

Expert Opinion

The finasteride riddle

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Abstract

Designed to test finasteride's potential to cut the incidence of prostate cancer, the Prostate Cancer Prevention Trial yielded a paradoxical finding: a decrease in low-grade PCa accompanied by an apparent increase in high-grade disease. As a result of these questionable benefits and apparent harms, the FDA has not approved finasteride for chemoprevention. While recently published follow-up data from PCPT suggests that concern over the risks of finasteride may be unfounded, it also shows that the drug has not saved lives. It may seem that the one remaining role for finasteride is as an adjunct to PSA testing, serving to reduce the risk of overdiagnosis. However, other harms connected to finasteride call even this secondary function into question.

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Introduction

The finasteride story begins some forty years ago with the discovery of a cluster of male pseudohermaphrodites in the Dominican Republic with a hereditary deficiency in 5- α reductase, the enzyme responsible for the conversion of testosterone into the more potent androgen, dihydrotestosterone (DHT). Resembling girls as children, these males have an undeveloped prostate as adults [1]. Given the numbers of aging men who suffer from benign prostatic hyperplasia (BPH), researchers began to wonder if the same enzyme deficiency could be induced in them with beneficial results. Finasteride, a 5- α reductase inhibitor (5-ARI), was synthesized. First tested on human subjects in 1986 and

approved as Proscar (5 mg) in 1992, finasteride enabled the non-surgical treatment of BPH, thereby contributing to the transformation of urology itself [2].

Finasteride and Cancer Prevention

But if a naturally occurring 5- α reductase deficiency suggested the possibility of inducing the same deficiency to treat a "benign" condition, it also suggested that reduced levels of DHT might lower the risk of a malignant one—prostate cancer (PCa), a disease in which DHT is implicated, and from which the Dominican pseudo-hermaphrodites appear to be exempt. Shortly after finasteride was approved as a BPH treatment, the

National Cancer Institute launched a large placebo-controlled trial to test the drug's preventive potential. The Prostate Cancer Prevention Trial (PCPT) ran from 1993 to 2003, when it was stopped because that potential had been realized: the finasteride group saw a 24.8% relative reduction in the incidence of PCa, the trial's primary endpoint [3].

While the idea of a pill that reduces cancer risk—in addition to relieving lower urinary tract symptoms and reducing the risk of acute urinary retention—is certainly attractive, two factors cast a cloud over the promise of finasteride. First, how meaningful was the 24.8% figure? According to the PCPT data, almost half the cancers in the study were found not as a result of suspicious PSA and/or digital rectal exam but the study protocol itself—specifically, a research or end-of-study (EOS) biopsy “offered” to subjects who had not been biopsied for cause. (The intent of the EOS biopsies was to right the imbalance of biopsies caused by the PSA-lowering effect of finasteride.) In their careful analysis of the PCPT data in 2010, FDA reviewers judged the findings of the research biopsies to be of questionable significance, in that the biopsies themselves were “not reflective of clinical practice” [4]. If large numbers of cancers detected in PCPT were not insignificant, how is it that cancer was found in fully 24.4% of the placebo group—men at *low* risk, according to the PCPT entry criteria—while the lifetime risk of PCa death stands at approximately 3.5%? Moreover, the FDA reviewers found that many biopsies that had actually been performed at the end of the study for research purposes were misclassified as for-cause. If one adjusts the numbers accordingly and considers only the cancers detected in for-cause biopsies as clinically significant, the take-home figure of 24.8% dwindles to 14%, and the findings of the PCPT become less impressive.

However, it was not so much the questionable benefits of finasteride as its possible harms that spoiled the festivities. At its conclusion in 2003 the PCPT yielded an unexpected and paradoxical result: in addition to the reduction of PCa by 24.8% in the treatment group, the study found a 26.9% increase in Gleason 7–10 cancers. Thus, while finasteride decreased the incidence of low-grade PCa—in particular, Gleason 6—it was for some reason associated with an increase of the cancers of greatest concern. (The REDUCE trial of the dual 5-ARI dutasteride yielded similar results in a population

at elevated risk) [5]. As a result of this inverted risk-benefit profile, in December 2010 the Oncologic Drugs Advisory Committee of the FDA recommended 17-0 against the use of finasteride for purposes of prevention. In 2011, the FDA ordered revisions to the labels of 5-ARIs stating that they are not approved for the prevention of PCa, and issued a notice stating that men treated with 5-ARIs for BPH were at elevated risk of high-grade PCa. While finasteride remains in use as a BPH treatment, in the decade since the striking results of the PCPT were filed it appears that few doctors have recommended the off-label use of the drug to reduce the risk of PCa.

