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The finasteride prostate cancer prevention trial (PCPT) – What have we learned?

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Abstract

In 2003, the first of two large NCI-sponsored prostate cancer chemoprevention trials was reported. The prostate cancer prevention trial (PCPT) demonstrated a 24.8% reduction in the prevalence of prostate cancer in men taking finasteride 5 mg/d for 7 years. However, despite the overall reduced risk of prostate cancer, men in the finasteride-treated arm of the study were more likely to develop high-grade disease. This article examines some of the controversies aroused by the PCPT and evaluates some of the arguments that have been advanced in an attempt to explain some of the unexpected outcomes of the study. In addition, some of the recent studies assessing the potential impact of an effective chemopreventive strategy on population mortality are reviewed. To conclude, there is some discussion of factors, which need to be openly discussed with male patients who might be considered for finasteride therapy.

Keywords: Prostate cancer; Chemoprevention; PCPT; Finasteride

1. Introduction

The interest of both the urological and scientific communities in prostate cancer chemoprevention was greatly heightened by the publication of the outcome of the first prospective, randomised controlled prostate cancer prevention trial (PCPT) [1]. An indication of the impact of this study is evidenced by the fact that this paper became the most frequently cited urological paper in 2003. To date, the PCPT has been the largest study ever conducted in the urological community, although in due course it will be overtaken by the larger SELECT prostate cancer prevention trial. The vital role of androgens in prostate carcinogenesis as well as the absence of benign prostatic hyperplasia (BPH) and prostate cancer in men with congenital deficiency of 5-α-reductase (5-AR) type 2 led to the supposition that blocking 5-AR may serve a chemopreventive function, forming the rationale underpinning the PCPT. The PCPT was established in 1993 and recruited 18 882 healthy volunteers aged 55 years or over with a normal digital rectal examination and a serum PSA less than 3 ng/ml. These men were randomised to receive either 5 mg of the 5-α-reductase inhibitor, finasteride, or placebo and were examined annually with a digital rectal examination (DRE) and serum PSA with suspicious findings resulting in biopsy. After 7 years, all subjects were scheduled to undergo end of study prostatic biopsies. The primary endpoint was the prevalence of biopsy-detected prostate cancer, and the study was powered to reveal a 25% reduction in prostate cancer incidence in the presence of finasteride [2]. The first results were expected in October 2004, but the study was terminated prematurely and the outcome reported in 2003 [1]. The results showed that finasteride administration resulted in a 24.8% reduction in prostate cancer incidence over the study period. This is the first prospective study to demonstrate such a large clinically relevant

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reduction in prostate cancer incidence. The risk reduction associated with finasteride among risk groups defined by age, family history, race and PSA was of the same general magnitude. However, the study also revealed that the finasteride-treated group developed a significantly higher proportion of high-grade tumours of Gleason score 7 and above (6.4%) compared with the placebo group (5.1%). Sexual side effects were also more problematic in the finasteride group whereas urinary symptoms were more common with placebo. These results have sparked much controversy and discussion. On the basis of the results of the PCPT, finasteride chemoprevention cannot be recommended unreservedly; a careful risk-benefit analysis with the patient must be undertaken [3]. Nevertheless, despite the obvious caveats, the study provided a valuable insight into the design and conduct of a large scale chemoprevention trial and certainly provides a rationale for further such trials. As is almost universal with studies of this scale, the PCPT produced some answers but also raised additional questions, which require clarification before perhaps the full impact of the PCPT can be realised. Questions arising over data interpretation from the PCPT include:

1. Why was the incidence of prostate cancer in both arms of the study higher than anticipated?
2. Were the cancers detected (especially cancers diagnosed by end of study biopsy) clinically relevant?
3. Does finasteride administration result in a true increased risk of high-grade disease or is this finding an artefact of the study design?

