The PCPT: New Findings, New Insights, and Clinical Implications for the Prevention of Prostate Cancer

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1. Introduction

The Prostate Cancer Prevention Trial (PCPT) was a randomised, placebo-controlled study of the effect of finasteride on the 7-yr prevalence of prostate cancer [1–3]. The study was based on the observation that androgens are not only involved in the growth of the prostate, but also play a key role in development of prostate cancer [4–6]. 5α-Reductase is involved in the conversion of testosterone to the more potent androgen dihydrotestosterone (DHT). There are two forms of the enzyme, type 1 and type 2, and the latter is the predominant isoenzyme found in the prostate. Individuals with congenital deficiency of type 2 5α-reductase have small prostates, undetectable prostate-specific antigen (PSA) levels, and no evidence of prostatic epithelium; they do not develop benign prostatic hyperplasia (BPH) or prostatic cancer [7]. Finasteride selectively inhibits type 2 5α-reductase, reducing both serum [8] and intraprostatic DHT [9].

The PCPT revealed that finasteride significantly reduced the 7-yr period-prevalence of prostate cancer compared with men receiving placebo. However, data from the study showed an unexpected increase in the prevalence of high-grade
tumours in the finasteride arm. This finding has been the topic of much discussion and further analyses of data from the PCPT have been conducted to determine whether it is a true effect or an artefact.

2. The PCPT

The primary end point of the PCPT was the prevalence of prostate cancer in men receiving finasteride or placebo over the 7-yr trial period. Secondary end points included associated mortality (including disease-specific mortality), adverse events (AEs), quality of life (also including sexual function), grade and stage of diagnosed cancers, accuracy of PSA and digital rectal examination (DRE) for diagnosing prostate cancer, and the incidence of BPH. During the study period, subjects underwent an annual DRE and PSA measurement; an abnormal DRE or raised PSA level (>4.0 ng/ml) during the study resulted in the recommendation of a biopsy (termed “for-cause” biopsy). However, because of the known effect of finasteride on reducing PSA levels [10], an end-of-study biopsy was also offered to all patients who did not have a diagnosis of prostate cancer. Results indicated a 7-yr prevalence of prostate cancer of 18.4% in the finasteride arm and 24.4% in the placebo arm among the 9060 subjects included in the final analysis of the study [1]. This represents a risk reduction of 24.8% between the two treatment arms (95% confidence interval [CI], 18.6–30.6; \( p < 0.001 \)). There was a 6% absolute reduction in prostate cancer incidence in patients treated with finasteride. Irrespective of whether detected by for-cause or by end-of-study biopsy, rates of prostate cancer were lower in the finasteride arm. Although there was some variance in the magnitude of the risk reduction effect, all subgroups benefited from finasteride therapy, irrespective of age, race, baseline PSA level, or family history of prostate cancer.

Although a clear overall benefit was seen, biopsy results revealed an unexpected trend: the rate of high-grade prostate cancer (Gleason score \( \geq 7 \)) was slightly, though significantly, raised in the finasteride group compared with placebo (6.4% vs. 5.1%, respectively, \( p < 0.005 \)). This effect was only seen in the for-cause biopsy group and not in the end-of-study biopsy. Given the implications of this increase in high-grade tumours on finasteride therapy for both chemoprevention of prostate cancer and management of BPH, data from the PCPT have been studied further.

3. Does finasteride induce high-grade cancer?

If finasteride had really induced high-grade prostate cancer, there would have been a continued divergence in the risk for high-grade tumours between the finasteride and placebo arms. This effect has been observed in clinical trials on tamoxifen in breast cancer, where the rate of endometrial cancers increased over time [11]. This was not the case in the PCPT. A closer examination of the results from the study revealed that although the incidence of high-grade prostate cancer was greater in the finasteride arm, this effect was seen within 1 yr of study commencement and the cumulative proportional incidence rose at a similar rate to that of placebo throughout the study (Fig. 1) [12].

Evidence of increased biologic aggressiveness of tumours detected in the finasteride group was explored through the histologic examination of high-grade tumours. Results showed that subjects with high-grade prostate cancer who received finasteride were less likely to have bilateral disease, despite a significantly smaller prostate sample.

<table>
<thead>
<tr>
<th>Table 1 – Secondary indicators of aggressive tumour growth in the biopsy samples from the Prostate Cancer Prevention Trial</th>
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<tbody>
<tr>
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<tr>
<td>Mean no. of biopsy cores</td>
</tr>
<tr>
<td>Median number cores positive</td>
</tr>
<tr>
<td>Median percent cores positive</td>
</tr>
<tr>
<td>Greatest linear extent (mm)</td>
</tr>
<tr>
<td>Bilateral cancer</td>
</tr>
<tr>
<td>Perineural invasion</td>
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<tr>
<td>Median prostate volume (ml)</td>
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</tbody>
</table>

Adapted from Lucia S et al. [13].
with an equivalent number of biopsy cores (Table 1) [13]. Other surrogate markers of tumour aggressiveness indicated no significant differences between finasteride and placebo samples.

