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## INVITED RESEARCH HIGHLIGHT

Prostate Cancer

# To screen or not to screen: the prostate cancer dilemma

Nelson N Stone<sup>1</sup>, E David Crawford<sup>2</sup>

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**The European Randomized Study of Screening for Prostate (ERSPC) has updated their previous seminal report on prostate cancer mortality comparing screened men to controls. Now with 13 years follow-up, the rate ratio of prostate cancer mortality was 0.79 favoring the screened population. The authors concluded that there was a “substantial reduction in prostate cancer mortality attributable to testing with prostate-specific antigen (PSA)” but they also stated that a “quantification of harms” needed to be addressed. The issue of harms was not addressed by the ERSPC (at least not in this report) and hence this additional statement most likely reflects the controversy currently surrounding the risks associated with over-diagnosis and treatment of indolent diseases inadvertently detected by a screening protocol.<sup>1</sup> In addition, the positive results from this trial conflict with those of the prostate, lung, colorectal and ovarian (PLCO)<sup>2</sup> study and require further elaboration.**

Part of the challenge with interpreting the ERSPC is a result of the study design. France entered the study late (2 years), the screening intervals varied from 2 to 4 years, the biopsy indication by PSA varied, and screening was discontinued at different time points in several of the countries. Despite these limitations, screening detected substantially more prostate cancers than in the control group, 10.2% of the population versus 6.8%. However, even though the intervention arm experienced a 21% decrease in prostate cancer mortality, the absolute decrease was only 0.6% (545 per 89 352) to 0.5%

(355 per 72 891); and this came at a burden of potential overtreatment in the patients with low-risk disease. The majority of the prostate cancers detected in the PSA arm had low-risk features (59.9%), whereas many fewer men in the control group were diagnosed with similar disease (41.6%). Unnecessary surgery or radiation has become a significant problem in the management of these men. Many clinicians chose to offer low-risk patients active surveillance (AS) rather than definitive therapy. However, this also creates an additional burden, as transrectal ultrasound biopsies are often repeated yearly, and PSA testing frequency is increased. Thirty to fifty percents of the men on AS eventually have surgery or radiation, and many have advanced disease at the time of treatment.<sup>3,4</sup> The problem created by screening is that too many patients are identified with low-risk disease. Approximately, 50% have disease that can be safely managed by AS, while the other half would be best managed by definitive or focal therapy. Unfortunately, the procedure used to make a diagnosis, the TRUS biopsy, cannot differentiate between these two groups.

The ERSPC study is often compared to the updated PLCO trial.<sup>2</sup> The latter trial, with similar 13 years follow-up offered PSA and digital rectal examination (DRE) screening to about half as many men. The major difference between the two was about 50% of the control arm previously had a PSA or DRE test, and this “contamination” may have influenced the overall results. The PLCO trial failed to find a difference in prostate cancer detection (11.1% vs 9.9%, screened vs not screened) and no improvement in cancer mortality. It is also worthwhile noting that prostate cancer deaths were not that dissimilar between the two studies with 0.41% versus 0.38% of the study population dying from the disease, respectively.

Where does that leave the physician who is trying to decide whether to offer early detection with PSA/DRE testing and how can our patients

make an informed decision given these data? First it is important to recognize the patient populations were different in the American and European trials. Men in the USA have been exposed to prostate cancer “screening” since 1989<sup>5,6</sup> and it is estimated that over 75% of the population have had PSA testing. Early diagnosis came later to the Europeans, and PSA testing is not universally done in all countries. It should, therefore, not be surprising that the studies were positive in Europe and negative in America. Where does that leave the Asian patients? PSA testing is not routinely performed in Japan, where penetration is estimated at 5%–10%.<sup>7</sup> In addition, more cancers are diagnosed at higher stage, and the death rate from the disease continues to increase.<sup>8</sup> The situation is probably not dissimilar in other Asian countries. These data would be an argument in favor of routine testing.

Nonetheless, a strategy needs to be developed to manage the majority of patients who are diagnosed with TRUS biopsy with low-risk disease. The danger in ignoring this problem is men may refuse testing putting them at risk for increased morbidity and death. The ERSPC study briefly mentioned multiparametric (mp) magnetic resonance imaging (MRI) as a technology to decrease over-diagnosis. Centers in Europe and the USA are utilizing mpMRI combined with targeted biopsies to identify high-grade disease. Men with elevated PSA get scanned and only biopsied when suspicious regions suggest high-grade disease. mpMRI is more likely to identify lethal cancers (Gleason score 8 and above) than low-grade disease.<sup>9,10</sup> The men with a nonsuspicious mpMRI study would then not be biopsied at all. The available evidence on this issue needs to be confirmed by large, preferably multicenter studies. Another strategy employs genetic and epigenetic assays of biopsy material whereby apparent low-risk disease is reassigned into a more aggressive category and only these patients are offered definitive

<sup>1</sup>Departments of Urology and Radiation Oncology, The Icahn School of Medicine at Mount Sinai, New York, NY, USA; <sup>2</sup>Department of Surgery, Division of Urology and Radiation Oncology, The Anschutz Cancer Center, The University of Colorado Health Sciences Center, Aurora, CO, USA.  
Correspondence: Prof. NN Stone  
([drnelsonstone@gmail.com](mailto:drnelsonstone@gmail.com))

therapy. Studies are underway to see if either of these two strategies can improve treatment decisions in the AS group.

One additional strategy should be mentioned. Several investigators have turned to saturation or mapping biopsies using a transperineal approach. Fifty to seventy-five percents of men on an AS protocol are found with multifocal or higher grade disease after a transperineal mapping biopsy (TPMB).<sup>11-13</sup> Crawford has investigated TPMB using a mapping software program whereby disease sites within the gland can be precisely localized affording a large number of patients a targeted focal therapy (TFT) option.<sup>14,15</sup> As more data is collected with mpMRI, genetic testing and TPMB, better selection of candidates for AS, TFT and definitive therapy should increase our confidence that PSA testing is the right choice for our patients.

### COMPETING INTERESTS

The authors declare that they have no competing interests.

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