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Review

Cancer Prevention Research

Opportunities for Preventing Esophageal Adenocarcinoma

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Abstract

Esophageal adenocarcinoma (EAC) is rapidly increasing in incidence in many Western societies, requires demanding treatment, and is associated with a poor prognosis, therefore preventive measures are highly warranted. To assess the opportunities for prevention, we reviewed the available literature and identified seven main potentially preventive targets. Preventive effects were found on the basis of medium-level observational evidence following treatment of gastroesophageal reflux disease (using both medication and surgery) and tobacco smoking cessation, which should be clinically recommended among exposed patients. Nonsteroidal anti-inflammatory drugs appear to prevent EAC, and the limited existing data also indicate a protective effect of medication with statins or hormone replacement therapy in women, but current evidence is insufficient to guide clinical decision-making regarding these drugs. The evidence is presently insufficient to assess the potentially preventive role of weight loss. Whether avoidance of eradication of *Helicobacter pylori* prevents EAC is not studied, but there is no evidence that such eradication increases symptoms of gastroesophageal reflux or prevalence of erosive esophagitis. The introduction of preventive actions should be tailored toward high-risk individuals, that is, older men with obesity and gastroesophageal reflux disease and individuals with Barrett esophagus rather than the population at large. *Cancer Prev Res; 9(11); 828–34. ©2016 AACR.*

Introduction

Esophageal cancer is the eighth most common cancer and the sixth most deadly cancer worldwide (1). There are 2 major histologic types of esophageal cancer, adenocarcinoma and squamous cell carcinoma (SCC). SCC is most common worldwide, whereas esophageal adenocarcinoma (EAC) is more common in the Western world, especially among white men (1–3). While the incidence of SCC is decreasing, EAC is characterized by a rapidly increasing incidence among white populations in high-income countries (3). The increase seems to have begun in the early 1970s, and in the United States, the annual incidence increased from 0.40 cases per 100,000 individuals in 1975, to 2.58 per 100,000 in 2009 (4, 5). Changes in prevalence of the main etiologic factors, that is, gastroesophageal reflux, obesity and infection with *Helicobacter pylori*, have most likely contributed to the increase (2). Potentially, curatively intended treatment of EAC requires demanding and extensive surgery, often followed by severe postoperative complications, including mortality and severe deterioration in health-related quality of life (2). Despite recent advances in detection and treatment of EAC, the overall prognosis remains poor, with a 5-year overall survival rate of approximately 15%. The 5-year survival rate following curatively intended treatment varies greatly (range, 24%–55%) in Western societies, a variation that at least partly depends on differences in selection of patients for surgery (6–8). The rapidly increasing incidence, demanding treatment and poor prognosis highlight the need for preventive measures, especially among high-risk individuals. Such high-risk groups might be those with a combination of risk factors of EAC or those with the premalignant condition Barrett esophagus, a specialized columnar metaplasia replacing the native squamous epithelium of the distal esophagus in response to chronic gastroesophageal reflux (9). We conducted a review assessing potential targets for preventing EAC.

Search criteria

The literature search to identify relevant studies assessing factors that might prevent EAC was conducted using PubMed, Web of Science, and the Cochrane library. The search strings were combinations of different exposures and EAC, with the primary aim of identifying relevant systematic reviews meta-analyses, and secondarily original studies. Because of the rare incidence of EAC, studies including high-grade dysplasia were also included, although there is a risk of interobserver variation regarding high-grade dysplasia (10, 11). We only included studies of human subjects and excluded case reports and publications in other languages than English. Backward and forward citation tracking was conducted to further identify relevant literature. The best level of evidence regarding each of these factors was rated according to the Oxford Centre for Evidence-based Medicine's level of evidence, where the level of evidence is graded as: 1 [randomized controlled trials (RCT)], 2 (cohort studies), 3 (case–control studies), 4 (case series), and 5 (expert opinions); grades 1 to 3 are further denoted as (a) systematic review or (b) individual study (12). Furthermore, the recommendations were assessed according to the Oxford Centre for Evidence-based Medicine's grades of recommendations, graded as: A (consistent level 1 studies),

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Table 1. Associations between the 7 preventive targets and risk of EAC, evidence of preventive effects, and the level of evidence according to the Oxford Centre for Evidence-based Medicine

