Review

Screening for Prostate Cancer With the Prostate-Specific Antigen Test
A Review of Current Evidence

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IMPORTANCE Prostate cancer screening with the prostate-specific antigen (PSA) test remains controversial.

OBJECTIVE To review evidence from randomized trials and related modeling studies examining the effect of PSA screening vs no screening on prostate cancer–specific mortality and to suggest an approach balancing potential benefits and harms.

EVIDENCE ACQUISITION MEDLINE, EMBASE, and the Cochrane Register of Controlled Trials were searched from January 1, 2010, to April 3, 2013, for PSA screening trials to update a previous systematic review. Another search was performed in EMBASE and MEDLINE to identify modeling studies extending the results of the 2 large randomized trials identified. The American Heart Association Evidence-Based Scoring System was used to rate level of evidence.

RESULTS Two trials—the Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial and the European Randomized Study of Screening for Prostate Cancer (ERSPC)—dominate the evidence regarding PSA screening. The former trial demonstrated an increase in cancer incidence in the screening group (relative risk [RR], 1.12; 95% CI, 1.07-1.17) but no cancer-specific mortality benefit to PSA screening after 13-year follow-up (RR, 1.09; 95% CI, 0.87-1.36). The ERSPC demonstrated an increase in cancer incidence with screening (RR, 1.63; 95% CI, 1.57-1.69) and an improvement in the risk of prostate cancer–specific death after 11 years (RR, 0.79; 95% CI, 0.68-0.91). The ERSPC documented that 37 additional men needed to receive a diagnosis through screening for every 1 fewer prostate cancer death after 11 years of follow-up among men aged 55 to 69 years (level B evidence for prostate cancer mortality reduction). Harms associated with screening include false-positive results and complications of biopsy and treatment. Modeling studies suggest that this high ratio of additional men receiving diagnoses to prostate cancer deaths prevented will decrease during a longer follow-up (level B evidence).

CONCLUSIONS AND RELEVANCE Available evidence favors clinician discussion of the pros and cons of PSA screening with average-risk men aged 55 to 69 years. Only men who express a definite preference for screening should have PSA testing. Other strategies to mitigate the potential harms of screening include considering biennial screening, a higher PSA threshold for biopsy, and conservative therapy for men receiving a new diagnosis of prostate cancer.

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In the United States, about 233 000 men will receive a diagnosis of and almost 30 000 will die of prostate cancer in 2014.[1] The lifetime risk of dying of prostate cancer is less than 3%, with about 2% of all prostate cancer deaths occurring before age 55 years, 28% occurring between age 55 and 74 years, and 70% at age 75 years or older.[2] Age, black ancestry, and family history, especially first-degree relatives receiving a diagnosis early in life, are the primary risk factors for prostate cancer (Box 1).[3]

In the United States, prostate-specific antigen (PSA) was introduced to evaluate treatment response in 1987 but was soon widely adopted for screening. Prostate-specific antigen screening has remained controversial because of uncertainty surrounding its benefits and risks and the optimal screening strategy.[4] A common PSA threshold for biopsy has been greater than 4.0 ng/mL, a cut point associated with a positive predictive value of about 30%[5] in men aged 50 years or more and a negative predictive value of about 85% in men of median age 69 years at biopsy.[6] And because most prostate cancer will never cause harm, PSA screening considerably increases the risk of receiving a diagnosis of prostate cancer, leading to treatment morbidity among men, with no possibility of benefit.

Before 2009, conflicting observational data and 2 small trials could not resolve this controversy.[7-9] Two large randomized trials published in 2009 that were expected to provide definitive conclusions yielded conflicting results. Therefore, the benefits and harms of prostate cancer screening continue to be debated.

Recent interest in more patient-centered care[10,11] emphasizes the importance of informing men about risks and benefits of PSA screening. However, recent clinical practice guidelines provided conflicting results[12-14] (Table 1). This review will critically assess and interpret results of the randomized controlled trials of PSA screening and treatment of screen-detected cancers, discuss methods that may improve the ability of the PSA to identify clinically meaningful prostate cancer, and discuss how clinicians can potentially maximize the benefit of PSA screening and reduce harms.

