Outcomes Associated With the Use of Finasteride: An Evaluation of this Medication as a Chemoprotective Agent and its Efficacy

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Outcomes Associated With the Use of Finasteride: An Evaluation of this Medication as a Chemoprotective Agent and its Efficacy

Abstract

Background: Whether a male should be placed on a well-studied pharmaceutical agent thought to have chemoprotective properties, is currently a question that is debated by clinicians. The purpose of this study is to determine the benefits versus harms associated with finasteride as a chemoprotective agent. Finasteride, has been used for the treatment of benign prostatic hyperplasia. It has been hypothesized that, since this medication resulted in the reduction of PSA levels, and a decrease in the size of the prostate, it would, in turn have a positive lowering effect on the incidence of prostate carcinoma. A significant number of men will be diagnosed with prostate cancer yearly. This disease may be preventable and is treatable to a certain degree. Screening and prevention modalities have been studied and continue today in an attempt to find better techniques for catching this disease early on. The earlier the cancer is discovered, the greater the chance of survival as there is less likelihood it has metastasized.

Methods: A systematic review of literature over the last twelve years was performed. A thorough literature search was performed using the search engines as follows: CINHAL, Ovid/MEDLINE, and ISI Web of Knowledge. The search was limited to include clinical studies, with English as the primary language. An evaluation of the abstract led to relevant studies, and additional sources were obtained through the bibliography of studies found to lead to other pertinent published information. Numerous studies were obtained and evaluated for relevance and quality. The keywords used included, prostatic carcinoma, prostatic neoplasm, finasteride, and prostatic intraepithelial neoplasia.

Results: A total of four articles were reviewed for this study. Many studies reported that finasteride does result in a reduction of PSA values by approximately half and in a decrease in the volume of the prostate gland. According to the Prostate Cancer Prevention Trial, finasteride was found to have caused an overall decrease in the incidence of prostate cancer in the treatment group, but in the carcinomas detected, they were an overall high-grade of cancer. A subsequent analysis of data from the same trial concluded the incidence of high-grade carcinoma in the treatment group on biopsy was downgraded to a lower-grade cancer at prostatectomy. This analysis demonstrated a narrowing of the gap between the treatment group and the control group in the incidence of high-grade disease. This narrowing was insufficient to confirm that finasteride was not the cause of the increased detection of high-grade cancers.

Conclusion: According to the aforementioned results from this review, it is apparent that finasteride cannot be used as a chemoprotective agent until there is further proof that it does not cause a higher incidence of high-grade disease. Due to the inconclusive data that resulted from such a vast study, more research needs to be performed in this area.

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Outcomes Associated With the Use of Finasteride: An Evaluation of this Medication as a Chemoprotective Agent and its Efficacy.

Catherine H. Cieslik

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Hillsboro, OR

For the Masters of Science Degree, August 2010

Faculty Advisor: Latha Reddy
Clinical Graduate Project Coordinators: Annjanette Sommers MS, PAC & Rob Rosenow PharmD, OD
Catherine was born and raised in Omaha, Nebraska, along with her six other siblings. Catherine is the last born out of the seven children and her parents are very excited for her becoming a medical professional. She graduated University of Nebraska-Lincoln with a degree in Biological Sciences before moving out to Portland, Oregon, to pursue a career in the medical field. Catherine has been living in Portland for the last five years. She has two sisters and a brother-in-law that also live in the area. Her entire family has been very supportive along the way during Physician Assistant School. She has a special appreciation for her family in Oregon. They supported her during her clinical year with cozy housing, delicious food, and care for her dog, Wynston. Catherine has been playing soccer ever since she signed herself up to play when she was six. In addition to soccer, she enjoys snowboarding, running, biking, and any other outdoor sports or activities. Catherine is looking forward to joining the medical community and contributing to it as a member and a clinician. She is inspired and motivated to make learning medicine a lifelong pursuit.
ABSTRACT

Background: Whether a male should be placed on a well-studied pharmaceutical agent thought to have chemoprotective properties, is currently a question that is debated by clinicians. The purpose of this study is to determine the benefits versus harms associated with finasteride as a chemoprotective agent. Finasteride, has been used for the treatment of benign prostatic hyperplasia. It has been hypothesized that, since this medication resulted in the reduction of PSA levels, and a decrease in the size of the prostate, it would, in turn have a positive lowering effect on the incidence of prostate carcinoma. A significant number of men will be diagnosed with prostate cancer yearly. This disease may be preventable and is treatable to a certain degree. Screening and prevention modalities have been studied and continue today in an attempt to find better techniques for catching this disease early on. The earlier the cancer is discovered, the greater the chance of survival as there is less likelihood it has metastasized.

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Conclusion: According to the aforementioned results from this review, it is apparent that finasteride cannot be used as a chemoprotective agent until there is further proof that it does not cause a higher incidence of high-grade disease. Due to the inconclusive data that resulted from such a vast study, more research needs to be performed in this area.

