American Cancer Society Comments on the United States Preventive Services Task Force Draft Prostate Cancer Screening Recommendation Statement

The American Cancer Society is a nationwide, community-based voluntary health organization dedicated to eliminating cancer as a major health problem by preventing cancer, saving lives, and diminishing suffering from cancer through research, education, advocacy, and service. The Society, operating through its national office and 12 geographic divisions throughout the United States, is the largest voluntary health organization in the United States.

The American Cancer Society appreciates the opportunity to comment on the draft prostate cancer screening recommendation statement, and we appreciate the United States Preventive Services Task Force's (USPSTF) effort to solicit comments from the public prior to finalizing a new recommendation. Our response was developed by the American Cancer Society Prostate Cancer Advisory Committee (ACS PCAC), a group of cancer screening and prostate cancer experts from varied disciplines. Previously, this group reviewed the published prostate cancer screening literature and wrote the Society's 2010 ACS prostate cancer screening guideline.[1] We re-assembled members of the ACS PCAC to review and discuss the Task Force draft recommendation statement, and to provide this response.

The Society agrees with many of the Task Force's conclusions. In particular we also are concerned that many men are be harmed by undergoing screening that leads to detection and treatment of prostate cancers that would never have become clinically apparent (overdiagnosis and overtreatment), and that routine screening in the absence of discussion and shared decision making is inconsistent with the evidence, the current recommendations from most organizations, and constitutes poor quality medical care.

It is our opinion, however, that the current scientific evidence supports a "C" recommendation for prostate cancer screening. We urge the Task Force to amend the proposed "D" recommendation to a "C" recommendation. We make this recommendation after considering and weighing the evidence somewhat differently than the Task Force, as outlined below.

The 2008 Task Force recommendation and the 2010 ACS recommendation for screening average risk men aged 50 years and older are similar with respect to uncertainty about the net benefit of screening, with neither organization recommending routine screening, and both organizations emphasizing the importance of shared decision making and personal preferences.[2,1] The Task Force currently recommends against screening men ages 75 and older because average life expectancy is less than 10 years. The ACS recommends that clinicians make an individual assessment of expected longevity and recommends against testing in men with an estimated longevity of less than 10 years.

While the 2001 ACS guidelines[3] and the 2008 Task Force recommendation[2] did not have the benefit of evidence from the prospective randomized trials, our 2010 ACS guideline[1] was informed by the 2009 publication of the U.S. Prostate, Lung, Colorectal, and Ovarian trial (PLCO) and the European Randomized Study of Prostate Cancer

(ERSPC) trial,[4, 5] whereas the Task Force 2010 update[6] not only has those data but also more recently published results from the Göteborg trial.[7]

As noted above, we believe prostate cancer screening merits a "C" recommendation. We note that the Task Force's definition of a "C" recommendation reads: "The Task Force recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is at least moderate certainty that the net benefit is small." The only other cancers that have received a "D" screening recommendation from the Task Force are ovarian, pancreatic, and testicular cancer. In support of these three "D" recommendations, the Task Force concluded that there is no substantive evidence of benefit to screen for these cancers. In support of their "D" recommendation for prostate cancer, the Task Force cites early and, especially in the case of the PLCO, immature results from the two major cancer screening trials, the European ERSPC and the US PLCO trials. The ACS PCAC does not interpret these studies as negatively as the Task Force.

With respect to the PLCO trial, the Task Force draft recommendation statement judges the PLCO results as negative, citing the non-significant increase in prostate cancer mortality in the group invited to screening. We regard the PLCO results as non-informative at this time due to the high rate of screening (44%) in both the invited and control group prior to the trial, the high rate of contamination in the control group during the trial, and the considerably lower-than-expected frequency of prostate cancer mortality (due in part to the high rate of pre-randomization PSA screening). Each of these factors contributed to a significant erosion of study power to observe a difference in mortality. As with the ERSPC trial, the PLCO results are early and additional years of follow-up are needed. The recent Cochrane review reached a similar conclusion, judging the PLCO to have a high risk of bias in the "incomplete outcome data domain," given that only 67% of study subjects have been followed-up at 10 years.[8]

With respect to the ERSPC, we disagree with focusing on the absolute benefit rather than the clinically relevant relative benefit (mortality rate ratio 0.8). We also disagree with the decision to place priority on the non-significant relative benefit for the entire age range in the study rather than the pre-specified core group (ages 55-69) in which the relative benefit was statistically significant. Finally, we do not share the Task Force's concern over the validity of the ERSPC results when the results are evaluated without the contribution of the Göteborg data, which enrolled younger men and has had longer follow-up (14 years) than either the PLCO or ERSPC. In fact, the rate ratio without Göteborg is 0.84, which is very close to the effect size when the ERSPC is analyzed with all centers (0.80). Given the similarity of the effect sizes, and the longer follow-up in the Göteborg study, it seems that the ERSPC findings without the Göteborg data should simply be interpreted in that context. In addition, like the PLCO, the results of the ERSPC results are also early and will be more definitive with additional years of follow-up.

