October 12, 2015

Albert L. Siu, MD, MSPH
Chairperson
U.S. Preventive Services Task Force
540 Gaither Road
Rockville, MD 20850

Re: U.S. Preventive Services Task Force (USPSTF) Draft Recommendation Statement: Aspirin to Prevent Cardiovascular Disease and Cancer

Dear Dr. Siu and Members of the U.S. Preventive Services Task Force:

The American Cancer Society (ACS) and the American Cancer Society Cancer Action Network (ACS CAN) are pleased to provide comments on the *Draft Recommendation Statement: Aspirin to Prevent Cardiovascular Disease (CVD) and Cancer*. ACS is a nationwide community-based voluntary health organization dedicated to eliminating cancer as a major health problem by preventing cancer, saving lives lost to cancer, and diminishing suffering from cancer through research, education, advocacy, and service. ACS CAN is the nonprofit, nonpartisan advocacy affiliate of ACS that supports evidence-based policy and legislative solutions designed to eliminate cancer as a major health problem. ACS and ACS CAN are pleased that the U.S. Preventive Services Task Force (USPSTF) has developed recommendations for aspirin use that take cancer prevention into account and is soliciting feedback on these recommendations from stakeholders.

It is appropriate that the USPSTF specifically considered colorectal cancer in its review, given the scientific evidence about aspirin and colorectal cancer that has emerged in recent years and the fact that colorectal cancer is the third leading cause of cancer death in both men and women in the U.S. This year, in the U.S, an estimated 132,700 people will be diagnosed with colorectal cancer and nearly 50,000 people will die from the disease.[1] ACS and ACS CAN are focused on reducing deaths from colorectal cancer by preventing it altogether and detecting it earlier, primarily through colorectal cancer screening. We are pleased that USPSTF has comprehensively reviewed the evidence on aspirin use and colorectal cancer and that the draft recommendations for aspirin use appropriately account for prevention of colorectal cancer.

Our comments focus on the specific questions on which the USPSTF has requested input.

1. How could the USPSTF make this draft Recommendation Statement clearer?

The draft recommendations for aspirin use may be perceived as having been driven solely by prevention of CVD, not prevention of colorectal cancer, since aspirin use is recommended only for individuals at higher risk of developing CVD. To avoid this misperception, we suggest the

[1] American Cancer Society. *Colorectal Cancer Facts & Figures 2014-2016*. Atlanta: American Cancer Society, 2014.

Recommendation Statement explicitly note that aspirin's benefits for colorectal cancer prevention meaningfully influenced the USPSTF's calculations of benefits and harms, and thereby increased the number of people for whom aspirin use is recommended.

The draft Recommendation Statement is clear about the initiation of preventive aspirin use in adults at various ages, including the determination that there is insufficient evidence for recommending the initiation of aspirin use after age 70. However, the draft Recommendation Statement is not clear about the **continuation** of aspirin use after age 70 by individuals who are at higher risk of cardiovascular disease and have already been using aspirin for many years. The draft recommendations for initiating aspirin use for certain individuals aged 50-59 who have a higher risk of cardiovascular disease are based on estimated net lifetime benefits from a simulation model that assumes continued aspirin use until death or the development of contraindications such as gastrointestinal bleeding. However, some clinicians may perceive the "I" grade for individuals 70 or older to mean that individuals who have appropriately used aspirin for primary prevention for many years should discontinue aspirin use when they reach age 70. According to the USPSTF simulation model, such discontinuation of aspirin use at age 70 would eliminate much of the estimated net lifetime benefit used to justify initiation of aspirin use at ages 50-59.

If USPSTF recommendations are to be guided by results from the simulation model, then the "B" grade for the recommendation for certain individuals in their 50s and the "C" grade for the recommendation for certain individuals in their 60s, should be clarified to indicate that the recommendations apply to initiating aspirin use with the intention of continuing use past the age of 70 unless contraindications are developed. This clarification should be included in the Recommendation Summary as some clinicians may not refer to the full Recommendation Statement in making recommendations to their patients about aspirin use. More generally, it would be helpful if the Recommendation Statement could explicitly address continuation of aspirin use by long-term users of aspirin when they reach the age of 70.

2. What information, if any, did you expect to find in this draft Recommendation Statement that was not included?

Because this recommendation concerns aspirin for prevention of both CVD and cancer, we expected the Recommendation Statement to include similar background information for prevention of both CVD and colorectal cancer, the type of cancer which is most emphasized in the recommendations. However, in several instances, information was presented about CVD prevention, but not about prevention of colorectal cancer.

The "Treatment and Dosage" section of the Recommendation Statement notes that low-dose aspirin use appears as effective as higher doses for prevention of CVD but says nothing about the dose of aspirin that may be effective for prevention of colorectal cancer. The evidence review report for prevention of cancer cites the scientific literature as indicating low-dose (e.g., 81 mg/day) and higher dose aspirin may have similar effects on colorectal carcinogenesis. We suggest

the Recommendation Statement note evidence concerning the effectiveness of low-dose aspirin in inhibiting colorectal carcinogenesis.