Keywords: prostatic carcinoma, prostatic neoplasia, finasteride, prostatic intraepithelial neoplasia.
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LIST OF ABBREVIATIONS

CI   Confidence Intervals
P    p value
RR   Relative Risk
PCPT Prostate Cancer Prevention Trial
PSA  Prostate Specific Antigen
DRE  Digital Rectal Examination
PIN  Prostatic Intraepithelial Neoplasia
HGPIN High-grade Prostatic Intraepithelial Neoplasia
Outcomes Associated With the Use of Finasteride: An Evaluation of this Medication as a Chemoprotective Agent and its Efficacy.

BACKGROUND

Prostate cancer is a devastatingly prevalent diagnosis in men of advanced ages. An estimated 192,000 cases were diagnosed in 2009, and approximately 27,000 deaths were predicted to occur.¹,² “The projected lifetime risk of developing cancer for a 50 year-old male is about 42%, of being diagnosed is 9.5%, and of dying from prostate cancer is 2.9%.”³ The incidence of prostate cancer has been on the rise and researchers are not certain as to why, but it may be due to environmental or genetic factors. The incidence is also more prevalent in African American men than Caucasian men.⁴

There are many factors involved when trying to predict the probability of survival from prostate cancer, especially the extent of the tumor at the time of diagnosis. The 5-year relative survival rate among men with cancer confined to the prostate is 91 to 97%. Once the cancer has extended beyond the prostate gland, survival decreases considerably. While men with advanced stage disease may benefit from palliative treatment such as radiation, or anti-androgen therapy, their tumors are not generally curable.³

In the early 1990s, the American Cancer Society approved the use of the Prostate Specific Antigen (PSA) serum test as a screening tool for detecting prostate cancer.³ A glycoprotein produced by the prostate epithelial cells, PSA levels may be elevated in men with prostate cancer. The cut-off value for a normal PSA is less than 4.0ng/ml. Many factors may temporarily elevate PSA without necessarily indicating a cancer, these include urinary retention, prostatitis, recent ejaculation, or a prostate biopsy.⁴ A conclusion that has been drawn from
current research over the last several years is that PSA may not directly represent the likelihood of dysplasia or carcinoma.  

A more accurate way of measuring risk is the PSA velocity, which is derived from calculations of the rate of change in PSA before the diagnosis of cancer was established. Increases of > 0.75 ng/ml per year are suggestive of cancer. Another screening modality is the digital rectal examination (DRE). If the prostate gland is found to be enlarged on exam, then patients are referred for biopsy, even if PSA is not elevated at the time.  

Androgens, such as testosterone, are hormones predominantly found in males, which directly impact the prostate gland. An enzyme called 5-alpha reductase converts testosterone to a more active androgen, dihydrotestosterone (DHT), the hormone that stimulates growth of the prostate. Finasteride is a 5-alpha reductase inhibitor. This medication works by the mechanism that inhibits the 5-alpha reductase enzyme from the conversion of free testosterone into DHT, the primary, and more potent, androgen that causes prostate hyperplasia.  

A 5-mg dose of finasteride was approved to treat benign prostatic hypertrophy (BPH) in 1992. Treatment with finasteride in men with BPH has been associated with a 17-30% reduction in prostate volume (average 19%) and a 50% decrease in circulating levels of prostate-specific antigen.  

Hypertrophy of the prostate gland is a normal aging process in men. Hypertrophy needs to be differentiated from hyperplasia, or proliferation of cells. Two researchers named Mc Neal and Bostwick, discovered a lesion which lined benign prostatic cells and was similar in structure to cells found more commonly in men with prostatic adenocarcinoma. The lesion was subsequently named prostatic intraepithelial neoplasia (PIN) and it is classified into low PIN or high-grade prostatic intraepithelial neoplasia (HGPIN). Frequently found preceding a
diagnosis of prostate cancer, HGPIN is morphologically similar to prostate cancer.\textsuperscript{11,10} Many other scientists and doctors believe high-grade PIN is currently associated with increased prostate cancer risk but whether HGPIN is a prostate cancer precursor is subject to debate. According to researchers in the Cote et al\textsuperscript{7} study, high-grade prostatic intraepithelial neoplasia is considered a premalignant lesion and has molecular and cellular changes similar to those seen in prostate cancer.\textsuperscript{7}

Whether a man should be placed on a pharmaceutical agent thought to have chemoprotective properties, like finasteride, is currently a question that is debated by many clinicians and patients alike. It is thought to have beneficial results in the reduction of PSA levels, decrease in the size of the prostate, and in turn, is hypothesized to cause a decrease in the incidence of prostate carcinoma.\textsuperscript{7}

The purpose of this study is to assess whether finasteride truly is a chemopreventive agent. The different outcomes this study will evaluate are the effects of finasteride on PSA levels, on the incidence of glandular cell proliferation changes, prostatic intraepithelial neoplasia, prostate cancer, and on the overall quality of life.

