Chemoprevention in Barrett’s esophagus and esophageal adenocarcinoma

Motasem Alkhayyat, Prabhat Kumar, Krishna O. Sanaka and Prashanthi N. Thota

Abstract: There has been a dramatic increase in the incidence of Barrett’s esophagus and esophageal adenocarcinoma over the past several decades with a continued rise expected in the future. Several strategies have been developed for screening and surveillance of patients with Barrett’s esophagus and endoscopic treatment of Barrett’s associated dysplasia and early esophageal cancer; however, they have not made a substantial impact on the incidence of cancer. Herein, chemoprevention becomes an attractive idea for reducing the incidence of cancer in Barrett’s patients. Several agents appear promising in preclinical and observational studies but very few have been evaluated in randomized controlled trials. Strongest evidence to date is available for proton-pump inhibitors and Aspirin that have been evaluated in a large randomized controlled trial. Other agents such as statins, metformin, ursodeoxycholic acid, and dietary supplements have insufficient evidence for chemoprevention in Barrett’s patients.

Keywords: aspirin, Barrett’s esophagus, chemoprevention, esophageal cancer, proton-pump inhibitors

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Introduction
Barrett’s esophagus (BE) is a condition characterized by metaplastic cellular transformation of the normal stratified squamous cell lining of the esophagus into intestinal columnar epithelium. This adaptive change is premalignant and may transform into esophageal adenocarcinoma (EAC) in a stepwise pattern through dysplasia–neoplasia sequence. Gastroesophageal reflux disease (GERD) is the major culprit for the development of BE, the other risk factors being age older than 50 years, male sex, Caucasian race, smoking, obesity, and family history of BE or EAC. The lifetime risk of EAC in BE varies between different studies: In a meta-analysis, Gatenby and colleagues reported a lifetime risk of EAC of one in eight to 14 people and lifetime risk of high-grade dysplasia (HGD)/EAC of one in five to six individuals with BE. In comparison, large population-based cohort studies showed a lower risk: one in 10 to 37 for EAC and one in eight to 20 individuals for HGD/EAC. The incidence of EAC has risen up at a rapid rate in the past three decades despite the success achieved with implementing endoscopic surveillance and advancement of treatment modalities for BE patients. The majority of EAC cases are diagnosed without prior history of BE diagnosis or reflux symptoms and carry an overall poor prognosis due to advanced stage at the time of diagnosis. Hence, BE-EAC is an attractive target for chemoprevention. An effective chemopreventive agent can reduce the risk of development of BE and EAC in general population and lead to longer surveillance intervals in known BE cases. In this review, we examine the current evidence for various agents in chemoprevention of BE and EAC such as proton pump inhibitors (PPI), aspirin and other nonsteroidal inflammatory drugs (NSAIDs), statins, metformin, and other candidate drugs (Table 1).

Proton-pump inhibitors
It is widely accepted that GERD plays a key role in the development of BE and EAC. In BE, ongoing acid reflux can lead to neoplastic progression by increasing proliferation, decreasing apoptosis,
### Table 1. Potential chemopreventive agents for BE and current evidence.

