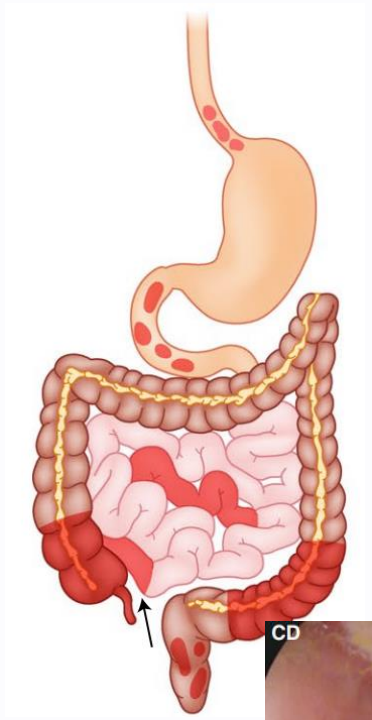
GI Conditions in Life Insurance

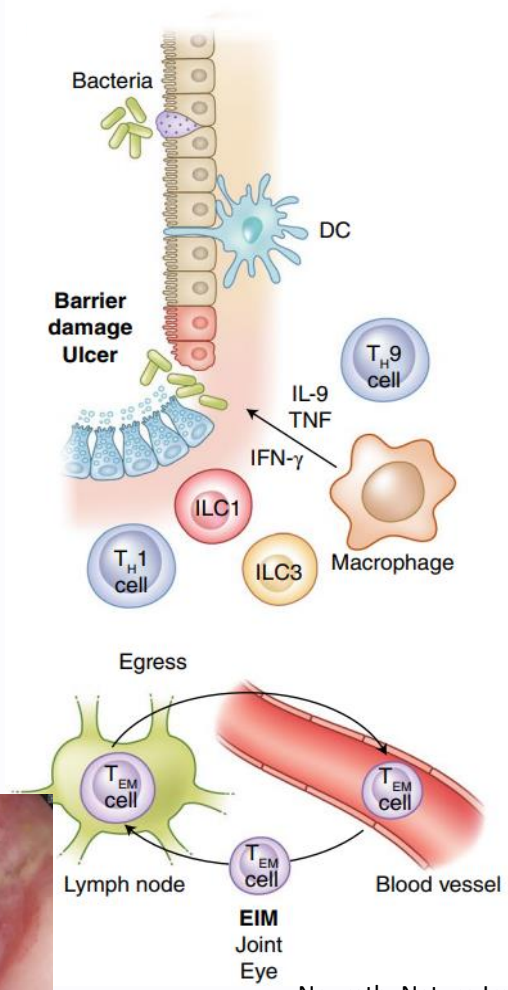
Updates on Inflammatory Bowel Disease and Barrett's Esophagus

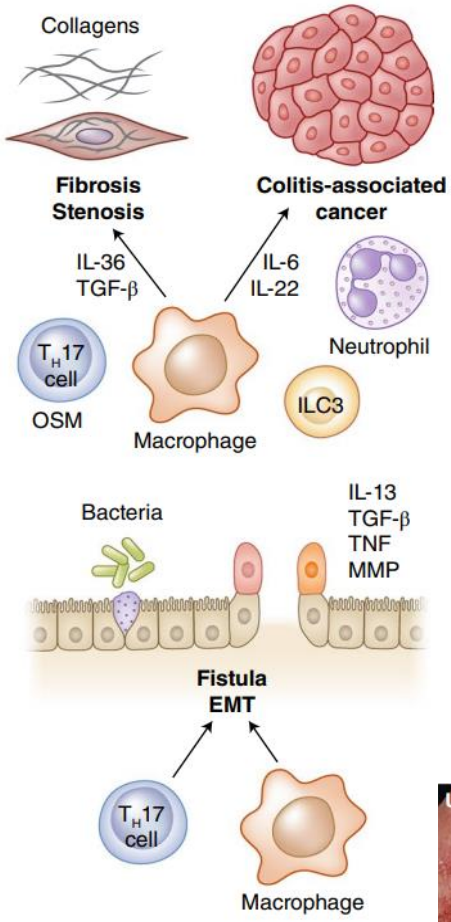
Tobias Schiergens

Inflammatory Bowel Diseases

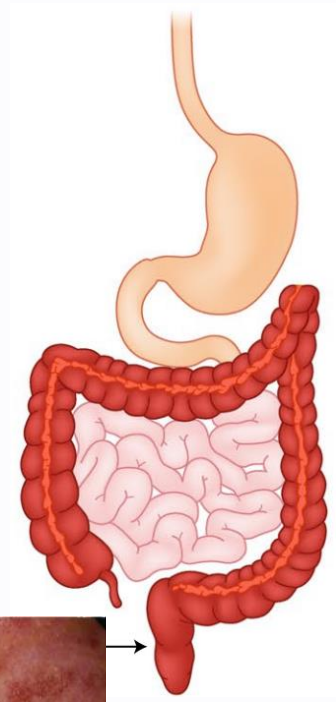
Crohn's Disease (CD)

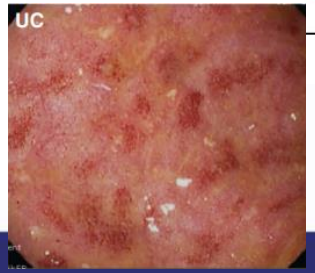






Ulcerative Colitis (UC)

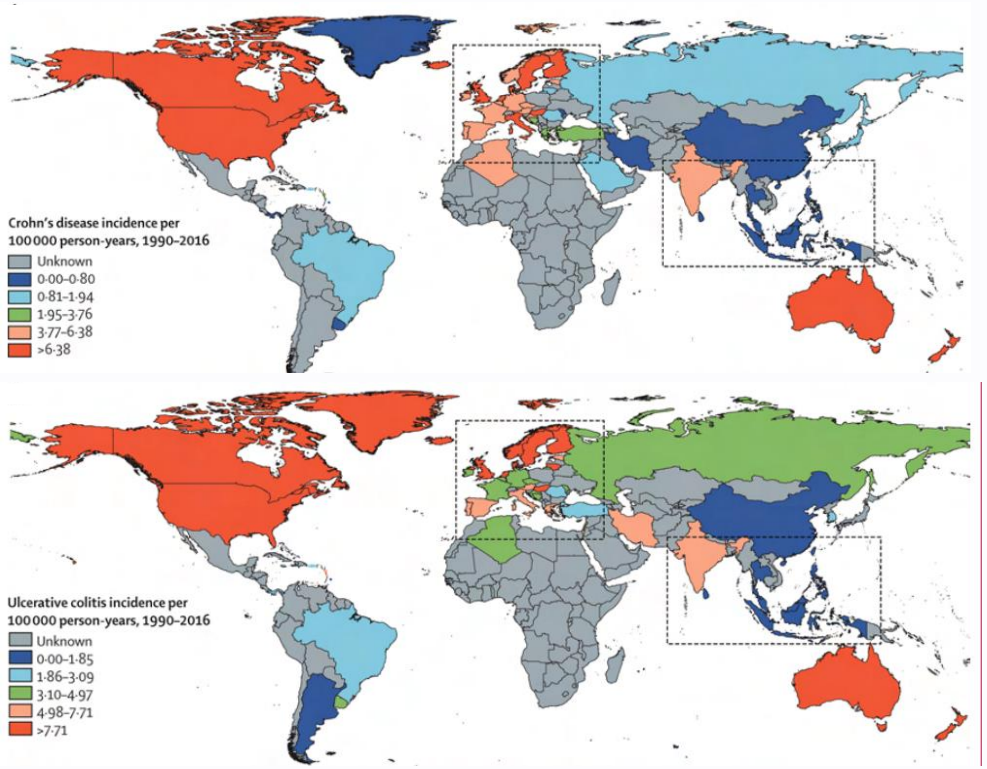




Neurath, Nature Immunology 2019;20:970

IBD – Epidemiology

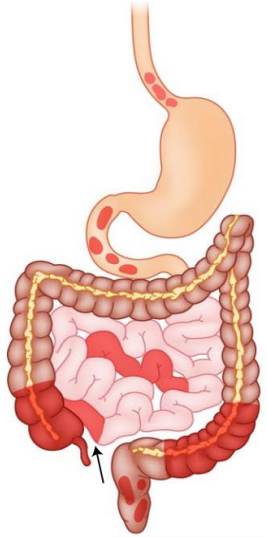
- 3.1 million (1.3%) of U.S. adults had ever received a diagnosis of IBD
- Accelerating incidence has stabilized in Western countries
- Higher prevalence of IBD among non-Hispanic whites
- Age of onset usually between 15 and 30 years
- Slight female predominance in adult-onset CD, slight male predominance in UC

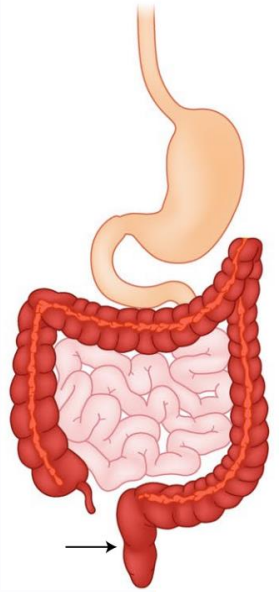


	Incidence per 100 000 person-years				Prevalence per 100 000			
	Crohn's disease		Ulcerative colitis		Crohn's disease		Ulcerative colitis	
	Lowest estimate	Highest estimate	Lowest estimate	Highest estimate	Lowest estimate	Highest estimate	Lowest estimate	Highest estimate
North America	6·30 (California, USA)	23·82 (Nova Scotia, Canada)	8·8 (Olmsted County, USA)	23·14 (Nova Scotia, Canada)	96·3 (California, USA)	318·5 (Nova Scotia, Canada)	139·8 (Quebec, Canada)	286·3 (Olmsted County, USA)

Centers for Disease Control and Prevention; CDC
Ng et al., Lancet 2017;390:2769

	Crohn's Disease	Ulcerative Colitis
Symptoms	Abdominal pain, diarrhea, nausea, vomiting, loss of appetite, weight loss, fever, fatigue	
Localization	Entire digestive tract -Small bowel involvement: ~ 80% -Perianal disease: ~ 40%	Colon and rectum, backwash ileitis
Inflammation	Transmural	Superficial mucosal
Histology	Granulomas, increased goblet cells	Crypt abscesses, depletion of goblet cells
Smoking	Aggravating	Protective
Endoscopy	Skip lesions, deep ulcers, cobblestone appearance	Continuous lesions, pseudopolyps
Complications	Strictures, fissures, fistulas, venous thromboembolism, colorectal cancer	Toxic megacolon, venous thromboembolism, colorectal cancer
Extraintestinal manifestations	Erythema nodosum, pyoderma gangrenosum, arthritis, ocular manifestations	
Associations	Gallstones	Primary sclerosing cholangitis (PSC)





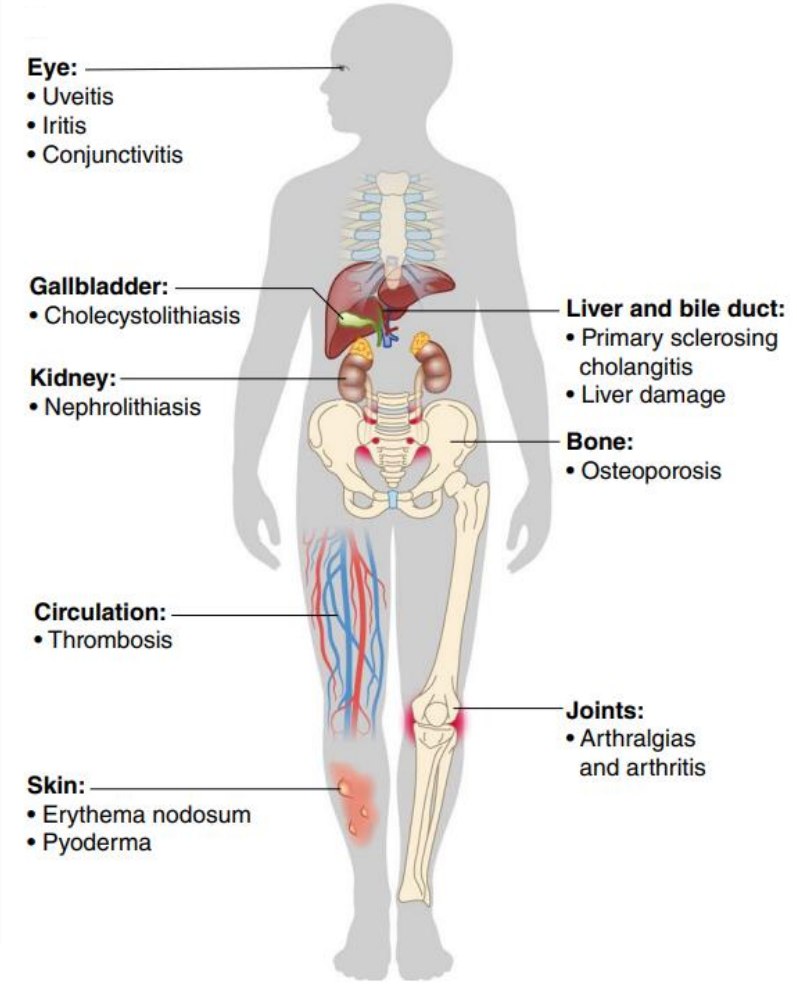
Neurath, Nature Immunology 2019;20:970
Schiergens, Basics Surgery, 2018, 4th ed., Elsevier

IBD – Extraintestinal Manifestations

<10%
EIM at diagnosis

25%
EIM in their lifetime

- Arthritis / arthropathy most frequent EIM
- Liver and lung most relevant for mortality
- EIM present prior to surgery will persist in about half of patients after colectomy. Complete cessation of EIM after colectomy may be less common in CD than in UC



Neurath, Nature Immunology 2019;20:970
Roth et al., United European GastroenterolJ.2021;9:773.