To reiterate, the ACS PCAC believes that median follow-up in the PLCO and ERSPC trial results is too short, especially given the Göteborg findings, and thus it is premature to judge the current rate ratios as final. Screening trials take time to show a

benefit and the benefit tends to grow with time.[10, 11] Relying on the data available as of March 2009 may underestimate the true benefit.

The results of the Göteborg study are discounted on the basis that they also were a study site for the ERSPC. We understand the concerns, but feel attention can and should be given to the Göteborg study as a stand-alone study as it was underway before the ERSPC was conceived, and always intended to publish results independently. In our judgment, these results add to the evidence supporting the possible benefits of prostate cancer screening, yet do not diminish the importance and value of informed and shared decision making related to the decision to be screened for prostate cancer.

Although not noted in the draft recommendation statement, concerns have been expressed about the randomization process in some of the ERSPC centers, including Göteborg. The control group men in Sweden, Finland, France, and Italy did not know they were in a study and still do not know they were in a study. Autier and colleagues have proposed that the lack of awareness of being in a trial could lead to differences in the diagnosis rate, although the extent of any potential impact on disease-specific mortality rates is unclear at this point and hopefully will be addressed in future ERSPC publications.[9]

Since publication of the ERSPC, concerns have been voiced about differential treatment in the study's screening and control groups. However, Wolter and colleagues reported that observed differences were mostly due to differences in treatment due to stage at diagnosis, and that study arm played a minor role in treatment selection.[9] While treatment of study subjects may have been more likely to take place in university hospitals, only two centers have been examined, with only one showing a greater likelihood of study subjects being treated in the university hospitals.[12] To the degree that concerns have been raised about differential treatment in the study, we hope the ERSPC investigators will resolve them in future publications.

With respect to the duration of follow-up, estimates of the number needed to invite, number needed to screen, and number needed to treat are premature. We believe there is good reason to be cautious about deriving estimates of overdiagnosis (48% - 67%) based on these early findings with limited years of follow-up, especially since these estimates are based on data from a single center (Rotterdam). Moreover, estimates of overdiagnosis from Europe do not easily transfer to the US. The group that produced the estimate of 67% overdiagnosis among all screen-detected cases found that this estimate dropped to 42% when they applied their model to US data.[13] Finally, the number needed to invite to prevent one prostate cancer death is highly dependent on follow-up and tends to be substantially overestimated with limited years of follow-up. Estimates based on projections under extended follow-up are less than half the number cited (1,410) after 9 years of follow-up in the European trial. [14, 15] Although there are differences between the Göteborg and ERSPC trials as a whole, the influence of longer follow-up is evident when comparing the estimate of the number needed to invite to prevent 1 prostate cancer death in the ERSPC with 9 years of follow-up (1410) vs. Göteborg with 14 years of follow-up (293).

With respect to additional evidence related to the benefit of screening, we recommend that the Task Force exclude the two meta-analyses showing no benefit as a

source of supportive evidence.[8, 16] Both meta-analyses included trials that the Task Force judged to be poor quality, and thus can not be considered as providing credible supporting evidence for the conclusion that the randomized trials have not shown a mortality benefit.

As noted above, we share the Task Force's concern that there are significant harms associated with prostate cancer screening. Further, too often shared decision making does not occur, and inappropriate screening and treatment is occurring in men with limited longevity who have very little likelihood of benefit due to their age or illness. However, the opportunity to prevent a cancer death in a healthy man under age 75 is highly valued by many individuals and clinicians. These individuals, even when informed of the risks of screening, often opt to pursue screening with sequential decision making at every step.

A "D" recommendation from the Task Force indicates that physicians should not offer the test. It represents a conclusion that harms outweigh benefits, or that there is fair evidence that screening is ineffective. In effect, a "D" rating states that the decision to offer or not offer screening has been made at the societal level and need not involve individuals. It is imperative that this rating be based on a realistic accounting of the harms and the benefits.