| Agent          | Type of study                      | Clinical effect                                                                 | Study population                        | References                |
|----------------|-----------------------------------|---------------------------------------------------------------------------------|------------------------------------------|---------------------------|
| **PPI**        | Observational [Rетrospective]     | HR for any dysplasia = 0.25 [95% CI = 0.13–0.47], p < 0.0001                   | 236 BE patients in a VA setting.         | El-Serag et al.¹²         |
|                | Observational [Prospective]       | ↑Risk of LGD in patients with delayed [>2 years] PPI use versus PPI use within 1 year [HR = 5.6, 95% CI = 2.0–15.7] | 350 BE patients.                        | Hillman et al.¹³          |
|                | Observational case-control study  | ↑Risk of EAC in patients on PPIs [OR = 2.39; 95% CI = 1.03–5.54].               | 1440 BE patients                        | Hvid-Jensen et al.¹⁴      |
| Meta-analysis  |                                    | ↓Risk of HGD/EAC in patients on PPIs [OR = 0.29; 95% CI = 0.12–0.79]             | 7 studies, 2813 BE patients              | Singh et al.¹⁵            |
|                | Observational case-control study  | ↑Risk of HGD/EAC in patients on PPIs [OR = 1.95; 95% CI = 1.00–3.81]             | 15,143 BE patients [control] versus 57 HGD/EAC cases [cases] | Masclée et al.¹⁴         |
| Meta-analysis  |                                    | No association with HGD/EAC [unadjusted OR = 0.43; 95% CI = 0.17–1.08]           | 9 observational studies, 5712 BE patients | Hu et al.¹⁷              |
| Randomized factorial trial | Esomeprazole 80 mg + aspirin 325 mg showed improved time to composite endpoint of death/HGD/EAC [time ratio = 1.27; 95% CI = 1.01–1.58] | 2557 BE patients                        | Jankowski et al.¹⁸        |
| Aspirin & NSAIDs | Observational study               | ↑COX-2 expression levels in 75% [15/20] NDBE, 83% [10/12] LGD, and 100% [24/24] HGD/EAC cases [p < 0.001] | 56 BE patients                      | Morris et al.¹⁹          |
| Systemic review & Meta-analysis |                                    | ↓EAC risk with aspirin/NSAIDs use [OR = 0.67; CI = 0.51–0.87] | Nine studies, general population | Corley et al.²⁰          |
| Phase IIb randomized placebo-controlled trial | No change in the proportion of biopsy samples with dysplasia or cancer LGD: median change with celecoxib = −0.09, IQR = −0.32 to 0.14, and with placebo = −0.07, IQR = −0.26 to 0.12; p = 0.64 | 222 BE patients with or without any dysplasia | Heath et al.²¹          |
|                | Observational [Prospective]       | ↓Risk of neoplastic progression with non-aspirin NSAIDs [RR = 0.43; 95% CI = 0.22–0.88] | 570 BE patients                        | Kastelein et al.²²        |
| Pooled analysis |                                    | ↓Risk of EAC with aspirin use >10 years [OR = 0.36, 95% CI = 0.18–0.71; p < 0.003] | Eight trials, 25,570 patients on aspirin evaluated for cancer mortality | Rothwell et al.²³        |
| Double-blind, placebo-controlled, phase 2 clinical trial | ↓PGE2 levels with esomeprazole [80 mg] + aspirin [81 mg/325 mg] in patients with BE with no dysplasia or LGD | 114 BE patients with no dysplasia or LGD | Falk et al.²⁴           |
| Meta-analysis  |                                    | ↓EAC risk with COX inhibitors [OR = 0.59; 95% CI = 0.45–0.77]                   | 11 studies, total of 317 EAC patients and 1999 BE controls | Beales et al.²⁵          |
| Meta-analysis  |                                    | ↓Risk of HGD/EAC with use of aspirin [RR = 0.64; 95% CI = 0.53–0.77] and NSAIDs [RR = 0.50; CI = 0.32–0.78] in BE patients | Nine studies, 5446 BE patients           | Zhang et al.²⁶           |
| Case-control study |                                    | ↓Risk of BE with regular aspirin/NSAIDs [OR = 0.59; 95% CI = 0.39–0.87] | 320 patients newly diagnosed BE patients [cohort] versus 317 without BE [controls] | Schneider et al.²⁷       |
| Prospective cohort study |                                    | ↓Risk of BE in women who used aspirin [OR = 0.85; CI = 0.72–0.99] | Of 27,881 women followed over 18 years, 667 women developed BE | Jovani et al.²⁸          |

