Microbiome, Inflammation and Cancer

Anita Afzali MD, MPH, FACG

Medical Director, OSU Inflammatory Bowel Disease Center

Abercrombie & Fitch Endowed Chair in Inflammatory Bowel Disease

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  - UCB, Abbvie, Janssen, Celgene, Takeda
- Board Member/Founder: IBD Horizons®

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Objectives

- Introduction to our microbiome
- Impact of diet and inflammation to the microbiome
- Effect of inflammation on cancer
- Review of inflammatory bowel disease and cancer

We are More Bacteria than Human

- Healthy adult harbors ~100 trillion bacteria in gut alone
- This is 10X the number of human cells we possess
- Humans possess 23,000 genes
- Microbiome contributes ~3,300,000
- Communal gut microbial genome (microbiome) is ~150 times larger than human genome

Microbiome, A Human Organ

- Reasonable to view microbiome as an organ
- Weighs ~1kg although is without distinct structure
- Organized system of cells more akin to immune system than liver
- Dominated by 4 large groups of bacteria or phyla:
  - Actinobacteria
  - Bacteroidetes
  - Firmicutes
  - Proteobacteria

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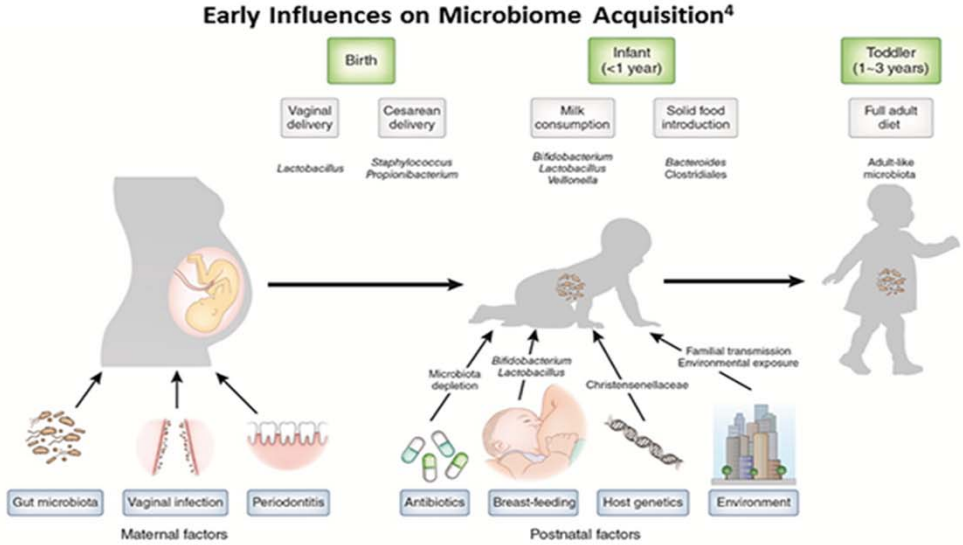
Development of Microbiota



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Tamburini S et al. Nat Med 2016

