Colonic Neoplasia Remotti

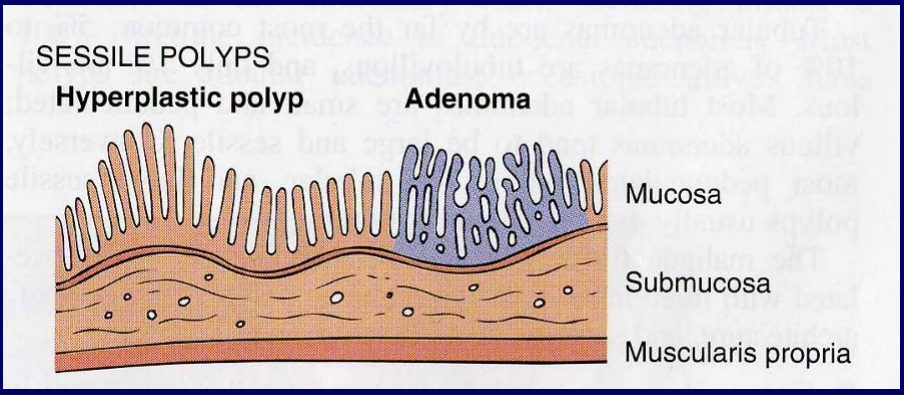
Colorectal adenocarcinoma – leading cancer in developed countries
In US, annual incidence of colorectal adenocarcinoma 150,000.
In US, annual deaths due to colorectal adenocarcinoma 57,000.

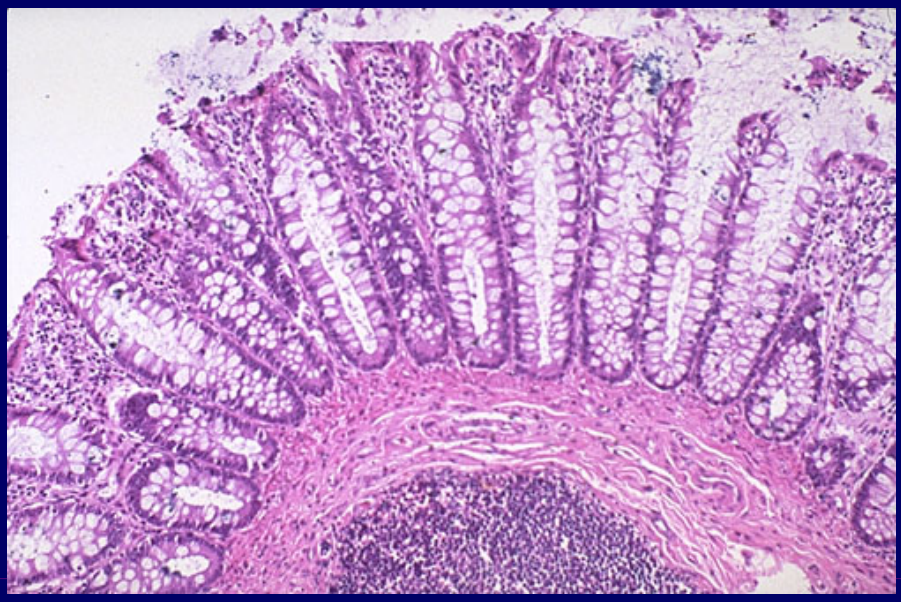
Colonic Adenocarcinoma (Overview of lecture)

- Precursor lesions (Adenoma- Carcinoma sequence)
- Pathologic staging of colorectal tumors

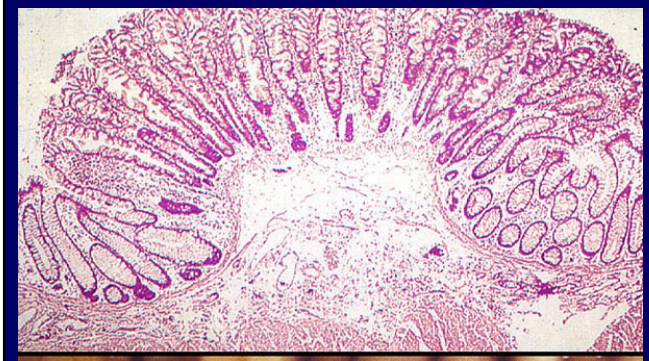
- Chronic inflammation (IBD, including UC and Crohns)
- Genetics (genetic predisposition)
  - FAP (germline mutation of APC gene)
  - HNPCC (germline mutation of mismatch repair gene)
- Molecular pathways of colorectal carcinogenesis
  - Suppressor pathway (APC/beta catenin)
  - Mutator pathway (DNA mismatch repair genes)

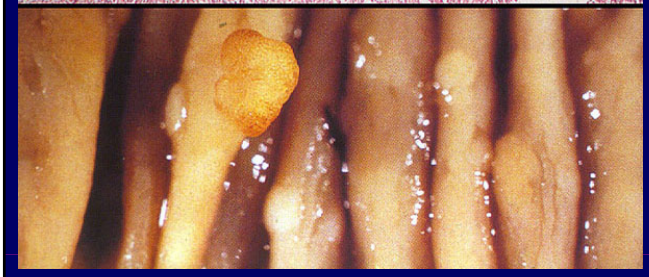
Colonic Polyps : Hyperplastic vs. Adenomatous





Colonic Polyps : Hyperplastic

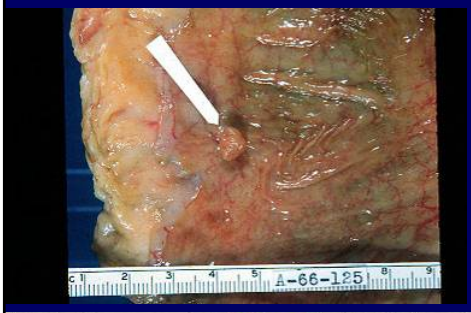


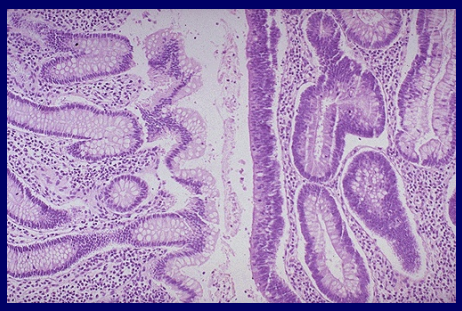


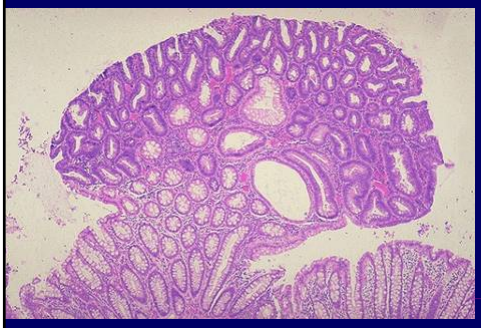
Saw tooth shape of surface epithelium

No dysplasia.

