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Chemoprevention in Barrett's Esophagus: Are we there yet, are we there yet...?

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Doc, what can I do to decrease my risk of dying from cancer?

This is perhaps the most commonly asked question from patients after they receive a Barrett's esophagus diagnosis, and one of the most challenging to answer. Chemoprevention, the use of pharmacologic agents or supplements to modify cancer risk, is an area of intense interest given the relative ease of administration. If effective, chemoprevention could be doubly appealing: it could both diminish cancer risk and decrease (or eliminate) the need for invasive, costly endoscopic procedures used for surveillance and treatment of Barrett's esophagus or dysplasia.

What information does the current study provide?

The current study by Nguyen et.al. updates the group's prior Veterans' Affairs (VA) epidemiologic study of chemoprevention with more subjects, additional follow-up time for proton pump inhibitors (PPI), and new data for aspirin/NSAIDs and statins.¹

The main findings of interest include the inverse associations found for PPIs and aspirin/NSAIDs. The incidence rate ratio for high grade dysplasia or esophageal adenocarcinoma among persons with at least one PPI prescription compared to non-users was remarkably low (IRR=0.42 95% CI: 0.21–0.82); data confined to the 13 patients with esophageal adenocarcinoma showed an even stronger reduction in risk (IRR=0.33, 95% CI: 0.11–0.98).

The data for aspirin/NSAIDs also showed an inverse association. Although this finding is intriguing, it is difficult to interpret given this medication class is widely available over the counter and the data set only evaluated prescription use. No associations were found for statin use.

The current study has many strengths including the extensive experience of the investigator group in the field of Barrett's esophagus; a considerable number of patients (given the rarity of esophageal adenocarcinoma) who developed either cancer (13) or high grade dysplasia (an additional 17 unique patients); its use of pharmacy records for much of the time interval (which show the medications actually dispensed); a manual record review to confirm the Barrett's esophagus diagnoses; the requirement for at least two endoscopies (ensuring the entire study

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population had at least some follow-up); and the uniform collection of data by a single endoscopist and pathologist. This combination of strengths is difficult to replicate in many settings.

There are several unavoidable weaknesses of the study that limit the ability to make firm conclusions. One is duration of follow-up: despite a long follow-up interval (1982–2004), the duration of follow-up for individual patients is relatively short for chemoprevention agents (a mean of 2.8 years for statins to 5.1 years for PPIs). Also, the sample size limited the power of the study and restricted the ability to conduct detailed analyses of dose and duration. Instead, the primary exposure definition was a single medication prescription. This is an inherent difficulty of doing research on patients with Barrett's esophagus, where relatively few patients are followed at any given center and few of those patients progress on to cancer or dysplasia. Finally, an unknown number of veterans had "dual insurance" or otherwise received medical care outside of the VA system. If either medications were received or a cancer diagnosis was made outside the VA, these events would not have been reported in the database.

Is there biological evidence to support the observed inverse associations?

The idea that acid inhibition could decrease the risk of Barrett's esophagus progressing to cancer is highly intuitive: we know that gastroesophageal reflux disease (GERD) can cause esophagitis, and that chronic inflammation in other organs (e.g., the lung and colon) is associated with an increased risk of neoplasia. Thus, it makes sense that reducing esophagitis by decreasing acid reflux may decrease the risk of Barrett's esophagus progressing to esophageal adenocarcinoma.

However, the biological data supporting a chemopreventive effect of acid suppression is conflicting. Some studies show acid suppression decreases markers of proliferation in Barrett's esophagus.^{2, 3} In contrast, other in vitro studies suggest that intermittent acid exposure or a predominance of bile in the refluxate (such as what might occur in someone on PPIs) may be more likely to induce proneoplastic changes than continuous acid exposure alone. In a laboratory model, brief exposure of Barrett's esophagus cells to bile salts, in the absence of acid, led to increased proliferation; however, a combination of bile salts and acid together inhibited cell proliferation.⁴ Another in vitro study also showed that acid exposure resulted in antiproliferative effects in nonneoplastic Barrett's epithelial cells, leading the authors to speculate that antisecretory medications in dosages higher than those required to heal esophagitis or relieve GERD symptoms could be detrimental.⁵

Are the inverse associations consistent with other studies?

A recent Australian study of 502 cancer-free Barrett's esophagus patients reported that those not on PPIs at the time of Barrett's esophagus diagnosis were 3.4 times more likely to have higher-risk endoscopic macroscopic markers (e.g., ulceration, nodularity, or stricture) or low-grade dysplasia than patients who were on a PPI at the time of diagnosis.⁶ No difference was seen in high-grade dysplasia or cancer rates between PPI-users and non-users. The same group previously reported that patients who delayed starting PPIs by 2 years or more after Barrett's esophagus diagnosis had a higher risk of high-grade dysplasia or cancer compared with patients who started shortly after their diagnosis.⁷

In contrast, surgical anti-reflux procedures, the most potent form of anti-reflux therapy, have not been convincingly demonstrated to decrease cancer risk compared with medical therapy, despite multiple studies with over 4000 years of patient follow-up.^{8, 9} This was not, however, a comparison with no therapy.

Could the results be due to bias or confounding?

The primary limitation of the current study is one hampering all epidemiology studies: confounding or the inability to control for other factors that may alter the chance of either the exposure (the medications of interest) or the outcome (dysplasia and esophageal adenocarcinoma). For example, the investigators did not have access to information related to socioeconomic status, tobacco and alcohol use, *H. pylori* status, dietary intake, and other factors that may be associated with both the exposure and the outcome and could therefore confound the results.

