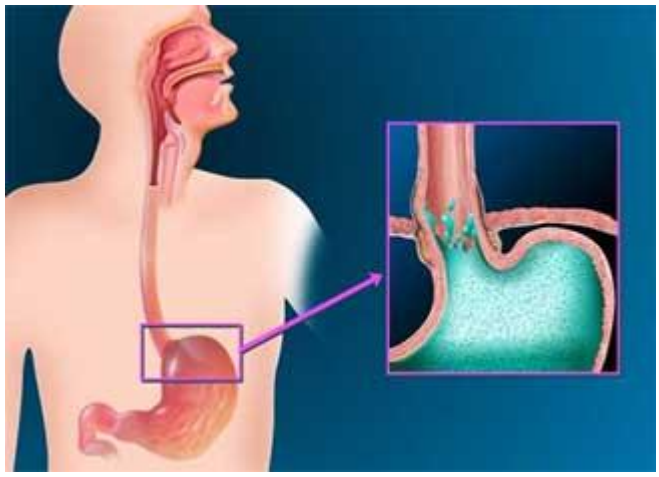
Cancer Association of South Africa (CANSA)

Fact Sheet
on
Barrett's Oesophagus

Introduction

Barrett's Oesophagus is a disorder in which the lining of the oesophagus is damaged. This damage occurs when parts of the oesophageal lining are repeatedly exposed to stomach acid, and are replaced by tissue that is similar to what is found in the intestine.



[Picture Credit: Barrett's Oesophagus]

Que, J., Garman, K.S., Souza, R.F. & Spechler, S.J. 2019.
"In patients with Barrett's esophagus (BE), metaplastic columnar mucosa containing epithelial cells with gastric and intestinal features replaces esophageal squamous mucosa damaged by gastroesophageal reflux disease. This condition is estimated to affect 5.6% of adults in the United States, and is a major risk factor for esophageal adenocarcinoma. Despite the prevalence and importance of BE, its pathogenesis is incompletely understood and there are disagreements over the cells of origin. We review mechanisms of BE pathogenesis, including transdifferentiation and transcommitment, and discuss potential cells of origin, including basal cells of the squamous epithelium, cells of esophageal submucosal glands and their ducts, cells of the proximal stomach, and specialized populations of cells at the esophagogastric junction (residual embryonic cells and transitional basal cells). We discuss the concept of metaplasia as a wound-healing response, and how cardiac mucosa might be the precursor of the intestinal metaplasia of BE. Finally, we discuss shortcomings in current diagnostic criteria for BE that have important clinical implications."

Understanding how the Oesophagus and Stomach Functions

When food is ingested, it passes down the oesophagus into the stomach. Cells in the lining of the stomach produce acid and other chemicals which help to digest the food. Stomach cells also make a thick liquid (mucus) which protects the lining of the stomach from damage caused by the acid. The cells on the inside lining of the oesophagus, are not protected from the acid produced in the stomach.

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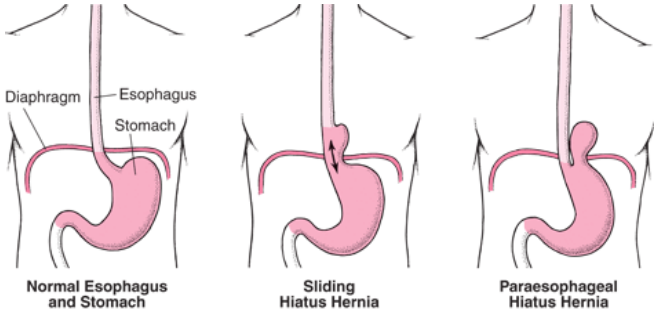
Causes and Risks for Barrett's Oesophagus

[Picture Credit: Hiatus Hernia]



The following are the two main causes of Barrett's Oesophagus:

Acid Reflux - this happens when the valve at the lower end of the oesophagus is weak and allows stomach contents to splash up into the oesophagus. Reflux of acid is very common and many people have symptoms at some point in their lives.

Gastro-Oesophageal Reflux Disease (GORD) - this is when stomach acid irritates the oesophagus.
The risk of having acid reflux is higher in individuals who:

- are overweight
- smoke tobacco
- consume large amounts of alcohol
- eat a lot of spicy or fatty foods
- are white males

The Risk of Oesophageal Cancer from Barrett's Oesophagus

It is known that Barrett's Oesophagus can increase one's risk for cancer of the oesophagus. Such individuals will also need to have regular examinations of the inside of the oesophagus. This is called an endoscopy.

