Chemoprevention of esophageal adenocarcinoma

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***Abstract*:** The incidence of esophageal adenocarcinoma (EAC) is rising rapidly in Western countries, and effective chemoprevention for this malignancy is lacking. Endoscopic surveillance of patients with Barrett's esophagus is currently employed to diagnose EAC at earlier stages, but this strategy has several limitations. Non-steroidal anti-inflammatory drugs and proton pump inhibitors are the most promising agents for prevention of EAC, and a randomized controlled trial of aspirin and esomeprazole is ongoing. Other agents under investigation include green tea, berries, and antioxidants. Cost-effectiveness analyses have shown that chemopreventive agents need to be highly effective at preventing EAC in order to have benefit beyond endoscopic surveillance.

***Keywords*:** esophageal cancer, adenocarcinoma, chemoprevention

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In Western countries, the incidence of esophageal adenocarcinoma (EAC) has risen at a rapid rate over the past 30 years [Kubo and Corley, 2002; Vizcaino *et al*. 2002]. The reasons for this alarming trend are not entirely understood, but the increasing prevalence of obesity and associated acid reflux likely play a significant role [Lagergren *et al*. 1999a,b]. Unfortunately, the overall survival of EAC remains low (~15%), and only 24% of esophageal cancer cases in the United States are diagnosed while still localized [Jemal *et al*. 2007].

Barrett's esophagus (BE) has long been recognized as the primary precursor lesion to EAC [Spechler, 2002]. In patients diagnosed with BE, periodic endoscopic surveillance is performed for the detection of high-grade dysplasia or early carcinoma. While this strategy results in diagnosis of adenocarcinoma at earlier stages (and possibly improved overall survival) [Corley *et al*. 2002; van Sandick *et al*. 1998; Wright *et al*. 1996], the overwhelming majority of new cases of adenocarcinoma never receive a prior diagnosis of BE [Schlansky *et al*. 2006].

There are several problems with relying solely on endoscopic surveillance for the prevention and early identification of EAC. Most BE patients are initially diagnosed after an upper endoscopy performed for symptoms of acid reflux. The prevalence of frequent gastro-esophageal reflux disease (GERD) symptoms in the United States is estimated at 20–25% [El-Serag *et al*. 2004b], but only a small proportion of these patients will have BE [Shaheen and Ransohoff, 2002]. Additionally, a high proportion of BE patients deny a history of reflux symptoms [Ronkainen *et al*. 2005; Rex *et al*. 2003]. Once BE is diagnosed, the incidence of progression to adenocarcinoma is low, estimated at ~0.5% per year [Shaheen and Ransohoff, 2002]; and therefore the number of surveillance endoscopies that need to be performed to significantly impact the overall survival in EAC is large.

As such, EAC is an attractive target for the development of an effective chemopreventive agent. In this paper, the published literature will be reviewed on the chemoprevention of EAC (Table 1).

Nonsteroidal anti-inflammatory drugs

Epidemiologic studies have consistently demonstrated a protective effect of nonsteroidal anti-inflammatory drug (NSAID) use on risk of EAC [Duan *et al*. 2008; Anderson *et al*. 2006; Vaughan *et al*. 2005; Bardou *et al*. 2004; Gammon *et al*. 2004; Corley *et al*. 2003; Farrow *et al*. 1998; Funkhouser and Sharp, 1995]. A cohort study using data from the National Health and Nutrition Examination Survey (NHANES) reported a 90% reduction in the risk of death from esophageal cancer (all cell types) among

Table 1. Chemopreventive interventions under investigation for esophageal adenocarcinoma and current levels of evidence.*

	Level of evidence
NSAIDs†	1
Proton pump inhibitors†	1–2
Green tea (Poly E) †	2
Folic acid	2
Black raspberries	3
Diet high in fruits and vegetables	2
Antioxidants	2
Superoxide dismutase	
Thioproline	
Retinoic acid (vitamin A)	2–3

NSAIDs, nonsteroidal anti-inflammatory drugs.
*Level 1: High-quality cohort studies; consistent findings across studies; Level 2: Lower-quality cohort or case-control studies; meta-analyses of lower-quality studies; inconsistent findings across studies; Level 3: Extrapolations from bench research.
†Currently being studied in randomized controlled trials.

aspirin users [Funkhouser and Sharp, 1995]. In Northern Ireland, regular NSAID use was associated with a reduced odds of both BE (OR 0.40; 95% CI 0.19–0.81) and EAC (OR 0.58; 95% CI 0.31–1.08) [Anderson *et al.* 2006]. The authors hypothesized that there may have been a confounding by indication, and that NSAIDs were possibly avoided in patients with GERD due to symptom exacerbation. In a secondary analysis, however, a higher proportion of patients with GERD symptoms than without were NSAID users.