Given these findings, what other factors might account for this increase in the observed incidence of high-grade cancer in the finasteride arm? A number of potential explanations have been explored including (1) the influence of finasteride therapy on histologic grading, (2) the effect of prostate size on cancer detection, and (3) the effect of finasteride on the performance of PSA in prostate cancer screening. These aspects are discussed in further detail below.

4. Histologic effect

Alterations in the microscopic appearance and immunophenotype of cells in the prostate and in adenocarcinomas, described as “substantial and characteristic” have been reported following androgen-deprivation therapy [14]. The authors observed that these changes were not often seen in untreated cancers and were distinct enough to be consistently identified, suggesting that the changes might be specifically linked to the treatment. However, one study on the effects of finasteride on Gleason score in 45 patients reported no effect of treatment on histologic grading [15]. Likewise, a review of data from the Proscar Long-Term Efficacy and Safety Study (PLESS) found no significant histologic differences between the finasteride and placebo arms in patients who developed prostate cancer [16]. More recent data come from a study of 56 patients with prostate cancer who had previously taken finasteride for 6 mo [17]. Histologic effects were compared with control prostate samples and samples from patients treated with a luteinising hormone-releasing hormone agonist (LHRHa) for 3 mo. Results indicated that finasteride did not induce a greater degree of morphologic change to that observed in the control group. In addition, no consistent hormonal therapy effect with finasteride treatment was observed compared with that seen with an LHRHa. The authors concluded that the morphologic changes due to long-term finasteride are not a likely cause of the greater percentage of high-grade tumours in the study arm.

5. Prostate volume effect

The effect of finasteride on reducing prostate volume has been well documented [18,19]. A 6-yr study with finasteride in 487 patients with BPH resulted in a mean reduction in prostate volume of 24% [20]. This reduction matches closely that observed in the PCPT: median prostate volumes were 25.5 ml in the finasteride arm and 33.6 ml in the placebo arm, a relative difference of 24.1% [1]. It has been shown that cancer detection rates decrease as prostate volume increases, as demonstrated in Fig. 2 [21–23] and that the accuracy of tumour detection and grading of biopsy samples improves with decreasing tumour size [24–26]. Further evidence comes from a study by Kulkarni et al who found that prostate volume was a significant predictor of high-grade disease on prostate biopsy, that is, smaller prostates were correlated with high-grade cancer [27]. This effect was lost when true histologic assessment was performed in radical prostatectomy specimens.

![Fig. 2 - Theoretical model showing prostate cancer detection bias associated with prostate volume.](image-url)
A mathematical model has examined the effect of prostate volume on cancer detection using data from the PCPT. Assuming a 1-ml total tumour volume presenting as four tumours, a prostate volume of 30 ml, six biopsy cores, and a 25% reduction in prostate volume with finasteride, the predicted increase in cancer detection due to change in prostate volume was 20% [28]. The authors of the study suggest that this compares well with the 25% increase in high-grade tumours seen in the PCPT. Based on published findings, it is likely that the increased detection of high-grade tumours in the finasteride arm (vs. placebo) is an artefact, resulting from a detection bias caused by the significant reduction in prostate volume.

### 6. PSA effect

Although the prevalence of high-grade prostate cancer was significantly greater in diagnosed tumours in the finasteride arm compared with placebo (37.0% [280 of 757] vs. 22.2% [237 of 1068] for placebo; \( p < 0.001 \)), this effect was primarily driven by the PSA-initiated for-cause biopsy subset of subjects. Differences between the two arms were not significant in for-cause biopsies recommended due to either abnormal DRE or abnormal DRE plus elevated PSA level. Likewise, differences in the end-of-study biopsies were also not significant. These findings raise the issue of a possible bias in the study design with respect to the role of PSA in detecting prostate cancer.

High PSA levels >4.0 ng/ml were established as predictors of prostate cancer in the early 1990s [29]; since then, detection of prostate cancer has increased markedly [30]. With the advent of the PCPT, the opportunity arose to assess prospectively the predictability of low PSA levels (0–4.0 ng/ml) with respect to all prostate tumours including those of high grade. This sub-analysis concentrated on the placebo arm of the PCPT and selected participants whose PSA levels had remained ≤4.0 ng/ml, had a normal DRE, had not undergone a for-cause biopsy or transurethral resection, but had undergone an end-of-study biopsy [31]. A total of 2950 of the 9459 men who were randomised to the placebo arm in the PCPT were eligible and included in the analysis. The results revealed that there was a natural progression of prostate cancer with increasing PSA levels, which also applied to high-grade tumours. As the PSA level increased, so did the prevalence of all prostate cancers including high-grade cancer (Fig. 3). Thus, a PSA level ≤0.5 ng/ml equated to a 6.6% risk of developing prostate cancer and a 0.8% risk of developing high-grade disease, whereas values of 3.1–4.0 ng/ml were associated with a 26.9% risk of developing cancer and a 6.7% risk of developing high-grade disease.