Crohn's Disease – Severity

- Classification based on age of onset, disease location, and disease behavior (Montreal Classification)
- Management based on disease manifestation, activity (CDAI), severity and risk
  - Symptoms
  - CRP, fecal calprotectin
  - Age at diagnosis
  - Distribution of bowel inflammation
  - Ulceration on colonoscopy
  - Perianal complications
  - Extra-intestinal manifestations
  - Prior surgery / intestinal resections
  - Penetrating or stricturing disease

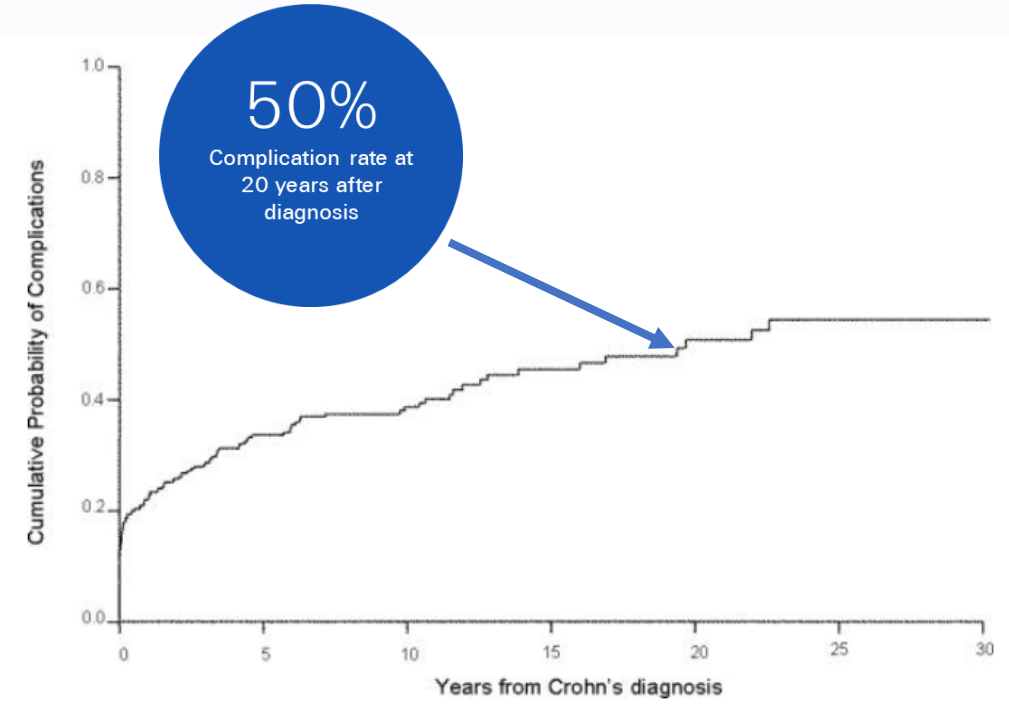
Age at diagnosis
A1 below 16 years
A2 between 17 and 40 years
A3 above 40 years
Location
L1 ileal
L2 colonic
L3 ileocolonic
L4 isolated upper disease*
Behavior
B1 nonstricturing, nonpenetrating
B2 stricturing
B3 penetrating
p perianal disease modifier¶

Regueiro et al., UpToDate.com
Sandborn et al., Gastroenterology. 2014;147:702

Crohn's disease – Disease course

- In ~ 20% prolonged remission after initial presentation
- Ileal involvement associated with a shorter time interval
- Risk factors associated with progressive disease:
  - Age < 40 years
  - Tobacco use
  - Perianal or rectal involvement
  - Steroid-dependent disease

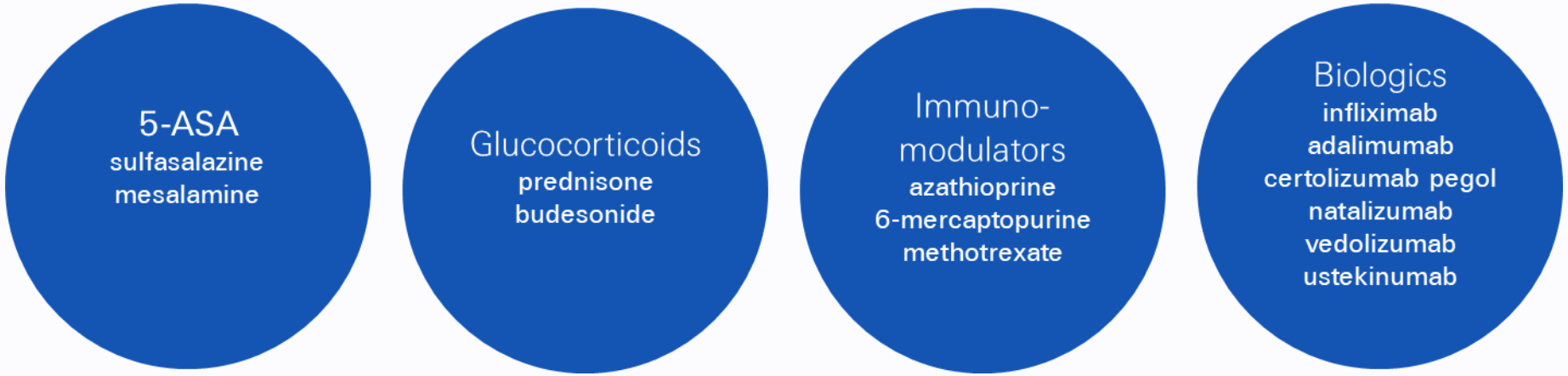
Penetrating or stricturing complications



Solberg et al., Clin Gastroenterol Hepatol 2007;5:1430
Thia et al., Gastroenterology 2010;139:1147
Beaugerie et al., Gastroenterology 2006;130:650
Cosnes et al., Gut 2012;61:1140

Crohn's Disease – Medical treatment

- Induction and maintenance of remission
- Managing relapse / refractory disease
- Management of complications

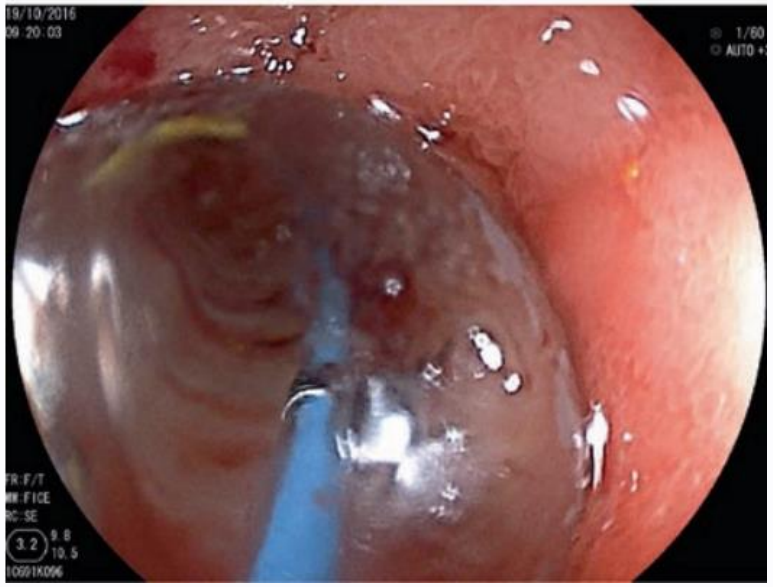


Regueiro et al., UpToDate.com
Sandborn et al., Gastroenterology. 2014;147:702

Crohn's Disease – Endoscopic treatment

Management of symptoms and / or complications

- Intestinal obstruction (fibrotic strictures)



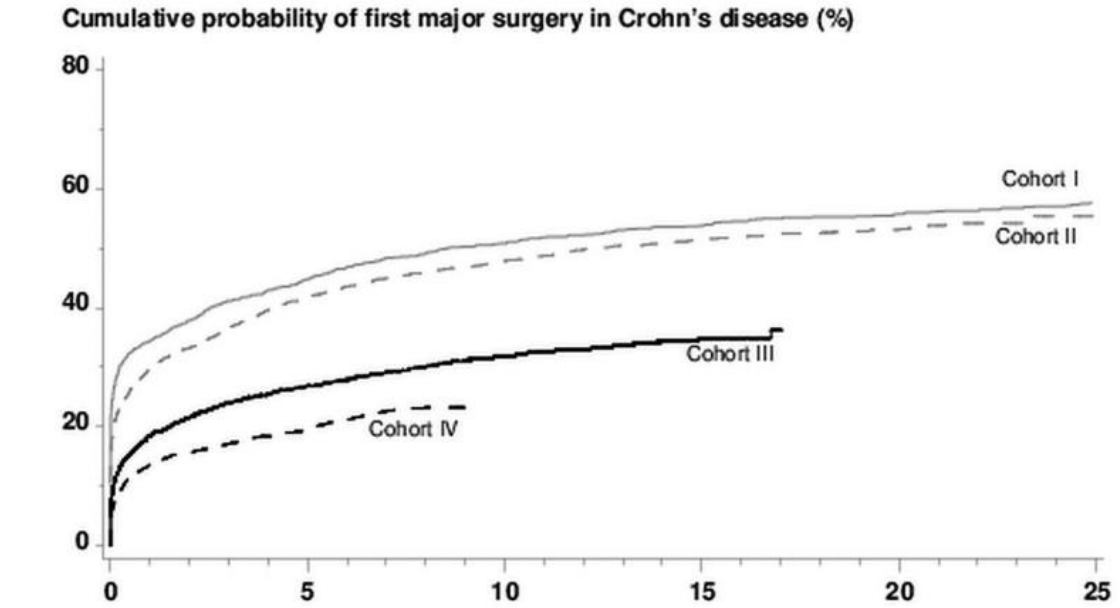
Hoffmann et al., Inflammatory Bowel Diseases, 2019, 3rd ed., Springer

Crohn's Disease – Surgical treatment

Management of symptoms and complications

- Bowel perforations, abscess, peritonitis
- Bleeding
- Intestinal obstruction (fibrotic strictures, conglomerates, etc.)
- Enteric fistulas / perianal fistulas
- Cancer

- Surgical treatment
  - Careful resections (ileo-colic)
  - strictureplasty
  - Oncologic surgery

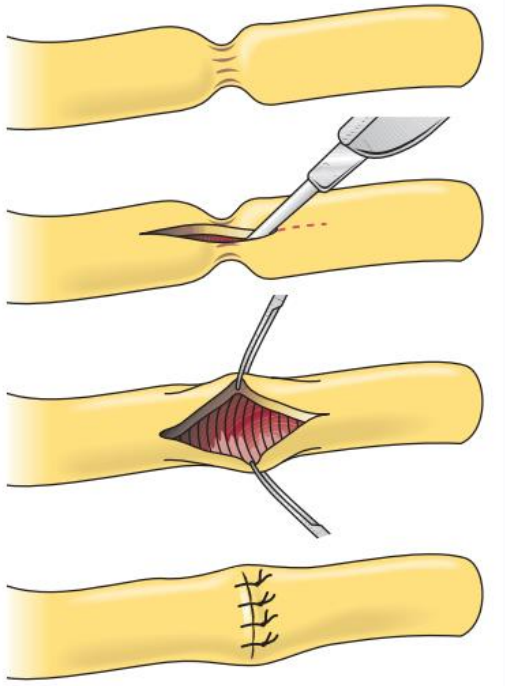


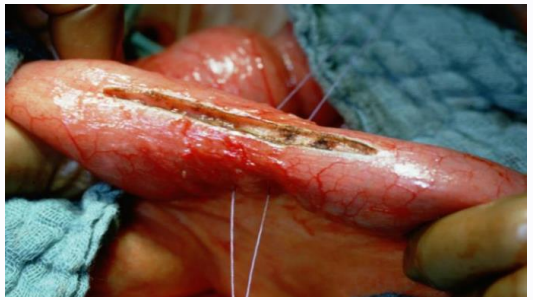
CP.	1 y.	5 yrs.	9 yrs.
Cohort I (1979–86)	34.4%	44.7%	50.3%
Cohort II (1987–94)	29.6%	41.7%	46.8%
Cohort III (1995–02)	18.4%	26.7%	31.1%
Cohort IV (2003–11)	13.6%	19.6%	23.3%

Schiergens, Basics Surgery, 2018, 4th ed., Elsevier
Rungoe et al. Gut 2014;63:1607

