

# Low-Dose Aspirin and Vitamin E Challenges and Opportunities in Cancer Prevention

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**T**HIS ISSUE OF JAMA INCLUDES 2 ARTICLES FROM THE Women's Health Study (WHS).<sup>1,2</sup> This 10-year long, placebo-controlled, randomized trial of low-dose aspirin and vitamin E included nearly 40 000 predominantly middle-aged women with no history of cancer or cardiovascular disease.<sup>3</sup> The WHS used a 2 × 2 factorial design to evaluate the effects of low-dose aspirin (100 mg) taken every other day and 600 IU of vitamin E (in the form of natural-source  $\alpha$ -tocopherol), also taken every other day. Neither alternate-day, low-dose aspirin nor vitamin E showed any evidence of efficacy in reducing overall cancer incidence or mortality.<sup>1,2</sup> With respect to noncancer outcomes, notable findings for low-dose aspirin included a reduction in stroke risk, no apparent effect on myocardial infarction, and an increased risk of gastrointestinal bleeding requiring transfusion.<sup>4</sup> Vitamin E had no apparent effect on either cardiovascular disease incidence or on gastrointestinal bleeding.<sup>2</sup>

In considering the meaning of the WHS results with respect to cancer prevention, it is important to note 2 strengths of the study. First, because of its relatively large size and substantial number of outcome events (2865 cases of cancer overall, including 1230 breast cancer cases, 269 colorectal cancer cases, and 583 cancer deaths), the WHS is unlikely to have missed true important effects on overall cancer incidence, breast cancer incidence, colorectal cancer incidence, or overall cancer mortality. Second, because the intervention period lasted 10 years, an unusually long time for a randomized trial, the effects of relatively long-term low-dose aspirin treatment and vitamin E supplementation could be evaluated. This is important given that short-term effects on cancer would not necessarily be expected.

Could long-term, low-dose aspirin treatment ( $\leq 150$  mg/d) produce any important reduction in risk of cancer? The WHS provides strong evidence that alternate-day, low-dose aspirin treatment does not, or at least not for women within the first 10 years of treatment. There was no suggestion of reduced risk for overall cancer incidence, breast cancer incidence, colorectal cancer incidence, or cancer mortality. This remained true even in analyses restricted to the second 5 years

of follow-up, when participants in the intervention group had already accrued a minimum of 5 years of aspirin exposure. To our knowledge, no other studies, either randomized trials or observational studies, have evaluated the effect of alternate-day, low-dose aspirin on cancer risk. A previous, considerably smaller, randomized trial examined alternate-day use of 325 mg of aspirin and found no association with colorectal cancer incidence.<sup>5</sup> However, the 5-year intervention period of this trial may have been too short to produce clear effects. Results from the WHS do not entirely rule out the possibility that taking low-dose aspirin every day, rather than every other day, could have some cancer prevention benefits. Evidence about the potential effects of daily low-dose aspirin on cancer risk is limited and includes some inconsistent findings. For example, a randomized trial found a dose of 81 mg/d reduced risk of colorectal polyp recurrence.<sup>6</sup> However, analyses of pharmacy databases in the United Kingdom and Denmark found no association between low-dose aspirin use and colorectal cancer incidence.<sup>7,8</sup>

The null results from WHS with respect to alternate-day, low-dose aspirin do not refute previous evidence that moderate or high doses of aspirin ( $\geq 325$  mg/d) may reduce the risk of certain cancers. In numerous observational studies, regular use of aspirin has consistently been associated with reduced risk of colon or colorectal cancer, with most studies reporting 30% to 50% reductions in incidence.<sup>9</sup> Two randomized trials have shown that aspirin treatment reduces the recurrence of colorectal adenomatous polyps in patients with previous polyps<sup>6</sup> or colorectal cancer.<sup>10</sup> Aspirin use has also been consistently associated with reduced risk of esophageal and stomach cancer, although there are fewer studies of these cancers than of colorectal cancer.<sup>9,11</sup> The totality of the evidence from laboratory studies, observational epidemiology, and randomized trials of colorectal polyp recurrence continues to support the hypothesis that moderate or high doses of aspirin may reduce the risk of colorectal cancer, and possibly the risk of certain other cancers as well.

The null results for vitamin E (in the form of  $\alpha$ -tocopherol) and cancer from the WHS add to the evidence from 2

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previous trials<sup>12,13</sup> that even relatively long-term  $\alpha$ -tocopherol supplementation is unlikely to have any substantial effect on cancer risk, at least in women. An unexpected reduction in prostate cancer incidence was observed among men randomized to  $\alpha$ -tocopherol in the Alpha-Tocopherol Beta Carotene (ATBC) trial, a study that included only male smokers.<sup>12</sup> However, this association was not observed in the Heart Outcomes Prevention Evaluation—The Ongoing Outcomes (HOPE-TOO) trial,<sup>13</sup> in postintervention follow-up of the ATBC trial,<sup>14</sup> or in 2 large prospective observational studies,<sup>15,16</sup> and may have been a result of chance. Although ongoing randomized trials<sup>17,18</sup> will eventually provide further information, the promise of  $\alpha$ -tocopherol as a cancer prevention agent appears to be dimming.

