

# Gleason grading controversies: what the chemoprevention trials have taught us

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## ABSTRACT

The recent Prostate Chemoprevention Trial (PCPT), which assessed the efficacy of finasteride in reducing prostate cancer incidence, showed promising results. However, patients who developed cancer had higher Gleason scores than those on placebo. Moreover, recent evidence has shown that the biopsy Gleason scores in patients on finasteride were actually more accurate compared with patients on placebo when matched with the final, radical prostatectomy (RP) scores. This accuracy was due to a reduction in prostate volume induced by the drug, and better performance of prostate-specific antigen correlation for identifying men with high-grade cancer. Re-evaluation of the results based on the pathology of the RP specimens and longer follow-up showed a 30% reduction in cancer incidence with finasteride and no significant differences in Gleason scores compared with placebo

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## Prostate cancer prevention strategies

Androgens, particularly dihydrotestosterone (DHT), contribute to the normal growth and development of the prostate gland. DHT is produced in the prostate from testosterone through the action of 5- $\alpha$ -reductase enzymes (5AR), of which there are two isoforms: type I and type II. Increased 5AR levels have been associated with hyperplastic tissue.<sup>1</sup> In BPH, levels of both enzymes are elevated; in malignant tissue, the level of 5AR-1 is predominantly higher.<sup>2,3</sup>

Androgen deprivation, initially through castration and subsequently through hormonal treatments, has been used successfully to treat advanced prostate cancer.<sup>4</sup> Other approaches to reducing androgen activity have included dietary modification, nutritional supplements and drug treatment. Although there is no specific association between diet and a reduction in androgen levels, some studies have shown a positive correlation between saturated fat intake and prostate cancer risk.<sup>5,6</sup> Diets high in fibre and low in fat are associated with lower incidences of prostate cancer, and it appears that a high-fat diet can increase hormonal bioavailability.<sup>6</sup> A few small studies have suggested that nutritional supplements, such as vitamins D and E, and lycopene, a vitamin A analog, reduce the risk of prostate cancer.<sup>6</sup> Both selenium and vitamin E have been associated with a decrease in prostate cancer incidence,<sup>7,8</sup> and the effect of these two supplements both alone and in combination has been under

investigation in the largest prostate cancer prevention study to date — the Selenium and Vitamin E Cancer Prevention Trial (SELECT).<sup>9</sup>

Chemoprevention is another approach to reducing androgen levels. Inhibition of the 5ARs has been shown to reduce BPH, and to be effective in preventing prostate cancer. In rats, inhibition of the 5ARs was shown to prevent the progression of microscopic to macroscopic prostate cancer.<sup>10</sup> Finasteride, which inhibits 5AR-2, has been used to treat BPH in humans, and has also been shown to reduce the incidence of prostate cancer as demonstrated in the Prostate Cancer Prevention Trial (PCPT).<sup>11</sup>

## Evaluation of prevention trials

Table 1 is a list of phase III trials, completed or in progress, that are testing the use of either drugs or nutritional supplements in reducing the risk of prostate cancer.<sup>12</sup> The PCPT, which evaluated finasteride initially, involved 18 882 participants with a 7-year follow-up.<sup>11</sup> Of the 9060 men who were included in the final analysis, prostate cancer was detected in 803 of 4368 (18.4%) treated with finasteride, and in 1147 of 4692 (24.4%) treated with placebo ( $p < 0.001$ ). Dutasteride is currently being tested in 8000 high-risk patients over a 4-year period in the REDUCE trial.<sup>13</sup>

The SELECT trial, designed to examine the effect of selenium and vitamin E in reducing prostate cancer incidence in 32 400 men, began in 2001 and was scheduled to run for 12 years.<sup>9</sup> However, in September 2008, the SELECT Data and Safety Monitoring Committee reviewed the existing data and enough were available to show that 200 mcg of selenium and 400 IUs daily of vitamin E in pill form do not prevent prostate cancer. Consequently, participants in SELECT were advised to stop taking their study supplements. However, follow-up will be

