Colorectal Cancer

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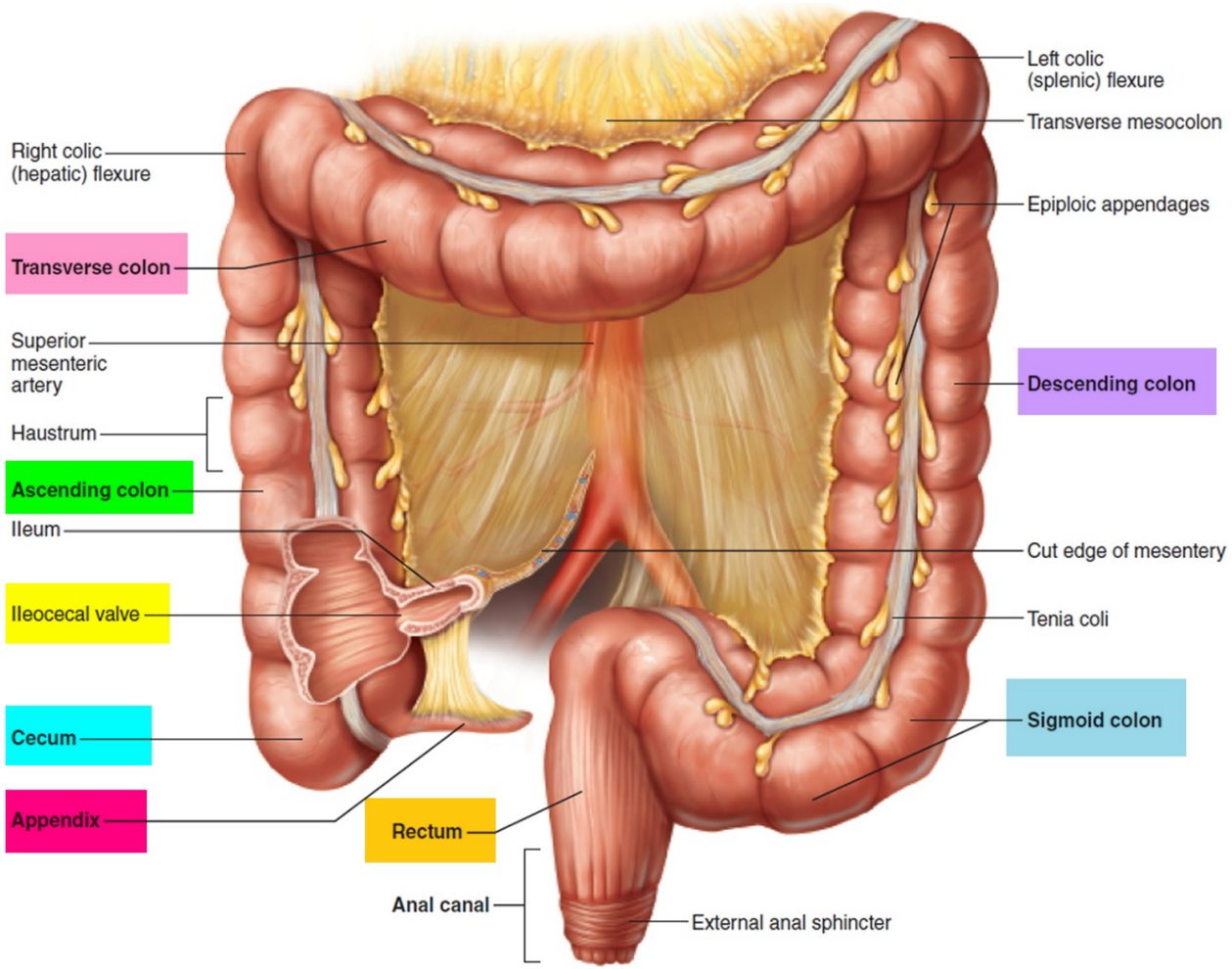
Outlines

