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REVIEW

Risk factors affecting the Barrett's metaplasia-dysplasia-neoplasia sequence

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Abstract

Esophageal adenocarcinoma has the fastest growing incidence rate of any cancer in the United States, and currently carries a very poor prognosis with 5 years relative survival rates of less than 15%. Current curative treatment options are limited to esophagectomy, a procedure that suffers from high complication rates and high mortality rates. Metaplasia of the esophageal epithelium, a condition known as Barrett's esophagus (BE), is widely accepted as the precursor lesion for adenocarcinoma of the esophagus. Recently, radio-frequency ablation has been shown to be an effective method to treat BE, although there is disagreement as to whether radio-frequency ablation should be used to treat all patients with BE or whether treatment should be reserved for those at high risk for progressing to esophageal adenocarcinoma while continuing to endoscopically survey those with low risk. Recent research has been targeted towards identifying those at greater risk for progression to esophageal adenocarcinoma so that radio-frequency ablation therapy can be used in a more targeted manner, decreasing the total health care cost as well as improving patient outcomes. This review discusses the current state of the literature regarding risk factors for progression from BE through dysplasia to esophageal adenocarcinoma, as well as the current need for an integrated scoring tool or risk stratification system capable of differentiating those patients at highest risk of progression in order to target these endoluminal therapies.

Key words: Barrett's esophagus; Esophageal adenocarcinoma; Endoscopy; Risk factors; Radiofrequency ablation; Antireflux surgery

Core tip: The transformation of Barrett's esophagus to dysplasia and finally to esophageal adenocarcinoma is a multifactorial process encompassing effects from multiple known and unknown risk factors. Previously, radiofrequency ablation was reserved for use in high risk patients with high-grade dysplasia, but recent evidence supports the expansion of this technique to be potentially used to treat additional patients at moderate risk of progression, such as those with long segments, long duration of symptoms, and those patients who are unable or unwilling to take proton-pump inhibitors's.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) has been estimated to affect nearly 20% of the United States population at any given time[1]. Of this group suffering from GERD, roughly 15% are estimated to have Barrett's esophagus (BE), a condition characterized by columnar-lined epithelium in the esophagus[2]. It is well established that BE is the link between GERD and esophageal adenocarcinoma (EAC), a neoplastic lesion with an extremely poor prognosis with 5-year survival rates of less than 15% and which currently has the fastest rising incidence rate of any cancer with approximately a 10-fold increased incidence rate among men aged 15-74 in the last 40 years[3-6]. Unfortunately, little progress has been made in treating this extremely aggressive cancer, with median survival time increasing only 3.2 mo over the last 30 years[7]. BE has been shown to be a paradigmatic model for progression from metaplastic disease through dysplasia to neoplasia[8]. In this review, we summarize the current literature regarding the etiology and pathophysiology of BE and EAC.

RESEARCH

We performed a literature review in the PubMed/Medline database using MeSH term "Barrett's Esophagus" combined with subheadings "etiology", "physiopathology", "therapy", "diagnosis" and "epidemiology" as well as MeSH term "Esophageal Neoplasms" with selected subheadings "diagnosis", "etiology", "physiopathology", "epidemiology" and "therapy" combined by Boolean operator AND with MeSH term "Adenocarcinoma" with selected subheadings "diagnosis", "epidemiology", "etiology", "pathophysiology" and "therapy". We reviewed abstracts published between 1980 and April of 2013 in English and selected articles relevant to topics discussed herein.

EPIDEMIOLOGY

Columnar lined epithelium has been shown to be present in almost 25% of individuals with GERD symptoms, and columnar lined epithelium with intestinal metaplasia is reported as affecting almost 15% of those with GERD symptoms. The probability of progressing to EAC from BE has been estimated to be approximately 0.5%/year[9,10], with the most convincing evidence provided in a meta-analysis of 47 studies by Yousef *et al*[11] showing a pooled cancer incidence of 6.4/1000 person-years for the 13 studies conducted in the United States and 6.1/1000 person-years for all 47 studies pooled. EAC incidence has increased roughly 10-fold in select demographics over the last 40 years, with only a small fraction being attributed to increasing obesity rates[12]. Recent data suggests this increase is slowing but still substantial, with average annual percentage increase in incidence rising 6.1% in men and 5.9% in women[13]. Other causes for this rapid increase in incidence have yet to be elucidated, but this continues to be a highly active area of research.