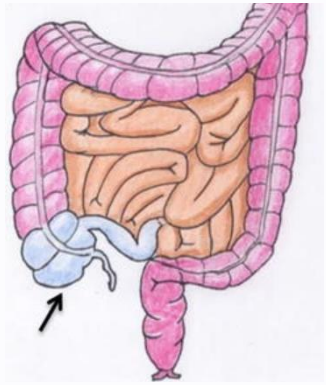
Crohn's Disease – Surgical treatment

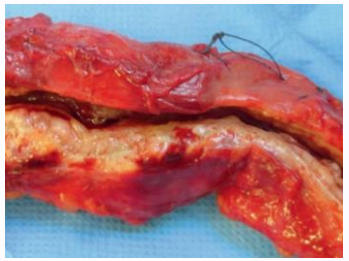
Strictureplasty

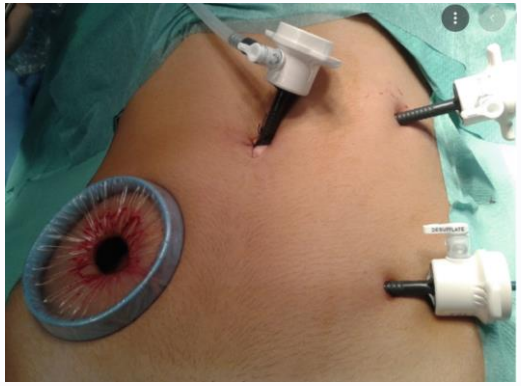


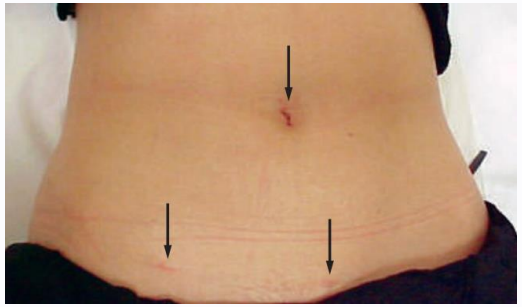


Resection



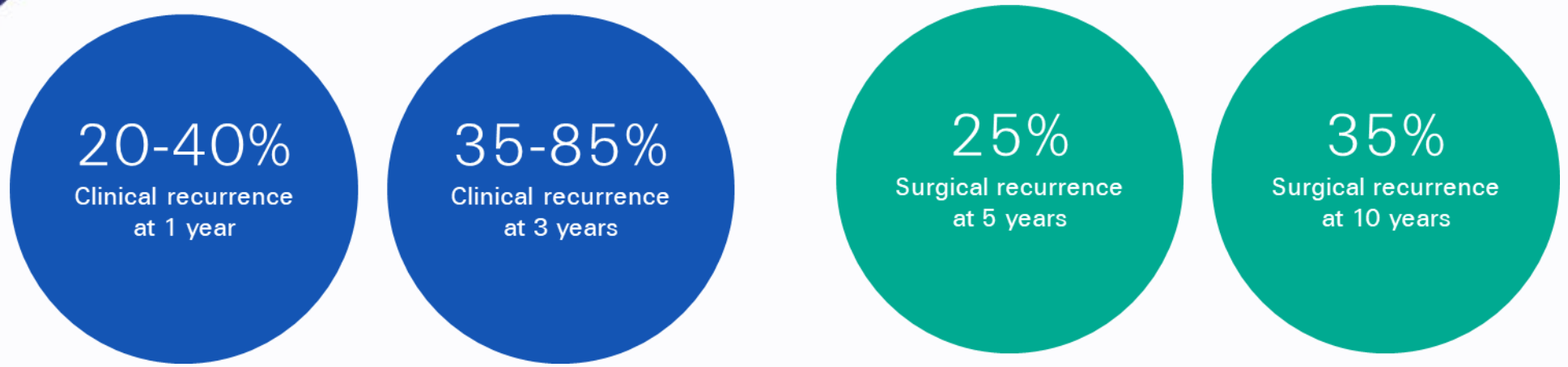






Schiergens, Basics Surgery, 2018, 4th ed., Elsevier
Hoffmann et al., Inflammatory Bowel Diseases, 2019, 3rd ed., Springer
Quon et al., Abdominal Imaging 2015;40:1034
Polle et al., Nat Rev Gastroenterol Hepatol 2007;4:324

Crohn's Disease – Surgical treatment: Recurrence

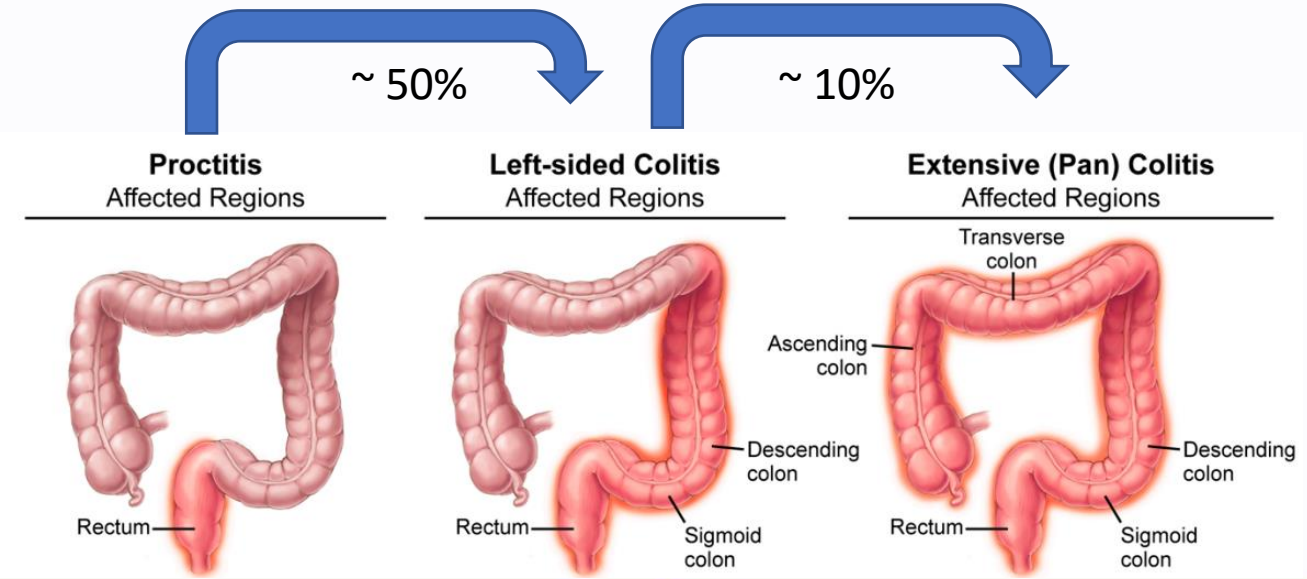


- Smoking: Recurrence at 10 years, clinical: OR 2.2; surgical OR 2.6
- Genetics, e.g. NOD2/CARD15 mutation
- Disease duration: OR ~ 1.10/a
- Disease extent: proximal gastrointestinal and diffuse disease that involves the colon
- Penetrating, fistulizing disease: OR 4.1
- Stricturing disease: OR 2.4
- Surgical technique: Side to side vs. end-to-end anastomosis

Schiergens et al., Z Gastroenterol 2017;55:57
Swoger et al., Gastroenterol Clin North Am 2012;41:303
Fumery et al., Aliment Pharmacol Ther 2017;45:381
Frolkis et al., Am J Gastroenterol 2014;109:1739
Reese et al., Int J Colorectal Dis 2008;23(12):1213
Alvarez-Lobos et al., Ann Surg 2005;242:693
Avidan et al., Digestion 2005;72:248
Sampietro et al., Clin Gastroenterol Hepatol 2009;7:183

Ulcerative Colitis – Severity and Disease Extent

- Clinical disease activity index, Montreal classification, Mayo scoring system
  - Symptoms (number of stools, bleeding, fever,)
  - Anemia, anorexia, albumin
  - Severe endoscopic disease (eg, deep ulcerations)
  - Systemic toxicity: CRP, fecal calprotectin
  - Extraintestinal manifestations
  - Age



Peppercorn et al., UpToDate.com
Kayal et al., Clin Med 2020;9:94
Hashash et al., UptoDate.com

Ulcerative Colitis – Medical treatment options

Mild to moderate disease

- **Proctitis or proctosigmoiditis:** Topical mesalamine (topical glucocorticoids), oral 5-ASA agents
- **Left-sided or extensive colitis:** combination of an oral 5-ASA agent plus rectal mesalamine / +/- budesonide MMX / systemic glucocorticoid therapy with prednisone

Moderate to severe disease

- TNF therapy (infliximab, adalimumab, golimumab) with or without an immunomodulator (eg, azathioprine) is used to induce remission
- vedolizumab (anti-integrin antibody), ustekinumab (anti-interleukin 12/23 antibody), glucocorticoids
- Non-responders: Janus kinase (JAK) inhibitors, tofacitinib, upadacitinib, ozanimod, iv glucocorticoids

Regueiro et al., UpToDate.com
Sandborn et al., Gastroenterology. 2014;147:702

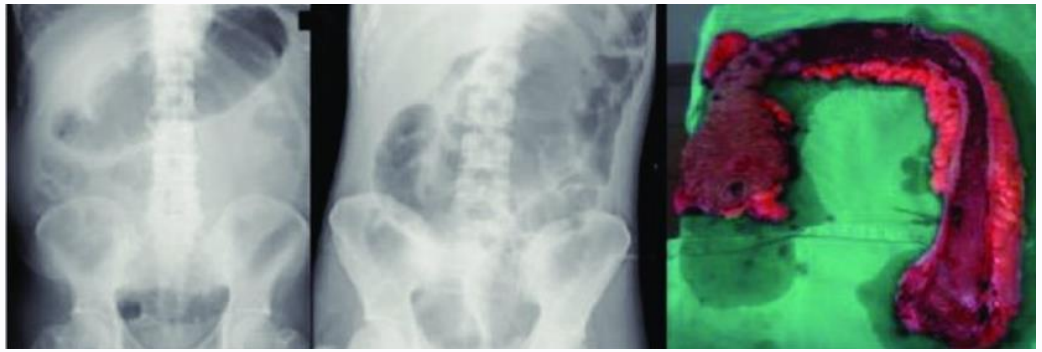
Ulcerative Colitis – Complications

Acute

- **Severe bleeding:** in up to 10 % of patients
- **Fulminant colitis and toxic megacolon:** > 10 stools per day, bleeding, abdominal pain, distension, and sepsis
- **Perforation:** most commonly as a consequence of toxic megacolon

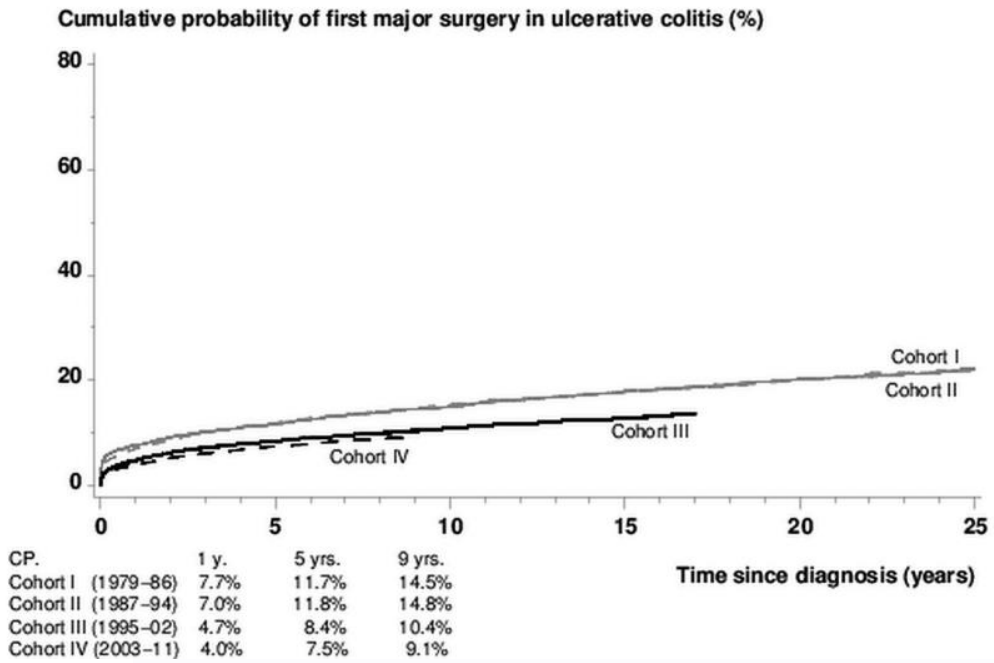
Chronic

- **Benign strictures:** in ~ 10%, most frequently in the rectosigmoid colon and may cause symptoms of obstruction
- **Dysplasia, colorectal cancer**



Peppercorn et al., UpToDate.com
Santos, Current Topics in Surgery 2021, DOI: 10.5772/intechopen.98987

Ulcerative Colitis – Surgery



CP.	1 y.	5 yrs.	9 yrs.
Cohort I (1979–86)	7.7%	11.7%	14.5%
Cohort II (1987–94)	7.0%	11.8%	14.8%
Cohort III (1995–02)	4.7%	8.4%	10.4%
Cohort IV (2003–11)	4.0%	7.5%	9.1%

Elective
Moderate to severe disease, persistent symptoms despite medical therapy, intolerance of medical therapy, dysplasia, cancer