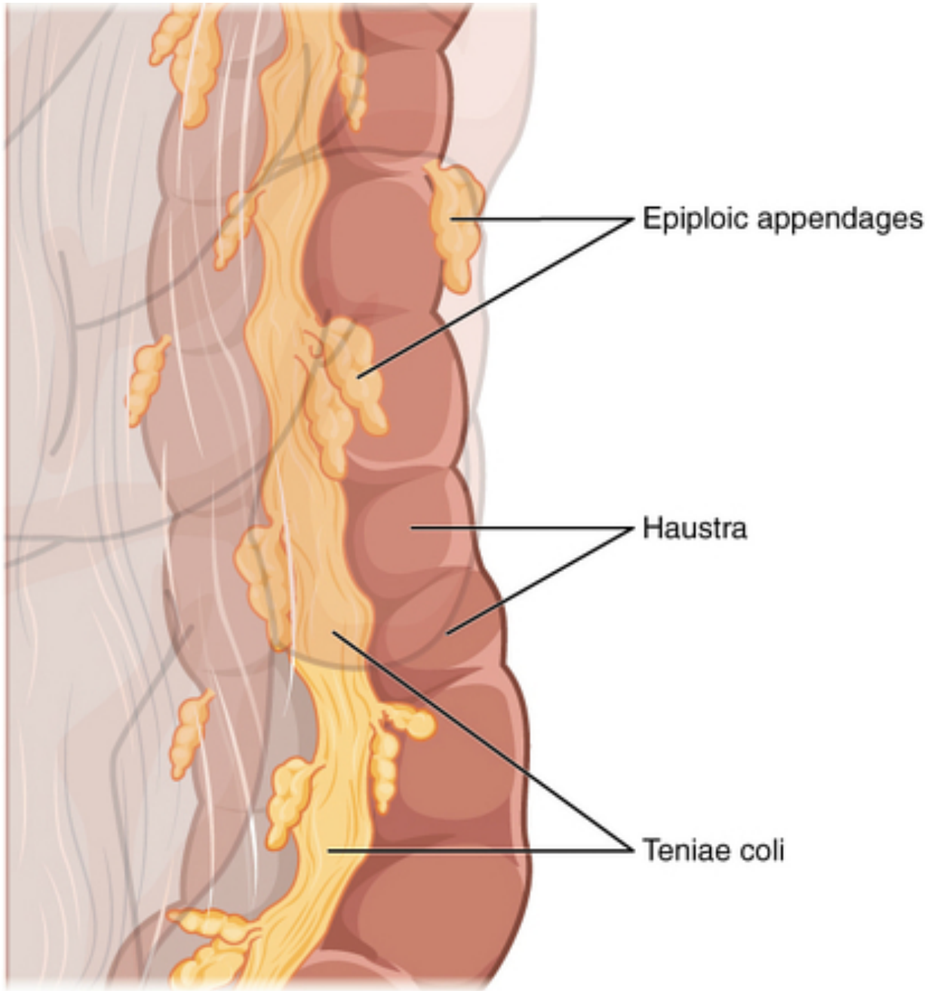
- Anatomy
- Epidemiology
- Risk and Protective factors
- Etiology
- Polyps and Lynch syndrome
- Pathology
- Screening
- Staging systems
- Clinical Presentation and Diagnosis
- Treatment
- Follow Up

Anatomy

- The large intestine is the terminal portion of the gastrointestinal tract and is derived from the midgut, hindgut, and cloaca.
- The large intestine length is approx. 1.5 m (5 ft) long.
- The large intestine is divided into the cecum and appendix, the ascending colon, transverse colon, descending colon, sigmoid colon, rectum, and anal canal.
- The large intestine is **less mobile** than the small bowel as the ascending and descending colon are fixed to the retroperitoneum.

Anatomy


Left colic (splenic) flexure
Transverse mesocolon
Right colic (hepatic) flexure
Epiploic appendages
Transverse colon
Descending colon
Superior mesenteric artery
Haustrum
Ascending colon
Ileum
Cut edge of mesentery
Ileocecal valve
Tenia coli
Sigmoid colon
Cecum
Appendix
Rectum
Anal canal
External anal sphincter


Epiploic appendages
Haustra
Teniae coli

Anatomy

	Midgut derivatives **Cecum, appendix, ascending colon, proximal 2/3 of the transverse colon**
Arterial blood supply	**Branches of the superior mesenteric artery (SMA)**
	Ileocolic artery: Ileocolic region, cecum and appendix.
	Rt colic artery: Ascending colon and hepatic flexure.
	Middle colic artery: Proximal 2/3rd of transverse colon
Venous drainage	Branches of the superior mesenteric vein → portal vein
Lymphatic drainage	Superior mesenteric lymph nodes: colon to splenic flexure
innervations	Visceral: superior mesenteric plexus