Colonic Polyps : Adenoma

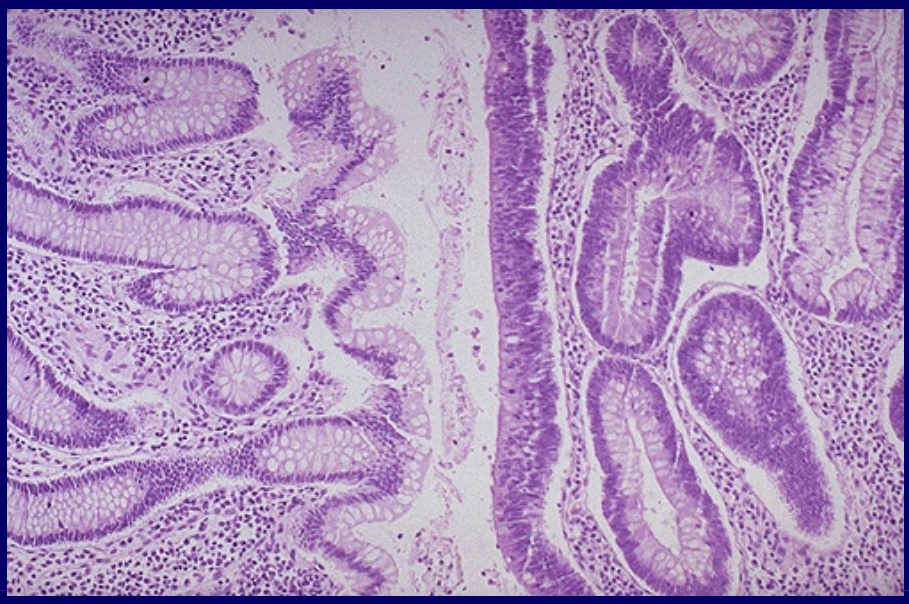






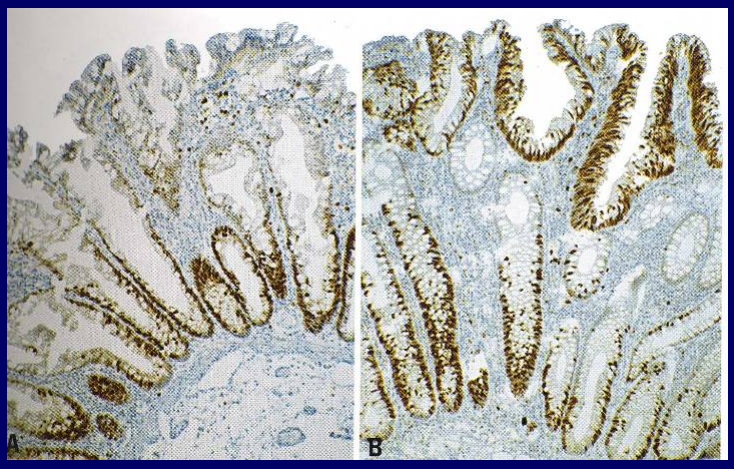
Adenomas by definition have dysplasia.

Lack of surface maturation



Colonic Polyps : Hyperplastic vs. Adenomatous

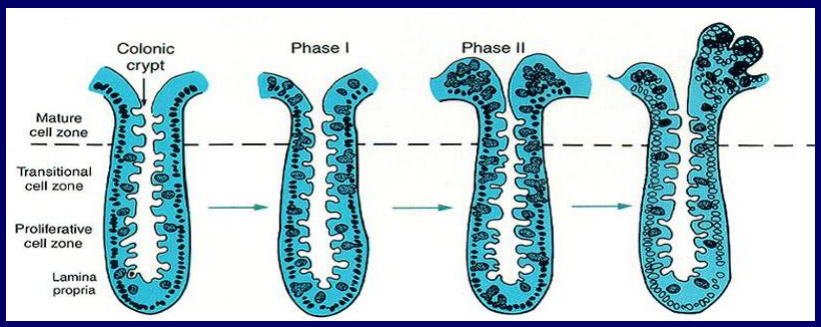
MIB-1 (immuno) nuclear staining
Adenoma- lacks surface maturation;



