

Does Finasteride Affect the Severity of Prostate Cancer? A Causal Sensitivity Analysis

Bryan E. SHEPHERD, Mary W. REDMAN, and Donna P. ANKERST

In 2003 Thompson and colleagues reported that daily use of finasteride reduced the prevalence of prostate cancer by 25% compared to placebo. These results were based on the double-blind randomized Prostate Cancer Prevention Trial (PCPT), which followed 18,882 men with no prior or current indications of prostate cancer annually for 7 years. Enthusiasm for the risk reduction afforded by the chemopreventive agent and adoption of its use in clinical practice, however, was severely dampened by the additional finding in the trial of an increased absolute number of high-grade (Gleason score ≥ 7) cancers on the finasteride arm. The question arose as to whether this finding truly implied that finasteride increased the risk of more severe prostate cancer or was a study artifact due to a series of possible postrandomization selection biases, including differences among treatment arms in patient characteristics of cancer cases, differences in biopsy verification of cancer status due to increased sensitivity of prostate-specific antigen under finasteride, differential grading by biopsy due to prostate volume reduction by finasteride, and nonignorable dropout. Via a causal inference approach implementing inverse probability weighted estimating equations, this analysis addresses the question of whether finasteride caused more severe prostate cancer by estimating the mean treatment difference in prostate cancer severity between finasteride and placebo for the principal stratum of participants who would have developed prostate cancer regardless of treatment assignment. We perform sensitivity analyses that sequentially adjust for the numerous potential postrandomization biases conjectured in the PCPT.

KEY WORDS: Causal inference; Principal stratification; Selection bias; Treatment effects.

1. INTRODUCTION

The Prostate Cancer Prevention Trial (PCPT) was a multicenter, double-blind, randomized trial that studied the effect of finasteride on the period prevalence of prostate cancer in healthy men screened for 7 years (Thompson et al. 2003). The 18,882 men aged 55 years or older with no history or current indicators of prostate cancer [prostate-specific antigen (PSA) ≤ 3.0 nanograms per milliliter (ng/mL) and digital rectal exam (DRE) normal] were randomized to receive either 5 milligrams of finasteride per day or placebo and were followed for 7 years. During annual follow-up participants were referred for a prostate biopsy if their PSA exceeded a threshold or their DRE was abnormal (suspicious for cancer). In addition, all participants not diagnosed with prostate cancer during the study were instructed to undergo an end-of-study prostate biopsy at their seventh and final visit.

Of the 10,168 men whose cancer status was known by either a positive midstudy biopsy or an end-of-study biopsy, prostate cancer was detected in 821 (16.6%) of 4,951 men on the finasteride arm compared with 1,194 (22.9%) of 5,217 men on the placebo arm, suggesting that finasteride lowered the risk of prostate cancer ($P < .001$). However, 299 (36.4%) of the 821 finasteride prostate cancer cases were more severe (Gleason score ≥ 7) compared to only 264 (22.1%) of 1,194 placebo prostate cancer cases ($P < .001$); see Table 1. Interpretation of the results is, therefore, challenging because the study suggested that finasteride reduced the overall risk of prostate cancer but accelerated growth of high-grade tumors (Scardino 2003).

While the apparent proportion of high-grade cancers among those diagnosed with cancer on finasteride is higher than that of those diagnosed with cancer on placebo, this may not be an

appropriate measure of finasteride's effect on disease severity. Those men diagnosed with cancer are a subset of those men initially randomized in the trial. As this subset was selected after randomization, there could be selection bias (Rosenbaum 1984). If the characteristics of men diagnosed with prostate cancer differ between treatment arms, then the apparent effect of finasteride on prostate cancer grade may be due to correlations between these differing characteristics and cancer grade, rather than the causal effect of finasteride. Additionally, using the number of cancers as the denominator (instead of the number of biopsies or the number randomized) ignores the possibility that finasteride prevented a large fraction of low-grade cases. An example of how postrandomization selection could influence results is shown in Figure 1.

To limit such potential selection bias, one could compare the prevalence of high-grade cancer among those who received a biopsy (as opposed to among those who were diagnosed with cancer). Of the 4,951 men who had a biopsy in the finasteride arm, 6.0% had a high-grade tumor whereas 5.1% of the 5,217 men with a biopsy in the placebo arm had a high-grade tumor, a difference that is borderline statistically significant; $P = .03$. Such an analysis may be important for public health purposes. However, it does not directly address the question of determining the effect of finasteride on cancer severity but represents the combined effects of finasteride on cancer prevalence and on cancer severity among prevalent cases.

A relevant population for addressing the effect of finasteride on cancer severity is the subgroup of patients who would have developed cancer regardless of treatment, but whose treatment may have affected severity (Robins 1995; Rubin 2000; Frangakis and Rubin 2002). The potential-outcomes framework (Neyman 1923; Rubin 1978) can be used to define this population. Specifically, as shown in Table 2, participants can be classified into four categories of paired potential outcomes (principal strata; Frangakis and Rubin 2002) under finasteride and

Bryan E. Shepherd is Assistant Professor, Department of Biostatistics, Vanderbilt University, Nashville, TN 37232 (E-mail: bryan.shepherd@vanderbilt.edu). Mary W. Redman is Assistant Member, Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109 (E-mail: mredman@fhcrc.org). Donna P. Ankerst is Professor, Department of Mathematics, Technical University, Munich, Germany (E-mail: ankerst@ma.tum.de). We thank Catherine Tangen, Phyllis Goodman, Ian Thompson, Alan Kristal, and William Dupont for their help with this manuscript. This article was supported in part by Public Health Service grant CA37429 from the National Cancer Institute and R01 DA023879-01 from National Institutes of Health.