ETIOLOGY AND PATHOPHYSIOLOGY

BE is caused by reflux of gastric contents into the esophagus, which causes damage to the stratified squamous epithelium. Not surprisingly, it has also been shown that GERD symptoms increase odds of EAC by 7.7 fold, odds which increase to 43.5 fold when comparing patients with long-standing and severe GERD symptoms[13]. It is currently contested as to whether gastric acid, bile reflux, or the combination is responsible. Several studies have shown increased intraluminal bilirubin content, a proxy for duodenal juice content, in patients with BE, suggesting that bile acid plays an important role in BE development[14]. Likewise, gallbladder function was shown to be impaired in patients with BE and EAC in a real-time ultrasonography experiment following a 10-h fast leading to increased duodenogastric reflux[15]. Cholecystectomy has also been shown to increase risk of EAC, albeit slightly[16,17]. The body's compensatory mechanism can but does not always include metaplasia in the form of simple columnar epithelium, which is thought to be more tolerant to the low pH[18,19]. BE is the most predictive risk factor for the development of EAC, with a relative risk for developing esophageal cancer of 11.3 when compared to the general population[20]. Much research recently has been focused on determining what the risk factors are for developing BE. Age has been shown to be correlated with increased risk of developing BE, with a low of 2 diagnoses per 100000 person-years for those aged 21-30 years and peaking at 31 diagnoses per 100000 person-years in those aged 61-70 years[21]. Males also experience BE incidence rates roughly twice that of females, although the reason for this difference remains to be elucidated[21].

Obesity and its related conditions have been shown to be a risk factor for many diseases, and BE is no exception. A meta-analysis by Cook *et al*[22] suggests that increasing obesity is correlated with an increased risk for BE development but only indirectly due to obesity's effect on GERD development. This view is contested by El-Serag *et al*[23], who suggest that increasing visceral adipose tissue to subcutaneous adipose tissue ratio is correlated with the presence of BE [adjusted OR = 1.47 (95%CI: 0.92 to 4.09)]

as well as Kendall *et al*[24], whose data shows a significant correlation between all measures of obesity tracked (waist circumference, waist-hip ratio, sagittal abdominal diameter, and waist-height ratio) and presence of BE in males even after adjusting for GERD symptoms. It has been proposed that the association between obesity and risk of BE is due to several factors including increased intra-abdominal pressure leading to worsening GERD, as well as increased circulating levels of leptin, adiponectin, and other chemicals secreted by adipose tissue, although this link remains to be confirmed. Recently, low birth weight and preterm birth have been implicated as a risk factor for BE, with several studies reporting those born very small for gestational age, < 3rd percentile in one study and < 2000 g in another, having between a three and eleven-fold increase in odds when compared to those born at a normal weight for gestational age[25,26]. Hiatal hernia has been shown to be another risk factor for BE, with size of hiatal hernia correlating with increasing risk of both BE as well EAC[27,28]. Metabolic syndrome, another obesity related factor, has been shown to increase risk for BE by two-fold relative to those without metabolic syndrome[29].

It is being currently debated as to whether *Helicobacter pylori* (*H. pylori*) infection leads to increased or decreased risk of developing BE, but two meta-analyses, of 49 studies conducted by Fischbach *et al*[30] and 19 studies conducted by Islami *et al*[31], both suggest that, although significant selection and information bias may be present in these studies, *H. pylori* infection appears to be associated with a decreased risk of BE. Aggressive eradication of *H. pylori* infection over the last 30 years may provide an explanation for a small portion of the drastic increase in incidence.

Along with being male and older age[32-34], those with low dietary antioxidant intake have also been shown to not only have an increased risk of developing BE, but also have an increased risk of developing EAC[35,36]. Similarly, length of GERD symptoms is a risk factor for both development of BE as well as EAC[36,37]. The reasons for males experiencing high incidence rates is not well understood, but it appears to be due to other reasons than differential exposure to known risk factors[38,39]. Hormonal factors, studied by comparing patients undergoing hormone therapy, do not appear to account for the discrepancy in EAC incidence rates between males and females[40]. Heme iron intake in the diet has been suggested as a risk factor corresponding to EAC development as well[41]. Dietary iron has been shown to be a growth factor for *H. pylori,* making this association one in need of further investigation.

Many studies recently have elucidated relationships between various risk factors and the development of EAC, a goal that has potential to directly affect patient outcomes and change clinical practice with respect to ablative therapy. Sikkema *et al*[42] conducted a prospective cohort study in which they found statistically significant associations between many risk factors and progression to high grade dysplasia (HGD) and/or EAC including esophagitis and length of BE segment, with a risk ratio of 1.11 per centimeter increase in length, and known duration of BE of greater than or equal to 10 years with a risk ratio of 3.2. Also, previous partial gastrectomy is linked to EAC development[43]. Patients who underwent esophagectomy for EAC were shown in a case-control study to have a 45% prevalence of colonic polyps when compared to control patients who also underwent screening colonoscopies, of whom only 14% were shown to have colon polyps[44]. Whether there is a predictive relationship between presence of colon polyps and risk of EAC is still a contested topic and deserves further attention. Also, early research shows no evidence of viral genomic sequences present in tumors[45]. The single most predictive clinical factor for progression to HGD and/or EAC found to date is the presence of low grade dysplasia (LGD) found during biopsy with a relative risk of 9.7 (95%CI: 4.4-21.5) according to Sikkema et al and 5.5 (95%CI: 1.1-28.6) according to Oberg *et al*[46] compared to those without LGD.

