

WHAT DO WE KNOW ABOUT PSA SCREENING NOW THAT IT'S 2009?



By William Cavanagh

Awaited with great anticipation and accompanied by a torrent of press releases and media analyses, two reports were issued earlier this year that sought to settle – or at least contribute significantly toward settling – a years-long debate related to the value of screening asymptomatic men for prostate cancer through the use of serum prostate specific antigen (PSA) testing.

Both studies were reported in the March 26, 2009 issue of the *New England Journal of Medicine*^{1,2}. The first of these was a report of the European Randomized Study of Screening for Prostate Cancer (ERSPC), which involved 182,000 men from seven continental European countries. Subjects who qualified for the study had no signs or symptoms of prostate cancer when they entered the study, and were randomized to a screening arm where they underwent serum PSA testing or to a control arm, where no “screening” serum PSA testing was undertaken.

The main objective of the study was an evaluation of the hypothesis that a PSA-screened population of men with no history of prostate cancer would

suffer fewer deaths from prostate cancer than an identical population of men who were not screened using PSA. Using a randomized controlled trial (see Levels of Evidence page 6), The ERSPC found the risk of prostate cancer diagnosis and death contained in Table 1.

threshold typically used in the U.S. (as in the PLCO report below).

We also note that there were 112 fewer deaths in the screened group. This difference amounted to a 20% reduction in deaths from prostate cancer attributable to PSA screening.

TABLE 1.

	Number of Men Overall	Prostate Cancers Diagnosed	PCa Deaths
Screened group	82,816	6,830 (8.2%)	214 (0.29%)
Unscreened group	99,184	4,751 (4.8%)	326 (0.36%)
Difference in Screened Group		+71%	-112 (-20%)

From Table 1, we note that there were significantly more men diagnosed with prostate cancer in the screened group (71% more). Given the nature of screening, we would expect as much: more PSA draws, more biopsies, more prostate cancers. We would especially consider this scenario a possibility in this study, where the threshold for a “positive” serum PSA test was maintained at 3.0 ng/ml, as opposed to the 4.0 ng/ml

The authors report the probability of this finding being due to pure chance (“p”) as less than 0.05, which in the context of a randomized controlled trial means that screening has proven to lead to fewer deaths. Normally a finding of this magnitude would be considered undeniable, scientific, “Level I” proof of an advantage to screening... game, set, match.

But underlying this mortality advantage of screening in the European study is the fact that when we consider the absolute difference between the groups we find that 0.36% deaths from prostate cancer in the unscreened group minus 0.29% deaths in the screened group amounts to about 0.07%, or seven deaths per 10,000 men. In other words, this study suggests that if 10,000 men went unscreened by PSA, seven more would die than if those same 10,000 men underwent PSA screening. That is the survival advantage demonstrated in absolute terms.

Looked at another way, in order to prevent one prostate cancer death in an unscreened population, roughly 1400 men (~10,000/7) would need to be screened. This fact is especially sobering when considering what happens to the prostate cancer detection rate in these 1400 men, which is boosted from 4.8% to 8.2% in this study by screening (see Table 1). The authors of this study estimate that 48 additional men would be diagnosed and treated (given the elevation in the detection rate resultant from screening) in order to realize the one man who would not die from prostate cancer.

PLCO Study in the U.S.

The second study that relates to this complicated, but important, topic is the PLCO (Prostate, Lung, Colon, and Ovarian) Cancer Screening Trial, a very large scale U.S. trial that was begun in 1992 and enrolled 155,000 men and women by the time enrollment was closed in 2001. This multi-institutional study from the National Cancer Institute was an effort to determine the possible advantages to screening methods that had emerged for the PLCO cancers.

The PLCO study has enrolled 76,693 men who were randomized to screening by PSA and annual digital rectal examination (DRE) or no screening, with the objective of evaluating the effect on mortality – dying

of prostate cancer – of screening men in the U.S., much like the ERSPC study sought to do for European men.

However, unlike the ERSPC study, the findings of the PLCO study at the time of this published analysis found no advantage to screening by PSA and DRE. At the time of the writing of the article, at which point the group had completed seven years of follow-up (on its way to 13 years for the final analysis) – the results were as seen in Table 2.

which the trial accrued its subjects (1992 – 2001), PSA screening was becoming widespread in the U.S. , and patients who were assigned to the non-screened group may have nevertheless undergone PSA testing, at physical examinations for instance, that were not governed by the PLCO study design. The study authors, however, do not believe this “contamination” to be significant enough to have lead to the lack of benefit to the screened group.

TABLE 2.

	Number of Men Overall	Prostate Cancers Diagnosed	PCa Deaths
Screened group	34,755	2,820 (8.1%)	50 (0.14%)
Unscreened group	34,590	2,322 (6.7%)	44 (0.13%)
Difference in Screened Group		+22%	+6 (+13%)

While we can make very little in the way of legitimate comparisons between the ERSPC study and the PLCO study, we can note that while the ERSPC study found a significant decrease in prostate cancer related mortality in the screening group, the PLCO study clearly has not (the fact that more men had died in the screening group is not “statistically significant”; that is, the rate at which men died from prostate cancer are more than likely identical between the screened and unscreened groups).