(continued)
| Agent                  | Type of study                  | Clinical effect                                                                 | Study population                                                                 | References                                                                 |
|------------------------|--------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Metformin              | Randomized phase 2 trial       | ↑Antioxidant expression preventing toxic bile acids from causing DNA damage and NF-κB activation in Barrett's tissue (p < 0.05) | 74 subjects with BE [52/74 (70%) with BE > 2 cm] | Loomans-Kropp et al. [31]                                                 |
| UDCA                   | Nonrandomized trial            | ↑Antioxidant expression preventing toxic bile acids from causing DNA damage and NF-κB activation in Barrett's tissue (p < 0.05) | 74 subjects with BE [52/74 (70%) with BE > 2 cm] | Loomans-Kropp et al. [31]                                                 |
| Green tea and phenols  | Phase 1b (double-blinded) placebo-controlled trial | ↑Catechin epigallocatechin-3-gallate (EGCG) in the esophagus | 44 BE patients enrolled, 11 received placebo, and 33 received Poly E | Joe et al. [38] |
| Omega 3-PUFA           | Randomized control trial       | ↓COX-2 concentrations in Barrett's tissue but no change in inflammatory cytokines | 52 BE patients | Valenzano et al. [41] |
| Zinc                   | Phase 1 pilot study            | ↑Apoptosis, ↑Tumor suppressor mRNAs, ↓Inflammatory state and ↓Epithelial-to-mesenchymal transition signaling in the cells | 10 BE patients | Valenzano et al. [41] |
| BE                     | Barrett's esophagus            | ↑8 expression and ↓NF-κB in Barrett's tissue as compared with the gastric tissue (p < 0.001) | 18 BE patients with LGD or no dysplasia. | Cummings et al. [37] |
| Folate                 | Meta-analysis                  | ↓Risk of EAC with higher dietary folate intake (OR = 0.50; CI = 0.39–0.65) | Six studies, general population | Zhao et al. [36] |
| Vitamin D              | Meta-analysis                  | ↓Risk of EAC with higher dietary folate intake (OR = 0.623; CI = 0.519–0.748). | Seven studies, general population | Thomas et al. [30] |
| UDCA                   | Nonrandomized trial            | ↑Catechin epigallocatechin-3-gallate (EGCG) in the esophagus | 44 BE patients enrolled, 11 received placebo, and 33 received Poly E | Joe et al. [38] |
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production of reactive oxygen species (ROS), DNA damage, and stimulating esophageal production of proinflammatory and proproliferative cytokines. Several studies demonstrated a greater frequency of pathological esophageal acid exposure among patients with BE compared with those with erosive esophagitis. PPIs, through acid-suppressive effects and by modulation of antioxidant and proinflammatory cytokine production, may potentially reduce carcinogenesis. 

While data regarding the effect of PPIs on the risk of developing BE among patients with GERD are scant, multiple studies investigated the impact of PPIs on the risk of BE progression and EAC development. Different reports, including one double-blinded randomized controlled trial (RCT), showed a decrease in the length of BE segment and appearance of squamous islands within the BE segment during prolonged PPI therapy. Complete regression, however, is rare to occur even among those who received long-term PPIs therapy. 

A growing body of evidence suggests that PPI use is associated with a lower risk of progression to HGD/EAC among patients with established BE. In a large meta-analysis of seven observational studies with a total of 2813 BE patients, PPI use was associated with a 71% reduction in the risk of HGD/EAC [adjusted odds ratio (OR) = 0.29; 95% confidence interval (CI) = 0.12–0.79]. There was a trend toward a dose–response relationship with PPI use for more than 2 to 3 years being more protective against EAC or HGD compared with a shorter duration of use; however, results were not statistically significant [three studies; PPIs use > 2–3 years versus < 2–3 years: OR = 0.45 (95% CI = 0.19–1.06) versus 1.09 (95% CI = 0.47–2.56)]. The strongest evidence for chemopreventive effect of PPIs comes from a well-conducted, randomized, multicenter, 2 × 2 factorial design, AspECT trial that enrolled a large sample size with long-term follow-up. The study enrolled 2557 patients with BE with confirmed intestinal metaplasia, and patients were followed up for a median of 8.9 years with almost complete data collection (99.9%). Using accelerated failure time (AFT) model, whereby a time ratio of greater than 1 indicates that the treatment prolonged the time to an event, the trial demonstrated that high-dose PPIs were superior to low-dose PPIs in the primary composite endpoint of time to mortality or development of HGD or EAC (time ratio = 1.27; 95% CI = 1.01–1.58). In fact, the use of high-dose esomeprazole (80 mg) combined with aspirin provided the most benefit, suggesting an additive effect of the two medications (time ratio = 1.59; 95% CI = 1.14–2.23). On Cox proportional hazards modeling, a 21% and 20% reduction in the composite endpoint were seen with high PPI versus low PPI and aspirin versus no aspirin, respectively. The more substantial reduction seen in observational studies may be due to the bias or confounding inherent to observational studies. Despite the presence of some limitations such as being nonblinded, predominantly White population, limited female enrollment, and using AFT that assumes constant effect of covariates over time, the AspECT trial provides evidence that the use of PPI can reduce progression in BE.

