In Response to Opportunity for Public Comment:

Vitamin D and Calcium Supplementation to Prevent Cancer and Osteoporotic Fractures in Adults: U.S. Preventive Services Task Force Recommendation Statement – DRAFT

July 9, 2012

The American Cancer Society and the American Cancer Society Cancer Action Network are pleased to provide comments on the U.S. Preventive Services Task Force (USPSTF) Draft Recommendation Statement on Vitamin D and Calcium Supplementation to Prevent Cancer and Osteoporotic Fractures in Adults. The American Cancer Society, Inc. (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. The American Cancer Society Cancer Action Network (ACS CAN) is the nonprofit, nonpartisan advocacy affiliate of ACS and supports evidence-based policy and legislative solutions designed to eliminate cancer as a major health problem. Our comments focus exclusively on the recommendation related to cancer prevention and do not address the recommendations related to the prevention of osteoporotic fractures.

Summary of Our Position

ACS and ACS CAN support the conclusion of the USPSTF that the current evidence is insufficient to assess the balance of the benefits and harms of vitamin D supplementation, with or without calcium, for the primary prevention of cancer in adults. While existing evidence suggests that vitamin D and calcium may play a role in preventing colorectal cancer, excessive intake of calcium may increase the risk for prostate cancer, and associations of vitamin D and calcium intake with other cancers are not consistent. We agree that more research is needed to understand the relationship of vitamin D and calcium dose and form in relation to the development of cancer in the colon, rectum, prostate, and other common cancer sites before a recommendation for vitamin D or calcium supplementation for reducing cancer risk should be made. Published randomized controlled trials on the relationship between calcium, vitamin D and cancer outcomes have several key limitations, including exposure of control groups to supplemental calcium and vitamin D, and the experimental groups taking fairly low doses of vitamin D.

The Relationship Between Vitamin D and Calcium Intake and Cancer Risk

The American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention\(^1\) states that increasing evidence from epidemiologic studies suggests that vitamin D may help prevent colorectal

cancer. Most nested case control studies from prospective cohorts have shown inverse associations between pre-diagnostic circulating 25(OH)D levels and colorectal cancer risk, as noted in the USPSTF supporting documentation. Several studies also suggest moderate consumption of foods high in calcium might help reduce the risk of colorectal cancer, and calcium supplementation modestly reduces the recurrence of colorectal adenomas, pre-malignant lesions for colorectal cancer. This effect for colorectal adenoma was stronger in participants with higher blood vitamin D levels. Randomized controlled trials in humans found that calcium and vitamin D change biological measurements in colorectal tissue in expected directions, and support larger clinical trials of these nutrients for colorectal cancer prevention.

However, there is some evidence that excess calcium and/or dairy product intake is associated with an increased risk of prostate cancer and evidence is mixed on the relationship between 25(OH)D levels and pancreatic cancer. Because of these concerns, ACS recommends that men meet but not exceed the recommended levels of calcium (as shown in Table 3 of the draft statement), primarily through food sources. Since women are not at risk of prostate cancer and are at a higher risk of osteoporosis, ACS recommends that women consume recommended levels of calcium primarily through food sources. ACS does not currently recommend the use of vitamin D or calcium supplements for cancer prevention. Individual decisions about whether to take supplements should be based on all potential risks and benefits and made in consultation with a medical professional.

To further the knowledge base on the relationship between vitamin D and cancer risk, data from the American Cancer Society’s Cancer Prevention Study II Nutrition Cohort are contributing to a large pooled analysis of data from 19 prospective cohorts to examine the relationships with pre-diagnostic blood 25(OH)D and colon, rectal, and breast cancers.

**Limitations of Existing Research**

Randomized controlled trials examining the relationship between vitamin D supplementation, with or without calcium, and risk for colorectal and other cancers that have been conducted to date have several key limitations, including small sample size and homogenous study populations. With reference to the Women’s Health Initiative, ranked as the best quality study in the USPSTF review, over half of the women were taking supplements outside of the trial at baseline, and all women were permitted to take non-trial supplements during the trial. This limitation was not noted in the USPSTF review. A recent reanalysis of Women’s Health Initiative data limited to women who were not taking calcium or vitamin D supplements at baseline found a significant inverse association with calcium and vitamin D supplementation for breast cancer and for all cancers; the association with colorectal cancer was inverse.

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but not statistically significant.\(^4\) The USPSTF review did appropriately acknowledge the limitation that experimental subjects in the Women’s Health Initiative were randomized to a relatively low dose of vitamin D, which may have been insufficient for colorectal cancer prevention.

Given these limitations, a final determination about the relationships of vitamin D and calcium supplementation with cancer should not be made on the basis of the results of the existing randomized controlled trials. It is possible that greater amounts of vitamin D are needed to impact cancer risk. A new trial examining the impact of daily supplementation of 2000 IU of vitamin D on cancer risk is currently enrolling participants.

**Future Research Needs**

While observational studies appear to indicate an inverse relationship between vitamin D and calcium intake and colorectal cancer risk, more research is needed to fill in certain knowledge gaps.

Some specific research questions that must be answered include:

- Do vitamin D and calcium interact in reducing cancer risk? If so, how?
- Is there an optimal blood level of circulating 25(OH)D for reducing cancer risk that does not increase risk of other diseases?
- What dose of vitamin D is needed to reach optimal 25(OH)D levels? Does amount needed vary in population subgroups?
- Does calcium and/or dairy product consumption reduce colorectal cancer risk?
- Does vitamin D intake influence pancreatic cancer risk?
- Does calcium and/or dairy intake increase prostate cancer risk?
- What is the mechanism for an increased prostate cancer risk related to calcium and/or dairy intake?
- Is this relationship limited to localized, or aggressive prostate tumors?
- Does vitamin D and calcium supplementation provide the same benefits or harms as the intake of these nutrients from natural sources?
- Does the impact of vitamin D or calcium supplementation vary based on baseline concentrations of these nutrients in the blood?

While randomized controlled trials examining some of these issues are currently underway, results will not be available for several years, and further research is still needed to address gaps in the evidence.

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Conclusion

ACS and ACS CAN look forward to the release of USPSTF’s final recommendation statement on vitamin D and calcium supplementation to prevent cancer, and strongly recommend the prioritization of additional research on the impact of vitamin D and calcium intake and supplementation on the risk for colorectal, prostate, and other cancers among various population groups. As the draft statement notes, approximately 572,000 cancer deaths occurred last year. ACS and ACS CAN support efforts to better understand how to create a world where fewer people suffer and die from cancer.

If you have any questions about these comments or if we can provide any additional information, please contact Marji McCullough, strategic director of nutritional epidemiology at ACS, at marji.mccullough@cancer.org or 404-929-6816, or Melissa Maitin-Shepard, senior policy analyst at ACS CAN, at melissa.maitin-shepard@cancer.org or 202-585-3205.

Thank you for your consideration of our comments.