Biomarkers have the potential to drastically improve our ability to risk stratify. p53 as well as KI-67, both proteins involved in cell cycle progression, have been shown to be expressed at higher levels in BE samples that progress to EAC[47-51]. Likewise, it has also been shown that cell-free circulating DNA methylation patterns correlate extremely closely (r = 0.92) with aberrant DNA methylation patterns in matched tumor tissue in patients with EAC and also that 911 loci for DNA methylation could perfectly discriminate between EAC and controls, suggesting that cell-free DNA methylation patterns could be used as a non-invasive method to screen premalignant lesions[52]. Promoter hypermethylation of p16 and APC is also strongly correlated with progression to EAC, with one study reporting hypermethylation of p16 and APC, either separately or together, in over 50% of HGD/EAC samples with hypermethylation of the same promoters totally absent in samples from patients with normal esophagus[53]. In a similar way, Mcm2 expression in BE is directly correlated with degree of dysplasia, with 91% of patients diagnosed with dysplasia or EAC in one prospective cohort showing Mcm-2-positive cytological brushings, while brushings from controls without BE showed no signs of Mcm-2 expression on the luminal surface[54]. COX-2 expression is upregulated in BE patients and degree of overexpression is correlated with risk of malignant transformation, suggesting that COX-2 expression could be used as a potential marker as well[55]. This increase in COX-2 expression has been shown to be strongly induced by deoxycholic acid incubation *in vitro* using OE-19 cells as a Barrett's model, suggesting a potential mechanism for this phenomenon[56]. Several bile acids have also been shown to induce the expression of other proteins important in cancer progression such as CDX2 as well as induce

NF-κB signaling[57]. Other notable biomarkers include increased DNA damage detected by Comet Assay, decreased Beclin-1 expression, increased cyclin A, cyclin B1, and cyclin D1 expression, and abnormal DNA content[49,58-65]. Notably, abnormal DNA content, measured by the number of chromosomes arms with loss, has been shown to be directly correlated with the progression from metaplasia, through low and high grade dysplasia, and finally to neoplasia[66]. Likewise, telomerase reverse transcriptase has been shown to be overexpressed in increasing levels along the metaplasia-dyplasia-neoplasia sequence of BE[67]. Whether these two markers can be used to differentiate between BE patients who will progress and those who will not remains to be studied. The field would benefit from further research into how these biomarkers can be integrated and utilized in a clinical setting as well as which can be used cost effectively to better predict risk of progression to EAC.

Interestingly, high serum leptin levels were associated with increased risk of EA, whereas increased levels of high molecular weight adiponectin conferred a protective effect, with a hazard ratio (HR) of 0.34 (95%CI: 0.14-0.82)[68]. The mechanism for this association might be due to leptin's effect on proliferation of adenocarcinoma cells independent of apoptosis or necrosis, as has been shown in BIC-1 and SEG-1 cells *in vitro*[69]. Type 2 diabetes mellitus has been shown to be more prevalent in those diagnosed with EAC, although the effect was attenuated after controlling for differences in BMI[70].

The consumption of several substances have shown to confer protective effects, with use of a multivitamin pill showing a HR of 0.38 (95%CI: 0.15-0.99) when compared to those not taking a multivitamin[71]. Vitamin D intake, however, was found to increase the risk of EAC, showing an OR of 1.99 (95%CI: 1.03-3.86), although vitamin D intake was not associated with BE or reflux esophagitis[72]. Taking proton-pump inhibitors (PPIs) has been shown to confer a protective affect against progressing from BE to EAC, with a hazard ratio of 0.41 (95%CI: 0.18-0.93) and 0.21 (95%CI: 0.07-0.66) for those using proton pump inhibitors at inclusion of the study or during the follow-up period, respectively; a finding supported by several other studies[73,74]. In addition to the use of proton-pump inhibitors, several studies recently have shown decreased rates of progression to EAC from BE when taking aspirin and/or statins, although the mechanism for this protection remains to be elucidated fully[75]. Sadaria *et al*[76] found that simvastatin attenuated growth and increased apoptosis in human esophageal adenocarcinoma (FLO-1) cells in tissue culture, providing one potential mechanism by which statins reduce risk of progression to EAC. One meta-analysis investigating this protective effect found a number needed to treat of 389 patients with statins to prevent one case of EAC[77]. ACE inhibitors could potentially provide a protective effect, although studies regarding this question were underpowered[78]. Medications that have relaxing effects on the lower-esophageal sphincter, specifically anticholinergics and theophyllines, have been associated with a roughly 1.5-2.5 fold increased risk of EAC, a relationship not seen for other types of cancers of the upper digestive tract[79,80].