Etiologic factor	Risk of EAC	Preventive measure	Best available evidence	Prevention of EAC	Level of evidence[a]
Gastroesophageal reflux disease	Weekly symptoms: OR, 4.92; 95% CI, 3.90–6.22 (15)	Medication with PPI	M-A of patients with BE	PPI vs. no PPI: OR, 0.29; 95% CI, 0.12–0.79 (20)	3a
	Daily symptoms: OR, 7.40; 95% CI, 4.94–11.1 (15)	Anti-reflux surgery	M-A of patients with BE	Antireflux surgery vs. medication: IRR, 0.46; 95% CI, 0.20–1.08 (23)	2a
Obesity	BMI 25–30: RR, 1.71; 95% CI, 1.50–1.96 (25) BMI $\geq$ 30: RR, 2.34; 95% CI, 1.95–2.81 (25) BMI $\geq$ 40: OR, 3.65; 95% CI, 2.50–5.34 (26)	Weight loss by obesity surgery	Not sufficient data		
Tobacco smoking	Ever vs. never: OR, 2.08; 95% CI, 1.83–2.37 (34)	Tobacco smoking cessation	Pooled analysis of 10 studies	Tobacco smoking cessation < 10 y: OR, 0.82; 95% CI, 0.60–1.13 (34)	3b
				Tobacco smoking cessation $\geq$ 10 y: OR, 0.71; 95% CI, 0.56–0.89 (34)	3b
H. pylori infection	Current infection: OR, 0.52; 95% CI, 0.37–0.73, (41) and OR, 0.59; 95% CI, 0.51–0.68 (42)	*H. pylori* eradication	M-A of eradication and risk of GERD and erosive esophagitis	Eradication and risk of erosive GERD: OR, 1.17; 95 % CI, 0.94–1.45 (43) Eradication and risk of GERD: OR, 0.84; 95% CI, 0.60–1.18 (44) Eradication and risk of erosive esophagitis: OR, 0.97; 95% CI, 0.72–1.31 (44)	2a
HRT		Medication with HRT	M-A of women receiving HRT	Ever vs. never: OR, 0.75; 95% CI, 0.58–0.98 (50)	3a
NSAIDs		Medication with NSAID	Pooled analysis of 6 studies	Daily vs. never: OR, 0.56; 95% CI, 0.43–0.73 (57)	3b
				Occasional vs. never: OR, 0.66; 95% CI, 0.44–1.00 (57)	3b
			M-A of 8 RCTs 20-year follow-up	Daily vs. placebo: HR, 0.36; 95% CI, 0.21–0.63 (58)	1a
Statins		Medication with statins	M-A of patients with BE	Users vs. nonusers: OR, 0.59; 95% CI, 0.45–0.78 (61)	3a
			M-A of patients irrespective of BE	Users vs. nonusers: OR, 0.72; 95% CI, 0.60–0.86 (61)	3a

Abbreviations: BE, Barrett esophagus; M-A, meta-analysis; RR, Rate ratio.

[a]Level of Evidence according to the Oxford Centre for Evidence-based Medicine's levels of evidence; the level of evidence is graded: 1 (RCTs), 2 (cohort studies), 3 (case–control studies), 4 (case series), and 5 (expert opinions); grades 1 to 3 are also denoted as a (systematic review) or b (individual study). Refer to ref. 12.

B (consistent level 2 or 3 studies or extrapolations from level 1 studies), C (level 4 studies or extrapolations from level 2 or 3 studies), and D (level 5 evidence of troublingly inconsistent or inconclusive studies of any level; ref. 12).

Seven potentially preventive measures

The literature search identified 7 factors of particular relevance for prevention: (i) treatment of gastroesophageal reflux, (ii) weight loss among obese individuals, (iii) tobacco smoking cessation, (iv) avoidance of eradication of *H. pylori*-infection, (v) hormone replacement therapy (HRT), (vi) use of nonsteroidal anti-inflammatory drugs (NSAID), and (vii) use of statins. The results of the literature search and evidence grade regarding each of the 7 factors are summarized in Table 1. We indicate population-based studies for studies employing this sampling frame, whereas the rest were non–population-based.

