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Harvard Medical School
Brigham and Women's Hospital

Women's Health Study Update

Women's Health Study researchers publish landmark trial findings

At long last, the main findings from the Women's Health Study (WHS) trial are here! Thanks to your longstanding commitment to taking the study pills and filling out the health questionnaires, we now have the results of the largest and longest trial of low-dose aspirin (100 mg every other day) and vitamin E supplementation (600 IU every other day) for the primary prevention of cardiovascular disease and cancer in initially healthy women. The trial included 39,876 female health professionals aged 45 years and older who were followed for an average of 10 years. Participants were monitored for the occurrence of major cardiovascular events – heart attack, stroke, or death from cardiovascular causes – as well as overall cancer rates and cancer deaths.

Aspirin and cardiovascular disease

During the course of the trial, 477 major cardiovascular events occurred among the 19,934 women assigned to the aspirin group, as compared with 522 among the 19,942 women in the placebo group, a 9% overall reduction that was not statistically significant. However, in a pattern seemingly different from that found in trials in men, this result was due almost entirely to a reduction in strokes without a reduction in heart attacks. Specifically, aspirin lowered the risk of total stroke by 17% and the risk of ischemic stroke by 24%, but had no benefit on heart attack or cardiovascular death. The benefit on stroke is of particular relevance to women, as cardiovascular events in women are more likely to be strokes than heart attacks, whereas the reverse is true in men. With respect to side effects, aspirin, as expected, increased the risk of bleeding. Serious gastrointestinal hemorrhages were significantly more common in women assigned to aspirin than in those assigned to placebo, and there was also a nonsignificant increase in the risk of hemorrhagic stroke.

The most consistent cardiovascular benefits of aspirin were found among women aged 65 years and older, a group that comprised 10% of the WHS study population yet suffered one-third of all cardiovascular events. Among these women, aspirin use led to a 26% reduction in risk of major cardiovascular events, with a benefit on both stroke and heart attack. In contrast, for younger women, aspirin appeared to provide little or no cardiovascular protection.

"From a clinical perspective, the cardiovascular data on aspirin suggest that many women, particularly those over age 65, are likely to attain a net benefit from preventive aspirin therapy," said lead author Paul Ridker, MD, MPH. "The clinical implications for women younger

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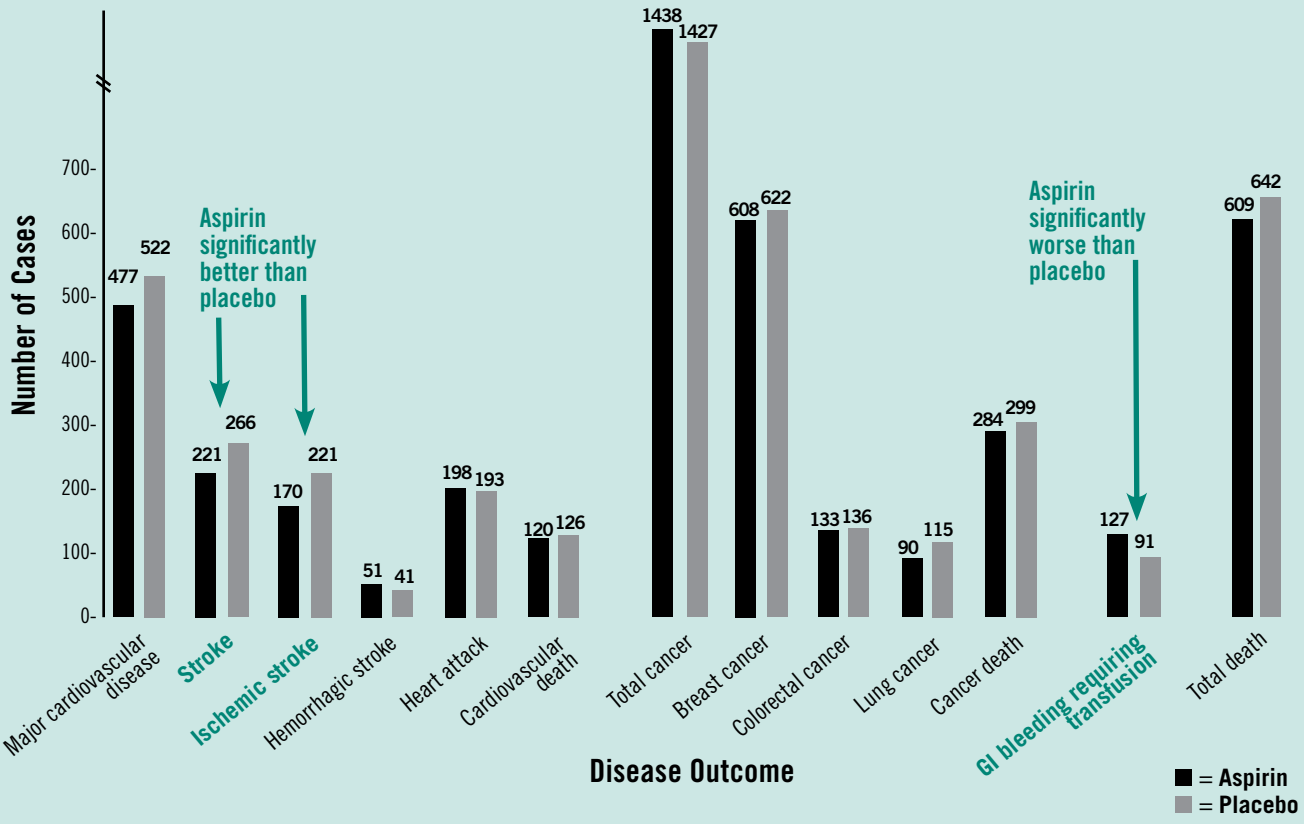
Drs. Nancy Cook, I-Min Lee, and Julie Buring, pictured left to right, published the long-anticipated WHS results on aspirin and cancer, and on Vitamin E, in the July 6, 2005 issue of the *Journal of the American Medical Association*.