**Table 1. Phase III chemoprevention clinical trials**

Trial	Population characteristics	No. of subjects	Agent v. placebo	Study length (years)
Prostate Cancer Prevention Trial (PCPT) <sup>11</sup>	Normal DRE; PSA < 3 ng/mL	18 882	Finasteride 5 mg/day	7
Reduction by Dutasteride of Prostate Cancer Events (REDUCE) Study <sup>13</sup>	High risk patients; PSA 2.5 – 10 ng/mL	8000	Dutasteride 0.5 mg/day	4
Selenium and Vitamin E Cancer Prevention Trial <sup>9</sup>	Normal DRE; PSA < 4 ng/mL	32 400	Vitamin E and/or selenium	12 (supplements terminated at 5 years with further follow-up)
Rofecoxib in prostate cancer risk reduction <sup>31</sup>	General	15 000	Rofecoxib (selective COX-2 inhibitor) 25 mg/day	Study terminated due to risk of cardiovascular disease
Physicians Health Study II <sup>32</sup>	Physicians	15 000	Beta-carotene, vitamins C and E	12

DRE = digital rectal exam; PSA = prostate-specific antigen; COX-2 = cyclooxygenase 2 inhibitors.

continued, as the data did suggest that vitamin E may slightly increase the chance of getting prostate cancer, and that selenium may increase the chance of getting diabetes mellitus, although these findings were not proven (<http://www.crab.org/select/>).

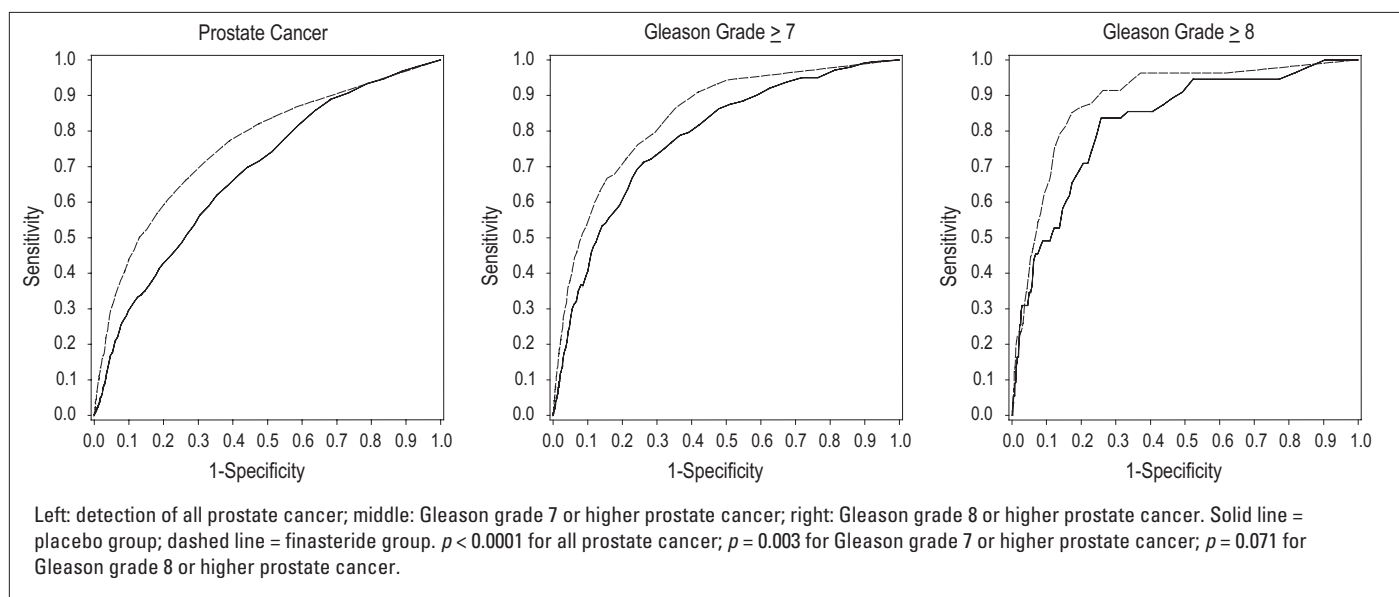
In the PCPT, men with a prostate-specific antigen (PSA) level of 3 ng/mL or lower and randomly assigned to treatment with 5 mg/day finasteride showed a 24.8% relative risk reduction in prostate cancer incidence, independent of family history, age or race.<sup>11</sup> However, Gleason scores of 7 or more were noted in more men on finasteride than on placebo; this generated controversy as to whether this agent should be used as a preventive measure.