Methods

A literature search was performed for PSA screening trials from January 1, 2010, to April 3, 2013, with a search strategy similar to that used by Ilic and colleagues[21,22] to update previous Cochrane reviews through July 2010. MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched for PSA screening studies and studies published in English, including randomized controlled trials of PSA screening for prostate cancer. Search terms included *prostate-specific antigen*, *PSA*, *mass screening*, *screening*, *prostatic neoplasms*, *prostate cancer*, *clinical trial*, *random*, and *placebo* and were adapted for each database.

An additional search in EMBASE and MEDLINE from 2005 to April 4, 2013, was performed for studies that modeled extended follow-up or alternative screening strategies, based on the results of the 2 large randomized trials. The same search terms were used, but the terms *clinical trial*, *random*, and *placebo* were replaced with *model*, *simulation*, and *computer simulation*, *medical decision*, *Markov model*, *decision analysis*, and *population health*.

The American Heart Association Evidence-Based Scoring System was used to rate the evidence as follows: level of evidence A, data from multiple randomized clinical trials; level B, data from either

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Box 1. Characteristics of Men at Higher Risk for Prostate Cancer

Black race

Family history, particularly if relation diagnosed before age 65 y

Known or suspected *BRCA1* or *BRCA2* mutation

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a single randomized trial or multiple nonrandomized studies; and level C, expert opinion.[23]

Results

Screening Studies

Three hundred thirty-nine articles were identified in the systematic review; 10 were reviewed and 5 are discussed. The evidence addressing the effectiveness of PSA screening is dominated by 2 trials: the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer screening trial from the United States[24,25] and the European Randomized Study of Screening for Prostate Cancer (ERSPC)[26,27] (Table 2). Three smaller trials do not contribute appreciably to the evidence base because they assessed 1-time screening and did not use intention-to-treat methods.[7,9,28] The PLCO randomized 76 685 men aged 55 to 74 years to annual PSA testing for 6 years and digital rectal examination for 4 years; men with suspicious results were referred to their usual source of care. About 4% of participants were black and 7% had a family history of prostate cancer.[24] After 13 years, prostate cancer cumulative incidence was approximately 11% in the screening group and 10% in the control group (108.4 vs 97.1 per 10 000 person-years; relative risk [RR], 1.12; 95% CI, 1.07-1.17; 10% is obtained by dividing the number of cancers by the number of men in the non-screening cohort; cumulative incidence is calculated with risk $= 1 - e^{-ID \times t}$ [where ID is incidence density and t is elapsed time]), and prostate cancer mortality was approximately 0.4% in both groups (3.7 and 3.4 per 10 000 person-years in the screening and usual care group, respectively; RR, 1.09; 95% CI, 0.87-1.36).[25] There was no statistically significant effect of age, pretrial PSA testing result, or comorbidity on the results. Limitations of the PLCO study include the low proportion of black men and men with a family history of prostate cancer, of biopsies among men with suspicious results (<50%),[29] and contamination of the control group by PSA testing, approximately 50% annually in the sixth year of screening.[24] These problems would lead to dilution of any true screening effect. Thus, PLCO is best considered a trial of more systematic vs less systematic screening, as also reflected by the small absolute difference in prostate cancer cumulative incidence between groups.

The European Randomized Study of Screening for Prostate Cancer randomized 182 160 men in 7 countries to PSA screening without digital rectal examination every 4 years (every 2 years in Sweden) or a control group; the main analysis focused on a prespecified group of participants aged 55 to 69 years at entry.[26] After 11-year follow-up, prostate cancer cumulative incidence was approximately 10% in the screening group and 6% in the control group (9.66 vs 5.95 per 1000 person-years; RR, 1.63; 95% CI, 1.57-1.69), and prostate cancer mortality was approximately 0.4% in the screening group and 0.5% in the control group (0.39 vs 0.5 per 1000 person-years;