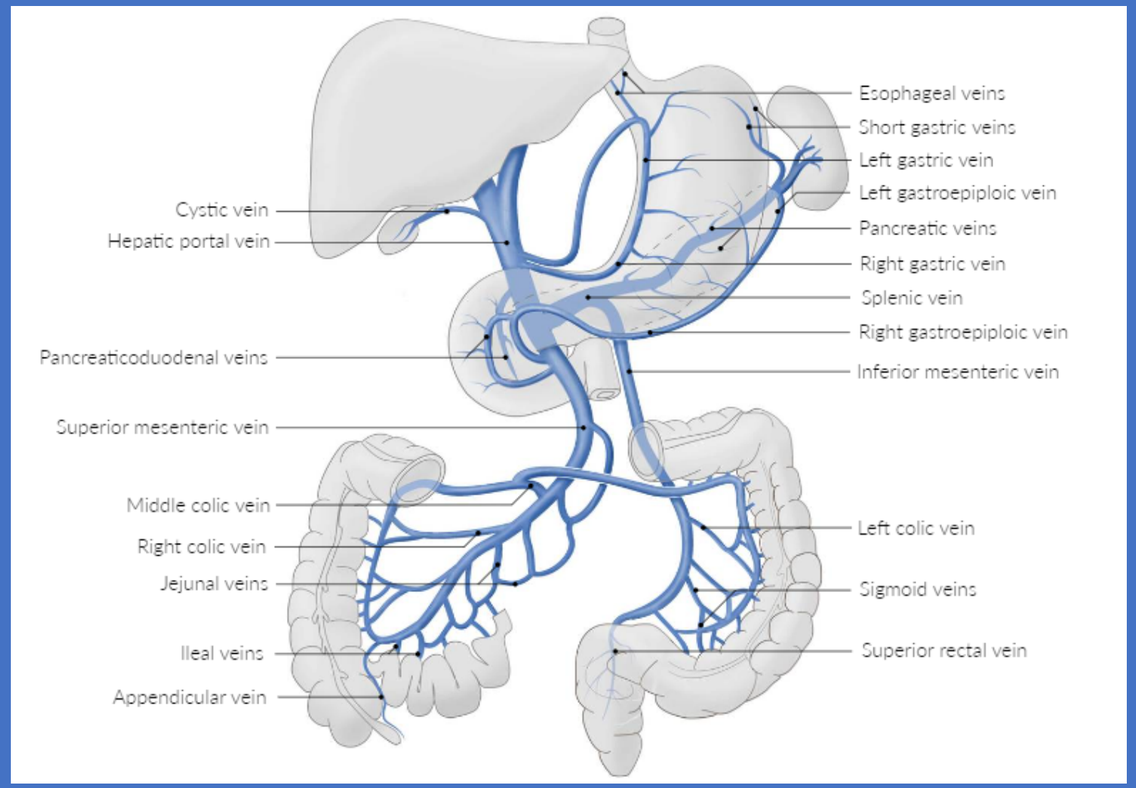
Anatomy

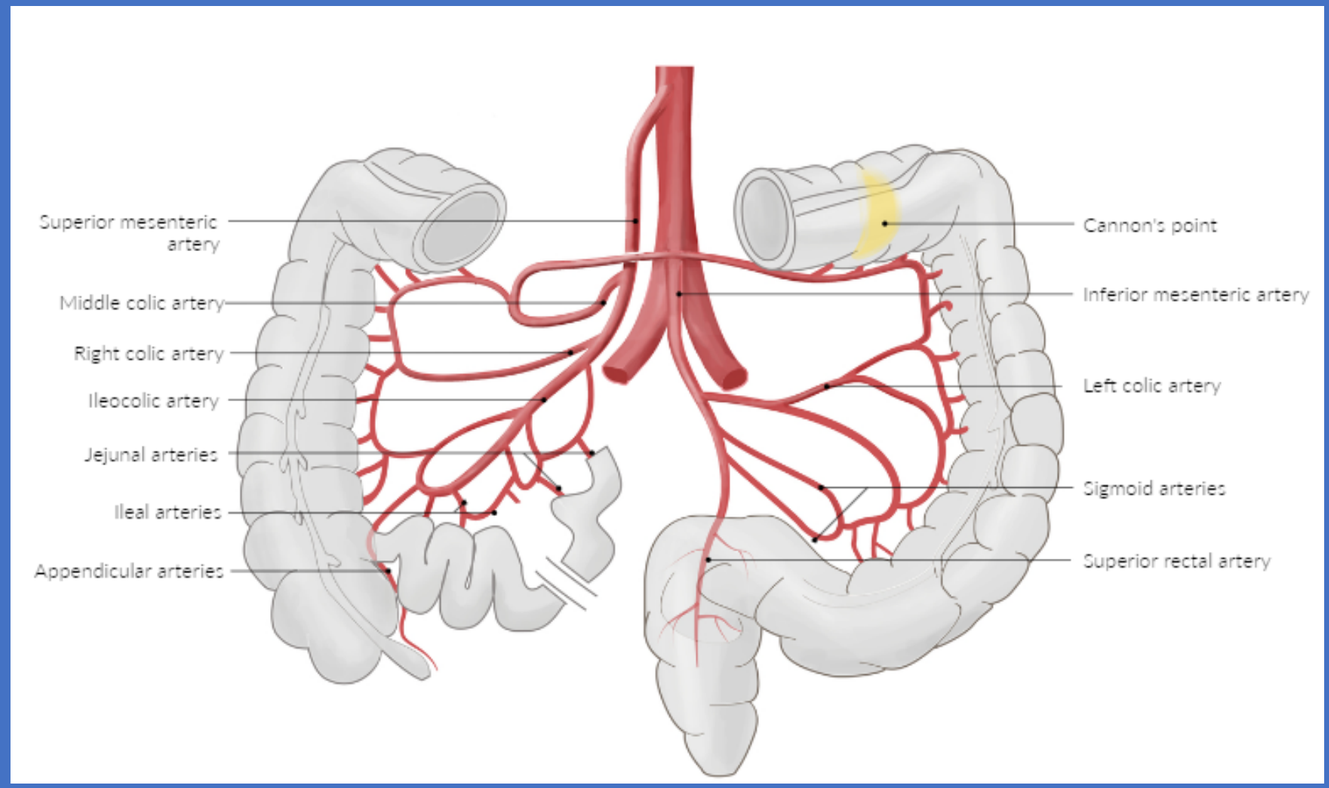
	Hindgut derivatives **Distal 1/3 of the transverse colon, descending colon, and sigmoid colon**
Arterial blood supply	**Branches of the Inferior mesenteric artery (IMA)**
	Lt colic artery: distal 1/3rd of transverse colon, Splenic flexure and descending colon.
	Sigmoidal arteries: Sigmoid colon.
Venous drainage	Left colic vein and sigmoid veins drain into the **inferior mesenteric vein** → splenic vein → portal vein
Lymphatic drainage	Inferior mesenteric lymph nodes: colon from splenic flexure to upper and middle rectum
innervations	Visceral: Inferior mesenteric plexus

Anatomy

	Rectum and anal canal	
	Above pectinate line	**Below pectinate line**
Arterial blood supply	**Superior rectal artery** (IMA)	**Middle rectal artery** (Internal iliac) **Inferior rectal artery** (Internal pudendal)
Venous drainage	Superior rectal vein → **inferior mesenteric vein** → splenic vein → **portal vein**	Middle and inferior rectal vein → internal pudendal vein → internal iliac vein → common iliac vein → **inferior vena cava**
Lymphatic drainage	1) Upper and middle rectum: **pararectal lymph nodes** → inferior mesenteric lymph nodes 2) Direct to **Internal iliac lymph nodes**	Superficial inguinal lymph nodes
innervatio	Visceral: Inferior mesenteric plexus	Somatic: inferior rectal branch of the

