Barrett's esophagus: Pathogenesis and malignant transformation

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INTRODUCTION

Barrett's esophagus is the condition in which metaplastic columnar mucosa that predisposes to cancer development replaces the stratified squamous mucosa that normally lines the distal esophagus. The condition develops as a consequence of chronic gastroesophageal reflux disease and predisposes to the development of adenocarcinoma of the esophagus [1]. Barrett's esophagus is considered short segment if the metaplastic columnar mucosa involves <3 cm of the distal esophagus and long segment if it involves ≥3 cm.

This topic will review the pathogenesis of Barrett's esophagus and the mechanisms of transformation into esophageal adenocarcinoma. The indications for screening for Barrett's esophagus and the clinical manifestations, diagnosis, and management of Barrett's esophagus are discussed in detail separately. (See "Barrett's esophagus: Epidemiology, clinical manifestations, and diagnosis" and "Barrett's esophagus: Surveillance and management".)

PATHOPHYSIOLOGY

Mechanism of esophageal injury — Barrett's esophagus results from chronic reflux esophagitis caused by the gastroesophageal reflux of acid and other noxious substances. (See "Complications of gastroesophageal reflux in adults".)

Acid exposure — Patients who have long-segment Barrett's esophagus are predisposed to reflux caustic gastric contents (often without warning symptoms) into an esophagus whose ability to protect itself is compromised by defective clearance mechanisms and diminished secretion of growth factors (table 1) [2]. In most cases, Barrett's esophagus appears to develop to its full extent over a short period of time (ie, <1 year), with little or no subsequent progression. Given the propensity for severe gastroesophageal reflux disease (GERD) in patients with long-segment Barrett's esophagus, it was initially assumed that the metaplasia progressed in extent over the years as columnar mucosa replaced more and more reflux-damaged squamous mucosa. However, for reasons that are unclear, such progression is rarely observed [3].

By contrast, patients with short-segment Barrett's esophagus often have few or no symptoms and signs of GERD. The development of the intestinal-type columnar metaplasia typical of Barrett's esophagus in patients with short-segment disease may be due to exposure to acid and noxious agents that accumulate at an acid pocket in the most proximal gastric cardia that escapes the buffering effects of food and remains highly acidic during the postprandial period [4,5]. (See "Pathophysiology of reflux esophagitis", section on 'Impaired esophageal emptying'.)

Other noxious agents

- **Nitroso compounds** – Potential consequences of persistent reflux include not only acid-peptic injury, but also exposure to high concentrations of nitric oxide (NO) generated from dietary nitrates in green, leafy vegetables. Most ingested nitrate is absorbed by the small intestine and excreted unchanged in the urine, but approximately 25 percent is concentrated by the salivary glands and secreted into the mouth where bacteria on the tongue reduce the recycled nitrate to nitrite. When swallowed, nitrite encounters acidic gastric juice, and the nitrite is converted rapidly to NO. After nitrate ingestion, high levels of NO have been demonstrated at the gastroesophageal junction [6]. NO can be genotoxic and, potentially, carcinogenic.

- **Bile** – The reflux of bile acids also appears to contribute to carcinogenesis in Barrett's esophagus. (See 'Molecular mechanisms' below.)

Development of Barrett's metaplasia — Barrett's esophagus develops through the process of metaplasia, in which one kind of fully differentiated (adult) tissue replaces another [7]. The metaplastic columnar cells of Barrett's esophagus are in some ways a favorable adaptation to chronic reflux since they appear to be more resistant to reflux-induced injury than the native squamous cells. Unfortunately, this metaplasia also predisposes to cancer development.