Urgent
Acute fulminant colitis refractory to medical treatment

Emergency
Perforation, toxic megacolon, massive hemorrhage

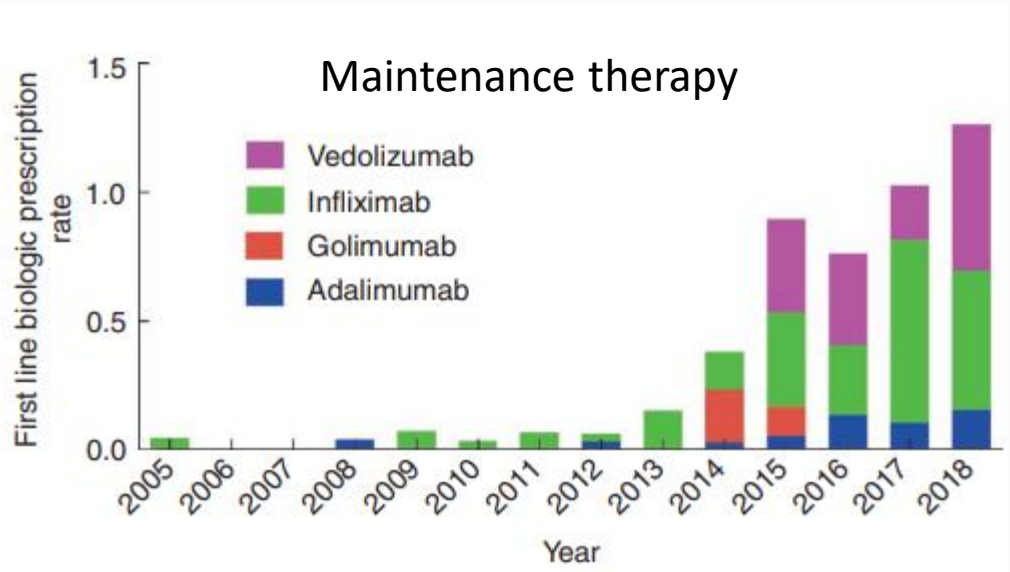
10-year colectomy risk

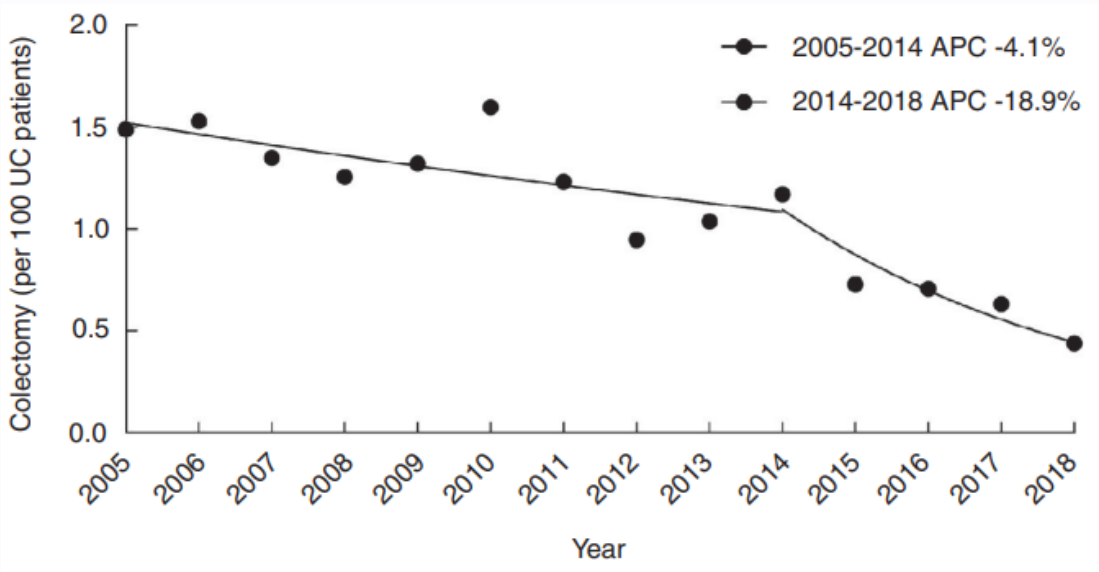
20%
Pancolitis

5%
Proctitis

Hoffmann et al., Inflammatory Bowel Diseases, 2019, 3rd ed., Springer
Rungoe et al., Gut 2014;63:1607

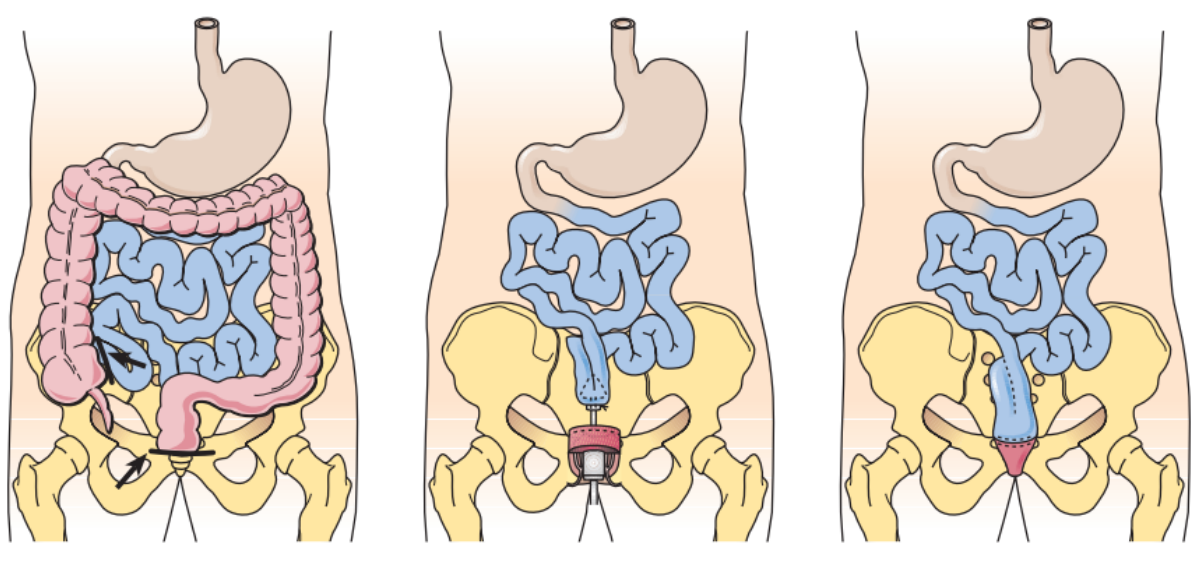
Ulcerative Colitis – Surgery





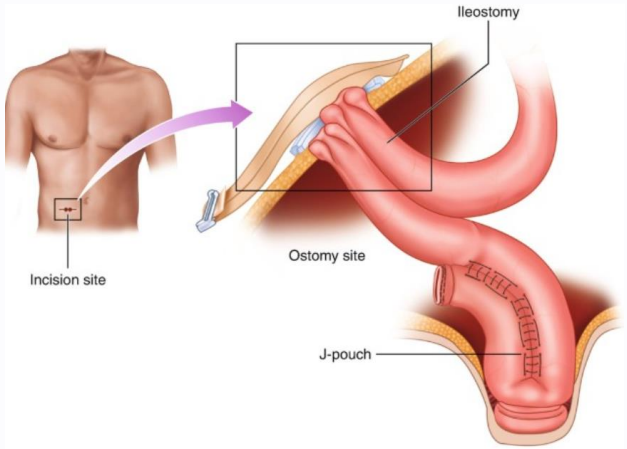
Jenkinson et al., Colorectal Dis 2021;23:1175

Ulcerative Colitis – Surgery



Elective restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA)
as one, two-, or three-stage procedure

- total abdominal colectomy and ileostomy
- completion proctectomy with an IPAA and loop ileostomy
- loop ileostomy gets reversed



Schiergens, Basics Surgery, 2018, 4th ed., Elsevier
Giambartolomei et al., Mental Conditioning to Perform Common Operations in General Surgery, 2020, Springer

Inflammatory Bowel Diseases – Cancer Risk

CD

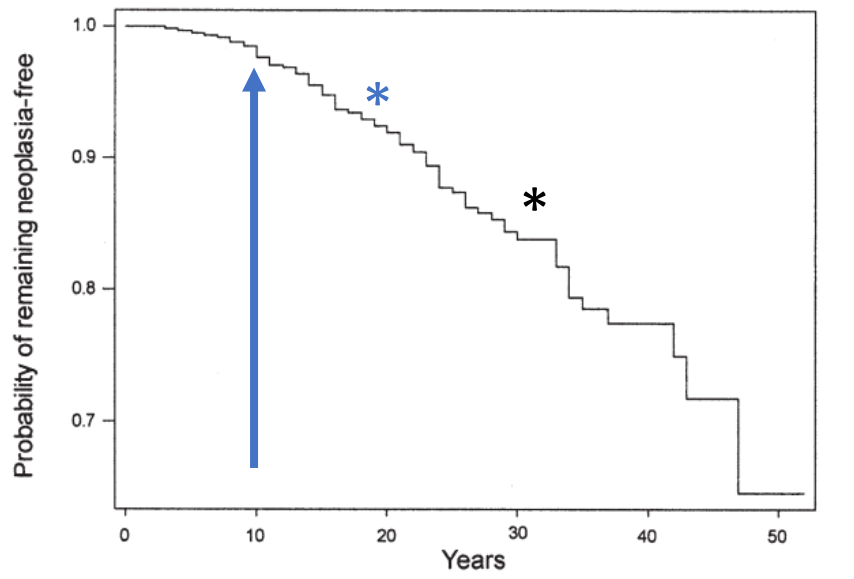
- CRC risk in longstanding CD involving the colon is probably comparable to UC
- (Weak) indications of increased risks: squamous cell carcinoma of the anus and skin, adenocarcinoma of the small bowel, duodenal neoplasia, testicular cancer, leukemia / hematologic malignancies

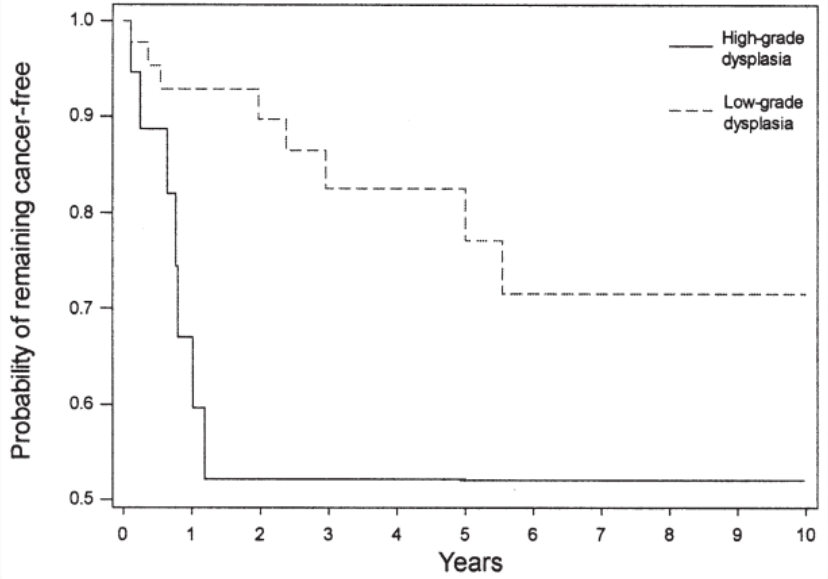
UC

- The **extent of colitis** and **duration of disease** are the two most important risk factors for CRC
- The CRC risk begins to increase at ~ 8 - 10 years

Cumulative incidence

- 3-5 % after 20 yrs. *
- 8-10 % after 30 yrs. *





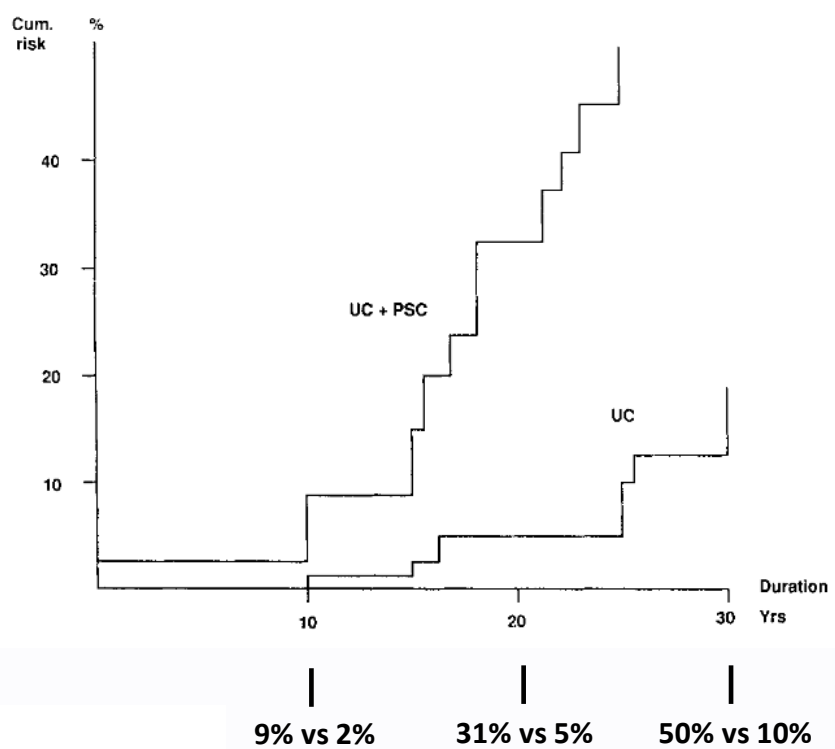
Hemminki et al., Ann Oncol. 2009;20:574
Levin, Cancer 1992;70:1313
Rutter et al., Gastroenterology 2006;130:1030

Inflammatory Bowel Diseases – Primary sclerosing cholangitis

!

90%
Prevalence of IBD in PSC, 80% thereof UC

5%
Prevalence of PSC in UC



- Median survival without liver transplantation: 10(-20) yrs.
- Cholestasis, P-ANCA (30-80%), IgM increase (40-50%)
- Colitis usually has a mild or quiescent course
- Higher risk of pouchitis and peristomal varices following proctocolectomy + IPAA
- Patients with concurrent PSC and IBD have a higher risk of colorectal cancer

Loftus et al., Gut 2005;54:91
Mertz et al., Ann Gastroenterol 2019;32:124
Broomé et al., Hepatology. 1995;22:1404.