In a separate prospective cohort study of patients with BE, current NSAID use was associated with a reduced risk of progression to EAC (HR 0.32; 95% CI 0.14–0.76) [Vaughan *et al.* 2005]. A meta-analysis of aspirin, NSAID use, and esophageal cancer reported a significantly reduced odds of EAC in aspirin and NSAID users (OR 0.67; 95% CI 0.51–0.87) [Corley *et al.* 2003].

The underlying mechanisms behind this protective effect are not entirely clear. One possible explanation is the inhibition of cyclooxygenase-2 (COX-2). Cyclooxygenase-1 (COX-1) is constitutively expressed in the gastrointestinal tract. COX-2 expression is generally not observed in normal gastrointestinal mucosa, but has been described in multiple epithelial malignancies [Howe and Dannenberg, 2002], although its expression is often heterogeneous [Abdalla *et al.* 2005]. The exact role that COX-2 plays in neoplastic progression to EAC has not been well elucidated. COX-2 is expressed at progressively increased levels from BE to dysplasia to adenocarcinoma [Mehta *et al.* 2006; Morris *et al.* 2001; Shirvani *et al.* 2000; Wilson *et al.* 1998]. Bile acid exposure in the esophagus results in increased COX-2 expression in BE as well [Zhang *et al.* 2001]. Inhibition of COX-2 *in vitro* and *in vivo* decreases expression of markers of cellular proliferation and induces apoptosis in both BE and EAC [Kaur *et al.* 2002; Buttar *et al.* 2002a; Souza *et al.* 2000], and results in decreased development of EAC in a rat model [Buttar *et al.* 2002b].

While randomized controlled trials using both COX-nonselective (aspirin) and COX-2 selective (celecoxib) inhibitors have demonstrated a reduced risk of the development of colorectal adenomas (RR 0.55–0.81) [Arber *et al.* 2006; Bertagnolli *et al.* 2006; Baron *et al.* 2003; Sandler *et al.* 2003], treatment with COX-2 selective inhibitors has not proved successful to date as a chemopreventive agent for EAC. The Chemoprevention for BE Trial (CBET) Study Group recently reported the results of a randomized controlled trial of celecoxib for the prevention of progression in patients with BE with low- or high-grade dysplasia [Heath *et al.* 2007]. No significant differences were seen between the celecoxib and placebo groups with respect to the proportion of patients who progressed or with respect to markers of progression, including COX-2 expression. The negative results of this study may have been partly due to various factors: there was a high rate of histologic regression in both subjects with baseline low-grade dysplasia (50%) and high-grade dysplasia (25%). Additionally, the histological endpoints of the study are difficult to interpret in light of both high-sampling error in endoscopic surveillance for BE as well as poor inter- and intra-observer variability among pathologists, particularly for the diagnosis of low-grade dysplasia.

Given the consistent protective effects of NSAID use for EAC in epidemiologic studies, there may be alternative mechanisms independent of cyclooxygenase that underlie the antineoplastic properties of NSAIDs. In one population-based case-control study, NSAID use was associated with a reduced odds of EAC only for tumors expressing cyclin D1, which is involved in cellular proliferation (OR 0.45; 95% CI 0.26–0.79) [Gammon *et al.* 2004].

There have been no randomized controlled trials using nonselective NSAIDs for the prevention

of EAC. The Aspirin for the Prevention of Esophageal Cancer Trial (AsPECT) is an ongoing large, multicenter randomized controlled trial that is evaluating the effects of aspirin 300 mg daily (vs no aspirin) on all-cause mortality and on the rate of progression to high-grade dysplasia or adenocarcinoma in patients with BE [Jankowski and Moayyedi, 2004]. The results of this study are eagerly anticipated.

