Note: This is a two-article spread with a shared commentary. Please scroll down for the second article.

THERAPEUTICS

Low-dose aspirin did not prevent cancer in healthy women

Cook NR, Lee IM, 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.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Hospitalists ★★★★★★☆

QUESTION

In healthy women ≥ 45 years of age, how effective is aspirin in preventing cancer?

METHODS

Design: Randomized placebo-controlled trial (Women's Health Study [WHS], a randomized 2 × 2 factorial trial).
Allocation: Concealed.*
Blinding: Blinded {participants, health care providers, data collectors, and outcome assessors}†.*
Follow-up period: Mean 10.1 years.
Setting: {A mail-based trial in female health care professionals in the United States}†.
Participants: 39 876 women ≥ 45 years of age (mean age 55 y) without a history of cancer (except nonmelanoma skin cancer), cardiovascular disease, or other major chronic illness and no history of adverse effects to aspirin who were not taking aspirin or nonsteroidal antiinflammatory drugs > once per week; anticoagulants or corticosteroids; or individual supplements of vitamin A, vitamin E, or β-carotene > once per week.
Intervention: Aspirin (100 mg every other d) (*n* = 19 934) or matching placebo (*n* = 19 942).
Outcomes: Total invasive cancer, excluding nonmelanoma skin cancer. Secondary outcomes were breast, colorectal, and lung cancer.
Patient follow-up: 97% for morbidity and 99% for mortality (intention-to-treat analysis).

MAIN RESULTS

Aspirin and placebo groups did not differ for incidence of total invasive cancer (Table). Groups also did not differ for incidence of breast, colorectal, or lung cancer (Table) or for total cancer mortality or site-specific cancer mortality, except for lung cancer mortality, which showed a reduction with aspirin (0.3% vs 0.4%; relative risk 0.70, 95% CI 0.50 to 0.99).

CONCLUSION

In healthy women ≥ 45 years of age, low-dose aspirin did not prevent total cancer or breast, colorectal, or other types of cancer.

Sources of funding: National Heart, Lung, and Blood Institute and National Cancer Institute.

For correspondence: Dr. N.R. Cook, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. E-mail ncook@rics.bwh.harvard.edu.

*See Glossary.

†Information provided by author.

Aspirin vs placebo to prevent total invasive cancer and breast, colorectal, and lung cancer at mean 10.1 years‡

Outcomes	Aspirin	Placebo	RRI (95% CI)	NNH
Total invasive cancer	7.2%	7.2%	1.0% (–8 to 6)	Not significant
			RRR (CI)	NNT
Total cancer death	1.4%	1.5%	5.0% (–11 to 19)	Not significant
Breast cancer	3.1%	3.1%	2.0% (–9 to 13)	Not significant
Colorectal cancer	0.7%	0.7%	3.0% (–24 to 23)	Not significant
Lung cancer	0.5%	0.6%	22% (–3 to 41)	Not significant

‡Abbreviations defined in Glossary; RRI, RRR, NNH, NNT, and CI calculated from data in article.

COMMENTARY

2 studies by Cook and Lee and their colleagues complete the reporting of primary outcomes from the Women's Health Study, a trial of low-dose aspirin and high-dose α-tocopherol in the primary prevention of CVD and cancer in generally healthy female health care professionals. The 10-year results were fairly convincingly negative, with no hint of a benefit for either intervention in the primary endpoints. So many comparisons were made examining secondary outcomes and subgroups that caution is needed in interpreting any of these marginally significant findings, such as vitamin E reducing CV death or aspirin increasing cancer in never-smokers.

The question then becomes, to whom and to what interventions do these results apply? Although all healthy women in the health care professions > 45 years of age were eligible, only 10% of the participants were > 65 years. Thus, it may be hard to apply these results to older women. Subgroup analysis suggested a benefit in the older age group with both vitamin E and low-dose aspirin (1) in the prevention of CVD. Doses of aspirin higher than the 100 mg every other day that was tested in the study by Cook and colleagues might decrease the incidence of colorectal cancer (2, 3) but would be expected to carry greater toxicity. The finding that α-tocopherol supplements had no benefit or might even increase mortality (4) is at odds with well-established epidemiologic data regarding diets high in vitamin E, including α-tocopherol and other antioxidants. Postulated causes include the displacement of other antioxidants, such as γ-tocopherol by α-tocopherol supplements (5). The observational epidemiologic data also reflect uncontrolled confounding by other factors (e.g., healthy diet).

