

ESÔFAGO DE BARRET E ADENOCARCINOMA ESOFÁGICO: A RELAÇÃO ENTRE METAPLASIA E O DESENVOLVIMENTO DE CÂNCER

BARRET'S ESOPHAGUS AND ESOPHAGEAL ADENOCARCINOMA: THE RELATIONSHIP BETWEEN METAPLASIA AND CANCER DEVELOPMENT

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RESUMO

O esôfago de Barrett (EB) é uma condição metaplásica do esôfago distal e um precursor estabelecido do adenocarcinoma esofágico (AE). Seu desenvolvimento está fortemente associado ao refluxo gastroesofágico crônico e à exposição do epitélio esofágico aos conteúdos gástrico e biliar. Embora a maioria dos pacientes com EB não evolua para câncer, um subgrupo desenvolve displasia e, posteriormente, AE por meio de um processo multifatorial que envolve alterações genéticas, epigenéticas, inflamatórias e celulares. Esta revisão bibliográfica teve como objetivo analisar a relação entre o esôfago de Barrett e o adenocarcinoma esofágico, enfatizando os fatores de risco, os mecanismos envolvidos na progressão maligna, os desafios diagnósticos e as abordagens atuais de vigilância e tratamento. Foi realizada uma revisão narrativa da literatura utilizando estudos baseados no PubMed/Medline e os dois artigos de revisão selecionados fornecidos para este estudo, com foco nas publicações disponíveis até dezembro de 2022 e nas revisões subsequentes de 2023 e 2022. A literatura indica que a doença do refluxo gastroesofágico, a obesidade, a adiposidade central, o sexo masculino, a idade avançada, o tabagismo e segmentos mais extensos de Barrett estão associados a um maior risco. A progressão envolve inflamação crônica, estresse oxidativo, sinalização anormal de fatores de crescimento, alterações nos genes TP53 e CDKN2A, aneuploidia e ativação de vias como NF- κ B, IL-6/STAT3, Wnt/ β -catenina e TGF- β /BMP. A vigilância endoscópica e a terapia de erradicação são importantes para pacientes com displasia ou neoplasia precoce. A identificação precoce de pacientes de alto risco permanece essencial para reduzir a progressão para adenocarcinoma esofágico avançado.

ABSTRACT

Barrett's esophagus (BE) is a metaplastic condition of the distal esophagus and an established precursor of esophageal adenocarcinoma (EAC). Its development is strongly associated with chronic gastroesophageal reflux and exposure of the esophageal epithelium to gastric and biliary contents. Although most patients with BE do not progress to cancer, a subgroup develops dysplasia and eventually EAC through a multistep process involving genetic, epigenetic, inflammatory, and cellular alterations. This literature review aimed to analyze the relationship between Barrett's esophagus and esophageal adenocarcinoma, emphasizing risk factors, mechanisms involved in malignant progression, diagnostic challenges, and current approaches to surveillance and treatment. A narrative literature review was conducted using PubMed/Medline-based studies and the two selected review articles provided for this study, focusing on publications available through December 2022 and the subsequent 2023 and 2022 reviews. The literature indicates that gastroesophageal reflux disease, obesity, central adiposity, male sex, older age, smoking, and longer Barrett's segments are associated with increased risk. Progression involves chronic inflammation, oxidative stress, abnormal growth-factor signaling, TP53 and CDKN2A alterations, aneuploidy, and activation of pathways such as NF- κ B, IL-6/STAT3, Wnt/ β -catenin, and TGF- β /BMP. Endoscopic surveillance and eradication therapy are important for patients with dysplasia or early neoplasia. Early identification of high-risk patients remains essential to reduce progression to advanced EAC.

Keywords: Barrett's Esophagus. Esophageal Adenocarcinoma. Gastroesophageal Reflux. Dysplasia. Metaplasia.

