

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Aspirin Chemoprevention in Barrett Esophagus: Is the Risk Worth the Benefit?



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G&H What is the prevalence of Barrett esophagus in the general population, and how often does this condition progress to cancer?

JAJ Barrett esophagus is an inherited condition that is triggered by environmental factors (usually gastroesophageal reflux disease) that cause a chronic inflammatory reaction at the lower end of the esophagus. According to conservative estimates, Barrett esophagus occurs in at least 2% of the general population, particularly in northern Europe. This figure may be even higher in areas such as western Scotland, where 3–4% of the local population may have Barrett esophagus. This high rate can perhaps be attributed to genetics as well as obesity, which are both major risk factors for Barrett esophagus.

The number of patients with Barrett esophagus that progresses to esophageal adenocarcinoma is likely quite low. It is thought that the lifetime risk of progression is no more than 5% for men and 3% for women. However, at least half of these patients—2.5% for men and 1.5% for women—will actually die from other causes with higher mortality rates, such as heart disease or pneumonia. In general, safe estimates for the number of individuals with Barrett esophagus that progresses to cancer are 0.3–0.5% per year.

G&H Is surveillance/early detection still considered to be the main strategy for preventing the progression of Barrett esophagus to cancer?

JAJ Yes, surveillance is still considered to be the main preventive strategy; however, the scientific basis for the

surveillance of Barrett esophagus patients has not yet been proven in a randomized controlled trial. Thus, the BOSS study, the largest Barrett esophagus study in the world, is randomizing 3,600 individuals with Barrett esophagus in the United Kingdom to surveillance every 2 years or surveillance at the time of need (ie, upon development of symptoms). Which of the 2 arms is most effective will only be known when the BOSS trial results are announced; therefore, the effectiveness of surveillance is not yet known. The rationale for the surveillance programs currently being used in Barrett esophagus patients—despite the lack of evidence for their effectiveness—lies in the commonly held belief that doing something is better than doing nothing; anecdotal reports indicate that if a physician is lucky enough to detect an early lesion, it can be managed before it becomes cancerous.

G&H Does aspirin have a role in the chemoprevention of esophageal cancer?

JAJ Several studies have examined the use of aspirin for preventing various cancers, including gastrointestinal cancers. The best evidence of aspirin's chemopreventive ability has been shown in young patients with inherited colorectal cancer. As previously mentioned, the lifetime progression rate of Barrett esophagus to cancer is 5% for men and 3% for women. In contrast, the progression rate of inherited colorectal cancer, particularly familial adenomatous polyposis, is 99% at 39 years of age, which is obviously a very serious risk. In addition, since these patients are young, they are

much less likely to develop side effects from aspirin use, as side effects are more common in older patients. Thus, it is probably not unreasonable for these younger patients to take aspirin for 10 years, perhaps even 20 years, of their lives.

In terms of esophageal cancer, data have suggested that aspirin (in a dose of at least 75 mg but perhaps as high as 300 mg or more per day) can decrease the rates of squamous-cell carcinoma and esophageal adenocarcinoma, the latter of which is usually associated with Barrett esophagus. The rate of this cancer reduction is thought to be 20–25%. The exact level of reduction seems proportional to both the duration of aspirin therapy as well as the dose.

G&H Have any studies examined the use of aspirin for preventing the progression of Barrett esophagus to esophageal cancer?

JAJ No data are yet available from large randomized studies with cancer endpoints regarding the use of aspirin for preventing the progression from Barrett esophagus to esophageal cancer. My colleagues and I are currently conducting the AspECT trial, which has recruited 2,500 patients to undergo treatment with aspirin (the active agent) and esomeprazole (the acid suppressive agent administered to prevent the development of ulcers that may occur from aspirin use); these patients have been followed for an average of 5 years to date. Thus far, the treatment appears to be relatively well tolerated and without many side effects, although we are still in the middle stages of the trial. It is still too early to determine whether the use of aspirin and esomeprazole leads to a reduction in cancer; this question will likely require at least 10 years—perhaps up to 20 years—of follow-up data.