Ever since the PCPT results appeared in 2003, many have suspected that the increase in high-grade cancer found in the finasteride group was an artifact of the study, in that finasteride shrinks the prostate, thereby making detection more likely. (There is also a theory that by suppressing Gleason ≤ 6 cancer, finasteride reduces interference with the high-grade cancer signal.) This explanation was post-hoc, however, and as such resembled an effort to explain away unwanted information. In the absence of solid evidence of finasteride's safety, the FDA was right to interpret the increase in high-grade cancer conservatively. Wrote FDA reviewers in response to the Merck application, “Chemoprevention strategies administer drugs to otherwise healthy individuals. Therefore, only the highest level of evidence that demonstrates a statistically persuasive and clinically meaningful benefit in the context of a favorable risk-benefit analysis supports the use of a drug for cancer chemoprevention”. The mixed results of the PCPT do not meet this standard.

The picture may or may not have changed with the emergence of data from the Health Professionals Follow-up Study in 2012. According to a report presented to a meeting of the New England section of the American Urological Association, study subjects who took finasteride for BPH at any time since 1986 showed a 25% reduced risk of PCa, a 39% reduced risk of Gleason 7 disease, and no increase or decrease of Gleason 8–10 disease. In the light of concerns raised by PCPT about high-grade cancer (defined in PCPT as Gleason 7–10), such reassurance was welcome.

However, the incidence of PCa is really a surrogate for the outcome that matters most—death. In the case of Gleason ≤ 6 disease, the surrogate endpoint is an

especially tenuous one, in that the cancer may not even manifest itself clinically. While the PCPT ran for a full decade, following the study population all the way to death would have required a much longer trial, and so the designers settled for the secondary outcome, as unreliable as it may be. (According to FDA reviewers, there were but five PCa deaths on the treatment arm of the PCPT and six on the placebo arm. By contrast, 400 died of cardiac disorders.) Now that we have reached the twenty-year mark since the launch of PCPT, one would like to know how the study population fared. Did the excess of high-grade cancers on the finasteride arm lead to an excess of deaths? Recently, a follow-up report on the PCPT population appeared, and in the PCPT tradition it yielded results encouraging on the one hand but deflating on the other.

The conclusion of the follow-up study reads:

Finasteride reduced the risk of prostate cancer by about one third. High-grade prostate cancer was more common in the finasteride group than in the placebo group, but after 18 years of follow-up, there was no significant between-group difference in the rates of overall survival or survival after the diagnosis of prostate cancer [6].

If the excess of high-grade cancer were actually fueled by finasteride, this effect has had time to manifest itself in an excess of mortality on the finasteride arm; yet no such excess has been detected. It appears, then, that the increase in high-grade cancers associated with finasteride in PCPT may actually have been an artifact of detection bias, as many theorized. It should be noted, however, that the study reports overall mortality, not prostate-cancer mortality, and that men with high-grade cancer in the PCPT placebo group could have seen anything from a 30% decrease in the risk of death to a 27% increase.

But if the risk of increased mortality suggested by PCPT did not materialize, neither did the promise of decreased mortality. It turns out that the reduced incidence of PCa in the finasteride group did not translate into fewer deaths; the risk-reduction was driven entirely by a decrease in cancers that rarely lead to death. Just as PCPT left questions about the meaning of a 24.8% decrease of an over-detected cancer of ambiguous significance, we are now left wondering what the point might be of taking a drug that reduces no risk except that of being diagnosed with a cancer of dubious clinical

import. Is the finasteride question much ado about little?

Even as the PCPT began in 1993, mass screening for PCa was catching on in the United States, and by the end of the decade millions of men had PSA testing in the aggressively promoted belief that early detection equals saved lives. (Of course, if all those who learned to think of themselves as survivors of PCa really had their lives saved, the death rate of the disease would have been higher than before screening.) The timing of all this bears comment. Over the ten years of the PCPT, doctors did not go ahead and prescribe finasteride off-label to prevent PCa; they waited for the results of the PCPT to see if it prevented PCa, and if so, with what accompanying risks. In the simultaneous case of PSA testing, doctors did not wait for the results of randomized trials to materialize; as if a public-health emergency existed, they went ahead and screened as many men as possible, even though the benefits of PSA testing were assumed while the harms that followed from testing—not least, impotence—were undeniable.