RR, 0.79; 95% CI, 0.68-0.91).[27] After 12 years of follow-up, the cumulative incidence of metastatic prostate cancer in 4 countries was approximately 0.7% in the screening group and 0.9% in the control group (0.67% vs 0.86% per 1000 men; hazard ratio, 0.70; 95% CI, 0.60-0.82).[30] The annual rate of PSA screening contamination in the control group was approximately 20%.[27]

Criticisms of the ERSPC include whether results are generalizable to US men and the possibility that differences in which medical facilities men received treatment between groups[31] might explain the results. A separate report from the Swedish field center showed a significant reduction in prostate cancer mortality, from approximately 0.9% to 0.5%, with screening at 14 years, approxi-

Table 1. Screening Recommendations of Major Societies (Limited to Guidelines Based on Systematic Reviews and Updated Since the Publication of the European Randomized Study of Screening for Prostate Cancer and Prostate, Lung, Colorectal, and Ovarian Screening Trial Randomized Controlled Trials)

Organization	Who Should Be Screened	Screening Interval	Basis
US Preventive Services Task Force, 2012[14]	Screening should not be offered		Systematic review
American Urological Association, 2013[15-17]	Men aged 55-69 y or ≥70 y with >10- to 15-y life expectancy: use shared decision-making approach Men at higher risk <55 y: individualize approach	Consider 2-y interval over annual screening; may individualize intervals based on initial PSA	Systematic review and meta-analysis of the literature, 1995-2013
American Society of Clinical Oncology, 2012[18]	Men with life expectancy >10 y: use shared decision-making approach		Updating of Agency for Healthcare Research and Quality literature review; PubMed search through 2012; expert opinion
American Cancer Society, updated 2010[13]	Men aged >50 y at average risk with >10-y life expectancy: use shared decision-making approach Men at higher risk (black, first-degree relative diagnosed before 65 y) at 45 y Men at appreciably higher risk (multiple family members diagnosed before 65 y) at 40 y	Base interval on initial PSA: annual if ≥2.5 ng/mL; biannual if <2.5 ng/mL Biopsy recommended for all men with PSA>4 ng/mL Biopsy for PSA levels between 2.5 and 4 ng/mL should be individualized	Systematic review of the literature and consensus process
American College of Physicians, 2013[12]	Men aged 50-69 y with life expectancy >10-15 y: use shared decision-making approach Men at higher risk (black, first-degree relative diagnosed before 65 y) at 45 y Men at appreciably higher risk (multiple family members diagnosed before 65 y) at 40 y	Consider longer intervals than 1 y between screening PSAs	Review of available guidelines
Canadian Urologic Society, 2011[19]	Men ≥50 y with a 10-y life expectancy: use shared decision-making approach Men ≥40 y at high risk Consider baseline PSA in men 40-49 y	Consider intervals up to every 4 y	Systematic literature search 2004-2010
European Association of Urology, 2013[20]	Baseline PSA≥40-45 y	Risk-adapted strategy based on initial PSA in men with life expectancy >10 y Screening intervals every 2-4 y for men with serum PSA>1.0 µg/L at 45-59 y and up to 8 y in men with serum PSA <1 µg/L	Systematic literature review and meta-analysis

Abbreviation: PSA, prostate-specific antigen.

Table 2. Prostate Cancer Incidence and Mortality in the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial

Site	Follow-up, Median, y	Prostate Cancer Detected			Died of Prostate Cancer		
		No./Total (Cumulative Incidence %)		Rate Ratio (95% CI)	No./Total (Cumulative Incidence %)		Rate Ratio (95% CI)
		Control	Screening		Control	Screening	
ERSPC[27]							
The Netherlands	11.1	896/17390 (5.2)	2028/17443 (11.6)		97/17390 (0.56)	69/17443 (0.40)	0.71 (0.52-0.96)
Belgium	12.1	311/4255 (7.3)	420/4307 (9.8)		25/4255 (0.48)	22/4307 (0.51)	0.89 (0.48-1.52)
Sweden	14	507/5951 (8.5)	759/5901 (12.9)		70/5951 (1.18)	39/5901 (0.66)	0.56 (0.38-0.83)
Finland	11	3175/48409 (6.6)	2838/31970 (8.9)		237/48409 (0.49)	139/31970 (0.43)	0.89 (0.72-1.09)
Italy	10.7	257/7251 (3.5)	374/7266 (5.1)		22/7251 (0.30)	19/7266 (0.26)	0.86 (0.46-1.58)
Spain	10.7	24/1141 (2.1)	69/1056 (6.5)		1/1141 (0.088)	2/1056 (0.19)	2.15 (0.2-23.77)
Switzerland	8.2	226/4955 (4.6)	475/4948 (9.6)		10/4955 (0.02)	9/4948 (0.18)	0.89 (0.36-2.20)
All sites[a]	11.0	5396/89352 (6.0)	6963/72891 (9.6)	1.63 (1.57-1.69)	462/89352 (0.52)	299/72891 (0.41)	0.79 (0.68-0.91)
				Relative Risk			Relative Risk
PLCO[25]	13	3815/38345 (9.9)	4250/38340 (11.0)	1.12 (1.07-1.17)	145/38345 (0.38)	158/38340 (0.41)	1.09 (0.87-1.36)

[a] For all sites, P = .001.

mately 4 times the absolute benefit in the ERSPC overall.[32] The importance of the independent Swedish report is questionable because the outcomes of most of the participants were included in the ERSPC report. Differences in the Swedish results may be due to chance. Suggested explanations for the larger benefit include that follow-up was longer, participants included younger men (aged 50 to 54 years), and there was implementation of biennial screening. However, the relatively similar absolute difference in prostate cancer mortality in the overall ERSPC results at 11-year follow-up makes it unlikely that the overall ERSPC results would reach Swedish levels after 3 additional years.[26,27] The low event rate among men aged 50 to 54 years in the overall ERSPC[26] and a low occurrence of interval cancers between Swedish and Dutch ERSPC participants[33] make inclusion of younger men or more frequent screening less likely explanations. In the ERSPC at 11-year follow-up, the number of participants needing to be invited to be screened to prevent a prostate cancer death was 1055, and the ratio of additional men receiving a diagnosis of prostate cancer to reduction in men who died of prostate cancer in the screening group was 37.[31]

A concern about both trials is follow-up duration. Prostate cancer mortality typically occurs late in life. Therefore, these trials include only about one-sixth of prostate cancer deaths that will eventually accrue; 11 to 13 years of follow-up may be too short to inform the decision of a man in his 50s.

Treatment Study

The recently published Prostate Cancer Intervention vs Observation Trial (PIVOT) has important implications for screening.[34] PIVOT randomized 731 men with localized prostate cancer to radical prostatectomy or observation. Approximately half had stage T1c cancers discovered by PSA screening. After a median follow-up of 10 years, overall mortality was approximately 47% with radical prostatectomy and 50% with observation (HR, 0.88; 95% CI, 0.71-1.08). The proportion of men who died of prostate cancer was 5.8% in the radical prostatectomy group and 8.4% with observation. Patient characteristics did not affect the results. A prespecified subgroup analysis found that among the approximately two-thirds of participants with baseline PSA level less than or equal to 10 ng/mL, overall mortality was approximately 46% with radical prostatectomy vs 44% with observation (RR, 1.06; 95% CI, 0.87-1.29), whereas for men with baseline PSA greater than 10 ng/mL, overall mortality was about 48% with radical prostatectomy vs 62% with observation (RR, 0.79; 95% CI, 0.63-0.99). This study demonstrates the excellent prostate cancer-specific outcomes for men receiving a diagnosis by screening, whether treated or not. The finding that radical prostatectomy provided a mortality benefit only to men with a PSA level greater than 10 ng/mL, albeit from a subgroup analysis, suggests that the traditional biopsy threshold of greater than 4.0 ng/mL could be increased without substantially decreasing benefits.