In most patients, reflux-induced mucosal damage is repaired by the regeneration of more squamous cells. In some patients, for reasons that are not clear, the reflux-damaged esophagus is repaired through a columnar metaplasia in which gastric and intestinal-type columnar cells replace squamous cells. While it was previously thought that Barrett's metaplasia is the result of transcommitment, in which progenitor cells in the esophagus that normally would differentiate into squamous cells instead differentiate into columnar cells, there is contrary evidence from other studies [8]. These studies suggest that Barrett's metaplasia might result from the proximal migration of stem cells from the gastric cardia [9], from the expansion of a nest of residual embryonic-type cells located at the gastroesophageal junction [10], or from a unique population of transitional basal cells located at the squamo-columnar junction [11]. There is also evidence to suggest that progenitor cells in esophageal submucosal glands and their ducts might give rise to Barrett's metaplasia [12]. Finally, in a rat model of reflux esophagitis, Barrett's metaplasia appears to occur when circulating stem cells from the bone marrow are transported through the blood to the damaged esophagus, where they differentiate into columnar cells [13].

MALIGNANT TRANSFORMATION

Risk and protective factors — The risk of developing cancer in patients with Barrett's esophagus increases with age and is higher in men, and in individuals with long segments of Barrett's mucosa [14-17].

Reflux of acid and bile salts can cause oxidative DNA damage and induce double-strand DNA breaks in Barrett's epithelial cells. Agents that induce double-strand breaks are considered carcinogens [18,19]. In support of this concept, the Barrett's metaplasia adjacent to esophageal adenocarcinomas frequently shows evidence of oxidative DNA damage, likely due to the reflux of acid and bile [20]. Effective acid suppression with a proton pump inhibitor has been associated with increased epithelial cell differentiation and decreased proliferation, suggesting that it has a favorable effect on dysplasia progression [21]. Inhibition of COX-2 has been shown to have antiproliferative and pro-apoptotic effects in Barrett's-associated esophageal adenocarcinoma cell lines. The COX-2 inhibitors may also hinder cell proliferation in vitro, suggesting a possible role in chemoprevention [22]. (See "Barrett's esophagus: Surveillance and management", section on 'Management of acid reflux'.)

The pattern of acid secretion may be an important determinant in the neoplastic progression of Barrett's metaplasia. An ex vivo study demonstrated that pulsed acid exposure increased cell proliferation, but continuous acid exposure decreased cell proliferation [23]. (See "Barrett's esophagus: Surveillance and management", section on 'Cancer risk'.)

H. pylori infection appears to protect the esophagus from gastroesophageal reflux disease (GERD), Barrett's esophagus, dysplasia in Barrett's esophagus, and esophageal adenocarcinoma, perhaps by causing a chronic gastritis that interferes with acid production [24,25]. *H. pylori* strains that express cytotoxin-associated gene A (cagA) appear to be especially damaging to the stomach, and especially protective for the esophagus. (See "Helicobacter pylori and gastroesophageal reflux disease".)

Transcriptionally active high-risk-human papillomavirus infection has been associated with Barrett's dysplasia and esophageal adenocarcinoma in some studies [26-28]. However, its etiologic significance in the progression of Barrett's dysplasia is unclear [29].

Histologic changes

Dysplasia — Esophageal columnar metaplasia predisposes to the development of adenocarcinoma [30]. Cancers in Barrett's esophagus develop as the result of genetic and epigenetic alterations that give the cells certain growth advantages, and cause morphological changes in the tissue that the pathologist can recognize as dysplasia. Dysplasia is a constellation of histological abnormalities, suggesting that one or more clones of cells have acquired sufficient genetic/epigenetic damage to render them neoplastic and predisposed to malignancy [31]. (See 'Molecular mechanisms' below.)

On histopathology dysplasia is characterized by a constellation of characteristic cytological and architectural abnormalities [32]. Cytologic abnormalities include nuclear enlargement, pleomorphism, hyperchromatism, and stratification. Atypical mitoses and loss of cytoplasmic maturation are also seen. Architectural changes include crowding of tubules and villiform surfaces. The presence of these abnormalities suggests that the tissue has sustained genetic/epigenetic damage, resulting in clonal proliferations of cells with abnormal differentiation and a predisposition to malignancy. Dysplasia is graded as low or high grade based upon the severity of architectural and cytologic features. (See "Barrett's esophagus: Surveillance and management", section on 'Management of dysplasia or intramucosal carcinoma'.)