2. The unexpected high incidence of prostate cancer

The PCPT has been criticised for being unrepresentative on the basis that the prevalence of prostate cancer in the placebo arm of the study was 24.4%, four times higher than the 6% assumed for the trial design. In addition this figure might seem even more exaggerated since the study group was already pre-screened such that entry criteria included a normal DRE and PSA < 3 ng/ml at the time of recruitment. It is now apparent that the 6% assumption was an error based on SEER (Surveillance, Epidemiology and End Results) incidence estimates, which relate to clinically evident cases and not to the prevalence of biopsy-detectable disease in a pre-screened population undergoing not only biopsy "for cause" but also end of study biopsy when there was no clinical indication [4]. It is noteworthy that the incidence of clinically evident tumours detected by "for cause" biopsies (*i.e.* abnormal DRE or elevation of the PSA during the study) was 7.2% at 7 years and more closely resembles the figure expected from the SEER data [4].

The outcome of the GSK-sponsored REDUCE trial is now eagerly awaited (despite differences in the agent being used and the study design) to see if the same phenomenon concerning high-grade tumours is apparent. In the REDUCE trial the effect of dutasteride 500 μg/d (a dual inhibitor of 5-AR type 1 and type 2) for 4 years is being assessed in men at increased risk of prostate cancer with a PSA 4–10 ng/ml who have already had a negative prostatic biopsy. The REDUCE trial is now fully recruited and as patients are to be biopsied at 2 and 4 years, further data concerning the possible induction of high-grade tumours by 5-ARIs should soon be available.

Urologists will be only to familiar with the high autopsy incidence of prostate cancer (30% for men aged 30–40 years; 50% for men aged 60–70 years, 100% for men >80 years [5]). The incidence of biopsy detectable prostate cancer in the PCPT is clearly not as high as these figures but the high rate of cancer detection in the PCPT does automatically raise the question whether the cancers detected in the PCPT trial were clinically relevant?

3. Were the cancers clinically relevant?

Of the 1950 prostate cancers detected in the PCPT study group, 1006 (52%) were detected after a "for cause" biopsy prompted by either an elevated PSA or an abnormal digital rectal examination. Currently, this is how many cases of prostate cancer are presented in the clinic and diagnosed. Such patients would be common place in clinical practice and treated in the appropriate way. There is little controversy surrounding this group of tumours. The major controversy surrounds the 944 cancers detected by end of study biopsies. The authors have reported that of these 944 tumours, 21.1% were in men with a PSA in the range 2.5–3.9 ng/ml, a range where studies have demonstrated and most urologists concur that clinically significant cancer is as common as in men with a PSA between 4 and 10 ng/ml [3]. Another 15.4% of cancers were high-grade (Gleason 7–10), a characteristic for which there is almost universal recognition of the potential for an aggressive natural history. These statistics have led the authors to conclude that of the cancers detected in the study, a minimum of 90% met criteria that are generally accepted to indicate clinical relevance. The as yet unanswered question is whether the Gleason 6 prostate cancers detected in the end of study biopsies will behave any differently from Gleason 6 prostate cancers detected in biopsies prompted by a PSA greater than 4 ng/ml or an abnormal DRE. It is further noted that of all the cancers detected in both study groups, only 75 (3.8%) were Gleason 2–4 tumours that are often considered clinically insignificant. The percentage proportion of tumours of different Gleason score diagnosed following "for cause" biopsy, end of study biopsy, and following RP in US and European settings is given in Table 1.

Table 1
Distribution of Gleason scores in PCPT for-cause biopsies (biopsies over the 7 years of the study prompted by an elevated PSA or abnormal digital rectal examination), PCPT end-of-study biopsies, and in large representative studies in the US and in Europe of patients undergoing radical prostatectomy

Gleason score	PCPT for-cause 897 (%)	PCPT end-of-study biopsies 928 (%)	Representative US radical prostatectomy series (%)	Representative European radical prostatectomy series (%)
2–4	5.5	2.8	11.1	2
5–6	57.1	77.7	61.2	61
7	24.6	16.5	22.6	34
8–10	12.8	3.0	3.8	3

4. Does finasteride result in an increased risk of high-grade cancer?

Perhaps the greatest controversy following the publication of the PCPT results is the issue of whether finasteride truly increases the risk of developing high-grade prostate cancer (HGPC) or whether this finding is an artefact of study design.

Several authors had predicted that this might be the case and have argued strongly in the literature that this is a real phenomenon. Several hypotheses have been advanced to explain the increase of HGPC as follows:

1. finasteride induces HGPC;
2. finasteride induces development of HGPC by changing the hormonal environment;
3. finasteride alters the morphology of prostate cancer cells similar to the known effect of androgen-deprivation therapy, such that they resemble HGPC;
4. finasteride causes a detection bias with regard to HGPC by reducing the prostate volume.

