

# Prostate Cancer Screening: Facts, Statistics, and Interpretation in Response to the US Preventive Services Task Force Review

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Recently, the US Preventive Services Task Force (USPSTF) published a review of the evidence for screening for prostate cancer<sup>1</sup> and made a clear recommendation against screening. By giving a grade of “D” in the recommendation statement that was based on this review, the USPSTF concluded that “there is moderate or high certainty that this service has no net benefit or that the harms outweigh the benefits.”<sup>2(p3)</sup>

Whether these harms of screening, overdiagnosis and overtreatment, are justified by the benefits in terms of reduced prostate cancer mortality is open to reasonable doubt. As such, we can understand why a guideline group might recommend against prostate-specific antigen (PSA) screening, particularly the way in which it is currently practiced in the United States. That said, the USPSTF report contained a number of important errors of fact, interpretation, and statistics.

*Definitive conclusions based on incomplete data.* When the review was published, the largest active prospective trial of PSA screening, the European Randomized study of Screening for Prostate Cancer (ERSPC), had not yet reported at its prespecified main follow-up time. The results from the ERSPC, which were used as a basis by the USPSTF, report on an interim analysis at a median follow-up of only 9 years.<sup>3</sup> To draw the conclusion that screening results “in small or no reduction in prostate cancer–specific mortality”<sup>1(p762)</sup> would suggest that definitive conclusions of no benefit can be drawn from an ongoing trial with equivocal results at interim follow-up. Also, the recent analysis of the ERSPC trial that used 2 additional years of follow-up (11 years) consolidated the previous findings that PSA screening significantly reduces prostate cancer mortality (relative risk, 0.79; 95% CI, 0.68 to 0.91;  $P = .001$ ).<sup>4</sup>

*Overall mortality, cancer-specific mortality, and statistical power.* One of the key questions addressed in the USPSTF report is whether “PSA-based screening decrease(s) . . . all-cause mortality.”<sup>1(p764)</sup> It is a basic misunderstanding to believe that the screening trials such as ERSPC or the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) trial could address the question of whether screening affects all-cause mortality. This is because it has much lower power than cancer-

specific mortality as a result of the statistical noise of deaths from other causes. As an illustration, imagine a trial that is designed to have 80% power to detect a decrease in cancer deaths at 10 years from 1% to 0.5%. Also assume that the intervention had precisely the effect hypothesized without increasing deaths from other causes, which occurred in approximately 20% of participants in each group. The  $P$  values for such a trial would be less than .01 for cancer-specific mortality but .5 for overall mortality; indeed, the trial would have less than 10% power to detect differences in all-cause mortality. These numbers are approximately those reported in the Göteborg trial.<sup>5</sup>

*Combining data from incompatible trials.* The USPSTF authors state that “our summary of the evidence [is that] most trials [of PSA screening] found no statistically significant effect on prostate cancer-specific mortality.”<sup>1(p767)</sup> They also cite two recent meta-analyses<sup>6,7</sup> and report the conclusions as “no pooled effect of screening.”<sup>1(p767)</sup> But combining PSA screening trials, whether formally or informally, involves treating different types of studies as comparable. The meta-analysis by Djulbegovic et al<sup>6</sup> and the updated Cochrane review<sup>7</sup> included two trials, the Quebec and the Norrköping trials, that have well-known, serious methodologic weaknesses. Of the remaining fair-quality trials, two demonstrated significant reductions in prostate cancer mortality: 20% after 9 years of follow-up and 44% after 14 years of follow-up in the ERSPC<sup>3</sup> and the Göteborg<sup>5</sup> trials. The third trial, PLCO,<sup>8</sup> did not demonstrate a protective effect of screening on prostate cancer mortality at a short follow-up (7 to 10 years). After the USPSTF report, the PLCO trial investigators reported on 10 to 13 years of follow-up with no statistically significant difference in risk at 13 years between the arms (risk ratio, 1.09; 95% CI, 0.87 to 1.36).<sup>9</sup>