INTRODUCTION

Barrett's esophagus (BE) is characterized by the replacement of the normal squamous epithelium of the distal esophagus by columnar-type epithelium, commonly associated with intestinal metaplasia. It is recognized as a precursor lesion for esophageal adenocarcinoma (EAC), a malignant neoplasm whose incidence has increased substantially in Western countries. Approximately 2% of adults may have BE, although its prevalence is difficult to establish because diagnostic criteria vary and intestinal metaplasia may be unevenly distributed throughout the affected mucosa.¹

Gastroesophageal reflux disease (GERD) is considered one of the principal factors involved in the development of BE. Chronic exposure to gastric acid, bile, pepsin, and other components of refluxate promotes epithelial injury and persistent inflammation. However, the relationship is complex because a considerable proportion of patients diagnosed with BE do not report typical GERD symptoms. Other factors, including male sex, advanced age, obesity, central adiposity, smoking, hiatal hernia, and a longer Barrett's segment, are also associated with increased risk.¹

The transition from BE to EAC does not occur in all patients and generally follows a multistep sequence involving metaplasia, low-grade dysplasia, high-grade dysplasia, and, finally, adenocarcinoma. During this process, chronic inflammatory stimulation and cellular stress contribute to genetic and epigenetic abnormalities that promote uncontrolled proliferation, genomic instability, and malignant transformation. Alterations involving tumor suppressor genes such as **TP53** and **CDKN2A**, together with aneuploidy and abnormal signaling pathways, have been associated with neoplastic progression.¹

Because EAC is frequently diagnosed at an advanced stage and has poor survival outcomes, understanding the biological relationship between BE and cancer is clinically relevant. Therefore, this review aimed to analyze the relationship between Barrett's esophagus and esophageal adenocarcinoma, focusing on risk factors, pathophysiological mechanisms of malignant progression, diagnostic challenges, surveillance, and current treatment strategies.

METHOD

A narrative literature review was performed based primarily on the scientific articles provided for this study. The literature search methodology described in the principal clinical review included the Ovid Medline/PubMed databases and publications available through December 2022.¹ The descriptors were combinations of **"Barrett's esophagus," "Barrett esophagus," "esophageal neoplasm," "esophageal adenocarcinoma," "gastroesophageal reflux disease," "dysplasia,"** and **"cancer."** Boolean operators **AND** and **OR** were used to combine the terms.

The selected literature focused on the definition, epidemiology, risk factors, progression from BE to EAC, molecular mechanisms, diagnosis, surveillance, and treatment. Articles that were not available in English, abstracts without complete articles, and non-peer-reviewed publications were excluded according to the methodology described in the principal review.¹ The present review synthesized the findings of the selected sources according to the structure proposed in the provided literature-review model.

RESULTS

Barrett's Esophagus and Risk of Malignant Progression

BE represents an important stage in the development of EAC, but malignant transformation is not inevitable. The progression is commonly described as a sequence from reflux-associated epithelial injury to metaplasia, low-grade dysplasia (LGD), high-grade dysplasia (HGD), and EAC.¹ The annual risk of progression from BE to EAC is relatively low in patients without dysplasia, which explains why endoscopic eradication therapy is not routinely recommended for nondysplastic BE.²

Several factors influence the probability of progression. Increasing age, male sex, obesity, central adiposity, smoking, GERD, hiatal hernia, and longer BE segments have been associated with increased risk.¹ In particular, central adiposity appears to have an independent association with BE and EAC, even after adjustment for overall body mass index. Smoking is also an established risk factor for EAC, with

epidemiological studies demonstrating approximately twice the risk among individuals who have smoked compared with never-smokers.¹

The extent of the metaplastic segment is also clinically relevant. A longer Barrett's segment is associated with a greater probability of progression to HGD or EAC. Consequently, contemporary surveillance strategies increasingly consider both the degree of dysplasia and the length of the BE segment when determining follow-up intervals.¹

Molecular Mechanisms of Progression

The progression from BE to EAC is driven by the interaction of chronic environmental injury and molecular alterations. Refluxed gastric acid, bile, and pepsin can induce chronic inflammation and oxidative stress, creating an environment favorable to cellular damage and genomic instability.¹ Pepsin exposure may also contribute to carcinogenesis, including through alterations in gene expression and signaling pathways associated with tumor development.¹

