cancer was then estimated using information from the subset of participants who underwent radical prostatectomy.

For these analyses, a man was defined to have an endpoint determination if he had a diagnosis of prostate cancer or if he underwent a negative EOS biopsy by June 23, 2003. Due to early closure of PCPT, 15,990 (85%) of the 18,882 randomized men had reached their 7-year anniversary when the study was reported and the trial unblinded. Endpoint determination was made in 5223 men in the placebo arm and 4958 men in the finasteride arm for a total of 10,181 (64%) of the 15,990 men, closely matching the expected 60% rate of endpoint determination that was specified in the protocol design assumptions (see Appendices 3 and 4). High-grade prostate cancer was defined as a Gleason score of 7 or higher.

3.9.5.1.1 Analysis 1: Predicting Prostate Cancer Prevalence if all Subjects had an Endpoint Determination

Methods

It is likely that men who did not have a known prostate cancer status at 7 years (i.e., did not have an endpoint determination) had a different probability of prostate cancer than those who did. For example, a man with a for-cause biopsy prompt was more likely to undergo a biopsy than a man at end of study who did not have a PSA or DRE biopsy prompt. In order to estimate the cancer prevalence if all subjects had an endpoint determined, an often-employed assumption is that there are measured study risk factors that explain who had a study endpoint determined and are related to the risk of prostate cancer. Under this assumption, for 2 men with similar risk factors, 1 with an endpoint determined and 1 without, the outcome data from the man with the endpoint determination informs the prostate cancer status for the other.

An approach that employs this assumption and can be used to estimate the prevalence of prostate cancer and high-grade disease is *inverse probability of censoring weighted (IPCW) estimation*. Use of this analytic approach is a 2-step process; the first step is to estimate the probability of having an endpoint determination by using information from men who did have an endpoint determination. The second step is to estimate the probability of prostate cancer. The probability of cancer is estimated by the weighted average of cancers within each treatment arm among men with an endpoint determination, using the IPCW method for calculating weights.

To estimate the probability of having an endpoint determination in the first step, logistic regression was used. To model the predicted probabilities, study factors related to both (1) having an endpoint determination and (2) having a diagnosis of prostate cancer were chosen. The baseline factors that were included in these analyses were treatment arm, age, ethnicity/race, baseline PSA value, and family history of prostate cancer. Post-randomization covariates that were included in this analysis were interim biopsy prompts based on PSA level or DRE and ever having a negative biopsy result during follow-up and before the end of the study. The weights were then calculated using these probabilities for men who did have an endpoint determination. The same weights and

approach were used to estimate the prevalence of high-grade cancers in each treatment arm [13].

This analysis accounts for biases related to the increased sensitivity of PSA and DRE with finasteride and the fewer biopsies conducted in the finasteride group compared to placebo.

Results

There were a number of characteristics that were associated with not having an endpoint determination. They include being randomized to finasteride (OR=0.89) and older age (OR=0.98 for each year of age). Factors associated with having an endpoint determination included White race vs. other race/ethnicities, a family history of prostate cancer, interim biopsy prompts based on PSA or DRE, and a prior negative interim biopsy. While higher PSA at randomization was marginally associated with having an endpoint determination (OR = 1.14, $p < 0.0001$), the association was no longer significant ($p=0.60$) when the other factors were adjusted for in the model [13]. See Appendix 11 for more details.

Estimated prostate cancer prevalence results from this analysis are presented in Table 26. The observed rates of prostate cancer for the 5223 men in the placebo group and 4958 men in the finasteride group with an endpoint determination were 22.9% and 16.6%, respectively. Had all subjects had an endpoint determination, the analysis suggests that the true rate of cancer in the 8024 men in the placebo group would have been 21.1% and in the 7966 men in the finasteride group would have been 14.7%. The estimated relative risk of prostate cancer if everyone had an endpoint determination is changed minimally from the observed data (0.72 vs. 0.70).

Similarly, while the observed rates of high-grade cancer in the placebo and finasteride groups were 4.8% and 5.8%, respectively, the analysis estimates that the true rates of high-grade cancer if everyone had a biopsy are 4.2% and 4.8%, respectively. The risk of high-grade disease associated with finasteride after accounting for the missing data decreased from an observed and significant 21% increased risk to a non-significant 14% increased risk ($p=0.12$) [13].

Table 26

Observed and Estimated Numbers and
Proportions of Men with Prostate Cancer Detected on Biopsy
Up To Unblinding Date of June 23, 2003

	Placebo arm N=8024	Finasteride arm N=7966	RR (95% CI)	P-value
Prostate cancer				
Observed	1194 (22.9%)	823 (16.6%)	0.72 (0.67-0.79)	<0.0001
Estimate of overall prevalence	1693 (21.1%)	1171 (14.7%)	0.70 (0.64-0.76)	<0.0001
High-grade cancer				
Observed	252 (4.8%)	288 (5.8%)	1.21 (1.02-1.42)	0.02
Estimate of overall prevalence	337 (4.2%)	382 (4.8%)	1.14 (0.96-1.35)	0.12

3.9.5.1.2 Analysis 2: Predicting High-Grade Prostate Cancer by Integrating Prostatectomy Grading Data

Methods

The goal of this analysis was to estimate the high-grade prostate cancer status if all men with prostate cancer had undergone prostatectomy. This analysis accounts for the effect of finasteride to improve the accuracy of Gleason grading based on prostate needle biopsy due to reduced gland volume. The analysis used information from 500 subjects diagnosed with prostate cancer by prostate biopsy who subsequently underwent a radical prostatectomy, a procedure that makes the entire gland available for precise Gleason grading of cancer. Participants could not have undergone hormonal therapy for prostate cancer and there must have been evidence of prostate cancer on the prostatectomy sample reviewed. This subset of men who underwent prostatectomy is not a randomized sample and, thus, not necessarily representative of all men diagnosed with prostate cancer in the PCPT; accordingly, adjustment for covariates, including those included in the first analysis as well as diagnosis of high-grade cancer on needle biopsy, were incorporated into a model. This second analysis proceeded as did the first analysis; first, a logistic regression model was used to estimate the probability of prostatectomy taking into account factors from the subset of men who underwent prostatectomy. Next, the prevalence of high-grade cancer was estimated from the group of men with high-grade disease determined by prostatectomy. The overall prevalence of high-grade cancer for

each treatment arm was then estimated by multiplying the high-grade estimates from this analysis and the estimates of prostate cancer from the first analysis. Measures of variability were estimated by resampling the observed data many thousands of times (i.e., by using bootstrap samples) to obtain an accurate variance measurement.

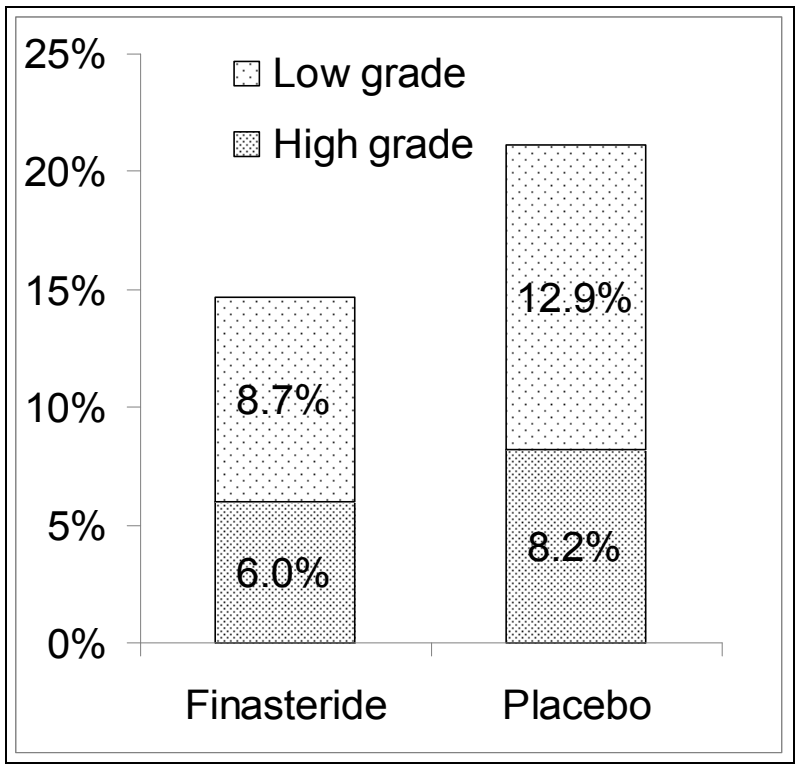
Results

While treatment group, family history, white race, a prior negative study biopsy, and high-grade cancer on biopsy did not significantly impact on whether a participant underwent prostatectomy, younger age, PSA at randomization, and biopsy prompt by PSA or DRE were positively and significantly associated with undergoing a prostatectomy [13] (see Appendix 9 for details).

The estimate of the number and rate of high-grade cancers from the analysis that incorporated the prostatectomy data is 478 (6.0%) in the finasteride arm and 658 (8.2%) in the placebo arm (Figure 14, below). The estimated relative risk reduction (finasteride vs. placebo) for Gleason score $\leq$ 6 cancer is 34% (RR [95% CI] = 0.66 [0.55-0.80], p=<0.0001) and for Gleason score $\geq$ 7 cancer is 27% (RR [95% CI] = 0.73 [0.56-0.96], p=0.02) [13].

Figure 14

Estimated Proportions of All Subjects with
Low-Grade and High-Grade Prostate Cancer
Incorporating Prostatectomy Data
Up To Unblinding Date of June 23, 2003



3.9.5.1.3 Summary

These two analyses reported in [13] systematically controlled for the PSA, DRE and needle biopsy detection biases, the unequal biopsy rates between the two groups, and potentially other factors when calculating the rate of prostate cancer in the 2 treatment groups. In the first analysis, the estimated relative risk for prostate cancer between treatment groups went from 0.72 to 0.70, but after accounting for the unequal biopsy rates and the PSA and DRE biases resulted in a risk ratio estimate for high-grade disease that was closer to 1.0 and no longer statistically significant. The second analysis also controlled for the increased sensitivity of needle biopsy for detecting high-grade prostate cancer with finasteride among men with a diagnosis of prostate cancer. The estimated 27% relative risk reduction in high-grade disease with finasteride suggests that it was highly unlikely that treatment with the drug actually increased the risk of high-grade cancer in the PCPT (Figure 14).

3.9.6 Additional Analyses by Investigators External to PCPT

In addition to the analyses summarized in this document (above) from SWOG or from Merck, analyses were performed by groups outside of the conduct of the PCPT. In each case, these independent analyses reached conclusions consistent with those reported by SWOG or by Merck. These are briefly summarized here.

1. Paul Pinsky (Division of Cancer Prevention, NCI) and colleagues requested and received the PCPT clinical data to perform their own analysis. They used a statistical model to extrapolate the radical prostatectomy Gleason score results to all men in the PCPT using a missing-at-random assumption. They estimated the rates of true high-grade (Gleason score 7-10) and true low-grade (Gleason score ≤ 6) disease, where "true" Gleason score is what was (or would have been) found on radical prostatectomy. They also estimated misclassification rates on biopsy of true high-grade and low-grade disease. The estimated relative risks for true low-grade and true high-grade disease for finasteride compared to placebo were 0.61 (95% CI: 0.51, 0.71) and 0.84 (95% CI: 0.68, 1.05), respectively. The misclassification rate of true high-grade disease (to low-grade disease on biopsy) was significantly lower for finasteride (34.6%) than for placebo (52.6%). Their results were consistent with those published by the PCPT study team. After accounting for the increased sensitivity of the prostate needle biopsy in the finasteride group, the increased prevalence of high-grade disease in that arm was no longer present [12].

2. Stuart Baker (Biometry Research Group, Division of Cancer Prevention, NCI) and colleagues requested and received clinical data from the PCPT to perform their own independent statistical analyses. Recognizing that the analyses conducted by SWOG of the combined biases of finasteride and placebo on the prevalence of prostate cancer and high-grade disease were very complex and challenging, they sought to independently replicate those findings with the same data sets from the trial. As stated by Dr. Baker, “with such an important result at stake, a transparent analysis was important”. Their analysis adjusting for family history, race and age resulted in a relative risk estimate for high-grade prostate cancer (Gleason score 7-10) for finasteride vs. placebo of 0.82 (95% CI: 0.64, 1.06). Prostate cancer prevalence among those without biopsy was imputed incorporating differences in positive findings from observed for-cause and EOS biopsies. Their estimate of the Gleason score 8-10 relative risk was 1.40 (95% CI: 0.71, 2.76) with a wide confidence interval due to few cancers falling into this category [16].

3. Bryan Shepherd (Department of Biostatistics, Vanderbilt University) and colleagues requested and received clinical data from the PCPT. They used a causal inference approach implementing inverse probability weighted estimating equations to address the question of whether finasteride caused more severe prostate cancer by estimating the mean treatment difference in prostate cancer severity between finasteride and placebo

for the principal group of participants who would have developed prostate cancer regardless of treatment assignment. They performed sensitivity analyses that sequentially adjusted for the numerous potential post-randomization biases conjectured in the PCPT. They concluded that, although not completely exhaustive, their sensitivity analyses account for most of the potential biases that could have artificially led to the paradoxical result of an increase in the absolute number of high-grade prostate cancer cases in association with a significant reduction in prostate cancer overall in the finasteride group. They believe the findings are probably due to the improved sensitivity of biopsy for detecting high-grade disease in finasteride compared to placebo, which, when accounted for, removes the statistical significance of the average causal effect of increased high-grade prostate cancer by finasteride [15].

Table 27, below, adapted from Baker et al. [16], provides a summary of the relative risk estimates from various analyses of the PCPT data. In general, when Gleason score 7 is included in the definition of high-grade disease, the relative risk estimates for finasteride suggest benefit in preventing these cancers; when the group of high-grade cancers is restricted to the smaller subset of Gleason score 8-10 cancers, the relative risk estimates are > 1 and the corresponding confidence intervals are wide.

Table 27

Estimated Relative Risks (Finasteride vs. Placebo) For
High-Grade Prostate Cancer
(Adapted from Baker et al. [16])

	Relative Risk of High-Grade Prostate Cancer (95% CI) Based on Gleason Score Grouping	
	7-10	8-10
Analyses conducted by SWOG		
Redman et al. [13]	0.73 (0.56, 0.96)	1.25[†]
Other Analyses		
Baker et al. adjusted analysis [16]	0.82 (0.64, 1.06)	1.40 (0.71, 2.76)
Pinsky et al. [60]	0.84 (0.58, 1.06)	1.39 (0.79, 2.50)
[†] No confidence interval reported, said to be imprecise.		

Note: The relative risk (finasteride vs. placebo) of 1.25 for Gleason score 8-10 prostate cancer as reported by Baker et al. in the table above is derived using prevalence estimates (1.0% and 0.8% for finasteride and placebo, respectively) from a separate analysis by Redman et al. that incorporated biopsy sensitivity into the model.

4. Number Needed to Treat (NNT) Analysis

Population-based application of a strategy of chemoprevention of prostate cancer: Focus on number of men at risk needed to treat to prevent one prostate cancer.

The implications of the PCPT for prostate cancer prevention must be put into context from a public health perspective. The population studied included men with a PSA ≤ 3.0 ng/mL at study entry, which constituted a group of men at low- to moderate-risk for prostate cancer at study initiation. If chemoprevention with finasteride were to be applied to a similar population, a large proportion of men would receive this agent. As about 16% of men are expected to develop prostate cancer in their lifetime in the U.S., and as the relative risk reduction with finasteride is approximately 25%, this strategy would result in (1) a large number of men who will never develop prostate cancer receiving medication unnecessarily and (2) 75% of the men who would have developed prostate cancer in the absence of chemoprevention still developing prostate cancer. If we presume that approximately 200,000 men will be diagnosed with prostate cancer annually in the U.S., over a 7-year period a 25% relative risk reduction could be as large as 350,000 men not diagnosed with prostate cancer. Certainly, focusing the use of finasteride to men at greatest risk would allow treatment of substantially fewer men and would reduce the number of cancers prevented.

A method to understand the utility of such an intervention is through the window of a *number needed to treat* (NNT) analysis. This analysis allows both an exploration of the population impact as well as the impact of this prevention strategy on subgroups with higher levels of risk of prostate cancer. Table 28, below, presents the number of men needed to treat with finasteride to prevent 1 case of prostate cancer. It includes all prostate cancers (including end-of-study biopsies), for-cause detected prostate cancers (only those men with a PSA > 4.0 ng/mL and/or an abnormal DRE), as well as those subjects with prostate cancer who had a PSA > 2.5 ng/mL and/or an abnormal DRE. This final group was included as there are extensive data indicating that in this group of men, prostate cancers have a similar risk of clinical significance as those in men with a PSA > 4.0 ng/mL. Additionally, the National Comprehensive Cancer Network guidelines recommend consideration of prostate biopsy for a PSA > 2.5 ng/mL [4]. The American Cancer Society's updated Guideline for the Early Detection of Prostate Cancer also recommends that men with a PSA > 2.5 ng/mL undergo risk assessment to consider prostate biopsy [37].

Table 28

Number Needed to Treat (NNT)
With Finasteride to Prevent
One Case of Prostate Cancer

Disease/Event	NNT[‡] to Prevent 1 Cancer Case
All prostate cancer	15-22[†]
For-cause prostate cancer	43-61[†]
For cause prostate cancer, plus cancer detected in EOS biopsy in men with PSA of 2.6-4.0 ng/mL at time of EOS biopsy	29-40[†]
[†] Reflects range from the SWOG to the MITT analysis [‡] Treatment duration of PCPT was 7 years	

It would appear that, depending on how PSA screening is employed in the general population, the impact of finasteride in preventing a man from having a diagnosis of prostate cancer would vary. If only those men with a PSA > 4.0 ng/mL or an abnormal DRE underwent prostate biopsy, between 43 and 61 men would require treatment with finasteride for 7 years to prevent 1 case of cancer. However, in the US today, PSA values between > 2.5 but ≤4.0 ng/mL (i.e., between 2.6 and 4.0 ng/mL) are also often used to recommend a biopsy in men at risk due to the prevalence of clinically significant cancer in this group of men; with this practice the NNT for 7 years to prevent 1 case of prostate cancer would be between 29 and 40 men.

Ideally, a preventive intervention would be applied only to the individual who, in the future, would develop disease and whose disease would be prevented with the intervention. For prostate cancer prevention, such a strategy would lead to an NNT of 1. Unfortunately, it is not possible to predict with certainty that disease will occur and, for most interventions, it is not possible to predict with certainty that the preventive strategy will be successful. To put the NNT numbers into perspective with other common prevention interventions, Table 29 displays some of these interventions. Although treatment periods are somewhat shorter and outcomes may be considered more grave, it can be seen that the NNTs with finasteride are in the range of other chemopreventive interventions. While these data are not provided to suggest that prevention of prostate cancer is analogous to the level of public health or personal concern associated with a diagnosis of breast cancer or a myocardial infarction, much of the evidence from quality of life studies of patients with prostate cancer does suggest that this diagnosis may rise to this level [61].