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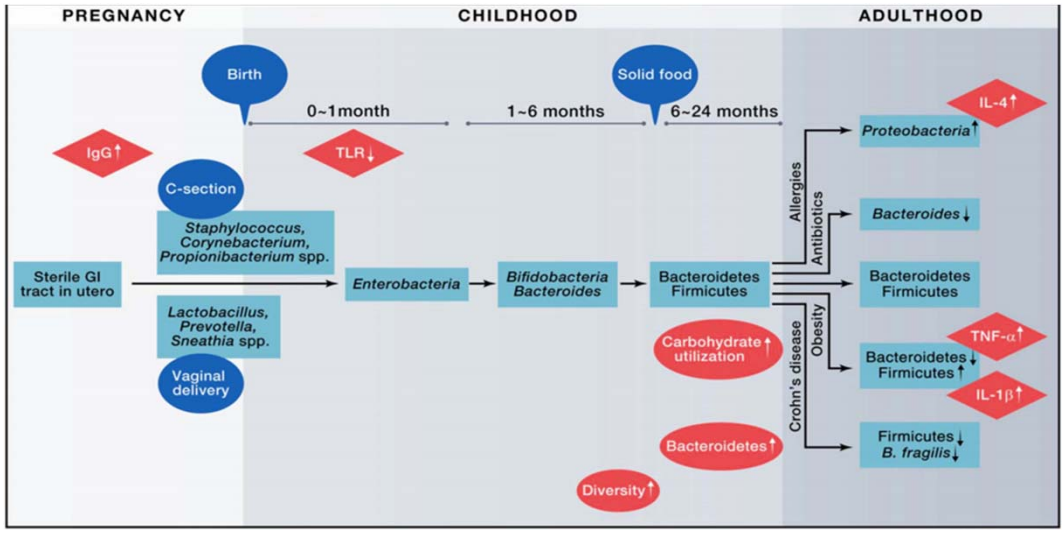
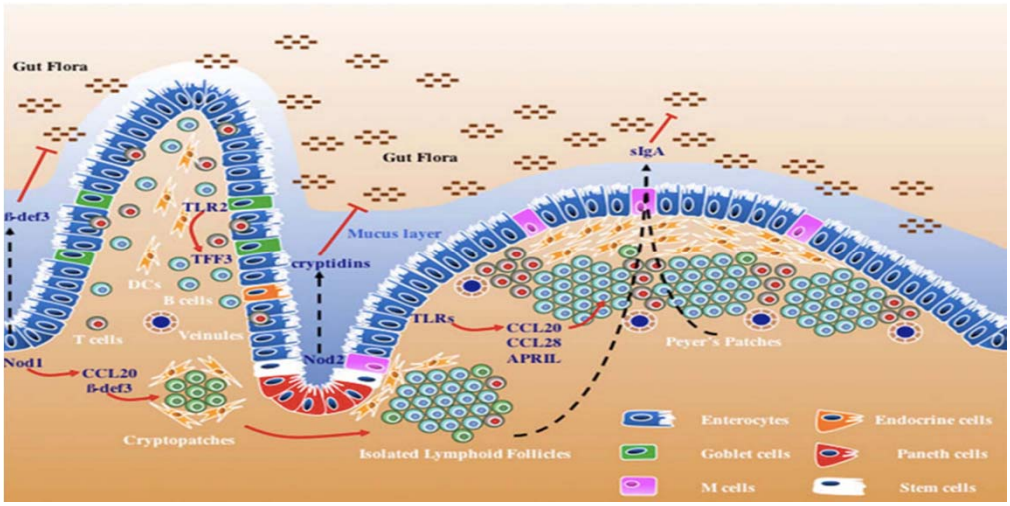
Development of the Microbiota

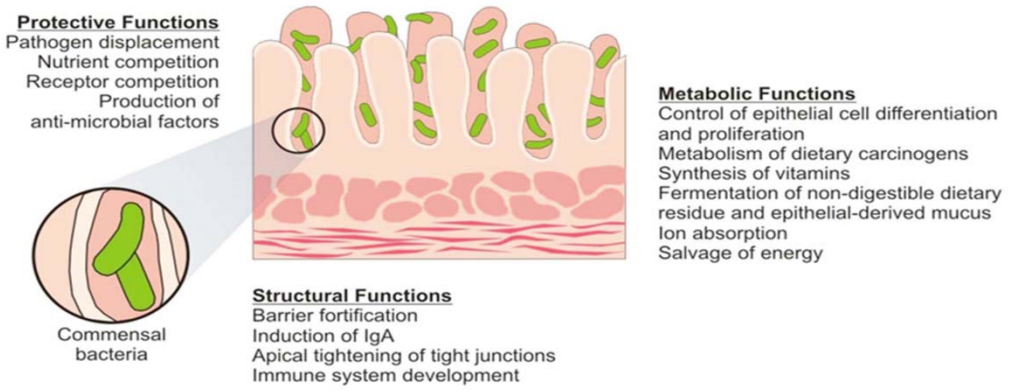


Single Layer of Intestinal Epithelial Cells Separates Trillions of Bacteria from Lamina Propria