Adverse Effects of Screening and Treatment

In the screening trials, the cumulative risk of a suspicious PSA test result followed by a negative biopsy result was 12% to 13% after 3 to 4 rounds of screening; overall, about 25% of biopsies performed found cancer, representing the positive predictive value of the test.[35] In one ongoing trial, adverse effects rated moderate or severe by men who underwent biopsy with PSA level 3 to 20 ng/mL were pain (7%), fever (6%), hematuria (6%), hematochezia (2%), and hematosper-

mia (27%).[36] In clinical trials, the risk of hospitalization after biopsy, usually for infection, has been 0.5% to 1.3%[35,36]; however, in a population-based study, 30-day hospitalization risk was approximately 7% compared with approximately 3% in controls.[37]

Results of the ERSPC demonstrated a 63% higher prostate cancer incidence in the screened group compared with the control group during 11-year follow-up.[38] These results suggest that overdiagnosis and resultant overtreatment are the primary adverse effects of PSA screening. This phenomenon is even more common in the United States, where aggressive treatment even for low-risk prostate cancer in men with limited life expectancies occurs commonly.[39,40] Perioperative mortality for radical prostatectomy is about 0.5%.[35] In PIVOT, participants who underwent radical prostatectomy had an 11% higher absolute risk of incontinence and 43% higher absolute risk of erectile dysfunction during 2-year follow-up.[34] During the long term, complications of surgery and radiotherapy appear similar.[41] Recent population-based studies suggest that these adverse effects have not decreased even with newer technologies.[42,43]

Statistical Modeling Studies

Statistical models have extrapolated results from the 2 large randomized trials to address additional questions about screening.[38,44-48] In this review, 202 articles were identified, 25 were reviewed, and 4 are discussed.

Influence of Length of Follow-up on PSA Screening Efficacy

Modeling studies use existing evidence to project longer-term outcomes. Some modeling studies suggest that with longer follow-up, PSA screening will be associated with a larger decrease in prostate cancer mortality.[49,50] Gulati et al[49] projected 25-year estimates of the number needed to screen and to treat to prevent 1 prostate cancer death for men aged 55 to 69 years at diagnosis. Over time, the number needed to screen and treat decreased substantially as a result of an increasing predicted decline in prostate cancer mortality. In Europe, the number needed to screen was 262 and number needed to treat was 9 after 25 years. With a range of overdiagnosis rates consistent with incidence in the United States, number needed to screen values were 186 to 220 and 2 to 5, respectively, substantially lower than after the 11-year follow-up from the ERSPC (1055 and 37, respectively).

Screening Strategy

Using modeling methods based on results from the ERSPC, Heijnsdijk et al[51] projected lifetime estimates of prostate cancer death with and without screening for men starting at age 55 years, extrapolating results of the ERSPC. If 1000 men aged 55 to 69 years were screened annually, 9 fewer prostate cancer deaths would occur compared with the number of deaths with no screening (in the ERSPC, just 1 fewer death per 1000 was observed after 11 years), and there would be a 37% relative reduction in prostate cancer mortality. If annual screening were extended to age 74 years, 11 fewer deaths would occur, with a 44% relative reduction in prostate cancer–specific death, but the number of cancers needed to detect to prevent 1 prostate cancer death would increase from 5 to 7; the number of quality-adjusted life-years gained by screening would be unchanged. The lack of difference in number of quality-adjusted life-years between screening to age 69 vs 74 years, despite a greater mortality benefit, reflects that substantially more men are overdiagnosed (45 vs 72/1000 men) and are treated unnecessarily when screened during a longer period. Although utility modeling in this study

was limited, the importance of quality of life can be observed in the sensitivity analyses performed. With varying utilities, the lifetime difference in quality-adjusted life-years between screening and not screening for 1000 men ranged from −21 to 97, indicating that the net benefit of screening appears highly dependent on individual preferences.

Wu et al[52] varied the interscreening interval and age range from the Finnish branch of the ERSPC during 25-year follow-up, including 1-time screening; periodic screening at 1-, 2-, 4-, and 8-year intervals; starting at age 55, 60, and 65 years; and ending at age 70 or 75 years. Varying the screening interval was associated with a greater effect on outcome than age at screening initiation. The greatest relative reduction in prostate cancer–specific mortality was observed in men screened annually between age 55 and 75 years (26.1%), with number needed to screen equal to 154 to prevent 1 prostate cancer death. The benefit decreased as the interval between screenings increased. If these men were screened every 2 years, the reduction decreased to 18.3%, and if they were screened every 4 years, it decreased to 10.4%. However, if annual screening was restricted to men aged 60 to 75 years, the relative reduction in prostate cancer–specific mortality decreased only to 25.5%; if restricted to men aged 65 to 75 years, it decreased to 21.7%. The absolute risk difference between the most effective screening protocol and no screening was at most 8.3 fewer prostate cancer deaths per 1000 men screened after 25 years, substantially more than the difference of 1.1 per 1000 men observed in the ERSPC after 11 years, but a small absolute benefit.