Table 29

Representative Numbers Needed to Treat (NNT)
For Other Medical Prevention Strategies

Disease/Event	Intervention	Comparator	NNT	Reference
Invasive breast cancer	Tamoxifen (69 mos)	Placebo	47	[62]
Myocardial infarction or cardiovascular death	Lipid lowering (primary prevention, 5 yrs)	No treatment	69	[63]
Myocardial infarction or cardiovascular death	Lipid lowering (secondary prevention, 5 yrs)	No treatment	16	[63]
Myocardial infarction	Aspirin (5 yrs)	No treatment	44[†]	[64]
[†] Based on an annual CHD event risk of 1.5%				

The data presented in Table 28, above, include a range for the NNT based on inclusion of men in the SWOG population or men in the MITT population as the denominator. Although prostate cancer was detected at all levels of PSA and among all risk groups (e.g., based on age, family history, race), it was much less common, for example, in men with low levels of PSA. As such, it is possible among these low to moderate risk men who participated in the PCPT to further examine the NNT based on the level of prostate cancer risk. Examining the 4775 finasteride and 5123 placebo participants who had an endpoint determination (i.e., the SWOG population), participants were stratified based on their PSA level at study entry, since this factor is strongly correlated with the probability of subsequent prostate cancer diagnosis. As can be seen in Table 30, below, as pre-study PSA level (and hence risk of prostate cancer) increases, the NNT to prevent 1 prostate cancer decreases. These data would suggest that, at a population level, men with lower levels of risk – in this case identified by a low PSA level (e.g., the NNT group with the lowest PSA between 0.0 and 0.9 ng/mL) – would have a lower level of benefit from a strategy of chemoprevention with finasteride, while men at levels of risk above this – in this case identified by a higher PSA level (e.g., men with PSA of 1.0 ng/mL or greater or 2.0 ng/mL or greater) – would have a higher and comparable level of benefit, with the NNT comparable to other commonly-accepted disease prevention strategies [65].

It is also important to understand how these analyses interact with the proposed label change. The purpose of this change is to facilitate a discussion between the physician and patient about the potential risks and benefits of finasteride treatment in the man with lower urinary tract symptoms from BPH. Because PSA is generally related to prostate volume, with levels generally higher in men with larger prostates and symptoms of BPH, it could be inferred that the numbers of men with BPH needed to treat to prevent 1 case of prostate cancer would more likely be in the lower ranges of these NNT values.

Table 30

Number Needed to Treat (NNT) with Finasteride to Prevent
One Case of Prostate Cancer by Baseline PSA Level (ng/mL)
For All Prostate Cancers and For-Cause Prostate Cancers

	NNT‡ to Prevent 1 Cancer Case	
Baseline PSA (ng/mL)	All Cancers	For-Cause Cancers
< 1.0	19-30†	64-105†
1.0-1.9	12-18†	37-56†
2.0-3.0	17	30-29†
† Reflects range from the SWOG to the MITT analysis ‡ Treatment duration of PCPT was 7 years		

5. Benefit-Risk Analysis for Chemoprevention of Prostate Cancer with Finasteride

As with any medical decision, be it therapeutic or preventive, a decision to embark on a medical strategy requires the medical practitioner and patient to understand both the benefits of the strategy as well as its potential risks. The list below summarizes risks and benefits of a strategy of prostate cancer chemoprevention with finasteride based on the outcomes of the PCPT. Regarding the primary reason for this strategy – reduction in the risk of prostate cancer – a man should be aware that finasteride would reduce the relative risk of a prostate cancer diagnosis by 26% and an absolute risk reduction of 6.5%. If he would have a recommendation for a prostate biopsy only for a PSA > 4.0 ng/mL, about 43-61 men would need 7 years of treatment with finasteride to prevent 1 case of prostate cancer. If he, like many men, would have a recommendation for a prostate biopsy for a PSA > 2.5 ng/mL, this number decreases to 29-40 men who would require treatment with finasteride to prevent 1 case of prostate cancer.

Considering the cancers that would be diagnosed, a strategy of cancer prevention with finasteride would result in an increased risk of finding and diagnosing high-grade tumors that are present in the prostate, tumors that have a greater risk of distant spread and death. While the observed imbalance in high-grade tumors reported in the PCPT was initially hypothesized to potentially result from administration of finasteride (i.e., that finasteride might cause an increase in the risk of developing these tumors), the best evidence available suggests that, if a high-grade cancer is present, finasteride improves the ability of prostate biopsy to detect this tumor by reducing prostate volume and by improving the detection ability of PSA. With the growing interest in active surveillance for prostate cancer among lower-grade tumors, finasteride would result in earlier detection of these high-grade (and high-risk) cancers and potentially reduce the risk of delayed treatment. Also, in some men, improved detection of prostate cancer with finasteride would result in

an earlier diagnosis, potentially improving the chance of cure. Concurrent with a reduction in risk, finasteride appears to also improve the ability of the commonly-applied screening methods, DRE and PSA, to detect prostate cancer and, in the case of PSA, to detect high-grade prostate cancer. By improving the performance of these diagnostic tests, a man *without* prostate cancer would have a lower likelihood that his physician would recommend an unnecessary biopsy, a test with a risk of bleeding and infection. Likewise, by improving the performance of these tests, a man *with* prostate cancer would be more likely to have a recommendation for biopsy if he were receiving finasteride.

The reduction in risk of prostate cancer has implications beyond the diagnosis of cancer itself. After a prostate cancer diagnosis, a man generally requires life-long follow-up for his disease including regular PSA testing. Even if cancer is controlled and does not recur, these follow-up visits and tests are associated with anxiety and cost. If cancer is diagnosed, there are a range of treatment options, all of which are associated with side effects that can range from minimal to severe. For men who opt for active surveillance, visits as frequently as quarterly are required and repeated prostate biopsies are necessary, each one with the risk of bleeding and infection. Some physicians recommend these biopsies annually. If cancer is then noted to grow in stage or grade, later treatment becomes necessary. For men who opt for surgery or radiation, side effects are greater and include urinary incontinence including the use of pads or diapers, impotence requiring use of oral medications like sildenafil (VIAGRA®), vacuum erection pumps and constriction bands to maintain erections, injections into the penis of medications that have a risk of priapism or Peyronie's disease, or placement of artificial penile prostheses that have risks of infection, bleeding, or mechanical failure. Other risks of surgery include bleeding, infection, urethral stricture, and rectal injury. For men who opt for radiation, there is a similar risk of impotence as with surgery. In addition to the risk of incontinence, radiation also has the risks of obstruction, increasing urinary frequency and urgency, as well as the risk of radiation cystitis with bladder contracture. Due to the radiation dose received by the anterior rectal wall, there is also the risk of rectal bleeding, tenesmus, fecal incontinence, and radiation proctitis. Finally, with radiation, there is a small increased risk of secondary malignancies, generally of the rectum and bladder. Overall, by reducing the risk of prostate cancer, both treatment and treatment-related complications described above would be expected to be reduced.

In addition to high-grade (Gleason score 7-10) tumors and tumors detected due to a PSA > 4.0 ng/mL or an abnormal DRE, there is increasing evidence suggesting that prostate cancers associated with PSA levels > 2.5 ng/mL are also clinically significant [66]. Tumors detected in the PCPT had a high likelihood of being clinically important by contemporary criteria: 67% of the total number of prostate cancers diagnosed in the PCPT (n=2153) in the SWOG population were detected by either a for-cause biopsy (PSA > 4.0 ng/mL and/or abnormal DRE; n=1090), an EOS biopsy associated with a PSA of 2.6–4.0 ng/mL at the time of biopsy (n=236), or an EOS biopsy associated with a PSA ≤ 2.5 ng/mL at the time of biopsy that led to a diagnosis of Gleason score 7-10 tumor (n=120). In addition, application of Jonathan Epstein's pathologic criteria for

defining potentially clinically insignificant tumors demonstrated that 75% of the cancers diagnosed in the PCPT were considered pathologically significant [67]. Further, it is important to place these results in contemporary context. With the initial PCPT publication in 2003 and the subsequent 2004 publication of the rates of prostate cancer by level of PSA [36], it was recognized that many significant prostate cancers were present at levels of PSA < 4.0 ng/mL. With this understanding, there has been an increased focus on detecting these tumors; data from 2004-2006 suggest that men with a PSA < 4.0 ng/mL represent 14% of incident prostate cancers [68]. Of these men, over 75% undergo radical treatment with either surgery or radiation therapy. As a result, the findings based on the EOS biopsies in the PCPT now represent the clinical circumstances of many men undergoing routine PSA screening.

For a man who considers finasteride treatment to prevent prostate cancer, the risks of potential prostate cancer diagnosis and treatment must be weighed against the risks of finasteride (i.e., its side effects). Sexual side effects including erectile dysfunction, decreased libido, and ejaculatory disorders are more common in men receiving finasteride. Breast enlargement (gynecomastia) is also reported more commonly with finasteride than in men not receiving this medication (4.6% vs. 2.8% in the PCPT).

There are also beneficial effects of finasteride on urinary symptoms that were reported in the PCPT, and these effects are consistent with the results of prior studies with finasteride in men with BPH [69]. A reduction in symptoms related to prostate enlargement was observed, including improvement in frequent urination and urinary urgency and a reduced risk of urinary retention and surgery (e.g., TURP) [1]. While finasteride 5 mg (PROSCAR®) is not indicated to reduce the risk of urinary complications of prostate enlargement in men without BPH, the observed beneficial effects on urinary symptoms are important due to the high prevalence of these symptoms, and of prostate enlargement, in an aging male population [70].

5.1 Benefits of Chemoprevention of Prostate Cancer with Finasteride

- Reduction in the relative risk of prostate cancer by 26%.

- Improved detection of high-grade prostate cancer through improved performance of PSA. As high-grade prostate cancer is the most common cause of death due to prostate cancer, improved detection of this higher-risk cancer could have significant benefits.

- Improved detection of high-grade prostate cancer through improved detection with prostate biopsy.

- Reduction in risk of urinary urgency and frequency, urinary retention, and surgery for obstructive urinary symptoms due to prostate enlargement.

- Reduction in risk of high-grade prostatic intraepithelial neoplasia (HGPIN). As HGPIN often leads to increased surveillance including repeated prostate biopsies, reduction in risk of HGPIN would reduce the anxiety and risk of infection and bleeding associated with repeated prostate biopsies. If HGPIN is a premalignant lesion, then reduction in the risk of HGPIN may reduce the risk of subsequent prostate cancer.

- If prostate cancer is present in an individual patient, because of improved performance of DRE and PSA there is a greater likelihood that prostate biopsy will be recommended.

- Reduction in risk of treatment of prostate cancer (surgery or radiation) as well as risks of treatment. Risks of surgery include urinary incontinence, impotence, stricture, bleeding, infection, and rectal injury. Risks of radiation include urinary incontinence or obstruction, impotence, and radiation proctitis or cystitis, as well as a risk of cancer caused by radiation, generally of the rectum or bladder.

- Reduction in anxiety associated with cancer diagnosis. As prostate cancer follow-up is generally life-long, the prolonged period of anxiety associated with this diagnosis would be avoided in men whose cancers are prevented.

5.2 Risks of Chemoprevention of Prostate Cancer with Finasteride

- Increased risk of a diagnosis of high-grade prostate cancer. While at the time the initial PCPT study results were published (2003) the clinical significance of the high-grade findings was unknown, subsequent analyses provide evidence to suggest that the observed increase in high-grade tumors is related to improved detection of high-grade prostate cancer due to improved sensitivity and diagnostic performance of PSA and prostate biopsy.

- Increased risk of sexual side effects including decreased libido, erectile dysfunction, and ejaculatory disorders.

- Increased risk of gynecomastia. In the PCPT, this side effect was seen in 4.6% of men receiving finasteride and 2.8% of men receiving placebo.

6. Conclusions

The data from the Prostate Cancer Prevention Trial (PCPT) provide compelling evidence that treatment with finasteride significantly reduces a man's risk of prostate cancer. A diagnosis of prostate cancer is associated with several potential sequelae, including anxiety as the man becomes a lifelong cancer survivor and the impact of treatment of the disease, most often radical radiation or radical surgery, both of which are costly and associated with short-term and long-term complications, notably urinary obstruction or incontinence, impotence, and bowel complications including bleeding and tenesmus.

With radiation therapy there is also a small increased risk of secondary malignancies, generally of the bladder and rectum. Despite finasteride's impact on the commonly-used methods of prostate cancer detection – PSA testing, DRE and needle biopsy – to improve their sensitivity to detect prostate cancer overall (and in the case of PSA and needle biopsy, to detect high-grade cancer), in the PCPT treatment with finasteride still reduced overall prostate cancer relative risk by 26% compared to placebo ($p<0.0001$). High-grade cancers represented a small number of tumors detected in the PCPT but were diagnosed more often in men receiving finasteride than in men receiving placebo. While at the time the results of the PCPT were initially published (2003) the clinical significance of the increased number of high-grade tumors observed with finasteride was unknown, subsequent analyses suggest that this finding was most likely because of improved detection of these aggressive tumors due to the action of finasteride on PSA and prostate biopsy, and potentially DRE, to improve the ability of these tests to detect these tumors. As these tumors are often missed by screening tests and by prostate biopsy, this effect of finasteride may actually improve the results of prostate cancer screening and detection.

In 2009, after reviewing the available evidence, the American Society of Clinical Oncology (ASCO) and the American Urological Association (AUA) jointly published a guideline on the use of 5α-reductase inhibitors in the prevention of prostate cancer [2]. Subsequently, the results of a second placebo-controlled prostate cancer chemoprevention trial, the REDUCE trial with dutasteride (AVODART®), a dual (type 1 and type 2) 5α-reductase inhibitor, were published and reported a relative risk reduction in prostate cancer overall generally similar to that reported in the PCPT [71].

Finasteride 5 mg (PROSCAR) has been marketed and used by men for the treatment of BPH for almost 2 decades. The drug has an established profile that was confirmed in the population of men without severe symptoms of BPH enrolled in the PCPT. As demonstrated in prior studies, treatment with finasteride was associated with a reduction in the risk of urinary symptoms associated with prostate enlargement, a common condition of aging men. Side effects of treatment were those previously associated with finasteride, including an increase in the incidence of sexual and breast-related adverse experiences compared to placebo. Breast cancer was reported in 1 man in each treatment group. Of note, the incidence of cardiovascular adverse experiences was significantly lower with finasteride than with placebo. Other medical events were generally comparable between finasteride- and placebo-treated subjects.

The number of men who must take finasteride to prevent 1 case of prostate cancer is comparable to other widely-used medical prevention interventions. In addition, men who are at a greater risk of prostate cancer due to higher PSA levels, a family history of prostate cancer, increased age, or African-American ethnicity (or a combination of these risk factors) are more likely to benefit from finasteride for the prevention of prostate cancer and may find this option more attractive than do lower-risk men.

Understanding that 1 man in 6 in the U.S. will be diagnosed with prostate cancer in his lifetime, and as about half of all men as they age will develop urinary symptoms from prostate enlargement, a disease that can be treated with finasteride, a man who has opted to undergo regular PSA testing for the early detection of prostate cancer and who is being treated, or considering treatment, with finasteride should be informed that he may reduce his risk of prostate cancer diagnosis and the consequences of the disease (anxiety, surgery, radiation, and the side effects of monitoring or treatment) by the use of finasteride.

7. Appendices

1. PROSCAR® (finasteride 5 mg) Current U.S. Product Circular and Proposed Draft Labeling
2. Design Options for the Prostate Cancer Prevention Trial
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Appendix 1

PROSCAR® (finasteride 5 mg) Current U.S. Product Circular and Proposed Draft Labeling

1A. PROSCAR® (finasteride 5 mg) Current U.S. Product Circular

1B. Proposed Draft Labeling

Appendix 1A. PROSCAR® (finasteride 5 mg) Current U.S. Product Circular

Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

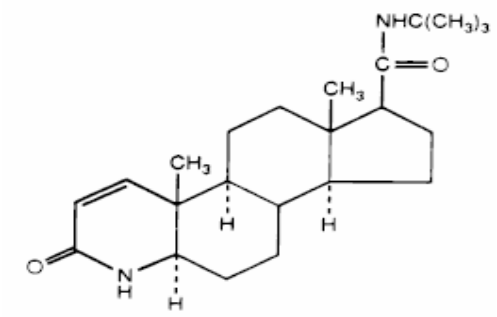
9631305

PROSCAR®
(FINASTERIDE)
TABLETS

DESCRIPTION

PROSCAR* (finasteride), a synthetic 4-azasteroid compound, is a specific inhibitor of steroid Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into 5α-dihydrotestosterone (DHT).

Finasteride is 4-azaandrost-1-ene-17-carboxamide, *N*-(1,1-dimethylethyl)-3-oxo-,(5α,17β)-. The empirical formula of finasteride is $C_{23}H_{36}N_2O_2$ and its molecular weight is 372.55. Its structural formula is:



Finasteride is a white crystalline powder with a melting point near 250°C. It is freely soluble in chloroform and in lower alcohol solvents, but is practically insoluble in water.

PROSCAR (finasteride) tablets for oral administration are film-coated tablets that contain 5 mg of finasteride and the following inactive ingredients: hydrous lactose, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, hydroxypropyl cellulose LF, hydroxypropyl methylcellulose, titanium dioxide, magnesium stearate, talc, docusate sodium, FD&C Blue 2 aluminum lake and yellow iron oxide.

CLINICAL PHARMACOLOGY

The development and enlargement of the prostate gland is dependent on the potent androgen, 5α-dihydrotestosterone (DHT). Type II 5α-reductase metabolizes testosterone to DHT in the prostate gland, liver and skin. DHT induces androgenic effects by binding to androgen receptors in the cell nuclei of these organs.

Finasteride is a competitive and specific inhibitor of Type II 5α-reductase with which it slowly forms a stable enzyme complex. Turnover from this complex is extremely slow ($t_{½}$ ~ 30 days). This has been demonstrated both *in vivo* and *in vitro*. Finasteride has no affinity for the androgen receptor. In man, the 5α-reduced steroid metabolites in blood and urine are decreased after administration of finasteride.

In man, a single 5-mg oral dose of PROSCAR produces a rapid reduction in serum DHT concentration, with the maximum effect observed 8 hours after the first dose. The suppression of DHT is maintained throughout the 24-hour dosing interval and with continued treatment. Daily dosing of PROSCAR at 5 mg/day for up to 4 years has been shown to reduce the serum DHT concentration by approximately 70%. The median circulating level of testosterone increased by approximately 10-20% but remained within the physiologic range.

Adult males with genetically inherited Type II 5α-reductase deficiency also have decreased levels of DHT. Except for the associated urogenital defects present at birth, no other clinical abnormalities related to Type II 5α-reductase deficiency have been observed in these individuals. These individuals have a small prostate gland throughout life and do not develop BPH.

*Registered trademark of Merck Sharp & Dohme Corp., a subsidiary of **Merck & Co., Inc.**

In patients with BPH treated with finasteride (1-100 mg/day) for 7-10 days prior to prostatectomy, an approximate 80% lower DHT content was measured in prostatic tissue removed at surgery, compared to placebo; testosterone tissue concentration was increased up to 10 times over pretreatment levels, relative to placebo. Intraprostatic content of prostate-specific antigen (PSA) was also decreased.

In healthy male volunteers treated with PROSCAR for 14 days, discontinuation of therapy resulted in a return of DHT levels to pretreatment levels in approximately 2 weeks. In patients treated for three months, prostate volume, which declined by approximately 20%, returned to close to baseline value after approximately three months of discontinuation of therapy.

Pharmacokinetics

Absorption

In a study of 15 healthy young subjects, the mean bioavailability of finasteride 5-mg tablets was 63% (range 34-108%), based on the ratio of area under the curve (AUC) relative to an intravenous (IV) reference dose. Maximum finasteride plasma concentration averaged 37 ng/mL (range, 27-49 ng/mL) and was reached 1-2 hours postdose. Bioavailability of finasteride was not affected by food.