Coevolution of Host and Microbiome

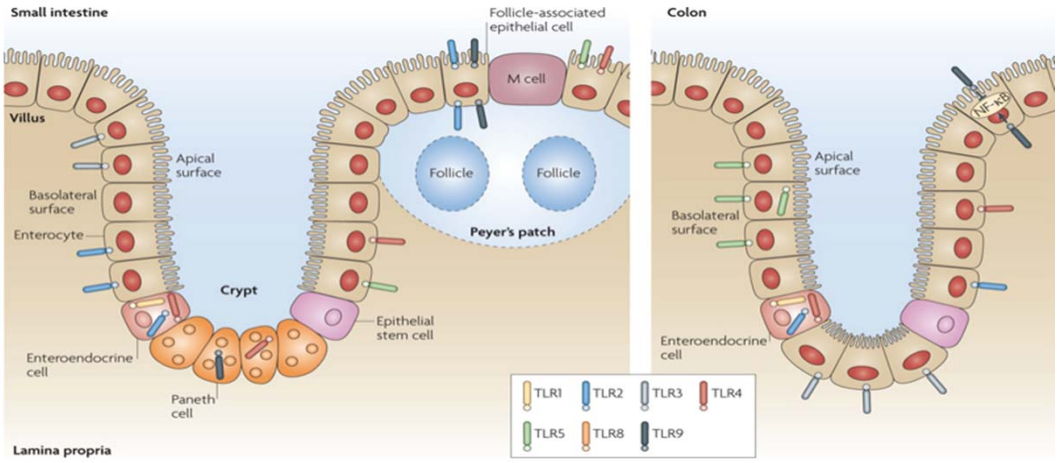
- Evolutionary aligned interests and interplay – neither wishes to harm
- Commensal bacteria provide benefits to host



Expansion of Host Metabolic Capacity by Microbiome

- Bacteria express glycoside hydrolase – converts glycans to useable sugars
  - No enzyme encoded in human genome is capable of digesting glycans, only bacterial enzymes!
- Many carbohydrates are digestible only by bacteria -> SCFA
  - Primary fuel for colonocytes
  - 10-15% of adult energy may be generated by SCFA production, stored as fat

Sensing of Bacteria by Intestinal Epithelial Cells



Abreu MT 2010

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Importance of Host-Microbiome Alignment

- Microbiome may cause disease directly or indirectly, when this delicate balance is disturbed
- Many diseases may result from this *dysregulation*:
  - Diabetes
  - Obesity
  - Metabolic syndrome
  - Stress/anxiety
  - Cardiovascular disease
  - Rheumatologic diseases
  - Inflammatory bowel disease (IBD)
  - Cancer

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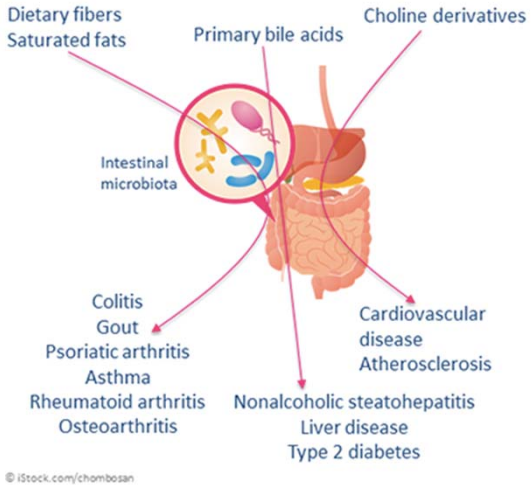
Diet, Microbiome and Inflammation are Connected

- Microbiome = complex microbial community that inhabits GI tract, respiratory tract, skin
- Altered microbiota = Dysbiosis
- May be factor in perpetuation of inflammatory diseases