**METHODS**

A thorough literature search was performed using the search engines as follows: CINHAL, Ovid/MEDLINE, and ISI Web of Knowledge. The search was limited to include clinical studies, and English as the primary language. An evaluation of the abstract led to relevant studies, and additional sources were obtained through the bibliography of studies found to lead to other pertinent information published. The results of the search only included articles from 1998 to current literature on this subject. The study types included randomized control
studies, and observational studies both prospective and retrospective. Case controlled studies, meta-analyses and case reports were excluded. Any studies on duasteride (another 5-alpha reductase), were also excluded to keep the focus on finasteride. The keywords used included, prostatic carcinoma, finasteride, and prostatic intraepithelial neoplasia.

RESULTS

In this systematic review of literature, two randomized control studies, and two retrospective cohort follow-up studies were examined. The first one, published in 1998, investigated the chemopreventive potential of finasteride by evaluating its effect on the prostate gland of men with elevated serum prostate-specific antigen. This study looked at the short-term effects of finasteride over a 12 month period, in participants who were already at risk. Another study from the results from the Prostate Cancer Prevention Trial (PCPT), looked at the influence of finasteride on the development of prostate cancer in participants with normal PSA values and a normal digital rectal exam, and without a prior diagnosis of prostate cancer. These studies examine whether finasteride affects the outcomes; cellular proliferation (i.e. PIN or HGPIN), the growth of prostatic carcinoma, and the effect on the quality of life for those individuals. Secondary outcomes measured included effects on PSA values, and volume of the prostate gland. Not all of the studies measured all of the outcomes, and may have measured them differently. Comparisons between the studies link similar information as closely as possible.

Additional studies reviewed, were observational prospective or retrospective studies, all using the data from the Prostate Cancer Prevention Trial that further evaluated findings, or reevaluated conclusions already published. Still other studies viewed were correspondence articles published related to the PCPT, and these publications were not included in the review,
since they were not individual studies, but they were used for background information and additional resources (Table 1: Summary Matrix of Review Articles).

The first article found, was “The effect of finasteride on the prostate gland in men with elevated PSA levels.” This was a blinded randomized control trial performed to determine the short-term effects (12 months) of finasteride on men with risk factors. The Cote et al study included men over the age of 50, with elevated PSA values (>4.0ng/ml). All patients received a pre-study biopsy that had to be negative in order for them to participate in the trial. There was a total of 52 men in the study, 27 in the treatment group, and 25 in the control group. The participants in the treatment group were given 5 mg of finasteride a day, and the control group received neither medication nor placebo. All patients underwent an end-study biopsy 12 months later.

This study showed a decrease in the PSA values of men treated with finasteride by a difference of 4.44ng/ml; whereas the control group had an increase in PSA of 0.50ng/ml over the course of the year. The difference between the two groups was 4.94ng/ml, which was statistically significant at p<0.001. There was an overall 48% reduction in mean PSA in the finasteride group (p<0.001), mean serum DHT level decrease of 67% (p<0.001), but a mean serum testosterone increase of 21% (p<0.001). All of these values were statistically significant.

There was no significant change in percent of glandular epithelium in either treatment or placebo group. The percent of hyperplastic epithelium was decreased by 8.3 percent over the 12 months in the treatment group (statistically significant with p=0.002). Whereas, in the control group, the percentage of decrease in hyperplastic cells was only 2.9%.

There were no cellular changes in either group of individuals that had pre-existing HGPIN on the end-of-study biopsy. The number of participants that had no high-grade PIN on
the pre-study biopsy but then did have HGPIN on the 12-month biopsy was 3 out of 19 in the treatment group (16%), and 6 out of 20 in the control group (30%), (p=0.45 was not statistically significant).7

The rates of prostate cancer were higher in the cohort that had pre-existing HGPIN. The number of individuals in the treatment group who had HGPIN in the pre-study biopsy, and had been diagnosed with prostate cancer was 6 out of the 8 (75%). No participants who had pre-existing HGPIN (5 individuals), in the control group, were diagnosed with prostate cancer. Only one individual out of 25 (4.0%) had prostate cancer on the 12-month biopsy in the control group. In the treatment group, 8 out of 27 patients (30%) total, were diagnosed with prostate cancer on the end-study biopsy. “This difference (six out of eight compared to zero out of five) was statistically significant (p=0.021).”7

Out of the 9 patients who were diagnosed with cancer, 6 from the treatment group underwent a radical prostatectomy. Of these individuals, 5 had bilateral disease with a Gleason score of 6-7. The individual who was diagnosed with prostate cancer from the observational group, also obtained a prostatectomy, which showed bilateral disease, although it was confined to the prostate. Nobody was reported to have lymph node invasion.7 This study also concluded, “finasteride-treated men in the study had a significantly increased detection rate of prostate cancer at 1 year. This excess was largely limited to men with HGPIN on pre-study biopsy. This study raises serious questions about the probable efficacy of finasteride in preventing prostate cancer.”7 This study did not report any information on medication side effects or quality of life for these individuals.