### Gleason grading controversies in the PCPT

For all biopsies evaluated in the PCPT, Gleason scores of 7, 8, 9 or 10 were noted in 280 of 757 (37%) men treated with finasteride, and in 237 of 1068 (22.2%) men treated with placebo. Among “for cause” biopsies, high-grade disease was reported in 188 of 393 (47.8%) men on finasteride and in 148 of 504 (29.4%) of men on placebo.<sup>11</sup> Overall, a higher grade disease was found in 6.4% of men treated with finasteride compared with only

5.1% of men treated with placebo, an observation that was disconcerting at first glance. Was it possible that finasteride changed the histology of the prostate such that a low-grade cancer would now appear as high grade, thereby negating the utility of the Gleason grading in determining prognosis? Yang and colleagues<sup>14</sup> showed that finasteride does not induce significant histological alterations in the prostate. Hence, the greater incidence of high-grade disease in the finasteride group was not due to a histological artefact as originally thought.<sup>14</sup> The Gleason grade has also since been proven to be a valid prognostic predictor in men on finasteride.<sup>15</sup> Men with prostate cancer and low testosterone levels have higher Gleason grades and worse outcomes than men with prostate cancer and normal testosterone levels.<sup>16</sup> Similarly, there was the possibility that finasteride may have been selected for high-grade tumours by the suppression of low-grade tumours.

The issue of the accuracy in determining the true Gleason grade in a biopsy has also been questioned. Unfortunately, errors in the predicted biopsy Gleason score are common. Gleason grading and scoring are largely subjective, and since not all pathologists may be equally proficient in reading



**Fig. 1.** Receiver operating characteristic curves for prostate-specific antigen in the Prostate Chemoprevention Trial.<sup>25</sup>

Gleason grades, especially on the small thin-needle core tissue samples obtained at biopsy, observer variation does occur. In a United Kingdom study, 9 uropathologists were asked to grade 81 slides, with a total of 47 slides being read more than once. For the first reading of the 81 slides, consensus agreement was 78%. For the 47 slides read more than once, intra-observer agreement was 77%. Problems in interpretation tended to occur at Gleason score levels of 2 to 4 and at 7.<sup>17</sup> In addition to errors in Gleason grading, biopsy sampling has a bearing on the tissue obtained for histological analysis. In a study to determine the sensitivity of the sextant biopsy protocol compared with a more extensive procedure, 15% of cancers went undetected using the standard sextant protocol.<sup>18</sup>

### Biopsy v. RP results in the PCPT

In a further evaluation of PCPT, prostate biopsy results were compared with those obtained from radical prostatectomy (RP).<sup>19</sup> Tumour grades at biopsy and prostatectomy were assessed for 206 men on finasteride and 283 on placebo. The difference in the number of high Gleason grade tumours in the finasteride group compared with the placebo group diminished at RP. While the biopsy results gave a difference of 42.7% v. 25.4% ( $p < 0.001$ ) for high-grade tumours detected in the finasteride and placebo groups, respectively, at prostatectomy, these figures were 46.4% v. 38.6% ( $p = 0.10$ ), a non-significant difference. Furthermore, no significant