Some data from retrospective case-control studies have suggested that individuals who take aspirin may develop less Barrett esophagus. In addition, data from John Inadomi, Chin Hur, Gary Falk, Paul Limburg, and other groups of researchers have shown that patients taking aspirin are much less likely to progress from esophagitis to Barrett esophagus.

G&H What is the rationale behind the use of aspirin as a chemopreventive strategy?

JAJ First, based upon case-control and cohort studies, aspirin is by far the most effective agent out of all the potential cancer-reducing agents; individuals who take aspirin have been shown to have less esophageal adenocarcinoma. Second, aspirin is relatively well tolerated in younger individuals. The most common side effects associated with the use of aspirin are found mainly in patients

65 years of age and older, and these complications are well known, as aspirin has been used for over 100 years. Third, most of the complications of aspirin can be avoided with concomitant administration of acid suppressive therapy such as proton pump inhibitors. Further long-term data on the use of aspirin and proton pump inhibitors will be provided by the AspECT trial.

G&H What are the most common complications associated with aspirin?

JAJ In patients 65 years of age and older who are taking aspirin, the risk of severe gastrointestinal bleeding increases from approximately 1% per year to 4% per year by 75 years of age, which is quite a significant risk. Prior to 65 years of age, the risk of gastrointestinal bleeding in patients taking aspirin is very low (approximately 0.2% per year).

Another complication associated with aspirin is a 60% increase in the risk of hemorrhagic stroke. However, that figure refers to the relative risk of hemorrhagic stroke; the absolute risk is very small (only a few percentage points). Nonetheless, patients are often very worried about the risk of developing a bleeding stroke.

The third major complication associated with aspirin is its interference with cardiac medications such as clopidogrel.

It is important to take these complications into account when managing patients because many physicians think that aspirin is a panacea and do not consider the small but serious risk of side effects, which accumulate over 10–20 years and could include death from peptic ulcer bleeding or hemorrhagic stroke. If the goal is to try to prevent 3–5% of patients with Barrett esophagus from progressing to cancer (half of whom will die from other causes anyway), it is essential to make sure that more harm is not caused than good in the process, particularly since this drug would have to be taken for at least 10 years.

G&H Based on the data that are currently available, which Barrett esophagus patients appear to respond best to aspirin?

JAJ Genetics appear to determine which patients respond best to aspirin and which patients are most resistant. My colleagues and I conducted a large genetic study of all the populations included in the AspECT trial and the related ChOPIN trial; the results of this genetic study were recently published in *Nature Genetics*. We identified 2 genetic factors that may predispose individuals to the development of Barrett esophagus. In the future, it may be possible to use these data to stratify which patients would benefit (and not be harmed) from aspirin use.

G&H What data are needed before the use of aspirin could be adopted as a chemopreventive strategy for patients with Barrett esophagus?

JAJ Long-term data are needed on the use of aspirin in Barrett esophagus patients, such as the results of the ongoing AspECT trial. An editorial by Inadomi in *Gastroenterology* discussed a short-term study in which aspirin appeared to prevent production of the growth-promoting substance prostaglandin in patients taking short-term aspirin therapy. This finding suggested that aspirin may affect tissue; however, no conclusions could be made because the study was not powered to examine hard endpoints. In his editorial, Inadomi noted that the study results were very compelling but that clinical implications of aspirin use could not be determined until the AspECT trial results were available. As the chief investigator of the AspECT trial, I agree with this statement because clear, randomized evidence is needed to demonstrate that the benefit of aspirin use is not merely theoretical and is not associated with too many risks.

G&H Has there been research on the use of agents other than aspirin for chemoprevention in Barrett esophagus patients?

JAJ Yes. Approximately 5 years ago, a trial was published in the *Journal of the National Cancer Institute* that showed no response at all with the use of COX-2

drugs in patients with Barrett esophagus. In addition, a few small chemoprevention trials have been conducted on other agents such as metformin, but results have not yet been published.

Suggested Reading

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