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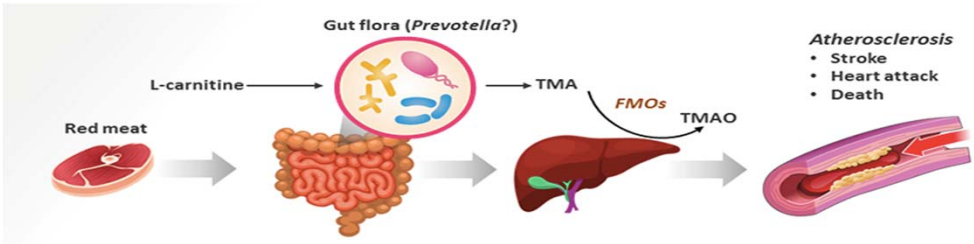
Link Between Diet, TMAO and Microbiome, and CV Risk



- Omnivores produce more TMAO than vegans/vegetarians following ingestion of red meat-derived L-carnitine through microbiota-dependent mechanism
- *Prevotella*-rich microflora had higher plasma levels of TMAO -> greater risk of CV disease

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Koeth RA et al. Nat Med 2013

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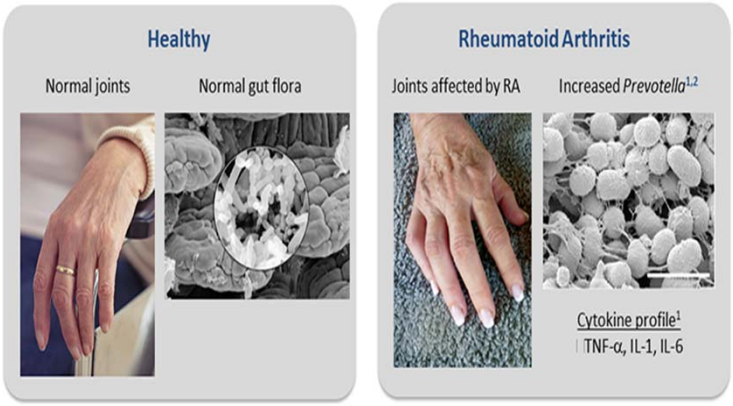
Rheumatic Diseases and Distinct Microbiomes



- Disease States
  - PA, AS, RA
- Distinct microbiome
- Different cytokine profile

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Scher GU et al. Arthritis Rheum 2016

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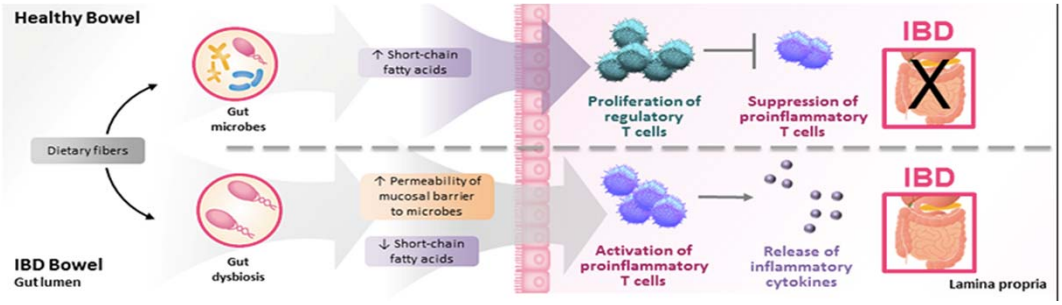
Role of Microbiome in IBD

- Gut microbiome - implicated in regulating intestinal adaptive immune responses
- Diet plays important role in intestinal immune function:
  - Bacterial metabolites from fiber expand T reg cells in gut, may prevent
  - High fats/sugar promote overgrowth of “inflammatory” bacterial species



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Smith PM et al. Science 2013