4.1. Does finasteride induce the development of HGPC?

This question could be rephrased, in practical terms, as follows: "does a prostate cancer destined to have a Gleason score 6 instead develop into a cancer with a Gleason score of $\geqslant 7$ and behave biologically and clinically accordingly?"

If this were the case, the authors have suggested that a gradual and progressive increase in the ratio of HGPC in the finasteride-treated group compared with the placebo group would be observed over the study period whereas this, in fact was not the case. The ratio was 2.5 during Year 1 and rose to its maximum level of 3.6 during Year 2. The lowest ratio was 1 seen during Year 4 and finished at 1.6 at the end of the Year 7 (Fig. 1).

4.2. Does finasteride induce the development of HGPC by changing the hormonal environment?

There are those who hold assiduously to the view that the results of the PCPT were entirely predictable and that there was biochemical, laboratory, epidemiological and clinical data indicating that the trial was flawed from the outset and that finasteride would promote prostate cancer [6]. In Gleason grades 1–3 prostate cancer, there is minimal 5-α-reductase activity and in Gleason grades 4 and 5 prostate cancer, there is none [7,8]. This led some authors to be highly sceptical concerning the rationale of the PCPT, although biochemical features of established cancer may not necessarily provide the best evidence for the biochemical pathways most suitably disrupted in chemopreventive strategies. Most recently, a further hypothesis has been generated as a biochemical explanation of the higher incidence of HGPC [9]. Imanov indicates that within the prostate the second estrogen receptor (ER-β) has a role suppressing proliferation

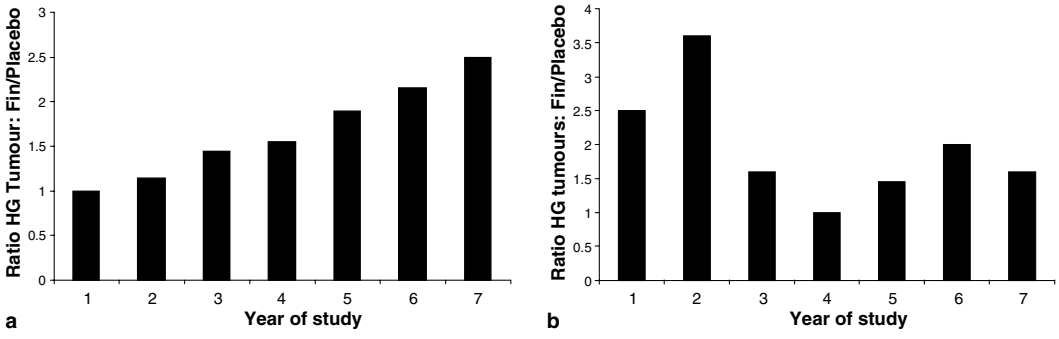

Fig. 1. Projected induction of high-grade prostate cancer expected on the basis of: (a) cumulative dose and (b) as observed in the PCPT. Incidence is expressed as ratio of finasteride/placebo groups. Adapted from Thompson [3].

and promoting differentiation, counterbalancing the androgen receptor which causes proliferation and secretion. These workers have recently discovered the putative natural ligand for ER-β. This turns out to be 5-α-androstane-3β, 17β-diol (3β-androstanediol) which is, in fact, a metabolite of dihydrotestosterone (DHT). They suggest that finasteride, by blocking the conversion of testosterone to dihydrotestosterone, inhibits the production of 3β-androstanediol, thus suppressing ER-β and preventing the differentiation of the prostatic epithelium. As a consequence, they recommend that in future chemoprevention trials finasteride should be used in combination with an ER-β agonist.

4.3. Does finasteride alter the histo-pathological morphology making Gleason scoring more difficult?

This question could be rephrased in practical terms as follows: "does a prostate cancer with a Gleason score 6 instead appear to the histopathologist to have a Gleason score of $\geqslant 7$ but behaves biologically and clinically as a Gleason score 6 tumour?"