Benefits and risks for women on aspirin or placebo, after 10 years of follow-up, Women's Health Study



There were 19,934 women in the aspirin group and 19,942 women in the placebo group.
Cardiovascular and gastrointestinal (GI) bleeding data from Ridker PM et al *N Engl J Med* 2005;352:1293-304; cancer data from Cook NR et al. *JAMA* 2005;294:470-55.

than age 65 are less clear. More research is needed to determine whether there are subgroups of younger women that benefit from aspirin therapy and whether a dose higher than that studied in the WHS is required for cardiovascular protection. Women considering the use of aspirin to prevent cardiovascular disease must weigh the balance of benefits and risks and thus should consult with their personal physicians before beginning therapy."

The results on low-dose aspirin and cardiovascular disease were published in the March 31, 2005 issue of the *New England Journal of Medicine.* (Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005;352:1293-1304.)

Aspirin and cancer

During the course of the trial, 1438 cancers occurred among women assigned to the aspirin group, as compared with 1427 among women in the placebo group, a difference that was not statistically significant. In addition, 284 women assigned to the aspirin group died of cancer, compared with 299 women in the placebo group, a nonsignificant 5% risk reduction. Thus, aspirin had little effect on the overall incidence of cancer or cancer-related deaths. The most common cancer among WHS participants was breast cancer, which accounted for 43% of cancer cases, followed by colorectal and lung cancer, which accounted for 9% and 7% of cases, respectively. Aspirin offered no protection against the development of breast cancer, colorectal cancer, or cancer of any other site in the body, with the possible exception of lung cancer. Women assigned to aspirin were 22% less likely to develop, and 30% less likely to die from, lung cancer than women assigned to placebo.

The findings suggest that low-dose aspirin is not effective in reducing risk of cancer in initially healthy women, although a beneficial effect on lung cancer cannot be ruled out. "We believe that the results for lung cancer need to be confirmed in future trials," said lead author Nancy Cook, ScD. "Based on the data currently available, we do not suggest that doctors recommend low-dose aspirin therapy for primary prevention of cancer."

It remains possible that a higher dose of aspirin than that tested in the WHS may protect against the development of cancer. Indeed, in August 2005, the Nurses' Health Study, which followed nearly 83,000 female nurses for two decades, reported that women who took more than 14 standard-dose (325-mg) aspirin tablets per week for longer than 10 years were one-third less likely to develop colorectal cancer than women who reported no regular aspirin use. However, this possible protective effect comes with a price – higher or more frequent aspirin doses cause greater gastrointestinal bleeding, a risk that may not be worth

taking for a healthy woman. The Nurses' Health Study was an observational study (i.e., the participants themselves chose whether or not to take medication), so the balance of benefits and risks of standard-dose aspirin need to be confirmed in a randomized clinical trial.

The WHS trial results on low-dose aspirin and cancer were published in the July 6, 2005 issue of the *Journal of the American Medical Association.* (Cook NR, Lee IM, Gaziano JM, Gordon D, Ridker PM, Manson JE, Hennekens CH, Buring JE. Low-dose aspirin in the primary prevention of cancer. The Women's Health Study: a randomized controlled trial. *JAMA* 2005;294:47-55.)