Treatment of gastroesophageal reflux

Gastroesophageal reflux disease (GERD) is a common condition with a reported prevalence ranging from 10% to 20% in most Western societies. GERD is also the main risk factor for EAC, an association established in the late 1990s (13, 14). A recent meta-analysis (including 5 population-based case–control studies) found that the OR of EAC was nearly 5 times higher among individuals experiencing weekly reflux symptoms (heartburn or acid regurgitation) than those with less frequent or no such symptoms [OR, 4.92; 95% confidence interval (CI), 3.90–6.22] and more than 7-fold increased for individuals experiencing daily reflux symptoms (OR, 7.40; 95% CI, 4.94–11.1; ref. 15). GERD can be treated medically, typically using proton-pump inhibitors (PPI), or surgically, with fundoplication. PPIs are generally considered to be the first line of treatment, whereas surgery is mainly an option if inadequate response is achieved from adequate doses of PPI or when treatment is believed to be ongoing for a long time, particularly in younger individuals (16). Studies have shown that long-term use of PPI increases the serum levels of gastrin, which in turn is believed to promote cell survival in the gastrointestinal tract and might facilitate carcinogenesis from Barrett esophagus, and it is debated whether this in a long-term clinical setting could increase the risk of EAC (17–19). Most earlier studies have failed to show reduction in risk of EAC following PPI use but rather indicated an increased risk. However, these results are debated, as they might be due to confounding by the severity of GERD, that is, those with severe GERD, who have the highest risk of EAC, are

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more likely to be prescribed PPIs than those with mild reflux. A recent meta-analysis (including 4 hospital-based cohort studies, 1 population-based cohort study, and 2 case–control studies) concluded that there was a decreased risk of EAC or high-grade dysplasia among patients with Barrett esophagus who used PPIs compared with non-users (OR, 0.29; 95% CI, 0.12–0.79; ref. 20). On the other hand, a recent Danish population–based case–control study assessing the risk of EAC following PPI treatment found an increased risk of high-grade dysplasia or EAC following treatment with PPIs, with a relative risk of 2.2 (95% CI, 0.7–6.7) and 3.4 (95% CI, 1.1–10.5) among long-term low- and high-adherence users, respectively (21). However, also, after combining this Danish study with the results from the previous meta-analysis (20), a protective effect of PPIs on EAC remained (22).

Fundoplication is generally performed laparoscopically, where the fundus of the stomach is wrapped completely or partially around the lower part of the esophagus. Because individuals eligible for fundoplication tend to have particularly severe GERD or GERD that did not respond satisfactorily to PPIs, a valid comparison with untreated patients is usually not feasible. Yet, a recent meta-analysis (including 10 cohort studies, of which 2 were population-based, and 2 RCTs) comparing patients undergoing fundoplication with medically treated patients indicated a nonsignificantly decreased pooled incidence rate ratio (IRR) of EAC in favor of surgery (IRR, 0.76; 95% CI, 0.42–1.39), and the risk estimate further decreased but remained nonsignificant in analyses restricted to patients with Barrett esophagus (IRR, 0.46; 95% CI, 0.20–1.08; ref. 23). In an analysis restricted to studies published after the year 2000, when the surgically treated patients typically underwent laparoscopic fundoplication, the IRR was statistically significantly decreased in patients with Barrett esophagus (IRR, 0.26; 95% CI, 0.09–0.79; ref. 23).

Taken together, there is medium-level evidence that medical treatment of GERD has a preventive effect on the development of EAC, although it is debated whether long-term use of PPI might actually have a carcinogenic effect on Barrett esophagus (evidence level 3a, grade of recommendation D). There is also medium-level evidence suggesting that prevention of EAC following surgical treatment of GERD goes in line with, or might be slightly more effective than, medical treatment (evidence level 2a, grade of recommendation B).

Weight loss

There is a strong association between high body mass index (BMI) and many cancer types, but a comprehensive meta-analysis (based on 221 datasets) concluded that EAC had the strongest association with BMI (24). A recent meta-analysis (22 studies; 14 case–control studies, of which 12 were population-based, and 8 population-based cohort studies) found that compared with individuals with normal BMI, the overall risk ratio (RR) of EAC was 1.71 (95% CI, 1.50–1.96) for individuals with a BMI 25–30 and 2.34 for those with a BMI $\geq$ 30 (95% CI, 1.95–2.81; ref. 25). A pooled analysis of 12 observational studies (10 population-based case–control studies and 2 population-based cohort studies) comparing individuals with a BMI < 25 with those with a BMI $\geq$ 40 found an OR of EAC of 3.65 (95% CI, 2.50–5.34; ref. 26). The available literature indicates a linear association between increasing BMI and risk of EAC. A meta-analysis (2 population-based cohort studies, 1 hospital-based cohort study, and 3 population-based case–control studies) concluded that abdominal or visceral adiposity, independent of BMI, significantly increased the risk of EAC (27). The increased risk of esophageal metaplasia and EAC due to obesity is attributable to mechanical effects of obesity (e.g., gastroesophageal reflux) but also metabolic and endocrine effects (such as macrophage activation and release of proinflammatory cytokines; ref. 28).