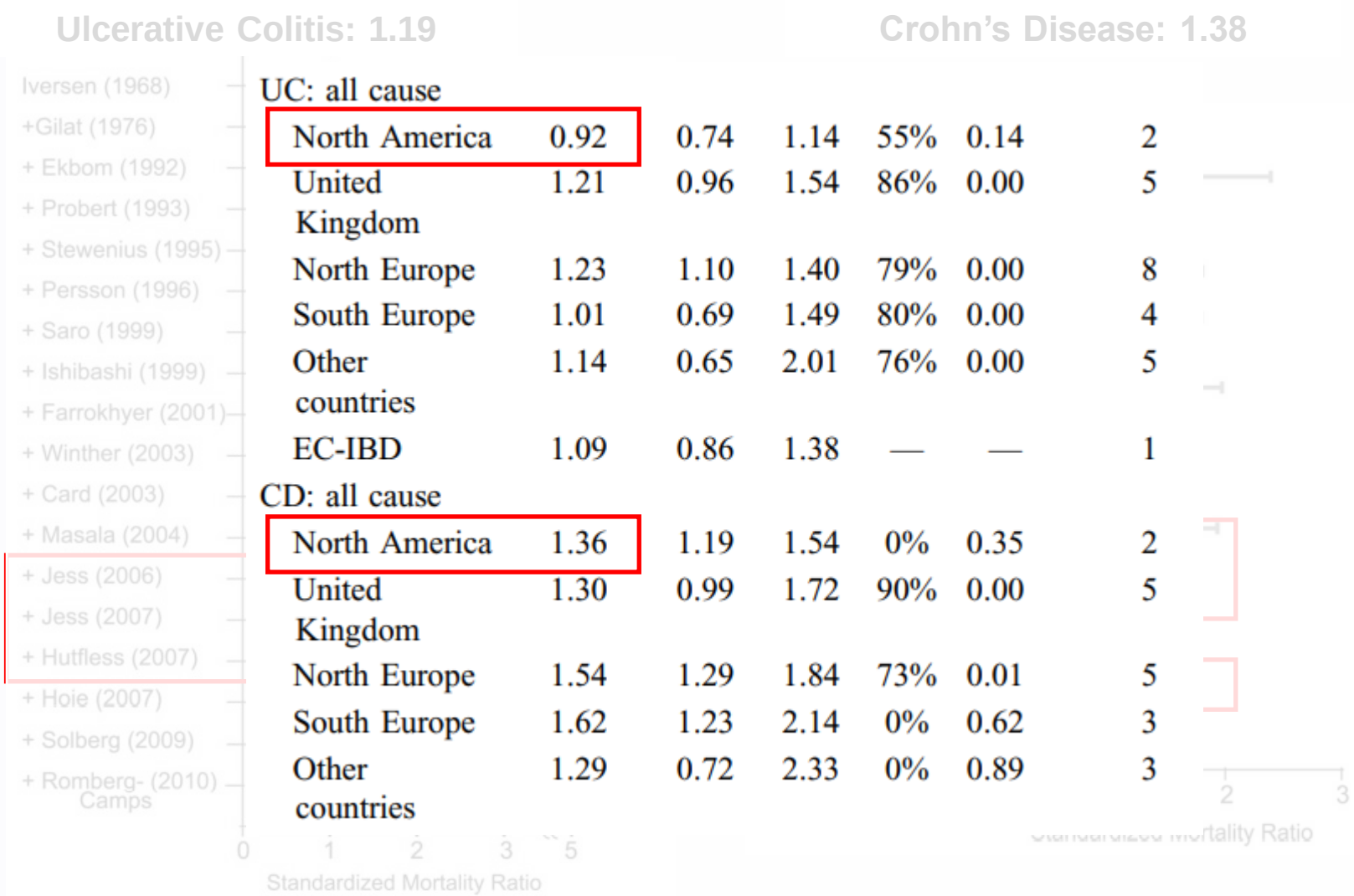
ORIGINAL ARTICLE

Crohn's Disease and Ulcerative Colitis Are Associated With Elevated Standardized Mortality Ratios: A Meta-Analysis

- 35 original articles
- 32,269 (CD) / 18,952 (UC) patients
- All-cause mortality UC: **HR 1.19** (95%-CI, 1.06–1.35)
- All-cause mortality CD: **HR 1.38** (95%-CI, 1.23–1.55)
- Mortality from **colorectal cancer, pulmonary disease, and non-alcoholic liver disease** was increased, whereas mortality from cardiovascular disease was decreased

	Summary SMR
Overall: UC	1.16
Overall: CD	1.46
CRC: UC	2.82
CRC: CD	3.12
Cardiovascular disease: UC	0.90
Cardiovascular disease: CD	1.00
Pulmonary disease: UC	1.41
Pulmonary disease: CD	1.60
Nonalcoholic liver disease: UC	2.26
Nonalcoholic liver disease: CD	2.82

Bewtra et al., Inflamm Bowel Dis 2013;19:599–613



UC: all cause						
North America	0.92	0.74	1.14	55%	0.14	2
United Kingdom	1.21	0.96	1.54	86%	0.00	5
North Europe	1.23	1.10	1.40	79%	0.00	8
South Europe	1.01	0.69	1.49	80%	0.00	4
Other countries	1.14	0.65	2.01	76%	0.00	5
EC-IBD	1.09	0.86	1.38	—	—	1
CD: all cause						
North America	1.36	1.19	1.54	0%	0.35	2
United Kingdom	1.30	0.99	1.72	90%	0.00	5
North Europe	1.54	1.29	1.84	73%	0.01	5
South Europe	1.62	1.23	2.14	0%	0.62	3
Other countries	1.29	0.72	2.33	0%	0.89	3

Bewtra et al., Inflamm Bowel Dis 2013;19:599–613

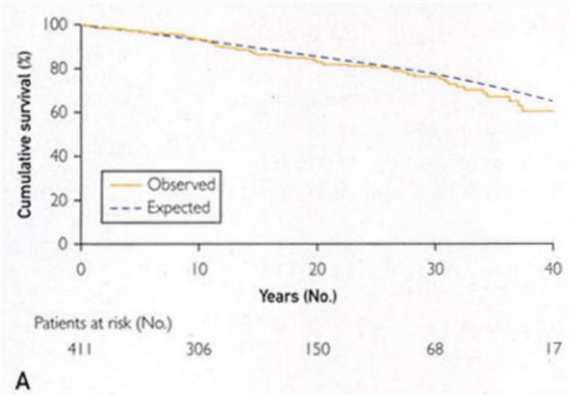
MAYO CLINIC

ORIGINAL ARTICLE

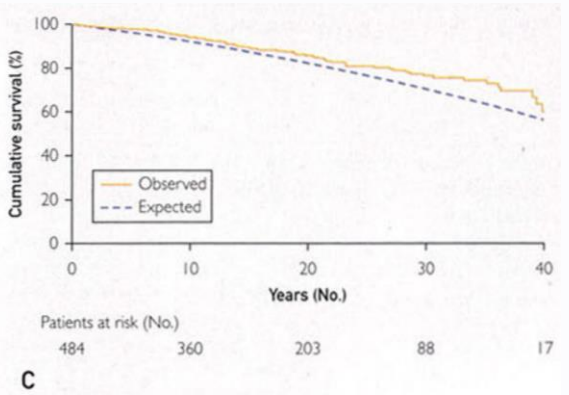
Overall and Cause-Specific Mortality of Inflammatory Bowel Disease in Olmsted County, Minnesota, From 1970 Through 2016

Check for updates

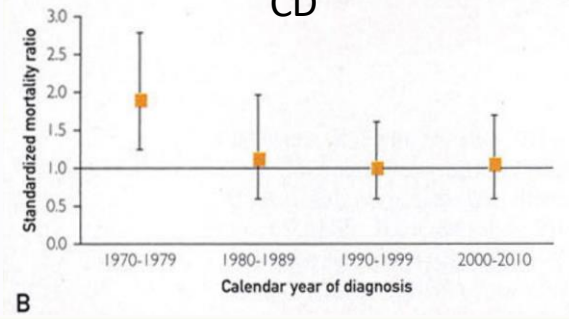
CD



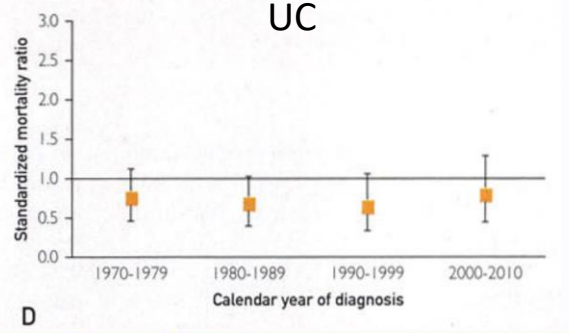
UC



CD



UC



Aniwan et al., Mayo Clin Proc 2018;93:1415

IBD – What's new?

Research

Understanding of Pathogenesis
- Inflammation processes, immunology
- Dysbiosis (microbiome, virome)

Personalized approaches
- NOD2
- IL-receptors
- ...

Therapy

Medical Treatment
- JAK-inhibitors
- IL-23 inhibitors
- S1P receptor modulators
- PDE4 inhibitors
- TLR9 agonist
- Cell-based (e.g., MSCs)
- Microbiota-based innovations, e.g., SER-287
- Nanoparticles

Diet

Complementary interventions

Challenges

Timing, selection, combination and sequence of the best therapy

Holistic healthcare
- Physical and mental wellbeing
- Quality of Life

Remission Induction and Maintenance strategies

Conventional therapies

- 5-ASA/Thiopurines/MTX
- Corticosteroids
- EEN (paediatric CD)
- Biological therapies or small molecules
- Surgery

CAMs supported by evidence as add-on therapy

- Curcumin
- *H. dysenterica*
- *A. paniculata*
- *A. absinthium*
- CDED
- ...

Improve quality of life

Achieve disease control

Assess the need for

- Dietary optimalisation
- Physical excercise
- Mind-body practices
- Psychological interventions
- Herbal and medicinal products

Outstanding questions

- Biomarkers/patient sub-groups
- Side effects?
- Dose/interval?
- Extra-intestinal symptom?
- Increase in flare intervals?
- Dietary therapy in adults?
- Dietary therapy in UC?

Long-term goals

Remission

Clinical/endoscopic/ biomarkers

Improved quality of life

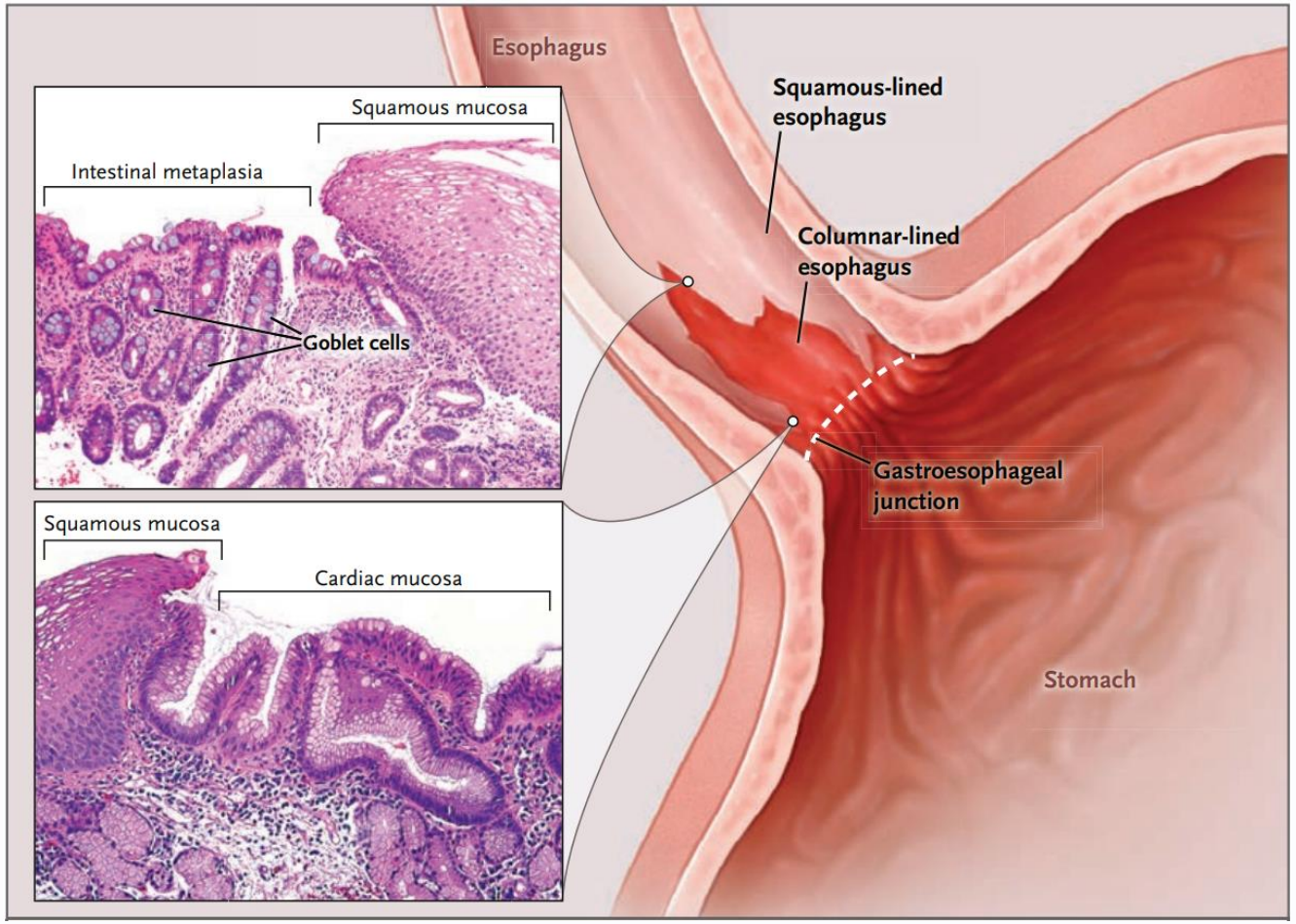
Study acronym	ClinicalTrials.gov identifier	Official title
ACHILLE	NCT04589338	Impact of Different Types of Physical Activity in Patients With Chronic Inflammatory Bowel Disease
IBD-FITT	NCT04816812	The IBD-FITT Study - Moderate-intensity Exercise for Patients with Inflammatory Bowel Disease With Moderate Disease Activity: a Randomised Controlled Trial
Special Physical Exercises	NCT04303260	Special Physical Exercises as a Therapeutic Intervention for Inflammatory Bowel Disease
Pre-Habilitation Exercise	NCT02849717	Pre-Habilitation Exercise Intervention for Patients Scheduled for Colorectal Surgical Resection
OATS	NCT04946448	COmbinAtion Therapy of dieT With biologicalS for Crohn's Disease: the OATS Study
iPENS	NCT04225689	The Intensive Post Exclusive Enteral Nutrition Study (iPENS): A Randomised Trial to Evaluate CD-TREAT Diet as a Food Reintroduction Regime in Children and Young Adults With Crohn's Disease
Semi-vegetarian Diet	NCT04835727	Effect of Semivegetarian Diet in Inflammatory Bowel Disease Patients With Clinical Remission
PIONIR	NCT05211518	Preventing IBD Onset in Individuals at Risk
ADDapt	NCT04046913	The ADDapt Diet in Reducing Crohn's Disease Inflammation
Intermittent Reduced Calorie Diet	NCT04147585	Effects of an Intermittent Reduced Calorie Diet on Crohn's Disease

Sudhakhar et al., Gut 2022, online Sep 28th

IBD – Most important questions

- Extent and severity?
- Treatment? Long-term corticosteroids, immunosuppressive drugs, anti-TNF agents?
- Complications? Anorexia? Underweight?
- Extraintestinal manifestation: Liver? Lung?
- Endoscopic surveillance?

