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Global Siemens Headquarters

Siemens AG
Wittelsbacherplatz 2
80333 Muenchen
Germany

Global Siemens Healthcare Headquarters

Siemens AG
Healthcare Sector
Henkestrasse 127
91052 Erlangen
Germany
Phone: +49 9131 84-0
www.siemens.com/healthcare

Global Division

Siemens Healthcare Diagnostics Inc.
511 Benedict Avenue
Tarrytown, NY 10591-5005
USA
www.siemens.com/diagnostics

www.siemens.com/diagnostics



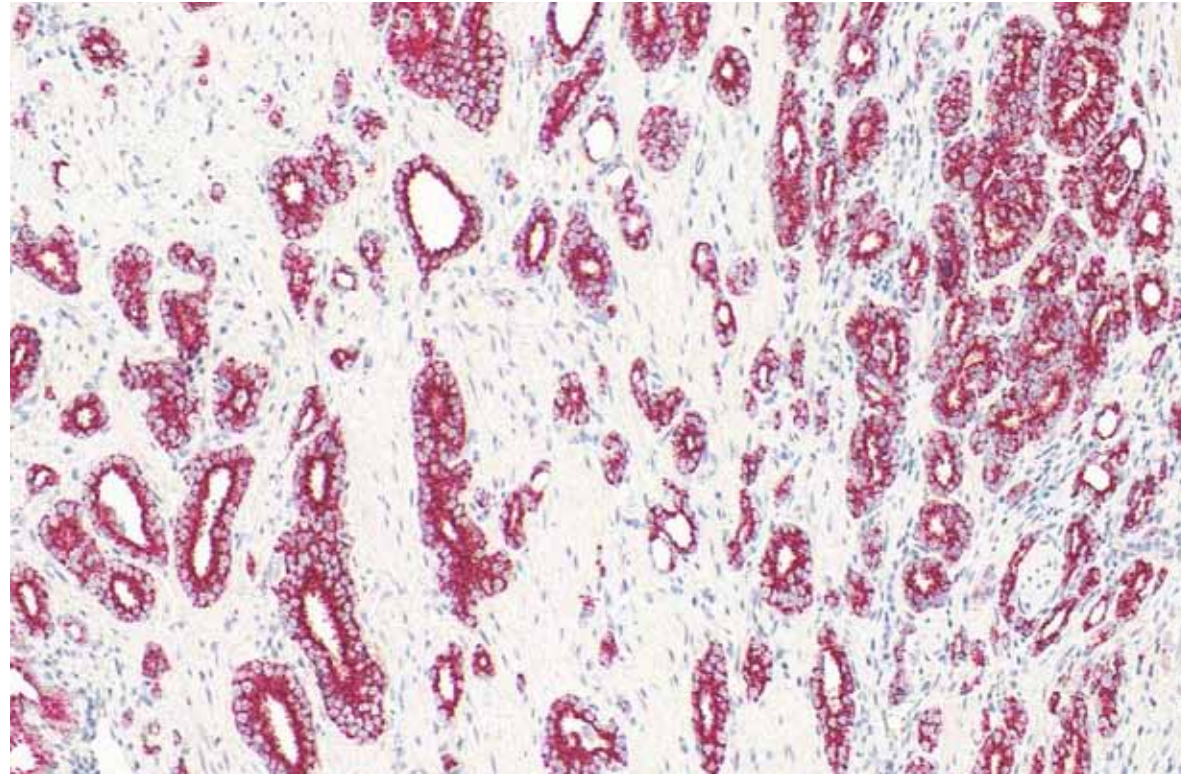
Prostate-Specific Antigen (PSA) Remains Relevant in the Early Detection of Prostate Cancer:

Insights into the Results of the European Randomized Study of Screening for Prostate Cancer (ERSPC) and Prostate, Lung, Colon, and Ovary (PLCO) Screening Trial Studies

Stephen B. Williams, MD, and Martin G. Sanda, MD
Division of Urologic Surgery
Beth Israel Deaconess Medical Center
Harvard Medical School, Boston, MA

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Prostate cancer tissue stained for P504S, a cytoplasmic protein, that is highly expressed in prostate cancer cells.

Introduction

Prostate cancer (CaP) remains the leading cancer diagnosis among men in the United States (U.S.), with approximately 192,000 cases diagnosed in 2009 and an estimated 217,730 new cases in 2010.¹ Prostate-specific antigen (PSA) testing has been successful in aiding in the early detection of CaP. Since the introduction of PSA testing, there has been a shift to earlier diagnosis of CaP from late-stage disease to early-stage disease; in the U.S., 91 percent of cases currently diagnosed are localized (early stage) disease.¹ PSA testing has led to an increased detection of clinically localized T1c CaP.