Despite the established association between BMI and EAC, the potentially preventive role of weight loss is uncertain. This is at least partly due to inherent problems in assessing weight loss as an exposure in larger cohorts and challenges in identifying a large enough cohort of individuals with voluntary weight loss that is both substantial and long-lasting. In this context, obesity surgery might be seen as a potential human model for assessing the risk of developing EAC following weight loss because of its drastic and stable long-term weight reduction starting from a specific date (29, 30). However, a recent systematic review identified only 11 cases of EAC occurring after obesity surgery, and statistical analyses were not conducted (31). In a subsequent population-based cohort study in Sweden, including 34,437 patients undergoing obesity surgery, only 8 participants developed EAC during follow-up, resulting in an HR of 0.9 (95% CI, 0.4–1.9) compared with nonoperated obese individuals (32). This might be explained by the rather short follow-up time in the studies published to date, where there might be a longer period of time before a risk reduction can be seen, or attributable to metabolic or endocrine effects due to obesity. Thus, no clearly preventive effect of obesity surgery was revealed, although the statistical power was low.

In summary, while obesity is associated with increased EAC risk, there is only limited evidence indicating that weight loss does *not* decrease the risk of EAC among obese individuals. However, long follow-up of large cohorts of patients, for example, those undergoing obesity surgery, should provide important knowledge regarding this topic (evidence level 2b, grade of recommendation B).

Tobacco smoking cessation

Tobacco smoking is associated with a moderately increased risk of EAC. A meta-analysis based on 33 studies (30 case-control studies, of which 13 were population-based, and 3 cohort studies, of which 2 were population-based) found an RR of 1.76 (95% CI, 1.54–2.01) for EAC, including the gastric cardia, when comparing ever and never smokers (33). A pooled analysis of 10 population-based case–control studies found an OR of 2.08 (95% CI, 1.83–2.37) when comparing ever and never smokers (34). The pooled analysis found that smoking cessation decreased the risk of EAC and that a longer time since smoking cessation reduced the risk increase in a time-dependent manner (34). Compared with current smokers, smoking cessation < 10 years entailed an OR of 0.82 (95% CI, 0.60–1.13) and smoking cessation of $\geq$10 years entailed an OR of 0.71 (95% CI, 0.56–0.89; ref. 34). However, the risk of EAC among previous smokers did not return to the level of non-smokers; even after $\geq$10 years of smoking cessation, the pooled analysis found a 1.7-fold risk of EAC compared with never smokers (34). There are currently no published cohort studies regarding smoking cessation.

Thus, there is consistent evidence showing that tobacco smoking cessation decreases the risk of EAC among tobacco smokers, although the risk might not return to the level of never smokers (evidence level 3b, grade of recommendation B).

Avoiding eradication of *H. pylori*

H. pylori is a gram-negative bacterium and has been determined to be a main risk factor for peptic ulceration and gastric