Barrett Esophagus – Columnar metaplasia



Spechler et al., N Engl J Med 2014;371:836

Reflux
↓
Esophagitis
↓
Barrett
↓
Cancer (EAC)
↓
Death

?

Barrett Esophagus – Prevalence in GERD

- Meta-analysis: > 40 studies, > 25,000 patients
- Pooled prevalence: 7.2% (95%CI, 5.4%-9.3%)
- Highest prevalence reported from North American Studies

14%
Dysplasia in cases of histologically confirmed Barrett

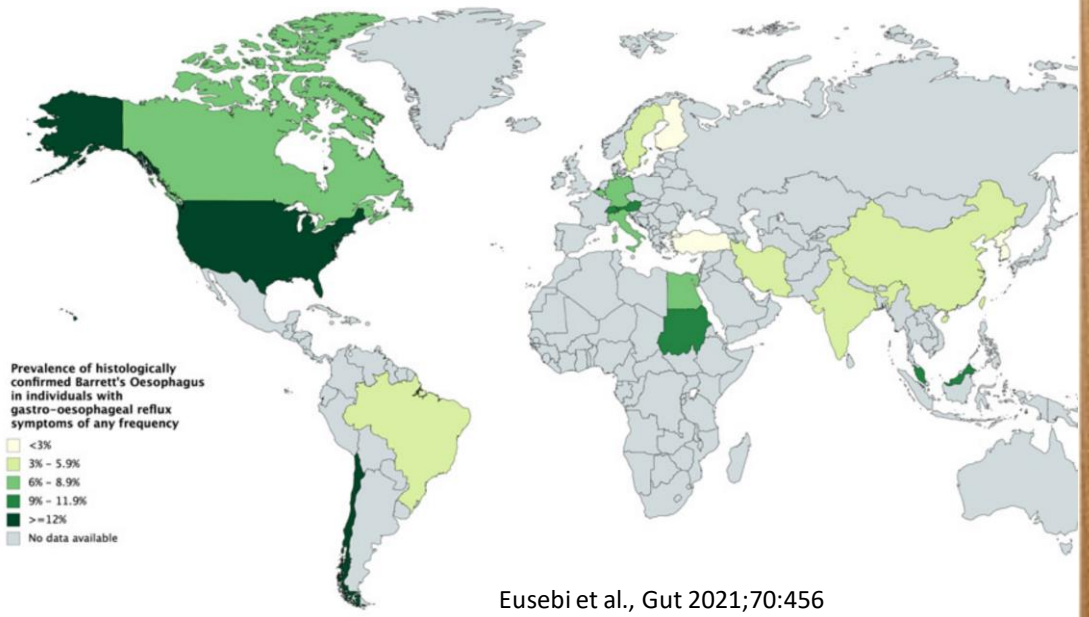
81%
of dysplasia cases low grade

Oesophagus

Original research

Global prevalence of Barrett's oesophagus and oesophageal cancer in individuals with gastro-oesophageal reflux: a systematic review and meta-analysis

Leonardo Henry Eusebi [1], Giovanna Grazia Cirota,[1] Rocco Maurizio Zagari,[1] Alexander Charles Ford [2]



Eusebi et al., Gut 2021;70:456

Barrett Esophagus – Extent of GERD

Reflux symptoms of any frequency

	Number of studies	Number of subjects	Pooled prevalence (%)	95% CI (%)
All studies	**42**	26 521	**7.2**	**5.4 to 9.3**
North American studies[16–18 20 23 25 27 32 37–39 55 59]	13	4158	14.0	10.8 to 17.7
European studies[22 24 29 34 36 40 43 45]	8	9211	4.9	1.9 to 9.1
Middle Eastern studies[31 33 41 47 53 56–58]	8	3392	3.0	1.7 to 4.7
Asian studies[30 35 48–52]	7	7414	4.1	1.4 to 8.2
African studies[28 42 46]	3	1196	8.0	6.3 to 9.9
South American studies[19 21 26]	3	1150	9.1	3.8 to 16.4

GERD as per the Montreal definition

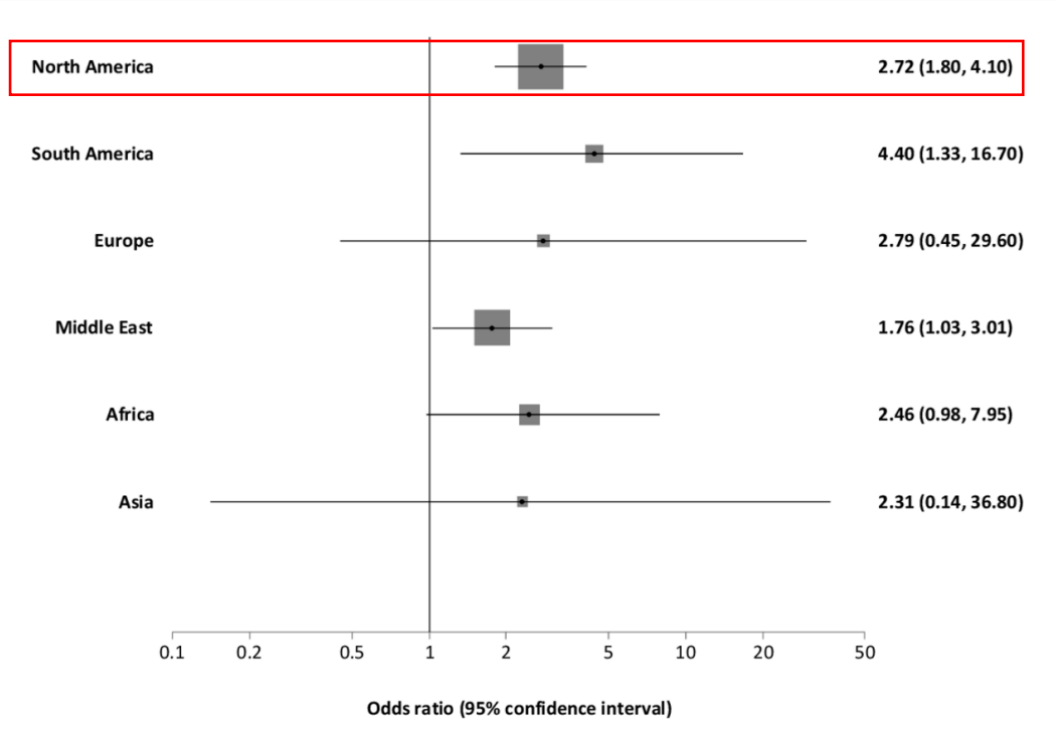
	Number of studies	Number of subjects	Pooled prevalence (%)	95% CI (%)
All studies	**24**	14 068	**8.2**	**6.2 to 10.3**
North American studies[25 27 32 37–39 59]	7	1066	14.3	11.0 to 18.0
European studies[22 29 34 36 40 45]	6	7616	5.7	2.3 to 10.6
Middle Eastern studies[33 41 53 56]	4	2422	3.8	1.6 to 6.9
Asian studies[30 50 51]	3	1125	6.1	1.9 to 12.6
African studies[42 46]	2	1091	7.1	6.1 to 9.2
South American studies[19 21]	2	748	12.5	10.2 to 15.0

14%

Prevalence of Barrett in GERD in North American studies

Eusebi et al., Gut 2021;70:456

Barrett Esophagus – Gender

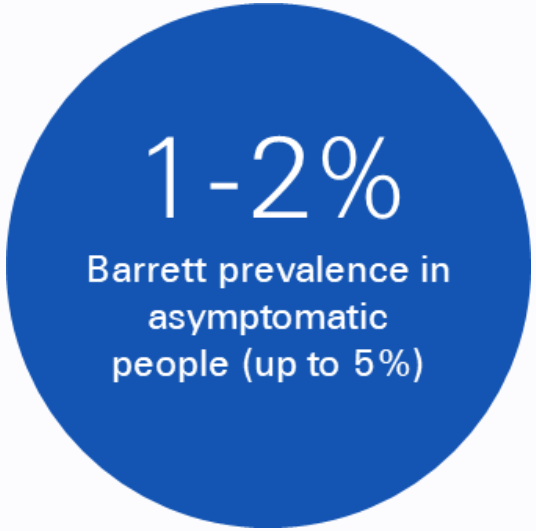


11% vs 5%

Prevalence Men vs Women with GERD, respectively

Eusebi et al., Gut 2021;70:456

Barrett Esophagus in individuals without reflux?



Ronkainen et al., Gastroenterology 2005;129:1825
Rex et al., Gastroenterology 2003;125:1670

Barrett Esophagus – Risk factors

- GERD
- Male gender
- BMI
- Age > 50 years
- Tobacco smoking
- Race
- (Diet)

Characteristic associated with Barrett esophagus	Type of study	No. of studies and participants	Associations
GERD[9]	Systematic review and meta-analysis	11 studies (1 cross-sectional and 10 cohort studies); N = 575 756 participants	GERD population: 7.21% (95% CI, 5.61%-8.81%); general population: 0.96% (95% CI, 0.75%-1.18%)
Sex[3]	Systematic review and meta-analysis	12 cohort studies	Men: 10.8% (95% CI, 6.6%-15.9%); women: 4.8% (95% CI, 2.7%-7.5%)
Age[8]	Cohort study	29 374 patients undergoing esophagogastroduodenoscopy	<50 y: 0.3%; ≥50 y: 1.1%; *P* = .02
Tobacco smoking[10]	Cohort study	1056 patients undergoing EGD	Smokers: 12%; nonsmokers: 1.1%; *P* <.001
Race[11]	Cohort	2100 patients undergoing EGD	White: 6.1%; Hispanic: 1.7%; Black: 1.6% *P* value (White vs Hispanic individuals) = .0002; *P* value (White vs Black individuals) = .004

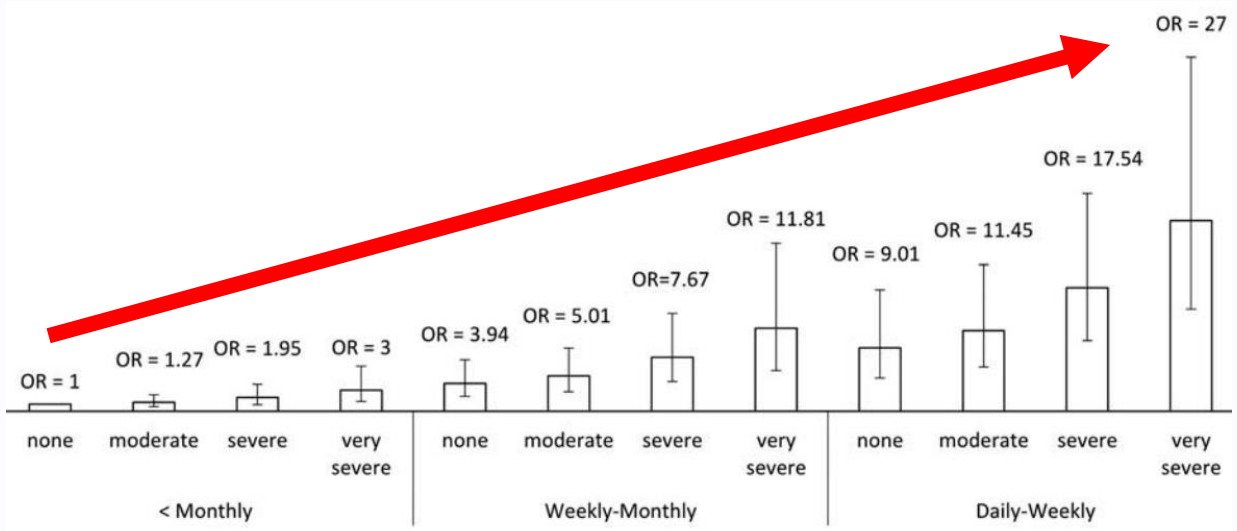
Sharma, JAMA 2022;328:663

Barrett Esophagus – Risk factors

- GERD
- Male gender
- BMI
- Age > 50 years
- Tobacco smoking
- Race
- (Diet)

ORIGINAL ARTICLE

Gastroesophageal Reflux Frequency, Severity, Age of Onset, Family History and Acid Suppressive Therapy Predict Barrett Esophagus in a Large Population