Iver, P.G. & Kaul, V. 2019.

"Barrett esophagus is a metaplastic change in the lining of the distal esophageal epithelium, characterized by replacement of the normal squamous epithelium by specialized intestinal metaplasia. The presence of Barrett esophagus increases the risk of esophageal adenocarcinoma several-fold. Esophageal adenocarcinoma is a malignancy with rapidly rising incidence and persistently poor outcomes when diagnosed after the onset of symptoms. Risk factors for Barrett esophagus include chronic gastroesophageal reflux, central obesity, white race, male gender, older age, smoking, and a family history of Barrett esophagus or esophageal adenocarcinoma. Screening for Barrett esophagus in those with several risk factors followed by endoscopic surveillance to detect dysplasia or adenocarcinoma is currently recommended by society guidelines. Minimally invasive nonendoscopic tools for the early detection of Barrett esophagus are currently being developed. Multimodality endoscopic therapy-using a combination of endoscopic resection and ablation techniques-for the treatment of dysplasia and early adenocarcinoma is successful in eliminating intestinal metaplasia and preventing progression to adenocarcinoma, with outcomes comparable to those after esophagectomy. Risk stratification of those diagnosed with Barrett esophagus is a challenge at present, with active research focused on identifying clinical and biomarker panels to identify those with low and high risk of progression. This narrative review highlights some of the challenges and recent progress in this field."

Alknasser, S., Agnihotram, R., Martel, M., Mayrand, S., Franco, E. & Ferri, L. 2019.

BACKGROUND: It is unknown why some cases of Barrett's esophagus progress to invasive malignant disease rapidly while others do so more slowly or not at all. The aim of this study was to identify demographic and endoscopic factors that predict dysplastic and neoplastic progression in patients with Barrett's esophagus.

METHODS: Patients with Barrett's esophagus who were assessed in 2000–2010 were assessed for inclusion in this retrospective study. Demographic and endoscopic variables were collected from an endoscopy database and the medical chart. Dysplastic and neoplastic progression was examined by time-to-event analysis. We used Cox proportional hazard regression modelling and generalized estimating equation methods to identify variables that were most predictive of neoplastic progression.

RESULTS: A total of 518 patients had Barrett's esophagus confirmed by endoscopy and pathology and at least 2 surveillance visits. Longer Barrett's esophagus segment (≥ 3 cm) (odds ratio [OR] 1.2, 95% confidence interval [CI] 1.1–1.3) and increased age (≥ 60 yr) (OR 3.5, 95% CI 1.7–7.4) were independent predictors of progression from nondysplasia to dysplastic or neoplastic grades. Presence of mucosal irregularities (OR 8.6, 95% CI 2.4–30.4) and increased age (OR 5.1, 95% CI 1.6–16.6) were independent predictors of progression from nondysplasia to high-grade dysplasia or adenocarcinoma.

CONCLUSION: Increased age, longer Barrett's segment and presence of mucosal irregularities were associated with increased risk of dysplastic and neoplastic progression. In addition to dysplasia, these factors may help stratify patients according to risk of neoplastic progression and be used to individualize surveillance. More prospective studies with larger samples are required to validate these results.

Incidence of Barrett's Oesophagus in South Africa

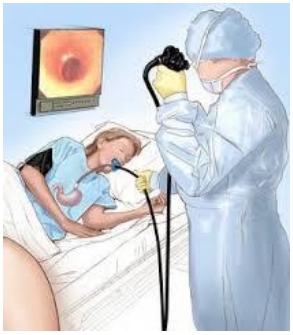
Barrett's Oesophagus is not a cancerous condition itself but rather a precursor to increased risk of dysplastic and neoplastic progression, therefore, the National Cancer Registry (2016) does not provide any information on its incidence in South Africa.

Mukaisho, K-I., Kanai, S., Kushima, R., Nakayama, T., Hattori, T. & Sugihara, H. 2019.

"Barrett's esophagus is considered a precancerous lesion of esophageal adenocarcinoma (EAC). Long-segment Barrett's esophagus, which is generally associated with intestinal metaplasia, has a higher rate of carcinogenesis than short-segment Barrett's esophagus, which is mainly composed of cardiac-type mucosa. However, a large number of cases reportedly develop EAC from the cardiac-type mucosa which has the potential to involve intestinal phenotypes. There is no consensus regarding whether the definition of Barrett's epithelium should include intestinal metaplasia. Basic researches using rodent models have provided information regarding the origins of Barrett's epithelium. Nevertheless, it remains unclear whether differentiated gastric columnar epithelium or stratified esophageal squamous epithelium undergo transdifferentiation into the intestinal-type columnar epithelium, transcommittment into the columnar epithelium, or whether the other pathways exist. Reflux of duodenal fluid including bile acids into the stomach may occur when an individual lies down after eating, which could cause the digestive juices to collect in the fornix of the stomach. N-nitroso-bile acids are produced with nitrites that are secreted from the salivary glands, and bile acids can drive expression of pro-inflammatory cytokines via EGFR or the NF-κB pathway. These steps may contribute significantly to carcinogenesis."