There already is evidence in the literature that conventional androgen-deprivation therapy (LHRH agonists/antagonists and anti-androgens) alters prostate cancer histomorphology with a shift towards higher grades (Fig. 2). Morphologically, most treated cancers have a variety of patterns of high-grade disease, including compressed glands, sheets of tumour cells, small cell clusters and single ribbons of cells [10,11]. This means that the Gleason scoring system becomes unreliable in the setting of hormonal therapy. Finasteride causes DHT deprivation but it does not produce androgen deprivation, and as might be expected, cellular testosterone is increased after finasteride. Whether finasteride causes histological changes in prostatic tissue has been addressed previously [12,13]. In a small number of patients, Civantos [12] reported mild histological changes related to finasteride therapy including vacuolated epithelial cells, prominent basal cells, acinar atrophy and small tumour glands. Most of these features were less common, heterogeneous and milder than in the group treated with androgen deprivation therapy (ADT). Yang [13] reported no significant histological differences in 103 prostate biopsies with and without prostate cancer from men treated with finasteride or placebo. They concluded that prostate cancer in needle biopsies from men treated with finasteride is unaltered and readily identified as cancer. These studies suggest that the impact of finasteride on prostate cancer histology is less than that seen with ADT.

Following the publication of the PCPT results, an expert panel of uro-pathologists was asked to review Gleason 8–10 needle biopsy cases. This panel began by reviewing cases from the medical therapy of prostate symptoms (MTOPS) study – in which long-term finasteride therapy was used to treat men with BPH – and were able to identify a finasteride treatment effect. They subsequently reviewed 141 cases of Gleason score 8–10 from the PCPT and concluded that approximately a third of cases in both finasteride and placebo groups reported 'degenerative changes/treatment effect'. The panel concluded therefore that whilst a grade effect may have been possible, there was no compelling evidence that finasteride affected tumour grade.

In an attempt to specifically address this issue, workers from Memorial Sloan-Kettering Cancer Centre in New York, studied the 5 year clinical outcome of 45 men who had undergone radical prostatectomy (RP) after having been on finasteride therapy for at least 6 months prior to their surgery [14]. The study involved a comparison of the actual outcome with that predicted by the Kattan nomograms using clinico-pathological data before and after surgery. In the study group, the mean duration of finasteride therapy before diagnosis of cancer was 23.6 months (range: 10–35 months), the mean serum PSA (corrected for finasteride) was 11.02 ng/ml (range: 0.92–36.48 ng/ml) and the

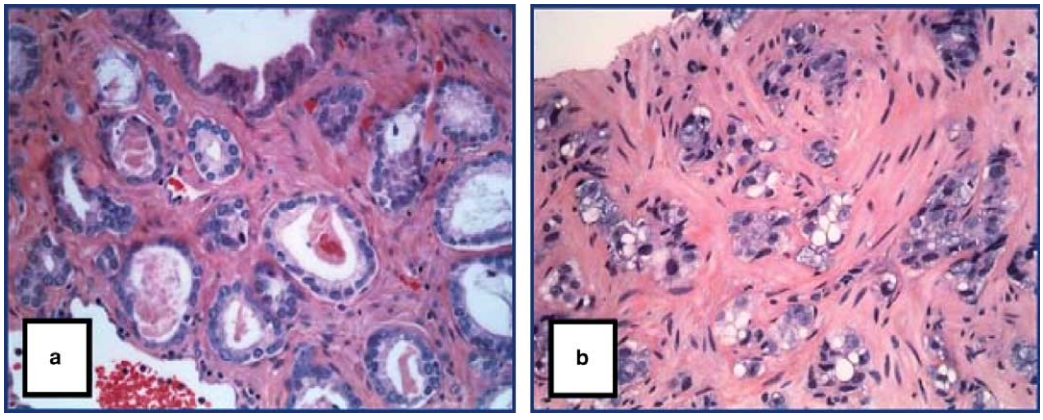

Fig. 2. Histopathological appearance of prostate cancer: (a) before and (b) after androgen deprivation therapy. From Rubin MA, *JCB* 2004, **91**, 478–482.