In 2009, two randomized controlled trials with conflicting results were published in the *New England Journal of Medicine*. These studies evaluated whether PSA testing provided a CaP-specific survival benefit.^{2,3} The role of PSA testing in CaP has come into question as a result of these two trials, prompting a reexamination of the impact that PSA testing has had on CaP.

European Randomized Study of Screening for Prostate Cancer (ERSPC): PSA Testing Provides a Survival Benefit

This trial was based in Europe and involved 162,873 men aged 55 to 69 years randomized to screening versus no screening for CaP. Patients with a prior diagnosis of CaP were excluded. Men were screened for CaP at 4-year intervals, except in Sweden, where the screening took place at 2-year intervals. Elevated serum PSA or an abnormal digital rectal examination (DRE) were indications for transrectal ultrasound-guided, sextant prostate biopsy.

Results of this study were evaluated after median follow-up of 9 years. Eighty-two percent of all men in the PSA group were tested at least once and 16 percent had a positive PSA test; 86 percent of these men were biopsied. The positive predictive value for CaP was 24 percent with an overall reduction in CaP-specific mortality of 20 percent (RR, 0.08; 95% confidence interval (CI), 0.65 – 0.98 [P = 0.040]).

The quality of the ERSPC trial has been criticized because the study is a compilation of data from seven different medical centers in different countries.⁴ However, the plan for combining results of concurrent parallel studies was predetermined at or before subject enrollment. The ERSPC study is not a meta-analysis study, a retrospective analysis of several independent studies; it is a prospective study, which typically provides a higher quality of evidence in comparison to meta-analysis studies.





Another criticism of ERSPC as class I evidence of the benefit of PSA testing is that the magnitude of survival benefit was marginal. As the length of follow-up was short at 9 years, its ability to demonstrate any CaP-specific survival benefit at less than 10 years is remarkable because CaP causes its greatest mortality 10 to 20 years after diagnosis. Clearly, results from longer follow-up of the ERSPC will provide important insights regarding the clinical significance and full magnitude of survival benefit associated with PSA testing.

Prostate, Lung, Colon, and Ovary (PLCO) Screening Trial: PSA Testing Provides No Survival Benefit

This trial was based in the U.S., and 76,693 men aged 60 to 74 years were randomized. Prerandomization PSA testing was limited to a single PSA test during the 3-year period prior to randomization. Participants in the CaP screening group were offered both PSA and DRE every year for 4 years and then annual PSA testing only for 2 years thereafter. Prostate biopsy was offered to men with PSA values of > 4 ng/mL and/or an abnormal DRE.

The PLCO study has five fatal flaws. First, the analysis was performed prior to the planned duration of follow-up: even though median follow-up was approximately 11 years, only 67 percent of the participants completed the minimum 10-year follow-up that had been required by the protocol. Second, although the median follow-up was approximately 11 years, the study was designed for at least 13-year follow-up.

Third, nearly half of patients had already undergone PSA testing prior to randomization, resulting in a preentry selection bias against demonstrating any benefit. Fourth, PSA testing in the control group increased to at least 52 percent after randomization, which resulted in a mere 33 percent difference in PSA testing rates between the two groups.⁴ Lastly, by using a single cutoff as an indicator for obtaining a prostate biopsy, some clinically significant cancers may have been missed unless revealed at later screens and/or by a positive DRE.⁶

Due to these major unexplained protocol deviations and the preselection bias, the PLCO study showed no significant CaP-specific mortality reduction in the PSA-tested group compared to the control group (RR, 1.13; 95% CI, 0.75 – 1.70). In addition, because PSA testing rates were 44 percent in the control group prior to randomization and up 52 percent after randomization, any sweeping conclusions derived from current and future results of this study are questionable. Interestingly, even with these flaws, this study demonstrated that men who had PSA testing in the control arm had a 25 percent decrease in CaP-specific mortality compared to those men who did not have PSA testing prior to randomization.

