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Perspective Roundtable: Screening for Prostate Cancer

Introduction

DR. THOMAS LEE: Welcome to a Perspective Roundtable of the *New England Journal of Medicine*. I'm Tom Lee, an associate editor of the *Journal*, and I'll be moderating a discussion today of two papers that are being published online this week of one of the most common and complex issues in medicine, screening for prostate cancer with prostate-specific-antigen testing.

With me are two colleagues with complementary clinical and academic expertise in this field. We have Mary McNaughton-Collins, a general medicine internist and health services researcher at Mass General Hospital and Harvard Medical School. And we have Phil Kantoff, who is director of the Lank Center for Genitourinary Oncology at Dana Farber Cancer Institute and a professor of medicine at Harvard Medical School. Thanks very much for joining us today.

First, let's try to put this topic in context. Phil, it's bread-and-butter medicine, but most physicians are confused, ambivalent and, even worse, inconsistent in what they do. Why is this topic so hard?

DR. PHILIP KANTOFF: Well, first of all, the PSA has been around for about 20 years, and to this date there's no primary evidence that PSA-based screening reduces prostate-cancer mortality. So we're operating without primary evidence of a benefit from the screening technique.

The use of PSA is associated clearly with an earlier diagnosis of prostate cancer. And we've also seen a reduction in the mortality from prostate cancer over the past 20 years during the period of time that it's been used. But we still don't know if it actually works, if there's a cause-and-effect relationship between use of PSA and reduction in mortality.

There's also the issue of tradeoffs. When you use a PSA, you diagnose prostate cancer, and the benefits of diagnosing that prostate cancer, generally, in its early form, are not seen for probably 10 to 15 years. Yet the downside effects of PSA screening are immediate if a patient undergoes treatment.

Screening Guidelines

DR. LEE: Mary, why don't you summarize the skeptic's position, the U.S. Preventive Services Task Force guidelines, for us?

DR. MARY McNAUGHTON-COLLINS: The guidelines are in conflict, in large part, because of the absence of convincing evidence that prostate-cancer screening produces more good than harm in men. And the skeptic definitely is concerned (I'd echo what Phil said) with the known harms — in particular, overdiagnosis and overtreatment, meaning finding and treating harmless cancers. So those harms, as Phil said, are incurred by men in the near term, and they endure. Then the potential uncertain benefit, in terms of mortality or morbidity reduction, is not realized until down the line, if at all.

So the United States Preventive Services Task Force has concluded that the evidence is insufficient to assess the balance of benefits and harms in men 75 years and younger. So they do not — cannot make a decision on screening there. However, they have come down outright against screening for men 75 years and older.

DR. LEE: So, Phil, your professional society and the urologists' professional society have a different perspective, right?

DR. KANTOFF: Correct. The American Urological Association was very quick in supporting the use of PSA-based screening, which includes PSA and digital rectal exam, initially in men of the age of 50, and have reduced their age cutoff to about 40.

Two other societies, the American Cancer Society, which incidentally was one of the first out of the box in recommending screening for prostate cancer, and the National Comprehensive Cancer Network (NCCN) have taken a slightly modified approach in suggesting that there should be some sort of discussion with the patient about the risk and benefits. But at the end of the day, they do support screening for prostate cancer with the PSA and digital rectal exam in men starting at the age of 50 in the case of the American Cancer Society, at the age of 40 in the case of the National Comprehensive Cancer Network. For the American Cancer Society, they have suggested that men at high risk — African American men, men with a positive family history — that screening should start earlier.

In reality, in the United States, over 50% of men over the age of 55 undergo screening, will report screening with PSA within the past couple of years.

Study Results

DR. LEE: Okay, so let's get to the studies. Mary, you've got the skeptic's position to defend. So why don't you tell us about the first of these studies, the PLCO study?

DR. McNAUGHTON-COLLINS: Sure, Tom. So PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening study, is a large randomized trial from the United States. The prostate component was designed to determine the effect of annual PSA screening and DRE on prostate-cancer-specific mortality. They enrolled about 76,000 men across 10 centers over the years 1993 to 2001. And the result, Tom: no mortality reduction with combined PSA and DRE screening over 11 years' median follow-up.

DR. LEE: Okay, Phil, you've read this paper carefully. So what do you think it proves and what do you think it doesn't prove?

DR. KANTOFF: In the PLCO study, the cutoff for doing a biopsy was 4 nanograms per milliliter. If we set up a study right now, that probably would not be the criteria for doing a biopsy. It would probably be lower, or we would use age-adjusted PSAs in order to trigger a biopsy. And of course, by using a higher criteria, you could miss some potential cancers and potentially some lethal cancers.

The second issue with the study is the issue of contamination: 52% of the men who were in the nonscreened arm had a PSA documented within the past few years in the study, as opposed to 85% in the screened arm. And as a result of it, it's not surprising to me that there was only a modest increase in the number of cancers that were diagnosed in the screened arm, only 20%.

But I think the most problematic part of this study is the relatively short follow-up period — average follow-up of 11 years. But the number of outcomes were actually very modest. One tenth of 1% of the entire population actually died of prostate cancer. Not surprisingly that the mortality for prostate cancer within the first 10 years is small, but with the numbers that they generated of about 50 and 44 in each arm, it's really hard to make a statement about differences in outcomes given that limitation.

DR. LEE: Why don't you tell us about the European study which came to a different conclusion?