The "Useful Resources" section mentions the USPSTF recommendation for prevention of CVD, including a healthy diet, physical activity, and smoking cessation, and provides a link to these recommendations. Furthermore, the "Additional Approaches to Prevention" section also notes and provides links to Community Preventive Services Task Force recommendations for prevention of CVD. In contrast, the Recommendation Statement does not mention resources or additional approaches for the prevention of either cancer in general or specifically of colorectal cancer. We believe it is important to note "additional approaches" to colorectal cancer prevention, including the USPSTF "A" recommendation for "screening for colorectal cancer using fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults, beginning at age 50 years and continuing until age 75 years".[2] As the USPSTF is aware, colorectal cancer screening continues to be under-used, and one of the most common reasons people provide for not being screened continues to be that their health provider did not discuss it with them.[3] The Community Preventive Services Task Force has also provided recommendations concerning promotion of colorectal cancer screening which should also be cited.[4] The Recommendations Statement should also note the strong evidence that a healthy diet and physical activity can lower risk of some cancers, particularly colorectal cancer,[5] and that tobacco cessation is critically important in helping prevent many types of cancer, including colorectal cancer.[6]

3. Based on the evidence presented in this draft Recommendation Statement, do you believe that the USPSTF came to the right conclusions? Please provide additional evidence or viewpoints that you think should have been considered.

---

[2] USPSTF. Final Recommendation Statement. *Colorectal Cancer: Screening, October 2008.* Available at http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/colorectal-cancer-screening. Accessed October 1, 2015.

[3] Shapiro JA, Klabunde CN, Thompson TD, Nadel MR, Seeff LC, White A. Patterns of colorectal cancer test use, including CT colonography, in the 2010 National Health Interview Survey. *Cancer Epidemiol Biomarkers Prev.* 2012;21:895-904.

[4] The Guide to Community Preventive Services. Cancer Prevention and Control: Client-Oriented Interventions to Increase Breast, Cervical, and Colorectal Cancer Screening. Updated February 25, 2014. Available at http://www.thecommunityguide.org/cancer/screening/client-oriented/index.html. Accessed October 5, 2015.

[5] Kushi LH, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV, Gapstur S, Patel AV, Andrews K, Gansler T. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin.* 2012;62(1):30-67.

[6] U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. *The health consequences of smoking: 50 years of progress: a report of the Surgeon General.* Atlanta: U.S. Department of Health and Human Services, 2014.

The USPSTF draft recommendation statement is based on a thorough review of the relevant scientific literature and reasonable assumptions about the risks and benefits of long-term aspirin use based on the scientific data available. The assumption of a reduction in risk of colorectal cancer after 10 years of aspirin use is justified by the scientific data. The USPSTF is to be commended for conducting a comprehensive risk/benefit analysis that appropriately includes benefits with respect to both CVD and colorectal cancer.

4. What resources or tools could the USPSTF provide that would make this Recommendation Statement more useful to you in its final form?

It would be useful to include a link in the Recommendation Statement to a recommended online CVD risk calculator, for example the American College of Cardiology and American Heart Association risk calculator used by the USPSTF simulation model. A link to an online risk calculator would make it easier for clinicians and patients to determine who meets the 10 percent 10-year CVD risk level at which aspirin use is recommended. It would also be helpful to include this link in the "Consumer Guide" for the new aspirin recommendation that will be posted on the USPSTF website.

5. The USPSTF is committed to understanding the needs and perspectives of the public it serves. Please share any experiences that you think could further inform the USPSTF on this draft Recommendation Statement.

As noted in the response to question 1, we believe it is important for the Recommendation Summary to be clear and comprehensive about the recommendation and the populations to which it applies, including whether individuals who begin taking aspirin at age 50-59 or age 60-69, as recommended in the current draft recommendation summary, should continue taking aspirin as they age out of these population groups. Many clinicians will rely only on the Recommendation Summary, and will not refer to the full Recommendation Statement in making recommendations to their patients about aspirin use. Experience in colorectal cancer screening has suggested that not recommending an intervention above a specified age cut-off may lead clinicians to discontinue the intervention, even for the healthiest older patients who would be most likely to benefit.[7, 8] We acknowledge there may be uncertainties, such as whether or not some reduced risk of colorectal cancer remains after discontinuing aspirin, that make it challenging to determine if and when aspirin use should be discontinued in aspirin users upon reaching the age of 70. However, we believe the Recommendations Statement should nonetheless explicitly address, rather than avoid, the issue of continuing aspirin use after age 70.

[7] Saini SD, Vijan S, Schoenfeld P, et al. Role of quality measurement in inappropriate use of screening for colorectal cancer: retrospective cohort study. *BMJ* 2014 Feb 26;348:g1247.