Vitamin E, cardiovascular disease, and cancer

There were 482 major cardiovascular events among the 19,937 women assigned to the vitamin E group and 517 among the 19,939 women assigned to the placebo group, a nonsignificant 7% reduction in risk. In the WHS cohort as a whole, vitamin E did not lower the risk of the specific outcomes of heart attack, stroke, or total mortality. However, vitamin E was associated with a significant 24% reduction in cardiovascular death, an unexpected finding that is not consistent with evidence from previous trials showing little effect on this outcome. In addition, among women aged 65 and older, vitamin E was associated with a significant 26% reduction in major cardiovascular events. Except for an increase in nosebleeds, which was likely due to chance, there were few side effects among women taking vitamin E. There was no increase in risk of other types of bleeding, including gastrointestinal hemorrhages and hemorrhagic stroke, associated with vitamin E.

"The intriguing findings on cardiovascular death deserve further study, but previous studies of vitamin E in patients with heart disease have not shown any benefit for cardiovascular death," said lead author I-Min Lee, MBBS, ScD. "Additionally, the finding of a decrease in major cardiovascular events among women aged 65 years and older has not been reported in previous studies. Moreover, this finding is not consistent with the overall lack of effect of vitamin E in trials of patients with heart disease, who tend to be older."

"This landmark trial has given women and their physicians important health information," said Elizabeth Nabel, MD, Director of the National Heart, Lung, and Blood Institute, which jointly sponsored the trial with the National Cancer Institute. "We can now say that despite their initial promise, vitamin E supplements do not prevent heart attack and stroke. Instead, women should focus on well-proven means of heart disease prevention, including leading a healthy lifestyle and controlling risk factors such as high blood pressure and high cholesterol."

With respect to cancer, 1437 cases of cancer occurred during follow-up among women assigned to the vitamin E group, as compared with 1428 among women in the placebo group, a difference

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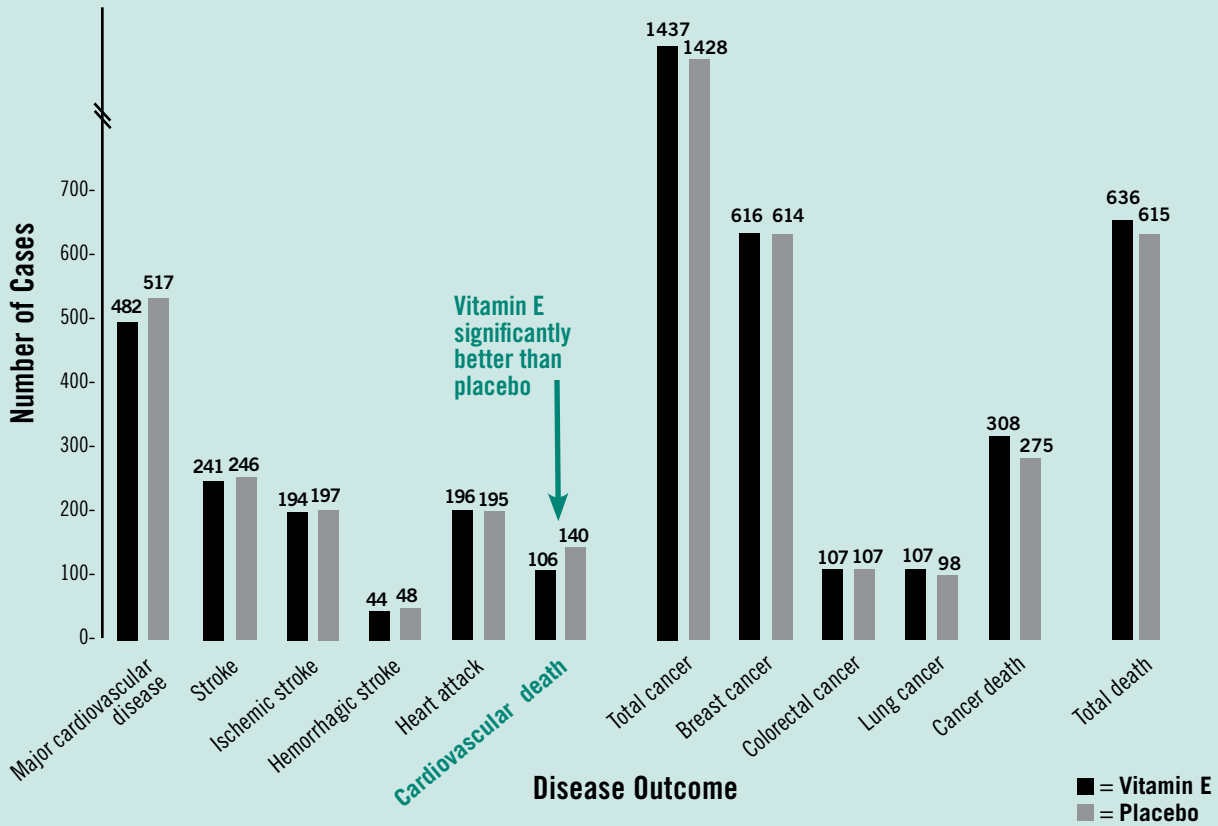
Benefits and risks for women on vitamin E or placebo, after 10 years of follow-up, Women's Health Study