But before we dismiss the PLCO study as evidence that PSA (and DRE) screening do not decrease the risk of dying from prostate cancer, we need to appreciate three important issues related to the PLCO prostate screening study.

First, it is possible that the “un-screened group” did in fact undergo some “informal” screening, and thus may have benefitted from PSA-detected cancer. Given the years over

Secondly, this study may be disclosing the possibility that successfully decreasing the death rate from prostate cancer may require that a lower threshold be set for investigation of prostate cancer: perhaps the 3.0 ng/ml limit set by the ERSPC trial, as opposed to the 4.0 ng/ml limit set by the PLCO study.

Third, and perhaps most important, the ERSPC trial had reported its results at a time of significantly later follow-up than the PLCO publication. Roughly speaking, the ERSPC study demonstrated that the difference in death from prostate cancer between the screened and unscreened groups began to widen at about ten years, and that this difference continued its diverging trend to at least 13 years. The PLCO study, based on its later start, reported its survival data based on a seven- to ten-year window. So there exists the very real possibility, based on the data presented in these two papers, that PLCO may yet demonstrate a survival benefit to screening once it closes its data collection at 13 years of follow-up. (Continued on Page 4)

“Whether or not to do PSA testing is not the issue; the issue is deciding what to do with the information the PSA provides.”

— Mark Scholz, M.D., Executive Director of the Prostate Cancer Research Institute



Yet, given these caveats that will have us continuing to watch the PLCO trial for its ultimate report, what do these studies tell us at this time about the value of PSA screening for prostate cancer? All told, over a quarter of a million men from around the world were enrolled into the most definitive of all studies – the randomized controlled trial. And in spite of lengthy (if incomplete) follow-up, and perhaps some difficult to overcome challenges in study execution, we see at best a modest decrease in the rate of prostate cancer death from screening – and one that some authorities believe must be considered in the context of a higher rate of cancer investigation, diagnosis, and treatment in screened populations.



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We must keep in mind that although PSA (to simplify the means of screening for a moment) does increase the ability of physicians to detect prostate cancer in a population of men, it does not perform very well as a diagnostic test: the lower the PSA “cut-off” that is used, the lower the specificity of the test, and the more men who undergo biopsy who have no disease. And while PSA may direct physicians to finding prostate cancers, the current state-of-the-art continues to struggle with identifying the prostate cancers that require aggressive treatment and those that do not. This current inability to discriminate between the cancers that kill and those that don’t will continue to plague the idea of PSA screening as a reasonable public health mission.

The primary reason for resisting the use of PSA screening in otherwise healthy populations of men lies in the notion, as demonstrated by the results of European ERSPC study, that the benefits of saving a relatively small number of lives must be weighed against the cumulative “collateral damage” that is inflicted upon the group as a whole. To put it in concrete terms from ERSPC, 48 men would be treated for their screening-detected prostate cancers for each man who ends up not dying from a prostate cancer that would have gone undetected if not for the screening. Given the costs and side effects associated with most localized prostate cancer treatments – major surgery, radiation treatments, impotence, incontinence, and so on – the case can be (and is) made that the theoretical balance does not favor the implementation of screening.

But what of the individual who – knowing full-well the risks of screening, where he may subject himself to diagnostic tests and treatments that are unnecessary in the long-run – decides that he wants to know his serum PSA every year? How do we tell an unscreened man dying of his prostate cancer that for his trouble 48 other men did not have to undergo unnecessary treatment, thus

preserving a rational calculus of cost and benefit to the population as a whole?

The answers to these perplexing and ethically-frightening questions are nowhere in sight, but potential solutions are not. Newer, better diagnostic tests that may differentiate the cancers that need treating are constantly under study. Novel therapies are emerging that may offer the kind of watershed moment that Dr. Huggins triggered two generations ago (see “Prostate Cancer Maverick: Charles Huggins, page 8.)


And even in the absence of “perfect” tests that instruct which prostate cancers absolutely need treatment and which do not, we are also getting better at drawing lines between localized prostate cancers that are worrisome and those that may be closely monitored. As Mark Scholz, M.D. (executive director of the Prostate Cancer Research Institute) put it recently: “whether or not to do PSA testing is not the issue; the issue is deciding what to do with the information the PSA provides.”

In the next issue of Insights, we will review the systems that are available to put the “information that PSA provides” to use, especially in terms of the wealth of research that has increased the precision with which men can be comfortable “watchfully waiting” and deferring definitive treatment. By minimizing the “collateral damage” aspect of prostate cancer treatment, we may yet find a solution to this intractable problem.

References

1. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality in a randomized European study. *The New England Journal of Medicine* 360:1320-1328, 2009.
2. Andriole GL, Crawford ED, Grubb RL, et al. Mortality results from a randomized prostate cancer screening trial. *The New England Journal of Medicine* 360:1310-1319, 2009.
3. See PCRI website at: www.PCRI.org

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