An interesting fact is that long-term PPI use leads to an increase in gastrin levels. Gastrin can increase BE cell survival and lead to cyclooxygenase (COX)-2 expression facilitating carcinogenesis. A case-control study of 1440 patients with BE from Denmark demonstrated an increased risk of EAC in patients on PPIs (OR = 2.39; 95% CI = 1.03–5.54). Another study from the United Kingdom observed an increased risk of HGD/EAC in BE patients using PPIs (OR = 1.95; 95% CI = 1.00–3.81). A follow-up meta-analysis that included these two studies, however, showed results that are leaning toward a chemopreventive effect of PPI but were statistically insignificant. A concern with PPIs is the purported elevated risk of osteoporosis, dementia, cardiovascular events, and renal insufficiency. A recent randomized trial has disputed previously reported associations between PPIs use and a variety of adverse events in observational studies. The study included nearly 18,000 patients, who were followed up over 3 years and showed no associations between PPI therapy and nearly all safety outcomes except for a slightly increased risk of enteric infections (1.4% with pantoprazole versus 1.0% with placebo).

Overall, given the suggested evidence of chemopreventive effect by PPIs and the favorable risk profile of these medications, American College of Gastroenterology current practice guidelines recommend once-daily PPIs therapy for patients with BE even if they are not experiencing GERD symptoms. Twice-daily PPI use is recommended for
poor control of reflux symptoms or esophagitis. Based on AspECT trial findings, however, the risks and benefits of increasing PPI to twice daily and adding Aspirin should be discussed with the patients even if they do not have symptoms.

**Aspirin and NSAIDs**

Over the last few decades, there has been a growing body of evidence on the use of aspirin and NSAIDs for cancer prevention as multiple studies have demonstrated a reduced risk of several gastrointestinal cancers with their use.\(^{23}\) Their chemopreventive effects are mediated through inhibition of COX pathways although COX-independent pathways have also been reported. The expression levels of COX-2 increase along the esophageal inflammation–metaplasia–dysplasia carcinoma sequence.\(^{19}\) Esophageal acid and bile exposure leads to production of inflammatory cytokines such as interleukin-1 and tumor necrosis factor, which subsequently increases COX-2 expression.\(^{50,51}\) Increased COX expression facilitates multiple steps in carcinogenesis, controlling cell cycle, angiogenesis, and apoptosis.\(^{19}\) COX-2 induction is associated with an increased production of prostaglandin E2 (PGE2), which modulates cell proliferation, cell death, and tumor invasion in many types of cancer.\(^{52}\) The COX-2 upregulation increases BE and EAC cell proliferation by induction of retinoblastoma tumor suppressor protein phosphorylation and upregulation of cyclins, cyclin-dependent kinases, and p53 LOH.\(^{53,54}\) The COX-2 can also regulate the expression of angiogenic factors, especially vascular endothelial growth factor mainly through a MAPK (mitogen-activated protein kinase)–dependent pathway.\(^{55}\)

In addition to binding to COX enzymes, aspirin, but not non-aspirin NSAIDs, blocks phosphorylation of IkB, which is a crucial step in NF-kB activation and expression of caudal-related homeobox transcription factor 2, which plays a key role in BE development.\(^{36}\) NSAIDs such as sulindac and its analogues have been shown to inhibit Akt pathway, an important mediator of cell proliferation and apoptosis in HCT116 and other cancer cell lines at supratherapeutic doses.\(^{57}\) NSAIDs can also activate the extrinsic apoptotic pathway by modulating the sensitivity of several tumor cells to Fas and tumor necrosis factor–related apoptosis-inducing ligand.\(^{58}\) Finally, NSAIDs are able to decrease intracellular content of glutathione that can lead to free radical damage in tumor cells.\(^{59}\)