As is expected, tobacco smoking has been shown repeatedly to increase the probability of progression to EAC. Interestingly, one study from the NIH Barrett's Esophagus and Esophageal Adenocarcinoma Consortium found an increased risk of progression to EAC with smoking and even showed a dose-response effect when considering pack-years, but there was a weaker association when considering cigarettes/day[81]. This study corroborates several other studies showing deleterious effects of smoking on risk of progression to EAC, estimating the risk at roughly double for those who smoke relative to those who do not smoke[82-85]. There appears to be no association between alcohol intake and risk of EAC according to several recent studies including meta-analysis, although this has been contested according to a matched case-control study out of North China[81,83,86-88].

Currently, no definitive genetic cause of BE or EAC has been identified. Several case reports, however, have found a remarkable history of BE and EAC among members of the same family, providing evidence that a subset of the population may be genetically susceptible to BE and potential progression to EAC[89-92]. Additionally, a single nucleotide polymorphism in the gene coding for epidermal growth factor (EGF) has been shown to be associated with decreased levels of EGF expression and has also been shown to be more prevalent in patients with BE and EAC[93]. Further research in this area could help identify specific genotypes that would allow clinicians additional tools when risk stratifying patients and making decisions regarding the management of patients with BE.

Surgical management of GERD has been shown to decrease odds of progression to EAC compared to no therapy, however a 2007 systematic review found that, in controlled studies, there was no statistically significant difference in EAC incidence rates between patients treated surgically and those treated medically. If data from uncontrolled case-series are included, the difference becomes significant. Interestingly, surgical management increased the probability of regression of BE and/or dysplasia by almost 15%[94]. This study shows puzzling results given the data from previous studies showing that fundoplication can reduce or even eliminate the reflux of bile acids into the esophagus, compared to medical therapy which only treats the reflux of hydrochloric acid[95]. One possible answer to this question could come from recent case-control data showing that, among patients who've undergone antireflux surgery, those with recurrent reflux symptoms are three times more likely to develop EAC than those without, underscoring the importance of addressing continuing reflux symptoms after antireflux surgery[96].

Randomized trials to date have only compared antireflux surgery to medical therapy in patients who were complete responders to medical therapy. This, unfortunately, is not the comparison of interest given the current role for surgery in GERD management. Patients selected for antireflux surgery in practice almost exclusively have failed medical therapy as their indication for surgical management. This suggests that there is some fundamental difference between patients who are responders and those who are not, and limits the usefulness of the comparison in these studies. The question of antireflux surgery *vs* continued medical management remains unanswered conclusively, but continues to be an active area of research and could benefit heavily from a randomized controlled trial comparing antireflux surgery to continued medical management in a population of patients who have continued reflux symptoms despite full dose medical therapy. Current data suggests that there is a role for antireflux surgery in the management of patients with BE, but the question of exactly which patients should be receiving these procedures remains to be answered.

CONCLUSION

As can be seen from the wealth of information outlined above, the risks associated with progression from BE to esophageal adenocarcinoma are multifactorial, with many different risk factors each contributing a relatively small portion to the overall risk of progression. This suggests that a single intervention aimed at reducing exposure to individual risk factors other than refluxed gastric contents is unlikely to have a drastic impact on increasing adenocarcinoma rates or to affect the risk for individual patients with Barrett's. Currently, no biomarkers have shown to be clinically useful in BE, but this continues to be an active area of research. More work is necessary to investigate the many risk factors at play and the populations that they apply to, in order to better understand the contributions to risk for any given clinical situation. Recent advancements in knowledge of risk factors and their contributions to progression have made clinical risk stratification models possible in order to target endoluminal therapies capable of eradicating Barrett's tissue and drastically decreasing risk of progression to adenocarcinoma. Currently, these tools are not widely available. Additional work is required to further develop and validate these tools in order to target patients at the highest risk of progression with either therapeutic intervention or endoscopic surveillance. One risk factor, the presence of LGD, has been very clearly shown to drastically increase the risk of progression to EAC by multiple studies. Given this information along with the known safety and efficacy of radiofrequency ablation and other endoluminal therapies, we believe that there is sufficient data to support the use of RFA in all Barrett's patients with LGD, even in the absence of additional risk factors. Additional stratification tools are required in order to dictate exactly which patients without LGD should receive RFA/endoluminal therapy and which should not, but given the evidence outlined above, patients with very long segment, patients who have had reflux symptoms for time periods of 10 years or greater, or patients who are unable or unwilling to take PPI's or are not antireflux surgery candidates should be considered carefully as potential candidates for endoscopic ablation.

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