Prostate Cancer

Screening guidelines and evidence

ERPSC
PLCO
55 year old man with no significant past medical history comes to your office for his annual physical exam. His friend was recently diagnosed with prostate cancer after being screened with a PSA test. He insists on PSA testing after you discuss risks and benefits. He wants “everything” done. What is the evidence and guideline based recommendation?

A) Order the PSA and perform DRE
B) Decline to order the PSA and do not perform DRE
C) Decline to order the PSA but perform DRE
D) Order the PSA but do not perform the DRE
E) Refer patient to urology
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D) **Order the PSA but do not perform the DRE**
E) Refer patient to urology
Screening for Prostate Cancer — The Controversy That Refuses to Die

Michael J. Barry, M.D.

In the United States, most men over the age of 50 years have had a prostate-specific–antigen (PSA) test,\(^1\) despite the absence of evidence from large, randomized trials of a net benefit. Moreover, about 95% of male urologists and 78% of primary care physicians who are 50 years of age or older report that they have had a PSA test themselves,\(^2\) a finding that suggests they are practicing what they preach. And indeed, U.S. death rates from prostate cancer have fallen about 4% per year since 1992, five years after the introduction of PSA testing.\(^3\) Perhaps the answer to the PSA controversy is already staring us in the face. At the same time, practice guidelines cite the unproven benefit of PSA screening, as well as the known side effects,\(^4,5\) which largely reflect the high risks of overdiagnosis and overtreatment that PSA-based screening engenders.\(^6\)

The first reports from two large, randomized trials that many observers hoped would settle the controversy appear in this issue of the Journal. In the U.S. Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, Andriele et al.\(^7\) report no mortality benefit from combined screen-
Randomized Trials

European Randomized Study of Screening for Prostate Cancer (ERPSC)
NEJM 2009;360(13):1320

• 162,387 in core group age 55-69
• Randomized to PSA screening on average of every 4 years vs no PSA screening.
• Primary outcome of rate of death.
• Followed from early 1990s to 2006.
182,160 Subjects 50–74 yr old underwent randomization
162,387 Were in the core age group (55–69 yr old)

160 Subjects 50–74 yr old died
144 Were 55–69 yr old

82,816 Were assigned to the screening group
72,890 Were 55–69 yr old
6830 Had prostate cancer
5990 Were 55–69 yr old

99,184 Were assigned to the control group
89,353 Were 55–69 yr old
4781 Had prostate cancer
4307 Were 55–69 yr old
## Table 2. Death from Prostate Cancer, According to the Age at Randomization.

<table>
<thead>
<tr>
<th>Age at Randomization</th>
<th>Screening Group</th>
<th>Control Group</th>
<th>Rate Ratio (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Deaths</td>
<td>Person-Yr (Death Rate per 1000 Person-Yr)</td>
<td>No. of Deaths</td>
</tr>
<tr>
<td>All subjects</td>
<td>261</td>
<td>737,397 (0.35)</td>
<td>363</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–54 yr</td>
<td>6</td>
<td>55,241 (0.11)</td>
<td>4</td>
</tr>
<tr>
<td>55–59 yr</td>
<td>60</td>
<td>316,389 (0.19)</td>
<td>102</td>
</tr>
<tr>
<td>60–64 yr</td>
<td>76</td>
<td>191,542 (0.40)</td>
<td>95</td>
</tr>
<tr>
<td>65–69 yr</td>
<td>78</td>
<td>135,470 (0.58)</td>
<td>129</td>
</tr>
<tr>
<td>70–74 yr</td>
<td>41</td>
<td>38,755 (1.06)</td>
<td>33</td>
</tr>
</tbody>
</table>

* The result of the chi-square test for heterogeneity among subjects in the core age group (55 to 69 years) was 2.44 (P=0.49).

‡ Rate ratios were calculated with the use of Poisson regression and compare the rate of death from prostate cancer in the screening group with the rate in the control group.
Table 3. Rate Ratios for Death from Any Cause and Death from Prostate Cancer, with Exclusions According to Location of Study Center.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rate Ratio (95% CI)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All deaths from any cause</td>
<td>0.99 (0.97–1.02)</td>
<td>0.50</td>
</tr>
<tr>
<td>All deaths from prostate cancer</td>
<td>0.80 (0.67–0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>Excluding the Netherlands</td>
<td>0.81 (0.67–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Excluding Finland</td>
<td>0.74 (0.58–0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Excluding Sweden</td>
<td>0.84 (0.70–1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>Excluding Belgium</td>
<td>0.79 (0.66–0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Excluding Spain</td>
<td>0.79 (0.67–0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Excluding Italy</td>
<td>0.79 (0.66–0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Excluding Switzerland</td>
<td>0.80 (0.68–0.96)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Rate ratios, which were calculated with the use of Poisson regression, compare the rate of death from prostate cancer in the screening group with the rate in the control group. The calculations were restricted to men in the core age group (55 to 69 years).

