Predictors of Progression to High-Grade Dysplasia or Adenocarcinoma in Barrett's Esophagus

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KEYWORDS

• Barrett's esophagus • Esophageal adenocarcinoma • Dysplasia • Risk factors
• Neoplastic progression

KEY POINTS

- Barrett's esophagus is the most well-established risk factor for the development of esophageal adenocarcinoma.
- Risk factors for neoplastic progression in patients with Barrett's esophagus include endoscopic findings (ie, erosive esophagitis), pathologic findings (ie, dysplasia), and clinical aspects (ie, male sex, older age, tobacco).
- Protective factors against neoplastic progression include medication use (ie statins, aspirin) and dietary considerations.

INTRODUCTION

The incidence of esophageal adenocarcinoma, a disease characterized by high mortality and an estimated 5-year survival rate of 20%, has increased dramatically in recent decades.[1,2] Barrett's esophagus is the most well-established risk factor for the development of esophageal adenocarcinoma.[3] The annual risk of progression from Barrett's esophagus to adenocarcinoma is approximately 0.33% per year.[4] When including both esophageal adenocarcinoma and high-grade dysplasia as a combined end point of progression, the incidence rate is approximately 0.9% to 1.0% per year.[5,6] Despite this neoplastic risk, the vast majority of patients with Barrett's esophagus die of causes other than esophageal adenocarcinoma.[7] At present, it remains unclear which patients

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with Barrett's esophagus progress on to neoplasia, a fact that makes current surveillance programs problematic. This article examines the endoscopic, pathologic, and epidemiologic risk factors for neoplastic progression in Barrett's esophagus (Table 1).

ENDOSCOPIC RISK FACTORS

Segment Length

While esophageal adenocarcinoma can develop in both short and long segments of Barrett's esophagus (traditionally defined as >3 cm), the understanding of the relationship between segment length and the risk of progression has evolved in recent years.[8] A 2012 meta-analysis found a lower annual incidence of esophageal adenocarcinoma in patients with short-segment Barrett's esophagus (<3 cm) than in the overall Barrett's esophagus population (0.19% vs 0.33% per year).[4] Work from the Northern Ireland Barrett's Esophagus Registry demonstrated an increased risk for progression to adenocarcinoma or high-grade dysplasia in long-segment Barrett's esophagus (hazard ratio [HR], 7.1; 95% confidence interval [CI], 1.74–29.04).[9] A recent case-control study from Berlin also found an association of segment length with progression to adenocarcinoma or high-grade dysplasia.[10] Patients with long-segment Barrett's esophagus had an increased risk of progression when compared with those with short-segment Barrett's esophagus (odds ratio [OR], 2.69; 95% CI, 1.48–4.88).

Newer studies have examined the relationship of segment length and risk of progression not only as a binary variable of long versus short but also as a continuous variable. In a large multicenter study, increasing segment length was an independent risk factor for neoplastic progression in patients with nondysplastic Barrett's esophagus.[11] Patients who progressed to adenocarcinoma or high-grade dysplasia had a longer Barrett's segment (6.1 cm vs 3.5 cm). Perhaps more importantly, the risk for neoplastic progression increased by 28% for every 1-cm increase in length of the Barrett's segment. Similarly, a Netherlands cohort study of more than 700 patients with nondysplastic Barrett's esophagus or low-grade dysplasia confirmed the concept of increasing risk with increasing segment length.[12] The relative risk of neoplastic progression to adenocarcinoma or high-grade dysplasia was 1.11 (95% CI, 1.01–1.2) per 1-cm increase in segment length. The recently completed SURF (Surveillance vs Radiofrequency Ablation) trial of radiofrequency ablation in patients with Barrett's esophagus with low-grade dysplasia also found segment length to be an independent predictor of neoplastic progression in the surveillance arm of the study (OR, 1.35 per cm; 95% CI, 1.04–1.76).[13]

Table 1
Risk factors for neoplastic progression to esophageal adenocarcinoma

Clinical	Older age White race Male sex Family history Tobacco Obesity
Endoscopic	Long-segment Barrett's esophagus Hiatal hernia Mucosal abnormalities Right hemisphere position
Pathologic	Intestinal metaplasia Dysplasia p53 Overexpression