The results of these three trials should not have been combined in the meta-analysis because the European and US trials did not address the same scientific question. The PLCO trial was conducted in the United States, where PSA testing was already widespread; this is in contrast to the ERSPC, which was conducted in Europe, where the background rates of PSA testing were very low. In the first year of the PLCO trial, 40% of men in the control arm underwent PSA testing,

with contamination reaching 52% by year six.<sup>8</sup> Contamination in the European trial was no more than 15%.<sup>10</sup>

*Comparison of confidence intervals.* The USPSTF authors claim that “chance could also explain the apparent discrepancy between the two trials [ERSPC and PLCO] because the risk estimate confidence intervals overlapped.”<sup>1(p767)</sup> This demonstrates a critical misunderstanding of confidence intervals. To understand whether two values differ, we look at the confidence interval for the difference, not the confidence interval for each value separately.

*Biologically implausible inference.* The USPSTF writes “the PLCO trial evaluated a shorter screening interval (annual [in PLCO] versus every 4 years [in ERSPC]), suggesting that more conservative screening and treatment strategies might be more effective than more aggressive ones.”<sup>1(p767)</sup> Less frequent screening may reduce the risk of overdiagnosis, but there is simply no plausible mechanism by which a much longer rescreening interval would improve cancer outcomes. There are numerous differences between the PLCO and ERSPC trials that might affect outcome, and the screening interval is only one factor.<sup>10</sup> The high rate of screening among controls in the PLCO trial<sup>11</sup> is the most likely explanation for the divergent results of PLCO and ERSPC, a phenomenon that reduces any differences between groups.

*Failure to address the time-to-event nature of the data.* The USPSTF authors state that “48 men received treatment for every prostate cancer–specific death prevented.”<sup>1(p767)</sup> This is false: the number was calculated from the number of men diagnosed, not the number treated. In Göteborg, for example, approximately 25% of men who were diagnosed with cancer were still on surveillance at last follow-up.<sup>5</sup> Moreover, this statistic depends on the length of follow-up. Models have estimated the number needed to diagnose for prostate cancer screening to decrease to approximately 20 at 12 years of follow-up in the ERSPC,<sup>12</sup> as a whole, and to decrease to approximately nine at 25 years of follow-up.<sup>13</sup> The empirical estimate from ERSPC at 11 years of follow-up is 37,<sup>4</sup> and that from the Göteborg randomized trial with 14 years of follow-up is 12.<sup>5</sup>

*Factual errors about the ERSPC reports.* The USPSTF writes: “None of the RCTs [randomized controlled trials] of PSA-based screening provided information on potential psychological harms, such as anxiety or adverse effects on health-related quality of life.”<sup>1(p765)</sup> This is not true. Three randomized PSA screening trials have reported no detrimental effect on men’s anxiety levels or generic health status.<sup>14-17</sup>

*Overestimation of the risk of radical prostatectomy.* The USPSTF claims that the 30-day perioperative mortality rate after radical prostatectomy is 0.5%. This is based on a study of Medicare claims from 1991 to 1994,<sup>18</sup> that is, older patients who were treated nearly 20 years ago. If this figure were accurate, it would imply, for example, that a typical high-volume center such as Memorial Sloan-Kettering Cancer Center or Johns Hopkins would experience four or five deaths per year. This is nowhere near the case; this is, at least in part, because risk increases with age,<sup>19,20</sup> and because men older than age 65 years constitute a small minority of radical prostatectomy series. Contemporary estimates of perioperative mortality that are based on all men treated are close to 0.1%.<sup>21</sup>

In conclusion, the best trials that are available to date, which are currently still in progress, have demonstrated that screening can reduce prostate cancer death by 20% to 44%.<sup>3-5</sup> To recommend against screening on the basis of “moderate or high certainty”<sup>2(p3)</sup> of no

benefit is one of a series of critical errors of fact, interpretation, or statistics that characterize the USPSTF report.