Hyperplastic Polyp

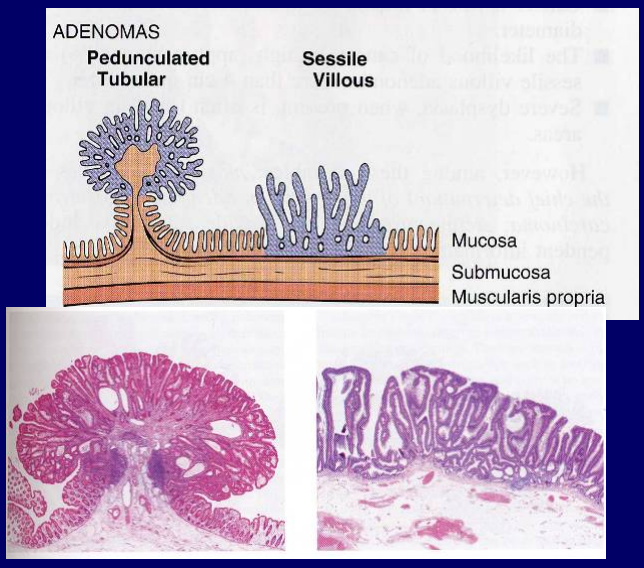
Adenoma

Abnormal proliferation is a hallmark of neoplasia

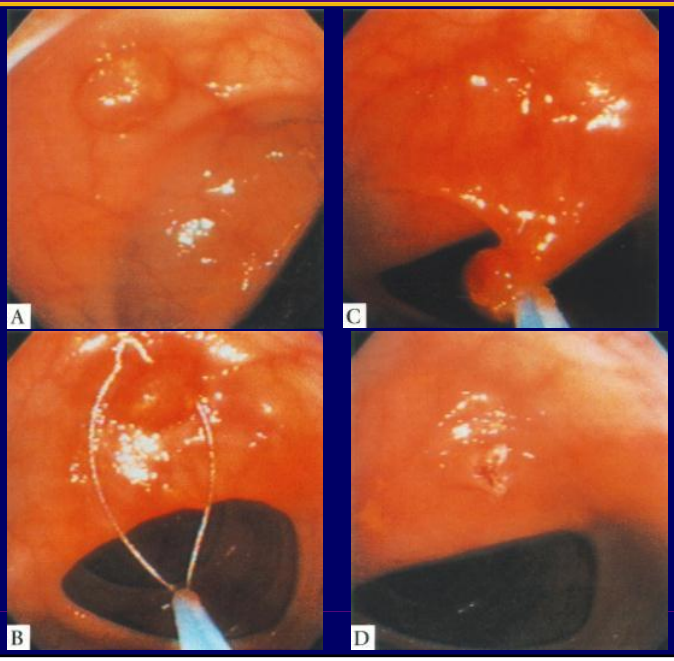


Lack of surface maturation
Proliferation extends to the surface

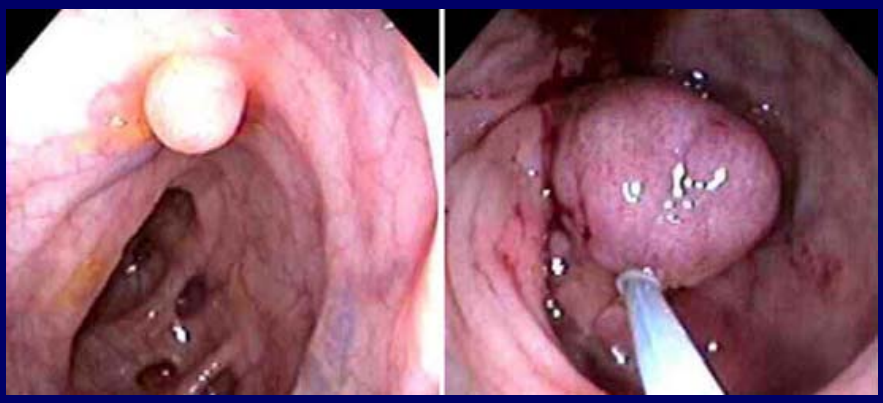
Adenomas – pedunculated vs sessile

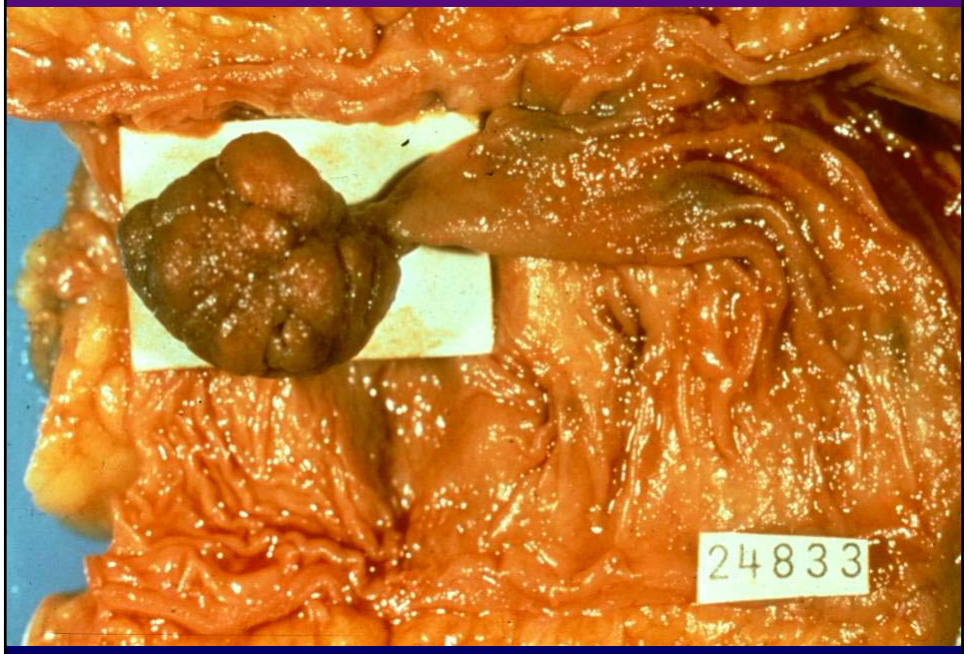


Endoscopic polypectomy

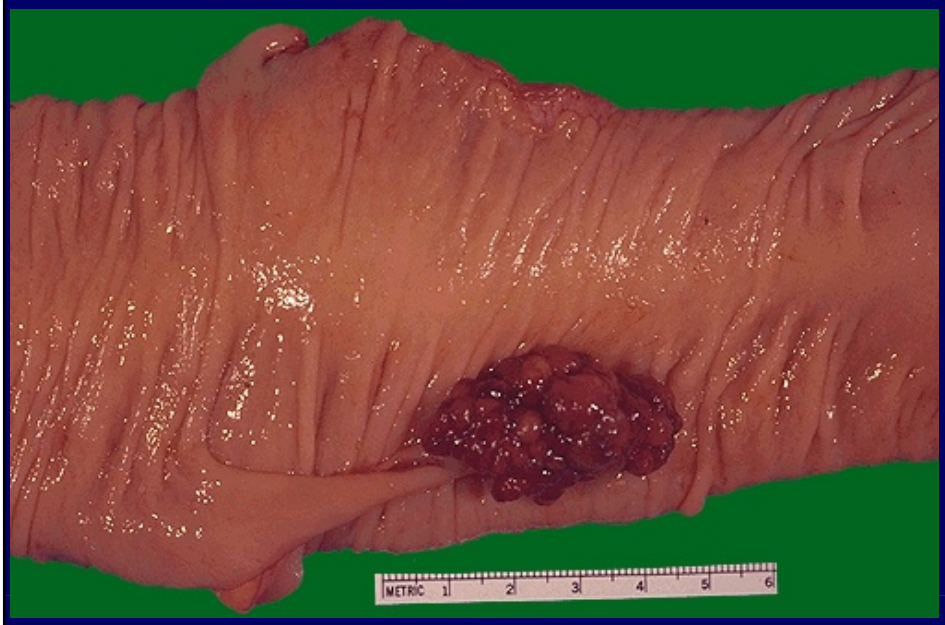


Adenoma on endoscopy

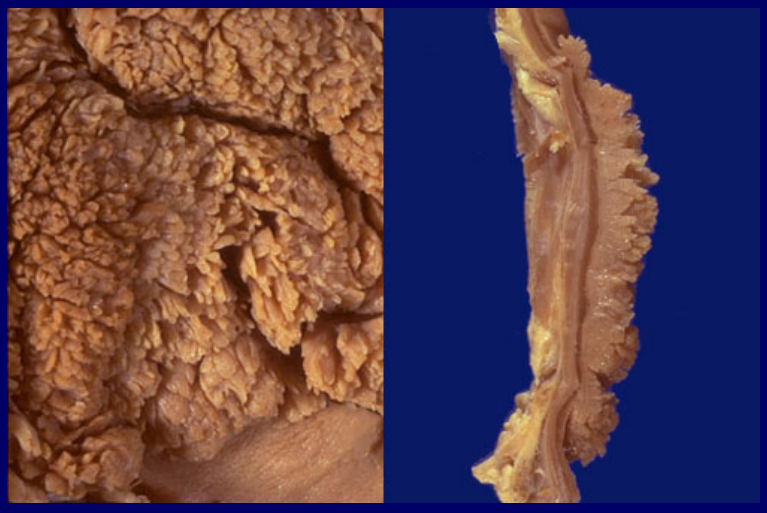




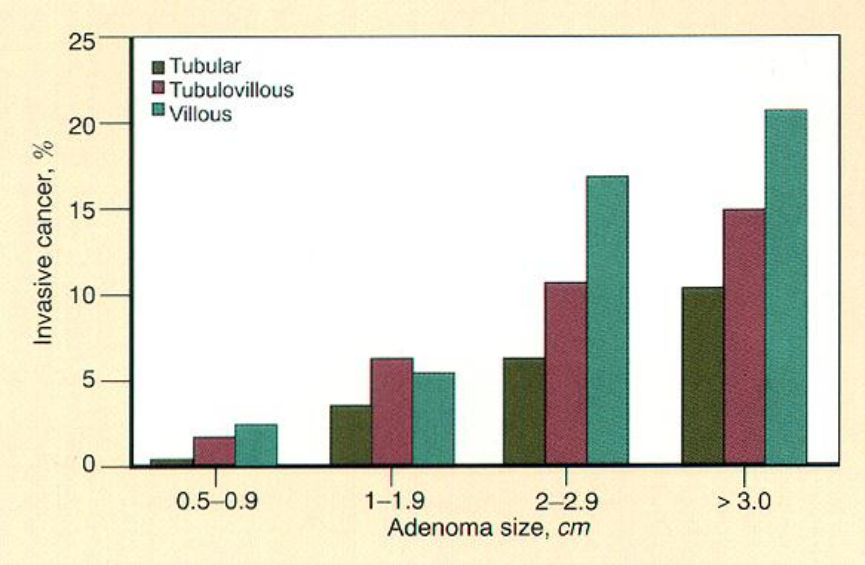