differences in pathological stage, nodal involvement, or margin status were evident between the finasteride and placebo groups. In the finasteride group, the Gleason score at biopsy identified high-grade disease present at RP more frequently than in the placebo group (69.7% v. 50.5% [ $p = 0.01$ ]). These data suggest that the biopsy material for the placebo group was subject to sampling error, likely due to the difference in prostate volume between the two groups. The median prostate volume for men on finasteride was 25.5 cm<sup>3</sup> compared with 33.6 cm<sup>3</sup> for men on placebo, a difference of 24%.<sup>11</sup> Logistic modeling has shown that the probability of detecting high-grade tumours is related to the sampling density such that the likelihood of detection decreases as the volume increases.<sup>20</sup> The model predicted 239 of the 243 high-grade cancers observed in the finasteride group. Furthermore, a retrospective study of 369 cases of prostate cancer, in which biopsy material could be compared with RP material, showed that larger prostate size resulted in fewer high-grade cancers diagnosed at biopsy.<sup>21</sup> Thus, finasteride may have improved the detection of cancer and the grade assignment.

Based on the results seen in the sample of men who had RP results available for comparison with biopsy results, a statistical model was used to extrapolate the RP Gleason results to *all* men in the PCPT.<sup>22</sup> The estimated relative risks for true low-grade and true high-grade (Gleason 7 to 10) disease for finasteride compared with placebo were

0.61 (95% CI 0.51-0.71) and 0.84 (95% CI 0.68-1.05), respectively. The misclassification rate of true high-grade disease to low-grade disease on biopsy was significantly lower for finasteride (34.6%) than for placebo (52.6%). Misclassification rates on biopsy were higher in the placebo arm; therefore, the rate of true high-grade disease may have been lower in the finasteride arm.

### PSA levels and prostate cancer incidence in the PCPT

Prostate cancers associated with lower PSA levels may represent indolent, clinically inconsequential tumours. Insignificant disease by the Epstein criteria includes disease with Stage T1c, PSA density less than 0.15 ng/ml/g, Gleason grade 6 or lower (no pattern 4 or 5) and extent of tumour on biopsy (less than three cores with tumour and no core with more than 50% tumour).<sup>23</sup> In the PCPT, only 24.5% of tumours diagnosed in the placebo group at biopsy could be classified as clinically insignificant using these criteria. Analysis of RP specimens in the placebo group showed disease with Gleason grade 7 or higher in 16% of men with PSA levels below 1.0 ng/mL, 33% of men at 1.1 to 2.5 ng/mL and 43% of men at 2.6 to 4 ng/mL.<sup>24</sup> The sensitivity v. the specificity for PSA has also been analyzed and median PSA density was found to be significantly higher in the finasteride group than in the placebo group with a statistically significant better sensitivity for detecting prostate cancer.<sup>25</sup> Receiver operating characteristic (ROC) PSA curves for detecting cancer v. no cancer showed that the area under the curve (AUC) was 0.757 and 0.681 ( $p = 0.001$ ) in the finasteride and placebo groups, respectively (Figure 1). For Gleason grades 7 or higher v. 6 or

lower or no cancer, the AUCs were 0.838 and 0.781 ( $p = 0.003$ ) in the two groups, respectively. For detecting Gleason grade 8 or higher v. 7 or lower, the AUCs were 0.886 and 0.824, respectively ( $p = 0.71$ ).<sup>25</sup> Men with higher PSA levels in the finasteride group were more likely to have cancer than men in the placebo group who also had higher PSA levels.