mean biopsy Gleason score 6 (range: 6–8). A comparison of the biopsy and RP specimen Gleason score, showed it was down-graded by 1 point in 6 men, up-graded by 1 point in 8, up-graded by 2 points in one and was consistent in 30 men. The 5 year actuarial freedom from recurrence was 86% which paralleled the projections of the nomograms predicting a mean 5 year freedom from recurrence of 83% (before) and 85% (after) RP. These authors concluded that finasteride does not appear to compromise the assignment of Gleason grade for use in prediction tools before or after RP in men undergoing prostate biopsy or RP. In determining the relevance of this study to the findings of the PCPT, it must be acknowledged that there were significant differences in the duration of finasteride therapy in this study compared with the PCPT. In due course, a similar analysis will be possible using data from patients with high-grade disease from the PCPT study to determine if the assigned Gleason score remains valid in predictive nomograms and clearly the clinical outcome of these patients can be directly compared with the outcome of other cohorts of men with similar high-grade tumours.

4.4. Does prostate gland reduction have an impact on biopsy outcome?

For those patients receiving finasteride, the median prostate volume was 25.5 cm^3 compared with 33.6 cm^3 for those men in the placebo group. The majority of men in both groups had biopsies in which six cores of tissue were obtained. The overall reduction in gland volume with finasteride was 24%. It has been estimated that 0.48% of the prostate was sampled in the finasteride group and 0.36% in the placebo group [5]. These figures are not particularly helpful as the transition zone (where cancers are rare) accounts for approximately 60% of the total gland volume and more meaningful figures would relate to the volume of the peripheral zone sampled at the time of prostatic biopsies. Using the figures quoted by Pitts [5] and correcting for the transition zone, 0.9–1.2% of peripheral zone tissue is physically removed by six biopsies and this figure would potentially rise to 2.4% if double the number of biopsies are taken (10–12 biopsies are standard practice currently). Assuming that a core of tissue probably represents what is happening in the prostatic tissue immediately adjacent to it on either side, it can be extrapolated that 12 biopsies would be representative of pathologic changes in at least 7% of the tissue in the peripheral zone. It has been suggested that with a 24% reduction in the gland volume it is more likely that biopsies will be positive for cancer. Adjusting for four base line risk factors (age, race, family history and PSA) the odds ratio (finasteride *vs.* placebo) of HGPC was 1.28 (95% CI, 1.08–1.53, $P = 005$). When adjustment included age, race, family history, PSA, number of biopsy cores and gland volume the odds ratio was 1.03 (95% CI, 0.4–1.26 $P = 0.80$).

The question arises whether finasteride has a similar or different effect on the larger transition zone of the prostate where BPH is the predominant pathology as opposed to the much smaller postero-inferior peripheral zone of the prostate where the majority of cancers arise. There are surprisingly few studies in the literature, which directly address this issue. In an early study, soon after the launch of finasteride, it was reported that finasteride had a greater effect on the periurethral (transition) zone of the prostate and although there was a small reduction in the volume of the peripheral zone, this did not reach statistical significance [15]. A later report, however, indicated that the effect of finasteride on prostatic epithelium was similar in the peripheral and transition zones for both morphometric and volumetric changes [16]. Based on this later study, it remains a possibility that volumetric changes in the finasteride-treated prostate influence the cancer detection rate.

5. Further pathological data from the PCPT

5.1. Pathological features of prostatectomy specimens

In the PCPT, tumours were more commonly up-graded after RP in the placebo group than the finasteride arm. 30.5% of patients in the placebo group had their tumours up-graded compared with 24.5% of men in the finasteride arm. Conversely, 12.5% of men in the placebo arm had their tumours down-graded compared with 19.85% in the finasteride arm. If a patient had a high-grade tumour at prostatectomy, the likelihood that this was found at biopsy was 70.3% in the finasteride arm compared with 50% in the placebo arm. In other words, grading appeared to be more accurate from biopsies in the finasteride arm than in the placebo arm. In the PCPT, 98% of tumours were clinically T1 or T2. Subsequent examination of prostatectomy samples showed a similar proportion of T3 tumours in the finasteride and placebo arms. There was also a very similar proportion of tumours with positive margins in each arm.

