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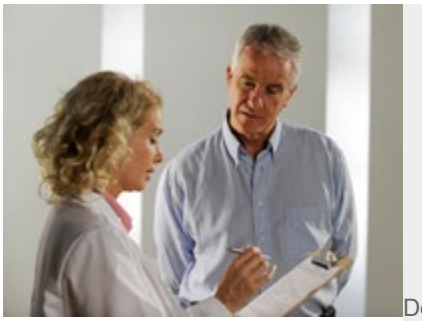
Long-Term Trial Results Show No Mortality Benefit from Annual Prostate Cancer Screening


Doctors and policy makers seek to understand which, if any, men may benefit from routine prostate cancer screening.

New data from the Prostate, Lung, Colorectal and Ovarian (PLCO) randomized screening trial show that, after 13 years of follow up, men who underwent annual prostate cancer screening with prostate-specific antigen (PSA) testing and digital rectal examination (DRE) had a 12 percent higher incidence of prostate cancer than men in the control group but the same rate of death from the disease. No evidence of a mortality benefit was seen in subgroups defined by age, the presence of other illnesses, or pre-trial PSA testing. The results were published January 6 in the *Journal of the National Cancer Institute*.

When the PLCO researchers published their initial prostate screening results in 2009, which also revealed no prostate cancer mortality or overall mortality benefit from annual screening, critics countered that participants had not been followed long enough to detect a difference in prostate cancer mortality, if one existed.

“The natural history of prostate cancer is so long that 10 to 15 years of follow up is usually the window we look for” when determining the effectiveness of a screening intervention, explained first author Dr. Gerald Andriole, who is chief urologic surgeon at the Siteman Cancer Center at Barnes-Jewish Hospital in St. Louis and the Washington University School of Medicine.

The persistent increase in incidence of prostate cancer in the screening arm of the study may indicate that regular screening can lead to overdiagnosis—finding tumors that never would have caused symptoms or death. “Even if there was just a tiny mortality benefit [from prostate cancer screening], overdiagnosis wouldn’t be so bad if we didn’t hurt people. But we do hurt people by finding a lot of trivial cancers that are most often overtreated,” explained Dr. Andriole.

The PLCO began in 1993 and enrolled men through mid-2001. More than 38,000 men were randomly assigned to annual screening for 6 years (including DRE for the first 4 years and PSA testing for all 6), and the same number of men were assigned to usual care.

Because prostate cancer screening is so common, more than half of the participants in the control arm underwent at least one prostate cancer screening test outside the trial. This contamination made it more difficult to determine whether annual testing affected mortality. However, “the level of screening in the

intervention arm was substantially greater than that in the control arm throughout the trial screening period," wrote the authors.

"Every time we screened [in the intervention arm] we got a bump of excess cases," said Dr. Philip Prorok, a lead NCI investigator on the study. "What we can't say for sure is whether we would have seen more of an effect on mortality had there been absolutely no screening in the control arm."

Another recent large trial, called the European Randomized Study of Screening for Prostate Cancer, did report a mortality benefit for prostate cancer screening. Although that trial had less contamination in the control arm, it had other limitations that could bias the results, such as differences in the treatments given to men in the screening and control arms.

To help reconcile the differing results from these two trials—the largest trials to date of organized prostate cancer screening—an effort is under way by the NCI-funded Cancer Intervention and Surveillance Modeling Network (CISNET) to use mathematical modeling to tease out how differences in the trial designs and populations may have contributed to the disparate trial results, explained Dr. Paul Pinsky, an NCI investigator on the PLCO trial and consultant to the CISNET project.

"Even though the results seem to be disparate, because one [trial] found a [statistically] significant protective effect [on prostate cancer mortality] and one didn't, it could be because of the ways the trials were designed and carried out," he said. The CISNET study began last year and is examining data from the two trials.

Men and their health providers agree that a more definitive answer is needed as doctors and policy makers seek to understand which, if any, men may benefit from routine prostate cancer screening. In October 2011, the United States Preventive Services Task Force released new draft guidelines for prostate cancer screening for public comment. The new draft guidelines, which are based in part on PLCO findings, recommend against routine PSA testing in men who do not have prostate cancer symptoms.

Some doctors think the new recommendations go too far in not accounting for the informed decisions of individual men. "If prostate cancer constitutes a continuum of disease and its overdiagnosis and overtreatment are mainly limited to low-grade disease, then instead of completely eliminating the potential benefits of screening along with the risks, why not consider managing low-risk patients differently?" asked Drs. Jeri Kim and John W. Davis of the University of Texas M. D. Anderson Cancer Center in a commentary published last month in *JAMA*.

Practice appears to be moving in this direction, with a greater emphasis on active surveillance instead of immediate treatment for some men who have prostate cancer that is thought to be at low risk of progressing. A big advance, explained Dr. Andriole, would be the ability to predict, even before a biopsy, whether a man with an elevated PSA level is likely to have an aggressive versus a nonaggressive cancer.

"There's a lot of effort now being put into this, and not just for prostate cancer, but for a lot of other cancer types as well," added Dr. Prorok. "If we diagnose someone with symptoms, or you find something on a screening test, can we eventually find a way to determine for which individuals the cancers are in fact aggressive and need more aggressive treatment, versus some that need less aggressive treatment or don't need any treatment at all?"

Researchers are looking for biomarkers, including genes and proteins, that may give clues to a cancer's aggressiveness. "If we could selectively change our criteria for biopsy such that only men who are at high risk for aggressive cancer get biopsied, we might be able to substantially shift the overall risk/benefit [ratio] of screening," said Dr. Andriole.

—*Sharon Reynolds*