Bakr et al., J Clin Gastroenterol 2018;52:873

Barrett Esophagus – Risk factors

- GERD
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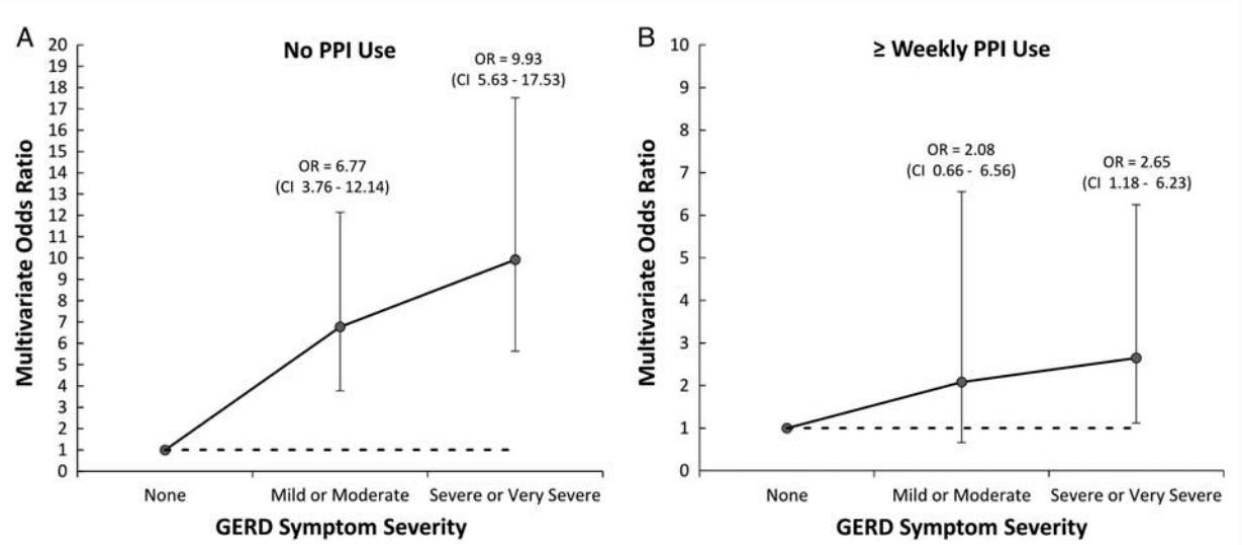
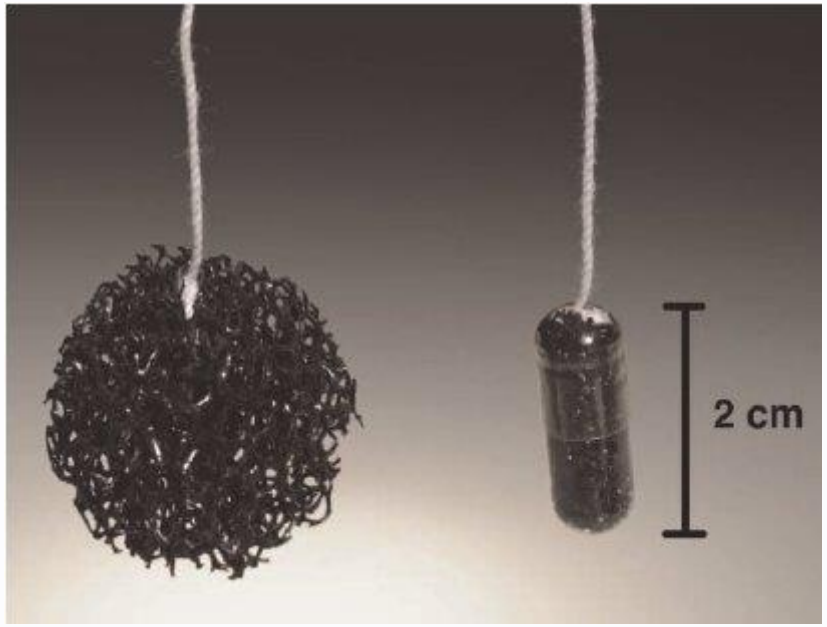


Bakr et al., J Clin Gastroenterol 2018;52:873

Barrett Esophagus – Diagnosis

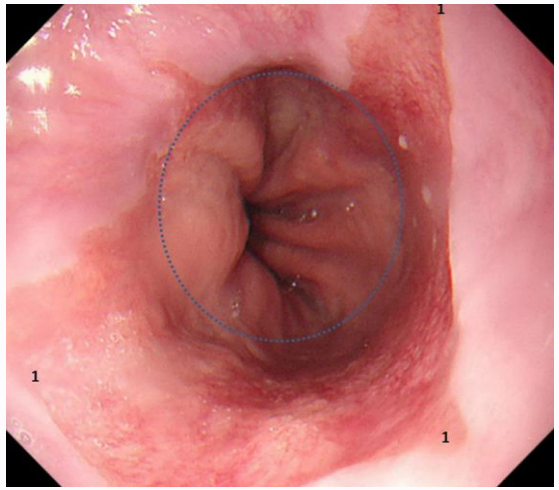
- **Conventional white light endoscopy**
- Unsedated transnasal ultrathin endoscopy*
- Swallowable, capsule sponge device** (biomarker-combined: trefoil factor 3, methylated DNA markers)

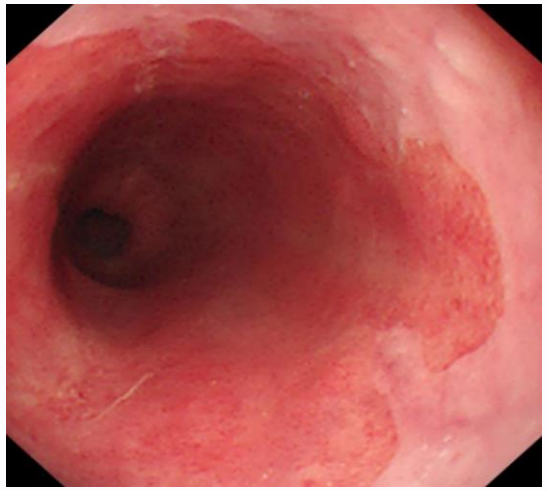


* The current ACG guidelines mention unsedated transnasal endoscopy as an alternative to conventional upper endoscopy
** Mentioned by the current ACG guidelines as potential methods for screening patients with chronic GERD and other risk factors

Sharma, JAMA 2022;328:663
Kadri et al., BMJ Clinical Research 2010;341:c4372

Barrett Esophagus – Short and Long Segment

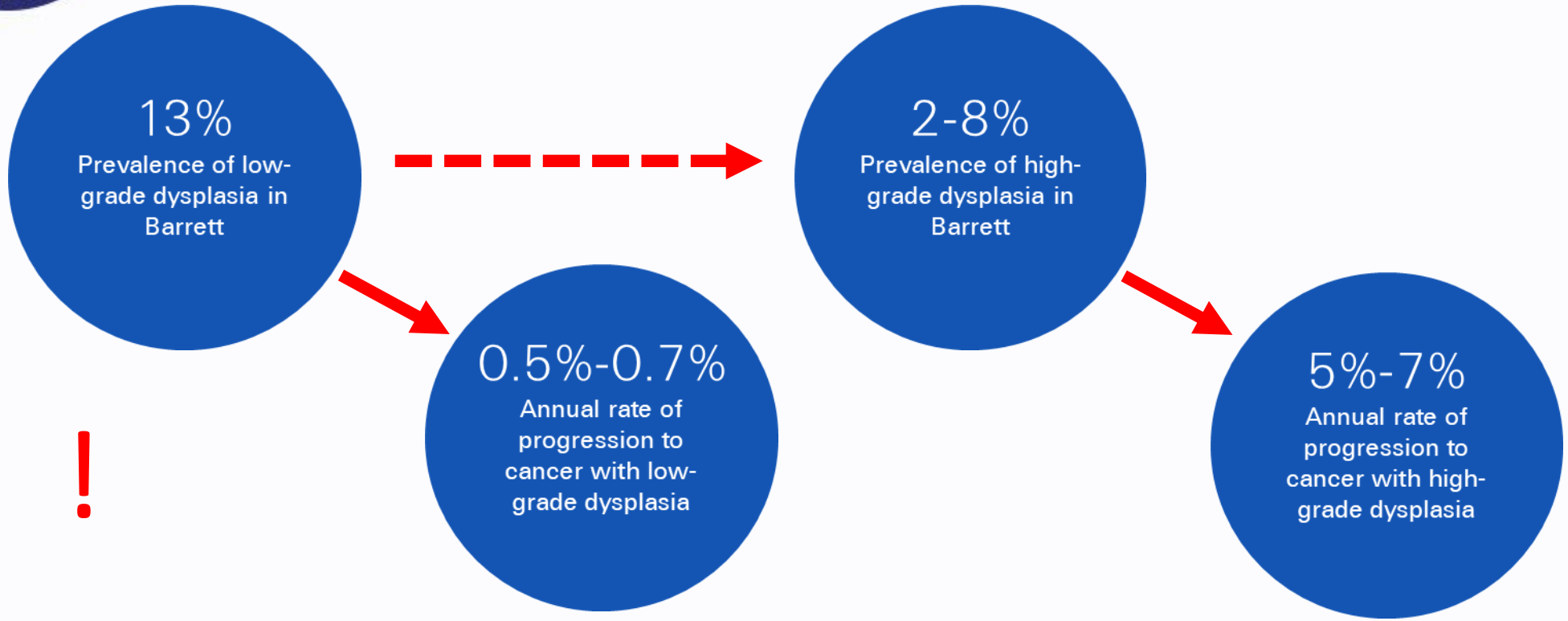




	Short-Segment	Long-Segment
Length (per definition)	1-3 cm	> 3 cm
Prevalence in GERD	6.7%	3.1%
Progression to Cancer w/o dysplasia	0.06 %/a	0.31 %/a

Sharma, JAMA 2022;328:663
Barrie et al., Surgical Endoscopy 2021;35:4756

Barrett Esophagus – Dysplasia and Risk for Adenocarcinoma



3-5% lifetime-risk of developing esophageal adenocarcinoma

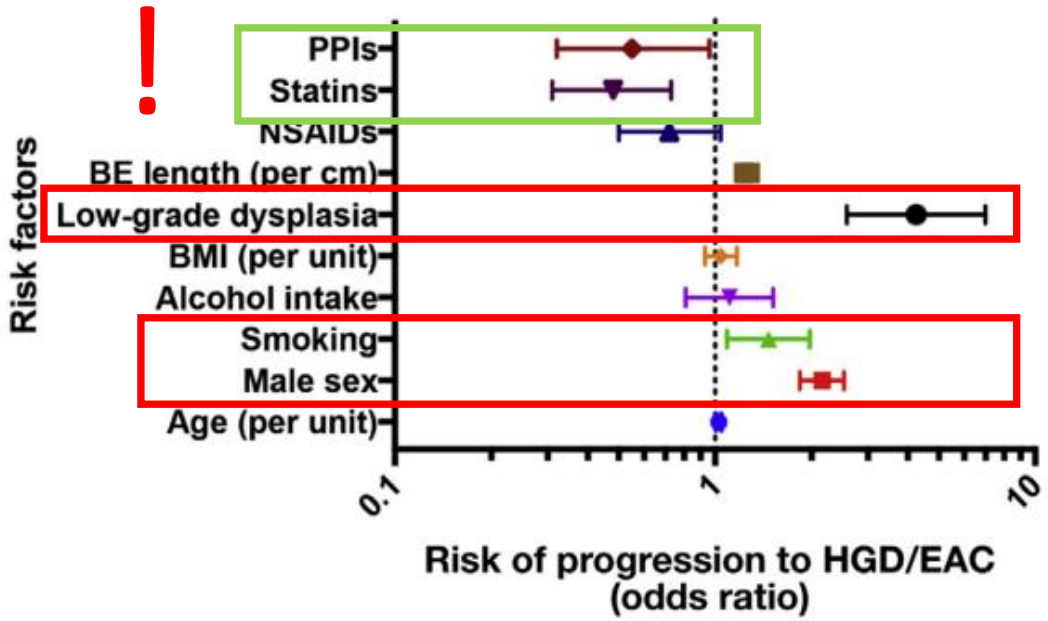
Singh et al., Gastrointest Endosc 2014;79:897
Sharma, JAMA 2022;328:663

SYSTEMATIC REVIEWS AND META-ANALYSES

Siddharth Singh, Section Editor

Factors Associated With Progression of Barrett's Esophagus: A Systematic Review and Meta-analysis

- 20 studies, reporting 1231 events in 74943 patients



Factor	Studies, n	OR (95% CI)	I^2
Demographic factors			
Age (per unit increase)	12	1.027 (1.007–1.046)	45
Male sex	11	2.16 (1.84–2.53)	0
Lifestyle factors			
Smoking	8	1.47 (1.09–1.98)	26
Alcohol	6	1.11 (0.81–1.52)	8
BMI (per unit increase)	6	1.04 (0.93–1.17)	53
BE characteristics			
Baseline LGD (vs NDBE)	11	4.25 (2.58–7.00)	87
BE length (per unit cm)	10	1.25 (1.16–1.36)	47
Medications			
NSAID	6	0.72 (0.50–1.04)	18
Statin	3	0.48 (0.31–0.73)	0
PPI	4	0.55 (0.32–0.96)	51

BE, Barrett's esophagus; BMI, body mass index; CI, confidence interval; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NDBE, nondysplastic Barrett's esophagus; NSAID, nonsteroidal anti-inflammatory drug; OR, odd's ratio; PPI, proton pump inhibitor.

