Point/Counterpoint: Early Detection of Prostate Cancer: Do the Benefits Outweigh the Consequences?

Presented by Peter R. Carroll, MD, MPH, and Andrew J. Vickers, PhD

Abstract
Few clinical issues have polarized the oncology community as much as screening for prostate cancer, with advocates of prostate-specific antigen (PSA) testing vocal on one side and skeptics just as vocal on the other. At the NCCN 19th Annual Conference, Dr. Peter R. Carroll and Dr. Andrew J. Vickers tackled the controversy surrounding early detection of prostate cancer, focusing attention on the randomized trial results at the heart of the matter; over-detection (the Achilles’ heel of screening); and the rationale behind the new, streamlined 2014 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer Early Detection, which emphasize selective early detection and treatment and are tightly aligned with the NCCN Guidelines for Prostate Cancer. (J Natl Compr Canc Netw 2014;12:768–771)

“Screening for prostate cancer has been a public health disaster,” announced Andrew J. Vickers, PhD, Attending Research Methodologist, Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York City. At the center of the debate is the question of whether the benefits of prostate-specific antigen (PSA) screening (namely the reduction in mortality) outweigh the harms (overdiagnosis and overtreatment). According to Dr. Vickers and his colleague Peter R. Carroll, MD, MPH, Professor and Chair, Department of Urology, University of California, San Francisco, the answer depends on screening younger men than in the past, adherence to strict criteria for biopsy, aggressive treatment of men with high-risk disease, and active surveillance for men with low-risk disease. Both Drs. Carroll and Vickers are members of the NCCN Guidelines Panel for Prostate Cancer Early Detection.

Randomized Trials on PSA Screening
The results of 2 key trials (from the United States and Europe) represent the primary basis of the U.S. Preventive Services Task Force (USPSTF) statement on screening for prostate cancer, reported Dr. Carroll. The USPSTF recommended against PSA-based screening for prostate cancer for men of any age in the general population. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial reported no benefit to prostate cancer screening after 7 to 10 years of follow-up. The rate of compliance with screening in the screening group was 85%, compared with 40% in the first year and 52% in the sixth year in the control group. Of note was the fact that approximately 74% of men in the usual care arm underwent screening at least once. However, Dr. Carroll offered some caveats regarding the conclusions of the PLCO trial. “It was not a trial comparing screening and no screening but rather a trial of controlled screening versus ad hoc or opportunistic screening. It did not test the hypothesis that screening would be of benefit,” he revealed.

In the European Randomized Study of Screening for Prostate Cancer (ERSPC), Schröder et al found PSA-
based screening significantly reduced mortality from prostate cancer. In the Göteborg arm of the ERSPC, "which started before ERSPC as an independent trial, there was a remarkable benefit, a 44% risk reduction," declared Dr. Carroll. Of particular note, nearly half the patients in this trial did not undergo initial treatment, which Dr. Carroll stated showed that lives can be saved without treating all patients.

Dr. Vickers cautioned against combining the results of the PLCO and ERSPC. "These are different trials asking different questions," he explained. Although there is much misunderstanding about the ERSPC, admitted Dr. Vickers, it was a "very large, well-conducted trial." In addition, the ERSPC had a younger mean age at the start of screening and a lower PSA threshold for referral. Furthermore, Dr. Carroll noted the importance of a median follow-up of 11 years in the ERSPC trial. "Anytime you look at detection or treatment of early-stage prostate cancer, any positive effect only becomes apparent at 8 to 9 years."

Updates from the ERSPC and the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) may shed more light on the debate regarding the benefit of early screening and subsequent treatment for prostate cancer, according to Dr. Carroll. With the upcoming results from the ERSPC reaching out to 13 or 14 years, the absolute impact of such screening should be made clearer, Dr. Carroll said. "You will see a continuing, long-term positive impact."

As for the SPCG-4 update comparing radical prostatectomy and watchful waiting in early-stage prostate cancer, extended follow-up confirmed a substantial reduction in prostate cancer–specific mortality, distant metastases, and the use of androgen deprivation in those treated with surgery, with the benefits more pronounced in men younger than age 65. "This is required reading for anyone interested in this subject," declared Dr. Carroll.

**Overdetection: The Achilles’ Heel of PSA Screening**

Prostate cancer mortality may be reduced with prostate cancer screening, but the risk of overdiaognosis, compounded by overtreatment, is substantial. Although the magnitude of overdetection has been debated, the exact numbers vary, with differences in time periods, age, comorbidities, region, definition, and screening practices adding to the mix (Figure 1). According to Dr. Carroll, “the risk of overdetection in the United States, based on how we currently screen and define it, is approximately 40%, suggesting that many of these men harbor very low-risk, low-grade tumors that do not require treatment. This is the part that the USPSTF got right,” said Dr. Carroll. In addition, almost all of the excess diagnosis in prostate cancer is in older men (> age 65), added Dr. Vickers.