Inflammatory pathways are particularly important in the transition toward dysplasia and cancer. Chronic exposure to refluxate can activate pathways such as nuclear factor kappa B (NF- κ B) and interleukin-6/signal transducer and activator of transcription 3 (IL-6/STAT3). Increased IL-6 expression has been associated with increasing degrees of dysplasia, suggesting a relationship between persistent inflammation and neoplastic progression.¹

Genetic and epigenetic alterations further contribute to malignant transformation. Loss of heterozygosity involving chromosome 17p, containing **TP53**, and chromosome 9p, containing **CDKN2A**, has been associated with neoplastic progression. Abnormalities in **TP53** are particularly associated with progression toward HGD and EAC, while alterations involving **CDKN2A** may occur earlier during the development of BE.¹ Aneuploidy and abnormal DNA methylation can additionally contribute to genomic instability and altered expression of tumor suppressor genes.¹

Other signaling pathways, including TGF- β /BMP, Notch, and Wnt/ β -catenin, participate in epithelial differentiation and neoplastic development. Wnt/ β -catenin signaling appears to have a particularly important role in dysplastic changes and malignant transformation rather than in the initial metaplastic process.¹ Thus, BE-to-EAC progression is better understood as a complex molecular evolution rather than a single pathological event.

Diagnosis, Surveillance, and Treatment

The diagnosis of BE involves endoscopic identification of salmon-colored mucosa extending proximally from the gastroesophageal junction and histological assessment of biopsied tissue. The requirement for intestinal metaplasia remains controversial internationally, although major American guidelines consider intestinal metaplasia an important component of the diagnosis.¹ Sampling error is an important limitation because goblet cells can have a mosaic distribution, meaning that inadequate biopsy sampling may fail to identify intestinal metaplasia.¹

Histological classification of dysplasia is essential because the degree of dysplasia strongly influences management. Confirmation by an experienced gastrointestinal pathologist is particularly important for LGD because substantial interobserver variability has been reported.² Patients with nondysplastic BE generally undergo endoscopic surveillance rather than eradication therapy because their annual risk of progression is low.²

For confirmed dysplasia or early EAC, endoscopic eradication therapy is the principal treatment strategy. It generally combines endoscopic resection of visible or raised lesions with ablation of the remaining flat Barrett's mucosa.² Endoscopic mucosal resection (EMR) is commonly used for focal lesions, whereas endoscopic submucosal dissection (ESD) can provide en bloc resection of larger or more complex lesions.²

Radiofrequency ablation (RFA) is the most widely available ablative technique. In patients with confirmed LGD, randomized trials have demonstrated increased eradication of intestinal metaplasia and reduced progression to HGD or EAC compared with surveillance.² Cryotherapy is another effective option and may be particularly useful when BE is refractory to RFA.² Following successful eradication, continued endoscopic surveillance remains necessary because recurrence may occur even years after treatment.²

CONCLUSION

Barrett's esophagus is a clinically important precursor to esophageal adenocarcinoma, but progression to cancer occurs through a complex and heterogeneous process rather than an inevitable sequence. Chronic reflux-associated injury, inflammation, oxidative stress, genetic alterations, epigenetic changes, and abnormal molecular signaling contribute to the transition from metaplasia to dysplasia and ultimately EAC. Risk is influenced by clinical characteristics such as male sex, older age, obesity, central adiposity, smoking, GERD, and longer Barrett's segments.

Early recognition of dysplasia and appropriate endoscopic surveillance are essential for identifying patients at increased risk. Endoscopic eradication therapy, particularly resection of visible lesions followed by ablation of residual Barrett's mucosa, has become central to the management of dysplastic BE and early EAC. Nevertheless, important uncertainties remain regarding the prediction of malignant progression, optimal surveillance intervals, and the role of molecular biomarkers. Further research is therefore necessary to improve risk stratification and personalize the prevention and treatment of esophageal adenocarcinoma.

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