Distribution

Mean steady-state volume of distribution was 76 liters (range, 44-96 liters). Approximately 90% of circulating finasteride is bound to plasma proteins. There is a slow accumulation phase for finasteride after multiple dosing. After dosing with 5 mg/day of finasteride for 17 days, plasma concentrations of finasteride were 47 and 54% higher than after the first dose in men 45-60 years old (n=12) and ≥70 years old (n=12), respectively. Mean trough concentrations after 17 days of dosing were 6.2 ng/mL (range, 2.4-9.8 ng/mL) and 8.1 ng/mL (range, 1.8-19.7 ng/mL), respectively, in the two age groups. Although steady state was not reached in this study, mean trough plasma concentration in another study in patients with BPH (mean age, 65 years) receiving 5 mg/day was 9.4 ng/mL (range, 7.1-13.3 ng/mL; n=22) after over a year of dosing.

Finasteride has been shown to cross the blood brain barrier but does not appear to distribute preferentially to the CSF.

In 2 studies of healthy subjects (n=69) receiving PROSCAR 5 mg/day for 6-24 weeks, finasteride concentrations in semen ranged from undetectable (<0.1 ng/mL) to 10.54 ng/mL. In an earlier study using a less sensitive assay, finasteride concentrations in the semen of 16 subjects receiving PROSCAR 5 mg/day ranged from undetectable (<1.0 ng/mL) to 21 ng/mL. Thus, based on a 5-mL ejaculate volume, the amount of finasteride in semen was estimated to be 50- to 100-fold less than the dose of finasteride (5 µg) that had no effect on circulating DHT levels in men (see also PRECAUTIONS, *Pregnancy*).

Metabolism

Finasteride is extensively metabolized in the liver, primarily via the cytochrome P450 3A4 enzyme subfamily. Two metabolites, the t-butyl side chain monohydroxylated and monocarboxylic acid metabolites, have been identified that possess no more than 20% of the 5α-reductase inhibitory activity of finasteride.

Excretion

In healthy young subjects (n=15), mean plasma clearance of finasteride was 165 mL/min (range, 70-279 mL/min) and mean elimination half-life in plasma was 6 hours (range, 3-16 hours). Following an oral dose of ^{14}C-finasteride in man (n=6), a mean of 39% (range, 32-46%) of the dose was excreted in the urine in the form of metabolites; 57% (range, 51-64%) was excreted in the feces.

The mean terminal half-life of finasteride in subjects ≥70 years of age was approximately 8 hours (range, 6-15 hours; n=12), compared with 6 hours (range, 4-12 hours; n=12) in subjects 45-60 years of age. As a result, mean $AUC_{(0\text{-}24\ hr)}$ after 17 days of dosing was 15% higher in subjects ≥70 years of age than in subjects 45-60 years of age (p=0.02).

Special Populations

Pediatric: Finasteride pharmacokinetics have not been investigated in patients <18 years of age.

Gender: Finasteride pharmacokinetics in women are not available.

Geriatric: No dosage adjustment is necessary in the elderly. Although the elimination rate of finasteride is decreased in the elderly, these findings are of no clinical significance. (See also Pharmacokinetics, Excretion, PRECAUTIONS, Geriatric Use and DOSAGE AND ADMINISTRATION.)

Race: The effect of race on finasteride pharmacokinetics has not been studied.

Renal Insufficiency: No dosage adjustment is necessary in patients with renal insufficiency. In patients with chronic renal impairment, with creatinine clearances ranging from 9.0 to 55 mL/min, AUC, maximum plasma concentration, half-life, and protein binding after a single dose of ^{14}C-finasteride were similar to values obtained in healthy volunteers. Urinary excretion of metabolites was decreased in patients with renal impairment. This decrease was associated with an increase in fecal excretion of metabolites. Plasma concentrations of metabolites were significantly higher in patients with renal impairment (based

on a 60% increase in total radioactivity AUC). However, finasteride has been well tolerated in BPH patients with normal renal function receiving up to 80 mg/day for 12 weeks, where exposure of these patients to metabolites would presumably be much greater.

Hepatic Insufficiency: The effect of hepatic insufficiency on finasteride pharmacokinetics has not been studied. Caution should be used in the administration of PROSCAR in those patients with liver function abnormalities, as finasteride is metabolized extensively in the liver.

Drug Interactions (see also PRECAUTIONS, *Drug Interactions*)

No drug interactions of clinical importance have been identified. Finasteride does not appear to affect the cytochrome P450-linked drug metabolism enzyme system. Compounds that have been tested in man have included antipyrine, digoxin, propranolol, theophylline, and warfarin, and no clinically meaningful interactions were found.

Mean (SD) Pharmacokinetic Parameters in Healthy Young Subjects (n=15)	
	Mean (± SD)
Bioavailability	63% (34-108%)*
Clearance (mL/min)	165 (55)
Volume of Distribution (L)	76 (14)
Half-Life (hours)	6.2 (2.1)

*Range

Mean (SD) Noncompartmental Pharmacokinetic Parameters After Multiple Doses of 5 mg/day in Older Men		
	Mean (± SD)	
	45-60 years old (n=12)	≥70 years old (n=12)
AUC (ng•hr/mL)	389 (98)	463 (186)
Peak Concentration (ng/mL)	46.2 (8.7)	48.4 (14.7)
Time to Peak (hours)	1.8 (0.7)	1.8 (0.6)
Half-Life (hours)*	6.0 (1.5)	8.2 (2.5)

*First-dose values; all other parameters are last-dose values

Clinical Studies

PROSCAR 5 mg/day was initially evaluated in patients with symptoms of BPH and enlarged prostates by digital rectal examination in two 1-year, placebo-controlled, randomized, double-blind studies and their 5-year open extensions.

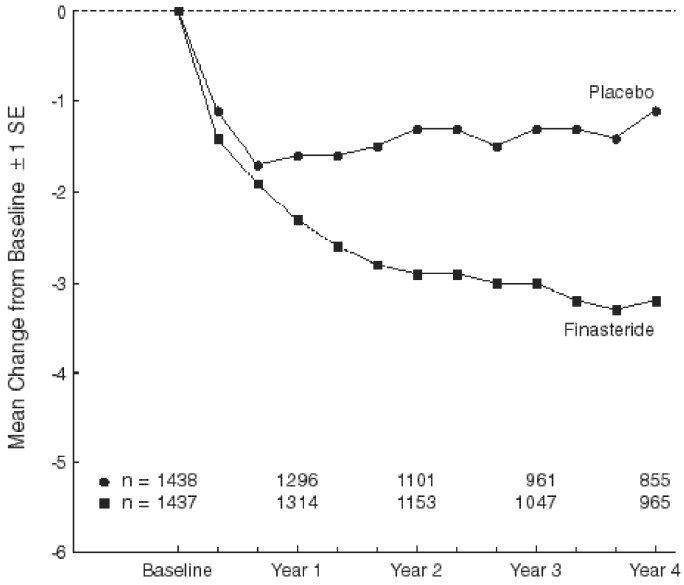
PROSCAR was further evaluated in the PROSCAR Long-Term Efficacy and Safety Study (PLESS), a double-blind, randomized, placebo-controlled, 4-year, multicenter study. 3040 patients between the ages of 45 and 78, with moderate to severe symptoms of BPH and an enlarged prostate upon digital rectal examination, were randomized into the study (1524 to finasteride, 1516 to placebo) and 3016 patients were evaluable for efficacy. 1883 patients completed the 4-year study (1000 in the finasteride group, 883 in the placebo group).

Effect on Symptom Score

Symptoms were quantified using a score similar to the American Urological Association Symptom Score, which evaluated both obstructive symptoms (impairment of size and force of stream, sensation of incomplete bladder emptying, delayed or interrupted urination) and irritative symptoms (nocturia, daytime frequency, need to strain or push the flow of urine) by rating on a 0 to 5 scale for six symptoms and a 0 to 4 scale for one symptom, for a total possible score of 34.

Patients in PLESS had moderate to severe symptoms at baseline (mean of approximately 15 points on a 0-34 point scale). Patients randomized to PROSCAR who remained on therapy for 4 years had a mean (± 1 SD) decrease in symptom score of 3.3 (± 5.8) points compared with 1.3 (± 5.6) points in the placebo group. (See Figure 1.) A statistically significant improvement in symptom score was evident at 1 year in patients treated with PROSCAR vs placebo (–2.3 vs –1.6), and this improvement continued through Year 4.

Figure 1
Symptom Score in PLESS



Results seen in earlier studies were comparable to those seen in PLESS. Although an early improvement in urinary symptoms was seen in some patients, a therapeutic trial of at least 6 months was generally necessary to assess whether a beneficial response in symptom relief had been achieved. The improvement in BPH symptoms was seen during the first year and maintained throughout an additional 5 years of open extension studies.

Effect on Acute Urinary Retention and the Need for Surgery

In PLESS, efficacy was also assessed by evaluating treatment failures. Treatment failure was prospectively defined as BPH-related urological events or clinical deterioration, lack of improvement and/or the need for alternative therapy. BPH-related urological events were defined as urological surgical intervention and acute urinary retention requiring catheterization. Complete event information was available for 92% of the patients. The following table (Table 1) summarizes the results.

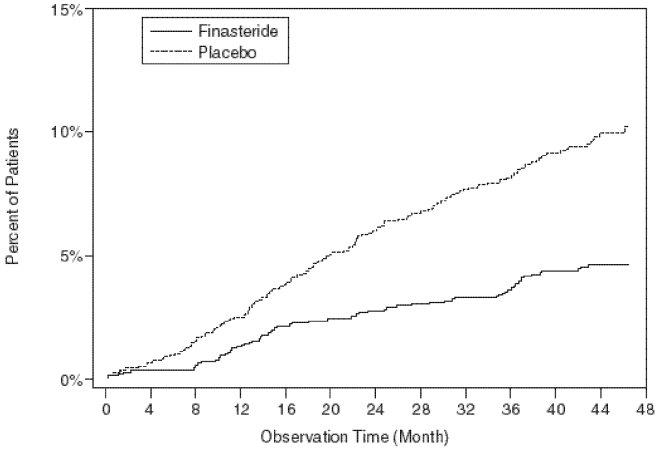
Table 1
All Treatment Failures in PLESS

	Patients (%) *				
Event	**Placebo N=1503**	**Finasteride N=1513**	**Relative Risk****	**95% CI**	**P Value****
All Treatment Failures	37.1	26.2	0.68	(0.57 to 0.79)	<0.001
Surgical Interventions for BPH	10.1	4.6	0.45	(0.32 to 0.63)	<0.001
Acute Urinary Retention Requiring Catheterization	6.6	2.8	0.43	(0.28 to 0.66)	<0.001
Two consecutive symptom scores ≥20	9.2	6.7			
Bladder Stone	0.4	0.5			
Incontinence	2.1	1.7			
Renal Failure	0.5	0.6			
UTI	5.7	4.9			
Discontinuation due to worsening of BPH, lack of improvement, or to receive other medical treatment	21.8	13.3			

*patients with multiple events may be counted more than once for each type of event
**Hazard ratio based on log rank test

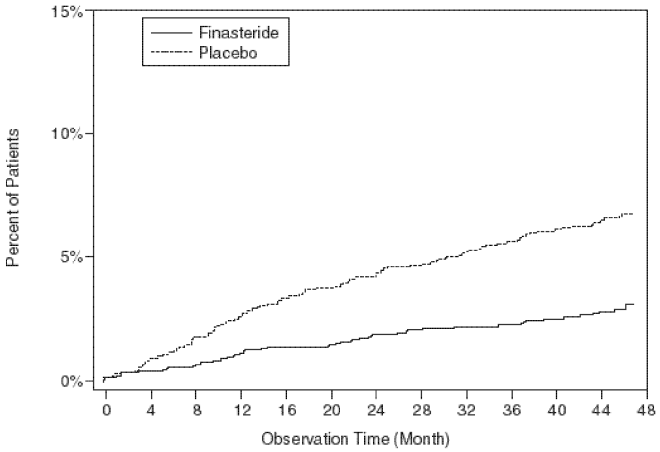
Compared with placebo, PROSCAR was associated with a significantly lower risk for acute urinary retention or the need for BPH-related surgery [13.2% for placebo vs 6.6% for PROSCAR; 51% reduction in risk, 95% CI: (34 to 63%)]. Compared with placebo, PROSCAR was associated with a significantly lower risk for surgery [10.1% for placebo vs 4.6% for PROSCAR; 55% reduction in risk, 95% CI: (37 to 68%)] and with a significantly lower risk of acute urinary retention [6.6% for placebo vs 2.8% for PROSCAR; 57% reduction in risk, 95% CI: (34 to 72%)]; see Figures 2 and 3.

Figure 2
Percent of Patients Having Surgery for BPH, Including TURP



Placebo Group				
No. of events, cumulative	37	89	121	152
No. at risk, per year	1503	1454	1374	1314
Finasteride Group				
No. of events, cumulative	18	40	49	69
No. at risk, per year	1513	1483	1438	1410

Figure 3
Percent of Patients Developing Acute Urinary Retention (Spontaneous and Precipitated)



Placebo Group				
No. of events, cumulative	36	61	81	99
No. at risk, per year	1503	1454	1398	1347
Finasteride Group				
No. of events, cumulative	14	25	32	42
No. at risk, per year	1513	1487	1449	1421

Effect on Maximum Urinary Flow Rate

In the patients in PLESS who remained on therapy for the duration of the study and had evaluable urinary flow data, PROSCAR increased maximum urinary flow rate by 1.9 mL/sec compared with 0.2 mL/sec in the placebo group.

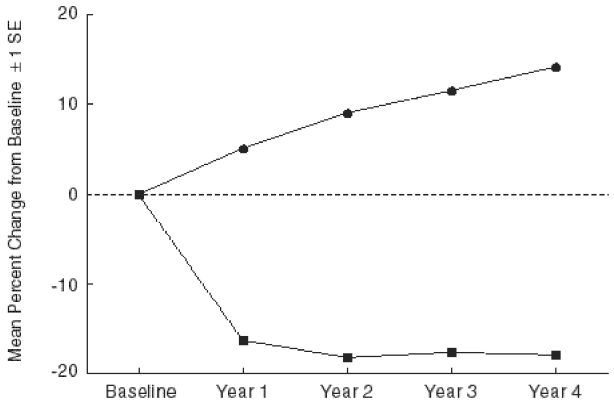
There was a clear difference between treatment groups in maximum urinary flow rate in favor of PROSCAR by month 4 (1.0 vs 0.3 mL/sec) which was maintained throughout the study. In the earlier 1-year studies, increase in maximum urinary flow rate was comparable to PLESS and was maintained through the first year and throughout an additional 5 years of open extension studies.

Effect on Prostate Volume

In PLESS, prostate volume was assessed yearly by magnetic resonance imaging (MRI) in a subset of patients. In patients treated with PROSCAR who remained on therapy, prostate volume was reduced compared with both baseline and placebo throughout the 4-year study. PROSCAR decreased prostate volume by 17.9% (from 55.9 cc at baseline to 45.8 cc at 4 years) compared with an increase of 14.1% (from 51.3 cc to 58.5 cc) in the placebo group ($p<0.001$). (See Figure 4.)

Results seen in earlier studies were comparable to those seen in PLESS. Mean prostate volume at baseline ranged between 40-50 cc. The reduction in prostate volume was seen during the first year and maintained throughout an additional five years of open extension studies.

Figure 4
Prostate Volume in PLESS



	Baseline	Year 1	Year 2	Year 3	Year 4
Placebo (●) n =	155	136	119	98	85
Finasteride (■) n =	157	144	130	116	102

Prostate Volume as a Predictor of Therapeutic Response

A meta-analysis combining 1-year data from seven double-blind, placebo-controlled studies of similar design, including 4491 patients with symptomatic BPH, demonstrated that, in patients treated with PROSCAR, the magnitude of symptom response and degree of improvement in maximum urinary flow rate were greater in patients with an enlarged prostate at baseline.

Medical Therapy of Prostatic Symptoms

The Medical Therapy of Prostatic Symptoms (MTOPS) Trial was a double-blind, randomized, placebo-controlled, multicenter, 4- to 6-year study (average 5 years) in 3047 men with symptomatic BPH, who were randomized to receive PROSCAR 5 mg/day (n=768), doxazosin 4 or 8 mg/day (n=756), the combination of PROSCAR 5 mg/day and doxazosin 4 or 8 mg/day (n=786), or placebo (n=737). All participants underwent weekly titration of doxazosin (or its placebo) from 1 to 2 to 4 to 8 mg/day. Only those who tolerated the 4 or 8 mg dose level were kept on doxazosin (or its placebo) in the study. The participant's final tolerated dose (either 4 mg or 8 mg) was administered beginning at end-Week 4. The final doxazosin dose was administered once per day, at bedtime.

The mean patient age at randomization was 62.6 years (±7.3 years). Patients were Caucasian (82%), African American (9%), Hispanic (7%), Asian (1%) or Native American (<1%). The mean duration of BPH symptoms was 4.7 years (±4.6 years). Patients had moderate to severe BPH symptoms at baseline with a mean AUA symptom score of approximately 17 out of 35 points. Mean maximum urinary flow rate was 10.5 mL/sec (±2.6 mL/sec). The mean prostate volume as measured by transrectal ultrasound was 36.3 mL (±20.1 mL). Prostate volume was ≤20 mL in 16% of patients, ≥50 mL in 18% of patients and between 21 and 49 mL in 66% of patients.

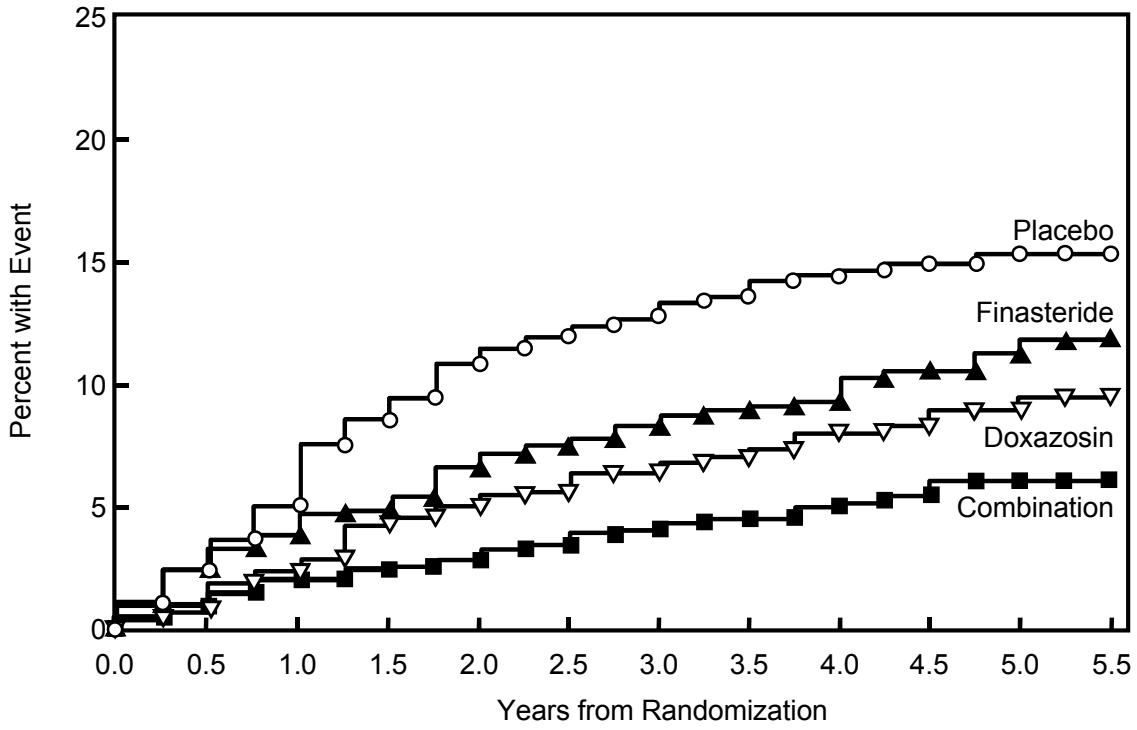
The primary endpoint was a composite measure of the first occurrence of any of the following five outcomes: a ≥4 point confirmed increase from baseline in symptom score, acute urinary retention, BPH-related renal insufficiency (creatinine rise), recurrent urinary tract infections or urosepsis, or incontinence. Compared to placebo, treatment with PROSCAR, doxazosin, or combination therapy resulted in a reduction in the risk of experiencing one of these five outcome events by 34% (p=0.002), 39% (p<0.001), and 67% (p<0.001), respectively. Combination therapy resulted in a significant reduction in the risk of the primary endpoint compared to treatment with PROSCAR alone (49%; p≤0.001) or doxazosin alone (46%; p≤0.001). (See Table 2.)