Undeniably, PSA screening leads to overtreatment, admitted both Dr. Vickers and Carroll. "Since the introduction of the PSA test in 1987, there has been a massive increase in the incidence of prostate cancer," stated Dr. Vickers. However, the benefits of early detection should not be overestimated, noted Dr. Carroll, as the risk of dying of prostate cancer is low, and screening lowers it further.

Furthermore, prostate cancer overdiagnosis has a strong relationship to age and PSA level. According to a recent study, the number of excess cases associated with the introduction of PSA screening in the United States would have been reduced by 85%, 68%, and 42% for age cutoffs of 60, 65, and 70, respectively, if PSA testing had been restricted to younger men. Thus, screening older men (> age 70) in only selected circumstances would reduce overdiagnosis and alter the benefit/harm ratio of PSA screening, the investigators concluded.

**Updated NCCN Recommendations Reflect Changes in Rationale**

In 2012, the NCCN Guidelines for Prostate Cancer Early Detection focused on screening early and often and using biopsy liberally, admitted Dr. Carroll. "It was a lengthy, circuitous path that we felt needed to be changed," he added, speaking on behalf of the NCCN panel. “We had to make the guidelines more streamlined, readable, and actionable.”

The screening strategy reflected in the revised 2014 guidelines centers on several key criteria: a younger target population of healthy men (with and without an increased risk because of family history and/or ethnicity); more explicit indications for use of biopsy in men with abnormal PSA levels; and selective treatment of men with high-risk disease (Table 1). The goal of the panel was to limit the problem of overdetection without substantially impacting lives saved.

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Although we have been screening close to 50% of men in the older age range (70–79), “the key ages at which we should be screening men for prostate cancer are between 45 and 60,” declared Dr. Vickers. The updated guidelines define the target population for screening as between 50 and 70 years of age, with a category 2A consensus.

Testing in younger patients (ages 45–50; category 2B) should be considered. For those with a PSA level greater than 1 ng/mL, repeat testing is indicated at 1- to 2-year intervals. According to Dr. Carroll, annual screening may be no better than every 2 years, which is different from recommendations in past NCCN Guidelines, and there are enough data to suggest that screening at 2 years is reasonable. For younger men with a normal digital rectal examination (DRE) and a PSA level 1 ng/mL or less, testing should be repeated at age 50.

Testing in men older than age 70 is considered a category 2B option. “Men in this group should be screened very cautiously,” stated Dr. Carroll. If the DRE is normal, the PSA level is less than 3 ng/mL, and no other indications for biopsy are present, repeated testing may be considered at 1- to 2-year intervals. Regardless of age, men should be screened based on overall health and life expectancy, he added.

In previous versions of the guidelines, the criteria for biopsy were liberal, including such factors as an elevated PSA level, abnormal clinical examination, a low free-to-total PSA ratio, and a high PSA velocity. In the 2014 NCCN Guidelines, the panel provided more explicit indications for biopsy and allowed for less-frequent testing. For instance, the only category 2A indication for biopsy is now a PSA level greater than 3.0 ng/mL. A DRE that is highly suspicious of cancer at any PSA level has a category 2B ranking, and Dr. Carroll emphasized that this does not include minor abnormalities. Removed from the current guidelines is the use of PSA velocity at a low PSA level as a sole indication for biopsy. “We now know that PSA velocity is basically nonpredictive of aggressive prostate cancer,” explained Dr. Vickers. “The use of PSA velocity alone, at very low baseline PSA levels, can lead to overdetection,” added Dr. Carroll.

For men with more aggressive, high-risk disease, Dr. Vickers noted that typically we have been undertreating them with primary androgen deprivation therapy. “PSA is not a good marker for prostate can-

![Figure 1](https://example.com/figure1.png)

**Figure 1** Rate of overdiagnosis in prostate cancer by year of diagnosis.
Table 1 Highlights of the 2014 NCCN Guidelines for Prostate Cancer

- Defines target population based on RCT
- Earlier testing, at age 45–50, single PSA, then selective
- Testing beyond age 70
- Less frequent testing
- Use of PSAV at low PSA removed explicit indication for biopsy
- Limits over detection with limited impact on lives saved
- Explicitly linked with NCCN Treatment Guidelines

| Table 1 | Abbreviations: PSA, prostate-specific antigen; PSAV, prostate-specific antigen velocity; RCT, randomized controlled trials. |

...cer, but it is fabulous marker for aggressive prostate cancer," he clarified.

In addition, when surgery is performed, he added, it often is in the hands of surgeons who lack the necessary experience with radical prostatectomy, which can result in less-than-optimal outcomes.8 “The learning curve of radical prostatectomy is about 250 to 300 cases,” revealed Dr. Vickers. His research7 showed that approximately 80% of surgeons performed fewer than 10 procedures each year and thus are unlikely to reach the plateau of the learning curve during their careers.

In closing, Drs. Vickers and Carroll emphasized that the NCCN Guidelines for Prostate Cancer Early Detection should not be used independently of the NCCN Guidelines for Prostate Cancer, as they are tightly aligned. Moreover, active surveillance is recommended in low-risk disease, thereby minimizing the harms of overtreating patients.9

References