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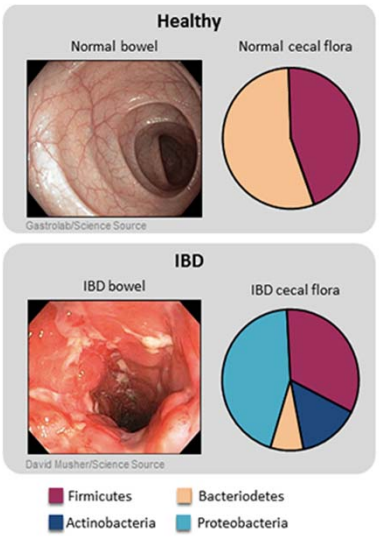
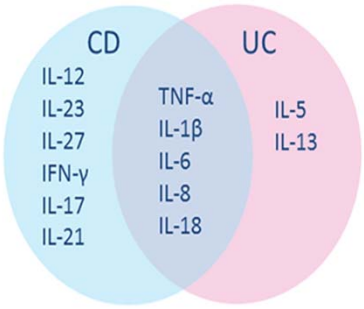
Differences in Microbiome associated with IBD





- Types of bacteria associated with UC/CD different than non-IBD
- Production of pro-inflammatory cytokines
- Distinct in UC vs CD

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Forbes JD et al. Inflamm Bowel Dis 2016

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Inflammation is Critical Component of Tumor Progression

- Cancers can arise from sites of chronic irritation, inflammation
- Vital component of tumor microenvironment are inflammatory cells
- Inflammation promotes neoplastic processes involved in proliferation, survival, migration
- Tumor cells have co-opted inflammatory signaling molecules and receptors

Tumors act as wounds that fail to heal

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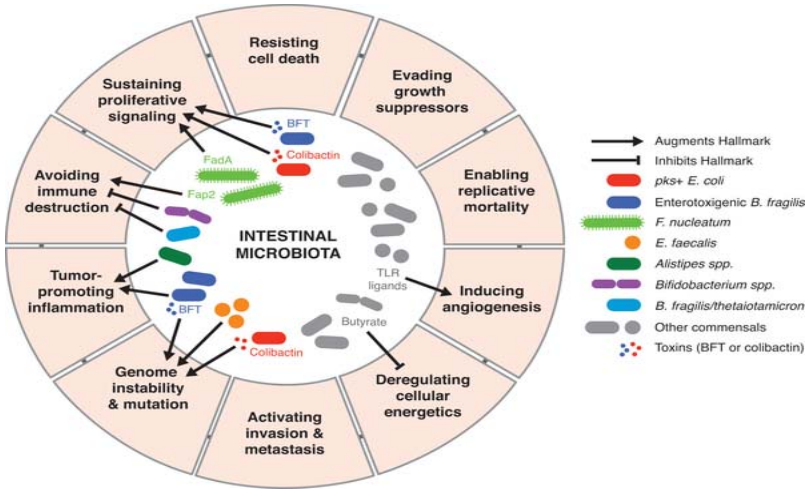
Microbial Influence in Inflammation and Cancer



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Fulbright LE et al. PLOS 2017

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Cancers associated with Inflammatory States

Inflammatory bowel disease	Colorectal cancer
Gastric intestinal metaplasia	Gastric cancer
Barrett's esophagus	Esophageal cancer
Chronic hepatitis	Hepatocellular carcinoma
Chronic pancreatitis	Pancreatic cancer
Oral leukoplasia	Head/neck cancer
Atypical adenomatous hyperplasia	Non-small cell lung cancer
Ductal carcinoma in situ	Breast cancer
Prostatic intraepithelial neoplasia	Prostate cancer
Bladder dysplasia	Bladder cancer
Cervical dysplasia	Cervical cancer
Actinic keratoses	Skin cancer