The next study is entitled “The influence of finasteride on the development of prostate cancer”5 – results of the PCPT. This was a blinded randomized control trial. It consisted of a
total of 18,882 men, 55 years or older, with a PSA level of 3.0 ng per milliliter or lower, normal digital rectal exam (DRE), and no other significant medical conditions. These participants were recommended for biopsy if they had an abnormal DRE, or if they had an elevated PSA. The Thompson et al. study was looking at the end-result of prevalence of prostate cancer during the seven year study. The participants were randomized to receive 5 mg of finasteride daily or placebo. At the end of the study, all the men were offered a biopsy due to the effects of finasteride on PSA levels, and to eliminate bias.\textsuperscript{5}

The Thompson et al. study did not report the decrease finasteride had on PSA values. The study had already confirmed from previous studies, that finasteride would cause a decrease in PSA values. Therefore, the study committee added a calculated factor of 2.3 ng/ml to each measurement of PSA in the treatment group.\textsuperscript{5}

The study found that the mean prostate volume for men in the finasteride cohort was 25.5 cm\(^3\), and in the placebo group it was 33.6 cm\(^3\) (a 24.1 % relative difference).\textsuperscript{5}

The rates of prostate cancer were reported for 9,060 men that were included in the final analysis. In the finasteride group, prostate cancer was diagnosed in 803 of the 4,368 (18.4\%) individual participants. While in the control group, cancer was detected in 1,147 out of the 4,692 (24.4\%), which was a relative risk reduction of 24.8\% (confidence interval (CI), 18.6 to 30.6\%; \(p<0.001\)). Prostate cancer was more prevalently detected in the observational group versus the treatment group in the case of both for cause biopsies and end-of-study biopsies.\textsuperscript{5}

In the finasteride group, there was a higher proportion of tumors with Gleason scores of 7-10 (280 of 757 graded tumor [37.0\%]), than the control group (237 of 1068 [22.2\%]). This was a statistically significant finding (\(p<0.001\)), relative risk of a high-grade tumor, 1.67 (CI, 1.44 to 1.93). The incidence of high-grade tumors in men in whom prostate cancer was
diagnosed in a for-cause-biopsy was 188 of 393 in the finasteride group (47.8%) and 148 out of 504 men in the placebo group (29.4%); \( p < 0.001 \); relative risk, 1.62 (CI, 1.37 to 1.93). According to the trial, most participants received a sextant biopsy (81.5% in treatment group, and 81.0% in control group). The majority of cancer detected was confined to the prostate, or was clinically localized.\(^5\)

Sexual problems including reduced volume of ejaculate, erectile dysfunction, loss of libido, and gynecomastia were more prevalent in the finasteride group (\( p < 0.001 \) for all comparisons). Urinary symptoms such as urgency, urinary frequency, prostatitis, urinary infection and retention, were more common in the placebo group (\( p < 0.001 \)). An equal number of men died in each group from prostate cancer.\(^5\)

The study, “\textit{Finasteride decreases the risk of prostatic intraepithelial neoplasia (PIN)}”\(^1\text{0}\) is an observational (retrospective cohort) study from data points taken from the Prostate Cancer Prevention Trial (PCPT). These participants were recommended for biopsy if they had an abnormal DRE, or if they had an elevated PSA. In this study they re-evaluate specifically the incidence of high-grade PIN in the individuals taking finasteride versus those who took placebo.\(^1\text{0}\)

The overall study found that there was a decrease in the risk of the incidence of high-grade PIN by 21% in the treatment group.\(^1\text{0}\) According to the study, men were considered for the evaluation for high-grade prostatic intraepithelial neoplasia if they were diagnosed with HGPIN or prostate cancer during the trial or at the end-of-study biopsy, or, if they had a negative end-of-study biopsy at 7 years. In this study, 4886 men were evaluated for HGPIN in the placebo group and 4568 in the finasteride group.\(^1\text{0}\)
The results of this study demonstrate that there was lower detection of HGPIN, and a greater number of negative prostate biopsies across the board in the finasteride arm. In the finasteride cohort, a normal end-of-study biopsy was 76.6% of participants, whereas, the placebo group only had 69.8% ‘normal’ participants. (This was statistically significant with relative risk (RR) = 0.77, CI 0.72-0.83, p<0.0001). The total detection of high-grade PIN was 6.0% of the finasteride group and a little higher at 7.1% for the placebo arm. The cumulative occurrence of HGPIN and prostate cancer in the treatment group was only 3.2% yet was higher in the placebo group at 4.6% (CI 0.56-0.85, p=0.004). The overall incidence of prostate cancer was higher at 18.2% in the placebo group, while it was only 14.2% with treatment by finasteride.