Table 2
Count and Percent Incidence of Primary Outcome Events
by Treatment Group in MTOPS

Event	Treatment Group				
	Placebo N=737 N (%)	Doxazosin N=756 N (%)	Finasteride N=768 N (%)	Combination N=786 N (%)	Total N=3047 N (%)
AUA 4-point rise	100 (13.6)	59 (7.8)	74 (9.6)	41 (5.2)	274 (9.0)
Acute urinary retention	18 (2.4)	13 (1.7)	6 (0.8)	4 (0.5)	41 (1.3)
Incontinence	8 (1.1)	11 (1.5)	9 (1.2)	3 (0.4)	31 (1.0)
Recurrent UTI/urosepsis	2 (0.3)	2 (0.3)	0 (0.0)	1 (0.1)	5 (0.2)
Creatinine rise	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total Events	128 (17.4)	85 (11.2)	89 (11.6)	49 (6.2)	351 (11.5)

The majority of the events (274 out of 351; 78%) was a confirmed ≥4 point increase in symptom score, referred to as symptom score progression. The risk of symptom score progression was reduced by 30% (p=0.016), 46% (p<0.001), and 64% (p<0.001) in patients treated with PROSCAR, doxazosin, or the combination, respectively, compared to patients treated with placebo (see Figure 5). Combination therapy significantly reduced the risk of symptom score progression compared to the effect of PROSCAR alone (p<0.001) and compared to doxazosin alone (p=0.037).

Figure 5
Cumulative Incidence of a 4-Point Rise in AUA Symptom Score by Treatment Group



Treatment with PROSCAR, doxazosin or the combination of PROSCAR with doxazosin, reduced the mean symptom score from baseline at year 4. Table 3 provides the mean change from baseline for AUA symptom score by treatment group for patients who remained on therapy for four years.

Table 3
Change From Baseline in AUA Symptom Score
by Treatment Group at Year 4 in MTOPS

	Placebo N=534	Doxazosin N=582	Finasteride N=565	Combination N=598
Baseline Mean (SD)	16.8 (6.0)	17.0 (5.9)	17.1 (6.0)	16.8 (5.8)
Mean Change AUA Symptom Score (SD)	-4.9 (5.8)	-6.6 (6.1)	-5.6 (5.9)	-7.4 (6.3)
Comparison to Placebo (95% CI)		-1.8 (-2.5, -1.1)	-0.7 (-1.4, 0.0)	-2.5 (-3.2, -1.8)
Comparison to Doxazosin alone (95% CI)				-0.7 (-1.4, 0.0)
Comparison to Finasteride alone (95% CI)				-1.8 (-2.5, -1.1)

The results of MTOPS are consistent with the findings of the 4-year, placebo-controlled study PLESS (see CLINICAL PHARMACOLOGY, *Clinical Studies*) in that treatment with PROSCAR reduces the risk of acute urinary retention and the need for BPH-related surgery. In MTOPS, the risk of developing acute urinary retention was reduced by 67% in patients treated with PROSCAR compared to patients treated with placebo (0.8% for PROSCAR and 2.4% for placebo). Also, the risk of requiring BPH-related invasive therapy was reduced by 64% in patients treated with PROSCAR compared to patients treated with placebo (2.0% for PROSCAR and 5.4% for placebo).

Summary of Clinical Studies

The data from these studies, showing improvement in BPH-related symptoms, reduction in treatment failure (BPH-related urological events), increased maximum urinary flow rates, and decreasing prostate volume, suggest that PROSCAR arrests the disease process of BPH in men with an enlarged prostate.

INDICATIONS AND USAGE

PROSCAR is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to:

-Improve symptoms

-Reduce the risk of acute urinary retention

-Reduce the risk of the need for surgery including transurethral resection of the prostate (TURP) and prostatectomy.

PROSCAR administered in combination with the alpha-blocker doxazosin is indicated to reduce the risk of symptomatic progression of BPH (a confirmed ≥4 point increase in AUA symptom score).

CONTRAINDICATIONS

PROSCAR is contraindicated in the following:

Hypersensitivity to any component of this medication.

Pregnancy. Finasteride use is contraindicated in women when they are or may potentially be pregnant. Because of the ability of Type II 5α-reductase inhibitors to inhibit the conversion of testosterone to DHT, finasteride may cause abnormalities of the external genitalia of a male fetus of a pregnant woman who receives finasteride. If this drug is used during pregnancy, or if pregnancy occurs while taking this drug, the pregnant woman should be apprised of the potential hazard to the male fetus. (See also WARNINGS, EXPOSURE OF WOMEN — RISK TO MALE FETUS and PRECAUTIONS, *Information for Patients* and *Pregnancy*.) In female rats, low doses of finasteride administered during pregnancy have produced abnormalities of the external genitalia in male offspring.

WARNINGS

PROSCAR is not indicated for use in pediatric patients (see PRECAUTIONS, *Pediatric Use*) or women (see also WARNINGS, EXPOSURE OF WOMEN — RISK TO MALE FETUS; PRECAUTIONS, *Information for Patients* and *Pregnancy*; and HOW SUPPLIED).

EXPOSURE OF WOMEN — RISK TO MALE FETUS

Women should not handle crushed or broken PROSCAR tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. PROSCAR tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed. (See CONTRAINDICATIONS; PRECAUTIONS, *Information for Patients* and *Pregnancy*; and HOW SUPPLIED.)

PRECAUTIONS

General

Prior to initiating therapy with PROSCAR, appropriate evaluation should be performed to identify other conditions such as infection, prostate cancer, stricture disease, hypotonic bladder or other neurogenic disorders that might mimic BPH.

Patients with large residual urinary volume and/or severely diminished urinary flow should be carefully monitored for obstructive uropathy. These patients may not be candidates for finasteride therapy.

Caution should be used in the administration of PROSCAR in those patients with liver function abnormalities, as finasteride is metabolized extensively in the liver.

Effects on PSA and Prostate Cancer Detection

No clinical benefit has been demonstrated in patients with prostate cancer treated with PROSCAR. Patients with BPH and elevated PSA were monitored in controlled clinical studies with serial PSAs and prostate biopsies. In these BPH studies, PROSCAR did not appear to alter the rate of prostate cancer detection, and the overall incidence of prostate cancer was not significantly different in patients treated with PROSCAR or placebo.

PROSCAR causes a decrease in serum PSA levels by approximately 50% in patients with BPH. This decrease is predictable over the entire range of PSA values, although it may vary in individual patients. Analysis of PSA data from over 3000 patients in PLESS confirmed that in typical patients treated with PROSCAR for six months or more, PSA values should be doubled for comparison with normal ranges in untreated men. This adjustment preserves the sensitivity and specificity of the PSA assay and maintains its ability to detect prostate cancer. PROSCAR may also cause decreases in serum PSA in the presence of prostate cancer.

Any confirmed increases in PSA levels from nadir while on PROSCAR may signal the presence of prostate cancer and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5α-reductase inhibitor. Non-compliance with PROSCAR therapy may also affect PSA test results.

Percent free PSA (free to total PSA ratio) is not significantly decreased by PROSCAR. The ratio of free to total PSA remains constant even under the influence of PROSCAR. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing finasteride therapy, no adjustment to its value appears necessary.

Information for Patients

Women should not handle crushed or broken PROSCAR tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to the male fetus (see CONTRAINDICATIONS; WARNINGS, EXPOSURE OF WOMEN — RISK TO MALE FETUS; PRECAUTIONS, *Pregnancy* and HOW SUPPLIED).

Physicians should inform patients that the volume of ejaculate may be decreased in some patients during treatment with PROSCAR. This decrease does not appear to interfere with normal sexual function. However, impotence and decreased libido may occur in patients treated with PROSCAR (see ADVERSE REACTIONS).

Physicians should instruct their patients to promptly report any changes in their breasts such as lumps, pain or nipple discharge. Breast changes including breast enlargement, tenderness and neoplasm have been reported (see ADVERSE REACTIONS).

Physicians should instruct their patients to read the patient package insert before starting therapy with PROSCAR and to reread it each time the prescription is renewed so that they are aware of current information for patients regarding PROSCAR.

Drug/Laboratory Test Interactions

In patients with BPH, PROSCAR has no effect on circulating levels of cortisol, estradiol, prolactin, thyroid-stimulating hormone, or thyroxine. No clinically meaningful effect was observed on the plasma lipid profile (i.e., total cholesterol, low density lipoproteins, high density lipoproteins and triglycerides) or bone mineral density. Increases of about 10% were observed in luteinizing hormone (LH) and follicle-

stimulating hormone (FSH) in patients receiving PROSCAR, but levels remained within the normal range. In healthy volunteers, treatment with PROSCAR did not alter the response of LH and FSH to gonadotropin-releasing hormone indicating that the hypothalamic-pituitary-testicular axis was not affected.

Treatment with PROSCAR for 24 weeks to evaluate semen parameters in healthy male volunteers revealed no clinically meaningful effects on sperm concentration, mobility, morphology, or pH. A 0.6 mL (22.1%) median decrease in ejaculate volume with a concomitant reduction in total sperm per ejaculate was observed. These parameters remained within the normal range and were reversible upon discontinuation of therapy with an average time to return to baseline of 84 weeks.

Drug Interactions

No drug interactions of clinical importance have been identified. Finasteride does not appear to affect the cytochrome P450-linked drug metabolizing enzyme system. Compounds that have been tested in man have included antipyrine, digoxin, propranolol, theophylline, and warfarin and no clinically meaningful interactions were found.

Other Concomitant Therapy: Although specific interaction studies were not performed, PROSCAR was concomitantly used in clinical studies with acetaminophen, acetylsalicylic acid, α-blockers, angiotensin-converting enzyme (ACE) inhibitors, analgesics, anti-convulsants, beta-adrenergic blocking agents, diuretics, calcium channel blockers, cardiac nitrates, HMG-CoA reductase inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, H_2 antagonists and quinolone anti-infectives without evidence of clinically significant adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a tumorigenic effect was observed in a 24-month study in Sprague-Dawley rats receiving doses of finasteride up to 160 mg/kg/day in males and 320 mg/kg/day in females. These doses produced respective systemic exposure in rats of 111 and 274 times those observed in man receiving the recommended human dose of 5 mg/day. All exposure calculations were based on calculated $AUC_{(0\text{-}24\ hr)}$ for animals and mean $AUC_{(0\text{-}24\ hr)}$ for man (0.4 µg•hr/mL).

In a 19-month carcinogenicity study in CD-1 mice, a statistically significant ($p \leq 0.05$) increase in the incidence of testicular Leydig cell adenomas was observed at a dose of 250 mg/kg/day (228 times the human exposure). In mice at a dose of 25 mg/kg/day (23 times the human exposure, estimated) and in rats at a dose of ≥40 mg/kg/day (39 times the human exposure) an increase in the incidence of Leydig cell hyperplasia was observed. A positive correlation between the proliferative changes in the Leydig cells and an increase in serum LH levels (2- to 3-fold above control) has been demonstrated in both rodent species treated with high doses of finasteride. No drug-related Leydig cell changes were seen in either rats or dogs treated with finasteride for 1 year at doses of 20 mg/kg/day and 45 mg/kg/day (30 and 350 times, respectively, the human exposure) or in mice treated for 19 months at a dose of 2.5 mg/kg/day (2.3 times the human exposure, estimated).

No evidence of mutagenicity was observed in an *in vitro* bacterial mutagenesis assay, a mammalian cell mutagenesis assay, or in an *in vitro* alkaline elution assay. In an *in vitro* chromosome aberration assay, using Chinese hamster ovary cells, there was a slight increase in chromosome aberrations. These concentrations correspond to 4000-5000 times the peak plasma levels in man given a total dose of 5 mg. In an *in vivo* chromosome aberration assay in mice, no treatment-related increase in chromosome aberration was observed with finasteride at the maximum tolerated dose of 250 mg/kg/day (228 times the human exposure) as determined in the carcinogenicity studies.

In sexually mature male rabbits treated with finasteride at 80 mg/kg/day (543 times the human exposure) for up to 12 weeks, no effect on fertility, sperm count, or ejaculate volume was seen. In sexually mature male rats treated with 80 mg/kg/day of finasteride (61 times the human exposure), there were no significant effects on fertility after 6 or 12 weeks of treatment; however, when treatment was continued for up to 24 or 30 weeks, there was an apparent decrease in fertility, fecundity and an associated significant decrease in the weights of the seminal vesicles and prostate. All these effects were reversible within 6 weeks of discontinuation of treatment. No drug-related effect on testes or on mating performance has been seen in rats or rabbits. This decrease in fertility in finasteride-treated rats is secondary to its effect on accessory sex organs (prostate and seminal vesicles) resulting in failure to form a seminal plug. The seminal plug is essential for normal fertility in rats and is not relevant in man.

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

PROSCAR is not indicated for use in women.

Administration of finasteride to pregnant rats at doses ranging from 100 µg/kg/day to 100 mg/kg/day (1-1000 times the recommended human dose of 5 mg/day) resulted in dose-dependent development of

hypospadias in 3.6 to 100% of male offspring. Pregnant rats produced male offspring with decreased prostatic and seminal vesicular weights, delayed preputial separation and transient nipple development when given finasteride at ≥30 µg/kg/day (≥3/10 of the recommended human dose of 5 mg/day) and decreased anogenital distance when given finasteride at ≥3 µg/kg/day (≥3/100 of the recommended human dose of 5 mg/day). The critical period during which these effects can be induced in male rats has been defined to be days 16-17 of gestation. The changes described above are expected pharmacological effects of drugs belonging to the class of Type II 5α-reductase inhibitors and are similar to those reported in male infants with a genetic deficiency of Type II 5α-reductase. No abnormalities were observed in female offspring exposed to any dose of finasteride *in utero*.

No developmental abnormalities have been observed in first filial generation (F_1) male or female offspring resulting from mating finasteride-treated male rats (80 mg/kg/day; 61 times the human exposure) with untreated females. Administration of finasteride at 3 mg/kg/day (30 times the recommended human dose of 5 mg/day) during the late gestation and lactation period resulted in slightly decreased fertility in F_1 male offspring. No effects were seen in female offspring. No evidence of malformations has been observed in rabbit fetuses exposed to finasteride *in utero* from days 6-18 of gestation at doses up to 100 mg/kg/day (1000 times the recommended human dose of 5 mg/day). However, effects on male genitalia would not be expected since the rabbits were not exposed during the critical period of genital system development.

The *in utero* effects of finasteride exposure during the period of embryonic and fetal development were evaluated in the rhesus monkey (gestation days 20-100), a species more predictive of human development than rats or rabbits. Intravenous administration of finasteride to pregnant monkeys at doses as high as 800 ng/day (at least 60 to 120 times the highest estimated exposure of pregnant women to finasteride from semen of men taking 5 mg/day) resulted in no abnormalities in male fetuses. In confirmation of the relevance of the rhesus model for human fetal development, oral administration of a dose of finasteride (2 mg/kg/day; 20 times the recommended human dose of 5 mg/day or approximately 1-2 million times the highest estimated exposure to finasteride from semen of men taking 5 mg/day) to pregnant monkeys resulted in external genital abnormalities in male fetuses. No other abnormalities were observed in male fetuses and no finasteride-related abnormalities were observed in female fetuses at any dose.

Nursing Mothers

PROSCAR is not indicated for use in women.

It is not known whether finasteride is excreted in human milk.

Pediatric Use

PROSCAR is not indicated for use in pediatric patients.

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total number of subjects included in PLESS, 1480 and 105 subjects were 65 and over and 75 and over, respectively. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. No dosage adjustment is necessary in the elderly (see CLINICAL PHARMACOLOGY, *Pharmacokinetics* and *Clinical Studies*).

ADVERSE REACTIONS

PROSCAR is generally well tolerated; adverse reactions usually have been mild and transient.

4-Year Placebo-Controlled Study

In PLESS, 1524 patients treated with PROSCAR and 1516 patients treated with placebo were evaluated for safety over a period of 4 years. The most frequently reported adverse reactions were related to sexual function. 3.7% (57 patients) treated with PROSCAR and 2.1% (32 patients) treated with placebo discontinued therapy as a result of adverse reactions related to sexual function, which are the most frequently reported adverse reactions.

Table 4 presents the only clinical adverse reactions considered possibly, probably or definitely drug related by the investigator, for which the incidence on PROSCAR was 1% and greater than placebo over the 4 years of the study. In years 2-4 of the study, there was no significant difference between treatment groups in the incidences of impotence, decreased libido and ejaculation disorder.

TABLE 4
Drug-Related Adverse Experiences

	Year 1 (%)	Years 2, 3 and 4* (%)

	Finasteride	Placebo	Finasteride	Placebo
Impotence	8.1	3.7	5.1	5.1
Decreased Libido	6.4	3.4	2.6	2.6
Decreased Volume of Ejaculate	3.7	0.8	1.5	0.5
Ejaculation Disorder	0.8	0.1	0.2	0.1
Breast Enlargement	0.5	0.1	1.8	1.1
Breast Tenderness	0.4	0.1	0.7	0.3
Rash	0.5	0.2	0.5	0.1

*Combined Years 2-4
N = 1524 and 1516, finasteride vs placebo, respectively

Phase III Studies and 5-Year Open Extensions

The adverse experience profile in the 1-year, placebo-controlled, Phase III studies, the 5-year open extensions, and PLESS were similar.

Medical Therapy of Prostatic Symptoms (MTOPS) Study

The incidence rates of drug-related adverse experiences reported by ≥2% of patients in any treatment group in the MTOPS Study are listed in Table 5.

The individual adverse effects which occurred more frequently in the combination group compared to either drug alone were: asthenia, postural hypotension, peripheral edema, dizziness, decreased libido, rhinitis, abnormal ejaculation, impotence and abnormal sexual function (see Table 5). Of these, the incidence of abnormal ejaculation in patients receiving combination therapy was comparable to the sum of the incidences of this adverse experience reported for the two monotherapies.

Combination therapy with finasteride and doxazosin was associated with no new clinical adverse experience.

Four patients in MTOPS reported the adverse experience breast cancer. Three of these patients were on finasteride only and one was on combination therapy. (See ADVERSE REACTIONS, *Long-Term Data*.)

The MTOPS Study was not specifically designed to make statistical comparisons between groups for reported adverse experiences. In addition, direct comparisons of safety data between the MTOPS study and previous studies of the single agents may not be appropriate based upon differences in patient population, dosage or dose regimen, and other procedural and study design elements.