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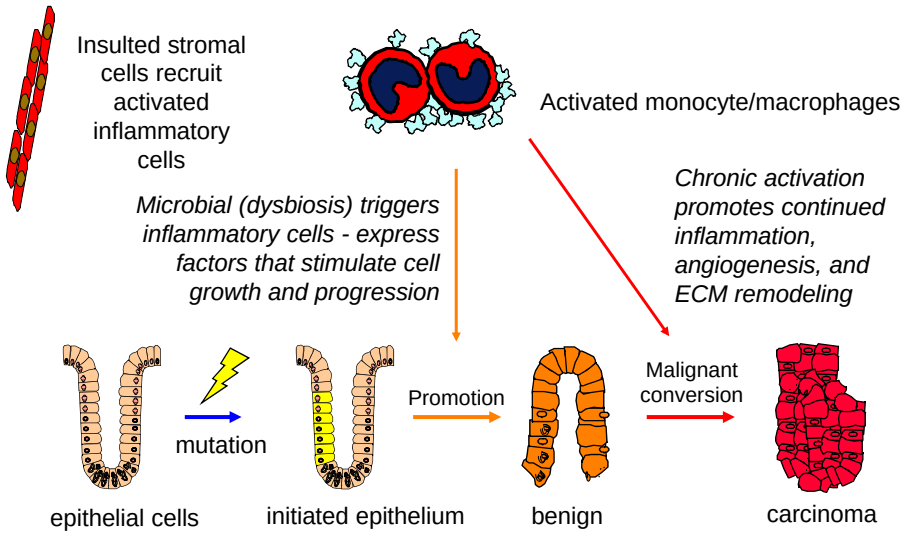
Chronic Inflammation Promotes Cancer



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Modified from Dan Dixon, Univ South Carolina

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Inflammatory Bowel Disease and Colorectal Cancer

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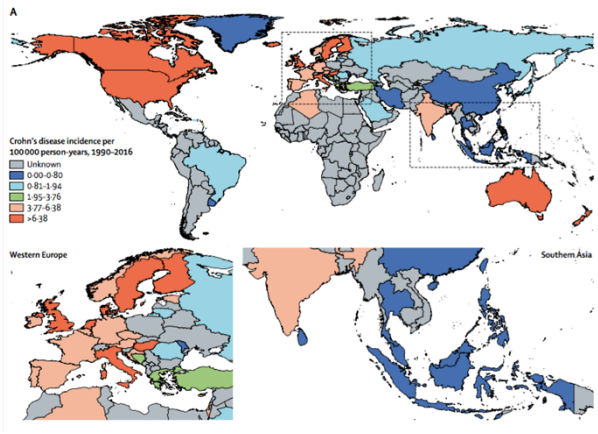
21st Century: IBD is a Global Disease

Incidence Crohn's Disease, 1990-2016



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SC Ng. Lancet October 2017

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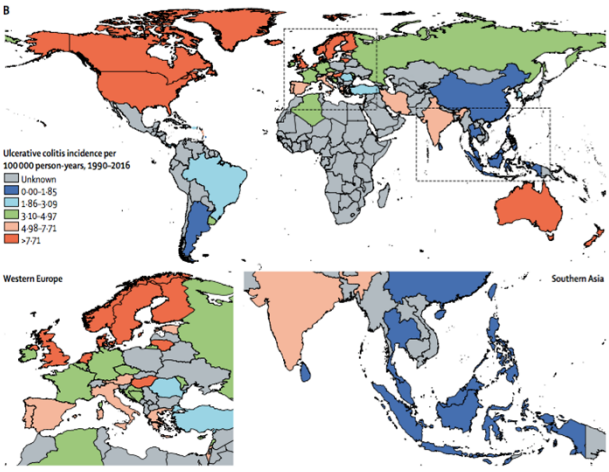
21st Century: IBD is a Global Disease

Incidence Ulcerative Colitis, 1990-2016



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SC Ng. Lancet October 2017

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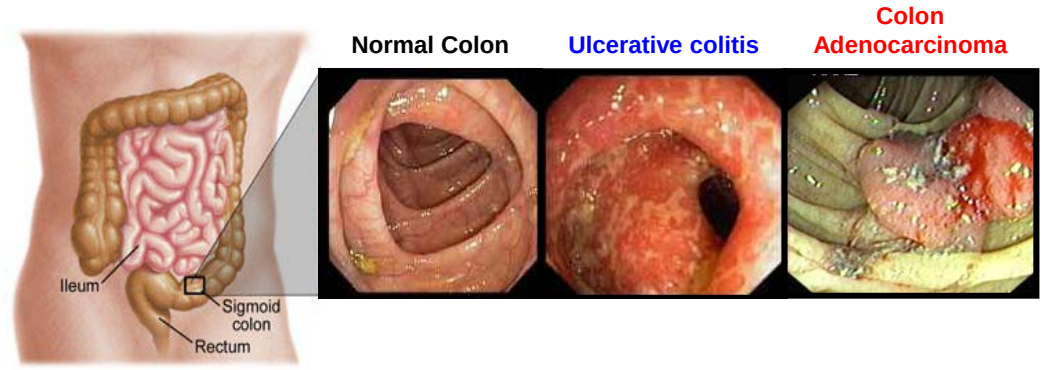
Chronic Inflammation is a Risk Factor for Cancer