Sessile adenoma



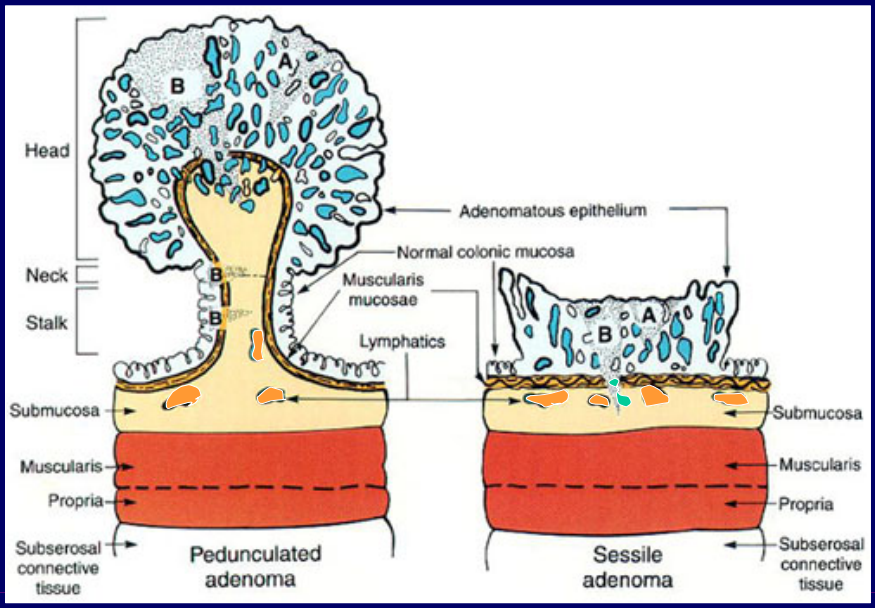
Sessile villous adenoma

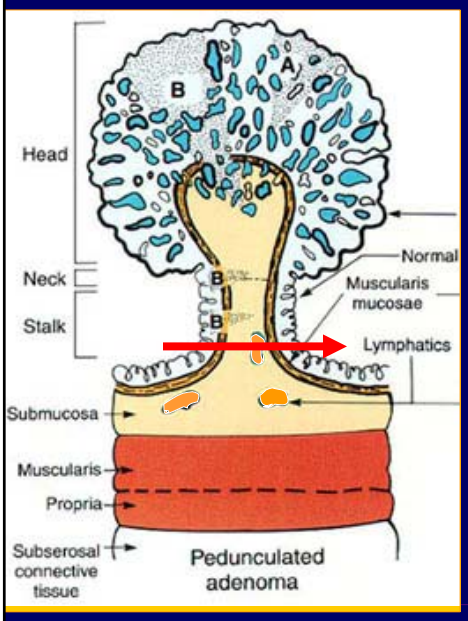


Percent of adenomas containing invasive cancer



Carcinoma within a polyp





Polypectomy is only Treatment

IF:

1) Stalk margin is negative
2) No lymphatic/vascular invasion
3) Tumor is <u>not poorly</u> differentiated.

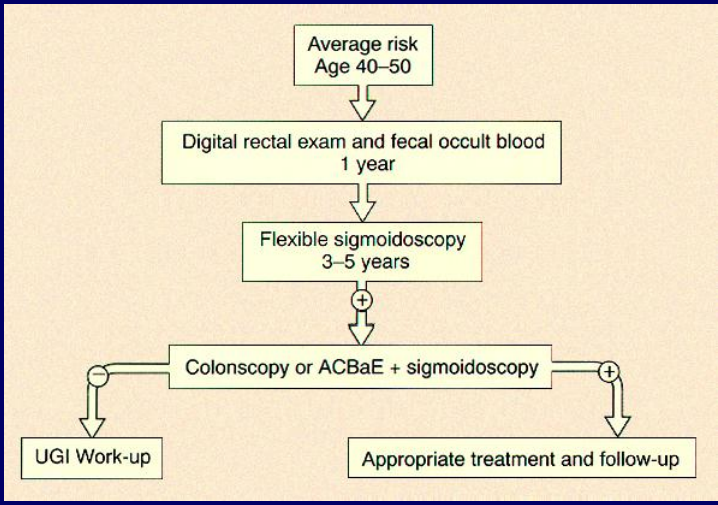
Adenoma – Carcinoma Sequence

Populations that have a high prevalence of adenomas have a high prevalence of colorectal carcinoma.