Signs and Symptoms of Barrett's Oesophagus

The exact causes of Barrett's Oesophagus are unknown, but it is thought to be caused in part by the same factors that cause GORD. Although people who do not have heartburn can have Barrett's Oesophagus, it is found about three to five times more often in people with this condition.



Diagnosis of Barrett's Oesophagus

To make a diagnosis of Barrett's Oesophagus an endoscopy of the oesophagus is usually done. A tube is inserted through the mouth and down the oesophagus to view the inside of the oesophagus to take a biopsy of the lining of the oesophagus.

[Picture Credit: Endoscopy]

Codipilly, E.C. & Iyer, P.G. 2019.

Purpose of review: There has been an exponential increase in the incidence of esophageal adenocarcinoma (EAC) over the last half century. Barrett's esophagus (BE) is the only known precursor lesion of EAC. Screening for BE in high-risk populations has been advocated with the aim of identifying BE, followed by endoscopic surveillance to detect dysplasia and early stage cancer, with the intent that treatment can improve outcomes. We aimed to review BE screening methodologies currently recommended and in development.

Recent findings: Unsedated transnasal endoscopy allows for visualization of the distal esophagus, with potential for biopsy acquisition, and can be done in the office setting. Non-endoscopic screening methods being developed couple the use of swallowable esophageal cell sampling devices with BE specific biomarkers, as well as trefoil factor 3, methylated DNA markers, and microRNAs. This approach has promising accuracy. Circulating and exhaled volatile organic compounds and the foregut microbiome are also being explored as means of detecting EAC and BE in a non-invasive manner. Non-invasive diagnostic techniques have shown promise in the detection of BE and may be effective methods of screening high-risk patients.

Snyder, P., Dunbar, K., Cipher, D.J., Souza, R.F., Soechler, S.J. & Konda, V.J.A. 2019.

"Risk stratification of patients with Barrett's esophagus (BE) presently relies on the histopathologic grade of dysplasia found in esophageal biopsies, which is limited by sampling error and inter-pathologist variability. p53 immunostaining of BE biopsies has shown promise as an adjunct tool but is not recommended by American gastroenterology societies, who cite insufficient evidence of its prognostic value. We have conducted a systematic review and meta-analyses to clarify this value. We searched for studies that: (1) used immunohistochemistry to assess p53 expression in esophageal biopsies of BE patients and (2) reported subsequent neoplastic progression. We performed separate meta-analyses of case-control studies and cohort studies. We identified 14 relevant reports describing 8 case-control studies comprising 1435 patients and 7 cohort studies comprising 582 patients. In the case-control study meta-analysis of the risk of neoplasia with aberrant p53 expression, the fixed- and random-effect estimates of average effect size with aberrant p53 expression were OR 3.84, $p < .001$ (95% CI 2.79-5.27) and OR 5.95, $p < .001$ (95% CI 2.68-13.22), respectively. In the cohort study meta-analysis, the fixed- and random-effect estimates of average effect size were RR = 17.31, $p < .001$ (95% CI 9.35-32.08) and RR = 14.25, $p < .001$ (95% CI 6.76-30.02), respectively. Separate meta-analyses of case-control and cohort studies of BE patients who had baseline biopsies with p53 immunostaining revealed consistent, strong, and significant associations between aberrant p53 immunostaining and progression to high-grade dysplasia or

esophageal adenocarcinoma. These findings support the use of p53 immunostaining as an adjunct to routine clinical diagnosis for dysplasia in BE patients."

Callahan, Z.M., Shi, Z., Su, B., Xu, J. & Ujiki, M. 2019.
"Surveillance of Barrett's esophagus (BE) is a clinical challenge; metaplasia of the distal esophagus increases a patient's risk of esophageal adenocarcinoma (EAC) significantly but the actual percentage of patients who progress is low. The current screening recommendations require frequent endoscopy and biopsy, which has inherent risk, high cost, and operator variation. Identifying BE patients genetically who are at high risk of progressing could deemphasize the role of endoscopic screening and create an opportunity for early therapeutic intervention. Genetic alterations in germline DNA have been identified in other disease processes and allow for early intervention or surveillance well before disease develops. The genetic component of BE remains mostly unknown and only a few genome-wide association studies exist on this topic. This review summarizes the current literature available that examines genetic alterations in BE and EAC with a particular emphasis on clinical implications."

