New Trial Data Do Not End the PSA Screening Debate

By Brian Vastag

To screen or not to screen? For prostate cancer, that is still the question, despite the release this spring of mortality data from two large trials that asked whether prostate-specific antigen (PSA) testing reduces the risk of dying from prostate cancer. In the United States, the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial found no mortality benefit for PSA screening after 7–10 years. Across the Atlantic, the European Randomized Study of Screening for Prostate Cancer (ERSPC) reported a 20% mortality benefit after 10 years of PSA screening.

Both studies were published in the March 26, 2009, New England Journal of Medicine. The data generated conflicting responses. The American Cancer Society (ACS) continued to not recommend routine screening. Instead, the ACS endorses shared decision making, with men and their physicians discussing the pros and cons of PSA screening before deciding on the blood test. The American Urological Association, by contrast, lowered to 40 years the age that “relatively healthy, well-informed” men should begin PSA testing. And a coalition of 13 advocacy groups focused on prostate cancer released a joint statement encouraging men to discuss the risk for prostate cancer with their physicians “and to request the appropriate use of PSA and DRE [digital rectal examination] tests until better options are available.”

Ruth Etzioni, Ph.D., a biostatistician at Fred Hutchinson Cancer Research Center in Seattle, said that interpretation of the two trials amounts to an oncologic Rorschach test: “The evidence is such that those people who are skeptical will still be skeptical, and those people who are enthusiastic will find something to be enthusiastic about.”

Whether either finding will affect actual practice is unknown. For men older than 50 years, PSA testing “is very common and I don’t think it’s going to change very much. It’s been very deeply ingrained in our practices for the last 10–15 years,” said Gerald Andriole, M.D., first author of the PLCO report and chief of the division of urologic surgery at the Washington University School of Medicine in St. Louis. Other PLCO authors include JNCI editor-in-chief Barnett Kramer, M.D., associate director for disease prevention at the National Institutes of Health in Bethesda, Md.

First Draft

Investigators for the PLCO trial, which begin in 1992 and enrolled nearly 77,000 men, caution that the published results are an initial report, with more data to come. Ideally, overall follow-up would stretch to 13–15 years, said Andriole. “These are initial results,” he said, published after the trial’s data safety monitoring board determined no mortality benefit existed for men receiving PSA tests annually for six years. “There’s still a possibility for the group as a whole that screening will be beneficial.”

Chris Berg, M.D., from the Division of Cancer Prevention at the National Cancer Institute, said that NCI will continue to fund the trial until all men have been monitored for at least 13 years. Berg, one of the study authors, helps run the PLCO. Prostate cancer often takes a long time to develop and progress, Berg said, so the current 7–10 years of follow-up is too short to know exactly what effect screening may ultimately have.

Four researchers interviewed for this article said they think that PSA testing does offer a mortality benefit for certain men—but that, for now, there’s no way to know...
Moving Ahead

Despite the continuing controversy—the debate over PSA testing has raged for 20 years—researchers in the field see hope for untangling the issues. They point to mathematical modeling and the huge repository of biological samples from the PLCO as two resources ripe for tapping.

Mathematical modeling takes trial data and then builds an ideal scenario, said Berg. For instance, modelers can input data from PLCO and construct a virtual trial that compares hypothetical men who receive no screening to men who get screened annually. Etzioni, who develops such models, is building one that will “quantify the expected savings [of life] of a 50-year-old man if he does get screened versus the expected likelihood of an unnecessary diagnosis.” Etzioni’s models may answer other questions, such as whether a 3-ng/mL cutoff or a 4-ng/mL cutoff offers more benefit, and whether annual PSA testing is necessary or if less frequent testing would suffice. Her work is supported by NCI’s Cancer Intervention and Surveillance Modeling Network (CISNET), which funds other researchers’ building similar models.

Modeling is becoming more accepted as a tool to extend clinical trial results, according to Berg. For instance, the USPSTF used models when building their colorectal and breast cancer screening guidelines. Models are “not as good as clinical trials,” said Berg. “But we cannot do a trial of the size and scope of PLCO to answer every question.”

Berg also pointed to the PLCO’s vast repository of blood, DNA, and prostate biopsy and tumor samples. She encourages researchers to mine these resources for clues as to which tumors are toothless lions and which need swift treatment. Finding biomarkers to tell which tumors belong in which categories is key to improving the value of PSA screening, she said. Although several such markers are under investigation, none has yet proven its worth in the clinic. “Somewhere in the PLCO biopsy collection is the answer to this dilemma,” she said, “if only we were smart enough to figure it out.”

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