Tips from Other Journals

Tips from Other Journals are written by the medical editors of *American Family Physician.*

The trade names of drugs listed in Tips from Other Journals are based on what is currently available and not necessarily the brand of drug that was used in the study being discussed.

Long-term Aspirin Use for Colorectal Cancer Prevention

Background: Colon cancer is the second leading type of cancer in developed countries. Studies have shown that aspirin in a dosage of at least 500 mg per day is effective in preventing colon cancer, although higher dosages may be contraindicated in persons at risk of bleeding. Rothwell and colleagues performed a meta-analysis to determine whether lower-dose aspirin regimens are effective in the primary prevention of colon cancer.

The Study: The authors evaluated four trials performed in the 1980s and 1990s, with end points focusing on cardiovascular outcomes. Studies with at least 1,000 participants and a median scheduled treatment period of at least 2.5 years were included. All of the studies were randomized and double-blinded except one that used physician volunteers as participants. The authors reviewed death registries, histology reports, and cancer registries to determine cause of death. Persons whose primary cause of death was colon cancer were counted, and control versus intervention groups were compared. Kaplan-Meier analysis of survival curves, log-rank test to assess significance, and hazard ratios to assess incidence and risk of death were performed. Results were stratified by the dosage of aspirin (75 to 300 mg versus 500 to 1,200 mg), the duration of treatment (at least 2.5 years versus 5 years), and by the location of colorectal cancer if discovered (colon proximal to the splenic flexure, descending colon, sigmoid colon, rectosigmoid junction, and rectum).

Results: A total of 14,033 participants were assigned to control or intervention groups across studies. There was no notable heterogeneity among studies; data were pooled with a median treatment duration of 6 years and median time to follow-up of 18.3 years. There was evidence for increased risk reduction with a longer treatment period, but no evidence of earlier diagnosis in the aspirin versus control groups when colorectal cancer presented during the trial. Pooled results showed that aspirin given at any dosage with a mean treatment duration of 5.8 years reduced long-term risk of colon cancer, with no benefit for rectal cancer. When the results could be divided based on location of the colon cancer, there was a significant benefit for prevention of colon cancer incidence and mortality occurring proximally to the sigmoid flexure (hazard ratio [HR] = 0.45, mortality HR = 0.34), but no effect was found in the distal colon. For persons using aspirin for at least five years, the risk of proximal colon cancer was decreased by 70 percent (HR = 0.35, mortality HR = 0.24) and there was also a decrease in the risk of rectal cancer (HR = 0.58, mortality HR = 0.47). The benefit of aspirin on colon cancer prevention was not increased with dosages greater than 75 mg per day. In patients treated with 75 to 300 mg of aspirin per day for five years, there was a 1.76 percent absolute reduction in the risk of fatal colorectal cancer.

Conclusion: The authors conclude that using aspirin in a dosage of at least 75 mg per day for five years or more may help prevent proximal colon cancer and rectal cancer. Although previous studies showed benefit only with higher dosages of aspirin, the authors suggest that patients may successfully decrease risk of colorectal cancer using lower dosages.

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Source: Rothwell PM, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet.* November 20, 2010;376(9754):1741-1750.

EDITOR'S NOTE: Evidence regarding which agents are effective in preventing colon cancer is limited. For example, there is insufficient evidence to support fiber supplementation and antioxidant use for primary prevention of colorectal cancer, and moderate evidence to support hormone therapy.[1] This study shows that aspirin in lower dosages may prevent colon cancer and related mortality. However, an accompanying editorial by Benamouzig and Uzzan notes some weaknesses of the study. The authors assert that there is still controversy about whether lowering the dosage of aspirin from 300 mg or 500 mg per day to 75 mg per day decreases the risk of bleeding.[2] Also, the question remains if these results are applicable to women; two of the four studies enrolled only men.[2] Conversely,

the maximal duration of the trials was seven years, but this study looks at the 20-year mortality rate, potentially underestimating the beneficial effects of aspirin. Surely some patients previously randomized to control groups chose to take daily aspirin once their trial was completed. Additionally, because an analysis of aspirin-related mortality was not performed, it seems the important question of safety remains.—J.P. and SUMI SEXTON, Associate Editor, *American Family Physician*

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Vitamin B Supplementation Does Not Reduce Cancer, CVD, or All-Cause Mortality

Background: Elevated plasma homocysteine levels have been proposed as a potentially modifiable risk factor for coronary heart disease. Vitamin B supplementation has been shown to lower homocysteine levels and cardiovascular disease (CVD) risk in patients with homocystinuria. However, vitamin B supplementation has not been shown to improve CVD outcomes in randomized trials in the larger population. Clarke and colleagues conducted a meta-analysis of large trials of vitamin B supplementation in patients at increased risk of CVD.

The Study: The authors included randomized, double-blind trials comparing vitamin B supplementation containing folic acid with placebo for the prevention of vascular disease. Eligible trials involved at least 1,000 participants who were treated for at least one year. The primary outcomes included the incidence of major vascular events (i.e., myocardial infarction or coronary death) and strokes (i.e., ischemic, hemorrhagic, or unclassified). Cancer incidence and total and cause-specific mortality rates from eligible studies were also reviewed.

Results: Eight trials involving 37,485 patients were analyzed, with a median treatment duration of five years (range = 2 to 7.3 years). All trials included folic acid supplementation at a dosage of 0.8 to 5.0 mg per day, except for one trial that used 40 mg per day. Seven trials used vitamin B_{12} (0.4 to 2.0 mg per day), and six trials also included vitamin B_6 supplementation.

Overall, vitamin B supplementation reduced plasma homocysteine levels by 25 percent, with the greatest reduction in patients with the highest initial homocysteine levels. However, no corresponding reduction in cardiovascular event rates occurred compared with the placebo groups. Similarly, no benefit was noted when compared with placebo in regard to cancer incidence or total mortality, including death from coronary heart disease (rate ratio [RR] = 1.02; $P = .65$), stroke (RR = 0.92; $P = .47$), or cancer (RR = 1.00; $P = .99$). Longer treatment duration was not associated with any clinical benefit.

Conclusion: Although vitamin B supplementation lowered plasma homocysteine levels, there was no corresponding benefit on the incidence of major vascular events, cancer, or all-cause mortality.

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Source: Clarke R, et al. Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer, and cause-specific mortality: meta-analysis of 8 randomized trials involving 37,485 individuals. *Arch Intern Med.* October 11, 2010;170(18):1622-1631.

EDITOR'S NOTE: Unfortunately, the interest in reducing homocysteine levels with vitamin B supplementation ultimately may be similar to previous interest in postmenopausal hormone therapy, vitamin E, and beta-carotene to improve a wide range of health issues.[1] Observational studies showed a promising association between the proposed intervention and a variety of outcomes; however, benefits were unable to be replicated with the preferred standard of research: randomized controlled trials. Some randomized trials even showed worsened outcomes, as with beta-carotene supplementation increasing the risk of lung cancer in male smokers, and high-dose antioxidant vitamin supplementation possibly increasing mortality rates.[2,3]

Besides the interest in vitamin B supplementation to reduce cardiovascular mortality, which is refuted in this study, observational data have suggested it may help slow cognitive decline. However, a well-powered, long-term study did not show any benefit for this purpose either.[4]

Despite the understandable interest by the public and physicians to improve health outcomes through vitamin supplementation, our efforts should be focused on promoting therapies proven to optimize health, such as exercising, eating right, and avoiding smoking. Although less convenient than taking a pill, these interventions have been shown to improve health outcomes.—K.T.M.

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