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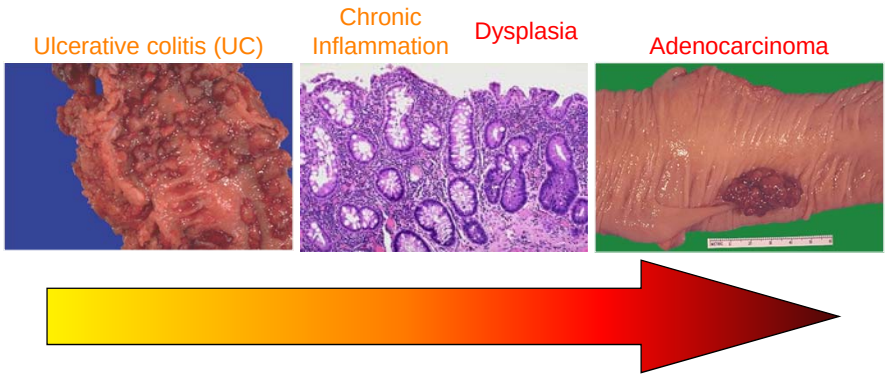
Chronic Inflammation is a Risk Factor for Cancer



- Patients with UC have a 5 to 7-fold greater risk of getting colon cancer
- UC persisting for 35-40 years increases the risk 20-35%
- Colon cancer associated with IBD has the worst prognosis
- Management with anti-inflammatory agents reduce incidence of cancer

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Increased Colorectal Cancer Risk in IBD

	UC RR (95% CI)	Crohn's colitis RR (95% CI)
Ekbom – Sweden[1,2]	5.7 (4.6-7.0)	5.6
Soderlund – Sweden[3]	2.7 (2.3-3.2)	2.1 (1.2-3.4)
Bernstein – Canada [4]	2.75 (1.9-4.0)	2.64 (1.7-4.1) [All CD]

Large Population-based studies >1000 pts

Overall, 2-3x risk for CRC

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Ekbom NEJM 1990, Lancet 1990
Soderlund GE 2009
Bernstein Cancer 2001

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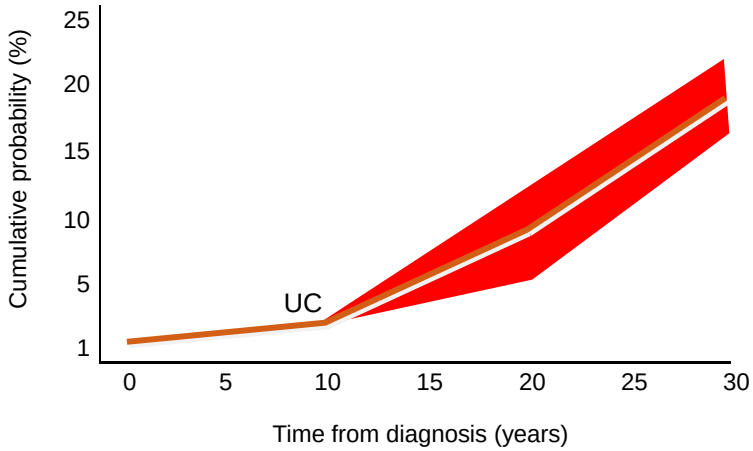
Disease Duration: Risk for CRC in Colitis Increases Over Time



