Knowledge and Use of Finasteride for the Prevention of Prostate Cancer

Robert J. Hamilton¹,²,³, Leila C. Kahwati², and Linda S. Kinsinger²

Abstract

Background: The knowledge about and use of chemopreventive agents for prostate cancer by physicians has not been described. The Prostate Cancer Prevention Trial (PCPT) showed that finasteride was effective in reducing the incidence of prostate cancer. We examined the influence of the PCPT on finasteride prescribing within the Veterans Health Administration (VHA).

Methods: We assessed trends on monthly new and total prescriptions for finasteride filled within the VHA from January 2000 to December 2005. Additionally, all VHA urologists and a random sample of VHA primary care physicians (PCP) were surveyed about their use of finasteride.

Results: The number of men starting finasteride grew over the study period. Publication of the PCPT was not significantly associated with any change in this pattern (P = 0.45). Fifty-seven percent of urologists and 40% of PCPs endorsed prescribing finasteride more frequently in 2006 than 5 years prior. However, among those who reported changing prescribing patterns, fewer than 2% reported being influenced by the PCPT. Sixty-four percent of urologists and 80% of PCPs never prescribe finasteride for prostate cancer chemoprevention; 55% of urologists cited concerns of inducing high-grade tumors, whereas 52% of PCPs did not know it could be used for chemoprevention.

Conclusions: The number of men starting finasteride in the VHA increased over time, but the change did not seem to be due to increased use of finasteride for chemoprevention. Publication of the PCPT seemed to have little influence over the study period.

Impact: Physicians may not readily accept the use of chemopreventive agents for prostate cancer.

Introduction

Chemopreventive agents for cancer prevention have been studied for a variety of cancers, including breast, colorectal, and prostate. However, their use has not been widely adopted, likely for several reasons. Physicians may not be familiar with chemopreventive indications for these agents, and they may be cautious about their use. Chemopreventive agents are used in people without the condition for which they are taking the chemopreventive medication; therefore, great care must be taken to be certain the benefits substantially outweigh the harms. Physicians may also be uncertain about which patients are most likely to benefit and therefore unlikely to initiate a discussion with patients about these drugs. Few studies have explored the actual use of chemoprevention for prostate cancer in clinical practice.

The class of drugs called 5-α reductase inhibitors (5-ARI) has been studied to determine their effectiveness in preventing prostate cancer. 5-ARIs inhibit the conversion of testosterone to dihydrotestosterone. Currently 5-ARIs are approved for two medical indications. Finasteride (5 mg) and dutasteride are approved for treatment of benign prostatic hyperplasia (BPH), whereas finasteride (1 mg) is approved for treatment of male pattern baldness. In July 2003, results of the Prostate Cancer Prevention Trial (PCPT) were published. This randomized controlled trial of over 8,000 men assigned to either finasteride 5 mg or placebo showed a 25% relative reduction in the incidence of prostate cancer in the finasteride arm (18.4% versus 24.4% placebo group; ref. 1). However, the proportion of high-grade tumors (Gleason grade ≥ 7) was 27% higher in finasteride users (6.4% versus 5.1%).

Recently, a second large randomized controlled trial entitled the Reduction by Dutasteride of Prostate Cancer Events published their results (2). This study of 6,729 men...
with a prior negative prostate biopsy randomized to receive dutasteride or placebo found a 23% reduction in the risk of prostate cancer after 4 years. A nonsignificant trend towards increased risk of high-grade disease was noted in the dutasteride arm.

Despite the evidence that 5-ARIs reduce the incidence of prostate cancer, the extent to which physicians and patients are aware of 5-ARIs as chemopreventive agents, how physicians assimilated the PCPT information, and whether this information has changed their finasteride prescribing patterns is not known. We sought to identify trends in finasteride prescriptions in the Veterans Health Administration (VHA) over time, determine whether these trends correlate with publication of the PCPT, and examine knowledge and use of finasteride among primary care physicians (PCP) and urologists in the VHA after publication of the PCPT. We hypothesized that the trends in finasteride prescriptions would correlate with the publication of the PCPT, and VHA urologists would be more likely than PCPs to prescribe finasteride for chemoprevention.