**Evidence for prevention of BE in general population**

There are few studies that have evaluated the effect of aspirin and NSAIDs on the development of BE with a preponderance suggesting protective effect. In the Nurses’ Health study, 667 patients developed BE among 27,881 women over 18 years of follow-up.\(^{28}\) Using multivariate analysis, women who regularly used aspirin had a lower risk of BE (OR=0.85; CI=0.72–0.99). Similar results were demonstrated in a case-control study where patients on regular aspirin had lower risk of BE especially among persons with GERD symptoms.\(^{27}\) In contrast, no beneficial effect was noted in a six-center pooled analysis where 1474 patients with BE were compared with two control groups: 2256 population-based controls and 2018 GERD controls (adjusted OR=1.00; 95% CI=0.76–1.32).\(^{60}\)

**Evidence for prevention of EAC in BE**

Studies evaluating the risk of EAC among BE exposed to aspirin also showed overall promising results in chemoprevention. In a meta-analysis published in 2014 evaluating nine large observational studies including 5446 patients with BE, aspirin use reduced the risk of HGD/EAC by 37% [relative risk (RR) = 0.63; CI = 0.43–0.94] and NSAIDS by 50% (RR = 0.50; CI = 0.32–0.78).\(^{26}\) A subsequent observational study of 15,134 patients with BE from the United Kingdom and Netherlands evaluating the risk of EAC, however, showed an adjusted risk of 1.3 (CI = 0.6–2.5) for NSAID use and 0.9 (CI = 0.4–1.8) for low-dose Aspirin use.\(^{16}\)

A combination of NSAIDs with other medications may induce synergism. For instance, in a prospective trial in patients with BE, a combination of esomeprazole and 325 mg dose of aspirin significantly reduced the levels of PGE2 concentrations in patients with BE.\(^{24}\) This was also demonstrated in the AspECT trial, where a high-dose esomeprazole (40 mg twice daily) combined with aspirin (300–325 mg) provided the most benefit, suggesting an additive effect of the two medications when combined together to decrease the primary composite endpoint (all-cause mortality, EAC, or HGD) in a dose–response relationship.\(^{18}\) Also, a combination of statins with COX-2
inhibitors is associated with lower EAC incidence of EAC in a meta-analysis of observational studies (OR = 0.26; CI = 0.1–0.68).25

Evidence for prevention of EAC in the general population

Multiple studies showed a chemopreventive effect of aspirin intake in EAC in the general population. A meta-analysis by Corley and colleagues20 included a total of nine (two cohort, seven case-control) studies with a total of 1813 patients with esophageal cancer. Pooled analysis showed that the use of aspirin and NSAIDS was protective against EAC (OR = 0.67; CI = 0.51–0.87). When stratified, aspirin use was protective (OR = 0.5; CI = 0.38–0.66) and NSAIDS had a borderline protective effect (OR = 0.75; CI = 0.54–1.0). In a recent meta-analysis of all observational studies on aspirin and cancers of the digestive tract sites, there was a 40% risk reduction with regular aspirin use (RR = 0.61; CI = 0.49–0.77, 10 studies).61 The evidence has been further corroborated by data extracted from RCTs for the primary and secondary prevention of vascular events.23,62,63 Results of the pooled analyses from eight trials evaluating the long-term cancer mortality of patients taking aspirin for prevention of vascular events found that aspirin use for more than 10 years significantly decreased the risk of EAC (OR = 0.36; CI = 0.18–0.71; p = 0.003) in 10 to 20 years of follow-up.23

The evidence for use of non-aspirin NSAIDs is weak: A prospective Dutch study of 570 patients with BE showed a 57% reduction in neoplastic progression with non-aspirin NSAIDS (RR = 0.43; CI = 0.22–0.88).22 In contrast, other studies show a lack of effect with NSAIDS. In a questionnaire-based, large prospective study (n = 311,115 individuals) followed for 7 years, there was no significant association between the use of NSAIDs and risk of EAC.24 An RCT of 100 patients with BE and low-grade dysplasia (LGD) or HGD using 200 mg of celecoxib twice daily for 48 weeks showed that celecoxib did not prevent malignant progression of BE.21 In addition, there was no difference compared with placebo group in terms of BE surface area, prostaglandin levels, mRNA level of COX enzymes, or methylation of tumor suppressor genes. This suggests a lesser role of chemoprevention by non-aspirin NSAIDs among the general population.