5.2. Other pathological features of high grade cancers from the PCPT

At the 2005 American Urological Association meeting, some of the authors of the original PCPT study reported on a pathological study of the needle biopsies of high-grade prostate cancers for other prognostic pathological features to better assess their biological aggressiveness [17]. The number and percent of cores positive for cancer, linear extent (mm) of cancer, bilaterality, and perineural invasion (PNI) were recorded with the

hypothesis being that if finasteride induced high-grade cancer pathological features would be worse in the finasteride arm of the study. This hypothesis, however, was not confirmed and the only feature that was significantly different was that prostate cancer was less likely to be bilateral in the finasteride group. It was also noted in this subgroup, that, in keeping with the overall study group, there was a significant reduction in the volume of the prostate. These observations led the authors to suggest that there was a potential detection-bias of HGPC in subjects receiving finasteride in the PCPT.

6. Estimated impact on mortality

Recently, there has been a report of the estimated impact of the PCPT on population mortality [18]. The authors estimated the number of person–years saved assuming a 24.8% reduction in the incidence of prostate cancer for 5 years among US men aged $\geqslant 55$ years. With a 24.8% reduction in the number of men with newly diagnosed prostate cancer, the authors estimated that 316,760 person–years would be saved due to finasteride in the US. An absolute increase of 6.9% in the proportion of men with high-grade cancer in the US cancer population (corresponding to the difference between the rate of HGPC in the placebo and finasteride arms of the PCPT) would reduce the number of person–years saved to 262,567. For each absolute increase of 5% in the proportion of men with high-grade tumours, the number of person–years saved would be reduced by approximately 39,000. Others have included data from the PCPT in a decision analysis model and report survival advantages for a finasteride-treated population of 1.7 months in 15 year cause-specific survival, and up to 3 months for cancers treated conservatively or surgically. Using such a model any improvement in life expectancy due to a preventive strategy aimed at the general population >1 month is regarded as significant [19].

7. The risk/benefit analysis and practical implications

At present, a man in USA has a lifetime risk of 17.3% of being diagnosed with prostate cancer and this would be reduced to 13% by taking long-term finasteride. In practical terms, this translates that with finasteride for every 100 men destined to develop prostate cancer, 4 will not as a consequence of therapy. Clearly, in view of the controversies surrounding data interpretation from the PCPT, there is no clear unequivocal message for physicians and their male patients. But it remains important that physicians facilitate patient understanding of the implications of taking a medical therapy which is currently only licensed for the treatment of BPH and not as a chemopreventive agent. The issue of HGPC is, in fact, included in the datasheet, which accompanies each prescription for the drug but it is unlikely that significant number of physicians prescribing finasteride for the treatment of BPH symptoms allude to this. What, therefore, are the benefits and what are the risks of taking long-term finasteride? Using the PCPT data, men taking finasteride had a 6% absolute reduction in the incidence of prostate cancer, and a reduction in urinary symptoms and complications. Conversely, there was an increased risk of sexual dysfunction in men taking finasteride and an increased risk of HGPC. The advantages and disadvantages are summarised in Table 2 (taken from [3]). How, therefore, do we advise men? As indicated by Thompson [3], central to discussions with male patients needs to be the bothersome of lower urinary tract symptoms, the patient's perception of sexual function and his philosophy concerning possible prostate cancer risk reduction. The size of the prostate is a further factor that could sway a physician in favour of a 5-ARI rather than an α-blocker for the treatment of BPH-related symptoms. For the man concerned about urinary symptoms, finasteride or finasteride in combination with a α-blocker would bring the benefits of maximal improvement in symptoms, a reduction in risk of BPH progression and an absolute reduction in the risk of prostate cancer. In a patient who is sexually active he may choose not to use finasteride or alternatively may prefer a trial of the agent to determine if sexual side effects are encountered. For the man concerned about prostate cancer and wishing to reduce his risk, finasteride could be considered, after appropriate counselling, if the appropriate regulatory changes in the licensing of finasteride are enacted in the future.

Table 2
Risks and benefits of finasteride

Benefit/risk	Absolute difference (%)	In favour of
Prostate cancer diagnosis	6	Finasteride
Genitourinary symptoms and complications	0.3–3.5	Finasteride
Sexual dysfunction or endocrine symptoms	1.7–13.1	Placebo
High-grade cancer diagnosis	1.3	Placebo

Adapted from Thompson *et al.* [3].

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