Materials and Methods

This study consisted of two components: an analysis of finasteride prescriptions over a 5-year period and a survey of VHA primary care and urology providers. Institutional Review Board approval was obtained from the Durham Veterans Affairs Medical Center.

Prescription data source

All filled outpatient prescriptions for 5 mg finasteride or 0.5 mg dutasteride between October 1, 1998 and December 31, 2005 were obtained from the VHA Pharmacy Benefits Management databases. As dutasteride prescriptions comprised <0.05% of the total 5-ARI prescriptions over this period, we use the term finasteride throughout the article to refer to both finasteride and dutasteride prescriptions.

Prescription data outcomes

Our primary outcome was change in new finasteride prescriptions over time. A new prescription was defined as the first prescription filled between January 1, 2000 and December 31, 2005 without a filled prescription between October 1, 1998 and December 31, 1999. Prescriptions were categorized according to month and year they were filled. For each month, crude new and total prescriptions were tabulated. We standardized crude monthly prescriptions based on the gender and age distribution of fiscal year 2006 VHA enrollees, obtained from administrative data.

To determine if VA physicians were limited by local or network-level formulary restrictions or guidelines for finasteride during the study period, we queried all 21 Veterans Integrated Service Network pharmacy formulary leaders by email.

Prescription data statistical analyses

To examine changes in new finasteride prescriptions over time, we used time series analysis, a set of techniques for modeling autocorrelation in temporally sequenced data (3). We used autoregressive integrated moving average models and exponential smoothing models. The models incorporated a ramp function to estimate impact of the PCPT on finasteride prescriptions. The autocorrelation, partial autocorrelation, and inverse autocorrelation functions were assessed for model parameter appropriateness. Data were modeled up to the point of publication of the PCPT in July 2003, and then model-derived monthly projections and 95% confidence intervals for the period after the PCPT were obtained and compared with actual new prescription rates. All P values were two sided. A similar analysis was conducted for total monthly finasteride prescriptions and new monthly prescriptions in men who had not also been prescribed an α-blocker in attempt to limit analyses to finasteride prescriptions that may have more likely been prescribed for chemoprevention rather than BPH. All analyses were done using SAS, version 8.2 (SAS Institute, Inc.).

Survey sample and administration

Potential survey respondents were identified using the VA Personnel and Accounting Integrated Data payroll system. Full- or part-time VHA physicians in urology, family or general practice, general internal medicine, or geriatrics were eligible. Residents, physician assistants, and nurse practitioners were excluded.

All 325 urologists were invited. We randomly selected 1,200 of the 4,557 PCPs to participate. Of this sample, we determined some were incorrectly identified as primary care or urology (n = 122), some were retired or no longer working at the VA (n = 9), or we could not locate a current email address or phone number (n = 15). The final sample included 302 urologists and 1,072 PCPs for a total of 1,374 subjects.

We used a modified Dillman approach to conduct this Web-based survey between September 15, 2006 to February 15, 2007 (4). Physicians were sent email invitations to participate. Physicians without email addresses were called and asked permission to send an email invitation or a hard copy of the survey. Nonrespondents were sent two reminder emails at 2 and 8 weeks.

Survey design

The Web-based survey, designed by our study team, is available upon request. It contained 45 questions in several domains, including practice patterns about diagnosis and treatment of BPH, frequency and indications for finasteride and α-blocker use in the setting of BPH, knowledge of issues surrounding finasteride use in the setting of BPH or cancer prevention, use of finasteride specifically as a preventive medication, issues discussed with patients pertaining to finasteride chemoprevention, resources physicians use to learn about finasteride chemoprevention, knowledge of issues surrounding finasteride use in the setting of BPH or cancer prevention, use of finasteride specifically as a preventive medication, issues discussed with patients pertaining to finasteride chemoprevention, resources physicians use to learn about finasteride.
chemoprevention, and demographics. The survey was pilot tested with eight PCPs and seven urologists, and was slightly modified based on their responses to improve readability and understandability. No questions were removed or added as a result of the pilot testing. Here, we report results only from the questions about use of finasteride for chemoprevention. Results are presented as frequencies.