DR. KANTOFF: The ERSPC study started, once again, over 15 years ago, and it involved a much larger group of patients, 182,000 patients. A much more heterogeneous study. It was conducted at seven different countries. They defined a core population of men, of about 162,000 men, who were between the ages of 55 and 69. And this is the group that they reported on.

The men were randomized to either screening with PSA, on average every 4 years, and a digital rectal exam twice over that period of time. In contrast to the PLCO study, the threshold, for the most part, of doing a biopsy was 3, which was less than the PLCO study, which standardly had 4 as the cutoff, although there was variability from country to country in terms of the criteria for doing the biopsy. The median follow-up in this study was 9 years, slightly less than the PLCO study.

There were about twice as many cases of prostate cancer diagnosed in the experimental arm, the screened arm, than in the nonscreened arm, speaking to the, although not documented, less contamination in the ERSPC study than in the PLCO study. In absolute numbers, there were 326 patients who died of prostate cancer in the nonscreened arm as compared to 214 patients who died of prostate cancer in the screened arm, which calculated out to be a 20% reduction in mortality, with a median follow-up of 9 years.

DR. LEE: Mary, this study is probably going to be quoted by some of our colleagues as proof that PSA testing should be used routinely. What's your take on that?

DR. McNAUGHTON-COLLINS: I think that there are limitations that deserve serious consideration. Firstly, the European study, as Phil said, it actually pulled together trials from different countries, but these different countries used different protocols. It wasn't a uniform study design.

Secondly, this study is an interim analysis, and it's the third interim analysis. And so the result of the 20% mortality reduction is only marginally statistically significant at 0.04, raising the question, which is curious, Tom, why stop now?

And thirdly, the numbers needed to screen, numbers needed to treat are high. The investigators themselves point out that to prevent one prostate cancer death, 1400 men need to be screened. But more problematic than that, about 48 men would need to be treated.

So I think the European investigators have some additional studies coming out, analyses on quality-of-life implications, on cost-effectiveness. And those papers will help round out this point. And those are eagerly awaited. But I think, at this juncture right now, it does behoove us, I think, to maintain a healthy skepticism about a screening program such as this, because any effective screening program, we know, requires more than just effectiveness. We have to find out more about quality of life or cost-effectiveness.

Risk-Benefit Balance

DR. LEE: So, Mary, as you look at these studies and other data, do you see evidence that our fears that we might harm patients with PSA testing might be realized?

DR. McNAUGHTON-COLLINS: I think that there is convincing evidence of harm, to answer your question, Tom. The two studies together show marginal to no benefit across several years of follow-up at the cost to so many men of overdiagnosis and overtreatment. So that deceptively simple PSA test inevitably leads to a cascade of biopsies, which lead to prostate-cancer diagnoses, leading to aggressive treatments for those prostate cancers, leading to men having substantial side effects from those treatments, urinary incontinence, sexual dysfunction. And the problem being that, for many of these men, they suffer those downstream troubles for a cancer that was never, ever destined to cause them harm in their lifetime.

So I think that that is a part of the problem. Once we can tell the indolent cancer that doesn't need to be treated from the aggressive cancer that does, I think the PSA screening controversy will diminish. And in the meantime, I think the onus is on us, to maintain that healthy skepticism about a screening program that's built on inconclusive data on whether or not we are helping more men than we're hurting.

DR. KANTOFF: I just want to agree with Mary in the sense that there's a lot of uncertainty about the downside effects, including getting a PSA and having the PSA anxiety, as we call it, associated with an elevated PSA, but not having prostate cancer, the morbidity of the biopsy itself, the overtreatment. I would like to begin to dissociate the whole process of PSA screening from treatment, because I do believe that many people who get diagnosed with prostate cancer do not need to be treated. And that's where much of the morbidity exists.

Clinical Practice

DR. LEE: I'd like to ask each of you to summarize what you're going to be saying to the patients, and friends and neighbors, that you talk to about this topic in the weeks ahead. Mary?

DR. McNAUGHTON-COLLINS: So, Tom, I think I would advise, looking at these papers, caution to patients, caution to physicians, and to neighbors and friends. I think that from my perspective, primary care physicians need to, with our patients, fully acknowledge the ongoing prostate-cancer-screening controversy. We need to encourage our patients to become informed, fully informed, to consider their preferences and values about their decision, this PSA test. And we physicians can help them to know that there's tradeoffs, that there are potential benefits and that there are potential harms.

And so, for men in my own practice, for some men the PSA decision is the right one. We check that box on the lab slip, and that's the right decision for them. For many of my men, once they're fully informed, they decide to forgo the PSA test. And for those men, that is the right decision. So I think right now, we're left with a shared decision-making process that is crucial and that works well to help us achieve quality decisions and outcomes for men considering PSA screening in 2009.

DR. LEE: Phil?

DR. KANTOFF: I think I'm not going to be saying a lot differently than what I was saying a week ago. What I learned, what I confirmed from these studies is that the mortality from prostate cancer in screened populations, in the first 10 years, is quite modest. And as a result of that, I more firmly feel that if somebody has a life expectancy of under 10 years, one could conceivably forgo screening.

In my opinion, I do think that there is going to turn out to be a reduction in mortality associated with PSA-based screening, but what I also firmly believe is that not everybody diagnosed with prostate cancer needs to be pigeonholed into a treatment paradigm. And we need to individualize, because clearly there are many patients who are diagnosed with prostate cancer that do not need to be treated, can be observed safely, and will not die of their cancer.

DR. LEE: I want to thank both of you, Mary McNaughton-Collins and Phil Kantoff, and thank our viewers for joining us.