PSA Testing Associated with a 44% Decrease in Prostate-Specific Mortality at 14 years

The Göteborg randomised population-based prostate-cancer screening trial was part of the European Randomised Study of Screening for Prostate Cancer (ERSPC) trial that showed a 20% prostate cancer-specific mortality benefit at 9-year follow-up for men undergoing PSA testing. In the Göteborg trial, PSA testing was associated with prostate-specific mortality risk reduction of 40% at 14-year follow-up: Swedish men born between 1930 and 1944 were randomized by computer in a 1:1 ratio either to a group invited for PSA testing every 2 years (n = 10,000) or to a control group (n = 10,000). Only men with elevated PSA were offered additional testing (digital rectal examination and prostate biopsies). At a median follow-up of 14 years, 1,138 men in the screening group and 718 in the control group were diagnosed with prostate cancer. The cumulative prostate-cancer incidence was 12.7% in the screening group and 8.2% in the control group, the hazard ratio was 1.64; 95% CI 1.50 – 1.80; P < 0.0001. The absolute cumulative risk reduction of death from prostate cancer at 14 years was 0.4% (95% CI 0.17 – 0.64), 0.9% in the control group vs. 0.5% in the screening group. The rate ratio of death from prostate cancer was 0.56, 95% CI 0.39 – 0.82; P = 0.002 in the group undergoing PSA testing compared to the control group. The rate of prostate cancer death for the group undergoing PSA testing compared to the control group was 0.44 (95% CI 0.28 – 0.68; P = 0.0002). Overall, 293 (95% CI 177 – 799) men needed to be tested for PSA and 12 men needed to be diagnosed with prostate cancer to prevent one prostate cancer death.

Hugosson J, et al. Mortality results from the Göteborg randomised population based prostate-cancer screening trial. *Lancet Oncology*. 2010 Aug;11 (8):725-32.



Prostate-Specific Antigen Is Relevant in the Early Detection of Prostate Cancer

PSA testing as an aid in the detection of CaP has led to an increased detection of clinically localized T1c CaP with concomitant stage migration.^{6,7} About 91 percent of U.S. men are now diagnosed with early-stage disease.¹ The conflicting results from the ERSPC (modest survival benefit) and PLCO (no survival benefit) studies that used simple PSA cutoff values as the basis for a recommendation for or against prostate biopsy have raised questions about the value of PSA testing.^{2,3} Strategies based simply on PSA and age cutoffs may be insufficient for identifying suitable

candidates for biopsy because the ultimate goal of early detection is to identify aggressive disease that harbors lethal potential and yet is amenable to definitive treatment. The ability to discern aggressive from indolent CaP is a centerpiece of ongoing efforts to refine CaP detection, clinical decision-making, and patient care.

One can argue that a more specific and sensitive marker is needed to identify clinically significant cancer. Current approaches to improving the sensitivity and specificity for CaP detection and minimizing unnecessary biopsies include assays that detect either free PSA or PSA bound to alpha-1-antichymotrypsin (complexed PSA).⁸ Percent free PSA has been extensively evaluated and shows an increased risk of CaP detection on needle biopsy as the percent free PSA decreases.⁹ Complexed PSA has been shown to reduce the number of unnecessary biopsies by 10 to 20 percent.^{2,6,12}

Markers that are under investigation for CaP detection include pro-PSA, PCA3, and TMPRSS2-ERG; none of these have been FDA cleared or approved. Pro-PSA is the precursor of PSA and is designed to be used in conjunction with total PSA and free PSA. Levels of pro-PSA have been shown to be significantly higher in men with unfavorable prostate biopsies.¹⁰ More data, however, are needed to substantiate this finding. PCA3 is a molecular marker that has demonstrated some clinical utility in guiding repeat biopsy decisions and for evaluating the likely significance of CaP in repeat biopsies.¹⁴⁻¹⁸ A recent study of men with one or two previous negative biopsies and scheduled for repeat biopsy showed a better diagnostic accuracy for the

PCA3 score than for the percent free PSA in predicting the outcome of a repeat biopsy.¹² Another novel marker is a gene fusion protein, TMPRSS2-ERG; it is being evaluated as a urine marker after DRE to help determine CaP risk.¹⁹ In addition to the markers discussed (pro-PSA, PCA3, and TMPRSS2-ERG), several other biomarkers are being studied; however, none can currently replace PSA as an aid in early detection of CaP.

Conclusion

New biomarkers are being investigated to aid in identifying men at risk for lethal CaP, and further studies are needed to define their roles. In current practice, PSA continues to have an important role in the early detection of CaP. The PLCO trial did not show a difference in survival benefit, but this trial had major protocol violations (PSA testing in the arm randomized to no PSA testing and premature analysis of results) that biased the study against showing any benefit. The results of the ERSPC trial demonstrated a survival benefit in patients who are evaluated for CaP using PSA. Recent results from the Göteborg randomized population-based arm of the ERSPC trial with median follow-up of 14 years have shown a 44 percent reduction in CaP-specific mortality using PSA.²⁰ PSA is a valuable aid in the early detection of CaP and has been shown to provide a mortality-specific benefit.

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