Proton pump inhibitors

EAC is associated with a history of acid reflux symptoms [Lagergren *et al.* 1999a; Chow *et al.* 1995], and acid reflux likely plays an important role in the development of BE [Shaheen and Ransohoff, 2002]. However, it is not clear if gastroesophageal reflux contributes to the neoplastic progression of BE to EAC. Patients with BE have increased acid exposure compared to non-BE heartburn patients, and proton pump inhibitors (PPIs) are effective at reducing intragastric pH and subsequent esophageal exposure to acidic reflux [Katz *et al.* 2007, 2006; Fiorucci *et al.* 1989; Gillen *et al.* 1987]. The use of PPIs has increased dramatically since their development more than 20 years ago, but the incidence of EAC has continued to rise at an alarming rate despite the widespread use of this class of medications.

The epidemiologic data do not convincingly support the use of PPIs for the prevention of neoplastic progression in patients with BE. Long-term PPI use in BE does not result in a significant change in the length of BE [Cooper *et al.* 2006]. Epidemiologic studies suggest that PPI use in patients with BE may be associated with lower rates of neoplastic progression [Hillman *et al.* 2008; Hillman *et al.* 2004]. In a study by El-Serag *et al.* [2004a] of veterans with BE, PPI use (compared to histamine H_2 antagonists and no acid suppression) had a lower risk of progression to dysplasia (HR 0.25; 95% CI 0.13–0.47). However, a case-control study from the UK demonstrated an increased risk of EAC in patients who received acid suppressive therapy (H_2 antagonists or PPIs) for GERD symptoms or BE (OR 5.42; 95% CI 3.13–9.39) [Garcia Rodriguez *et al.* 2006], and a separate population-based case-control study from the United States failed to show an association between acid suppression with H_2 antagonists and risk of EAC [Farrow *et al.* 2000]. Many of these studies have been limited by confounding by indication, inadequate assessment of adequacy of surveillance intervals and biopsy sampling, and reasons for not taking PPIs in the comparison groups.

Acid exposure in BE-associated EAC cell lines has been shown to activate the proliferative and anti-apoptotic MAPK pathway and increase COX-2 expression [Souza *et al.* 2004, 2002]. However, more recent *in vitro* studies suggest that acid exposure has antiproliferative effects in nondysplastic BE [Feagins *et al.* 2007; Zhang *et al.* 2007]. These seemingly discrepant findings may be due to differential responses to acid exposure in nondysplastic vs cancer cell lines. Additionally, early *ex vivo* studies using endoscopic biopsy specimens suggested that pulsed acid exposure (as compared to continuous acid exposure) resulted in increased cellular proliferation [Fitzgerald *et al.* 1996], although interpretation of these results is complicated by the presence of multiple cell types (including stroma and immune cells) in biopsy specimens.

Acid exposure does not result in genetic changes normally associated with enhanced cellular proliferation in BE cell lines, while results have been mixed in studies of BE-associated adenocarcinoma cell lines [Hao *et al.* 2007; Morgan *et al.* 2004]. An *in vivo* study of BE tissue demonstrated reduced cellular proliferation after six months of effective acid suppression with lansoprazole [Ouatu-Lascar *et al.* 1999]. A separate study of patients with BE who received PPI therapy demonstrated reduced p16 and increased cyclin D1 expression as compared to BE patients not receiving acid suppressive therapy [Umansky *et al.* 2001]. Effective acid suppression (as demonstrated by pH monitoring) in BE patients resulted in reduced cellular proliferation but had no effect on apoptosis or COX-2 expression [Lao-Sirieix *et al.* 2006].

There are hypothetical concerns that PPIs could promote neoplastic progression in BE. PPI therapy often results in secondary hypergastrinemia [Koop *et al.* 1990]. Both experimental and epidemiologic data support a role for gastrin in the development of colorectal neoplasia [Georgopoulos *et al.* 2006; Thorburn *et al.* 1998; Sobhani *et al.* 1993; Smith and Solomon, 1988; Kusyk *et al.* 1986]. In BE cells, gastrin binds to the CCK-2 receptor, which enhances proliferation and has antiapoptotic effects [Harris *et al.* 2004; Haigh *et al.* 2003].

Elevated tissue gastrin expression was associated with increased cellular proliferation and COX-2 expression in a series of patients with BE [Abdalla *et al*. 2004].