Table 5

Incidence ≥ 2% in One or More Treatment Groups

Drug-Related Clinical Adverse Experiences in MTOPS

Adverse Experience	Placebo (N=737) (%)	Doxazosin 4 mg or 8 mg* (N=756) (%)	Finasteride (N=768) (%)	Combination (N=786) (%)
Body as a whole				
Asthenia	7.1	15.7	5.3	16.8
Headache	2.3	4.1	2.0	2.3
Cardiovascular				
Hypotension	0.7	3.4	1.2	1.5
Postural Hypotension	8.0	16.7	9.1	17.8
Metabolic and Nutritional				
Peripheral Edema	0.9	2.6	1.3	3.3
Nervous				
Dizziness	8.1	17.7	7.4	23.2
Libido Decreased	5.7	7.0	10.0	11.6
Somnolence	1.5	3.7	1.7	3.1
Respiratory				
Dyspnea	0.7	2.1	0.7	1.9
Rhinitis	0.5	1.3	1.0	2.4
Urogenital				

Abnormal Ejaculation	2.3	4.5	7.2	14.1
Gynecomastia	0.7	1.1	2.2	1.5
Impotence	12.2	14.4	18.5	22.6
Sexual Function Abnormal	0.9	2.0	2.5	3.1

*Doxazosin dose was achieved by weekly titration (1 to 2 to 4 to 8 mg). The final tolerated dose (4 mg or 8 mg) was administered at end-Week 4. Only those patients tolerating at least 4 mg were kept on doxazosin. The majority of patients received the 8-mg dose over the duration of the study.

Long-Term Data

There is no evidence of increased adverse experiences with increased duration of treatment with PROSCAR. New reports of drug-related sexual adverse experiences decreased with duration of therapy.

During the 4- to 6-year placebo- and comparator-controlled MTOPS study that enrolled 3047 men, there were 4 cases of breast cancer in men treated with finasteride but no cases in men not treated with finasteride. During the 4-year, placebo-controlled PLESS study that enrolled 3040 men, there were 2 cases of breast cancer in placebo-treated men, but no cases were reported in men treated with finasteride. The relationship between long-term use of finasteride and male breast neoplasia is currently unknown.

In a 7-year placebo-controlled trial that enrolled 18,882 healthy men, 9060 had prostate needle biopsy data available for analysis. In the PROSCAR group, 280 (6.4%) men had prostate cancer with Gleason scores of 7-10 detected on needle biopsy vs. 237 (5.1%) men in the placebo group. Of the total cases of prostate cancer diagnosed in this study, approximately 98% were classified as intracapsular (stage T1 or T2). The clinical significance of these findings is unknown. This information from the literature (Thompson IM, Goodman Pμ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003;349:213-22) is provided for consideration by physicians when PROSCAR is used as indicated (see INDICATIONS AND USAGE). PROSCAR is not approved to reduce the risk of developing prostate cancer.

Post-Marketing Experience

The following additional adverse effects have been reported in post-marketing experience:

- hypersensitivity reactions, including pruritus, urticaria, and swelling of the lips and face
- testicular pain
- male breast cancer.

OVERDOSAGE

Patients have received single doses of PROSCAR up to 400 mg and multiple doses of PROSCAR up to 80 mg/day for three months without adverse effects. Until further experience is obtained, no specific treatment for an overdose with PROSCAR can be recommended.

Significant lethality was observed in male and female mice at single oral doses of 1500 mg/m^2 (500 mg/kg) and in female and male rats at single oral doses of 2360 mg/m^2 (400 mg/kg) and 5900 mg/m^2 (1000 mg/kg), respectively.

DOSAGE AND ADMINISTRATION

The recommended dose is 5 mg orally once a day.

PROSCAR can be administered alone or in combination with the alpha-blocker doxazosin (see CLINICAL PHARMACOLOGY, *Clinical Studies*).

PROSCAR may be administered with or without meals.

No dosage adjustment is necessary for patients with renal impairment or for the elderly (see CLINICAL PHARMACOLOGY, *Pharmacokinetics*).

HOW SUPPLIED

No. 3094 — PROSCAR tablets 5 mg are blue, modified apple-shaped, film-coated tablets, with the code MSD 72 on one side and PROSCAR on the other. They are supplied as follows:

NDC 0006-0072-31 unit of use bottles of 30

NDC 0006-0072-58 unit of use bottles of 100

Storage and Handling

Store at room temperatures below 30°C (86°F). Protect from light and keep container tightly closed.

Women should not handle crushed or broken PROSCAR tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent

potential risk to a male fetus (see WARNINGS, EXPOSURE OF WOMEN — RISK TO MALE FETUS, and PRECAUTIONS, *Information for Patients* and *Pregnancy*).

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Appendix 1B. Proposed Draft Labeling

Note: The current PROSCAR® (finasteride 5 mg) U.S. Product Circular can be found in Appendix 1A. Proposed changes are underlined in the text below.

INDICATIONS AND USAGE

Monotherapy

PROSCAR is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to:

-Improve symptoms

-Reduce the risk of acute urinary retention

-Reduce the risk of the need for surgery including transurethral resection of the prostate (TURP) and prostatectomy.

Combination with Alpha-Blocker

PROSCAR administered in combination with the alpha-blocker doxazosin is indicated to reduce the risk of symptomatic progression of BPH (a confirmed ≥4 point increase in AUA symptom score).

ADVERSE REACTIONS

Clinical Trials Experience, Long-Term Data

In the PCPT study, 9060 of the 18,882 men enrolled had prostate needle biopsy data available for analysis. In the PROSCAR group, 280 (6.4%) men had prostate cancer with Gleason scores of 7-10 detected on needle biopsy vs. 237 (5.1%) men in the placebo group. Additional analyses, including analysis of data from the cohort of men who underwent prostatectomy, suggest that the increase in the prevalence of high-grade (Gleason scores 7-10) prostate cancer observed in the PROSCAR group in this study may be explained by a detection bias due to the effects of PROSCAR on prostate volume and PSA, both of which facilitated diagnosis. Of the total cases of prostate cancer diagnosed in this study, approximately 98% were classified as intracapsular (clinical stage T1 or T2) at diagnosis. The clinical significance of the Gleason 7-10 data is unknown.

CLINICAL STUDIES

Other Studies

The Prostate Cancer Prevention Trial (PCPT) was a 7-year placebo-controlled trial that enrolled 18,882 men ≥55 years of age with a normal digital rectal examination and a PSA of ≤3.0 ng/mL. At the end of the study, 9060 men had prostate needle biopsy data available for analysis. In this study, prostate cancer was detected in 803 (18.4%) men receiving PROSCAR and 1147 (24.4%) men receiving placebo *[see Adverse Reactions (6.1)]*. The observed reduction in the prevalence of prostate cancer was consistent across subgroups defined by age, race, family history of prostate cancer, PSA at study entry, and prostate volume at biopsy. This information is provided for consideration by physicians when treating men, or evaluating men for treatment, with PROSCAR for BPH. [1]

REFERENCES

1. Use of 5-alpha Reductase Inhibitors for Prostate Cancer Chemoprevention: American Society of Clinical Oncology-American Urological Association 2008 Clinical Practice Guideline

Appendix 2

Design Options for the Prostate Cancer Prevention Trial

Several design options were considered prior to reaching the final study design of the Prostate Cancer Prevention Trial (PCPT) [72; 57]. These options are summarized in Table 1, below. An initial proposal (Design Option 1) was to establish a central laboratory to measure prostate-specific antigen (PSA) levels but withhold results from study investigators until the end of the trial. Diagnosis of prostate cancer would be the primary endpoint. The chief clinical indicator for prostate biopsy and, thus, detection of prostate cancer would be digital rectal examination (DRE). This approach was rejected because the investigators felt that the use of PSA in clinical practice was too ingrained in the U.S. by the time the PCPT protocol was being developed. Reliance on DRE alone for screening is not sensitive in detecting early-stage disease, is operator-dependent, and might bias detection since finasteride had been shown to decrease prostate volume approximately 20% within 6 months [45; 47]. In addition, study accrual could have suffered if PSA information was withheld. Finally, if participants were to seek PSA testing outside the trial, as might be expected if PSA results were not provided to the study investigators, differential biopsy rates in the 2 study arms would be likely due to the effect of finasteride on PSA (median PSA is reduced approximately 50% in men with benign prostatic hyperplasia (BPH)) [45; 69].

A second approach (Design Option 2) incorporated PSA "indexing." As with Design 1, the primary endpoint would be diagnosis of prostate cancer. Men in the placebo group would have a biopsy if their PSA exceeded a specific value, e.g., 4.0 ng/mL, or if percent change in PSA over time exceeded a specified cutoff value. A different cutoff value would apply for men in the finasteride group that would be chosen to equalize the biopsy rates for the 2 arms of the trial. As in Design 1, all PSA samples would be tested in a central laboratory. However, in the PSA indexing approach, the study investigators would be notified by the central laboratory whether the PSA result was elevated or not. Design 2 was rejected because of concerns with using an indexed PSA to primarily drive diagnosis of prostate cancer when diagnosis of prostate cancer is the primary endpoint, especially as a validated long-term method of indexing PSA, one that would not bias differences between groups in PSA-driven prompts for prostate biopsy and subsequent prostate cancer diagnosis, did not exist at that time. (PSA indexing was retained in the final study design (Design 5), but the primary endpoint was augmented to include the result of the 7-year, end-of-study biopsy.)

A third proposal (Design Option 3) for mitigating the potential bias due to PSA was to conduct multiple biopsies in a 10% sample of the study population (a so-called vanguard group). These men would undergo DRE and PSA annually and periodic prostate biopsies (e.g., after 1 year of treatment and then every other year for 8 to 10 years). Their PSA

data would be used to set cutoff values to trigger biopsies in the subjects who would be enrolled after them. The endpoint would be diagnosis of prostate cancer. Although this design would yield valuable data on the natural history of prostate cancer and the performance of PSA and DRE, it had the obvious drawback of making participation in the vanguard unappealing because of repeated biopsies. Because a large dropout rate after 1 or 2 biopsies would likely invalidate this design, it was rejected.

Design Option 4 was "a large simple trial" [73]. Participants would have followed local standards of care with no attempt to standardize diagnostic or treatment regimens. The primary endpoint would be mortality from prostate cancer, the most clinically relevant of all potential endpoints, rather than diagnosis. This design would not be affected by the detection of unimportant tumors (e.g. "latent", "occult," Stage A1) or other tumors that might cause no ill effects during the participant's lifetime. To implement Design 4, all investigators would have to acknowledge that PSA bias would undoubtedly lead to an early excess of prostate cancers detected in the placebo group and agree that the trial would not be stopped unless the Data and Safety Monitoring Committee (DSMC) determined that some preset highest acceptable difference in cancer detection rate had been exceeded. In the end, the required size of such a trial led to its rejection: randomization of 51,000 men to a 15-year study would have been required to detect a 26% reduction in prostate cancer deaths (90% power, 5% two-sided test).

Design Option 5 was the study design selected for the PCPT. It included both PSA indexing and end-of-study (EOS) biopsies and used the DSMC to monitor for the critical assumptions included in the study design during the conduct of the trial (see Appendix 3). Based on other assumptions used to determine the sample size required for the trial (see Appendix 4), Design Option 5 was predicted to yield sufficient power (≥90%) to detect a clinically meaningful difference (≥25%) between treatment groups in the primary endpoint (prevalence of prostate cancer over 7 years).

Table 1

Design Options for the Prostate Cancer Prevention Trial

Design Option	Endpoint	Ascertainment plan	Strengths	Weaknesses
1	Diagnosis of prostate cancer, any stage	Usual clinical practice; central laboratory withholds results of PSA from participants and physicians	Important information regarding PSA and prostate cancer detection at end of the trial	PSA, unadjusted for finasteride use, would likely bias endpoint; controversial medical practice because centrally-measured PSA values would not be reported
2	Diagnosis of prostate cancer, any stage	Central laboratory, indexed PSAs	Attempts to control PSA bias	Relation between PSA and endpoint not evaluable. At study inception, adjustment for PSA uncertain in short run and unknown beyond 3-4 years.
3	Diagnosis of prostate cancer, any stage	Central laboratory; PSA algorithm based on multiple biopsies of a vanguard group	Dynamic data-based PSA algorithm	Vanguard accrual difficult; sensitivity of vanguard PSA algorithm low
4	Mortality from prostate cancer	Usual clinical practice	Clinically relevant endpoint – standard diagnostic process	Extremely large sample size, long follow-up, probably high drop-in and drop-out rates.
5	Prostate biopsy result after 7 years of treatment (includes prostate cancer diagnosis, any stage, during the trial and at end of study)	Central laboratory, indexed PSAs	Unbiased ascertainment if critical assumptions hold; assumptions can be checked	Numerous critical assumptions required; endpoint in some participants ascertained only because of end-of-study biopsy, inconsistent with usual clinical practice

[72]

Appendix 3

Critical Assumptions in the Design of the Prostate Cancer Prevention Trial

The primary endpoint of the Prostate Cancer Prevention Trial (PCPT), the period prevalence of prostate cancer over 7 years, was subject to a number of potential known (and unknown) biases [57]. Therefore, the study design of the PCPT considered these potential sources of bias and incorporated design elements to address biases that could be mitigated. Potential sources of bias, primarily those that might impact the *detection* of prostate cancer, included:

(a) Changes in prostate-specific antigen (PSA) due to finasteride's mechanism of action (finasteride was known to reduce PSA by approximately 50% in men with benign prostatic hyperplasia (BPH)) [45; 69]. PSA testing was one mechanism by which a recommendation for prostate biopsy would be made to detect prostate cancer during the PCPT.

(b) Changes in the prostate due to finasteride's mechanism of action: finasteride treatment was known to reduce prostate volume by approximately 20% in men with BPH. The performance of the digital rectal examination (DRE), another mechanism by which a recommendation for prostate biopsy would be made to detect prostate cancer during the PCPT, and of prostate biopsy, the mechanism by which prostate cancer would be diagnosed in nearly all participants during the PCPT, could be affected by this effect on prostate volume.

(c) Non-adherence to the active study drug, or the *drop-out* rate

(d) Potential use of finasteride outside of the study, or the *drop-in* (contamination) rate

(e) Differences in the percentage of men undergoing surgical treatment, such as transurethral resection of the prostate (TURP), for management of BPH, with the potential to diagnose prostate cancer as a result of the procedure.

To ensure that these biases did not affect the integrity of the PCPT, a number of critical assumptions were developed. These assumptions were dynamically monitored by the PCPT Data and Safety Monitoring Committee (DSMC) at their semi-annual meetings during which they reviewed the accumulating data. These data provided the evidence regarding the accuracy of the key assumptions. If necessary, mid-course corrections to the study design could be made, e.g., adjustments to the PSA algorithm or enhanced searches for participants lost to follow-up. Some of the critical assumptions were more difficult to test than others.

Key critical assumptions include the following:

1. Finasteride-induced PSA change results in a simple downward shift in the PSA distribution and therefore generally preserves the ranking of the affected participants.

2. Finasteride does not affect the screening properties (sensitivity or specificity) of the DRE, the transrectal ultrasonography, or the prostate biopsy.

3. The procedures used to assess adherence of individual participants at each visit at which a PSA is obtained are sufficiently sensitive and reliable to detect degrees of non-adherence affecting PSA level interpretation.

4. Factors affecting loss to for-cause and end-of-study (EOS) biopsies are similar in both treatment arms so that the groups of participants who do not have biopsies due to death, loss to follow-up, and biopsy refusal will be comparable between the 2 arms.

5. Any bias resulting from TURPs conducted in BPH incident cases will be negligible.

Critical Assumption 1: ***Finasteride-induced PSA change results in a simple downward shift in the PSA distribution and therefore generally preserves the ranking of the affected participants.***

Monitoring plan

From previous studies in men with BPH, finasteride was known to reduce median PSA levels by 50% [47; 48]. At the time that the PCPT initiated, physicians prescribing finasteride 5 mg (PROSCAR) for the treatment of BPH in men in whom PSA testing was also being done to screen for prostate cancer were advised to double the measured PSA to adjust for this effect of finasteride. A similar reduction was assumed for the population of men in the PCPT, many of whom did not have BPH. Implicit in this assumption was that subjects developing prostate cancer would also have PSA reduced by 50% with finasteride.

In 1993, the clinical use of PSA was such that a PSA level > 4.0 ng/mL would prompt a prostate biopsy. However, due to the approximately 50% reduction of PSA with finasteride, if the laboratory- measured PSA values were used for the men on finasteride, a subject who on placebo would have a measured PSA value of 4.0 ng/mL would instead be measured and reported with a PSA value of ~2.0 ng/mL and a biopsy would not have been prompted. Thus, if unadjusted PSA values were used to prompt a biopsy in a man receiving finasteride, the fall in PSA produced by finasteride would reduce biopsy prompts and conceal a prostate cancer that would otherwise have been detected. This bias would make finasteride appear to reduce the prevalence of prostate cancer simply

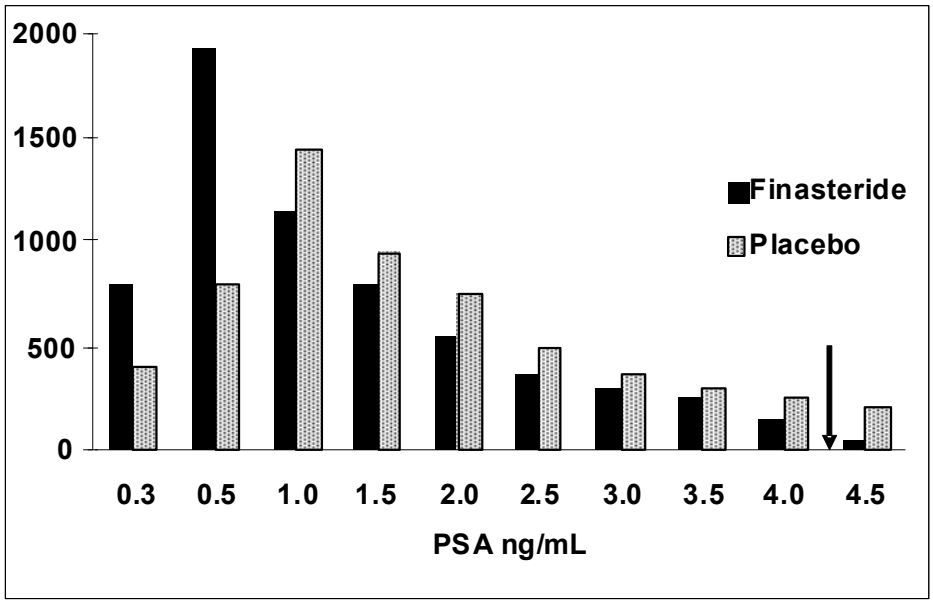
due to the differential biopsy rate and not due to cancer prevention. **This detection bias would favor finasteride.**

A solution for this potential bias due to PSA was to adjust PSA values in men on finasteride by a procedure referred to as *PSA indexing*. In Figure 1, below, a hypothetical distribution of PSA values for men on finasteride or placebo is presented. With the 50% reduction in PSA values, the finasteride distribution is shifted to the left. With this distribution, a certain percent of the men on the placebo arm will have a PSA value > 4.0 ng/mL and will be recommended to undergo a prostate biopsy while at the same cutpoint a substantially smaller percent of men on the finasteride arm will have a value > 4.0 ng/mL.