(continued on page 9)

Vitamin E did not prevent cardiovascular disease and cancer in healthy women

Lee IM, 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.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Hospitalists ★★★★★★☆

QUESTION

In healthy women ≥ 45 years of age, how effective is vitamin E in preventing cardiovascular disease (CVD) and cancer?

METHODS

Design: Randomized placebo-controlled trial (Women's Health Study [WHS], a randomized 2 × 2 factorial trial).
Allocation: Concealed.*
Blinding: Blinded {participants, health care providers, data collectors, and outcome assessors}†.*
Follow-up period: Mean 10.1 years.
Setting: {A mail-based trial in female health professionals in the United States}†.
Participants: 39 876 women ≥ 45 years of age (mean age 55 y) without a history of cancer (except nonmelanoma skin cancer), CVD, or other major chronic illness; no history of adverse effects to aspirin; and not taking aspirin or nonsteroidal antiinflammatory drugs > once per week; anticoagulants or corticosteroids; or individual supplements of vitamin A, vitamin E, or β-carotene > once per week.
Intervention: Vitamin E (600 IU of α- tocopherol every other d) (n = 19 937) or matching placebo (n = 19 939).
Outcomes: A composite endpoint of first major CV event (nonfatal myocardial infarction [MI], stroke, or CV death), and total invasive cancer excluding nonmelanoma skin cancer. Secondary outcomes were individual CV events and main site-specific types of cancer (breast, lung, and colon).
Patient follow-up: 97% for morbidity and 99% for mortality (intention-to-treat analysis).

MAIN RESULTS

Vitamin E did not reduce the composite endpoint of first major CV event and did not reduce total invasive cancer more than placebo (Table). Vitamin E also did not reduce MI (relative risk [RR] 1.01, 95% CI 0.82 to 1.23), stroke (RR 0.98, CI 0.82 to 1.17), or main site-specific types of cancer (breast RR 1.00, CI 0.90 to 1.12; lung RR 1.09, CI 0.83 to 1.44; colon RR 1.00, CI 0.77 to 1.31). Vitamin E reduced CV death more than placebo (0.5% vs 0.7%; RR 0.76, CI 0.59 to 0.98).

CONCLUSION

In healthy women ≥ 45 years of age, vitamin E did not prevent CVD and cancer.

Sources of funding: National Heart, Lung, and Blood Institute and National Cancer Institute.

For correspondence: Dr. I.M. Lee, Brigham and Women's Hospital, Boston, MA, USA. E-mail ilee@rics.bwh.harvard.edu.

*See Glossary.

†Information provided by author.

Vitamin E vs placebo to prevent cardiovascular disease (CVD) and cancer at mean 10.1 years‡

Outcomes	Vitamin E	Placebo	RRR (95% CI)	NNT
First major CV event§	2.4%	2.6%	7.0% (–5 to 18)	Not significant
			RRI (CI)	NNH
Total invasive cancer	7.2%	7.2%	1% (–6 to 8)	Not significant

‡Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.
§Composite endpoint comprises myocardial infarction, stroke, and CV death.

COMMENTARY *(continued from page 8)*

The bottom line for clinicians is that, for healthy women 45 to 64 years of age (who represented 90% of the participants in these 2 studies), there is no substantial benefit to long-term use of low-dose aspirin or high-dose vitamin E supplements. Studies specifically addressing these interventions in older women would be useful.

Laura Rees Willett, MD
Robert Wood Johnson Medical School
New Brunswick, New Jersey, USA

References

1. **Ridker PM, Cook NR, Lee IM, et al.** A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med. 2005;352:1293-304.
2. **Asano TK, McLeod RS.** Nonsteroidal anti-inflammatory drugs and aspirin for the prevention of colorectal adenomas and cancer: a systematic review. Dis Colon Rectum. 2004;47:665-73.
3. **Chan AT, Giovannucci EL, Meyerhardt JA, et al.** Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. JAMA. 2005;294:914-23.
4. **Miller ER 3rd, Pastor-Barriuso R, Dalal D, et al.** Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med. 2005;142:37-46.
5. **Huang HY, Appel LJ.** Supplementation of diets with alpha-tocopherol reduces serum concentrations of gamma- and delta-tocopherol in humans. J Nutr. 2003;133:3137-40.