On the basis of the evidence of a benefit from the largest trial (ERSPC), some authors recently suggested that this best supports a grade C recommendation, rather than D, for men 55 to 69 years. This would imply recommending “against routinely providing the service”<sup>22(p1952)</sup> while indicating that “there may be considerations that support providing the service in an individual patient.”<sup>22(p1952)</sup>

Nevertheless, we consider it reasonable to recommend against the way that PSA screening and associated treatments are currently implemented in the US, which causes unnecessary imbalances between the harms versus benefits of screening on a population level. First, PSA screening is often used in men who are unlikely to benefit from early detection because of short life expectancy and competing mortality; PSA tests are given to one third of men older than age 70 years with a greater than 50% risk of death within 5 years<sup>23</sup> and 15% of men older than age 65 years with advanced lung or GI tract cancers.<sup>24</sup> Current guidelines<sup>25</sup> also recommend a biopsy of the prostate for a wide variety of indications.<sup>25</sup> For example, men with a low PSA are recommended to have a biopsy if they have a positive digital rectal exam, although this is insufficiently informative in a screening setting,<sup>26</sup> and a high PSA velocity, which is similarly of limited benefit.<sup>27</sup>

The potential negative consequences from PSA screening, including psychological effects, false positives, and biopsy complications, might reasonably be regarded as acceptable for the individual man<sup>28</sup> if it were not for the burden of adverse effects from treatment for screen-detected tumors. Perhaps the most harmful consequence of PSA testing in the United States is that patients are almost always advised by their doctors to undergo curative treatment even if their risk of eventual death from prostate cancer is low. Surveys show that 99% of urologists and radiation oncologists would recommend treatment to a 65-year-old man with low-risk prostate cancer<sup>29</sup>; empirical studies show that fewer than 10% of men with low-risk disease are offered active surveillance.<sup>30</sup> This management of PSA-detected tumors needs to be reconsidered and individualized. Compounding this problem, much treatment is given by low-volume providers,<sup>31</sup> increasing the risk of treatment-related complications<sup>32</sup> and decreasing treatment effectiveness.<sup>33,34</sup>

We believe that implementation of the following three simple guidelines would immediately improve PSA screening outcomes in the United States. We also believe that these rules of thumb will have a greater practical impact than the USPSTF’s blanket rejection of the PSA test, something which is unlikely to influence practice.

*First, avoid PSA tests in men with little to gain.* There is no justification for recommending PSA screening in asymptomatic men with a short life expectancy. Hence, men older than age 70 years should only be tested in special circumstances, such as higher than median PSAs that are measured before age 70 or excellent overall health. Moreover, because a baseline PSA is strongly predictive of the future risk of aggressive prostate cancer,<sup>35,36</sup> men with low PSAs (eg, less than 1 ng/mL) can undergo testing less frequently, such as every 7 to 8 years,<sup>37</sup> with screening possibly ending at age 60 if the PSA remains at 1 ng/mL or less.<sup>36</sup> Men with PSAs that are above age median but below biopsy thresholds can be counseled about their elevated risk and actively encouraged to return for regular screening and more comprehensive risk assessment.<sup>38</sup>

*Second, do not treat those who do not need treatment.* A high proportion of men with screen-detected prostate cancer do not need

immediate treatment and can be managed by active surveillance.<sup>39</sup> Indeed, some would argue that most screen-detected cancers do not need immediate curative treatment: men with low-risk prostate cancer such as Gleason 6 at biopsy and clinical stage T1 or T2a have a low risk of death as a result of prostate cancer.<sup>40</sup>

Third, refer men who do need treatment to high-volume centers. Although it is clearly not feasible to restrict treatment exclusively to high-volume centers, shifting treatment trends so that more patients are treated by high-volume providers will improve cancer control and decrease complications.<sup>41</sup>

PSA testing is not likely to go away, and on the basis of the ERSPC results—which do indicate reductions in mortality—this is perhaps a good thing. Our goal should therefore be to maximize the benefits of PSA testing and minimize its harms. Following the three rules outlined here could dramatically improve the ratio of harms to benefits from PSA screening.

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