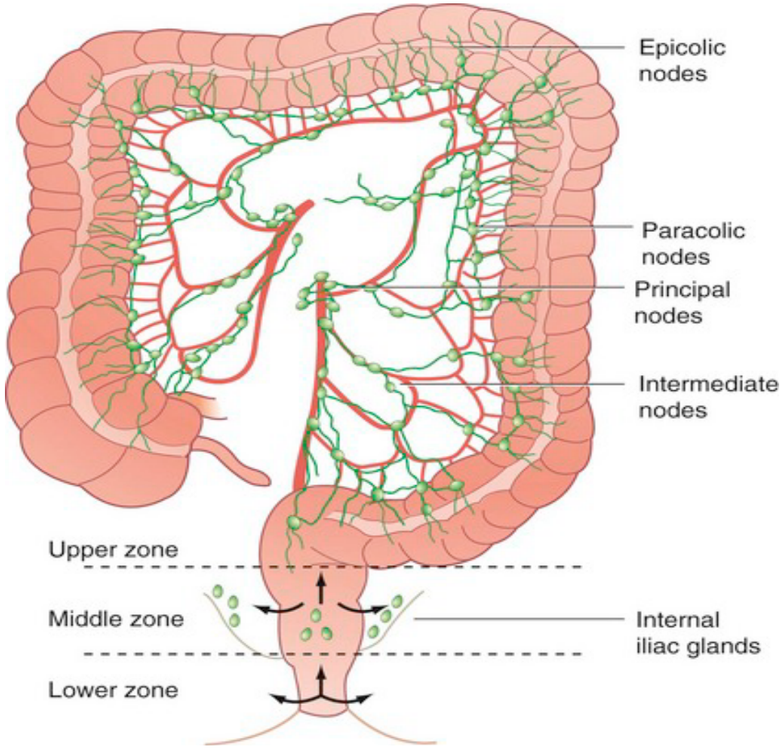
Anatomy

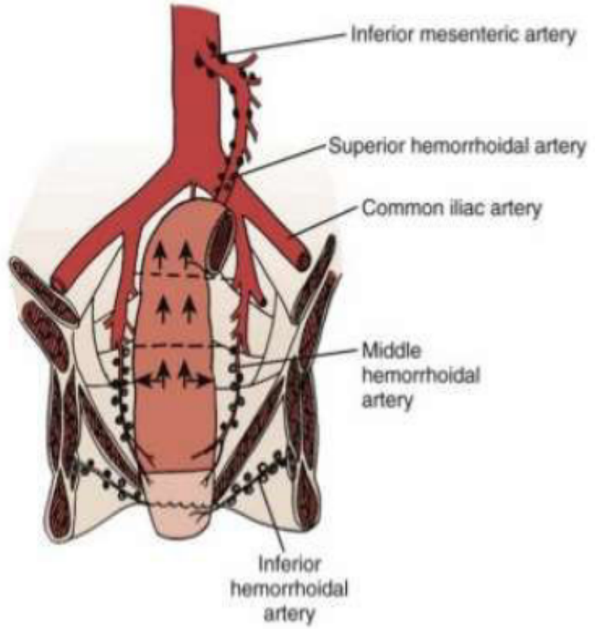

Esophageal veins
Short gastric veins
Left gastric vein
Left gastroepiploic vein
Pancreatic veins
Right gastric vein
Splenic vein
Right gastroepiploic vein
Inferior mesenteric vein
Left colic vein
Sigmoid veins
Superior rectal vein
Cystic vein
Hepatic portal vein
Pancreaticoduodenal veins
Superior mesenteric vein
Middle colic vein
Right colic vein
Jejunal veins
Ileal veins
Appendicular vein


Cannon's point
Inferior mesenteric artery
Left colic artery
Sigmoid arteries
Superior rectal artery
Superior mesenteric artery
Middle colic artery
Right colic artery
Ileocolic artery
Jejunal arteries
Ileal arteries
Appendicular arteries

Anatomy and Functions

- **Innervations**:
  - **The parasympathetic nerve**
    - Right and transverse colon is through the **vagus nerve.**
    - Distal colon and the rectum are supplied by (**the pelvic splanchnic nerves)** from S2,3,4.
  - **The sympathetic system**
    - supplies the blood vessels through the **greater and lesser splanchnic nerve.**
- **Lymphatic drainage:**
  - Most of the lymph nodes passes into the intestinal lymph trunks, and on to the **cisterna chyli** – where it ultimately empties into the **thoracic duct**.
- **Functions:**
  - Absorbs water and electrolytes
  - Absorbs vitamins





Colorectal Cancer

Epidemiology

- Worldwide:
  - Colorectal cancer is the third most diagnosed cancer in male and second in female.
  - Colorectal cancer is the second leading cause of cancer death.
- Incidence and mortality: male > female (UpToDate).
- It predominantly affects older individuals, with the majority of cases occurring in people aged 40-50 and above.

Risk factors

- **Age**: older age (> 40 years)
- **Race**: more in black people.
- **Gender**: male>female (UpToDate).
- **Hereditary syndromes**
  - Family history: Approx. 25% of individuals with colorectal cancer (CRC) have a positive family history.
  - Familial adenomatous polyposis
  - Hereditary nonpolyposis colorectal cancer
- **Associated conditions**
  - Colorectal adenomas and serrated polyps, Inflammatory bowel disease, Endocarditis and bacteremia due to S. gallolyticus and DM type 2.
- **Lifestyle**: Alcohol and Tobacco
- **Cholecystectomy**: slight increase in the risk of right-sided colon cancer, possibly as a consequence of increased bile acid exposure.
- **Diet**: Obesity, Processed meat and High-fat and low-fiber
- **Pathogens**: Streptococcus bovis, Clostridium septicum.