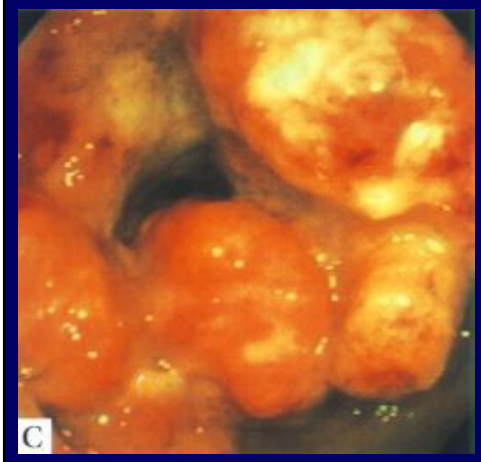
•The distribution of adenomas within the colorectum is similar to that of colorectal carcinoma.
•Peak incidence of adenomas antedates the peak for colorectal carcinoma.
•Adenomatous epithelium is often co-existent with adenocarcinoma.

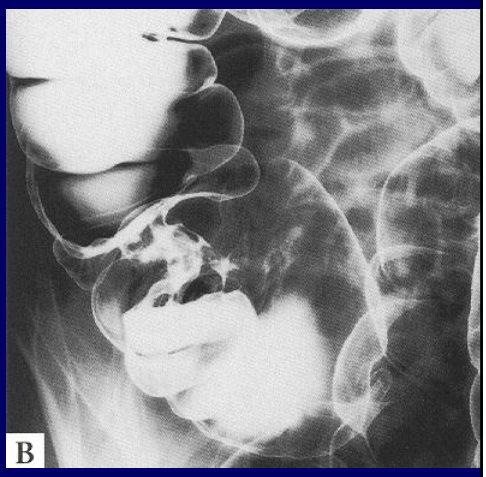
•Screening programs that carefully follow patients for the development of adenomas and remove all that are identified, reduce the incidence of colorectal cancer.

Algorithm for colon cancer surveillance

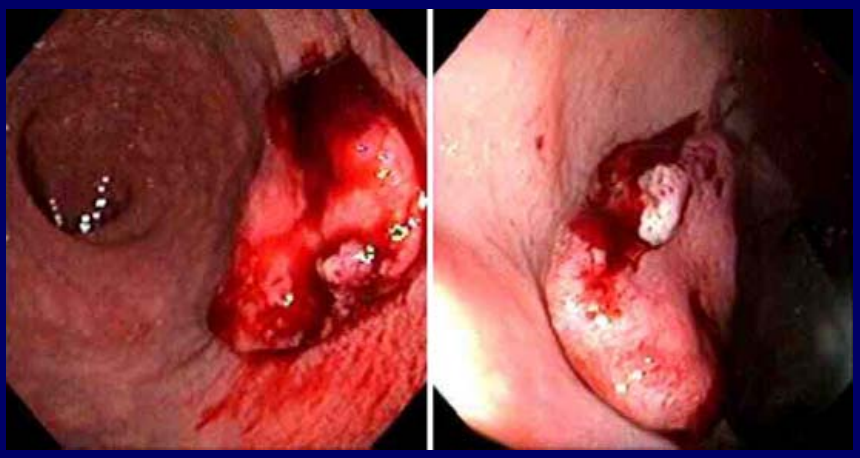


Adenocarcinomas and carcinomas affecting colon

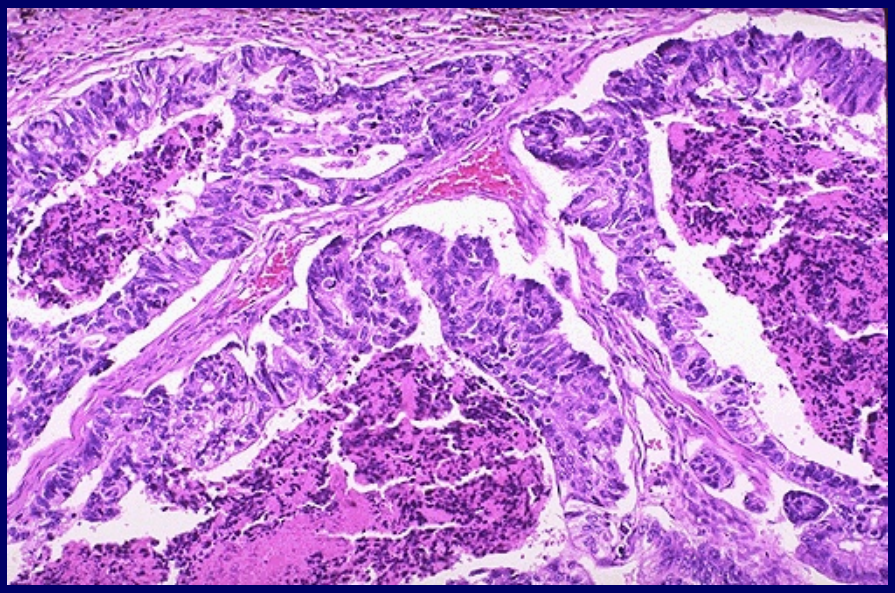




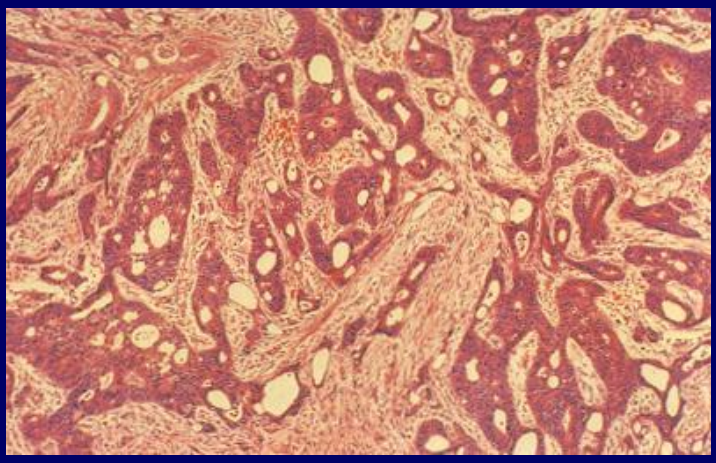
Colon cancer -endoscopy



Adenocarcinoma

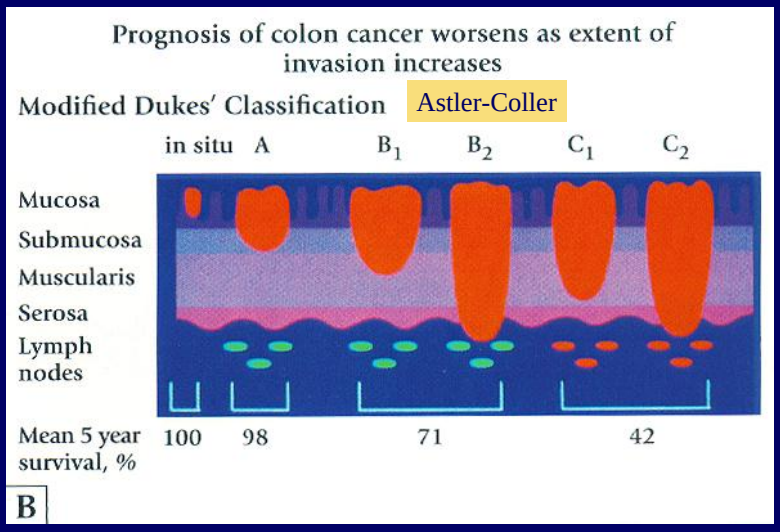


Invasive adenocarcinoma



Irregular infiltrative glands within submucosa
Desmoplastic " loose fibrotic" tissue response

Survival probabilities according to stage of disease (b)



TNM classification of colorectal adenocarcinoma

T- Primary tumor

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (intraepithelial or intramucosal invasion of lamina propria)***
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through muscularis propria into subserosa or into pericolic/perirectal fat.
T4	Tumor directly invades other organs or structures and/or perforates visceral peritoneum.