More recently, analyses of the receiver operating characteristics (ROC) of PSA have been conducted, suggesting that PSA performance is improved in patients receiving finasteride, in terms of overall detection of cancer, as well as for high-grade cancers. In an analysis of the 5112 men in the placebo arm who underwent PSA screening and a prostate biopsy in the PCPT, 1111 cases of prostate cancer were detected, of which 240 were Gleason score > 7 and 55 were Gleason score > 8 [32]. Of the 4579 men in the finasteride arm, 695 were diagnosed with cancer; 264 were Gleason score > 7 and 81 were Gleason score > 8. Analysis showed that area under the ROC curve for finasteride was greater than for placebo, both for cancer detection and for high-grade disease. These data suggest that there was a bias towards greater detection of prostate cancer, including high-grade prostate cancer, in the finasteride group compared with placebo. Therefore, the improved performance of PSA in men receiving finasteride may have played a role in the increased detection of observations regarding high-grade cancer in the PCPT.

From a clinical perspective, increased specificity of PSA testing may translate into fewer false-positive results and consequently a reduction in unnecessary biopsies. Similarly, increased sensitivity of PSA testing may result in fewer false-negative biopsies and fewer men with prostate cancers left undetected.

**Fig. 3** – Prevalence of all tumours and high-grade tumours in the placebo group of the Prostate Cancer Prevention Trial stratified by prostate-specific antigen (PSA) level [31].
Table 2 – Incidence of medical events and adverse events in the Prostate Cancer Prevention Trial

<table>
<thead>
<tr>
<th>Event</th>
<th>Finasteride (n = 9423)</th>
<th>Placebo (n = 9457)</th>
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<tbody>
<tr>
<td><strong>Effects on sexual functioning or endocrine effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced volume of ejaculate</td>
<td>5690 (60.4)</td>
<td>4473 (47.3)</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>6349 (67.4)</td>
<td>5816 (61.5)</td>
</tr>
<tr>
<td>Loss of libido</td>
<td>6163 (65.4)</td>
<td>5635 (59.6)</td>
</tr>
<tr>
<td>Gynaecomastia</td>
<td>426 (4.5)</td>
<td>261 (2.8)</td>
</tr>
<tr>
<td><strong>Genitourinary effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPH</td>
<td>488 (5.2)</td>
<td>823 (8.7)</td>
</tr>
<tr>
<td>Increased urinary urgency or frequency</td>
<td>1214 (12.9)</td>
<td>1474 (15.6)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>398 (4.2)</td>
<td>597 (6.3)</td>
</tr>
<tr>
<td>Transurethral resection of the prostate</td>
<td>96 (1.0)</td>
<td>180 (1.9)</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>418 (4.4)</td>
<td>576 (6.1)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>90 (1.0)</td>
<td>126 (1.3)</td>
</tr>
</tbody>
</table>

BPH = benign prostatic hyperplasia.
Reproduced with permission from Thompson et al. [1].

7. Urologic effects of finasteride

In the PCPT, finasteride was associated with significantly fewer genitourinary effects, with fewer BPH diagnoses (5.2% vs. 8.7% for placebo). Similarly, there were significantly fewer cases of acute urinary retention, urinary urgency/frequency, transurethral resections of the prostate, prostatitis, and urinary tract infections compared with placebo (all p < 0.001). Finasteride was well tolerated over the 7-yr study period of the PCPT. It was associated with a slightly greater incidence of sexual or endocrine AEs (p < 0.001 vs. placebo; Table 2) [1].

8. Conclusions

The PCPT demonstrated that finasteride treatment decreased the risk of prostate cancer by 25% over a 7-yr period. The accumulated body of evidence strongly suggests that the increase in high-grade tumours in the finasteride arm is an artefact resulting from a detection bias driven by two principle factors. First, finasteride treatment leads to a significant reduction in prostate volume, and second, treatment is associated with improved performance of PSA to detect prostate cancer (and high-grade prostate cancer). Importantly, the prostate volume reduction seen in finasteride-treated subjects probably led to increased detection of all prostate cancers, indicating that the risk reduction with this drug was probably greater than that actually reported.

References