“Finasteride and High-Grade Prostate Cancer in the Prostate Cancer Prevention Trial” was an observational (retrospective cohort) study from data points taken from the Prostate Cancer Prevention. The PCPT was a blinded randomized control trial. The Lucia et al study uses data points to re-analyze and assess whether the higher incidence of high-grade prostate cancer among men taking finasteride in the PCPT was due to finasteride’s potential effects on tumor morphology or to prostate size.

“Prostate biopsies with Gleason score 8-10 were examined histologically for hormonal effects, and those with Gleason score 7-10 were examined for pathologic surrogates of disease extent. Tissue samples from radical prostatectomies from both groups were examined for tumor grade and extent. The study compared the grade at biopsy and at prostatectomy between the groups.

The tumor grade at biopsy, and, afterwards, at prostatectomy were compared for the 206 finasteride treated men, and 283 placebo-arm tumors, in which, cancer grades on both specimens were available. Among these patients that received both biopsy and prostatectomy, the difference
in the percentage of high-grade (Gleason 7-10) cancers between the finasteride and placebo groups at biopsy (88 of 206 [42.7%] versus 72 of 283 [25.4%], respectively, diminished at prostatectomy (89 of 192 [46.4%] versus 105 of 272 [38.6%], respectively. A closer look of the data shows that there was no statistical significance between the presence of high-grade tumors between the groups at prostatectomy.\textsuperscript{12}

Overall this study produced results that showed tumors were more likely to be downgraded at prostatectomy in the finasteride group than in the placebo group; (19.8%) finasteride, (12.5%) placebo. Additionally, tumor grades were more commonly upgraded in the placebo than in the finasteride group; (30.5%) placebo, (24.5%) finasteride. The difference between upgrading or downgrading between the two groups was statistically significant (p=.03).\textsuperscript{12}

Out of all the patients who underwent a prostatectomy and were diagnosed with high-grade disease (Gleason $\geq$ 7), it was more likely to have been detected at biopsy in the finasteride arm (69.7%) than in the placebo group (50.5%), (p=.01).\textsuperscript{12} And furthermore, the pathologic extent of disease which include: core positive for cancer, linear extent of tumor, aggregate, bilateral involvement, and perineural invasion, was significantly lower on average in the finasteride arm as compared to the placebo group.\textsuperscript{12}

The mean prostate gland volume in men with a biopsy Gleason score 7-10, was significantly less in the finasteride group than in the placebo group (25.1cm$^3$ vs. 34.4 cm$^3$, respectively) (p<.001).\textsuperscript{12}

This study did not report on PSA values or side effects of medication as this was already reported in the main study of the Prostate Cancer Prevention Trial.
DISCUSSION

The two main studies differ, as the Cote et al\textsuperscript{7} study, found that there was an increase in the incidence of high-grade prostate cancer in the finasteride treatment group, whereas, the PCPT published by Thompson et al\textsuperscript{5} revealed that the incidence of high-grade cancer was greater in the treatment group, but it was due to the improvement in the ability to detect the cancers due to a reduction in the size of the gland. They believed this to be the reason more cancers where found to be in the treatment group, not because the drug itself contributed to increase growth of more aggressive cancerous cells.\textsuperscript{5,7}

The articles included in this review each have their own limitations. Cote et al\textsuperscript{4} was a small study cohort, which only ran for 12 months, was not placebo-controlled, and did not mention presence of PIN at the beginning of the study in the methods. The study found that the increase incidence of prostate cancer detected was significant. This significant difference could have been contributed to the fact that they already had some degree of PIN on the pre-study biopsy, but the only requirement was that they did not have prostate cancer. This made a difference in their study results as many scientists believe HGPIN is more closely linked to prostate cancer.\textsuperscript{7}

The study did not make clear how they grouped the male participants in regards to their initial PSA value. It would help to know whether they were stratified evenly across both the treatment and control groups. Not all the populations for each of the studies were equal. In this particular study the men were already at higher risk than in the PCPT study, because they had an elevated PSA value at the start of the study. One would expect that, since these men were at higher risk for prostate cancer, there would be more prevalence even in the control group, although only one individual was diagnosed with prostate cancer.
The small study sample could have contributed to the results of this study being influenced, which could explain the significant difference in the presence of prostate carcinoma between the treatment and observation groups of 30% vs. 4.0%, respectively. The study hypothesizes that the increase detection in the finasteride branch could be due to occult cancer present at the beginning of the study, or because detection was more accurate due to the overall reduction in the size of the gland. “This questionable bias was stated to be less than directly proportional to the reduction in prostatic volume, approximately 19%, which was insufficient to explain the increased cancer rate in the finasteride group.” This study does admit that the difference in the incidence of prostate cancer is not solely due to chance. It also suggests that finasteride might actually stimulate the growth of human prostate cancer. This study did not measure any of the other side effects of the medication finasteride, such as decreased libido or its positive effects on urinary symptoms.