Given the apparent conflicting effects of acid suppression on markers of neoplasia in the laboratory and inconclusive epidemiologic data, it is not possible to support the use of PPIs solely for the prevention of EAC. Hopefully, the AsPECT trial described above will help address the role of PPIs in the prevention of adenocarcinoma in patients with BE. Patients will be assigned to esomeprazole either 80 mg daily or 20 mg daily (which can be increased based on symptoms) [Jankowski and Moayyedi, 2004]. While the trial does not have a placebo arm, the 2×2 design will allow for the assessment of differences in effect of high-dose vs low-dose PPI therapy on neoplastic progression in BE.

Green tea

Epidemiologic studies from Asia suggest that high consumption of green tea is associated with a reduced risk of various epithelial malignancies [Cabrera *et al*. 2006]. In a cohort of nearly 70,000 women in China, regular green tea consumption was associated with a significantly decreased risk of colorectal cancer (RR 0.63; 95% CI 0.45–0.88) [Yang *et al*. 2007]. A meta-analysis also demonstrated an inverse relationship between green tea consumption and colorectal cancer (OR 0.82; 95% CI 0.69–0.98) [Sun *et al*. 2006]. The association between green tea consumption and risk of EAC has not been directly studied, in part due to the low incidence of EAC in Asia.

Several antineoplastic properties have been identified among green tea metabolites, which include epigallocatechin-3-gallate (EGCG) and other catechins. EGCG inhibits cell growth, induces apoptosis, and reduces COX-2 expression [Masuda *et al*. 2003, 2001]. EGCG also has antioxidant properties and may have anti-inflammatory properties as well [Saffari and Sadrzadeh, 2004; D'Alessandro *et al*. 2003].

There is currently an ongoing placebo-controlled phase IB trial of polyphenon E (Poly E), a compound containing EGCG (data unpublished). Patients with BE and no dysplasia or low-grade dysplasia will receive either Poly E or placebo for six months. The primary aim of the study is to demonstrate safety and determine the maximum tolerated dose. Secondary aims of the study include evaluation of the effects of Poly E on expression of various neoplastic biomarkers, including cyclin D1, COX-2, and Ki-67.

Folic acid

Folic acid is a water soluble vitamin B present in many foods. Folate plays an important role in DNA synthesis and methylation, and deficiency of this vitamin can result in DNA damage and abnormal DNA methylation [Choi and Mason, 2000]. Population-based case-control studies have showed that the highest levels of folate intake are associated with a significantly reduced odds of EAC [Chen *et al*. 2002; Mayne *et al*. 2001], and results of a recent meta-analysis demonstrated that high folate intake is associated with a reduced risk of EAC (RR 0.50; 95% 0.39–0.65) [Larsson *et al*. 2006]. Additionally, there are functional polymorphisms of methyl tetrahydrofolate reductase (MTHFR) that play important roles in folate metabolism, and the relationship between folic acid intake and cancer risk may vary between individuals with differing polymorphisms [Larsson *et al*. 2006].

While epidemiologic data also strongly suggest an association between high folate intake and reduced risk of colorectal cancer [Larsson *et al*. 2005; Baron *et al*. 1998; Giovannucci *et al*. 1998, 1995], a recent randomized placebo-controlled trial demonstrated no benefit of folate on the risk of recurrent adenomas [Cole *et al*. 2007]. Therefore, until a randomized controlled trial is performed in esophageal cancer, folic acid cannot be recommended for the prevention of EAC.

Berries

Freeze-dried berries, particularly blackberries, raspberries, strawberries, and cranberries, have gained interest as a chemopreventive agent. Like green tea, berries contain high concentrations of polyphenols. Additionally, they contain folic acid and antioxidants such as beta carotene and vitamins C and E [Stoner *et al*. 2007]. Diet supplementation with freeze-dried black raspberries results in decreased COX-2 expression in the rat esophagus [Chen *et al*. 2006]. In an open-labeled study, ten patients with nondysplastic BE took daily freeze-dried black raspberries for six months. After a six-month period, there was

a reduction in various urinary markers of oxidative stress [Kresty *et al.* 2006]. The results of tissue analysis from the total study population (target 20) have not yet been reported.