† P values have not been corrected for multiple testing.
European Randomized Study of Screening for Prostate Cancer (ERPSC)
NEJM 2009;360(13):1320

CONCLUSIONS
PSA-based screening reduced the rate of death from prostate cancer by 20% but was associated with a high risk of overdiagnosis.
Randomized Trials

Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial
NEJM 2009; 360:1310-1319

• From 1993-2001, 76,693 men at 10 US Centers randomized
• Annual Screening vs Usual Care
• PSA testing for 6 years and DRE for 4 years
A Prostate Cancers

Cumulative No. of Cases

Year

Screening
Control
B Prostate-Cancer Deaths

Cumulative No. of Deaths

Year

0 1 2 3 4 5 6 7 8 9 10

Screening

Control
Randomized Trials

Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial
NEJM 2009; 360:1310-1319

CONCLUSIONS
After 7 to 10 years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two study groups.
<table>
<thead>
<tr>
<th>Population</th>
<th>Men aged 55 to 69 y</th>
<th>Men 70 y and older</th>
</tr>
</thead>
</table>
| **Recommendation**  | The decision to be screened for prostate cancer should be an individual one.  
|                     | Grade: C                                     | Do not screen for prostate cancer.  
|                     | Grade: D                                     |

From: Screening for Prostate Cancer US Preventive Services Task Force Recommendation Statement

Table. Estimated Effects After 13 Years of Inviting Men Aged 55 to 69 Years in the United States to PSA-Based Screening for Prostate Cancer

<table>
<thead>
<tr>
<th>Effect</th>
<th>No. of Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men invited to screening</td>
<td>1000</td>
</tr>
<tr>
<td>Men who received at least 1 positive PSA test result</td>
<td>240</td>
</tr>
<tr>
<td>Men who have undergone 1 or more transrectal prostate biopsies</td>
<td>220\textsuperscript{b}</td>
</tr>
<tr>
<td>Men hospitalized for a biopsy complication</td>
<td>2</td>
</tr>
<tr>
<td>Men diagnosed with prostate cancer</td>
<td>100</td>
</tr>
<tr>
<td>Men who initially received active treatment with radical prostatectomy</td>
<td>65</td>
</tr>
<tr>
<td>Men initially received active surveillance</td>
<td>30</td>
</tr>
<tr>
<td>Men who initially received active surveillance who went on to receive active treatment with radical prostatectomy or radiation therapy</td>
<td>15</td>
</tr>
<tr>
<td>Men with sexual dysfunction who received initial or deferred treatment</td>
<td>50</td>
</tr>
<tr>
<td>Men with urinary incontinence who received initial or deferred treatment</td>
<td>15</td>
</tr>
<tr>
<td>Men who avoided metastatic prostate cancer</td>
<td>3</td>
</tr>
<tr>
<td>Men who died of causes other than prostate cancer</td>
<td>200</td>
</tr>
<tr>
<td>Men who died of prostate cancer despite screening, diagnosis, and treatment</td>
<td>5</td>
</tr>
<tr>
<td>Men who avoided dying of prostate cancer</td>
<td>1.3</td>
</tr>
</tbody>
</table>

From: Screening for Prostate Cancer US Preventive Services Task Force Recommendation Statement

USPSTF 2018 Video

https://jamanetwork.com/learning/video-player/16386161
45 year old woman presents to your clinic for her annual exam. She asks you about colon cancer. She has no prior history of polyps and no family history of cancer. What do you recommend based on the American Cancer Society Guidelines (2018)?

A) High sensitivity stool test  
B) Colonoscopy  
C) CT colonography  
D) Flexible Sigmoidoscopy  
E) Any of the above if patient agrees after discussing risks/benefits  
F) Wait until 50 years old old if patient prefers after discussing risks/benefits  
G) E or F
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Trends in Colorectal Cancer Incidence < 50 years old

There is limited direct evidence of screening effectiveness in adults younger than 50 years, in large part because of early expert judgments, based on disease burden, that screening should begin at age 50 years.
<table>
<thead>
<tr>
<th>Recommendations&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>The ACS recommends that adults aged 45 y and older with an average risk&lt;sup&gt;b&lt;/sup&gt; of CRC undergo regular screening with either a high-sensitivity stool-based test or a structural (visual) examination, depending on patient preference and test availability. As a part of the screening process, all positive results on noncolonoscopy screening tests should be followed up with timely colonoscopy.</td>
</tr>
<tr>
<td>The recommendation to begin screening at age 45 y is a qualified recommendation.</td>
</tr>
<tr>
<td>The recommendation for regular screening in adults aged 50 y and older is a strong recommendation.</td>
</tr>
<tr>
<td>The ACS recommends that average-risk adults in good health with a life expectancy of greater than 10 y continue CRC screening through the age of 75 y (qualified recommendation).</td>
</tr>
<tr>
<td>The ACS recommends that clinicians individualize CRC screening decisions for individuals aged 76 through 85 y based on patient preferences, life expectancy, health status, and prior screening history (qualified recommendation).</td>
</tr>
<tr>
<td>The ACS recommends that clinicians discourage individuals over age 85 y from continuing CRC screening (qualified recommendation).</td>
</tr>
</tbody>
</table>

**Options for CRC screening**

**Stool-based tests**
- Fecal immunochemical test every y
- High-sensitivity, guaiac-based fecal occult blood test every y
- Multitarget stool DNA test every 3 y

**Structural examinations**
- Colonoscopy every 10 y
- CT colonography every 5 y
- Flexible sigmoidoscopy every 5 y