The Thompson et al study only tested men 55 years old or older, with normal digital rectal exams, and PSA level of 3.0 ng/ml or below. Unlike the Cotes et al paper, this study only looked at older healthy individuals. The study by Cotes et al, tested the effects on men with already elevated PSA values and the effects finasteride may have had on this population. It would also be beneficial that if the medication finasteride is going to be used as a potential chemopreventive agent, it should be studied long-term. This study was ended prematurely, although if the study set out to evaluate the efficacy of a medication over a long-term period it should have continued to collect data beyond just seven years. The study states that the number of participants in the study makes up for the early termination of the study, yet it still does not account for the additional data they could have collected had it been continued for the original allotted time period.
This study used two different methods of measuring the PSA values: tandem E assay (hybritech) until 2000, then the Access assay (Beckman Coulter) thereafter. This may induce bias due to the mere difference in the design of the test. Another bias in this study was the adjustment to PSA values, which consisted of a doubling of the PSA values for finasteride-treated men, but on the basis of the goal of an equal percentage of biopsies in each group. That did not last however. Instead, the factor was changed to 2.3 at the beginning of the man’s fourth year in the study. The designers of the study had an interesting rationale as to why they added this factor, but it was inconsistent to begin the change in the middle of the study. Initially, they just reported PSA values as elevated or not elevated, but in 1995 as clinical practice changed, values began to be reported for men with elevated PSA levels. There were so many variables with the measuring and calculating of PSA values, that this adds question to the validity of the study. The study design was changed to perform an end-of-study biopsy on everyone to account for these changes.\textsuperscript{5}

The authors of the Prostate Prevention Cancer Trial noted that the magnitude of the risk reduction did not differ according to PSA levels, age, race/ethnicity, or family history of prostate cancer. This conclusion is limited to men with a normal initial reading of PSA (<4.0ng/ml).\textsuperscript{5} This is an important discovery because it suggests that once finasteride is cleared for use it will be available to treat men of all ages and races equally.

Prostate biopsies were not consistent: the guidelines were, that a minimum of six specimens were obtained, but while most men received 6, some did received up to 12 specimens. According to UpoDate, current standards are that the sextant biopsy has been effectively replaced by extended biopsy, which sample more aspects of the prostate, mainly the lateral parts. On average, 10-12 locations are sampled on a modern prostate core biopsy.\textsuperscript{4} Another discrepancy
was that specimens were sent to two different sites depending on whether it was a needle biopsy or a transurethral resection of the prostate, although there was only one referee pathologist. Another limitation of this study is that they did not perform a pre-study biopsy, or at least they did not mention it as having being done. Prerequisites of the study maintained that there was a normal DRE, normal PSA levels, and no coexisting conditions. A man can still be suffering from prostate cancer while screening values remain within “normal ranges”. The cut-off values for a “normal PSA” are calculated values from previous studies and observations that represent the median safe range for the general male population. As this study confirms later, there is no longer a PSA threshold below which prostate cancer cannot be found.⁵

There were numerous men that were excluded from obtaining an end-of-study biopsy either by choice or by guidelines from the study. Men were excluded if they had a diagnosis made or had the biopsy performed more than 7 years and 90 days after the initial randomization of the study. Other reasons men refused biopsies included: doctor recommendations against it, the men refused it on their own terms, or there was a coexisting condition contraindicating a biopsy. Others that were not included in the final analysis were lost to follow-up, died during the trial, had a previous diagnosis of cancer, or did not complete the study.

A total of 9822 men were not evaluated with end-of-study biopsies, and therefore, were not included in the final analysis of the trial. This was slightly over half the number of participants at the start of the trial. The total number of men analyzed in the finasteride group for a diagnosis of prostate cancer was 4368 and in the placebo group was 4692. This difference was not statistically significant, but potentially, if more men in the finasteride group had received biopsies, then it would have closed the gap, which could have led to a statistically significant result.
It is perplexing that cancer detected in the finasteride group was a higher grade, Gleason 7-10 grade cancer. The Thompson et al\textsuperscript{5} study claims that finasteride did not actually produce an increase in aggressive prostate cancers, rather cell changes on biopsy were possibly due to an appearance in the cells that mimic high-grade disease. The Lucia et al\textsuperscript{12,12} study supports this notion as it claims that increased incidence of higher grade cancers could be from histological changes induced by the medication that imitate high-grade disease and therefore, result from androgen-deprivation therapy. This concept is still debatable. Perhaps this is another consequence of ending the study before the seven years had run and giving up the opportunity to acquire more complete data. Moreover, the study was discontinued by the data and safety committee, “on the basis of sensitivity analyses, since the study objectives had been met and the conclusions were highly unlikely to change with additional diagnoses of prostate cancer and end-of-study biopsy results”.\textsuperscript{5}

This study found a relative risk reduction of 24.8\% in the incidence of prostate cancer. What this means in real terms this is not terribly important as it translates to treating 70 men for at least 7 years to prevent one case of prostate cancer.\textsuperscript{13}