Management of Barrett's Oesophagus
Once Barrett's Oesophagus has been identified, patients usually undergo periodic surveillance to detect possible cancerous changes in time.

Pharmacologic treatment for Barrett's Oesophagus is usually the same as that for GORD.

The diet for patients with Barrett's Oesophagus is the same as that recommended for patients with GORD. Patients should try and avoid the following:

- Fried or fatty foods
- Chocolate
- Peppermint
- Alcohol
- Coffee
- Carbonated beverages
- Citrus fruits or juices
- Tomato sauce
- Ketchup
- Mustard
- Vinegar
- Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs)

Treatment of Barrett's Oesophagus
Treatment for Barrett's Oesophagus depends on the degree of dysplasia found in the oesophagus cells and the person's overall health. It may include:

- Periodic endoscopy to monitor the cells in your oesophagus.
- Treatment for GORD.
- Endoscopic resection
- Radiofrequency ablation
- Cryotherapy
- Photodynamic therapy
- Surgery in which the damaged part of the oesophagus is

Kwiecien, S., Magierowski, M., Majka, J., Ptak-Belowska, A., Wojcik, D., Sliwowski, Z., Magierowska, K. & Brzozowski, T. 2019.
"Turmeric obtained from the rhizomes of Curcuma longa has been used in the prevention and treatment of many diseases since the ancient times. Curcumin is the principal polyphenol isolated from turmeric, which exhibits anti-inflammatory, antioxidant, antiapoptotic, antitumor, and antimetastatic activities. The existing evidence indicates that curcumin can exert a wide range of beneficial pleiotropic properties in the gastrointestinal tract, such as protection against reflux esophagitis, Barrett's esophagus, and gastric mucosal damage induced by nonsteroidal anti-inflammatory drugs (NSAIDs) and necrotizing agents. The role of curcumin as an adjuvant in the treatment of a *Helicobacter pylori* infection in experimental animals and humans has recently been proposed. The evidence that this turmeric derivative inhibits the invasion and proliferation of gastric cancer cells is encouraging and warrants further experimental and clinical studies with newer formulations to support the inclusion of curcumin in cancer therapy regimens. This review was designed to analyze the existing data from in vitro and in vivo animal and human studies in order to highlight the mechanisms of therapeutic efficacy of curcumin in the protection and ulcer healing of the upper gastrointestinal tract, with a major focus on addressing the protection of the esophagus and stomach by this emerging compound."

Singh, T., Sanghi, V. & Thota, P.N. 2019.
"Barrett esophagus is found in 5% to 15% of patients with gastroesophageal reflux disease and is a precursor of esophageal adenocarcinoma, yet the condition often goes undiagnosed. Patients with reflux disease who are male, over age 50, or white, and who smoke or have central obesity or a family history of Barrett esophagus or esophageal adenocarcinoma, should undergo initial screening endoscopy and, if no dysplasia is noted, surveillance endoscopy every 3 to 5 years. Dysplasia is treated with endoscopic eradication by ablation, resection, or both. Chemoprotective agents are being studied to prevent progression to dysplasia in Barrett esophagus. The authors discuss current recommendations for screening and management."

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Sources and References Consulted or Utilised

Alknasser, S., Agnihotram, R., Martel, M., Mayrand, S., Franco, E. & Ferri, L. 2019. Predictors of dysplastic and neoplastic progression of Barrett's esophagus. *Can J Surg*. 2019 Apr 1;62(2):93-99.

Barrett's Oesophagus
http://www.barretts-oesophagus.co.uk/patients_what.htm

Callahan, Z.M., Shi, Z., Su, B., Xu, J. & Ujiki, M. 2019. Genetic variants in Barrett's esophagus and esophageal adenocarcinoma: aliterature review. *Dis Esophagus*. 2019 Mar 19. pii: doz017. doi: 10.1093/dote/doz017. [Epub ahead of print]

Cancer Research UK
http://www.cancerresearchuk.org/about-cancer/cancers-in-general/cancer-questions/what-is-barretts-oesophagus

Centre for Digestive Diseases
http://www.cdd.com.au/pages/disease_info/barretts_oesophagus.html

Codipilly, E.C. & Iyer, P.G. 2019. Novel screening tests for Barrett's Oesphagus. *Curr Gastroenterol Rep*. 2019 Jul 25;21(9):42. doi: 10.1007/s11894-019-0710-9.

