PROSTATE CANCER

Mortality unaffected by finasteride treatment

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Long-term results of the landmark Prostate Cancer Prevention Trial (PCPT) have confirmed that, although finasteride is associated with increased detection of high-grade disease, there is no concomitant effect on overall survival. It is hoped that this finding will reassure clinicians who have been wary of using finasteride as a chemopreventative agent for prostate cancer.

The PCPT was first reported in 2003, demonstrating a significant 25% reduction in risk of prostate cancer for patients who took daily finasteride compared with placebo. Unfortunately, and somewhat paradoxically, men who did develop prostate cancer while taking finasteride were more likely to have high-grade disease than those in the placebo group (27% increased risk). As a result, the FDA ruled that finasteride (and dutasteride, another 5 α -reductase inhibitor) must carry a warning on their labels to state that they might increase the risk of high-grade prostate cancer and have not been approved for chemoprevention.

Unsurprisingly, physicians have been put off prescribing finasteride to their patients, despite accumulating evidence that the observed increase in the rate of high-grade tumours can be explained by the finding that finasteride-induced prostate gland shrinkage increases the sensitivity of PSA testing for the detection of high-grade disease. Now, a team of researchers led by Ian Thompson, Phyllis Goodman and Catherine Tangen—investigators for the original trial—have re-analysed the PCPT data for evidence of increased mortality in men who received finasteride, hoping to distinguish between a detection artefact and a genuine increased incidence of lethal high-grade prostate cancer in these patients.

For the original trial, 18,882 men with no evidence of prostate cancer were recruited at 222 centres across the USA and Canada and randomized to receive either 5 mg finasteride or placebo once daily for 7 years, during which time they underwent annual digital rectal examination and PSA testing. At final analysis, 803 of 4,368 men in the finasteride group (18.4%) and 1,147 of 4,692 men in the placebo group (24.4%) had been diagnosed with prostate cancer, corresponding to a 24.8% reduced risk for finasteride (95% CI 18.6–30.6; $P < 0.001$).

For this new *post hoc* analysis, Thompson and colleagues collected data on prostate cancer incidence for an additional year after the primary study was published. Their results confirm the benefit of finasteride treatment, reporting updated figures for prostate cancer detection in 989 of 9,423 men in the finasteride group (10.5%) and 1,412 of 9,457 men in the placebo group (14.9%), now corresponding to a 30% reduced risk of prostate cancer for men who took finasteride (95% CI 0.65–0.76; $P < 0.001$).

Next, investigators re-analysed the incidence of high-grade disease in the PCPT. Using Gleason score 7–10 as the definition of high-grade prostate cancer, they found that 333 of the cancers detected in the finasteride group were high grade (3.5%) compared with 286 in the placebo group (3.0%; RR 1.17, 95% CI 1.00–1.37; $P = 0.05$), once again confirming the findings of the original study.

Finally, Thompson and his team evaluated the survival data of men who participated in the PCPT. Cause of death was recorded on the death certificate for men who died during the trial. For men who were alive at the end of the trial, survival status was assessed using the

Social Security Death Index (if their Social Security number was known) up until October 2011. Data for men without a Social Security number were censored on the last date they were known to be alive.

As of October 2011, a total of 5,034 deaths were reported in the PCPT, with no difference in survival between groups. 2,358 deaths occurred in the finasteride group and 2,496 in the placebo group, corresponding to 15-year survival rates of 78.0% for finasteride and 78.2% for placebo (unadjusted HR 1.02, 95% CI 0.97–1.08; $P = 0.46$). 10-year survival rates for men diagnosed with low-grade prostate cancer were 83.0% for men who received finasteride and 80.9% for those who received placebo. For men with high-grade disease, 10-year survival rates were 73.0% and 73.6% for men who received finasteride and placebo, respectively.

Investigators were unable to evaluate prostate-cancer-specific mortality because the Social Security Death Index does not include information regarding the cause of death, which is an obvious limitation of this study. Whether finasteride has an effect on prostate-cancer-specific mortality is yet to be determined.

These findings seem to achieve the investigators' goal of demonstrating that increased detection of high-grade prostate cancer is, in fact, an artefact of finasteride treatment rather than a true increase in incidence, and might help to convince clinicians to consider finasteride chemoprevention for their patients who wish to undergo PSA screening.

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Original article Thompson, I. M. *et al.* Long-term survival of participants in the prostate cancer prevention trial. *N. Engl. J. Med.* doi:10.1056/NEJMoa1215932