Daily postdiagnosis aspirin use has been linked with lower mortality from prostate cancer in patients diagnosed with high-risk, nonmetastatic prostate cancer, according to a recent study (J Clin Oncol. 2014;32:3716-3722).

Although previous studies have reported mixed results regarding the postdiagnosis use of aspirin and prostate cancer-specific mortality (PCSM), the current study includes a larger cohort than previous articles as well as data regarding aspirin dose, which, according to the authors, is lacking in other studies.

Study Findings
The authors analyzed the American Cancer Society’s Cancer Prevention Study II Nutrition Cohort, a prospective study of cancer incidence initiated in 1992. At the time of enrollment, participants (including 86,402 men) filled out questionnaires regarding their demographic, lifestyle-related, and medical risk factors. Aspirin use was reported at the time of enrollment, in 1997, and every 2 years thereafter through June 2009.

Eric Jacobs, PhD, strategic director of pharmacoepidemiology in the Epidemiology Research Program at the American Cancer Society in Atlanta, and colleagues identified 10,422 men from the cohort who developed prostate cancer during follow-up through 2009. After excluding patients with distant metastases, clinically apparent lymph node involvement, and/or missing information, a total of 8427 men were included in the analysis of prediagnosis aspirin use and 7118 men in the analysis of postdiagnosis aspirin use.

Deaths with prostate cancer coded as the underlying cause found via linkage to the National Death Index were counted as PCSM; overall mortality was not examined.

Aspirin users and nonusers in the analytic cohort were similar with regard to age at diagnosis, stage of disease, Gleason score, treatment type, and level of education. As the authors expected, more aspirin users than nonusers had cardiovascular disease or diabetes, because the primary indication for daily aspirin use is the prevention of cardiovascular events.

Analyses using Cox proportional hazards models adjusted for age at diagnosis, race, calendar year of diagnosis, tumor extent, lymph node involvement, Gleason score, initial treatment type, use of cholesterol-reducing drugs, cardiovascular disease, and prediagnosis prostate-specific antigen level found that prediagnosis aspirin use was not statistically significantly associated with PCSM at a mean follow-up of 9.3 years, and postdiagnosis aspirin use was not significantly associated with PCSM at a mean follow-up of 6.4 years.

However, in a subset analysis of high-risk patients (defined as those with a T classification of 3 or less and/or a Gleason score of 8 or less), postdiagnosis aspirin use was associated with a lower PCSM (hazards ratio [HR], 0.60; 95% confidence interval [95% CI], 0.37-0.97). For low-dose, postdiagnosis aspirin use in high-risk patients, PCSM was found to be significantly reduced (HR, 0.50; 95% CI, 0.27-0.92). For higher-dose aspirin use, there was a nonsignificant decrease noted in PCSM (HR, 0.73, 95% CI, 0.40-1.34).

However, differences between the dose-specific risk estimates were not statistically significant and did not support a difference by dose. Low-dose was defined as 162 mg or less and a higher dose as anything greater than 162 mg.
KEY POINTS

- Prediagnosis aspirin use was not found to be statistically significantly associated with PCSM with a mean follow-up of 9.3 years.
- Postdiagnosis aspirin use in the entire cohort was not significantly associated with PCSM with a mean follow-up of 6.4 years.
- However, in a subset analysis of high-risk patients (defined as those with a T classification of 3 or higher and/or a Gleason score of 8 or higher), postdiagnosis aspirin use was associated with a lower PCSM (HR, 0.60; 95% CI, 0.37-0.97).

Associations between PCSM and daily aspirin use either prediagnosis or postdiagnosis did not appear to differ significantly by age at diagnosis, follow-up time, cardiovascular disease, diabetes, treatment type, or use of cholesterol-reducing drugs.

“The main finding is that among this large cohort of men diagnosed with nonmetastatic prostate cancer, those who used aspirin daily and those who did not had about the same risk of dying from prostate cancer,” says Dr. Jacobs. “However, in a subgroup of men diagnosed with potentially more aggressive prostate cancers, risk of dying from prostate cancer appeared somewhat lower among those who took daily aspirin after their diagnosis, even low-dose aspirin.”

Implications and Limitations

The results of this large prospective study indicated that postdiagnosis daily aspirin use was associated with a 40% lower PCSM in patients initially diagnosed with high-risk prostate cancer, although not in the entire cohort. The authors note that the results of previous studies are mixed: 3 prior studies have shown an HR of approximately 0.50 for PCSM and postdiagnosis aspirin use in patients diagnosed with prostate cancer regardless of risk category, but others have not shown such an association.

Paul Godley, MD, PhD, MPP, professor in the division of hematology/oncology at the University of North Carolina at Chapel Hill School of Medicine, says that although it is interesting, the current study does not have practice implications.

“In contrast to recommendations for aspirin use among patients who have had a myocardial infarction or a stroke, the study by [Dr.] Jacobs and colleagues did not evaluate men who were actually randomly assigned by researchers to take or not take aspirin,” says Dr. Godley. “It is an observational study of prostate cancer-specific mortality among men who reported taking (or not taking) aspirin. Observational studies are not adequate substitutes for randomized clinical trials evaluating the efficacy of medications. Since such a trial of aspirin is under development, it would be very premature to recommend aspirin to increase survival among men with high-risk prostate cancer. Bottom line, the data is insufficient at this point to make a recommendation to prostate cancer patients.”

Dr. Jacobs agrees that the findings of the current study do not mean that men with prostate cancer should begin taking aspirin in the hopes of lowering their risk of dying of their cancer. “Previous studies of aspirin and prostate cancer mortality among men with prostate cancer have shown mixed results. Further, aspirin use can also cause serious side effects such as gastrointestinal bleeding,” he says.

In addition to being an observational study, treatment information was self-reported, and the study lacked data regarding PSA levels, biochemical disease recurrence, and clinical disease recurrence.

“The associations found could have been due to unmeasured differences between prostate cancer patients who used aspirin and those who did not,” Dr. Jacobs adds. “In particular, prostate cancer progression could have caused some men to stop, or not start, using aspirin, sometimes termed reverse causation. However, we did design the analysis to minimize the possibility of reverse causation,” he says.

The authors of the study note in their discussion that randomized trials are needed, and that such a trial is currently underway in the United Kingdom. The Add-Aspirin trial will randomly assign patients with nonmetastatic, intermediate-risk, or high-risk prostate cancer to adjuvant aspirin at doses of 100 mg or 300 mg, or placebo daily for at least 5 years. The primary outcome is 5-year, biochemical disease recurrence-free survival. Results are not expected for approximately 10 years. The authors also note that their current study implies that future studies should concentrate on high-risk patients and do not need to include high doses of aspirin.

“I do not think there is a shortcut to get a definitive answer,” adds Dr. Godley. “We will have to await the completion of a prospective, randomized trial specifically designed to administer aspirin for the potential prevention of prostate cancer recurrence in high-risk, early-stage disease.”

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