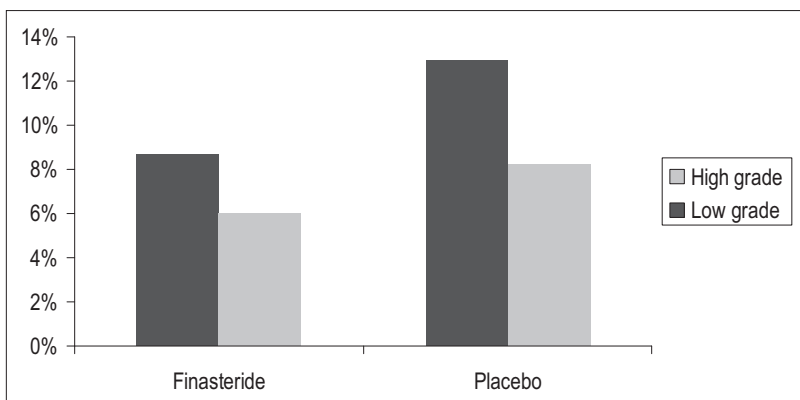
### Re-evaluation of PCPT using most recent data

The PCPT results have been re-evaluated using data collected for three months longer than in the original report, and adjusted for bias as determined by the RP and PSA data.<sup>26</sup> The results (Figure 2) showed a cancer rate of 14.7% in the finasteride arm v. 21.1% in the placebo arm, with a 30% risk reduction with finasteride (RR 0.7). Estimated rates of high-grade cancer using the RP data were 6% for the finasteride group v. 8.2% for the placebo group. The estimated risk reduction with finasteride for Gleason grade 6 or lower was 34% (RR 0.66;  $p < 0.0001$ ) and for Gleason grade 7 or higher was 27% (RR 0.73;  $p = 0.02$ ).<sup>26</sup> Thus, correction for reporting bias showed that finasteride does not increase the risk of high-grade cancer.

### Where do we go from here?

Prostate cancer prevention is an attractive proposition in men at risk, and chemoprevention has shown efficacy, as demonstrated in the PCPT. Finasteride has not yet been widely used for risk reduction because the initial results, which showed an increased risk of high-grade disease, have dissuaded physicians. However, recent data have shown that the increased risk of high-grade disease as demonstrated by initial findings was in effect an artefact.

Dutasteride is currently under investigation for its efficacy in reducing the risk of prostate cancer in at-risk men in the 4-year REDUCE study.<sup>13</sup> It is also being used for treatment, in order to extend the time to progression in men with low-risk localized prostate cancer who would otherwise undergo watchful waiting in the 3-year Reduction by Dutasteride of Clinical Progression Events in Expectant Management (REDEEM) study.<sup>27</sup> The REDUCE trial is expected to provide evidence to address key questions in the risk reduction of prostate cancer: What is the magnitude of risk reduction in men at higher risk than in PCPT; is there a clinical benefit to dual 5AR blockade; can dutasteride prevent high-grade disease; and, finally, who are the ideal candidates for prostate



**Fig. 2.** Estimated numbers of subjects with low-grade and high-grade cancer in the Prostate Chemoprevention Trial using prostatectomy data. Among patients on finasteride, 8.7% and 6% developed low-grade and high-grade cancer, respectively, compared with 12.9% and 8.2% for those on placebo.<sup>26</sup>

cancer risk reduction? First results of the REDUCE study are expected in 2009.

Chemoprevention for men at risk could likely be tailored more specifically if further work is carried out on genetic predisposition for prostate cancer. Functional polymorphisms have been observed in the 5AR-2 gene and there are variants associated with high activity and those with low activity.<sup>28</sup> The low-activity V89L variant has been associated with prostate cancer<sup>29</sup> and, interestingly, in a French study, an increased risk of aggressive prostate cancer was associated with this variant.<sup>30</sup> Furthermore, finasteride exhibits differing degrees of efficiency in inhibiting different variants with as much as a 60-fold variation in activity.<sup>28</sup> Thus, the relationship between androgen deprivation and cancer risk is complex and needs to be investigated more fully, and men with a given polymorphism may benefit more or less from 5AR inhibition with finasteride. Although chemoprevention may prove to be efficacious in reducing prostate cancer incidence, the benefit of gain will have to be weighed against the possibility of adverse events in otherwise healthy men when considering treatments for prostate cancer risk reduction.

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