Furthermore, the distortions that make PSA testing look more effective than it is were already known when mass screening began. Both “lead-time bias” (the illusion that detecting cancer earlier extends survival) and “length-time bias” (the tendency of screening to detect slower, more indolent malignancies) were understood well enough to be cited in a 1993 editorial by one of the prime movers of PSA testing, William Catalona [7]. Dr. Catalona also took the position that it is more convenient for the doctor to fold a PSA into the patient’s blood-work than to secure informed consent [8]. To compound the neglect of informed consent, at the time prostate-cancer screening established itself in the United States, “the popular media had not yet fully publicized the dilemmas and controversies of treatment for prostate carcinoma” [9]. To men with little knowledge of PCa, well might the dramatic increase in diagnosed cancer as a direct result of mass screening seem like evidence of the urgent necessity of screening itself.

With the screening of the eligible male population—whether informed or not—in shopping malls, parking lots, churches, and workplaces as well as clinics, American urology set in motion a program that may have contributed to a reduction of PCa mortality, but at the cost of untold overtreatment with serious adverse effects. It is presumably because of the harms that flow

from screening that perhaps only 50% of male internists in the United States undergo PSA testing [10].

Now that the hope of saving lives with finasteride seems to have gone up in smoke, its one remaining preventive role is to buffer the harms of PSA testing itself—harms that have caused professional bodies, one after another, to scale back their endorsements of mass screening and affirm the importance of informed consent. Finasteride, it seems, is not a life-saver but a bit of insurance. Take it and you reduce the risk of being diagnosed with a cancer of doubtful significance, like so much detected in the PCPT. Whatever headline about finasteride the PCPT yielded, it also showed just how much latent PCa is there to be found if you are really determined to find it.

Finasteride and Adverse Events

As it happens, finasteride does have another use in prevention, albeit not preventive medicine. Marketed in a 1-mg dosage as Propecia, it serves to prevent hair loss—another affliction those born with a 5-ARI deficiency are spared. Readers of this journal may not be aware that lawyers in the United States are actively recruiting men to join a number of suits against Merck, the maker of Propecia, on the grounds that the drug causes permanent sexual impairment among other woes. Propecia was approved by the FDA in 1997.

In the PCPT population (median age at randomization: 63), a high percentage of the finasteride group reported loss of libido (65.4%) and erectile dysfunction (67.4%), though the corresponding numbers in the placebo group were almost as high: 59.6% and 61.5%. The American Society of Clinical Oncology/American Urological Association evidence-based guideline on the use of 5-ARIs for chemoprevention notes adverse events associated with the drugs, including decreased libido and erectile dysfunction, but judges them reversible [11]. In 2011 the FDA ordered revision of the labels of both Propecia and Proscar to reflect reports of erectile dysfunction that persisted after cessation of treatment, and in 2012, in response to further reports, it ordered further revisions “despite the fact that clear causal links between finasteride (Propecia and Proscar) and sexual adverse events have NOT been established” (FDA’s emphasis). Evidently the same regulatory body that rigorously reviewed the PCPT data down to the last

digit felt compelled to lend some credence to word-of-mouth information. Concerning Proscar, the FDA wrote in 2012:

FDA reviewed 131 cases of erectile dysfunction and 68 cases of decreased libido associated with the use of finasteride 5 mg submitted to the drug sponsor’s worldwide safety database between 1992 and 2010. Where information was available, these reported events of erectile dysfunction and decreased libido lasted for at least several weeks after drug discontinuation.

Thus in at least some of the 199 “cases” of sexual problems “associated” with finasteride (5 mg) no information was available to the FDA itself. We seem to be witnessing a snowball effect, whereby unverified reports—in a word, rumors—somehow achieve regulatory recognition.

Trying to trace reports of the irreversible sexual effects of finasteride to their source is indeed like trying to track down a rumor. (If sexual problems allegedly continued “for at least several weeks” after Proscar was stopped, the problems were not irreversible.) As I write, lawyers allege that men’s lives are being ruined by Propecia, and as if trying to leverage anecdote into reality these lawyers cite a study in the *Journal of Sexual Medicine* that cites European regulatory notices that cite reports of “persistence of erectile dysfunction after discontinuation of treatment with Propecia.” As for the study itself, it tested no interventions; lists among its own limitations a post-hoc approach, selection bias, and recall bias; admits the subjects were recruited from one of the authors’ practices and from a Propecia help forum; and notes that subjects attributed to the drug not only their sexual complaints but a number of problems from fatigue to “cognitive difficulties” [12]. The reason blinded, placebo-controlled trials are run in the first place is to correct for the sort of biases and loose causal attributions built into this study.