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adenocarcinoma (35–37). A systematic review including 37 studies from 22 countries found that the infection is generally acquired during childhood and the prevalence is more than 50% in many populations (38). Infection with *H. pylori* can lead to atrophy of the gastric mucosa, resulting in lower volume and acidity of gastric juices, which in turn could decrease the risk of EAC (39). In keeping with this hypothesis, a meta-analysis of 20 studies (11 case–control studies and 9 cohort studies) found a 40% lower prevalence of *H. pylori* among patients with GERD compared with patients without GERD (OR, 0.60; 95% CI, 0.47–0.78) (40), and 2 recent meta-analyses (including 9 cohort studies and 9 case–control studies of which 3 were population-based, and including 15 case–control studies, of which 8 were population-based) found that ongoing infection with *H. pylori* was associated with a nearly halved risk of EAC (OR, 0.52; 95% CI, 0.37–0.73 and OR, 0.59; 95% CI, 0.51–0.68; refs. 41, 42). These findings indicate that broad eradication strategies might not be justified in high-risk individuals of EAC. However, no studies have assessed the association between *H. pylori* eradication and EAC. Nevertheless, a recent meta-analysis (including 7 RCTs and 5 cohort studies) found no significant association between eradication of *H. pylori* infection and prevalence of symptomatic GERD or endoscopically documented GERD (43). Another meta-analysis (including 16 cohort studies), although with some overlap with the previously cited meta-analysis, found no association between *H. pylori* eradication and symptomatic GERD or erosive esophagitis when analyzing the studies based on subgroups for geographic region, age, baseline disease, or length of follow-up (44).

Taken together, the limited literature has no direct evidence to determine whether eradication of *H. pylori* increases the risk of EAC, that is, whether avoidance of eradication might be justified in some individuals. However, such eradication does not seem to increase the risk of GERD or erosive esophagitis, and as these are risk factors of developing EAC, this might indicate that there is no increased risk for EAC per se (evidence level 2a, grade of recommendation D).

HRT

A possible explanation for the strong male predominance of EAC, with an average 3- to 6-fold higher incidence among men (45), is differences in levels of endogenous exposure to female sex hormones. If this hypothesis is true, preventive effects of exogenous HRT might be evident. HRT is administered mainly for climacteric symptoms in postmenopausal women and has been shown to be effective for treating vasomotor symptoms, vaginal atrophy, and sexual problems, as well as in preventing osteoporosis and bone fractures (46–49). A meta-analysis including 5 studies (2 population-based cohort studies, 2 case–control studies, and 1 pooled analysis of 4 case–control studies) found a decreased OR of EAC among ever users of HRT, compared with never users (OR, 0.75; 95% CI, 0.58–0.98); however, no subanalyses based on dosage, type, or duration were possible due to few and small studies (50). A recent case–control study found an increased risk of GERD symptoms (HR, 1.57; 95% CI, 1.45–1.70) when comparing ever users of HRT with never users, but no increased risk of Barrett esophagus (HR, 1.15; 95% CI, 0.81–1.63) or EAC (HR, 0.89; 95% CI, 0.28–2.82) was found (51).

Thus, the available literature addressing HRT in relation to risk of EAC to date is limited but might suggest a preventive effect (evidence level 3a, grade of recommendation B).

NSAIDs

NSAIDs inhibit COX on a systemic level, either unselected or COX2 specifically, and are usually administered for their analgesic, anti-inflammatory, and antipyretic effects (52, 53). COX2 is an inflammatory enzyme necessary for the production of prostaglandins and other inflammatory mediators, and there is an increased expression of COX2 in patients with Barrett esophagus and EAC, hence indicating the possibility of chemoprevention if targeting this mechanism (54–56). A pooled analysis of 6 studies (5 population-based case–control studies and 1 population-based cohort study) found a reduced risk of EAC among ever users of any NSAID, including aspirin, compared with never users (OR, 0.68; 95% CI, 0.56–0.82; ref. 57). Compared with never users, a slightly stronger reduction was indicated among daily users of any NSAIDS, including aspirin (OR, 0.56; 95% CI, 0.43–0.73) than occasional users (OR, 0.66; 95% CI, 0.44–1.00; ref. 57). A meta-analysis (including 8 RCTs) found that daily treatment with aspirin was followed by a reduction in 20-year risk of death due to EAC (HR, 0.36; 95% CI, 0.21–0.63; ref. 58). Another meta-analysis (including 9 case–control studies, of which 4 were population-based, and 1 population-based cohort study) assessing NSAID use and risk of EAC found an OR of 0.64 (95% CI, 0.52–0.79) among users of aspirin and 0.65 (0.50–0.85) among users of non-aspirin NSAIDs, compared with never users (59).

In summary, treatment with NSAIDs appears to decrease the risk of developing EAC (evidence level 1a, grade of recommendation A), but introduction of NSAID as chemoprevention solely for this purpose requires further research.