Diet

Various epidemiological studies have examined the associations between dietary patterns and risk of EAC. Two separate population-based case-control studies demonstrated a significantly reduced odds of EAC among individuals with the highest amounts of fruit and vegetable intake [Terry *et al.* 2001; Cheng *et al.* 2000]. However, a large cohort study of over 500,000 patients from Europe (the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST)) found no significant association between fruit (HR 0.84; 95% CI 0.60–1.17) or vegetable (HR 0.72; 95% CI 0.32–1.64) intake and risk of EAC [Gonzalez *et al.* 2006]. A separate cohort study of over 490,000 patients who took part in the NIH-AARP Diet and Health Study reported no association between fruit and vegetable intake and risk of EAC (OR 0.98; 95% CI 0.90–1.08) [Freedman *et al.* 2007].

Studies of fiber consumption on EAC risk are also inconclusive. In a case-control study from Italy, increasing fiber intake was associated with decreased odds of esophageal cancer (all cell types) (trend OR 0.70; 95% CI 0.51–0.96) [Soler *et al.* 2001]. In a randomized controlled trial of 87 patients with BE followed for three years, following a low-fat, high-fiber diet was not associated with any change in tissue expression of Ki-67 and presence of aneuploidy, two markers associated with neoplastic progression in BE [Kristal *et al.* 2005].

Carbonated soft drinks increase acid reflux symptoms such as heartburn [Fass *et al.* 2005]. In a population-based case-control study, increased consumption of carbonated soft drinks was surprisingly associated with a decreased odds of EAC (OR 0.47; 95% CI 0.29–0.76) [Mayne *et al.* 2006]. This effect was largely due to the consumption of diet soft drinks, which in theory may be associated with other healthy habits. A separate population-based case-control study from Sweden found no association between high-carbonated soft drink consumption and odds of EAC (OR 0.89; 95% CI 0.49–1.64) [Lagergren *et al.* 2006].

Antioxidants

Chronic inflammatory states such as reflux esophagitis can result in the generation of free radicals derived from oxygen and nitrogen [Federico *et al.* 2007]. These free radicals can promote carcinogenesis via numerous different means, including direct DNA damage and inhibition of DNA repair mechanisms, inhibition of apoptosis, and activation of cellular proliferation pathways. Antioxidants, such as carotenoids and vitamins C and E, bind with reactive oxygen and nitrogen species to neutralize their damaging effects. In a population-based case-control study from Sweden, both high beta-carotene use (OR 0.5; 95% CI 0.3–0.9) and high overall antioxidant use (OR 0.5; 95% CI 0.3–0.9) were associated with a reduced odds of EAC [Terry *et al.* 2000].

The enzyme superoxide dismutase (SOD) plays an important role in protection against the effects of oxidative stress [Farhadi *et al.* 2002]. Tissue SOD levels are lower in BE than in normal squamous esophageal mucosa. In one study, patients with BE and dysplasia were found to have *increased* levels of tissue SOD compared to nondysplastic BE [Sihvo *et al.* 2002]. A separate study demonstrated decreased SOD expression with more advanced neoplasia in BE [Hermann *et al.* 2005]. Rats fed diets supplemented with manganese-SOD developed significantly fewer EACs as compared to control rats [Martin *et al.* 2007; Piazuelo *et al.* 2005].

Nitric oxide and other reactive nitrogen species are also hypothesized to play a role in the carcinogenic effects of both acid and bile reflux [Clemons *et al.* 2007; Iijima *et al.* 2003]. Thiazolidine-4-carboxylic acid, or thioproline, has been shown to be an effective nitrite-trapping agent [Tsuda and Kurashima, 1991]. In animal models of gastroduodenal reflux, two separate studies reported that significantly fewer rats who received diets enriched with thioproline developed EAC as compared to control rats [Sasaki *et al.* 2007; Kumagai *et al.* 2004]. There are no published studies to date of the use of thioproline for the prevention of neoplastic progression in BE.

Given the experience of the Beta Carotene and Retinol Efficacy Trial, in which subjects who received beta-carotene and vitamin A had an increased risk of lung cancer [Omenn *et al.* 1996], a randomized controlled trial

demonstrating efficacy is mandatory before antioxidant use can be advocated for the prevention of EAC.