Adenocarcinoma — Esophageal adenocarcinoma in patients with Barrett's esophagus is thought to evolve through a sequence of genetic alterations that are associated with dysplastic changes of progressive severity. Barrett's esophagus is thought to be the precursor of adenocarcinoma of the esophagus and of the gastroesophageal junction (GEJ). Adenocarcinomas that straddle the GEJ are approximately twice as common as adenocarcinomas that clearly arise from the esophagus (picture 1) [33]. With straddling tumors, it can be difficult to determine whether the neoplasm arose from the columnar

epithelium in the distal esophagus or in the proximal stomach (the gastric cardia), especially when there is no evidence of Barrett's metaplasia in the esophagus. These tumors cannot be distinguished from one another morphologically, and they share a number of epidemiologic features including an association with GERD, a strong predilection for White males, and a rapidly rising incidence in Western countries [33]. (See "Epidemiology and pathobiology of esophageal cancer", section on 'Adenocarcinoma' and "Barrett's esophagus: Surveillance and management", section on 'Management of invasive esophageal adenocarcinoma'.)

Biochemical studies are also consistent with the hypothesis that Barrett's esophagus is the precursor for most GEJ tumors. In one series, for example, similar profiles of intestinal-type proteins were detected by immunofluorescence microscopy in Barrett's esophagus and in 26 cases of adenocarcinoma with or without obvious Barrett's in tumors from both esophagus and cardia [34]. These profiles were not seen in normal stomach or esophageal mucosa, in peptic esophagitis, or in squamous cell carcinoma.

Molecular mechanisms — Carcinogenesis in metaplastic cells begins with genetic and epigenetic alterations that either activate proto-oncogenes, disable tumor suppressor genes, or both [30,35]. Neoplastic progression observed in patients with Barrett's esophagus commonly includes alterations in the tumor suppressor genes p53 (also known as TP53) and p16 (also known as CDKN2A), and in the cyclin D1 proto-oncogene [30,36,37]. In addition to these changes, aneuploid or tetraploid populations can be found by flow cytometry in more than 90 percent of adenocarcinomas, and these same flow cytometric abnormalities may predict progression in Barrett's epithelium prior to malignant transformation [35]. Before cells acquire enough genetic and epigenetic damage to become frankly malignant, the earlier alterations can cause morphologic changes that can be recognized on histologic examination as dysplasia. When enough genetic and epigenetic abnormalities accumulate, a clone of malignant cells emerges that has the ability to invade adjacent tissues and to proliferate in unnatural locations. (See 'Dysplasia' above.)

The evolution of genetic changes leading from Barrett's esophagus to adenocarcinoma is incompletely understood. Traditionally, carcinogenesis in Barrett's esophagus was assumed to result from a gradual, step-wise accumulation of alterations in tumor suppressor genes, followed by oncogene activation, genomic instability, and malignant transformation. These early DNA abnormalities endow the cells with certain growth advantages, permitting them to hyperproliferate. During hyperproliferation, the cells acquire more genetic changes that eventuate in autonomous cell growth (neoplasia) [38]. It now appears that most tumors in Barrett's metaplasia develop though a "genome-doubled pathway" in which p53 mutation is acquired first, with subsequent whole genome doubling that results in genomic instability,

oncogene amplification, and malignant transformation [20]. This genome-doubled pathway results in cancer development far more quickly than the traditional pathway of step-wise accumulation of genetic alterations.

The gastroesophageal reflux of bile acids also appears to contribute to carcinogenesis in Barrett's esophagus. Bile acids cause both DNA damage and activation of the NF-κB pathway in Barrett's metaplastic cells. Ordinarily, severe DNA damage that might predispose to malignancy triggers apoptosis (programmed cell death), which destroys those cells that have potentially carcinogenic mutations [39]. However, NF-κB activation prevents apoptosis in Barrett's metaplasia. Thus, bile acid reflux can simultaneously damage DNA and activate a process that enables the survival of cells with cancer-causing mutations. (See 'Other noxious agents' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Barrett's esophagus".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Barrett's esophagus (The Basics)")
- Beyond the Basics topics (see "Patient education: Barrett's esophagus (Beyond the Basics)")

SUMMARY

- Barrett's esophagus is the condition in which metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal esophagus. (See 'Introduction' above.)