For all of the published studies, is it acid suppression itself that is decreasing risk? Or could it just be that patients with symptomatic GERD are both more likely to be treated with acid suppression and less likely to have early neoplastic changes?

Interestingly, only 67% of patients with Barrett's esophagus in the current study received at least one PPI prescription. This is substantially lower than what was reported by some members of the same research group in a study of 7,732 veterans with Barrett's esophagus where 91.5% of patients filled at least one PPI prescription in the first year following diagnosis.¹⁰

Why did the current study report a lower proportion of treated patients in a comparable veterans population? If a physician recommended a PPI, we might expect at least one prescription to be dispensed even if a patient were intolerant or noncompliant. Why were some patients not treated, even at an experienced center where each patient received at least two endoscopies separated by at least six months? Possibilities include physician-determined factors (e.g., no treatment because there was no evidence of GERD symptoms or esophagitis), patient-determined factors (e.g., did not want medications), and potential biases (e.g., patient received medications outside the VA system). Future studies elucidating why some people are treated and others are not would provide key insights into whether acid suppression itself influences cancer risk or whether confounding factors might explain the differences seen. That a single prescription is inversely associated with disease risk raises the specter of confounding.

The importance of confounding as a potential cause of the study's findings cannot be underestimated. A well known example is a large study that suggested a link between coffee consumption and pancreatic cancer.¹¹ The study showed a strong association (OR= 2.7, 95% CI 1.6 to 4.7 for 3 or more cups per day), evidence of a dose effect (more risk with greater coffee consumption), and the authors adjusted for many potential confounders that had been carefully measured through in-person interviews. However, the coffee-cancer association was subsequently discredited by other studies. The associations observed were felt to have resulted from biased controls, other gastrointestinal patients without cancer; these patients likely had a lower-than-expected coffee consumption for various reasons associated with their gastrointestinal ailments.^{12–15} The lesson from such studies is clear: if large epidemiologic studies with detailed data on confounders cannot fully statistically adjust for potential biases, we must be doubly cautious in reaching treatment decisions when using smaller data sets with little information on confounders.

Is there any harm to using these medications?

A crucial question when deciding on chemoprevention is the downside to taking the medication. For example, a cost-effectiveness model of selective cyclo-oxygenase inhibitors suggested that even if they were effective at decreasing the risk of neoplastic progression in Barrett's esophagus, any benefits could be outweighed by increased deaths from myocardial infarctions. In contrast, if a potential chemopreventive agent were inexpensive, had few known side effects, and might work, some patients may "hedge their bets" and take the medication until more definitive studies came along.

Unfortunately, there is an emerging body of evidence suggesting that acid suppression medications are not without risk, and that effects may be dose related. For example, PPI use has been found to be associated with a small but significant increased risk of clostridium difficile infections,¹⁶ food borne bacterial infections,¹⁷ and pulmonary infections. Recent studies have also suggested a possible small increase in the risk of hip fractures in patients taking acid suppressing medications.^{18–20}

Are there other reasons to use these medications?

For many patients with Barrett's esophagus, there are clear other indications for using the medications studied; thus, whether the patient should be on the agent is a "no-brainer". Potent acid suppression, such as with a PPI, is necessary to heal and maintain healing of esophagitis. Patients with GERD symptoms also have a clear indication for acid suppression. These patients should be on a PPI in a dose sufficient to heal their esophagitis or adequately treat their GERD symptoms. But not all patients with Barrett's esophagus have GERD. The treatment of patients who lack both esophagitis and GERD is less clear; some patients with Barrett's esophagus may not have chronic GERD. Other causes for Barrett's esophagus may include a remote episode of non-GERD vomiting-induced esophagitis, radiation injury, or other pathways. Such patients, who lack ongoing pathologic reflux, would be unlikely to benefit from pharmacologic acid inhibitors, even if they were effective at decreasing cancer risk in GERD patients.

Similarly, many patients with Barrett's esophagus have another indication for anti-platelet agents (i.e., aspirin). The United States Preventative Services Task Force recommends the use of aspirin for men age 45 to 79 years when the potential benefit due to a reduction in myocardial infarctions outweighs the potential harm due to an increase in gastrointestinal hemorrhage. Risk calculators are available on the internet (e.g. <http://www.framinghamheartstudy.org>) and many if not most Barrett's esophagus patients likely qualify for aspirin therapy.

Balancing the potential benefits and risks: what do we say to patients?

Chemoprevention is an exciting but unproven method for decreasing cancer risk in patients with Barrett's esophagus. The limitations of epidemiologic data underscore the need for a cautious approach, particularly for agents which may have some risk and for a condition in which the overall likelihood of dying from esophageal adenocarcinoma is low.²¹

Evidence to date supports the following

1. Pharmacologic acid suppression to eradicate esophagitis and relieve GERD symptoms in symptomatic patients.
2. The use of aspirin in patients with other indications for anti-platelet therapy, which likely include a substantial portion of patients with Barrett's esophagus. It is unknown if the cardioprotective dose may also be a chemopreventive dose.

At this time there is insufficient evidence to support

1. Routine use of high-dose PPI therapy beyond that needed for symptom relief and mucosal healing.
2. Invasive tests (such as pH probes) to monitor the degree of acid suppression in persons who have complete mucosal healing and minimal symptoms.
3. Routine use of aspirin in persons not at increased risk for cardiovascular disease.

Finally, randomized controlled trials, such as the Aspirin Esomeprazole Chemoprevention Trial (Aspect), will provide a more definitive assessment of the effects of acid suppressing medications and aspirin as chemoprevention agents in Barrett's esophagus.

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