[8] Van Hees F, Habbema JDF, Meester RG, et al. Should colorectal cancer screening be considered in elderly persons without previous screening?: A Cost-Effectiveness Analysis. *Ann Intern Med* 2014;160:750-759.

6. Do you have other comments on this draft Recommendation Statement?

The "Research Needs and Gaps" section would benefit from mentioning two important areas where research is needed in order to improve future calculations of the benefits and harms of long-term aspirin use. First, although evidence is strongest for colorectal cancer, aspirin may also lower risk of other cancers. In particular, there is considerable evidence that aspirin use is likely to lower risk of esophageal cancer. Although no statistically significant reduction in risk of esophageal cancer was observed during the relatively short intervention period of seven trials of daily aspirin use, there was a statistically significant approximately 60 percent reduction in the death rates from esophageal cancer in analyses of 20 years of follow up, including post-intervention follow up, available from three of these trials.[9] Observational studies also consistently show that aspirin use is associated with lower risk of esophageal cancer.[10] Further research, ideally from randomized trials, is needed to determine if benefits with respect to esophageal and potentially other cancers should be included in future calculations of the benefits of long-term aspirin use.

A second area where additional research is needed is the estimation of harms due to aspirin-induced major gastrointestinal bleeding. In the USPSTF simulation model, the incidence of aspirin-induced bleeding was derived partly from baseline rates of major gastrointestinal bleeding among older non-users of aspirin in a less economically developed area of southern Italy.[11] Rates of gastrointestinal bleeding may be substantially higher in that population than in the contemporary United States, resulting in an overestimation of the harms of aspirin use. Additional research is needed to better estimate the baseline risks of major gastrointestinal bleeding at various ages in general populations in the contemporary United States.

Under "Recommendations of Others" the draft Recommendations Statement cites a section of the ACS website, and notes that "The American Cancer Society recommends against the use of aspirin and other NSAIDs as a colorectal cancer prevention strategy." The website section cited does not mention any ACS recommendations about aspirin use. ACS has not published any formal recommendations about aspirin use and cancer, so it is not entirely accurate to say ACS has "recommended against" use, which suggests a conflict between ACS recommendations and the USPSTF draft recommendations. We would prefer that ACS's perspective be summarized as shown below:

[9] Rothwell PM, Fowkes FG, Belch JF, et al. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet* 2011;377:31–41.
[10] Thun MJ, Jacobs EJ, Patrono C. The role of aspirin in cancer prevention. *Nat Rev Clin Oncol* 2012;9(5):259-67.
[11] De Berardis G, Lucisano G, D'Ettorre A, et al. Association of aspirin use with major bleeding in patients with and without diabetes. *JAMA* 2012 Jun 6;307(21):2286-94.

"The American Cancer Society recognizes the evidence that long-term regular aspirin use has both harms and benefits, including reduced risk of colorectal cancer, but has not formally reviewed this evidence and does not currently have recommendations for or against aspirin use."

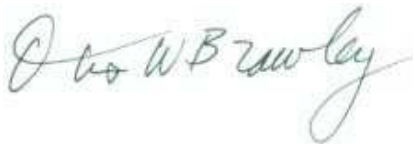
In addition, we wish to remind USPSTF of its enormous power in shaping access to and cost sharing for life-saving preventive services for millions of people across the country. Evidence of this is the Affordable Care Act's requirement that all non-grandfathered insurance plans cover, with no cost-sharing, all USPSTF's "A" and "B" rated preventive services. There are no coverage requirements for C-rated preventive services, even though the service may be recommended for some individual patients. USPSTF also provides industry, clinicians, and consumers with useful guidance regarding evidence-based preventive services.

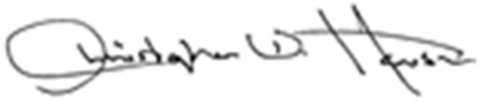
In order to ensure that USPSTF's full recommendation is used to inform insurance coverage decisions, we urge you to clearly and fully describe the recommendation in the summary statement. This should include both recommendations for initiation of aspirin use and recommendations for continuation of aspirin use among those who have previously initiated, even if they no longer meet the initiation criteria. It should be clear which individuals should be included in the population for the recommendation with the "B" rating and which fit into the populations for the recommendations with a "C" or "I" rating, given that the differences in grading of the recommendations will have significant implications for insurance coverage.

Thank you again for the opportunity to provide input on this important recommendation.

For additional information, please contact Eric J. Jacobs, PhD, Strategic Director, Pharmacoepidemiology at the American Cancer Society, at eric.jacobs@cancer.org or 404-329-7916, or Melissa Maitin-Shepard, MPP, Senior Analyst, Policy Analysis & Legislative Support at ACS CAN, at melissa.maitin-shepard@cancer.org or 202-585-3205.

Sincerely,





Otis W. Brawley, MD
Chief Medical Officer
American Cancer Society

Christopher W. Hansen
President
American Cancer Society Cancer Action Network