The relatively small absolute prostate cancer–specific mortality benefit to screening was also reported by Wever et al,[53] who used data from the ERPSC-Rotterdam and Goteborg to compare annual screening to no screening starting at various ages, ending at age 75 years. The authors found that in men who began screening at age 55 to 59 years, the absolute risk of dying from prostate cancer was 2.94% in men who did not undergo screening vs 1.89% in men who were screened. In men aged 65 to 69 years, the risk of dying of prostate cancer without screening was 2.64% compared with 1.81% with screening. Again, the age at screening initiation did not substantially affect prostate cancer–specific mortality outcomes.

Models attempt to provide answers to clinical questions under conditions of uncertainty, and the results depend on the assumptions they must make. Any attempt to model effects of PSA screening requires assumptions regarding rate of diagnosis with and without screening and prostate cancer–specific and overall survival. These assumptions can introduce bias into results. By discussing only studies extrapolating from the 2 trials, we have attempted to minimize this bias. In general, modeling studies extending the results of the ERSPC suggest that more favorable tradeoffs between overdiagnosis and overtreatment and prostate cancer mortality reductions will be observed during a longer time. Models also suggest that most of the benefit of PSA screening can be achieved with less intensive screening of a more limited target population than has generally been practiced in the United States.

Discussion

Recommendations for Decision Making in Clinical Practice
The decision whether to screen for prostate cancer with PSA should be shared between patient and clinician. As part of this discussion, the benefits and harms of screening should be presented, and a review of the current literature suggests that the ERSPC may provide the best esti-

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Box 2. Recommendations for Screening With PSA

Focus Screening Discussions on Men Aged 55 to 69 Years

This is the age group defined a priori in whom a mortality benefit was demonstrated in the ERSPC. Although some clinicians will extend these conversations to men aged 50 to 54 years or younger, especially with risk factors, and men aged 70 to 74 years in excellent health, many men outside these limits, particularly older and sicker men with limited life expectancies, are currently being screened.

Use PSA Screening Every Other Year as the Default Frequency

Screening can be annual in men near a biopsy threshold or less frequently (ie, every 3-4 years) in men with PSA levels less than 1 ng/mL.

Consider a Higher Biopsy Threshold

Although the ERSPC showed a benefit of screening with a biopsy threshold of 3 ng/mL, the results do not allow an analysis of the effect of a higher biopsy threshold on prostate cancer incidence and mortality. PIVOT suggests that the greatest benefit to treatment is realized with baseline PSA levels of 10 to 20 ng/mL. Consideration of biopsy at a PSA threshold of 4.0 ng/mL seems reasonable, and further analyses from PIVOT (particularly regarding the outcomes of higher-grade cancers diagnosed at lower PSA levels) and confirmatory evidence from the Protect trial[55] may make an even higher biopsy threshold warranted.

Consider Surveillance or Watchful Waiting

Either active surveillance (the strategy of close surveillance with serial PSA tests, examinations, and biopsy with treatment administered at a sign of more aggressive disease) or watchful waiting (observation with only palliative treatment offered at disease progression) may be the optimal treatment strategy for men with lower-risk prostate cancers, particularly with a lower PSA level at diagnosis or Gleason score lower than 7.

ERSPC indicates European Randomized Study of Screening for Prostate Cancer; PIVOT, Prostate Cancer Intervention vs Observation Trial; PSA, prostate-specific antigen.