Statins

Statins are usually prescribed as prevention of cardiovascular disease but may also have cancer preventive effects. Statins have antiproliferative, proapoptotic, anti-invasive, and radiosensitizing properties in preclinical studies (60). A meta-analysis (13 studies: 5 cohort studies, of which 2 were population-based, 7 case–control studies, of which 6 were population-based, and 1 *post hoc* analysis of 22 RCTs) of individuals without Barrett esophagus found an adjusted OR of 0.72 for developing esophageal cancer (95% CI, 0.60–0.86), and a subanalysis of patients with Barrett esophagus (5 studies: 3 cohort and 2 case–control studies, of which 1 was population-based) found a 43% reduction in risk of EAC (adjusted OR, 0.59; 95% CI, 0.45–0.78) among users of statins compared with never users (61). However, these results are debated, as a meta-analysis of only RCTs failed to show significant reduction in risk, although this was based on a smaller number of esophageal cancer cases (total 164 cancer cases compared with 9,285 cancer cases), and no separate analysis of only EAC was performed (62).

Thus, most available studies indicate a preventive effect on the development of EAC of treatment with statins (evidence level 3a, grade of recommendation B), but the literature is too limited to allow robust conclusions and therefore statins should not be used solely for EAC chemoprevention.

High-risk individuals for EAC

To determine who might benefit from preventive measures, high-risk individuals for EAC need to be identified. A recent Australian prediction model study aiming to identify individuals at high risk of developing EAC found that men older than 70 years with a BMI $\geq$ 30, who were current smokers, experiencing at least weekly symptoms of GERD, were medicated with PPIs, and had

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never used NSAIDs were at the highest risk (63). The model revealed that the absolute 5-year risk in individuals who fulfilled all of these criteria was 837 per 100,000 person-years, whereas the corresponding risks among individuals who were at least 60 years old and 50 years old were 506 and 185 per 100,000 person-years, respectively (64). A similar study in Sweden identified the highest risk (533 per 100,000 person-years) among male smokers, aged 70–74 years, with a BMI $\geq$ 25.5, experiencing weekly symptoms of GERD for at least 5 years, and requiring antireflux medication (64). An earlier study on the same Swedish study showed that age, sex, BMI, and reflux symptoms were the strongest predictors of developing EAC, although these factors have not been found to solely explain the male predominance (65, 66). Individuals with Barrett esophagus have already entered the metaplasia–dysplasia–adenocarcinoma axis. A meta-analysis concluded that the overall risk of Barrett esophagus to progress to EAC was 6.1 per 1,000 person-years and twice as high among men as women (67), but recently, 2 large and well-designed studies showed that the annual risk of EAC in persons with nondysplastic Barrett esophagus may be lower than previously reported, that is, 0.12% and 0.16% (68, 69).

Overall, these studies indicate that older men with obesity and GERD are at the highest risk of developing EAC and might benefit most from preventive measures. Individuals with Barrett esophagus also constitute a high-risk population, in whom preventive measures might be cost-effective.

Conclusions

This review indicates several promising targets for prevention of EAC among high-risk individuals in the clinical setting. The strongest evidence of preventive effects was seen following treatment of GERD, particularly after antireflux surgery in individuals with Barrett esophagus. There is medium-level evidence of a preventive effect of tobacco smoking cessation in relation to the risk of EAC. There is no substantial evidence showing that weight loss, including weight loss after obesity surgery, reduces the risk of EAC, although available studies are few in number and have a limited follow-up. Whether eradication of *H. pylori* increases the risk of EAC is unknown, but there is no evidence that eradication of *H. pylori* increases the risk of GERD, which would be believed to mediate any increased risk of EAC. HRT might decrease the risk of EAC, but the available studies are few in number and more research is required. Use of NSAIDs, both aspirin and non-aspirin, seems to prevent EAC, and results from RCTs are approaching. Regarding treatment with statins, the available literature shows a strong risk reduction of EAC among patients with Barrett esophagus. Yet, more research is needed to establish this association. Among these potential options for preventing EAC, clinicians should recommend treatment of GERD and tobacco smoking cessation. There is a need for more research on these as well as other targets before clinical recommendations can be made, and it remains to be established which individuals are most favorable for any such preventive actions.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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Authors' Contributions

Conception and design: J. Maret-Ouda, J. Lagergren
Development of methodology: J. Maret-Ouda, H. El-Serag, J. Lagergren
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Maret-Ouda
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H. El-Serag, J. Maret-Ouda, J. Lagergren
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