*** In the colon, unless a tumor invades into the submucosa, it is not considered an invasive adenocarcinoma.

TNM classification of colorectal adenocarcinoma

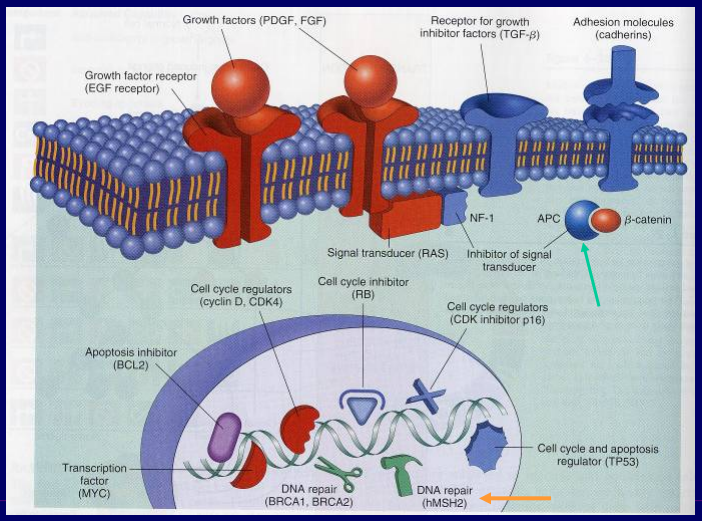
N-Regional Lymph Nodes

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes

M- Distant Metastases

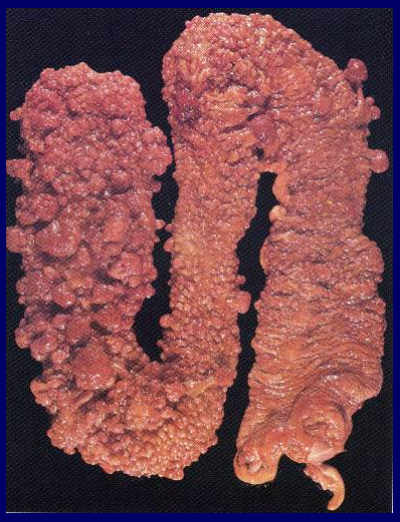
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Major classes of proteins encoded by cancer-associated genes:
Tumor suppressor genes, DNA repair genes, Protooncogenes,
Proteins regulating apoptosis.



Familial Adenomatous Polyposis

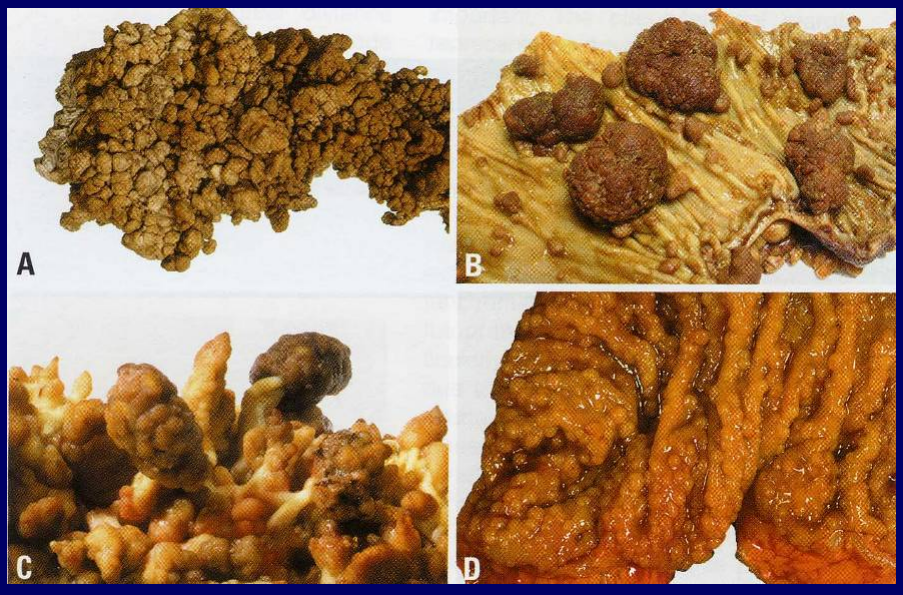
Familial adenomatous polyposis (FAP)



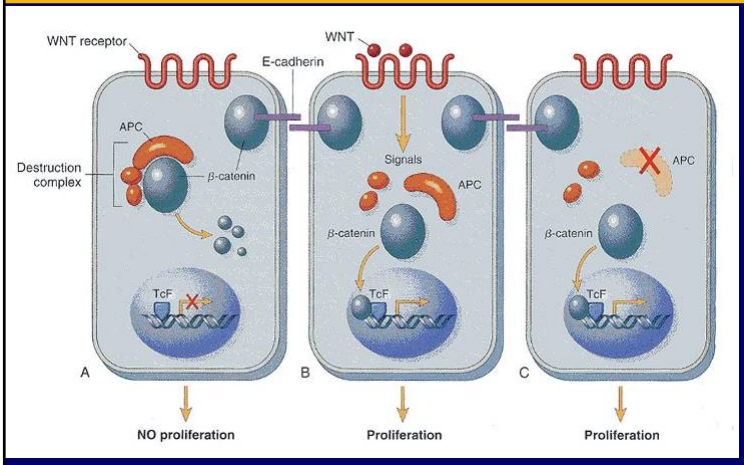
APC- tumor suppressor gene
Germline mutation of APC gene
Patients develop thousands of polyps by their 2nd decade.
The second APC gene must be lost for adenoma formation.
Virtually 100% risk for developing Colorectal adenocarcinoma; also high risk of ampullary carcinoma.

Earliest precursor lesion –
"aberrant crypt"

Familial Adenomatous Polyposis (FAP)



WNT signaling pathway involves APC/beta-catenin and Tcf-4.



