Effect of 5α-Reductase Inhibitor Use on Mortality From Prostate Cancer

William D. Figg, PharmD, MBA; Ian M. Thompson, MD

The role of androgens as a key driver of prostate carcinogenesis has been known for 50 years. In the early 1990s, with the development of finasteride, a selective inhibitor of the type 2 isoenzyme of 5α-reductase (5-AR) that lowers intraprostatic dihydrotestosterone levels, it was hypothesized that 5-AR inhibition might prevent prostate cancer. Two phase 3 studies, the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, were designed to investigate the effect of finasteride (PCPT) and dutasteride (REDUCE) on prostate cancer incidence.

The PCPT was initiated in 1993 as the first large population-based trial to test a chemopreventive strategy against prostate cancer. This prospective, randomized, double-blinded, and placebo-controlled trial enrolled 18,882 men 55 years or older with a normal digital rectal examination (DRE) result and serum prostate-specific antigen (PSA) level of 3.0 ng/mL or lower (to convert to micrograms per liter, multiply by 1) and assigned them to treatment with finasteride, 5 mg/d, or placebo. Results of the PCPT were reported in 2003. Based on recommendations of an independent data and safety monitoring committee, a decision was made to close the study because there was convincing evidence that the primary study objective had been met: a significantly reduced risk of prostate cancer. Finasteride reduced the prevalence of prostate cancer by 24.8%. The prevalence of Gleason grade 7 to 10 cancers was 6.4% in the finasteride group compared with 5.1% in the placebo group. Risk reduction in prostate cancer was apparent in men undergoing biopsy for cause and in men undergoing end-of-study biopsy. Prostate volumes were 24% smaller in men taking finasteride than in those receiving placebo. The concerning finding of the study was the higher prevalence of Gleason grade 7 to 10 cancers in the finasteride group.

The following theories could explain the paradoxical increase in high-grade disease:
1. Histologic artifact associated with finasteride use may result in incorrect grading of prostate cancers.
2. Finasteride may be more effective at preventing development of cancers with Gleason grade 2 to 6 than with Gleason grade 7 to 10.
3. A reduction in gland volume may improve high-grade cancer detection in men receiving finasteride, resulting in a proportionally higher rate of detection of high-grade cancers in this group.
4. The performance characteristics of PSA measurement and DRE for prostate cancer detection among men receiving finasteride may have been affected by finasteride, changing the rate of detection of high-grade disease.

Subsequent studies confirmed the first and fourth theories; the first theory appeared to not be operative, and the second was the clinical result. In 2011, the FDA not only denied the application for dutasteride as a chemoprevention agent, a warning of a potential for increased risk of high-grade prostate cancer with the use of 5-AR inhibitors (5-ARIs) used in the treatment of benign prostatic hypertrophy was issued. On the basis of this package insert warning, some physicians changed their practice to minimize the use of 5-ARIs for men who could benefit from their use. Since then, few studies have provided insight into whether such a concern was warranted.

As reported in this issue of JAMA Oncology, Azoulay and colleagues took a unique approach to address this controversy. Rather than reanalyze the 2 prevention trials and assess survival at later time points, they looked at 4 linked health care databases from the United Kingdom. This allowed them to analyze 13,892 men with newly diagnosed prostate cancer between a 10-year period. Their hypothesis was that men who had received a 5-ARI prior to the diagnosis of prostate cancer should be more commonly diagnosed as having high-grade disease and ultimately have worse outcomes. After 4.5 years of follow-up, 5001 deaths occurred in the study population, with 2439 deaths from prostate cancer. They found that 5-ARI use before the diagnosis of prostate cancer was not associated with an increased risk of prostate cancer-specific mortality or all-cause mortality. These results augment the long-term follow-up findings of the PCPT, showing no mortality increase in the finasteride group.

The role of 5-ARIs as chemopreventive agents for prostate cancer remains uncertain. On the one hand, reduction of low-
grade tumor incidence is unlikely to translate to a reduction in prostate cancer mortality; on the other hand, such a reduction could reduce disease overdetection and overtreatment, a serious concern that led the US Preventive Services Task Force to recommend against PSA screening. The study by Azoulay et al suggests that 5-ARI use is unlikely to increase prostate cancer mortality in men receiving them for BPH, reassuring those men on the symptom relief they may provide.

ARTICLE INFORMATION

Author Affiliations: Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland (Figg); Department of Urology, University of Texas Health Science Center at San Antonio, San Antonio (Thompson).

Corresponding Author: William D. Figg, PharmD, MBA, Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, 9000 Rockville Pike, Bldg 10, Room SA01, Bethesda, MD 20892 (figgw@helix.nih.gov).


Conflict of Interest Disclosures: None reported.

REFERENCES


CORRECTION

Incorrect Academic Degree: In the Original Investigation titled “Difference in Association of Obesity With Prostate Cancer Risk Between US African American and Non-Hispanic White Men in the Selenium and Vitamin E Cancer Prevention Trial (SELECT)” published online April 16, 2015, in JAMA Oncology (doi:10.1001/jamaoncol.2015.0513), an author’s name appeared with an incorrect academic degree. “Ruth Etzioni, MD” should be replaced with “Ruth Etzioni, PhD.” This article was corrected online.