It seems circulating anecdotes of debilitating sexual problems were picked up by European regulators and validated by a methodologically deficient study which in turn serves as an authority for the lawyers. But if anecdotes can be amplified into something like evidence, sexual problems themselves can be amplified by anxiety about such problems.

A well-conducted study also published in the *Journal of Sexual Medicine* shows the power of even cautious language to inflame sexual problems. Struck by the

difference between rates of sexual side effects associated with finasteride in clinical trials and the higher rates observed in practice, researchers in Italy devised an experiment to account for it. One hundred twenty middle-aged men diagnosed with BPH were randomly divided into two groups, one of which received 5 mg finasteride described only as a “compound of proven efficacy for treatment of BPH,” while the other received the same drug along with the notice that “it may cause erectile dysfunction, decreased libido, and problems of ejaculation, but these are uncommon.” In contrast to the PCPT population, the study subjects ranged in age from 45 to 65 and had no sexual dysfunction at the start. At one year, each of the adverse events occurred about three times more often in Group II, with erectile dysfunction leading the list—no less than 30.9% of men in Group II reported it. Just as a consent form in a clinical trial can cue subjects even in the placebo group into experiencing specified side effects, so the “counseling” received by Group II prompted these patients to experience the very troubles they were advised of, and which they undoubtedly hoped to avoid.

In total, no less than 43.6% of the advised men reported one sexual dysfunction or another, compared with 15.3% of men in Group I—such was the anxiogenic effect of the disclosure language [13]. (Contrary to circulating reports, none of the dysfunctions was irreversible.) As if the negative expectations set up by this language drowned out all reassurance, the statement that sexual harms due to finasteride are uncommon became untrue over the course of the study. Should a doctor then keep silent about these harms, lest he or she magnify them? That would be unethical, given that “the sexual dysfunction related to taking finasteride for BPH...might be the sort of side effect that would be material to some patients’ decision whether to undergo the treatment” [14].

Far from being an anomaly, the findings of the BPH study are consistent with the entire body of research on what is known as the nocebo effect (the reverse of the placebo effect). Moreover, similar results emerged from a study in which men taking the antihypertensive drug metoprolol were randomly sorted into three groups, of which one was told METO might induce erectile dysfunction, though “this side effect is rather uncommon”; one was told the drug was METO but given no information about sexual effects; and one was neither given

the name of the drug nor informed of sexual effects. After 60 days, the incidence of erectile dysfunction was 32% in group 1, 13% in group 2, and 8% in group 3 ($P<0.01$) [15].

Taken together, these studies point to the perhaps unsuspected risks of informed consent [16].

Conclusion

While PSA testing does not set up negative expectations like a study of the nocebo effect, it does play on anxiety, does tend to snowball (as suggested by its rapid evolution over the 1990s from experimental beginnings to the largest mass screening program in the United States), and is driven by the power of emotive messages. Consider an analogy, then, between the Propecia phenomenon and mass PSA testing. Propecia causes sexual problems, but probably not of the devastating severity alleged by interested lawyers; PSA testing may reduce PCa deaths, but probably not by as much as the public has been led to believe, and in any case it also leads inexorably to overtreatment. Men can become so convinced of the harms of Propecia that they attribute their problems to it, from anxiety itself to “mental foginess.” Men can also become so convinced that PSA testing saves lives that they firmly believe themselves survivors even if the cancer they had removed was unlikely ever to cause problems.

It is because PSA testing grew into a mass movement, with the excesses inseparable from such a movement, that the urologists who set this phenomenon going are now looking for ways to rein in its harms. Introduced to the market around the same time as PSA testing itself, finasteride has been nominated for this role. However, finasteride brings its own harms: sexual harms. If these can be tripled by disclosure language that plays them *down*, then use of finasteride by healthy men as an adjunct of PSA testing would be ill-advised—unless they want to take a drug like sildenafil to manage the risks of the finasteride being taken to lessen the risks of screening for PCa.

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