In Figure 2, below, the PSA values on the finasteride arm have been adjusted such that the same percent of men will have a PSA value > 4.0 ng/mL and thus be recommended for a biopsy. This adjusting, or indexing procedure, ensured, on an annual basis, a similar number of biopsy recommendations in both groups, and that the recommendations would be given to those with the highest PSA values.

Figure 1

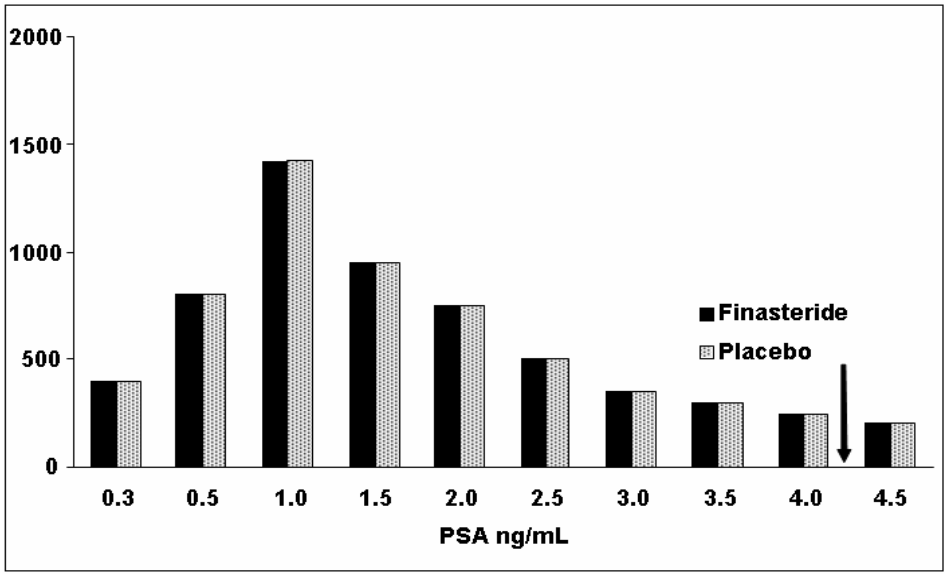
Theoretical PSA Distribution For Men on Placebo and Men on Finasteride Prior to Adjustment



Arrow reflects 4.0 ng/mL PSA upper limit of normal; prostate biopsy would be recommended in men with PSA values above this level.

Figure 2

Theoretical PSA Distribution for Men on Placebo and Men on Finasteride After Adjustment



Arrow reflects 4.0 ng/mL PSA upper limit of normal; prostate biopsy would be recommended in men with PSA values above this level.

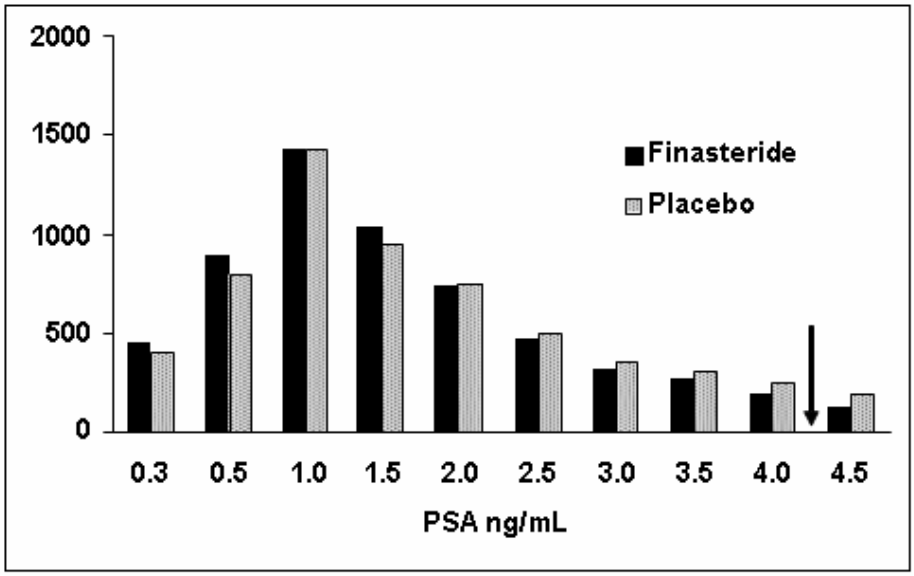
In order to monitor and index the PSA values, PSA was analyzed centrally. The results from the central laboratory were sent to the PCPT Statistical Center where they were adjusted based on the treatment assignment and whether or not study drug was being taken. At the outset of the study, the initial index for patients on finasteride was selected based on data from the studies completed prior to the start of the PCPT and was a multiplication factor of 2.0, the same multiplication factor recommended for men receiving finasteride 5 mg for the treatment of BPH who were also having PSA measured as part of prostate cancer screening [47; 48]. (For example, a laboratory-measured PSA of 1.4 ng/mL in a man in the finasteride arm was reported as a PSA of 2.8 ng/mL.)

With ongoing monitoring by the DSMC of the indexing value and the rates of biopsy recommendations in the 2 treatment arms during the PCPT, a trend of decreasing biopsy recommendations (due to both PSA and DRE) in the finasteride arm was detected. The distribution appeared more like that shown in Figure 3, below. To re-establish similar biopsy rates in the 2 treatment arms, the PSA indexing factor was changed from 2.0 to 2.3 at the participant's fourth year on study. However, while a change in the PSA multiplier had the desired effect of achieving better balance in the number of for-cause biopsies in the 2 treatment arms, there were still more biopsies conducted in men in the placebo group (for analyses that addresses this imbalance in the number of biopsies in the

2 treatment arms, see Sections 3.9.4.3 and 3.9.5). Further adjustment of the PSA indexing factor was not done, however, because of the concern that a further increase in this factor could result in biopsying an increasing number of men on finasteride who indeed may not have had cancer.

Figure 3

Theoretical PSA Distribution After 4 Years on Study:
Adjustment Using a PSA Indexing Value of 2.0



Arrow reflects 4.0 ng/mL PSA upper limit of normal; prostate biopsy would be recommended in men with PSA values above this level.

These assumptions formed the basis for the belief that PSA indexing in the finasteride arm would result in comparable groups of participants in each arm who have a PSA-prompted recommendation for a for-cause biopsy. (If a participant had a biopsy prompted by an elevated PSA and the result was negative for cancer, future biopsy recommendations were made if the PSA had risen 50% above the value that prompted the recommendation for the original biopsy or if the adjusted PSA value was > 10 ng/mL.) To determine whether the PSA indexing factor worked equally across all men on finasteride, we examined normalized rank plots for PSA for men in the 2 treatment groups. These plots were used to investigate whether finasteride "preserved the rank" of a man's PSA value when compared to all of the other men (e.g., if the man's baseline PSA was the highest in his treatment arm, did he retain the highest rank after finasteride administration, and if he was lowest, did he remain lowest?). This assessment was qualified by (1) the fact that an unknown proportion of participants will have a PSA that is modulated by physiological changes that are independent of finasteride, and (2) the

inherent variability in the PSA measurement. The assumption was that finasteride would, on average, reduce PSA level by 50%, but for an individual participant there is a range of how much the PSA value is reduced. If there were an imbalance with respect to certain participant characteristics, then an attempt would have been made to modify the PSA algorithm.

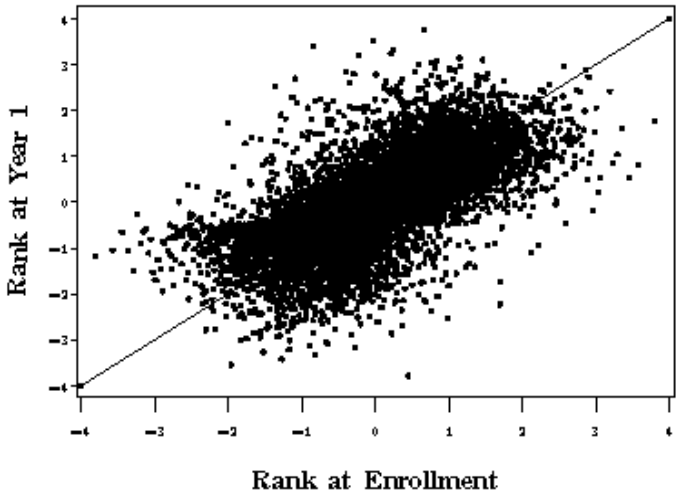
Monitoring results

We examined whether or not the above assumptions hold true by examining normalized rank plots for the finasteride and placebo groups (Figure 4, below). On the horizontal axis, the rank of the participant's PSA at baseline, with the lowest ranking PSAs representing the lowest absolute value of PSA; the vertical axis shows the ranking of PSAs after 1 year of treatment. For a perfect monotonic shift, all points would be on the 45-degree line. As one can see, even in the placebo group there is scatter around the 45-degree line, which is expected given physiologic changes and the variability in PSA measurement. The same general pattern for the finasteride group is seen but the scatter appears to be somewhat more pronounced. (Pearson correlation coefficient for placebo = 0.84, for finasteride = 0.67). This increase in scatter could be because the normal tissue in the smaller, finasteride-treated prostate produces less PSA but any tumor within the finasteride-treated prostate may produce PSA at a rate closer to that of tumors in the placebo arm (i.e., the appropriate PSA adjustment for men on finasteride with prostate cancer may be different than that for men on finasteride without prostate cancer). The scatter pattern is similar over subsequent years but with an increased scattering for both arms over time.

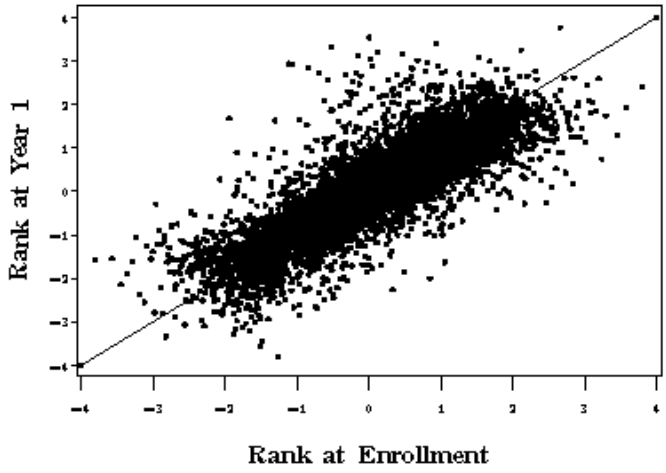
Figure 4

Rank Plots of PSA at Baseline vs. Year 1

Finasteride



Placebo



[57]

The DSMC was charged with deciding whether or not to modify the PSA algorithm over the duration of the PCPT if certain assumptions proved incorrect. The final PCPT study design attempted to ensure that the number of recommendations for a prostate biopsy was as equal as possible and that the number of men being prompted for a recommendation for a for-cause biopsy was as similar as possible in the 2 treatment groups. Accordingly, the PSA algorithm for adjusting PSA values in men on finasteride (i.e., multiply the measured PSA value by 2.0) was modified during the conduct of the PCPT. However, even with the use of PSA indexing it was still possible that the screening properties of PSA (i.e., sensitivity and specificity) could be affected by treatment with finasteride. A detailed analysis of the PCPT data to test the hypothesis that the effect of finasteride on PSA impacted the detection of prostate cancer, including high-grade prostate cancer, is presented in Section 3.9.4.1 of this document.

Critical Assumption 2: ***Finasteride does not affect the screening properties (sensitivity or specificity) of the digital rectal examination (DRE) or the prostate biopsy, including the transrectal ultrasonography (TRUS) used with the prostate biopsy***

Monitoring plan

This assumption was needed because while it was known that finasteride reduces the size of the prostate by approximately 20%, it was not known what influence this reduction in prostate volume had on the sensitivity and specificity of the diagnostic tests for prostate cancer, including the DRE and prostate biopsy. The validity of this assumption was investigated by comparing DRE results in the 2 treatment arms for all participants with for-cause biopsies. Analysis of prostatectomy samples at the end of the study provided additional data on the sensitivity and specificity of prostate needle biopsy in the presence and absence of finasteride.

Monitoring results

The results based on the monitoring plan above are presented in the body of this document (see Section 3.9.4.2). Additional information pertaining to the impact of prostate volume reduction due to finasteride on the results of prostate biopsy has been extensively evaluated. For example, the chance that a standard technique for prostate biopsy will identify a prostate cancer is directly proportional to the ratio of tumor volume to prostate gland volume as well as the number of biopsy cores [74; 75; 76; 77]. With a reduced gland volume for men on finasteride, and an equal number of biopsy cores (a 6-core, or sextant, biopsy was the recommended technique during the time the PCPT was developed and for most of its course[†]), a larger proportion of the prostate would be sampled in finasteride-treated men relative to placebo-treated men (i.e., there would be increased *sampling density* in the finasteride group). With this increased sampling density, there was an increased chance to detect prostate cancer and, in particular, high-grade prostate cancer. The manner by which this can occur can be illustrated as follows:

- Assume that 2 prostates both have the same volume of cancer: 1 cc of Gleason grade 3 cancer and 0.5 cc of Gleason grade 4 cancer. If the prostate were removed and examined in its whole, the final score would be Gleason grade 3+4 (Gleason score 7) prostate cancer. If we assume that one prostate is 40cc in volume and the other is 20% smaller (32cc) due to the action of finasteride, if a total of 6 biopsy cores were obtained from each prostate, biopsy of the smaller prostate would be more likely to find cancer since a larger proportion (1.5cc/32cc vs. 1.5cc/40cc) of the prostate would be sampled.

- Additionally, in the smaller prostate, there would be a greater likelihood that at least 1 biopsy needle would strike the Gleason grade 4 cancer, ensuring that the Gleason score on biopsy would be 7. This is in comparison to the larger prostate in which the Gleason grade 4 cancer would more likely be missed (i.e., not sampled), leading to a lower Gleason score (3+3, or 6, instead of 7 in this example). As a result, after finasteride treatment and with a smaller prostate, there would be a greater likelihood of detecting cancer and a greater likelihood of assigning a higher, more accurate, Gleason score.

[†] With growing evidence that laterally-directed biopsies better sampled the peripheral zone of the prostate, which is where most prostate cancers develop, the PCPT study sites were instructed to direct biopsy needles laterally in a manner mirroring then standard U.S. practice [78]. This recommended change in biopsy technique was sent to the PCPT clinical sites in November 2000, prior to when the majority of EOS biopsies had been conducted.

This potential bias was against finasteride. This hypothetical effect (unsupported by evidence in 1992) has since proved to be correct [79; 74]. Evidence suggests that the standard 6-core (sextant) biopsy of the prostate used at the time the PCPT initiated is more likely to detect prostate cancer in smaller glands, and given that cancer is detected, more likely to detect high-grade disease. In the Gleason scoring system used in the PCPT, any amount of high-grade disease found on needle biopsy, no matter how small, resulted in the assignment of high-grade cancer [27]. Prostate volume was estimated by transrectal ultrasonography (TRUS). Table 1, below, illustrates the significant, 25% difference in median prostate volume in the 2 treatment groups in the PCPT and shows that the proportion of men who had 6 cores obtained was similar in both treatment groups. The effect of prostate volume on Gleason score could be examined by comparing the Gleason score at biopsy (the sample) to that at prostatectomy (the whole gland). By looking at the change in score, how well the biopsy performed in predicting the final Gleason score could be examined. A detailed analysis of the PCPT data to test the hypothesis that the effect of finasteride on prostate volume impacted the detection of prostate cancer, including high-grade prostate cancer, is presented in Section 3.9.4.2 of this document.

Table 1

Prostate Volume and Number of Biopsy Cores

	Finasteride	Placebo
Prostate volume (cm^3) median	25.1	33.5
Number of biopsy cores		
Less than 6	1.9%	2.1%
Exactly 6	80.1%	79.3%
Greater than 6	18.0%	18.6%

[57]

Critical Assumption 3: ***The procedures used to assess adherence of individual participants at each visit during which a PSA is obtained are sufficiently sensitive and reliable to detect degrees of non-adherence affecting PSA level interpretation.***

Monitoring Plan

The study design and sample size calculation took into account *non-adherence*, defined as men randomized to finasteride who did not take their study drug, and *contamination*, defined as men randomized to placebo who took finasteride outside of the study, effects that are an added source of bias that can dampen the estimate of the true difference between treatment groups.

The reporting of treatment-adjusted PSA levels depended on the participant's known treatment status (i.e., whether or not he was taken off treatment and was no longer taking the study drug), and, if categorized as on treatment, that he was actually taking the study drug to which he was assigned. If the pill count measures did not accurately reflect if a participant was adherent to taking the study drug, then men on finasteride who were not actually taking study drug (when they said they were) would have a reported PSA level that had been adjusted (upwards) inappropriately. The result would be that more men in the finasteride arm would be prompted for a biopsy than should have been. **This would result in a bias against finasteride.**

As a result of contamination, men in the placebo arm who were taking finasteride outside of the study would have a reduced PSA level. The Statistical Center would not be aware of this and the PSA level received from the Central Laboratory would not be adjusted (upwards) when it should have been. As a result, more men in the placebo group would have a reported PSA level that was reduced (due to the action of finasteride). The result would be that fewer men in the placebo arm would be prompted for a biopsy than should have been. **This would result in a bias against finasteride.**

Serum dihydrotestosterone (DHT) is an excellent marker for finasteride use, as DHT levels are substantially reduced in a man on finasteride. DHT levels were measured in a 5% random sample of participants from whom serum had been collected and stored for PSA measurements. This biomarker was then compared to the results from the biannual pill counts and allowed for assessment of whether the pill count was an accurate measure of adherence. An accurate measure of adherence was necessary for the appropriate PSA adjustment to be made.

The DSMC monitored participant adherence in a *post-hoc* analysis by examining DHT levels and changes in DHT as well as by comparing DHT levels to pill counts. The PCPT statistical design assumed a non-adherence rate of 14% and a contamination rate of 5%, and these assumptions proved to be accurate: the final non-adherence rate was 12.6% and the final contamination rate was 4.9%. As stated above, the treatment effect of finasteride vs. placebo would potentially be reduced by deviations from protocol-assigned treatment.

Monitoring results

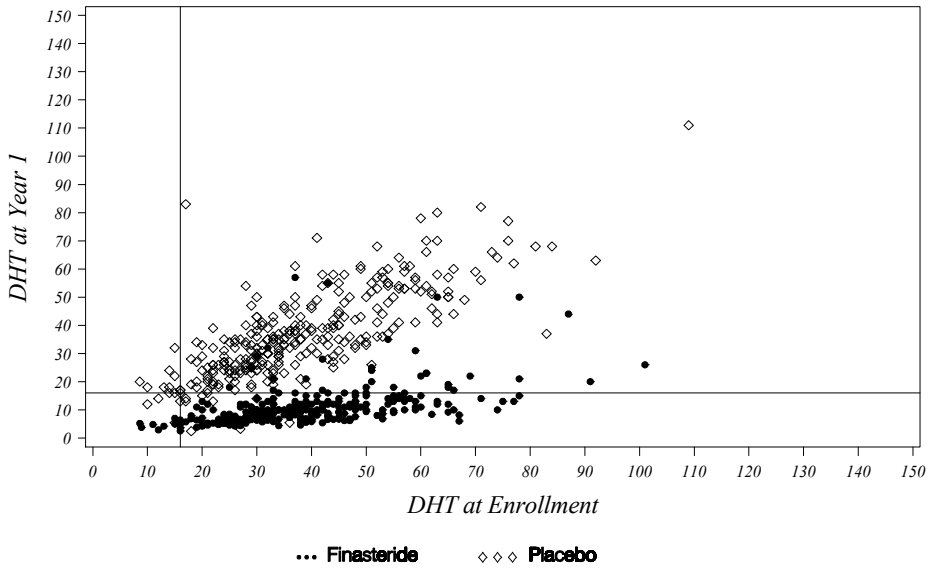
A DHT cutpoint for measuring adherence, based on the lower 5% distribution of the DHT level of all men at baseline, was determined (16 ng/dL). A participant on placebo was considered to have contaminated the placebo arm if his DHT level fell to ≤16 ng/dL and a participant on finasteride was considered to have been non-adherent if his DHT was >16 ng/dL.