Should the null results with respect to cancer from this large, well-conducted, long-term randomized trial, or from other chemoprevention trials, be considered discouraging news for cancer chemoprevention in general? There have been some successes in cancer chemoprevention, such as the use of tamoxifen to prevent breast cancer in high-risk women.<sup>19</sup> However, currently, no agent has been shown to do for cancer what statins do for cardiovascular disease, namely substantially and relatively safely reduce disease occurrence in individuals not at especially high risk. Pharmacological primary prevention of diseases as heterogeneous as cancer is inherently difficult. Randomized trials of cancer chemoprevention will undoubtedly produce many null results. Nevertheless, continued systematic research on cancer chemoprevention, including long-term randomized trials of carefully chosen agents, is essential given the large potential benefits. At the same time, it is unrealistic to expect the discovery of an agent that will produce substantial reductions in overall cancer rates in the immediate future.

With this in mind, it is important to remember that effective methods for reducing cancer incidence and mortality have already been discovered, but are underapplied. For instance, colorectal cancer screening is greatly underused,<sup>20</sup> providing an important cancer prevention opportunity for physicians and other health care professionals. Reducing tobacco use is essential for cancer prevention, and strong evidence indicates that policy measures, such as increases in tobacco excise taxes and clean indoor air regulations, are effective in reducing tobacco use.<sup>21</sup> In addition, clinicians can play an invaluable role in cancer prevention by asking patients about tobacco use and ensuring that patients who use tobacco receive appropriate counseling and treatment.<sup>21</sup>

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## REFERENCES

1. Cook NR, Lee I-M, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. *JAMA*. 2005;294:47-55.
2. Lee I-M, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA*. 2005;294:56-65.
3. Rexrode KM, Lee I-M, Cook NR, Hennekens CH, Buring JE. Baseline characteristics of participants in the Women's Health Study. *J Womens Health Gend Based Med*. 2000;9:19-26.
4. Ridker PM, Cook NR, Lee I, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med*. 2005;352:1293-1304.
5. Gann PH, Manson JE, Glynn RJ, Buring JE, Hennekens CH. Low-dose aspirin and incidence of colorectal tumors in a randomized trial. *J Natl Cancer Inst*. 1993;85:1220-1224.
6. Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med*. 2003;348:891-899.
7. Garcia Rodriguez L, Huerta-Alvarez C. Reduced risk of colorectal cancer among long-term users of aspirin and non-aspirin nonsteroidal anti-inflammatory drugs. *Epidemiology*. 2001;12:88-93.
8. Friis S, Sorensen HT, McLaughlin JK, Johnsen SP, Blot WJ, Olsen JH. A population-based cohort study of the risk of colorectal and other cancers among users of low-dose aspirin. *Br J Cancer*. 2003;88:684-688.
9. Harris RE, Beebe-Donk J, Doss H, Doss DB. Aspirin, ibuprofen, and other nonsteroidal anti-inflammatory drugs in cancer prevention: a critical review of non-selective COX-2 blockade [review]. *Oncol Rep*. 2005;13:559-583.
10. Sandler RS, Halabi S, Baron JA, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *N Engl J Med*. 2003;348:883-890.
11. Thun MJ, Henley SJ. Nonsteroidal anti-inflammatory drugs as anticancer agents. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2004:541-549.
12. Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med*. 1994;330:1029-1035.
13. Lonn E, Bosch J, Yusuf S, et al. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA*. 2005;293:1338-1347.
14. Virtamo J, Pietinen P, Huttunen JK, et al. Incidence of cancer and mortality following  $\alpha$ -tocopherol and beta-carotene supplementation: a postintervention follow-up. *JAMA*. 2003;290:476-485.
15. Chan JM, Stampfer MJ, Ma J, Rimm EB, Willett WC, Giovannucci EL. Supplemental vitamin E intake and prostate cancer risk in a large cohort of men in the United States. *Cancer Epidemiol Biomarkers Prev*. 1999;8:893-899.
16. Rodriguez C, Jacobs EJ, Mondul AM, Calle EE, McCullough ML, Thun MJ. Vitamin E supplements and risk of prostate cancer in U.S. men. *Cancer Epidemiol Biomarkers Prev*. 2004;13:378-382.
17. Christen WG, Gaziano JM, Hennekens CH. Design of Physicians' Health Study II: a randomized trial of beta-carotene, vitamins E and C, and multivitamins, in prevention of cancer, cardiovascular disease, and eye disease, and review of results of completed trials. *Ann Epidemiol*. 2000;10:125-134.
18. Klein EA. Selenium and vitamin E cancer prevention trial. *Ann N Y Acad Sci*. 2004;1031:234-241.
19. Fisher B, Costantino JP, Wickerham LD, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst*. 1998;90:1371-1388.
20. Seeff LC, Nadel MR, Klabunde CN, et al. Patterns and predictors of colorectal cancer test use in the adult U.S. population. *Cancer*. 2004;100:2093-2103.
21. US Department of Health and Human Services. *Reducing Tobacco Use: A Report of the Surgeon General*. Atlanta, Ga: US Dept 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; 2000.