Krishnamoorthi et al., Clin Gastroenterol Hepatol 2018;16:1046

Barrett Esophagus – Preventing Progression to Cancer

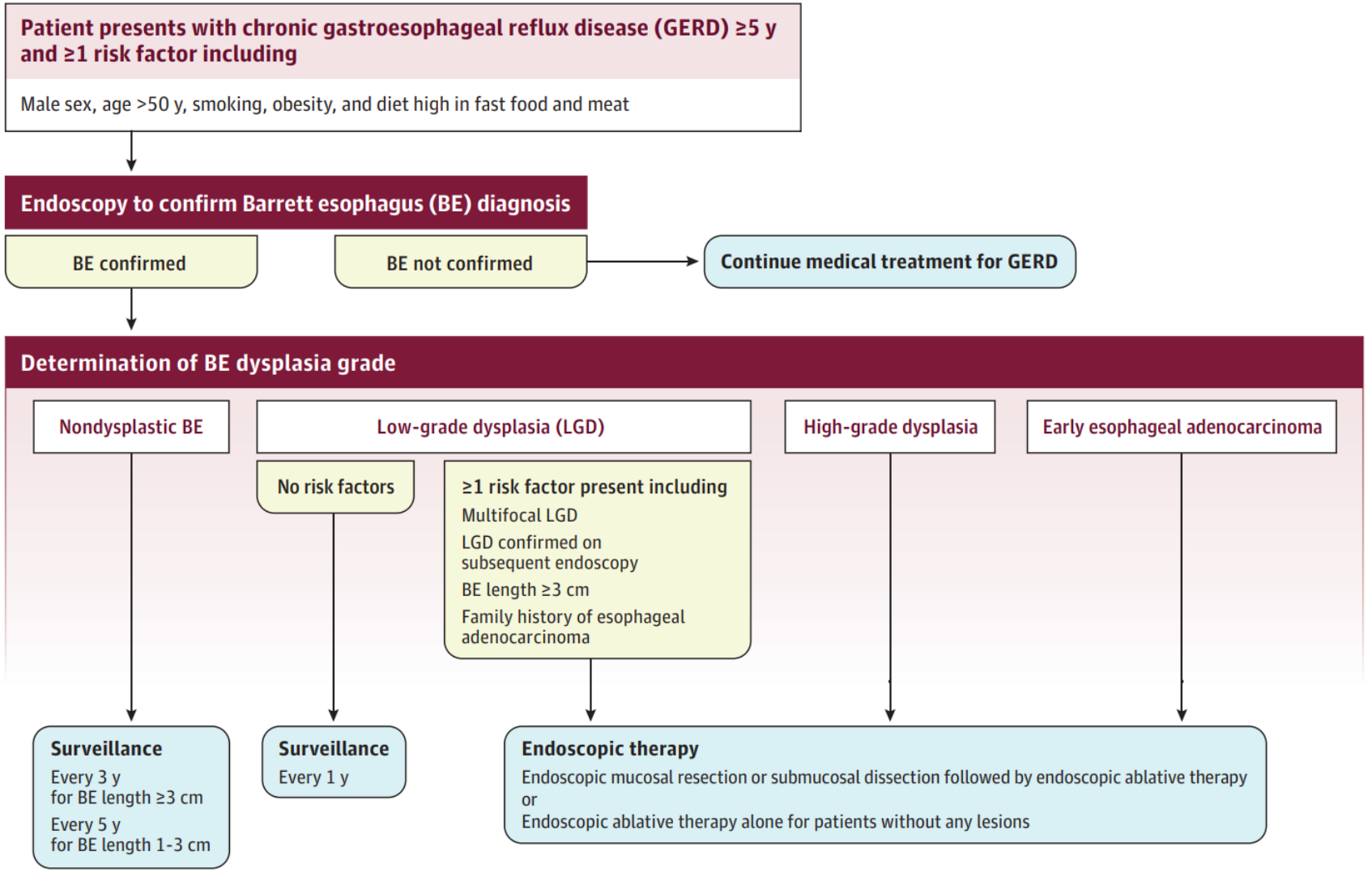
- Chemoprevention
- Endoscopic therapy

Chemoprevention			
Jankowski et al,[34] 2018 *	2557 Patients with Barrett esophagus from the UK	High-dose PPI (esomeprazole 40 mg twice-daily) with acetylsalicylic acid (n = 577); low-dose PPI (esomeprazole 20 mg once-daily) with acetylsalicylic acid (n = 571); high-dose PPI only (esomeprazole 40 mg twice-daily) (n = 704); low-dose PPI only (esomeprazole 20 mg daily) (n = 705)	Composite end point: time to all-cause mortality, esophageal adenocarcinoma, or high-grade dysplasia; at 8.9 y follow-up: high-dose PPI with acetylsalicylic acid, 52/572 (0.09); high-dose PPI only, 139/1270 (0.11); low-dose PPI with acetylsalicylic acid, 99/699 (0.14); low-dose PPI only, 174/1265 (0.14)
Endoscopic therapy for Barrett esophagus			
Shaheen et al,[35] 2009	127 Patients with Barrett esophagus and dysplasia from the US	RFA (n = 84); sham (n = 43)	CE-IM at 12 mo: 77.4% (RFA) vs 2.3% (sham); $P < .001$
Phoa et al,[36] 2014	136 Patients with Barrett esophagus with low-grade dysplasia	RFA (n = 68); surveillance (n = 68)	CE-IM at 3 y: 88.2% (RFA) vs 0% (surveillance); $P < .001$
Terheggen et al,[37] 2017	40 Patients with Barrett esophagus with focal high-grade dysplasia or early adenocarcinoma ≤3 cm	Endoscopic mucosal resection (n = 20); endoscopic submucosal dissection (n = 20)	R0 resection rates: 12% (endoscopic mucosal resection) vs 59% (endoscopic submucosal dissection); $P = .01$
Barret et al,[38] 2021	82 Patients with Barrett esophagus with low-grade dysplasia	RFA (n = 42); surveillance (n = 40)	CE-IM at 3 y: 35% (RFA) vs 0% (surveillance); $P < .001$

Abbreviations: CE-IM, complete eradication of intestinal metaplasia; PPI, proton-pump inhibitor; RFA, radiofrequency ablation.

* ACG and AGA recommend acid exposure elimination to prevent progression of Barrett esophagus to esophageal adenocarcinoma

Sharma, JAMA 2022;328:663-71
Jankowski et al., Lancet 2018;392:400



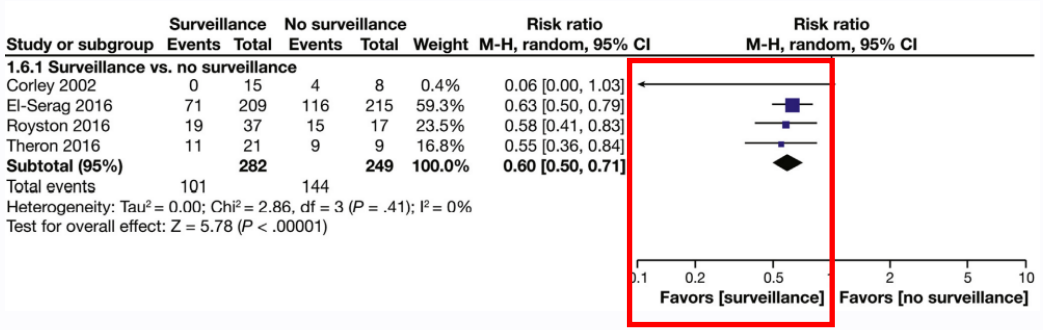
This algorithm has not been validated in randomized clinical trials.

Sharma, JAMA 2022;328:663

CLINICAL—ALIMENTARY TRACT

The Effect of Endoscopic Surveillance in Patients With Barrett's Esophagus: A Systematic Review and Meta-analysis

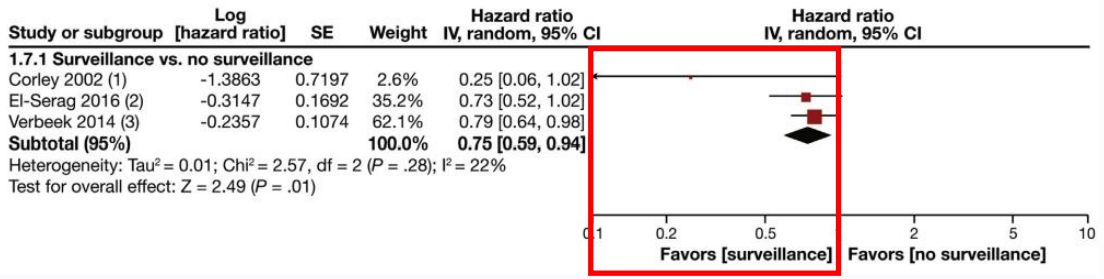
EAC-related mortality



Study or subgroup	Surveillance Events	Surveillance Total	No surveillance Events	No surveillance Total	Weight	Risk ratio M-H, random, 95% CI
1.6.1 Surveillance vs. no surveillance						
Corley 2002	0	15	4	8	0.4%	0.06 [0.00, 1.03]
El-Serag 2016	71	209	116	215	59.3%	0.63 [0.50, 0.79]
Royston 2016	19	37	15	17	23.5%	0.58 [0.41, 0.83]
Theron 2016	11	21	9	9	16.8%	0.55 [0.36, 0.84]
Subtotal (95%)		**282**		**249**	**100.0%**	**0.60 [0.50, 0.71]**
Total events	101		144			

Heterogeneity: Tau² = 0.00; Chi² = 2.86, df = 3 (*P* = .41); I² = 0%
Test for overall effect: Z = 5.78 (*P* < .00001)

All-cause mortality



Study or subgroup	Log [hazard ratio]	SE	Weight	Hazard ratio IV, random, 95% CI
1.7.1 Surveillance vs. no surveillance				
Corley 2002 (1)	-1.3863	0.7197	2.6%	0.25 [0.06, 1.02]
El-Serag 2016 (2)	-0.3147	0.1692	35.2%	0.73 [0.52, 1.02]
Verbeek 2014 (3)	-0.2357	0.1074	62.1%	0.79 [0.64, 0.98]
Subtotal (95%)			**100.0%**	**0.75 [0.59, 0.94]**

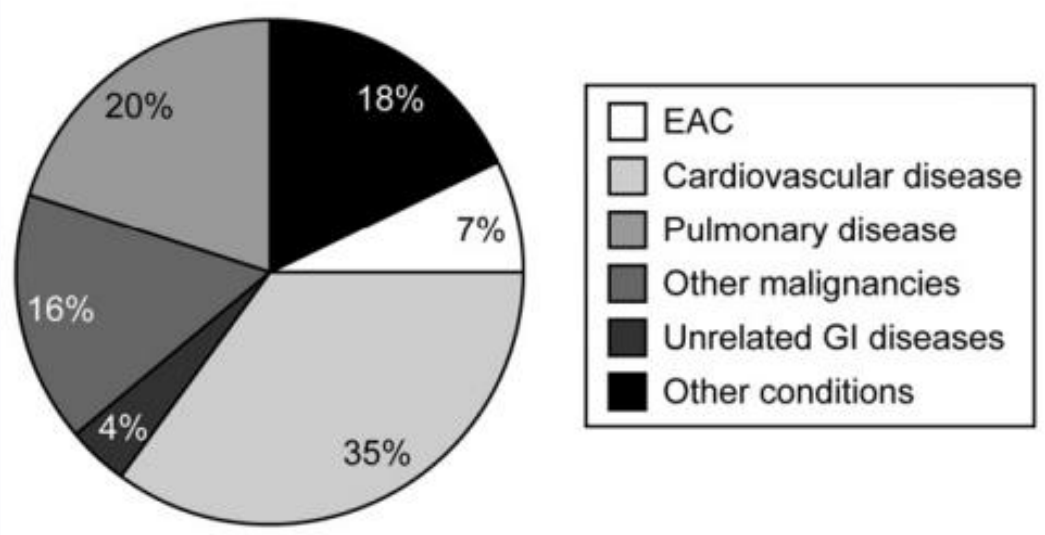
Heterogeneity: Tau² = 0.01; Chi² = 2.57, df = 2 (*P* = .28); I² = 22%
Test for overall effect: Z = 2.49 (*P* = .01)

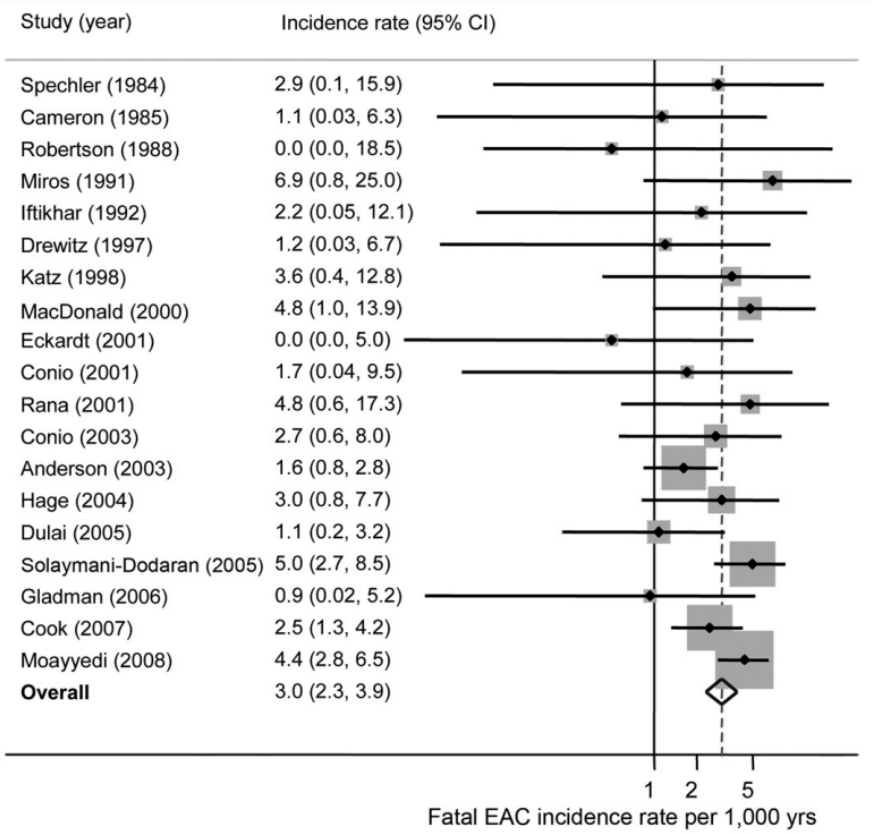
!

Codipilly et al., Gastroenterology 2018;154:2068

Risk of Esophageal Adenocarcinoma and Mortality in Patients With Barrett's Esophagus: A Systematic Review and Meta-analysis

- 51 studies
- 14,109 patients, 61,804 person years
- Fatal adenocarcinoma was 3.0/1000 person-years





Sikkema et al., Clin Gastroenterol Hepatol 2010;8:235

Barrett Esophagus – Most important questions

- Is there dysplasia – low- or high-grade? Metaplasia only?
- Long- or Short-Barrett?
- Appropriate surveillance / treatment?
- Cardiovascular and pulmonary co-morbidities!

Thank you!

Prof. Dr. Tobias Schiergens

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