One major concern about using aspirin and NSAIDS is the potential formation of gastric ulcers and risk of hemorrhagic stroke. In a large-scale study including 19,114 patients to evaluate the safety of taking 100 mg daily aspirin in healthy elderly (above 70 years old), investigators found a slightly increased risk of major hemorrhage compared with placebo group (8.6 versus 6.2 per 1000 persons, respectively).65 When combined with acid-suppressing medication (PPI), however, the risk of gastrointestinal bleeding decreases. In the AspECT trial, only 1% of participants had a serious adverse event relating to aspirin use despite using high-dose aspirin (300–325 mg), which could be lower if low-dose aspirin was used.18 In case of selective COX-2 inhibitors, although there is less risk of gastrointestinal ulceration and bleeding, there is a slightly increased the risk of cardiovascular events and nephrotoxicity.66

In summary, with the current available evidence on chemoprevention and an overall great safety profile with concomitant use of PPI, aspirin use can be recommended to decrease the risk of progression of BE and incidence of EAC.

Statins

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, more commonly called as statins, have been shown to exert immunomodulatory, anti-inflammatory, anti-angiogenic, and antiproliferative functions by inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR), the rate-limiting enzyme of the mevalonate pathway that is involved in proliferation, apoptosis, and modulation of cell signaling.67 A cell study found that in OE33 and BIC-1 EAC lines, simvastatin, lovastatin, and pravastatin all reduced the number of cancerous cells by around 30% and inhibited their proliferation.68 Clinical studies also have shown a great chemopreventive promise. A nested case-control study found that a group of patients with BE who had taken a statin had a 35% lower risk of developing EAC than the group that had no statin prescriptions, even when adjusting for confounding variables.29 In a recent case-control study based on SEER-Medicare database, there was an 85% reduced risk of EAC with use of statins (OR = 0.15; CI = 0.13–0.17) in the general population and a similar risk reduction in BE population with statin use (OR = 0.13; CI = 0.08–0.21).31 A meta-analysis published in 2017 showed a 40% risk reduction of EAC
with statin use in patients with BE (OR = 0.59; CI = 0.50–0.68), as well as in the general population (OR = 0.57; CI = 0.43–0.76). There was also a tendency for a dose- and duration-dependent decrease in the cancer incidence with long-term statin use. Given that statins have been effective in preventing EAC development in both cell lines and humans, they merit further research and use as viable options to prevent carcinogenesis in patients with BE.

**Metformin**

Metformin is a widely used antidiabetic agent that improves insulin sensitivity and peripheral glucose utilization. The reduced incidence of cancers in diabetic patients on metformin has highlighted its role in chemoprevention of many cancers. Metformin activates adenosine monophosphate (AMP)-activated protein kinase (AMPK). This increases insulin-dependent glucose uptake into cells and inhibits mTOR via TSC2/1, resulting in the downregulation of ribosomal protein S6 kinase (S6K1) that leads to a decrease in protein synthesis and cell proliferation. Metformin also has AMPK-independent, indirect antiproliferative effects that are related to lower systemic levels of insulin and insulin resistance. Non-AMPK-dependent protective pathways include reduction of insulin, insulin-like growth factor-1, leptin, inflammatory pathways, and potentiation of adiponectin, all of which may have a role in tumorigenesis. Observational studies on metformin and EAC in BE, however, have shown no effect. In an SEER database study, the use of metformin had a 24% reduced risk of EAC (OR = 0.76; CI = 0.62–0.93) among the total study population. Among individuals with BE, however, there was no observed association between metformin use and EAC risk (metformin: OR = 0.85; CI = 0.39–1.84). In a randomized phase 2 trial of 74 patients with BE, metformin 2000 mg per day was given for a total of 12 weeks. The percent change in the median level of pS6 K1 did not differ significantly between the trial and placebo groups. Hence, there is no evidence to support the use of metformin in BE patients for chemoprevention.

