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The Risks and Benefits of 5α-Reductase Inhibitors for Prostate-Cancer Prevention

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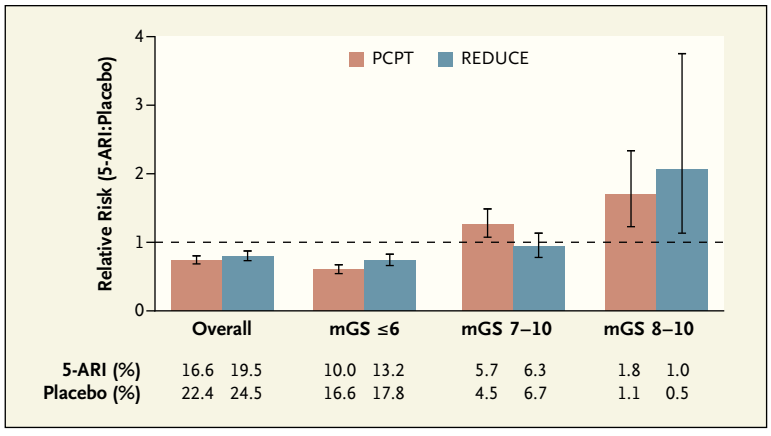
The use of 5α-reductase inhibitors for prevention of prostate cancer continues to be widely discussed within the scientific and medical communities.[1] Much of this discussion has been fueled by the findings of two large randomized, placebo-controlled trials — the Prostate Cancer Prevention Trial (PCPT) with finasteride and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial (ClinicalTrials.gov number, NCT00056407).[2,3] Together, these trials showed an overall relative reduction of 23 to 25% in prostate-cancer diagnoses, a seemingly significant benefit from drugs aimed at preventing one of the most common cancers in men. However, the observed reduction resulted from a decreased incidence of only low-grade prostate cancer (Gleason score, ≤6). In fact, in both trials, there was an absolute increase in the incidence of high-grade prostate cancers in the chemoprevention group.

Evaluating the potential chemopreventive benefits of 5α-reductase inhibitors and assessing the potential increased risk for high-grade prostate cancers have been central issues for the Food and Drug Administration (FDA). There has been much hope for an FDA-approved chemopreventive agent for prostate cancer, and there is clearly ongoing off-label use of 5α-reductase inhibitors for this indication.[4] The FDA has been actively evaluating the relevant data and held a meeting of its Oncologic Drugs Advisory Committee to address this topic in December 2010.[5]

Both chemoprevention trials were conducted in men who were at risk for prostate cancer but did not have diagnosed prostate cancer at study entry. The FDA analysis of the trials confirmed that there was a relative reduction of approximately 25% in the overall incidence of prostate cancer and a significantly increased incidence of high-grade prostate cancers. During the FDA review of the REDUCE trial, we requested that biopsy specimens be reassessed, according to the modified Gleason scale, by an independent pathologist who was unaware of the earlier scores. The central pathologist for PCPT performed this reassessment.[5] The use of modi-



Relative and Absolute Risk of Prostate Cancer According to Modified Gleason Score (mGS), PCPT and REDUCE Trial.

The abbreviation 5-ARI denotes 5α-reductase inhibitors. I bars indicate 95% confidence intervals.

fied Gleason scores is consistent with current recommendations for prostate-cancer grading and the grading system used in PCPT; modified Gleason scores were not originally reported in the REDUCE trial.[3]

The reassessment revealed no reduction in the incidence of tumors with modified Gleason scores between 7 and 10 — a finding that was consistent with the published data. However, an absolute increase of 0.5% in the incidence of tumors with modified Gleason scores of 8 to 10 (relative risk, 2.06; 95% confidence interval [CI], 1.13 to 3.75) was observed with dutasteride treatment. This increase is similar to the absolute increase of 0.7% in the incidence of such tumors observed with finasteride treatment (relative risk, 1.70; 95% CI, 1.23 to 2.34) (see graph). These results suggest that one additional man would receive a diagnosis of high-grade prostate cancer (modified Gleason score, 8 to 10) for every 150 to 200 men treated long-term with a 5α-reductase inhibitor.

It has been suggested that detection bias, attributable to the fact that 5α-reductase inhibitors reduce serum levels of prostate-specific antigen (PSA) and prostate volume, led to an increase in detection of high-grade prostate cancer in the finasteride group of the PCPT.[5] Indeed, the sensitivity of an elevated PSA level (a PSA level above 4 ng per milliliter in the placebo group or, in the finasteride group, above the adjusted value designed to correct for a finasteride-induced PSA reduction of approximately 50%) for the detection of prostate cancer, including high-grade tumors, was increased in the finasteride group of the PCPT. The observation that the increased risk of high-grade tumors (modified Gleason score, 8 to 10) with finasteride or dutasteride persisted in analyses of scheduled biopsies independent of PSA results argues against PSA-related detection bias as the cause of the observed increase in the incidence of high-grade tumors. Approximately 56% of all prostate cancers in the PCPT and 90% of those in the REDUCE trial were diagnosed by means of scheduled biopsies.[5]