Results

Prescription data
A total of 237,286 patients had a new prescription for finasteride between January 1, 2000 and December 31, 2005. Figure 1 illustrates the number of new finasteride users per month. Use of finasteride increased over this time period. After publication of the PCPT, the observed number of new users per month was less than what was predicted if rates observed before the PCPT publication had continued (“expected”). However, this difference was not statistically significant ($P = 0.45$). A similar trend was seen in examining total finasteride use ($P = 0.78$; Fig. 2).

In attempt to limit analyses to finasteride prescriptions that may have more likely been prescribed for chemoprevention rather than BPH, we examined finasteride use among men who did not fill a prescription for an α-blocker within the VHA between 1998 and 2006. Among users meeting this criterion ($n = 52,996$), a similar trend was observed: new finasteride use did not change significantly after publication of the PCPT ($P = 0.76$).

Survey data
Of the 1,072 invited PCPs, 464 (43.3%) responded, whereas 135 of the 302 (44.7%) invited urologists responded. The demographic characteristics of these respondents are shown in Table 1.

Urologists reported currently prescribing finasteride for any indication more frequently than PCPs (Fig. 3) and were more likely to report prescribing finasteride more frequently now than compared with 5 years ago (57% of urologists versus 40% of PCPs). However, among those who reported changing prescribing patterns, fewer than 2% of either group reported being influenced by the PCPT (0.8% of urologists and 1.4% of PCPs). A total of 64% of urologists and 80% of PCPs stated they never prescribe finasteride chemoprevention, and when asked why, 55% of urologists cited concerns of inducing high-grade tumors as the leading reason, whereas 52% of PCPs reported not knowing it could be used for chemoprevention.

Of physicians who reported using finasteride for chemoprevention, few said they use it broadly (6% of urologists; 8% of PCPs), whereas the majority (71%) of urologists and many (41%) PCPs said they would reserve it for those they perceived to be at high risk for prostate cancer. Yet, when all respondents were asked specifically which patient factors would make them more likely to prescribe finasteride for chemoprevention, both groups listed moderate to severe BPH as the most influential factor (Fig. 4).

Respondents rated patient interest in prostate cancer chemoprevention as low; 84% of PCPs and 57% of urologists reported patients had asked them about chemoprevention “never” or “only a few times.” Similarly, few physicians in either group brought up the topic with patients: 84% of PCPs and 37% of urologists said they never raised the issue; and only 14% and 51%, respectively, reported “occasionally” raising it.

Figure 5 illustrates that overall, 34% of PCPs and 66% of urologists felt the benefits of finasteride as a preventive medication either outweighed or equaled the risks.
Responses to the query about prescribing restrictions were obtained from 19 of 21 (90%) Veterans Integrated Service Network Formulary Leaders. Eleven (58%) reported having restrictions of some kind on finasteride use. Four Veterans Integrated Service Networks reported only urologists could prescribe finasteride, whereas five reported any physician could prescribe finasteride if a nonformulary request was submitted. Four reported the only allowed indication was for treatment of BPH in combination with an α-blocker.

Discussion

This analysis of VHA pharmacy data, and a survey of VHA PCPs and urologists found that publication of the PCPT, a large and rigorous study which showed that finasteride can prevent prostate cancer (1), did not change prescribing patterns for finasteride in the VHA. Our study is the first, to our knowledge, to explore the use of finasteride as a chemopreventive agent in practice. Increasing numbers of men were prescribed finasteride from 2000 to 2005, even after adjusting for growth and changes in the VHA population. But the rate of growth in the use of finasteride, for either new or existing prescriptions, did not significantly change after results of the PCPT became available.

Our survey confirmed these findings. We found the majority of both PCPs and urologists reported never prescribing finasteride for chemoprevention. Although most nonprescribing urologists were concerned about inducing high-grade disease, the majority of PCPs were not aware finasteride could be used for chemoprevention. Thus, publication of the PCPT, with its mixed message (both benefits and harms) and lack of clear guidance for practice, had differential effects on these two groups of providers: PCPs did not seem to hear the message at all and urologists heard mostly the potential harms.