There were 19,937 women in the vitamin E group and 19,939 women in the placebo group.
Data from Lee IM et al. *JAMA* 2005;294:56-65.

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that was not statistically significant. Vitamin E was not related to risk of developing breast, colon, or lung cancer, nor was it predictive of cancer deaths overall or at any site in the body. "On the basis of these findings, we cannot recommend vitamin E supplements for the prevention of cancer," said Dr. Lee.

"Thank you for forwarding a copy of the results from the cardiovascular component of the Women's Health Study trials. it was an honor to participate."

– Marie M. Wilson, RN, Port St. Lucie, Florida

The importance of the WHS results are highlighted by a recent national survey indicating that an estimated 44% of U.S. women take vitamin supplements containing vitamin E, and 11% take high-dose (400 IU or more per day) vitamin E supplements. Given the WHS findings, women may wish to reconsider their vitamin E supplement use, if they are taking such supplements for the purpose of preventing cardiovascular disease or cancer. The bottom line is that, for all of us, eating healthy foods and adhering to a healthy lifestyle—getting regular physical activity; maintaining a healthy weight; not smoking; and controlling high blood pressure, cholesterol, and 0diabetes—remain the best choice for long-term cardiovascular disease and cancer prevention.

The vitamin E results were published in the July 6, 2005 issue of the *Journal of the American Medical Association* (Lee IM, Cook NR, Gaziano JM, Gordon D, Ridker PM, Manson JE, Hennekens CH, Buring JE. 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.)

"Thank you for sending the much-anticipated results. I enjoyed being a part of such an important research study and look forward to participating in the follow-up."

– Jan Selwitz-Segal, dental hygienist, Boston, Massachusetts

The larger lesson from the WHS

From a policy standpoint, the Women's Health Study results, especially the findings on aspirin and cardiovascular disease, highlight the need to examine medical interventions in both women and men rather than routinely generalizing the results from one gender to another. "The WHS overwhelmingly demonstrates the importance of studying medical therapies among women as well as men," said Julie Buring, ScD, Principal Investigator of the WHS. "We finally have a solid foundation of data from women for women to make rational decisions about the use of aspirin and vitamin E in preventing cardiovascular disease and cancer."

Where does the WHS go from here?

Although the WHS was specifically designed to test whether aspirin and vitamin E affect risk of cardiovascular disease and cancer, WHS researchers are also examining how these interventions affect other medical conditions, including diabetes, loss of memory or other cognitive abilities, rheumatoid arthritis, and vision disorders such as cataract and age-related macular degeneration. In addition, we will continue to mail health questionnaires to study participants on an annual basis. These questionnaires are very similar to the ones that you have previously completed. Your responses will enable us to build upon the wealth of data already collected to explore new questions about health promotion and disease prevention among women. In fact, as of September 2005, more than 80% of WHS participants had already responded. As always, please feel free to write, call, or e-mail us with questions or comments about the WHS follow-up study (our mailing address, phone number, and e-mail are provided on this page). Thank you again for your extraordinary dedication and ongoing commitment to the Women's Health Study!

Q&A

Q Can I fill out my annual WHS questionnaires online?

We are looking into whether it is feasible to offer WHS participants the option of filling out their annual questionnaires electronically, on a privacy-secured website. It is possible that we will have the technological capability to do this within the coming year. More details will be forthcoming in future communications.

Q What writing implement should I use to complete the annual questionnaires?

The questionnaires are designed to allow recognition of marks made with a #2 pencil or a ballpoint pen. In either case, please make sure that the response bubbles are completely filled in and that your pencil or pen marks are dark. This ensures that the optical scanner will record your answers accurately.

If you have questions regarding the WHS, please let us know. Julie Buring, ScD, the study's Principal Investigator, will answer them in upcoming issues of *Update*.

A query to WHS *Update* readers

Are there topics related to women's health that you would like to see addressed in this newsletter, or experiences related to your participation in WHS that you would like to share with other women? If so, please let us know! Our contact information is:

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