As for detection bias due to 5α-reductase inhibitors' reduction of prostate volume by approximately 20%, it is possible that core needle biopsies may uncover more cancers, including high-grade tumors, in smaller prostates because of increased sampling density. Proponents of this hypothesis accounted for the intergroup difference in prostate volume either by statistically adjusting for prostate volume at the time of biopsy (using logistic-regression analysis or the Peters–Belson method) or by circumventing any potential for sampling bias by extrapolating from the Gleason scores for a subgroup of patients who had had prostatectomies to patients without prostatectomy data (weighted imputation estimation). These analyses resulted in estimates of the relative risk of high-grade prostate cancer (Gleason score, 7 to 10) in the finasteride group ranging from no increase to a relative decrease of 27%. Since conventional criteria define "high-grade" as a Gleason score of 8 to 10 and 75% of the increase in tumors with modified Gleason scores of 7 to 10 observed in the finasteride group involved tumors with a score between 8 and 10, the FDA repeated the same analyses, statistically adjusting for prostate volume and using a modified Gleason score of 8 to 10 as the definition of a high-grade tumor. The results of those analyses do not support the contention that increased sampling density is responsible for the increased incidence of high-grade tumors in the finasteride group (see table for opposing risk estimations for tumors with a modified Gleason score of 7 to 10 and those with a score of 8 to 10). Although questions concerning detection bias remain, none of the post hoc exploratory analyses provide convincing evidence that the increased incidence of high-grade disease observed in both trials can be dismissed.

Analyses of these trials indi-

Exploratory Analyses of Prostate Volume and Detection Bias for Tumors with a Modified Gleason Score of 7 to 10 versus 8 to 10 in the Prostate Cancer Prevention Trial (PCPT).*

Variable	Method	Result	Modified Gleason Score, 7–10	Modified Gleason Score, 8–10
Prostate volume	Logistic regression	Odds ratio (95% CI)	1.03 (0.84–1.26)	1.51 (1.01–2.26)
	Peters–Belson method	No. observed	243	73
		No. predicted	239	47
Prostatectomy	Weighted imputation estimation	Relative risk (95% CI)	0.73 (0.56–0.96)	1.25
			0.82 (0.64–1.06)	1.40 (0.71–2.76)
			0.84 (0.68–1.05)	1.39 (0.78–2.50)

* The logistic regression in the analysis of prostate volume was adjusted for treatment group, baseline covariates (age, baseline PSA level, family history of prostate cancer, and race), prostate volume, and number of biopsy cores. The Peters–Belson method was used to predict the number of high-grade prostate cancers in the finasteride group on the basis of a regression model developed using patients in the placebo group, with adjustment for all covariates listed above except treatment group; significant differences between the number of predicted and observed high-grade cancers in the finasteride group suggest that detection bias due to prostate volume does not explain the higher incidence of high-grade cancers seen with finasteride. In the prostatectomy analysis, weighted imputation was used to estimate the relative risk of high-grade prostate cancer using information from the subgroup of patients who had a prostatectomy specimen submitted to the PCPT Core Pathology Laboratory to impute the outcome for all other patients. Results shown are from three publications using similar analytic methods. Data are from the Oncologic Drugs Advisory Committee briefing information.[5]

cate that the reduction in prostate-cancer risk with both drugs was limited to tumors with a modified Gleason score of 6 or lower. Prospectively collected data in REDUCE showed that 80% of such tumors met the Epstein pathological criteria for "very-low-risk" disease, which indicates that a reduction in their incidence is unlikely to be clinically significant. An analysis of biopsies performed in response to an elevated PSA level or an abnormal digital rectal examination, as would be done in clinical practice, revealed a smaller reduction in the relative risk of prostate cancer (14%; 95% CI, 4 to 23%) than that reported for all cancers in men receiving finasteride. Therefore, the trade-off inherent in using a 5α-reductase inhibitor for prostate-cancer prevention is the acceptance of one additional high-grade cancer in order to avert three to four potentially clinically relevant lower-grade cancers.

The conclusion drawn by the advisory committee in December was that finasteride and dutasteride do not have a favorable risk–benefit profile for the proposed use of chemoprevention of prostate cancer in healthy men. The FDA agrees with this assessment. The effects of finasteride or dutasteride on the incidence of metastatic prostate cancer and prostate-cancer–specific morbidity and mortality have not been evaluated.

Strategies for reducing cancer risk expose people who do not have and may never develop cancer to a drug and its potential adverse effects. In these circumstances, a high level of certainty about benefits and risks of intervention is warranted. The labels of approved 5α-reductase inhibitors, which are currently indicated for the treatment of symptomatic benign prostatic hyperplasia and male-pattern hair loss, have been modified to include the observation of high-grade prostate cancers in the relevant trials. In addition, health care professionals prescribing 5α-reductase inhibitors to men who opt for PSA screening should be aware that these agents reduce PSA values and that any increase in the PSA level above the lowest value obtained may signal the presence of prostate cancer, even if the value remains in the normal range for men not taking such an agent.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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