In malignant cells with loss of APC, beta catenin degradation is prevented, so WNT signaling response is continually activated.

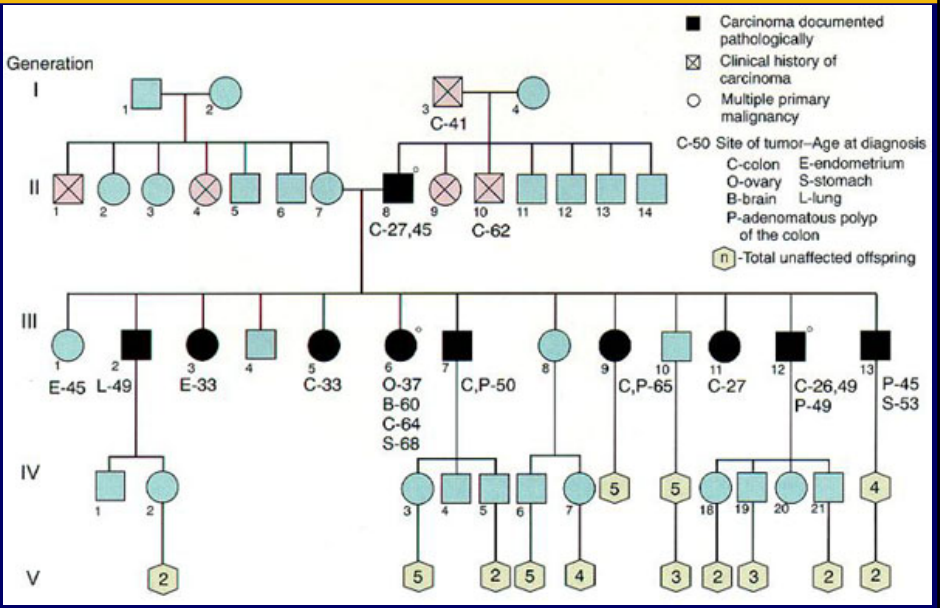
WNT-soluble factor that induces cellular proliferation by binding to its cytoplasmic receptor Preventing degradation of beta-catenin allowing it to translocate to the nucleus where it acts as a transcriptional activator in conjunction with Tcf-4.

APC protein- antiproliferative effect; integral part of complex that destoys beta-catenin.

HNPCC

Hereditary Non-Polyposis Colon Cancer

Inheritance in family with cancer family syndrome



HNPCC

Clinical Criteria for HNPCC

Amsterdam criteria: At least 3 relatives with colon cancer and all of the following:

-One affected person is a first degree relative of the other two affected persons

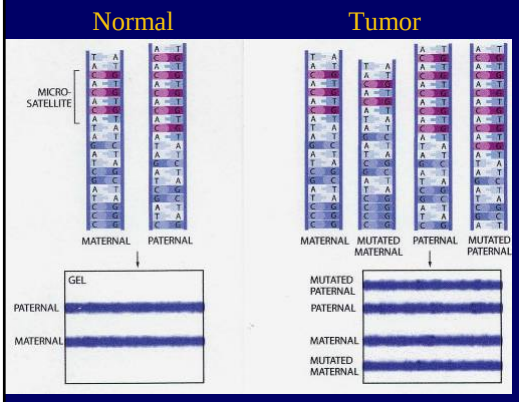
-Two successive generations affected.

-At least one case of colon cancer diagnosed before age 50 y

-FAP excluded

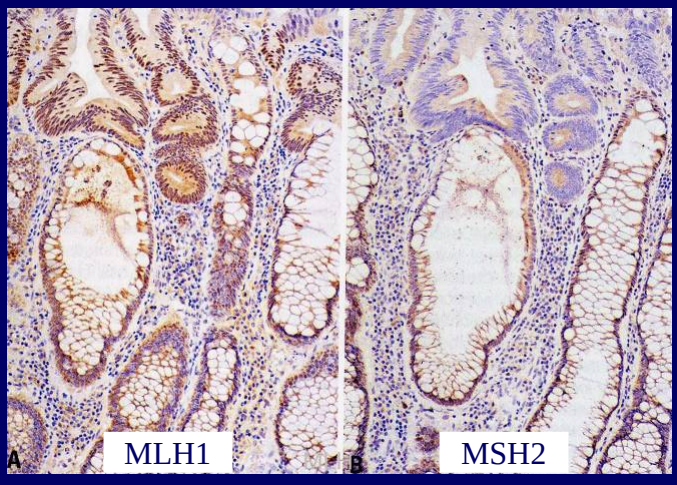
Modified Amsterdam criteria*: same as Amsterdam criteria except cancer can involve (colon, endometrium, small bowel, ureter or renal pelvis) instead of only colon cancer.*

Microsatellite Instability- the result of mismatch repair gene mutations



Microsatellites are simple repetitive DNA sequences (mono or dinucleotide repeats); Most microsatellites are in non-coding regions but a few are in coding regions of critical genes TGF-beta RII, IGFIIR, Tcf-4, BAX.

Immunohistochemical Staining for mismatch repair enzymes



Tubular adenoma in an HNPCC patient.
Neoplastic epithelium shows of loss of MSH2 expression, which correlates with mutation of the MSH2 mismatch repair gene.

Summary of clinical, pathological and genetic features of HNPCC

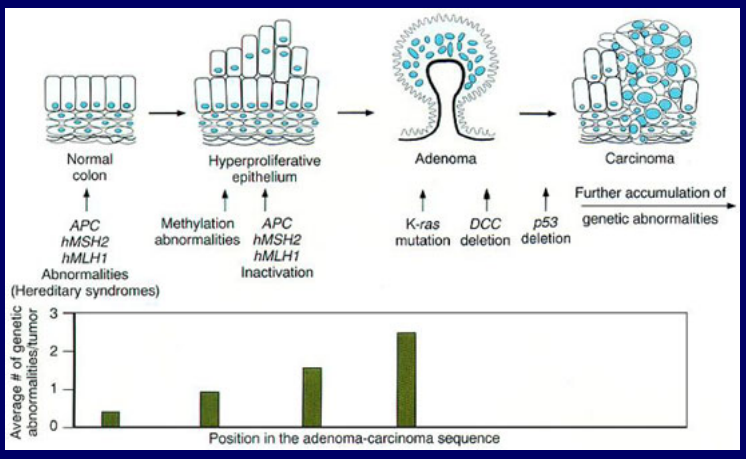
- Familial clustering of colorectal and/or endometrial cancer
- Excess risk of cancer of the ovary, ureter/renal pelvis, small bowel, stomach, brain, hepatobiliary tract, and skin (sebaceous tumors)
- Development of multiple cancers at an early age
- Features of colorectal adenoma include:
  i. variable numbers (one to a few)
  ii. high degree of dysplasia
  iii. rapid progression from adenoma to carcinoma (additional mutations rapidly accumulate – ACCELERATED TUMORIGENESIS)
  iv. high frequency of MSI
- Features of colorectal cancer include:
  i. predilection to proximal colon
  ii. improved survival
  iii. multiple colorectal tumors
  iv. increased proportion of mucinous tumors, poorly differentiated tumors, and tumors with marked host lymphocytic infiltrate at tumor margin.