The growth in use of finasteride likely reflects increased use for BPH. VHA providers are encouraged to use finasteride for BPH with symptoms not relieved by α-blockers alone (5). Just after the PCPT was published, the Medical Therapy of Prostate Symptoms trial was published (6). This large randomized controlled trial confirmed that long-term use of finasteride, especially in combination with an α-blocker, was safe and effective in reducing the risk of BPH progression. The results of this study and other evidence supporting the combined use of finasteride with α-blockers for BPH treatment (7, 8) may account for the growth in finasteride prescriptions.

Interestingly, the majority of both PCPs and urologists cited "moderate to severe BPH" as the patient factor that would make them most likely to consider prescribing finasteride for prostate cancer chemoprevention. BPH is not a risk factor for prostate cancer, yet physicians indicated this as a more influential factor than known prostate cancer risk factors such as family history, African-American race, and elevated prostate-specific antigen. As there is already strong evidence to start finasteride in men with BPH refractory to α-blocker monotherapy from the Medical Therapy of Prostate Symptoms trial (6), this suggests physicians are still uncertain about using finasteride solely for chemoprevention and prefer when its use may already be indicated for treatment of BPH.

Many VHA urologists seem cautious about using finasteride for chemoprevention due to concerns about a potential increased risk of high-grade tumors. Since the initial publication of the PCPT, several studies have done further analyses to assess this and other concerns about the safety and utility of finasteride in preventing prostate cancer. A set of articles (9-11) published since the PCPT suggests finasteride does not increase the risk of...
high-grade disease and the majority of cancers prevented by finasteride are clinically significant. Finasteride’s effect on the prostate gland leads to a detection bias due to changes in prostate volume and improved sensitivity of prostate-specific antigen. Pinsky et al. (9) used modeling techniques to apply the findings in a sample of radical prostatectomy specimens to the entire population of men with prostate cancer in the PCPT. They concluded that because of misclassification bias, the rate of true high-grade disease may have been lower in the finasteride arm. Also using mathematical models, Redman and colleagues (10) estimated high-grade cancer rates of 8.2% in the placebo group and 6.0% in the finasteride group. This translated into a 27% risk reduction in high-grade disease for finasteride users, a finding opposite that of the PCPT. The third study, by Lucia and others (11), examined whether finasteride prevented mostly smaller growing, less consequential prostate cancers. They reexamined biopsies from all PCPT participants and determined only 25% of cancers met criteria proposed by Epstein for clinically insignificant disease (12). These three studies strengthen the case for using finasteride for prostate cancer chemoprevention. They do not, however, provide direct evidence of prostate cancer mortality reduction. As these findings were published after our survey and prescription data analysis, our data do not reflect these most recent analyses.

There may be other factors that inhibit physicians from prescribing finasteride that were not captured in our study. For instance, we did not explore physicians’ interpretations of the relative risk increase of high-grade tumors (27%) compared with the absolute risk increase (1.3%). Perhaps some physicians’ concerns stemmed from a lack of understanding of the meaning of relative versus absolute risk difference. Furthermore, physicians may have felt that they do not have the time in a busy clinic to engage in a lengthy, complicated discussion about the risks and benefits of finasteride chemoprevention. Physician reluctance may also reflect the absence of guidelines recommending use of finasteride chemoprevention at the time of our study. Since our study concluded, the American Society of Clinical Oncology and the American Urological Association jointly developed a clinical practice guideline recommending that men with prostate-specific antigen of ≤3.0 ng/mL who are undergoing regular prostate cancer screening may benefit from a discussion of the risks and benefits of finasteride for the prevention of prostate cancer (13). Such a guideline, in conjunction with the studies described above providing clarity on the risk of high-grade tumors, may help increase awareness among PCPs and ease concerns about finasteride safety among urologists.

