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Lengthy Aspirin Use Linked to Reduced Heart Deaths in Women

By Judith Groch, Senior Writer, MedPage Today

Reviewed by Zalman S. Agus, MD; Emeritus Professor at the University of Pennsylvania School of Medicine.

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MedPage Today Action Points

- Explain to interested patients, that the positive aspirin results of this observational study contrast with findings from an earlier large randomized study that found no benefit.
- Explain to patients who ask that these observational results are insufficient to alter current clinical recommendations which are based upon clinical trials.

Review

BOSTON, March 26 -- Healthy women who took low-to-moderate doses of aspirin for at least five years had a reduced risk of death from any cause but especially cardiovascular disease, according to a large observational study.

Women who reported using aspirin currently had a 25% lower risk of all-cause death compared with those who never used aspirin regularly, reported Andrew Chan, M.D., of Harvard Medical School here, and colleagues, in the March 26 issue of the *Archives of Internal Medicine*.

The association was stronger at five years, with a 38% reduced risk of death from cardiovascular disease, while at 10 years the cancer death risk was 12% lower for aspirin users, said Dr. Chan.

The data came from a prospective, nested, case-control study of 79,439 women enrolled since 1980 in the Nurses' Health Study who had no history of cardiovascular disease or cancer.

All told, there were 9,477 deaths from any cause during 24 years of follow-up, with 1,991 deaths from cardiovascular disease, and 4,469 from cancer.

In an accompanying editorial, John A. Baron, M.D., of Dartmouth Medical School in Lebanon, N.H., sounded a skeptical note.

He pointed out that the Women's Health Study, carried out during more than 11 years and including 40,000 women, found no effect on cardiovascular or other mortality in healthy women, leaving confusion about aspirin's role.

"Is aspirin really that good or is there some other explanation for the findings that differ so much from those of the WHS and other primary prevention trials?" he asked.

In the current study, the investigators assessed the relative risk of death according to aspirin use before diagnosis of incident cardiovascular disease or cancer and during the corresponding period for each control subject.

The apparent benefit was largely confined to low-to-moderate doses of aspirin (one to 14 standard tablets a week), whereas higher doses (more than 14 tablets) were not beneficial.

Among women who reported current aspirin use, the multivariate relative risk of all-cause death was 0.75 (95% confidence interval, 0.71-0.81) compared with women who never used aspirin regularly.

The risk reduction was more apparent for death from cardiovascular disease (RR, 0.62, CI, 0.55-0.71), than for cancer deaths (RR, 0.88, CI, 0.81-0.96).

Use of aspirin for one to five years was associated with significant reductions in cardiovascular mortality (RR, 0.75; CI, 0.61-0.92). In contrast, a significant reduction in risk of cancer deaths was not observed until after 10 years of aspirin use (P for linear trend=0.005).

The lower risk of cancer deaths was statistically significant for death from colorectal cancer (multivariate RR, 0.72, CI, 0.56-0.92), they reported. Although current aspirin use did not seem to confer an overall significant benefit for breast or lung cancer deaths, women who used aspirin for longer than 20 years seemed to have a modest benefit for these cancers, the researchers said.

The benefit associated with aspirin was confined to low and moderate doses and was significantly greater in older participants (P for interaction<0.001) and those with more cardiac risk factors (P for interaction=0.02).

Because of previous data suggesting a higher risk of hemorrhagic stroke, the researchers checked and found a nonstatistically significant increased risk of death from stroke among aspirin users.

These results seem to be biologically plausible, Dr. Chan wrote. Aspirin therapy may influence cardiovascular disease and cancer through its effect on common pathogenic pathways, such as inflammation, insulin resistance, oxidative stress, and Cox enzyme activity.

Because thrombosis and platelet aggregation are relatively acute events, it is not surprising that the benefit of aspirin for vascular disease was observed within five years, the investigators said. "The slower benefit for cancer is also consistent with the slower, stepwise progression of carcinogenesis."

Study limitations included the observational nature of the study and the fact that aspirin use was self-selected. Thus, despite the strong biologic plausibility of these results, it is possible that the findings could be related to the reason for which participants used aspirin. Thus residual confounding could not be completely excluded, and the findings could not assign causality.

Furthermore, because the study matched cases of deaths with noncases, it was possible to assess only those that were fatal.

The researchers wrote that because the study was observational, "these results should be interpreted cautiously and are insufficient evidence to alter current clinical recommendations. Nevertheless, these data support a need for continued investigation of the use of aspirin for chronic disease prevention."

In his editorial, Dr. Baron noted that the difference between the Nurses' Health Study and the aggregated data from the Women's Health Study and other trials is too large to be explained by potential weaknesses in the randomized studies.

"At the same time," Dr. Baron wrote, "one has to consider that the observational NHS may not have been able to deal with the differences between aspirin users and nonusers."

Although the common finding in both studies of enhanced effects in older women leaves room for the possibility that aspirin reduces cardiovascular mortality in those patients, a large reduction in cardiovascular mortality in middle-aged women seems unlikely, he said.

"Therefore, these new findings by Chan et al cannot overcome the accumulated evidence that aspirin is not particularly effective for the primary prevention of death from cardiovascular disease in women," Dr. Baron concluded.

The authors of the Nurses' Health Study had no financial disclosures to report. Among the institutional grants was a GlaxoSmithKline Institute for Digestive Health Research award.

Dr. Baron, the editorial writer, reported no financial disclosures.

Additional source: Archives of Internal Medicine

Source reference:

Chan AT, et al ["Long-term Aspirin Use and Mortality in Women"](#) *Arch Intern Med* 2007; 167: 562-572.

Additional source: Archives of Internal Medicine

Source reference:

Baron JA ["Can Aspirin Keep Mortality at Bay?"](#) *Arch Intern Med* 2007; 167:535-536.

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