PCPT Summary

One in six men in the US can expect to be diagnosed with prostate cancer during their lifetime. Treatments for this disease including surgery and radiation have significant risk of sexual, urinary, and bowel complications and side effects. Prostate cancer is a disease whose development and progression rely, in part, on androgens including testosterone and its more potent metabolite, dihydrotestosterone (DHT). The conversion of testosterone to DHT is catalyzed in the prostate by the enzyme five alpha reductase (5AR). The most common isoform of this enzyme, the Type 2 form, is the predominant form in the prostate. Type 2 5AR is inhibited by finasteride, an agent used for treatment of urinary symptoms due to benign prostatic hyperplasia (BPH). As this agent significantly reduces androgen stimulation of prostatic cells, it was hypothesized that its administration may reduce the risk of prostate cancer.

The Prostate Cancer Prevention Trial (PCPT) randomized 18,882 men with a PSA less than or equal to 3.0 ng/mL and a normal prostate examination to either finasteride or placebo. Men were followed annually with PSA tests and prostate examinations. Annually, an abnormal prostate exam or, in the placebo group, a PSA above 4.0 ng/mL prompted a biopsy recommendation; in the finasteride group the PSA level that prompted a biopsy recommendation was adjusted to a level that resulted in a similar number of biopsy recommendations. Men who completed 7 years of treatment and were cancer-free were recommended to undergo an end-of-study prostate biopsy. The primary objective of the study was total cancers detected over 7-years (period prevalence).

Fifteen months prior to the final anticipated end-of-study biopsy, the Data and Safety Monitoring Committee recommended study closure as the primary objective of the study had been met: finasteride was associated with a 24.8% reduction in risk of prostate cancer. Fewer cancers (803 versus 1147) were detected in the finasteride group of the study. The risk reduction was noted among men with Gleason 6 or lower (lower grade) tumors which constituted 67% of all cancers detected. Conversely, high grade tumors were more commonly detected among men receiving finasteride: There were 6 more Gleason 7 tumors (190 vs 184) and 37 more Gleason 8-10 tumors (90 vs 53). These results were published in 2003 in the New England Journal of Medicine (NEJM 2003; 349:215-224).

Subsequent analyses of these data have helped to understand this paradox of fewer cancers yet more high grade tumors. The reason appears to be related to detection biases caused by finasteride: (1) finasteride significantly improves the sensitivity of PSA for detecting both cancer and high grade cancer, (2) finasteride significantly improves the sensitivity of digital rectal examination for cancer detection, and (3) biopsy in men receiving finasteride appears to more accurately grade tumors resulting in less undergrading than in the larger prostates among men receiving placebo. Several studies modeling the impact of these biases suggest that there is either no actual increase in risk of high grade tumors or that the risk of high grade tumors is lower with finasteride. Finasteride administration was also associated with a 21% relative risk reduction in the detection of high grade prostatic intraepithelial neoplasia, a lesion considered to be a possible precursor to prostate cancer.

Side effects of finasteride fall into two categories. Regarding urinary side effects, urinary symptoms and complications as well as surgical procedures performed due to prostate enlargement, a

common condition of aging, are reduced. Conversely, sexual side effects and gynecomastia are more common with finasteride.

The composite of these data suggest that finasteride administration to men at risk of prostate cancer can significantly reduce the risk of the diagnosis of the disease and thereby reduce the side effects and complications of its treatment. The benefits in terms of improved urinary symptoms are balanced by sexual side effects. For a disease that affects nearly 200,000 men in the U.S. annually and that can be expected to increase in frequency with the aging of the U.S population, the impact on public health and the quality of life of tens of thousands of patients annually could be substantial.

In 2012, an analysis on the survival of the participants was performed and published in the New England Journal of Medicine (NEJM 2013; 39: 603-610). Updated survival information was obtained from the Social Security Death Index which does not include cause of death. The paper concluded that after 18 years of follow-up there was no significant difference in survival between the placebo and finasteride group either overall or after the diagnosis of prostate cancer. Future plans include an updated analysis with cause of death information that will be obtained from the National Death Index where cause-specific mortality will be analyzed.