Results of the PCPT were widely publicized in the lay press (14), but still most PCPs reported they were not aware of finasteride for chemoprevention. We were not able to determine an explanation for this lack of awareness, although it is likely multifactorial. The National Cancer Institute, which funded the PCPT, presented the results in a clear, unbiased fashion using its established social marketing and public relations principles (14). However, the mixed results of the PCPT complicated the overall message of potential chemoprevention of finasteride. Thus, during the initial window of enthusiasm surrounding the trial, the main message may have been confusing, and this could have inhibited wider spread of the potential of finasteride to prevent prostate cancer. With the publication of the subsequent analyses and guidelines, more is understood about finasteride. Yet, the initial window of enthusiasm about the trial has passed, and thus, dissemination of these new findings may be slower. Nonetheless, we expect that since the completion of this study, knowledge of finasteride for chemoprevention has likely increased both among PCPs and urologists. Another reason for low rates for this use of finasteride may be the prescribing limitations placed on primary care providers in the VHA for use of certain medications. However, only 4 of the 21 regions of VHA had such restrictions in place during the study period.

Our findings raise the question of whether physicians hesitate to use medications for cancer chemoprevention in general (15). Similar to finasteride, tamoxifen and raloxifene have been studied for the prevention of breast cancer.
cancer (16), and aspirin have been studied for the prevention of colorectal cancer (17). Physicians may have low confidence in the effectiveness these medications as chemopreventive agents, concerns about exposing otherwise healthy patients to potential adverse drug effects, uncertainty about the length of time required to prescribe the drugs, and doubts about cost effectiveness (18). They may also have difficulty assessing which patients are most likely to benefit and in providing the counseling needed to reach a shared decision with patients about taking the drug. Lack of expressed patient interest may be another factor limiting use of these medications. Use of cancer chemopreventive agents is difficult to measure as these drugs all have other indications and the indications for use are not routinely recorded in drug databases. Several studies of tamoxifen and raloxifene use for breast cancer chemoprevention show that neither drug is being widely used by physicians or women at increased risk for breast cancer (19-25). Although aspirin is commonly used for cardiovascular disease prevention (26), its use for colorectal cancer prevention is also not known. Thus, the threshold for patients and physicians...
to accept the worthiness of chemopreventive agents seems to be high. Our study has several limitations. For our analysis of prescription data, the indication for each prescription was not available; thus, we were unable to determine whether a given prescription was primarily intended for treatment of BPH or prostate cancer chemoprevention. Because we could not accurately determine the number of men eligible to be prescribed finasteride, we have reported only the number of prescriptions and not a percentage of men who were prescribed finasteride over time. We assumed the proportion of men with BPH remained stable over the time period of the study. In addition, we analyzed the data by excluding men who had also been prescribed an α blocker, in an attempt to examine only those with finasteride prescriptions that were likely to have been prescribed for chemoprevention rather than BPH. Furthermore, as we were not able to ascertain which type of physician wrote each prescription, we were unable to analyze trends in prescriptions separate for PCPs and urologists. We had access to only VA prescription data, so the extent to which patients received finasteride from non-VA health care providers is not known. Our survey had only a modest response rate, but is comparable with other physician surveys. We do not know how the lack of Food and Drug Administration approval for the chemopreventive use of finasteride influences physician prescribing practices, particularly among PCPs who may be less comfortable using finasteride for “off-label” uses. Finally, we did not survey patients directly in this study and thus did not gain insight into whether patients would be keen to take finasteride for chemoprevention even if offered.

Conclusions

We observed the publication of the PCPT was not associated with any change in monthly finasteride prescriptions within the VHA, and few physicians reported changing their prescribing practices based on the PCPT findings. Many PCPs did not know finasteride could be used for chemoprevention, whereas urologists were concerned about high-grade disease. Our findings, if confirmed in other settings, suggest the PCPT had little immediate influence on finasteride use. Even when aware of randomized controlled trial evidence of benefit, physicians seem to be cautious in the chemopreventive setting, in which the patients who are candidates for treatment are otherwise healthy and thus the potential for harm looms large. For prostate cancer, greater use of 5-ARIs for chemoprevention will likely require increased awareness among PCPs, acceptance by urologists of the new evidence disputing the risk of high-grade disease, and greater interest among men who might benefit from taking it.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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