The final study that was a reanalysis of the Prostate Cancer Prevention Trial, by the main author, M. Scott Lucia. He was the blinded pathologist who worked on the PCPT from 2001 until the end of the study. This study by Lucia et al\textsuperscript{12}, helps to explain why there was an increased incidence of high-grade prostate cancer among men in the finasteride arm of the PCPT. One belief is that due to the effects of finasteride on PSA, DRE, and prostate volume, it has increased the detection of existing high-grade cancer. This study helps to support this conclusion, as it found that finasteride causes a decrease in prostate volume, which is in accordance with finding from previously mentioned studies. And due to this reduction in size, finasteride
increases the sensitivity of PSA and DRE for prostate cancer. Part of the reason that this may have contributed to the detection of high-grade disease, was the selective inhibition of low-grade cancer in men with cancers that contain both low-grade and high-grade components. “This in turn, would have increased the relative proportion of high to low-grade cancer, thereby favoring detection of the high-grade component by needle biopsy”.12

According to the current, updated (2005) version of the Gleason grading system, “low-grade cancers are rarely seen on needle biopsy because they are predominantly located anteriorly in the prostate, in the transition zone, and they tend to be small. A diagnosis of Gleason score 2-4 should be made on biopsy, rarely if ever, according to the new guidelines. For practical purposes this change has now translated into the virtual disappearance of Gleason score 2–4 on needle biopsy in contemporary practice.”14 The tumor grade on prostatectomy when compared to biopsy showed that, when high-grade disease was present at prostatectomy it was more likely to have been detected at biopsy in the finasteride group (62 of 89 [69.7%]) as opposed to (53 of 105 [50.5%]) (p=.01), in the placebo group. The Lucia et al12 argues that this comparison indicates that finasteride increased the sensitivity of prostate biopsy for high-grade disease.12 But if by today’s standards low-grade disease is undetectable on biopsy, then this would make sense that only high-grade is being detected and thus finasteride does not necessarily improve the sensitivity.

Although this was a promising discovery, it would also be hard to comprehend the idea of placing men on finasteride solely for the purpose of increasing the effectiveness of a prostate biopsy.

“The detection and grading of cancer on biopsy is subject to two factors: the ratio of tumor volume to prostate volume (which affects overall detection) and the relative proportions of
Gleason patterns that exist within the tumor (which affect grading).\textsuperscript{12} The reduced volume of the prostate gland made it more likely to detect, especially if the there was any substantial amount of high grade disease.\textsuperscript{12}

The Lucia et al\textsuperscript{12} study has shown that there were more cancers in the finasteride group that were downgraded. This finding supports the previous hypotheses that finasteride improves detection of high-grade disease on biopsy, mainly by decreasing gland size, and selective inhibition of low-grade tumors. Unfortunately, this may also lead to over detection, over treating, or falsely treating an otherwise harmless grade of dysplasia. Although this study claims to have found a downgrading on prostatectomy in the finasteride group, it does not have any evidence supporting or refuting whether finasteride causes an increased growth of high-grade cancers in some men, despite the decrease in low-grade cancer.\textsuperscript{12} “The analysis of prostatectomies from the PCPT does indicate that the relative increase in high-grade tumors in the finasteride group is less than originally believed.\textsuperscript{12} This is a promising result from a pathologist’s point of view, but it is not hopeful for putting this medication on the market as a chemopreventive agent.

The controversy as to whether finasteride is a chemoprotective agent is ongoing and deserves more analysis. Further new studies need to be performed to determine the efficacy of this drug. Analyzing and re-evaluating the same data from the Prostate Cancer Prevention Trial has been tried and it is time to have new clinical trials performed with more thoroughness and more up to date data.

**CONCLUSIONS:**

A significant amount of men will be diagnosed with prostate cancer yearly, but the average American man’s risk of dying from prostate cancer is only about 3%.\textsuperscript{6} The most
important risk factor for prostate cancer is age, but there is a significantly larger prevalence in
the African-American population than in the Caucasian population. The average white male has
a greater incidence of the disease than the average Asian-American. The higher incidence of
prostate cancer did not correlate with the increased presence of testosterone in men across ethnic
backgrounds.\textsuperscript{7} Screening and prevention modalities have been studied and continue today in an
attempt to find better techniques for catching this cancer early. The earlier the cancer is
discovered, the more likely it is not to have metastasized, and therefore, there is a greater chance
of survival.