- Barrett's esophagus develops through the process of metaplasia, in which one kind of fully differentiated (adult) tissue replaces another. Metaplasia commonly is a consequence of chronic inflammation, and Barrett's metaplasia results from chronic reflux esophagitis caused by the gastroesophageal reflux of acid, bile, and other noxious substances. (See 'Mechanism of esophageal injury' above and 'Development of Barrett's metaplasia' above.)

- The risk of developing cancer in patients with Barrett's esophagus increases with age and is higher in men, and in individuals with long segments (>3 cm) of Barrett's mucosa. *H. pylori* infection appears to protect the esophagus from gastroesophageal reflux disease, Barrett's esophagus, dysplasia in Barrett's esophagus, and esophageal adenocarcinoma, perhaps by causing a chronic gastritis that interferes with acid production. (See 'Risk and protective factors' above.)

- Traditionally, cancers in Barrett's esophagus were assumed to evolve gradually through a sequence of genetic and epigenetic alterations that gave the cells certain growth advantages, and caused morphological changes in the tissue that could be recognized on histopathology as dysplasia. It now appears that most tumors in Barrett's metaplasia develop though a "genome-doubled pathway" that can progress quickly to malignancy. (See 'Histologic changes' above and 'Molecular mechanisms' above.)

- Neoplastic progression observed in patients with Barrett's esophagus commonly includes alterations in the tumor suppressor genes p53 (also known as TP53) and p16 (also known as CDKN2A), and in the cyclin D1 protooncogene. (See 'Molecular mechanisms' above.)

REFERENCES

1. Shaheen NJ, Falk GW, Iyer PG, et al. Diagnosis and Management of Barrett's Esophagus: An Updated ACG Guideline. Am J Gastroenterol 2022; 117:559.
2. Fass R, Hell RW, Garewal HS, et al. Correlation of oesophageal acid exposure with Barrett's oesophagus length. Gut 2001; 48:310.

3. Cameron AJ, Lomboy CT. Barrett's esophagus: age, prevalence, and extent of columnar epithelium. Gastroenterology 1992; 103:1241.
4. Fletcher J, Wirz A, Young J, et al. Unbuffered highly acidic gastric juice exists at the gastroesophageal junction after a meal. Gastroenterology 2001; 121:775.
5. Fletcher J, Wirz A, Henry E, McColl KE. Studies of acid exposure immediately above the gastro-oesophageal squamocolumnar junction: evidence of short segment reflux. Gut 2004; 53:168.
6. Iijima K, Henry E, Moriya A, et al. Dietary nitrate generates potentially mutagenic concentrations of nitric oxide at the gastroesophageal junction. Gastroenterology 2002; 122:1248.
7. Spechler SJ. Laser photoablation of Barrett's epithelium: burning issues about burning tissues. Gastroenterology 1993; 104:1855.
8. Que J, Garman KS, Souza RF, Spechler SJ. Pathogenesis and Cells of Origin of Barrett's Esophagus. Gastroenterology 2019; 157:349.
9. Quante M, Bhagat G, Abrams JA, et al. Bile acid and inflammation activate gastric cardia stem cells in a mouse model of Barrett-like metaplasia. Cancer Cell 2012; 21:36.
10. Wang X, Ouyang H, Yamamoto Y, et al. Residual embryonic cells as precursors of a Barrett's-like metaplasia. Cell 2011; 145:1023.
11. Jiang M, Li H, Zhang Y, et al. Transitional basal cells at the squamous-columnar junction generate Barrett's oesophagus. Nature 2017; 550:529.
12. Owen RP, White MJ, Severson DT, et al. Single cell RNA-seq reveals profound transcriptional similarity between Barrett's oesophagus and oesophageal submucosal glands. Nat Commun 2018; 9:4261.
13. Sarosi G, Brown G, Jaiswal K, et al. Bone marrow progenitor cells contribute to esophageal regeneration and metaplasia in a rat model of Barrett's esophagus. Dis Esophagus 2008; 21:43.
14. Lagergren J, Bergström R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999; 340:825.
15. Reid BJ, Levine DS, Longton G, et al. Predictors of progression to cancer in Barrett's esophagus: baseline histology and flow cytometry identify low- and high-risk patient subsets. Am J Gastroenterol 2000; 95:1669.
16. Gopal DV, Lieberman DA, Magaret N, et al. Risk factors for dysplasia in patients with Barrett's esophagus (BE): results from a multicenter consortium. Dig Dis Sci 2003; 48:1537.

