Shrinkage of prostate led to overestimation of cancer risk in trial

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Reanalysis of data from the first long-term randomized trial of a chemopreventive agent for prostate cancer shows that the excess prevalence of high-grade prostate cancer in the drug-treated group may be attributable to shrinkage of the prostate at the time of biopsy.

The study of the Prostate Cancer Prevention Trial, led by University of Illinois at Chicago professor of pathology Dr. Peter Gann, is published in the Sept. 12 issue of the *Journal of the National Cancer Institute*.

The Prostate Cancer Prevention Trial evaluated the drug finasteride, which blocks production of a male hormone within the prostate and is proven effective in treating benign prostatic hyperplasia, or enlargement of the prostate. The trial was stopped in 2003 when finasteride was found to reduce the risk of prostate cancer by nearly 25 percent. However, men assigned to the finasteride group had a greater prevalence of high-grade cancer.

Gann said the results were confusing for clinicians and patients because the drug appeared to retard the development of prostate cancer and decrease its prevalence, but the increased risk of high-grade cancer was unexplained and worrisome.

Researchers reasoned one possible explanation was that because finasteride shrinks the prostate gland, it increases the likelihood that a biopsy will detect high-grade cancer.

"It's logical that if you shrink the size of the gland and then stick needles in it, you're more likely to find cancer if it exists," Gann said.

A second possible source of bias in the trial that may have contributed to overestimation of prostate cancer risk in the finasteride group is that the drug lowers the blood level of prostate-specific antigen by approximately 50 percent. The PSA level is a biological marker doctors use to detect disease, so PSA levels measured in men taking finasteride are routinely adjusted upward. This calculation may have led to overestimation of baseline PSA levels among men in the finasteride group who were already harboring high-grade tumors at the start of the study.

"This is a very unusual situation -- though it will become more common in the future -- where the drug affects the marker we use to find the cancer," said Gann.

Using data from the Prostate Cancer Prevention Trial study, Gann and colleagues developed statistical models that took into account the size of the prostate gland and the number of needle cores that were taken during biopsy. In essence, the researchers compared finasteride to placebo among men with an equivalent number of needle samples per unit of gland volume.

The analyses showed that adjusting for changes in gland size due to the drug could account for all of the excess high-grade tumors.

"Once we did this adjustment, all the excess high-grade went away, and the effect of the drug on low-grade cancer was even stronger, as we would expect," Gann said.

"This drug may have been much better than people thought," Gann said, "and the fears about its impact on high grade tumors may have been exaggerated based on this bias alone."

However, he said, the findings must be interpreted cautiously, and the new results alone do not justify definitive changes in clinical practice or widespread use of the drug.

"Our goal is to improve scientific understanding of what happened in this very important and expensive trial."

Source: University of Illinois at Chicago