HNPCC clinical characteristics

HNPCC CLINICAL CHARACTERISTICS

	HNPCC	Sporadic
Mean age at diagnosis, *y*	44.6	67
Multiple colon cancers, %	34.5	4 - 11
Synchronous	18.1	3 - 6
Metachronous	24.3	1 - 5
Proximal location, %	72.3	35
Excess malignancies at other sites	Yes	No
Mucinous and poorly differentiated cancers	Common	Infrequent
RER + %	79	17

Molecular genetic events in evolution of colon cancer



The progression to colorectal cancer is associated with an accumulation of genetic alterations, including alterations in oncogenes (K-ras), tumor suppressor genes (APC, DCC, p53), and DNA repair genes (hMSH2, hMLH1). The exact sequence of events is approximate and may vary in sporadic cancers compared with those arising in hereditary syndromes or inflammatory bowel disease.

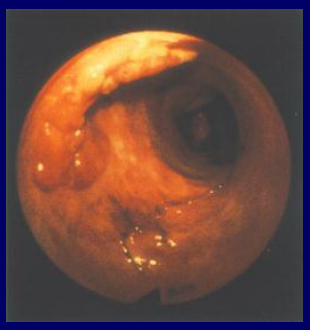
Genes altered in colon cancer

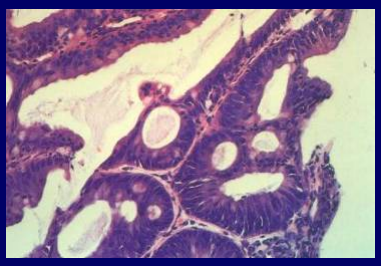
GENES ALTERED IN COLON CANCER

Gene	Chromosome	Sporadic tumors with alterations, %	Class	Function
K - *ras*	12	50	Protooncogene	Signal transduction
APC	5	60	Tumor supressor	?Cell adhesion Anti-proliferative function
DCC	18	70	Tumor supressor	?Cell adhesion
p53	17	75	Tumor supressor	Cell cycle control (G1/S arrest)
hMSH2	2		DNA Mismatch repair	Maintains fidelity of DNA replication
hMLH1	3		DNA Mismatch repair	Maintains fidelity of DNA replication

Dysplasia and Carcinoma in Inflammatory Bowel disease

Dysplasia-associated lesion/mass (DALM) in Ulcerative Colitis



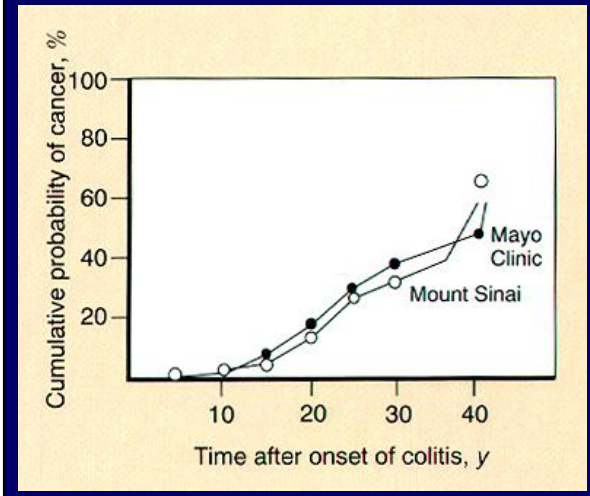


High grade Dysplasia

Risk of dysplasia in UC correlate with EXTENT and DURATION of disease.
UC patients with pancolitis are at highest risk.
Ulcerative proctitis (disease limited to rectum) -negligible risk.

DALM – (dysplasia associated lesions)
greater than 50% chance of coexistent invasive adenocarcinoma.

Probability of developing colorectal carcinoma in ulcerative colitis

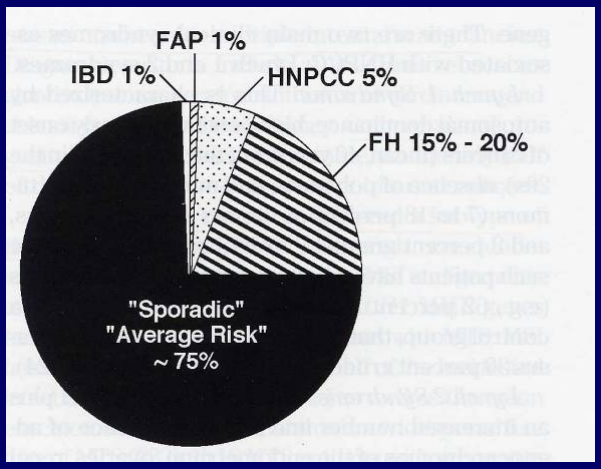


Cumulative risk of developing adenocarcinoma correlates with duration of UC:

5% in 5 years
15% in 25 years
30-50% in 40 years

1% per year cumulative incidence of carcinoma after 10 years duration of disease.

Bresalier RS, Kim YS, In Gastrointestinal Disease: Pathophysiology/Diagnosis/Management, edn 5. Edited by Sleisenger MH, Fordtran JS. Philadelphia: WB Saunders; 1993 1449-1493



Estimates of the predisposing causes of Colorectal Carcinoma

Current screening (average risk)

FOBT Flex sig	FOBT annual Flex sig - 5yr	Positive tests Colonoscopy
Colonoscopy	every 10 yr	
Barium Enema	every 5 yr	

Current screening (increased risk)

1 adenoma <1cm	3-6 yr after initial polypectomy	Colonoscopy
Adenoma>1cm, Multiple adenomas	3 yrs after initial polypectomy	
Curative resection of colon cancer	Within 1 yr	If normal , repeat in 3yr.

Current screening (high risk)

FAP (family hx)	puberty	Genetic testing
HNPCC (family hx)	age 21	Genetic testing, 1-2 yr until age 40, then annually
IBD	Risk greater with Pancolitis, >10yr duration	Every 1-2 yr.

Colonic Neoplasia

Colonic Adenocarcinoma (Summary)

- Precursor lesions (Adenoma- Carcinoma sequence)
- Pathologic staging of colorectal tumors

- Chronic inflammation (IBD, including UC and Crohns)
- Genetics (genetic predisposition)
  - FAP (germline mutation of APC gene)
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- Molecular pathways of colorectal carcinogenesis
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