17. Weston AP, Badr AS, Hassanein RS. Prospective multivariate analysis of clinical, endoscopic, and histological factors predictive of the development of Barrett's multifocal high-grade dysplasia or adenocarcinoma. Am J Gastroenterol 1999; 94:3413.
18. Zhang HY, Hormi-Carver K, Zhang X, et al. In benign Barrett's epithelial cells, acid exposure generates reactive oxygen species that cause DNA double-strand breaks. Cancer Res 2009; 69:9083.
19. Peng S, Huo X, Rezaei D, et al. In Barrett's esophagus patients and Barrett's cell lines, ursodeoxycholic acid increases antioxidant expression and prevents DNA damage by bile acids. Am J Physiol Gastrointest Liver Physiol 2014; 307:G129.
20. Stachler MD, Taylor-Weiner A, Peng S, et al. Paired exome analysis of Barrett's esophagus and adenocarcinoma. Nat Genet 2015; 47:1047.
21. Ouatu-Lascar R, Fitzgerald RC, Triadafilopoulos G. Differentiation and proliferation in Barrett's esophagus and the effects of acid suppression. Gastroenterology 1999; 117:327.
22. Buttar NS, Wang KK, Anderson MA, et al. The effect of selective cyclooxygenase-2 inhibition in Barrett's esophagus epithelium: an in vitro study. J Natl Cancer Inst 2002; 94:422.
23. Fitzgerald RC, Omary MB, Triadafilopoulos G. Dynamic effects of acid on Barrett's esophagus. An ex vivo proliferation and differentiation model. J Clin Invest 1996; 98:2120.
24. Erőss B, Farkas N, Vincze Á, et al. Helicobacter pylori infection reduces the risk of Barrett's esophagus: A meta-analysis and systematic review. Helicobacter 2018; 23:e12504.
25. Castro C, Peleteiro B, Lunet N. Modifiable factors and esophageal cancer: a systematic review of published meta-analyses. J Gastroenterol 2018; 53:37.
26. Rai N, Jenkins GJ, McAdam E, et al. Human papillomavirus infection in Barrett's oesophagus in the UK: an infrequent event. J Clin Virol 2008; 43:250.
27. Kunzmann AT, Graham S, McShane CM, et al. The prevalence of viral agents in esophageal adenocarcinoma and Barrett's esophagus: a systematic review. Eur J Gastroenterol Hepatol 2017; 29:817.
28. El-Serag HB, Hollier JM, Gravitt P, et al. Human papillomavirus and the risk of Barrett's esophagus. Dis Esophagus 2013; 26:517.
29. Iyer A, Rajendran V, Adamson CS, et al. Human papillomavirus is detectable in Barrett's esophagus and esophageal carcinoma but is unlikely to be of any etiologic significance. J Clin Virol 2011; 50:205.
30. Morales CP, Souza RF, Spechler SJ. Hallmarks of cancer progression in Barrett's oesophagus. Lancet 2002; 360:1587.
31. Spechler SJ. Disputing dysplasia. Gastroenterology 2001; 120:1864.