Vitamin A

Retinoic acid is excreted in bile, undergoes enterohepatic recirculation, and may therefore be present in significant amounts in gastroduodenal refluxate in the esophagus. Abnormal or decreased retinoic acid activity is thought to play a role in the development of various malignancies [Sun and Lotan, 2002]. A population-based case-control study from the United States reported a reduced odds of EAC in the highest quartile of dietary intake of vitamin A (OR 0.5, $p = 0.05$) [Chen *et al.* 2002]. A recent cross-sectional *in vitro* study demonstrated decreased tissue levels of retinoic acid in BE-associated dysplasia (compared to nondysplastic BE) as well as increasing expression of CYP26A1, a key enzyme involved in retinoic acid metabolism [Chang *et al.* 2007a]. However, there is also evidence suggesting that esophageal exposure to retinoic acid may promote the development of intestinal metaplasia [Chang *et al.* 2007b] and may play a role in neoplastic progression to EAC [Hormi-Carver *et al.* 2007; Lord *et al.* 2001]. Given the conflicting laboratory data and the results of the Beta Carotene and Retinol Efficacy Trial [Omenn *et al.* 1996], vitamin A cannot, at present, be recommended for the prevention of EAC.

Medications

Male sex is an independent risk factor for EAC and may be a significant risk factor for progression in patients with BE, possibly due to the protective effects of exposure to estrogen and progesterone. However, several population-based case-control and cohort studies have failed to demonstrate a significant association between hormone replacement therapy or other forms of estrogen exposure and risk of EAC [Chandanos *et al.* 2006; Lindblad *et al.* 2006; Lagergren and Jansson, 2005; Lagergren and Nyren, 1998].

Angiotensin converting enzyme inhibitors (ACEIs) have anti-inflammatory properties in addition to their blood pressure lowering effects [Ferrario and Strawn, 2006]. A single population-based case control study in the UK showed no significant association between ACEI use and risk of EAC (OR 0.71; 95% CI 0.43–1.17) [Sjoberg *et al.* 2007].

Cost effectiveness of chemoprevention

The utility of chemoprevention of EAC depends on several factors, including efficacy, cost, and safety. At present, endoscopic surveillance of patients with BE is relied upon as the sole means of attempting to improve outcomes in and decrease the disease burden of EAC.

Sonnenberg and Fennerty [2003] performed a cost-effectiveness study of chemoprevention with NSAIDs for EAC. The primary Markov model from these analyses assumed a progression rate of 0.5% per year from BE to EAC and a 50% efficacy for NSAIDs in preventing EAC. The authors concluded that NSAIDs in addition to endoscopic surveillance in BE patients was cost effective, with an incremental cost-effectiveness ratio <$30,000 per life-year saved. One of the limitations of the model was the lack of incorporation of low- and high-grade dysplasia as disease states and their associated shorter endoscopic surveillance intervals.

Hur *et al.* [2004] performed a cost-effectiveness study of chemoprevention with aspirin for patients with BE. The model included the health states of BE with no dysplasia, low-grade, and high-grade dysplasia, with varying surveillance intervals for each one. They found that a combination of aspirin therapy and endoscopic surveillance resulted in both decreased cost as well as increased quality-adjusted life years (QALYs). One of the principal assumptions of the models was that aspirin would also decrease the risk of EAC by 50%. In the sensitivity analyses, the combination strategy was only superior to endoscopic surveillance alone if aspirin reduced the risk of EAC by at least 40%.

Given the relatively low incidence of EAC in patients with BE, any chemopreventive agent needs to be both extremely effective at preventing EAC as well as extremely safe in order to be a cost-effective addition to endoscopic surveillance.

Conclusions

To date, NSAIDs and PPIs are the best-studied potential agents for the prevention of EAC. For several years, PPIs have been prescribed to the large majority of patients who carry a diagnosis

of BE, yet the overall incidence of EAC continues to rise. The protective effects of NSAIDs are consistent in the published epidemiologic studies. It is hoped that the randomized controlled AsPECT trial will provide important answers with regard to the utility of NSAIDs and PPIs for the prevention of EAC. Other agents, such as folic acid, green tea, and black raspberries, are promising candidates but have yet to be rigorously studied in humans. Hopefully, the results of future randomized controlled trials combined with improved risk stratification will result in chemopreventive strategies that will successfully reduce the incidence of and improve overall outcomes in EAC.

Conflict of interest statement

None declared

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