Eaden JA et al. Gut 2001

➢Overall prevalence of CRC in any UC patient is 3.7%

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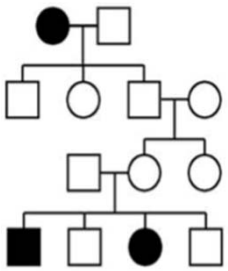
Disease Distribution:
Anatomical Extent of Inflammation Increases Risk for CRC

UC	Ekbom (1)	Soderlund (2)
Proctitis	1.7 (0.8-3.2) NS	1.7 (1.2-2.4)
Left-sided colitis	2.8 (1.6-4.4)	-
Pan-colitis	14.8 (11.4-18.9)	5.6 (4.0-4.7)

Meta-Analysis:
- Extensive Colitis – SIR 6.4 (2.4-17.5) (3)
- Extensive Colitis – SIR 4.8 (3.9-5.9) (4)

1. Ekbom NEJM 1990
2. Soderlund GE 2009
3. Lutgens IBD 2013
4. Jess CGH 2012

Family History:
Increases Risk of CRC in IBD Patients



- Large population-based cohort study
- 19,876 UC or CD patients

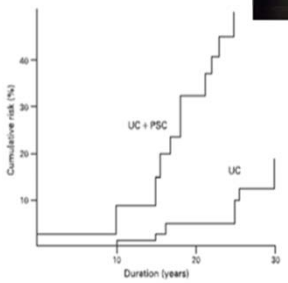
- Results:
  - First degree relative with CRC: RR 2.5 (1.4-4.4)
  - First degree relative with CRC: <50 yrs: RR 9.2 (3.7-23)

Askling, Gastroenterology 2001

Concomitant Inflammatory Diseases: Primary Sclerosing Cholangitis Increases Risk for CRC

- 5% of extensive UC patients
- 5% neoplasia risk (p <0.001)

Colitis Duration	PSC	No PSC
10y	9%	2%
20y	31%	5%
25y	50%	10%



- Meta-analyses:
  - Neoplasia OR 4.79 (3.58-6.41)
  - CRC RR 9.13 (4.52-18.5)

Broome, Hepatology 1995
Soetikno, GIE 2002
Jess, GE 2012

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Severity of Inflammation: More mucosal inflammation increases risk for CRC

- An independent risk factor
- Case-control study (1)
  - Significant effect of histological inflammation score (p<0.001)
  - OR neoplasia 4.69 (95% CI 2.10-10.48; p<0.001) for each score unit increase
- Cohort study (2)
  - Histological inflammation
  - HR neoplasia 3.0 (95% CI 1.4-6.3)
- Macroscopically normal colonoscopy – no inflammation (3)
  - CRC risk over 5 yr period no higher than general population (age & sex matched)

1. Rutter, Gastro 2004
2. Gupta, Gastro 2007
3. Rutter, Gut 2004

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Additional Factors: Increased Risk for CRC in IBD

- **Post-inflammatory polyps** = pseudopolyps
  - OR 2.3-2.5 for neoplasia
  - Suggests chronicity of inflammation
- **Young age** at diagnosis of IBD
  - Meta-analysis of pop-based studies:
  - Young age in UC – SIR 8.6 (3.8-19.5)
  - IBD Diagnosis < 30y – SIR 7.2 (2.9-17.8)
  - Absolute risk of CRC at young age remains low
  - Probably not independent risk factor, but composite risk of:
    - Disease duration ahead; extensive; more severe inflammation
- **Men** with UC had greater risk of CRC SIR 2.6 (2.2-3.0)
  - Women SIR 1.9 (1.5-2.3)

Rutter, Gut 2004
Velayos, Gastro 2006
Jess, CGH 2012
Lutgens, IBD 2013

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The Power of the Microbiome

"All diseases begin in the gut." - Hippocrates

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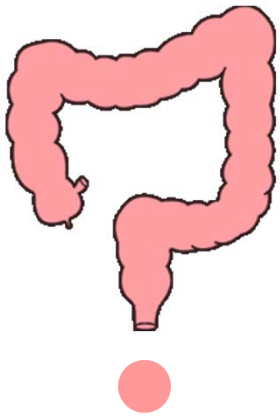
Questions



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