32. Goldblum JR. Barrett's esophagus and Barrett's-related dysplasia. Mod Pathol 2003; 16:316.
33. Cameron AJ, Lomboy CT, Pera M, Carpenter HA. Adenocarcinoma of the esophagogastric junction and Barrett's esophagus. Gastroenterology 1995; 109:1541.
34. Mendes de Almeida JC, Chaves P, Pereira AD, Altorki NK. Is Barrett's esophagus the precursor of most adenocarcinomas of the esophagus and cardia? A biochemical study. Ann Surg 1997; 226:725.
35. Galipeau PC, Cowan DS, Sanchez CA, et al. 17p (p53) allelic losses, 4N (G2/tetraploid) populations, and progression to aneuploidy in Barrett's esophagus. Proc Natl Acad Sci U S A 1996; 93:7081.
36. Souza RF, Morales CP, Spechler SJ. Review article: a conceptual approach to understanding the molecular mechanisms of cancer development in Barrett's oesophagus. Aliment Pharmacol Ther 2001; 15:1087.
37. Weston AP, Banerjee SK, Sharma P, et al. p53 protein overexpression in low grade dysplasia (LGD) in Barrett's esophagus: immunohistochemical marker predictive of progression. Am J Gastroenterol 2001; 96:1355.
38. Ormsby AH, Goldblum JR, Rice TW, et al. Cytokeratin subsets can reliably distinguish Barrett's esophagus from intestinal metaplasia of the stomach. Hum Pathol 1999; 30:288.
39. Huo X, Juergens S, Zhang X, et al. Deoxycholic acid causes DNA damage while inducing apoptotic resistance through NF-κB activation in benign Barrett's epithelial cells. Am J Physiol Gastrointest Liver Physiol 2011; 301:G278.

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GRAPHICS

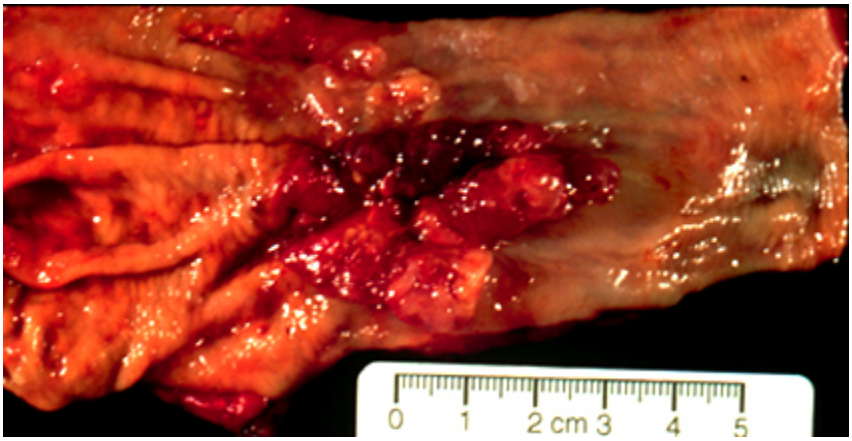
Physiologic abnormalities that may contribute to gastroesophageal reflux disease (GERD) in Barrett's esophagus

Abnormality	Contribution to GERD
Gastric acid hypersecretion with or without duodenogastric reflux	Gastric contents available for reflux are highly caustic to the esophagus due to high concentrations of acid and, with duodenogastric reflux, bile
Extreme hypotension of the lower esophageal sphincter	Impairment in primary antireflux barrier
Poor esophageal contractility	Reduced ability to clear esophagus of refluxed material
Diminished esophageal pain sensitivity	Reduced warning of esophageal injury which can also decrease compliance with antireflux therapy
Decreased salivary secretion of epidermal growth factor	May delay healing of esophagus

Adapted from: Spechler SJ. Barrett's esophagus. Semin Gastrointest Dis 1996; 7:51.

Graphic 66514 Version 3.0

Esophageal adenocarcinoma



Esophageal adenocarcinoma at the gastroesophageal junction in a patient with Barrett's esophagus.

Courtesy of Robert Odze, MD.

Graphic 50584 Version 1.0

Contributor Disclosures

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