**Potential chemopreventive agents in BE:**

Several dietary supplements and medications have been reported to be beneficial for prevention of EAC in patients with BE. The evidence comes from observational studies or small clinical trials and hence does not support clinical implementation at this time. Some of the promising agents are discussed next.

**Ursodeoxycholic acid**

Carcinogenesis in BE is associated with oxidative DNA damage from hydrophobic bile acids such as deoxycholic acid. The ursodeoxycholic acid (UDCA) is a naturally occurring competitive inhibitor of deoxycholic acid and has been shown to prevent DNA damage and NF-κB activation caused by toxic bile acids in BE epithelial cells. In fact, in an animal study of mice fed a UDCA-containing diet for 40 weeks, the incidence rates of BE and EAC were 20% and 10%, respectively, as opposed to incidence rates of 60% for both conditions in a control group. The chemopreventive role of UDCA in humans may be somewhat more complicated. In a clinical study of 29 patients with BE, UDCA given at a daily dose of 13 to 15 mg/kg/day for 6 months, favorable changes in gastric bile acid composition were observed but markers for oxidative DNA damage (8-hydroxydeoxyguanosine, 8OHdG), cell proliferation (Ki67), and apoptosis (cleaved caspase-3) were not reduced in BE. Clearly, additional research is required to determine whether treatment with UDCA is a viable chemopreventive option against EAC in patients with BE.

**Folate**

Folate deficiency is thought to increase the risk of cancer via mediation by p53 tumor suppressor gene or by decreasing intracellular S-adenosylmethionine that inhibits cytosine methylation in DNA, activating proto-oncogenes, inducing malignant transformations, causing DNA precursor imbalances, misincorporating uracil into DNA, and promoting chromosome breakage. There are several observational studies but no RCTs to evaluate folate levels or supplementation in protection against EAC. In a meta-analysis, individuals in the highest folate intake category were at half the risk of developing EAC compared with those in the lowest category (OR = 0.50; CI = 0.39–0.65). In a more recent meta-analysis, higher folate intake was associated with a 38% reduced risk of EAC.

**Vitamin D**

Calcitriol, the biologically active metabolite of Vitamin D, is an attractive chemopreventive agent due to its anticarcinogenic properties, that is,
apoptosis, differentiation, antiproliferation, and angiogenesis inhibition. In a meta-analysis of several observational studies, higher levels of serum vitamin D was associated with an increased risk of cancer (EAC or squamous cell cancer, OR = 1.39; CI = 1.04–1.74), with the majority of participants coming from China; however, no significant increased risk for EAC (OR = 1.45; CI = 0.65–2.24) was found. No association was observed between vitamin D intake and risk of cancer overall (OR = 1.03; CI = 0.65–1.42). In an only trial in BE patients, vitamin D supplementation failed to show any changes in the tumor suppressor 15-hydroxyprostaglandin dehydrogenase gene expression. Large-scale prospective studies with accurate measurement of vitamin D status are needed before chemoprevention with vitamin D is recommended, as current evidence does not support a chemopreventive role of vitamin D against EAC.

**Green tea and polyphenols**

Over the past decade, an array of epidemiological research studies has been done, establishing the anti-cancer activity of different green tea–derived compounds rich in catechins like epigallocatechin-3-gallate (EGCG). Various laboratory studies suggest that green tea polyphenols play a role in slowing down cell proliferation and induce apoptosis. Green tea plays a role in activating detoxifying enzymes such as quinone reductase, ornithine decarboxylase, and glutathione S transferase that are shown to have a preventive role against tumor development. A phase 1b clinical trial of 44 patients with BE treated with green tea–derived polyphenon E over 6 months demonstrated a clinically significant accumulation of the catechin EGCG in the esophagus.