Eluri, S. & Shabeen, N.J. 2017. Endoscopic eradication therapy in Barret's esophagus.
Tech Gastrointest Endosc. 2017 Jul;19(3):137-142. doi: 10.1016/j.tgie.2017.06.001. Epub 2017 Jun 12. PMID: 29269998.

Endoscopy
http://www.tbeeb.net/a-1187.htm

Iver, P.G. & Kaul, V. 2019. Barret Esophagus. *Mayo Clin Proc*. 2019 Sep;94(9):1888-1901. doi: 10.1016/j.mayocp.2019.01.032.

Kwiecien, S., Magierowski, M., Majka, J., Ptak-Belowska, A., Wojcik, D., Sliwowski, Z., Magierowska, K. & Brzozowski, T. 2019. Curcumin: a potent protectant against esophageal and gastric disorders. *Int J Mol Sci*. 2019 Mar 24;20(6). pii: E1477. doi: 10.3390/ijms20061477.

MacMillan Cancer Support
http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Oesophagusgullet/Pre-cancerousconditions/Barrettsoesophagus.aspx

McDevitt, D. & Mason, A. 2018. Treating Barret esophagus with radiofrequency ablation.
Nursing. 2018 Jan;48(1):26-32. doi: 10.1097/01.NURSE.0000527594.94344.6f. No abstract available. PMID: 29280837.

Medscape
http://emedicine.medscape.com/article/171002-overview

Mukaisho, K-I., Kanai, S., Kushima, R., Nakayama, T., Hattori, T. & Sugihara, H. 2019. Barrets's carcinogenesis. *Pathol Int*. 2019 Jun;69(6):319-330. doi: 10.1111/pin.12804. Epub 2019 Jul 10.

National Cancer Institute
http://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials

Parasa, S., Vennalaganti, S., Gaddam, S., Vennalaganti, P., Young, P., Gupta, N., Thota, P., Cash, B., Mathur, S., Sampliner, R., Moawad, F., Lieberman, D., Bansal, A., Kennedy, K.F., Vargo, J., Falk, G., Spaander, M., Bruno, M. & Sharma, P. 2017. Development and validation of a model to determine risk of progression of Barret's esophagus neoplasia. *Gastroenterology*. 2017 Dec 19. pii: S0016-5085(17)36713-6. doi: 10.1053/j.gastro.2017.12.009. [Epub ahead of print]. PMID: 29273452.

Patient.co.uk
http://www.patient.co.uk/health/barretts-oesophagus-leaflet

Que, J., Garman, K.S., Souza, R.F. & Spechler, S.J. 2019. Pathogenesis and cells of origin of Barret's Oesophagus. *Gastroenterology*. 2019 Aug;157(2):349-364.e1. doi: 10.1053/j.gastro.2019.03.072. Epub 2019 May 10.

Sami, S.S. & Iyer, P.G. 2018. Recent advances in screening for Barret's esophagus. *Curr Treat Options Gastroenterol*. 2018 Jan 13. doi: 10.1007/s11938-018-0166-2. [Epub ahead of print] Review. PMID: 29330747.

Singh, T., Sanghi, V. & Thota, P.N. 2019. Current management of Barrett Esophagus and esophageal adenocarcinoma. *Cleve Clin J Med*. 2019 Nov;86(11):724-732. doi: 10.3949/ccjm.86a.18106.

Snyder, P., Dunbar, K., Cipher, D.J., Souza, R.F., Soechler, S.J. & Konda, V.J.A. 2019. Aberrant p53 immunostaining in Barrett's esophagus predicts neoplastic progression: systematic review and meta-analyses. *Dig Dis Sci*. 2019 Mar 26. doi: 10.1007/s10620-019-05586-7. [Epub ahead of print]

Tan, W.K., di Pietro, M. & Fitzgerald, R.C. 2017. Past, present and future of Barrett's oesophagus. *Eur J Surg Oncol*. 2017 Jul;43(7):1148-1160. doi: 10.1016/j.ejso.2017.02.004. Epub 2017 Feb 16.

WebMD
http://www.webmd.boots.com/heartburn-gord/guide/barretts-oesophagus?page=3

Zakko, L., Lutzke, L. & Wang, K.K. 2017. Screening for Barrett's esophagus. *Minerva Med*. 2017 Feb;108(1):28-42. doi: 10.23736/S0026-4806.16.04864-3. Epub 2016 Oct 28.