The Society believes that the Task Force may not have given sufficient consideration to the perceived societal value of avoiding a prostate cancer death – an outcome highly valued by many individuals, and an opportunity that some men and families will choose even in the face of substantial risk of harm. For this reason, the Society's 2010 guideline recommends that physicians be armed with effective communication tools and engage appropriately selected, healthy men in a shared and informed decision to screen or not screen for prostate cancer.[1]

The Society recognizes that many primary care clinicians are continuing to order this test without informing their patient of the risks and potential harms and without soliciting their preference.[17, 18] This practice constitutes poor quality medical care and is not recommended. But we also support the right of men to participate in this important decision. It is incumbent on organizations such as the ACS and others to help develop and disseminate effective and practical shared decision making tools to facilitate high quality decision making.

In summary, we are in general agreement with the Task Force that there are significant limitations and risks associated with prostate cancer screening, but we disagree with three core conclusions in the draft recommendation statement related to the current evidence. In our opinion:

- We believe the evidence from the European trials is more supportive of a possible benefit than has been interpreted by the Task Force.
- The overdiagnosis associated with screening is significant but not as high as the estimate in the Task Force's statement.
- The estimate of the number needed to invite to prevent one prostate cancer death is overstated.

We agree that important questions remain to be answered from these studies, and that continued follow-up is imperative. However, based on our interpretation of the current evidence related to benefits and harms, we recommend that the Task Force reconsider their interpretation of the data and upgrade prostate cancer screening to a "C" recommendation. Issuing a "C" recommendation would provide men with the opportunity to integrate their personal values into the screening decision.

Respectfully,

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References

1. Wolf AM, Wender RC, Etzioni RB, et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. CA Cancer J Clin. 2010;60:70-98.
2. United States Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2008;149:185-191.
3. Smith RA, von Eschenbach AC, Wender R, et al. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. Also: update 2001--testing for early lung cancer detection. CA Cancer J Clin. 2001;51:38-75; quiz 77-80.
4. Andriole GL, Crawford ED, Grubb RL, 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med. 2009;360:1310-1319.
5. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009;360:1320-1328.
6. United States Preventive Services Task Force. Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Draft Statement. Agency for Health Care Policy and Research. Available at: http://www.uspreventiveservicestaskforce.org/draftrec3.htm. Accessed October 7, 2011, 2011.
7. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. Lancet Oncol. 2010;11:725-732.
8. Ilic D, O'Connor D, Green S, Wilt TJ. Screening for prostate cancer: an updated Cochrane systematic review. BJU Int. 2011;107:882-891.
9. Autier P, Boyle P, Buyse M, et al. Is FOB screening really the answer for lowering mortality in colorectal cancer? Recent Results Cancer Res 2003:254-63
10. Tabar L, Vitak B, Chen TH, et al. Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades. Radiology. 2011;260:658-663.
11. Hanley JA. Measuring mortality reductions in cancer screening trials. Epidemiol Rev. 2011;33:36-45.
12. Wolters T, Roobol MJ, Steyerberg EW, et al. The effect of study arm on prostate cancer treatment in a large screening trial (ERSPC). Int J Cancer. 2009.
13. Draisma G, Etzioni R, Tsodikov A, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. J Natl Cancer Inst. 2009;101:374-383.
14. Gulati R, Mariotto AB, Chen S, Gore JL, Etzioni R. Long-term projections of the harm-benefit trade-off in prostate cancer screening are more favorable than previous short-term estimates. J Clin Epidemiol. 2011;64:1412-1417.
15. Loeb S, Vonesh EF, Metter EJ, Carter HB, Gann PH, Catalona WJ. What is the true number needed to screen and treat to save a life with prostate-specific antigen testing? J Clin Oncol. 2011;29:464-467.

16. Djulbegovic M, Beyth RJ, Neuberger MM, et al. Screening for prostate cancer: systematic review and meta-analysis of randomised controlled trials. BMJ. 2010;341:c4543.
17. Hoffman RM, Couper MP, Zikmund-Fisher BJ, et al. Prostate cancer screening decisions: results from the National Survey of Medical Decisions (DECISIONS study). Arch Intern Med. 2009;169:1611-1618.
18. McFall SL, Smith DW. Lack of follow-up of prostate-specific antigen test results. Public Health Rep. 2009;124:718-725.