DHT levels at baseline vs. the first year of follow-up are presented in Figure 5, below, and in Table 2, below. A cross-classification of pill counts and DHT levels for men on finasteride is presented in Table 3, below. There was agreement between the 2 measures in over 87% of the times both pill count and DHT level were available. The pill count threshold proved to perform as well as more complicated adherence rules that utilize a biomarker [80].

As state above, the actual non-adherence rate in the finasteride arm (12.6%) and contamination rate in the placebo arm (4.9%) were close to those assumed in the PCPT statistical design. This means that these 2 sources of bias for prompts (due to PSA) for a biopsy recommendation – more prompts in 12.6% of the men on the finasteride arm due to non-adherence and fewer prompts in 4.9% of the men on the placebo arm due to contamination – were operational in the PCPT.

Figure 5

DHT (ng/dL) at Baseline vs. Year 1



[57]

Table 2

DHT (ng/dL) at Baseline vs. Follow-up Year

		Finasteride		Placebo	
Baseline	Year 1	Number of Men		Number of Men	
≤ 16	≤ 16	21		11	
	> 16	0		14	
> 16	≤ 16	361		14	(2.9%)†
	> 16	47	(10.9%)‡	441	
Total		429		480	
Baseline	Year 6				
≤ 16	≤ 16	9		8	
	> 16	1		4	
> 16	≤ 16	173		13	(4.9%)†
	> 16	26	(12.4%)‡	241	
Total		209		266	

† Percent of men on the placebo arm who were categorized as taking finasteride outside of the study (contamination)
‡ Percent of men on the finasteride arm who were categorized as on treatment but were not taking their study drug (non-adherence)

[57]

Table 3

DHT (ng/dL) vs. Pill Count
Finasteride Arm Only
All Years Combined
(N=2333)

	Pill count < 80%	Pill count ≥ 80%
	Number (%) of men	Number (%) of men
DHT ≤16	75 (3.2%)†	1994 (85.5%)‡
DHT >16	38 (1.6%)‡	226 (9.7%)†

† Disagreement
‡ Agreement

[57]

Critical Assumption #4: ***Factors affecting loss to for-cause and EOS biopsies are similar in both treatment arms so that the groups of participants who do not have biopsies due to death, loss to follow-up, and biopsy refusal will be comparable between the 2 arms.***

Monitoring plan

In addition to attempting to equalize the number of for-cause biopsies, and thus chances for prostate cancer detection in each group, by adjusting PSA values in the finasteride group, an important consideration was whether or not men being prompted for a recommendation for a prostate biopsy were comparable in the 2 treatment groups. The men prompted for a biopsy were compared in terms of reason for biopsy prompt as well as baseline characteristics, including baseline PSA, age, race, and American Urological Association (AUA) symptom score. The reasons for not having a prostate biopsy were also compared in each treatment group.

Monitoring results

The characteristics of men recommended for a for-cause biopsy are presented in Table 4, below. Figure 6, below, shows the number of for-cause biopsy recommendations over time and Figure 7, below, presents the number of for-cause biopsies done by year.

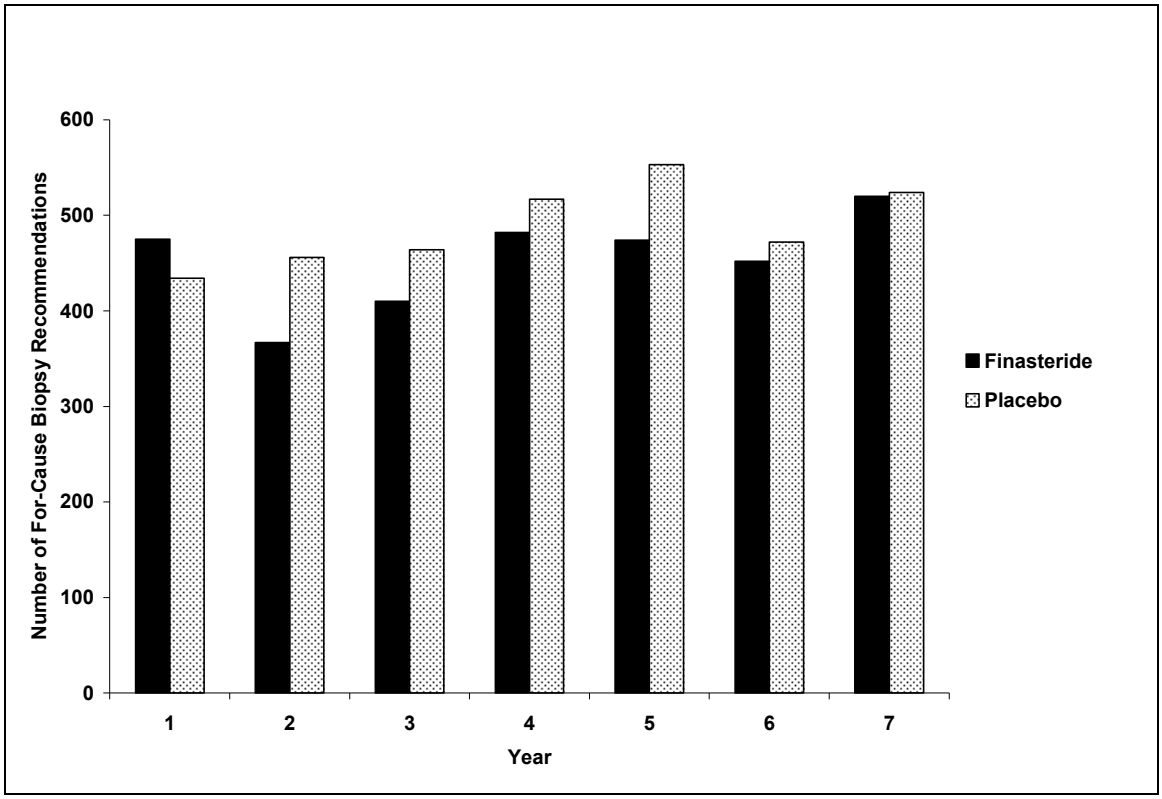
Table 4

Characteristics of Participants With For-Cause Biopsy Recommendation
As of February, 2003

	Finasteride (n=2094)		Placebo (n=2300)	
Age (at randomization)				
Median	63		63	
Range	55 - 85		55 - 83	
55-59	534	(25.5%)	601	(26.1%)
60-64	667	(31.8%)	710	(30.9%)
65+	893	(42.6%)	989	(43.0%)
Race				
White (Non-Hispanic)	1927	(92.0%)	2130	(92.6%)
Black (Non-Hispanic)	69	(3.3%)	85	(3.7%)
Hispanic	71	(3.4%)	50	(2.6%)
Asian/Pacific Islander	20	(1.0%)	17	(0.7%)
Other/Unknown	7	(0.3%)	9	(0.4%)
Baseline PSA				
Median	1.5		1.6	
≤ 1.0	614	(29.3%)	699	(30.4%)
1.1 - 2.0	830	(39.6%)	835	(36.3%)
2.1 - 3.0	650	(31.0%)	765	(33.3%)
3.1 - 4.0	0	(0.0%)	1	(0.04%)
Prostate Cancer in First-Degree Relative				
Yes	364	(17.4%)	378	(16.4%)
Reason Biopsy Recommended				
PSA				
Never	1002	(47.9%)	1152	(50.1%)
Ever	1092	(52.1%)	1148	(49.9%)
DRE				
Never	903	(43.1%)	948	(41.2%)
Ever	1191	(56.9%)	1352	(58.8%)
Baseline AUA Symptom Score				
Median	6.0		6.0	

Figure 6

Number of For-Cause Biopsy Recommendations Over Time



[57]

Figure 6, above, demonstrates that in the second and third years there was a decreasing number of biopsy recommendations for men receiving finasteride. (Because this figure shows annual biopsy recommendations, a participant may be represented more than once.) Had the PSA index not been changed at Year 4, there would have been 222 fewer biopsy recommendations in the finasteride study group. The number of biopsy recommendations averaged 471 per arm per year with a low of 367 and a high of 553. The total number of biopsy recommendations, including men at Year 7 (i.e., recommendation for the EOS biopsy) was 3309 recommendations in 2122 men on finasteride and 3544 biopsy recommendations in 2348 men on placebo (p=0.29 for between-group difference in total number of biopsy recommendations; p=0.10 for between-group difference in number of men).

For-cause and EOS biopsy refusals

While an attempt was made to equalize the total number of for-cause biopsy recommendations in the 2 treatment arms, another potential source of bias could be a differential rate of for-cause biopsy refusal and different reasons for biopsy refusal in the 2 treatment arms. It was important that the groups of participants who had and did not have for-cause biopsies should be as comparable as possible, and that the factors affecting the loss of for-cause biopsies be similar in the 2 groups so as not to lose participants' endpoint data differentially. It was also important that the final EOS biopsy rate be similar between the 2 treatment arms; this was particularly important because if there had been an inequality in the for-cause biopsy rate, then the EOS biopsy became the opportunity to equalize the chance for prostate cancer detection as it was the combined rate of cancer diagnosis (total prostate cancers based on for-cause plus EOS biopsies) that contributed to the primary endpoint of prostate cancer prevalence over 7 years.

In Tables 5 and 6, below, the reasons that for-cause and EOS biopsies, respectively, may not have been done included participant (and primary care physician) refusal, death, and loss of participant to follow-up. The overall for-cause biopsy completion rates were 49.0% on finasteride and 52.3% on placebo. (For biopsies conducted at Year 7 of the study that, in general, were considered EOS biopsies and not for-cause biopsies, there were additional reasons for a biopsy not being done, including site error and a participant having moved or died).

The overall endpoint determination ascertainment rate, which encompasses ascertainment of for-cause and EOS biopsies, was 59.6% in the finasteride group and 63.0% in the placebo group. While the overall ascertainment rate was similar to the 60% rate that was estimated in planning the PCPT (see Appendix 4), the reasons for non-ascertainment were different from what had originally been anticipated.

The reasons that for-cause biopsies were refused were equally distributed in the 2 treatment arms. At the onset of the study, there had been concern that for participants on finasteride, an additional repeat PSA test outside of the study would be done. Since such PSA values would not be adjusted for the effect of finasteride on PSA, they could have appeared to be in the normal range, leading to a 'negative repeat test' following an elevated *adjusted* PSA. This does not appear to have happened as the number of biopsy refusals due to a “Negative Repeat Test,” due to either a repeat PSA that no longer was (or appeared to be) elevated or a repeat DRE that no longer was abnormal, is equal in the two treatment arms.

For the entire randomized population, the loss to follow-up rate was less than expected (7.2% actual vs. 15% expected over 7 years) and the PCPT study population had a lower death rate than originally estimated (6.2% actual vs. 20% expected over 7 years). The EOS biopsy refusal rate was substantially higher than originally estimated (20.0% actual vs. 5% expected). These EOS biopsy refusals include not just participant refusal but also biopsies that could not be done because of a co-existing condition (e.g., a condition requiring the use of warfarin) or because of a personal physician recommendation against biopsy due to increased age (median age at participants' 7-year anniversary in the study was 69 years).

Table 5

Reasons For-Cause Biopsy Not Done

	Finasteride	Placebo
Number of participants ever refused	1034	1083
Number of biopsies refused†	1470	1529
Participant refusal	309 (21.0%)	275 (18.0%)
Negative repeat screening test	309 (21.0%)	306 (20.0%)
PSA and DRE not abnormal	203 (13.8%)	194 (12.7%)
Previous negative biopsy	166 (11.3%)	190 (12.4%)
MD recommended against	325 (22.1%)	385 (25.2%)
Intercurrent illness	34 (2.3%)	36 (2.4%)
Other/Unknown	124 (7.7%)	143 (8.0%)

† May be more than one biopsy recommendation per participant

[57]

Table 6

Reasons EOS Biopsy Not Done

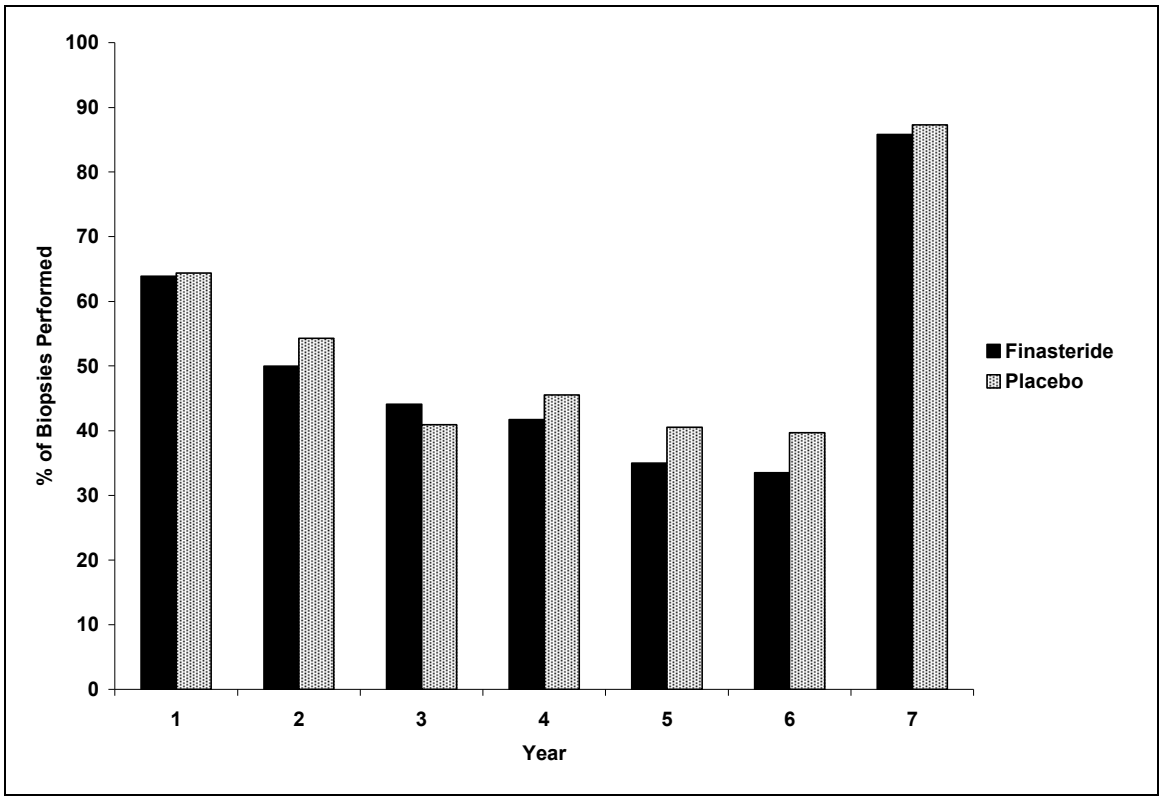
	Number of Biopsies	
	Finasteride	Placebo
Potential biopsies not done[†]	3290	3016
Lost to follow-up	703	657
Participant death	599	573
Refusal:		
Participant refusal	1401	1183
Negative repeat test	0	1
PSA + DRE not abnormal	2	4
Previous negative biopsy	6	10
MD recommended against	135	167
Intercurrent illness	184	175
Unable to complete procedure[‡]	10	8
Site error	8	11
Participant moved	16	16
Unknown	178	171

[†] Includes 48 participants in the finasteride group and 40 participants in the placebo group whose EOS biopsy was performed greater than 90 days after a participant's 7-year anniversary and hence not included in the primary efficacy analysis.
[‡] Due to equipment malfunction, participant inability to tolerate procedure, etc.

[57]

Figure 7

Percent of Recommendations For For-Cause Biopsies That Were Performed Over Time



[57]

<u>Critical Assumption 5</u>: ***Any bias resulting from transurethral resections of the prostate (TURPs) in benign prostatic hyperplasia (BPH) incident cases will be negligible.***

Transurethral resection of the prostate (TURP) is a surgical treatment for benign prostatic hyperplasia (BPH). Because in the procedure prostate tissue is removed and pathologically examined, a TURP provides the potential for prostate cancer detection. Because finasteride is a treatment for BPH that reduces the need for TURP, it was expected that fewer men in the finasteride arm would undergo a TURP during the PCPT, resulting in fewer chances for prostate cancer detection due to the procedure. **This is a potential source of bias in favor of finasteride.**

Monitoring plan

Finasteride has been shown to be effective in the treatment of BPH. If it should also be preventative for BPH, then more participants in the placebo than in the finasteride arm would have a TURP, which could lead to incidental discovery of more prostate cancers in the placebo arm. It is for this reason that trial entry criteria excluded men with significant

urinary obstructive symptoms. The TURP and resultant prostate cancers that were found due to TURP in the 2 study arms over time were to be presented to and monitored by the DSMC.

Monitoring results

In Table 7, below, the numbers of TURPs and prostate cancers detected as a result of the procedure are presented. Almost twice the number of men on placebo had a TURP compared to men on finasteride; however, this increased number of TURPs detected just 3 more prostate cancers in the placebo group than in the finasteride group – a small number compared to the overall number of prostate cancers detected.

Table 7

Number of Transurethral Resections of the Prostate (TURPs) and Prostate Cancer Detected

	Finasteride	Placebo
Number of participants with a TURP	97	182
Number of prostate cancers found as a result of the TURP	15	18

During the course of the PCPT, the most common treatment for BPH changed from an emphasis on surgical management with TURP to a predominantly pharmacologic approach, most often using alpha-adrenergic receptor blockers (e.g., terazosin, doxazosin). The result was that there were fewer TURPs performed during the PCPT than expected, with < 1.6 % of all prostate cancers diagnosed from a TURP in either treatment arm. Thus, this potential source of prostate cancer detection bias did not prove operational in the PCPT.

Summary and Conclusions Regarding Critical Assumptions

Multiple potential sources of bias were considered in the design of the PCPT. Because a critical mechanism for prostate cancer detection was a prompt for a recommendation for a prostate biopsy due to an elevated annual PSA test and/or abnormal annual DRE, it was recognized that the potential for bias due to the effects of finasteride on PSA or DRE might result in an imbalance in the number of for-cause biopsies performed, although the direction of such an imbalance was not known. With the potential for an imbalance in for-cause biopsies, the chance to detect prostate cancer could be biased. Thus, during the course of the PCPT, both the number and the reasons for prompts for a recommendation for a prostate biopsy were monitored by the DSMC. Nonetheless, while it was examined whether or not the men prompted for a prostate biopsy appeared comparable in the 2

treatment arms, and while the PSA indexing algorithm was adjusted (from 2.0 to 2.3) during the trial in an attempt to equalize the number of for-cause biopsies, it was not possible to ensure that the 2 treatment groups were fully comparable with respect to these factors. This was especially true for the prompts for a recommendation for a prostate biopsy based on the DRE, for which there was no adjustment factor that could be employed.

