

# Dutasteride and Prostate Cancer Risk

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Andriole GL, Bostwick DG, Brawley OW, et al.: Effect of dutasteride on the risk of prostate cancer. *N Engl J Med* 2010, 362:1192–1202.

## Rating

- Of importance

## Introduction

In a previously published and heavily discussed paper [1], the type 2 5- $\alpha$ -reductase inhibitor (5ARI) finasteride was shown to reduce the risk of prostate cancer by a substantial 25% as compared to placebo in men at no known risk of developing prostate cancer. This decrease in incidence was tainted by an elevated proportion of Gleason score 7 to 10 cancers among those diagnosed with prostate cancer while on finasteride.

This elevation was later shown to be caused by the size reduction of the gland and perhaps by pathological changes caused by the drug.

The fact that we are now in the possession of a newer drug (dutasteride) that inhibits both type 1 (expression of which is more enhanced in patients with prostate cancer) and type 2 5- $\alpha$ -reductase in the prostate [2] urges researchers to test its efficacy among patients at a higher

risk of developing prostate cancer (Reduction by Dutasteride of Prostate Cancer Events [REDUCE] trial) [3].

## Aims

To investigate the potential role of 4-year-long dutasteride versus placebo in decreasing the risk of incident prostate cancer proven by biopsy among men at an increased risk of developing the disease.

## Methods

This was a multicenter, randomized, double-blind, placebo-controlled, parallel group study. Men were given either dutasteride, 0.5 mg, or placebo for 4 years. All subjects had to have a recent 6- to 12-core prostate biopsy before entry and an elevated 2.5 to 10 ng/mL prostate-specific antigen (PSA). Patients agreed to have a 10-core transrectal ultrasound (TRUS)-guided prostate biopsy at 2 and 4 years. For cause, biopsies were at the treating physicians' discretion. All biopsies were read centrally. The primary endpoint of the study was prostate cancer detected on biopsy after 2 and 4 years of treatment. To maintain the blinded nature of the study, PSA levels for men on dutasteride as reported to the physicians were doubled because the drug was shown [4] to reduce serum levels by approximately 50%. Patients were seen at 6-month intervals and on each visit had a serum PSA determined and completed a validated widely accepted International Prostate Symptom Score (IPSS) questionnaire regarding their lower urinary tract symptoms (LUTS). Prostate volume was determined by TRUS at entry and every 2 years thereafter.

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## Results

For this study, 8,122 men were randomized and eligible to continue on study. Over 80% of patients on both arms had at least one postbaseline needle biopsy of the prostate. During the 4-year study period, 20% of men on the dutasteride arm versus 25% of men on the placebo arm were diagnosed with prostate cancer. Thus, a relative 22.8% risk reduction and an absolute 5.1% risk reduction was noted. Risk reduction for the first 2 years was similar to the last 2 years of the study. There was no significant difference in the number of men in each study arm that were diagnosed with tumors with a Gleason score of 7 to 10 ( $P=0.81$ ). A similar observation of similar case numbers was made regarding men with tumors with higher Gleason scores of 8 to 10 ( $P=0.15$ ). The risk of cancer detection was significantly statistically lower across all prespecified subgroups, including age, family history of prostate cancer, baseline PSA, baseline gland volume, and baseline IPSS. Men on dutasteride as compared to placebo had significantly lower rates of either high-grade intraepithelial neoplasia ( $P<0.001$ ) or atypical small acinar proliferation ( $P=0.04$ ) on their biopsies. Men on dutasteride had a significant decrease in their prostate volume in comparison to an observed increased gland volume in those on placebo. Accordingly, men on dutasteride had a greater mean reduction in their IPSS and lower risk of acute urinary retention and the need for surgery related to benign prostatic hyperplasia.

## Discussion

Among men at an increased risk of prostate cancer, the current REDUCE study has demonstrated that dutasteride, a dual 5ARI, reduces the incidence of prostate cancer being detected on biopsy. This reduction was observed mainly among men with tumors with Gleason scores of 5 and 6. The authors suggest that most tumors diagnosed during the 4-year trial were already present at the time of randomization but were not detected in the baseline biopsy. They propose that the major effect of dutasteride was in the shrinkage of prostate tumors or inhibition of their growth. This, they admit, goes along with modeling data from the previous Prostate Cancer Prevention Trial (PCPT) [5]. The authors argue that the relative size decrease in the dutasteride group versus increase in the placebo group could have resulted in an increased number of cancers detected in the dutasteride group because detection on biopsy specimens is a function of the tumor gland and prostate gland volume. In effect, the observation of a 23% relative decrease in the diagnosis of prostate cancer among the dutasteride group strongly supports the positive effects

of the drug on tumor shrinkage and inhibition of tumor growth. Improved PSA and digital rectal examination sensitivity, as shown in the PCPT analysis [6], may further enhance the detection of prostate cancer among the dutasteride group members, and again attests to a more accentuated beneficial effect of dutasteride.

The authors also mention the fact that, in addition to the observed reduction in prostate cancer risk, men on dutasteride for 4 years had a significantly decreased risk of acute urinary retention and/or need for surgery. They argue that these benefits should be weighed against the adverse events profile mainly related to sexual function observed in a minority of men.

The authors conclude that, among men with increased risk of developing prostate cancer and severe outcomes of benign gland hypertrophy, dutasteride reduces both risks. The drug should be considered among these men.

## Editor's Comments

One important aspect of this trial among others is in the fact that it substantiates a previous study (PCPT), thus reinforcing the conclusion that prolonged use of 5ARIs may decrease the risk of developing prostate cancer. Level 1a evidence regarding the potential use of this family of drugs no longer can be ignored. Furthermore, the current REDUCE trial was conducted among a higher-risk group of men than the PCPT. The results of the current study may help better define who are the potential men to best suit this long-term chemoprevention. Certainly, those at higher risk of developing the disease and concomitantly suffering from LUTS may best benefit. The REDUCE trial also helps elucidate the long and much debated issue of the PCPT initial report that 27% higher Gleason score biopsies were seen among those diagnosed with prostate cancer and taking finasteride as compared to the placebo group. Subsequent analysis of the PCPT data came to the conclusion that the odds ratio to develop such high Gleason score tumors was in fact 1.03; namely, no such increase could be seen. In the current trial, where emphasis was made of central (blinded) pathology reading, there was no increase in the number of high Gleason scores, (7–10 or 8–10), noted among the dutasteride group versus the placebo group.

Even if the main drug effect of dutasteride is seen on Gleason score 5 and 6 (which may cause some to question their clinical/oncological importance), the mere reduction in the total number of men diagnosed with the disease and spared the anxiety involved in being diagnosed, let alone the burden of treatment among those treated for the diagnosed disease, is, to me, an incentive to propose its use to men with higher risk of developing the disease.

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