**Curcumin**

Curcumin, the active ingredient of Asian spice turmeric, exhibits anti-inflammatory, antioxidant, antiapoptotic, antitumor, and antimetastatic activities and suppresses multiple signaling pathways responsible for inflammation, apoptosis, and cellular death. It appears to have a beneficial effect by preventing NF-κB activity induced by bile in esophageal cell lines. In a pilot study of patients with BE supplemented with 500 mg curcumin tablet for 7 days showed a doubling in the apoptotic frequency compared with non-supplemented control patients. A major downside is the poor availability of curcumin; hence, different types of formulations have been designed for improving the bio-availability of curcumin such as nano curcumin, asymmetric curcuminoid analogues, curcumin analog P1, EF31, and C-5.

**Omega 3-polyunsaturated fatty acids**

There is an upregulation of COX pathway in BE and EAC; omega 3-polyunsaturated fatty acids (PUFA) compete with arachidonic acid and lead to reduced COX-mediated inflammation. In an RCT of 52 patients with BE treated for 6 months with eicosapentaenoic acid, there was a decline in COX-2 protein concentrations but no significant difference in the change in inflammatory cytokines, PGE2 and leukotriene B4, or cellular proliferation.

**Zinc**

Zinc is an essential mineral that is integral to many enzymes and transcription factors that regulate key cellular functions such as DNA damage signaling and repair, replicative enzymes such as DNA and RNA polymerases, and transcription factors such as tumor protein p53. Therefore, a zinc deficiency can lead to loss of DNA integrity and increased cancer risk. There has been extensive work on the chemopreventive action of zinc in esophageal cancer in rodent models; however, those studies were mainly in squamous cell cancer not in adenocarcinoma. In a pilot placebo-controlled trial of 10 BE patients, oral zinc supplementation for 2 weeks showed increased apoptosis, upregulation of tumor suppressor mRNAs, a decreased inflammatory state, and decreased epithelial-to-mesenchymal transition signaling in the cells.

**Post-ablation chemoprevention in patients with BE**

According to the current guidelines, endoscopic eradication therapy (EET) is recommended for BE patients with confirmed dysplasia. After successful EET, the rate of recurrence of intestinal metaplasia is reported in up to 20–32% with an annual rate of ~5%/year. Although these recurrent metaplasia/dysplasia patients responded well to the repeat EET, and very few showed progression, this is a potential cause of concern. Post ablation chemoprevention can play a role in preventing these recurrences. Currently, lifelong PPI
therapy is recommended after successful EET although evidence is low. A prospective randomized phase II trial of 23 patients focusing on the role of aspirin in preventing recurrence after successful EET was recently completed. The CDX2 mRNA levels in esophageal mucosa in trial group (taking aspirin) were compared with the placebo group. The results are yet to be reported (NCT02521285).

**Conclusion**

To date, PPIs, aspirin, and NSAIDs are the most studied and most promising potential chemoprotective agents for the prevention of BE and EAC. Aspirin appears to have beneficial effect in both general population and BE patients while PPIs appear to be effective in BE patients only. Although PPIs have been prescribed for decades for patients with BE, the overall incidence of EAC continues to rise. The AspECT trial showed decrease in the composite endpoint of HGD/EAC and mortality with high-dose aspirin and PPI with no significant increase in adverse events; therefore, this combination should be discussed in patients with BE. The chemoprotective effects of NSAIDs are generally consistent in the available epidemiologic studies, yet their clinical utility is still under investigation given their high risk of adverse events. Other agents, such as metformin, statin, and nutritional supplements, including folic acid, green tea, and vitamin D, are promising candidates but have yet to be rigorously studied in clinical trials. In the future, any chemopreventive efforts should be tailored to individual patient risk profile with potential benefits outweighing the risks. Several of these agents have beneficial role not only in prevention of multiple cancers but also in chronic diseases such as cardiovascular disease, stroke, diabetes, and dementia. Creation of comprehensive risk prediction models incorporating genetic and acquired factors will help in identifying patients who will benefit the most from these agents. Future RCTs regarding the utility of different potential agents in preventing multiple cancers and other chronic diseases can provide guidance on implementation of public health strategies in a cost-effective manner.

**Author contributions**

All authors have contributed to designing the study, collecting the data, and drafting the manuscript. All authors approved the final version of the manuscript.

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**ORCID iD**

Prashanthi N. Thota  
https://orcid.org/0000-0001-7179-4774

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