Because of the design of the PCPT and the potential for bias, it is imperative that the results based solely on the for-cause biopsies be interpreted with caution. While critical assumptions were monitored and changes made to the study design to minimize the effect of potential biases (e.g., by changing the PSA indexing algorithm during the trial), it was not possible to entirely correct for all biases, including potential bias due to a 25% between-group, treatment-related median difference in prostate volume. The protocol-specified EOS biopsy, while not prompted by commonly-applied measures used in clinical practice (such as elevated PSA or abnormal DRE), was considered to be the optimal way to (1) correct for most potential biases that might influence results based solely on for-cause biopsies and (2) meet the primary study objective. While an endpoint of period prevalence that relied on results of EOS biopsies may be considered less related to clinical practice than an endpoint that relied only on disease incidence generated from biopsies prompted by commonly-applied clinical criteria (e.g., elevated PSA or abnormal DRE), the inclusion of the EOS biopsies in the primary endpoint provided the best evidence to test the hypothesis as to whether finasteride affected the development of prostate cancer.

Details regarding how well the critical assumptions incorporated into the PCPT study design have been met are provided in this Appendix. The success of the PCPT depended on these assumptions and the constant scrutiny by the DSMC to monitor for potential biases and design assumptions. Monitoring was possible due to central laboratory measurement of PSA and DHT and detailed data collection that allowed for appropriate analyses to be provided to the DSMC. While monitoring by the DSMC could not eliminate all potential biases, it was necessary, and effectively used, to minimize them. (For a detailed description of the totality of the different biases, including statistical methods to address them, see the analyses by Redman et al. [13], which are summarized in Section 3.9.5.)

Appendix 4

Assumptions Used in Determining the Sample Size of the Prostate Cancer Prevention Trial

The Prostate Cancer Prevention Trial (PCPT) planned for randomization (1:1) of 18,000 men to finasteride 5 mg or placebo, which provided for 92.1% power (type I error of 5%, 2-sided) to detect an adjusted between-group difference of 24.7% in the primary endpoint of period prevalence of prostate cancer over 7 years [72]. The calculations that led to this planned sample size were based on the following assumptions:

a) A conservative estimate of 6% prevalence of diagnosed prostate cancer in the placebo group, based on data from Cooner and Corder [50; 51].

b) A reduction of 25% in the period prevalence of prostate cancer (primary endpoint) was determined to be of clinical and public health interest.

c) The proportion of men in the finasteride group who stopped taking study drug (i.e., the drop-out, or non-adherence, rate) was estimated to be 14%. The proportion of men in the placebo group who took finasteride outside the study (i.e., the drop-in, or contamination, rate), which included men who took finasteride for treatment of BPH despite this being actively discouraged per protocol, was estimated to be 5%. Both assumptions were based on estimates derived from the Carotene and Retinol Efficacy Trial (CARET), a primary prevention study using vitamin A to prevent lung cancer [81].

d) The proportion of men with an endpoint determination (i.e., known prostate cancer status at 7 years), which was defined as a diagnosis of prostate cancer during the 7-year study or a negative end-of-study (EOS) biopsy at 7 years, was estimated to be 60%. This proportion was based on an expected 40% of men without an endpoint determination due to the following reasons:

- Estimated 20% mortality (exclusive of prostate cancer), based on the predicted median age of 63 years at study entry
- Additional 15% loss to follow-up for any reason other than death (based on the experience in the CARET)
- Additional 5% biopsy refusal rate, based on the belief that most men, particularly those who reached their study 7-year milestone, would be motivated to find out whether or not they had prostate cancer.

If needed, adjustment to the sample size during the trial was possible based on monitoring of design assumptions by the DSMC. Once the PCPT was unblinded and results available, it was apparent that the period prevalence of prostate cancer in the placebo group was substantially higher than projected (24.4% vs. 6%), in large part due to the use of the EOS biopsy that increased the amount of prostate cancer that otherwise would not have been detected. The relative risk reduction with finasteride was as projected (25%), the contamination and non-adherence rates were slightly less than projected, and the percent of men with an endpoint determination was similar to that projected (60%).

Appendix 5

Distribution of Gleason Scores at Time of Diagnosis
MITT Population

Gleason Score	All Cancers		Cancers Diagnosed in Biopsies Performed For Cause[†]		Cancers Diagnosed in End-of-Study Biopsies[‡]	
	Finasteride Group (N[§]=9423)	Placebo Group (N[§]=9457)	Finasteride Group (N[§]=9423)	Placebo Group (N[§]=9457)	Finasteride Group (N[§]=9423)	Placebo Group (N[§]=9457)
	n[‖] (%)	n[‖] (%)	n[‖] (%)	n[‖] (%)	n[‖] (%)	n[‖] (%)
2	4 (0.0)	8 (0.1)	3 (0.0)	7 (0.1)	1 (0.0)	1 (0.0)
3	1 (0.0)	9 (0.1)	0 (0.0)	7 (0.1)	1 (0.0)	2 (0.0)
4	16 (0.2)	37 (0.4)	7 (0.1)	22 (0.2)	9 (0.1)	15 (0.2)
5	76 (0.8)	129 (1.4)	38 (0.4)	60 (0.6)	38 (0.4)	69 (0.7)
6	488 (5.2)	855 (9.0)	186 (2.0)	319 (3.4)	302 (3.2)	536 (5.7)
7	228 (2.4)	216 (2.3)	128 (1.4)	112 (1.2)	100 (1.1)	104 (1.1)
8	52 (0.6)	27 (0.3)	35 (0.4)	21 (0.2)	17 (0.2)	6 (0.1)
9	39 (0.4)	30 (0.3)	31 (0.3)	25 (0.3)	8 (0.1)	5 (0.1)
10	9 (0.1)	6 (0.1)	9 (0.1)	5 (0.1)	0 (0.0)	1 (0.0)
2 to 6	585 (6.2)	1038 (11.0)	234 (2.5)	415 (4.4)	351 (3.7)	623 (6.6)
7, 8, 9 or 10	328 (3.5)	279 (3.0)	203 (2.2)	163 (1.7)	125 (1.3)	116 (1.2)
8,9 or 10	100 (1.1)	63 (0.7)	75 (0.8)	51 (0.5)	25 (0.3)	12 (0.1)
Not graded	66 (0.7)	90 (1.0)	45 (0.5)	62 (0.7)	21 (0.2)	28 (0.3)
All cancers	979 (10.4)	1407 (14.9)	482 (5.1)	640 (6.8)	497 (5.3)	767 (8.1)

[†] Includes cancers diagnosed in biopsies performed for cause either during the study or at the end of the study and those diagnosed after interim procedures.
[‡] Excludes cancers diagnosed in biopsies performed for cause at the end of the study.
[§] N = Number of MITT participants in the treatment group.
[‖] n = Number of participants with the corresponding Gleason score.

Appendix 6

Number (%) of Participants With Specific Adverse Experiences Meeting
SWOG Toxicity Criteria and Confirmed As Drug-Related
By the SWOG Operations Office
Incidence ≥4 Participants in One or More Treatment Groups
All Participants Randomized

	Finasteride (N = 9423)		Placebo (N = 9459)	
	n	(%)	n	(%)
Participants Confirmed as Having One Or More Drug-Related Adverse Experiences	282	(3.0)	306	(3.2)
Cardiac Disorders	**113**	**(1.2)**	**118**	**(1.2)**
Arrhythmia	19	(0.2)	15	(0.2)
Cardiac Disorder	6	(0.1)	5	(0.1)
Cardiac Failure Congestive	5	(0.1)	5	(0.1)
Myocardial Ischaemia	81	(0.9)	91	(1.0)
Eye Disorders	**5**	**(0.1)**	**2**	**(<0.1)**
Gastrointestinal Disorders	**7**	**(0.1)**	**12**	**(0.1)**
Gastritis	2	(<0.1)	4	(<0.1)
General Disorders And Administration Site Conditions	**4**	**(<0.1)**	**2**	**(<0.1)**
Hepatobiliary Disorders	**3**	**(<0.1)**	**9**	**(0.1)**
Infections And Infestations	**9**	**(0.1)**	**17**	**(0.2)**
Infection	6	(0.1)	10	(0.1)
Urinary Tract Infection	0	(0)	4	(<0.1)
Investigations	**6**	**(0.1)**	**5**	**(0.1)**
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**62**	**(0.1)**	**61**	**(0.1)**
Bladder Cancer	2	(<0.1)	8	(0.1)
Colorectal Cancer	11	(0.1)	10	(0.1)
Hepatic Neoplasm Malignant	4	(<0.1)	2	(<0.1)
Lung Neoplasm Malignant	8	(0.1)	11	(0.1)
Non-Small Cell Lung Cancer	8	(0.1)	5	(0.1)
Small Cell Lung Cancer Stage Unspecified	4	(<0.1)	5	(0.1)
Nervous System Disorders	**25**	**(0.3)**	**33**	**(0.3)**
Cerebrovascular Disorder	15	(0.2)	24	(0.3)
Multiple Sclerosis	5	(0.1)	1	(<0.1)
Nervous System Disorder	0	(0)	4	(<0.1)

Number (%) of Participants With Specific Adverse Experiences Meeting SWOG Toxicity Criteria and Confirmed As Drug-Related By the SWOG Operations Office
Incidence ≥4 Participants in One or More Treatment Groups
All Participants Randomized (Cont.)

	Finasteride (N = 9423)		Placebo (N = 9459)	
	n	(%)	n	(%)
Psychiatric Disorders	**5**	**(0.1)**	**3**	**(<0.1)**
Loss Of Libido	4	(<0.1)	2	(<0.1)
Renal And Urinary Disorders	**4**	**(<0.1)**	**5**	**(0.1)**
Respiratory, Thoracic And Mediastinal Disorders	**8**	**(0.1)**	**7**	**(0.1)**
Pulmonary Fibrosis	2	(<0.1)	4	(<0.1)
Skin And Subcutaneous Tissue Disorders	**2**	**(<0.1)**	**6**	**(0.1)**
Urticaria	2	(<0.1)	6	(0.1)
Vascular Disorders	**31**	**(0.3)**	**26**	**(0.3)**
Aneurysm	5	(0.1)	3	(<0.1)
Haemorrhage	2	(<0.1)	4	(<0.1)
Hypertension	11	(0.1)	7	(0.1)
Thrombophlebitis	12	(0.1)	11	(0.1)

Although a participant may have had two or more adverse experiences, he is counted only once within a category. The same participant may appear in different categories.

Appendix 7

Sensitivity of Prostate-Specific Antigen (PSA) for Detection of Prostate Cancer Sensitivity of PSA for Detection of Prostate Cancer Overall, Gleason Score ≥ 7 Cancer, and Gleason Score ≥ 8 Cancer For Standard Cutoffs of PSA on Placebo and For Cutoffs on Finasteride Chosen to Match Specificities of PSA on Placebo (From Thompson et al., 2006) [9]

PSA Placebo Cutoff (ng/mL)	PSA Finasteride (unadjusted)	Specificity Placebo and Finasteride†	Sensitivity Placebo	95% CI Sensitivity Placebo	Sensitivity Finasteride	95% CI Sensitivity Finasteride
Prostate cancer vs. no prostate cancer						
1.0	0.4	40.8	81.8	(79.5, 84.1)	86.8	(84.3, 89.3)
1.5	0.6	59.0	67.0	(64.2, 69.8)	77.3	(74.2, 80.4)
2.0	0.9	71.2	53.5	(50.6, 56.4)	66.0	(62.5, 69.5)
2.5	1.1	80.0	42.8	(39.9, 45.7)	56.8	(53.1, 60.5)
3.0	1.2	85.4	35.0	(32.2, 37.8)	52.2	(48.5, 55.9)
4.0	1.6	92.7	24.0	(21.5, 26.5)	37.8	(34.2, 41.4)
6.0	2.8	98.1	5.1	(3.8, 6.4)	13.8	(11.2, 16.4)
8.0	3.7	99.2	2.0	(1.2, 2.8)	6.6	(4.8, 8.4)
10.0	5.6	99.6	0.8	(0.3, 1.3)	2.9	(1.7, 4.1)
Gleason score ≥ 7 cancer vs. Gleason score ≤ 6 or no prostate cancer						
1.0	0.4	37.3	92.1	(88.7, 95.5)	95.5	(93.0, 98.0)
1.5	0.6	55.2	83.8	(79.1, 88.5)	90.9	(87.4, 94.4)
2.0	0.9	67.9	75.0	(69.5, 80.5)	79.5	(74.6, 84.4)
2.5	1.1	77.2	66.7	(60.7, 72.7)	72.0	(66.6, 77.4)
3.0	1.2	82.9	56.7	(50.4, 63.0)	67.8	(62.2, 73.4)
4.0	1.6	90.5	39.2	(33.0, 45.4)	53.0	(47.0, 59.0)
6.0	3.0	97.9	11.7	(7.6, 15.8)	19.3	(14.5, 24.1)
8.0	4.1	99.1	4.2	(1.7, 6.7)	9.5	(6.0, 13.0)
10.0	6.5	99.6	1.7	(0.1, 3.3)	4.2	(1.8, 6.6)
Gleason score ≥ 8 cancer vs. Gleason score ≤ 7 or no prostate cancer						
1.0	0.4	36.3	94.5	(88.5, 100.5)	96.3	(92.2, 100.4)
1.5	0.6	53.8	89.1	(80.9, 97.3)	96.3	(92.2, 100.4)
2.0	0.9	66.4	85.5	(76.2, 94.8)	91.4	(85.3, 97.5)
2.5	1.1	75.7	78.2	(67.3, 89.1)	87.7	(80.5, 94.9)
3.0	1.2	81.5	67.3	(54.9, 79.7)	86.4	(78.9, 93.9)
4.0	1.7	89.5	49.1	(35.9, 62.3)	64.2	(53.8, 74.6)
6.0	3.2	97.7	25.5	(14.0, 37.0)	22.2	(13.1, 31.3)
8.0	4.3	99.0	9.1	(1.5, 16.7)	13.6	(6.1, 21.1)

† Confidence intervals for specificities were on average within ± 0.9% (largest ± 1.5%) from the estimates reported in the table for both finasteride and placebo

Appendix 8

Sensitivity and Specificity of Digital Rectal Examination for Detection of Prostate Cancer
Stratified by Increased Prostate-Specific Antigen (PSA) at DRE
(From Thompson et al., 2007) [10]

	% Sensitivity (Number/Total Number)			% Specificity (Number/Total Number)		
Outcome	Finasteride	Placebo	P-value	Finasteride	Placebo	P-value
Increased PSA at biopsy (adjusted greater than 4.0 ng/mL):						
Prostate Ca	16.9 (39/231)	11.2 (30/267)	0.090	90.2 (212/235)	92.5 (272/294)	0.35
Gleason 7 or higher	22.1 (28/127)	17.0 (16/94)	0.40	90.1 (299/332)	92.2 (427/463)	0.31
Gleason 8 or higher	40.8 (20/49)	22.2 (6/27)	0.13	90.0 (369/410)	91.3 (484/530)	0.50
PSA not increased at biopsy (adjusted 4.0 ng/mL or less):						
Prostate Ca	23.5 (109/464)	18.4 (155/844)	0.031	91.8 (3,351/3,649)	92.0 (3,411/3,707)	0.80
Gleason 7 or higher	29.9 (41/137)	24.7 (36/146)	0.35	90.8 (3,610/3,974)	90.6 (3,985/4,398)	0.73
Gleason 8 or higher	34.4 (11/32)	50.0 (14/28)	0.30	90.3 (3,685/4,079)	90.4 (4,081/4,516)	0.97

Appendix 9

Comparison of the Characteristics of Men With and Without Prostatectomy
Up To Unblinding Date of June 23, 2003
(From Redman et al., 2008) [13]

	No Prostatectomy N=1517	Prostatectomy N=500	P-value†
Treatment arm			
Finasteride	617 (41%)	206 (41%)	0.80
Placebo	900 (59%)	294 (59%)	
Age at randomization	64.6±5.6	61.1±4.2	<0.0001
Race			
White	1,403 (92%)	466 (93%)	0.11
Other	114 (8%)	34 (7%)	
Family history of prostate cancer			
Yes	317 (21%)	117 (23%)	0.90
No	1,200 (79%)	383 (77%)	
PSA at randomization	1.6±0.8	1.7±0.7	0.006
Prior negative biopsy			
Yes	206 (14%)	67 (13%)	0.78
No	1,311 (86%)	433 (87%)	
Biopsy prompt for PSA			
Yes	350 (23%)	154 (31%)	0.01
No	1,167 (77%)	346 (69%)	
Biopsy prompt for DRE			
Yes	281 (19%)	123 (25%)	<0.0001
No	1,236 (81%)	377 (75%)	
High-grade tumor on biopsy			
Yes	391 (26%)	149 (30%)	0.07
No	1,126 (74%)	351 (70%)	

† From a multivariate logistic regression model with prostatectomy (yes/no) as the outcome, adjusting for other factors in the table

Appendix 10

Gleason Score Based on Needle Biopsy and at Radical Prostatectomy
Prostatectomy Cohort

Gleason Score Based on Needle Biopsy[1]	**Gleason Score at Radical Prostatectomy**[3]									
	Finasteride N = 206					Placebo N = 283				
	2-5	6	7	8-10	NG[2]	2-5	6	7	8-10	NG[2]
2-5	0	14	6	1	1	10	28	8	1	3
6	7	65	20	0	4	12	100	43	0	6
7	2	12	28	6	2	1	13	38	3	1
8-10	0	3	14	14	7	0	3	5	7	1

[1] 3 men on finasteride and 3 men on placebo who had a prostatectomy had a biopsy that could not be graded.
[2] NG = Not graded (because of antiandrogen therapy between biopsy and prostatectomy).
[3] Extended Mantel-Haenszel correlation statistic (increase, unchanged, decrease) between groups p = 0.03.

[11]

Appendix 11

Comparison of the Characteristics of Men With and Without an Endpoint Evaluated Up To Unblinding Date of June 23, 2003 (From Redman et al., 2008) [13]

N (%) / Mean ± S.D	Endpoint evaluated		OR[†] (95% CI)	P-value[†]
	No n = 5,809	Yes n = 10,181		
Treatment arm				
Finasteride	3,008 (52%)	4,958 (49%)	0.89 (0.84-0.95)	0.0007
Placebo	2,801 (48%)	5,223 (51%)	1.0 (reference)	
Age at randomization[‡]	63.4 ± 5.9	62.9 ± 5.4	0.98 (0.97-0.99)	<0.0001
Race				
White	5,297 (91%)	9,483 (93%)	1.37 (1.21-1.55)	<0.0001
Other	512 (9%)	699 (7%)	1.0 (reference)	
Family history of PCA				
Yes	782 (13%)	1,698 (17%)	1.23 (1.12-1.35)	<0.0001
No	5,026 (87%)	8,484 (83%)	1.0 (reference)	
PSA at randomization[§]	1.2 ± 0.7	1.3 ± 0.7	0.99 (0.94-1.04)	0.60
Prior negative study biopsy				
Yes	463 (8%)	1,349 (13%)	1.60 (1.43-1.80)	<0.0001
No	5,345 (92%)	8,833 (87%)	1.0 (reference)	<0.0001
Biopsy prompt for elevated PSA				
Yes	69 (1%)	803 (8%)	6.80 (5.32-8.84)	<0.0001
No	5,739 (99%)	9,381 (92%)	1.0 (reference)	
Biopsy prompt for suspicious DRE				
Yes	82 (1%)	830 (8%)	5.66 (4.52-7.18)	<0.0001
No	5,726 (99%)	9,352 (92%)	1.0 (reference)	

[†] From a multivariable logistic regression model with endpoint evaluated (yes/no) as the outcome, adjusting for other factors in the table.
OR = odds ratio, CI = confidence interval.
[‡] OR represents the difference in odds of endpoint comparing men 1-year apart in age.
[§] OR for each 1-unit increase in PSA level.

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