As it stands today, we are still using PSA values as a methodology for detecting cancer,
staging prostate cancer, and for detecting the recurrence of carcinoma of the prostate. The PCPT
results conclude that there is no longer a PSA threshold below which, prostate cancer cannot be
found. A better means of measurement would be to use the PSA density, which represents the
change of PSA over a period of time.\textsuperscript{3,5}

The clinical question as to whether or not a clinician should place their patients on
finasteride as a protective agent against prostate cancer is still unanswered. To date, finasteride is
approved for use in men with benign prostatic hyperplasia. The benefit of this medication, is that
it can decrease the size of the gland and lower PSA values, which may actually be a unwise
move on the part of a clinician. If an indolent cancer is growing in a patient on finasteride, the
standard modalities for screening may not pick up on a cancer that is not reflected on PSA values
or digital rectal examinations thereby masking the cancer. These new findings should be taken
seriously and should change the course of how we screen men while on finasteride.
Finasteride may have contributed to higher detection of prostate cancer, but if it is still unanswered as to whether it causes an increase incidence of high-grade cancers, it should not be used as a chemopreventive agent.

Furthermore, does preventative treatment for prostate cancer actually prolong life result in a better quality of life? The risk of a male dying from prostate cancer in his lifetime is low. So if this medication may not prolong life, it may not be worth the associated sexual dysfunction and other side-effects. The PCPT found, that, those taking finasteride had an increase in sexual side effects including, reduced volume of ejaculate, erectile dysfunction, loss of libido, and gynecomastia. There was a decrease in symptoms associated with genitourinary side effects. At this point in time, this medication should be reserved for those individuals who can actually benefit but not for those individuals trying to prevent prostate cancer.
REFERENCES


<table>
<thead>
<tr>
<th>Author/Title/Journal</th>
<th>Patients/Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome(s)</th>
<th>Validity (Jadad score)</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Cote et al&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Men with elevated PSA</td>
<td>5 mg of finasteride daily</td>
<td>No medication given</td>
<td>(all measured after the 12-month trial period) -PSA, -DHT, and -free T levels -Percent of glandular epithelium -Percent of hyper-plastic epithelium: PCNA index -PIN and prostate cancer presence</td>
<td>3</td>
<td></td>
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<tr>
<td>Thompso n et al&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Men 55 years of age or older with a normal digital rectal examination and a PSA level of 3.0 ng/ml or lower</td>
<td>Finasteride 5 mg per day for seven years</td>
<td>Placebo for seven years</td>
<td>Prevalence of prostate cancer during the course of the trial and on end-of-study biopsy.</td>
<td>5</td>
<td>This was a relative small sample size for the testing population. Additionally, the study was short in duration, only lasting 12 months.</td>
</tr>
<tr>
<td>Lucia et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Men 55 years of age or older with normal digital rectal examination and a PSA level of 3.0 ng/ml or lower</td>
<td>Finasteride 5mg per day for seven years</td>
<td>Placebo for seven years</td>
<td>Compared the rating of prostate cancer at biopsy versus the grade at prostatectomy.</td>
<td>5</td>
<td>This study found a downgrading at prostatectomy from the tumor grade at biopsy in the finasteride group.</td>
</tr>
<tr>
<td>Thompso n et al&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Men 55 years of age or older with normal digital rectal examination and a PSA level of 3.0 ng/ml or lower</td>
<td>Finasteride 5mg per day for seven years</td>
<td>Placebo for seven years</td>
<td>Evaluated the impact of finasteride on the risk of a needle biopsy diagnosis of high-grade prostatic intraepithelial neoplasia.</td>
<td>5</td>
<td>This study demonstrated that there was a 21% overall decrease risk of HGPIN in the finasteride group. Although the PCPT study found a small but significant increase in the diagnosis of high grade prostate cancer in the treatment group.</td>
</tr>
</tbody>
</table>
TABLE 2: Comparison of Outcomes from All the Studies

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Cotes et al(^4)</th>
<th>Thompson et al(^{10,12}) - PCPT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Finasteride</td>
<td>Control</td>
</tr>
<tr>
<td>PSA (ng/ml) difference</td>
<td>-4.44</td>
<td>0.50</td>
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<tr>
<td>HGPIN found on end-of-study biopsy</td>
<td>3/19 (16%)</td>
<td>6/20 (30%)</td>
</tr>
<tr>
<td>Prostate CA and HGPIN</td>
<td>6/27 (22.2%)</td>
<td>0/25 (0.0%)</td>
</tr>
<tr>
<td>HGPIN on pre-study biopsy</td>
<td>6/8 (75%)</td>
<td>0/5 (0.0%)</td>
</tr>
<tr>
<td>Prostate CA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HGPIN in pre-study biopsy</td>
<td>2/19 (11%)</td>
<td>1/20 (5.0%)</td>
</tr>
<tr>
<td>Prostate CA on end-of-study biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td># of Gleason grade 7-10 at biopsy</td>
<td>8/27 (30%)</td>
<td>1/25 (4.0%)</td>
</tr>
<tr>
<td># of Gleason grade 7-10 at prostatectomy</td>
<td>6 (Gleason 6-7)/27 (22.2%)</td>
<td>1 (Gleason score not assigned)/25 (4.0%)</td>
</tr>
</tbody>
</table>