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mates of outcomes relevant to a man making a decision about the value of PSA screening for his future health. After 11 years of follow-up, the ERSPC data suggest that a small but statistically significant reduction in prostate cancer mortality can be achieved with approximately 1 fewer death per 1000 men screened. This potential benefit must be weighed against the risks of false-positive results, the complications of prostate biopsy, and, most important, a higher risk of receiving a diagnosis of prostate cancer amounting to approximately 37 extra prostate cancer diagnoses per 1000 men screened. In the United States, these men are treated with surgery or radiation, leading to substantial adverse effects. However, modeling studies suggest that this relatively high ratio of harms to benefits should decrease with longer follow-up, and a man in his 50s making a decision about PSA testing might well consider the longer-term outcomes relevant to his decision, in particular given that the life expectancy for a man aged 50 years in the United States is 30 years.[54] Moreover, given different values and preferences, it is likely that different men will see even the shorter-term tradeoffs differently, leading some to choose screening when fully informed, and others not. Therefore, involving well-informed men in the decision whether to screen for prostate cancer is the best way forward.

Clinicians should discuss the pros and cons of PSA screening with average-risk men aged 55 to 69 years (starting at age 45 to 50 years

for black men and men with a first-degree relative with prostate cancer before age 70 years, though acknowledging that this earlier screening for high-risk men is not supported by direct evidence). The clinician should discuss the most important outcomes, including the possibility of false-positive results, risks of biopsy, and potential diagnosis with prostate cancer unnecessarily leading to treatments with considerable adverse effects.[12] The 1 fewer prostate cancer death per 1000 men screened documented in the ERSPC after 11 years should be communicated as a maximum benefit over that time, as well as the uncertainty about the benefit during a longer period. Findings of this review are consistent with recent guideline recommendations that only well-informed men who actively choose screening should have PSA testing. Some clinicians, consistent with the USPSTF recommendation, may choose not to raise the question of PSA screening with men who do not inquire about PSA screening. However, this approach may result in a health care disparity if only men well educated and well informed enough ask about PSA screening.

Numerous randomized trials have shown that a shared decision-making approach, when supported by patient decision aids, can improve knowledge, reduce decisional conflict, improve the accuracy of risk perceptions, and reduce patient passivity in decision making. In a meta-analysis of 11 trials of PSA decision aids, uptake of screening was reduced by 15%, but all these trials were conducted before the publication of PLCO and ERSPC.[55] A number of recent guidelines have included lists of the important benefits and harms of screening for discussion (American College of Physicians, American Cancer Society, American Society of Clinical Oncology),[12,13,18] and 2 offer patient decision aids (http://stage.asco.org/sites/default/files/psa_pco_decision_aid_71612.pdf and http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-024618.pdf).

Additional Considerations Regarding PSA Screening

The concept of overdiagnosis leading to overtreatment as an important adverse effect of a diagnostic intervention is now more widely recognized. Traditionally, the theory that cancers should be detected and treated as early as possible to maximize the chance of a cure has been pervasive. However, many of the harms of PSA screening are attributable to that theory not only through overdiagnosis but also through earlier diagnosis of cancers destined to cause harm. The results of the PIVOT trial in particular suggest that this mindset should evolve to diagnosing and treating prostate cancers only as early as necessary. Identifying the "escape from cure" point, the point at which prostate cancer ceases to be curable, is challenging, though the relatively favorable number needed to treat for surgery for men in PIVOT with PSA levels of 10 to 20 ng/mL and the lack of benefit for men with lower PSA levels suggest that for cancers that are curable at all, escape from cure may occur later than previously thought.

Reducing the Ratio of Harms to Benefits

The results of the 2 large RCTs, the related modeling studies, and PIVOT suggest strategies that may result in a more favorable harms-to-benefits ratio. Less intensive and more focused screening for well-informed men who request screening should reduce harm while maintaining most of any benefit. These recommendations include concentrating screening on men aged 55 to 69 years, increasing the interval between screening tests, increasing the biopsy threshold, and considering surveillance the preferred strategy for men with low-risk prostate cancer (**Box 2**).

Conclusions

Because trials have not directly compared different approaches, a reasonable strategy is to inform and involve men not only in the decision whether to screen but also in any subsequent decisions about biopsy and treatment.

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