examination with palliative treatment of symptoms) and active surveillance (periodic monitoring with PSA tests, physical examinations, and repeated prostate biopsy with attempted curative treatment for signs of disease progression or worsening prognosis) if prostate cancer is diagnosed through PSA screening. Watchful waiting and active surveillance may help prevent the conversion of overdiagnosis to overtreatment, mitigating the harms of screening that are so accurately portrayed by the task force.

To make a grade C recommendation appropriate, we primary care clinicians must ensure there is no more routine, indiscriminate PSA screening — and no washing our hands of responsibility once the patient is referred to a specialist for prostate-cancer treatment. We owe it to our patients to provide them with the kind of guidance about this screening test that they need and deserve. That’s the way to help put the controversy to rest . . . one man at a time.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Stratifying Risk — The U.S. Preventive Services Task Force and Prostate-Cancer Screening

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On October 11, 2011, the U.S. Preventive Services Task Force (USPSTF) issued a draft report on prostate specific antigen (PSA)-based screening for prostate cancer, giving it a grade D recommendation. Grade D means that “the USPSTF recommends against the service” because it has concluded that “there is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.”

This recommendation contradicts the view that PSA-based screening saves lives by reducing the risk of death from prostate cancer. The task force acknowledges that “clinical decisions involve more considerations than evidence alone” and that “clinicians should understand the evidence but individualize decision making to the specific patient or situation.” The latter recommendation, which I support, is in line with several guidelines recommending individualized decisions after the provision of balanced information on the risks and benefits of screening. Such information is unfortunately not currently available in the form of an internationally accepted document, though a proposal for such a document is part of the Prostate Cancer Risk Calculator, which is based on data from the European Randomized Study of Screening for Prostate Cancer (ERSPC, for which I am the international coordinator), and is available online (www.prostatecancer-riskcalculator.com).

The current draft USPSTF recommendation is meant to apply to the general population of men who might be at risk for clinically relevant prostate cancer. The review and recommendations presented by the task force attempt to balance the risks and benefits of screening against those of treatment. The document presents a high-level review of current knowledge. The recommendations are in line with several sets of U.S. guidelines, as well as with the recommendations made in 2009 by the ERSPC group, which state that any deliberation over introducing population-based screening must take into account unresolved questions about potential harms — mainly, the problems of overdiagnosis and overtreatment.

But the USPSTF report has a number of key weaknesses. First, it relied heavily on a meta-analysis that combined higher- and lower-quality evidence. The Cochrane recommendations for establishing scientific truth state that “a systematic review of all relevant randomized controlled trials is the highest level of evidence.” Yet clearly the randomized, controlled trials included in the PSA-screen-
ing meta-analysis are of varying levels of quality and relevance and should be weighted accordingly. In an article by Chou et al. that seems central to the USPSTF report, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, the ERSPC, and the Göteborg screening trials are weighted equally as “fair” — an assessment that seems unjustified, given the report’s criticisms of the PLCO trial. That trial had an excessive contamination rate (52%) in the control group; more than 40% of subjects had undergone PSA testing before randomization; the biopsy rate was only about 40% among men who screened positive; follow-up was only 7 years with 98% complete mortality data; and the power calculation was changed in 1995, with serious effects — all limitations that the task force seems not to have considered in crafting its recommendations. Moreover, according to the revised evaluation plan for the study published in 2000, a 13-year follow-up was to be required after the anticipated completion of recruitment in 2001.

The USPSTF report also notes that “overall mortality was the primary outcome addressed in all prostate-cancer screening studies assessed by the Task Force.” This statement is incorrect, at least as far as the ERSPC and Göteborg trials are concerned. Overall mortality provided a parameter for assessing randomization rather than serving as an end point in itself. Randomized, controlled trials of screening are meant to contribute to reducing cancer-related mortality in general, which is a recognized goal in the United States and around the world; reducing prostate-cancer–related mortality is an important part of that effort.

The task force report considered, methodologically correctly, only the results of the intention-to-screen analysis. The absolute and relative differences between study groups change, however, when analyses are adjusted for subjects’ noncompliance with screening. The resulting data are important because they show the effects in men who are actually screened. In the ERSPC as a whole and the Göteborg substudy, such adjusted analyses showed relative differences of 27% after 9 years of follow-up and 56% after 14 years of follow-up in prostate-cancer mortality in favor of screening. In addition, the high number needed to screen and the number needed to treat reported in the ERSPC are likely to improve with longer follow-up, as the data of the Göteborg study show. And in the ERSPC, the proportion of screening-detected cancers that were considered insignificant because they were indolent is estimated to be in the range of 30%; the remainder of estimated overdiagnosis can be considered to be due to patients’ life expectancy. Finally, prostate-cancer morbidity was an important secondary end point of the ERSPC, which showed that screening has a pronounced effect on the relative risk of metastatic disease, reducing it by 41%, according to preliminary analyses.

The authors of the USPSTF document, in their search for risk factors that may increase the likelihood of aggressive prostate cancer and may therefore outweigh the potential harmful effects of screening (mainly the diagnosis of indolent disease), considered free PSA levels as well as racial and family risk factors. They failed, however, to consider published and well-documented information on readily available clinical risk modifiers, such as the results of digital rectal examination (DRE) and transrectal ultrasonography, which have been included in risk calculators as a result of multivariate analyses. For example, according to the ERSPC-based risk calculator, in a 65-year-old man who decides to undergo prostatic biopsy on the basis of a PSA level of 4.0 ng per milliliter, there is a 21% chance that cancer will be found on sextant biopsies. If the same man undergoes routine urologic examinations that include a DRE and a volume estimate of his prostate by either transrectal ultrasonography or other means, the expected outcomes of the biopsy change dramatically. If he is found to have a normal DRE, no suspicious lesions on transrectal ultrasonography, and a prostatic volume of 55 ml, his risk of a positive biopsy result decreases to 8%. With abnormal results on DRE and transrectal ultrasonography and a prostatic volume of 25 ml, however, his risk of a positive biopsy would be 65%. Thus, the inclusion of other results strongly modifies the PSA-driven indication for biopsy. The effect on a population basis has been described by Roobol et al. as a dramatic reduction in “unnecessary,” biopsies and a substantial increase in the positive predictive value of PSA.

Risk stratification is currently also the only mechanism to reduce overdiagnosis that can be applied before undertaking biopsies. For example, if we decide not to perform biopsies in men in whom the probability of finding cancer is 12.5% or lower, we will avoid performing 33% of PSA-
indicated biopsies and miss only a few aggressive cancers. Until there are marker substances or imaging technologies that permit selective detection of aggressive cancers, such risk stratification should be routinely used by clinicians.

Overtreatment can be at least temporarily avoided by offering active surveillance to men who have a low risk of prostate cancer. These men would be taking a small risk of having progressive disease that goes unnoticed.

All these considerations suggest that PSA screening should not be dismissed as uniformly nonbeneficial. Rather, decisions about screening should be made on an individual basis, by an informed patient and his clinician, after weighing that patient’s particular risk factors.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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This article (10.1056/NEJMpa1112140) was published on October 26, 2011, at NEJM.org.


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