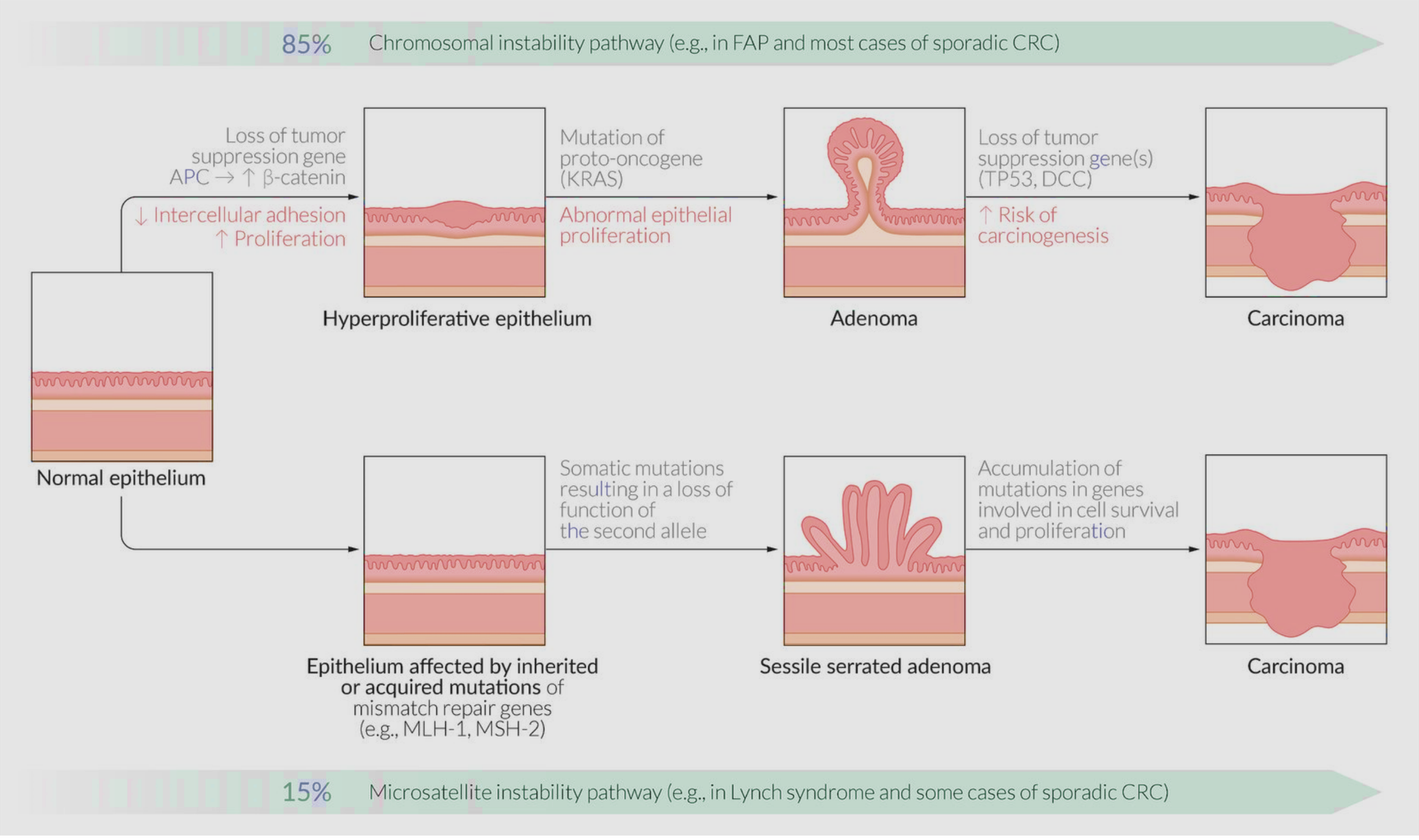
Protective factors

- High fiber diet
- Folic acid and folate
- Aspirin
  - Low-dose aspirin can reduce the risk of colorectal cancer by 40% for people who meet specific criteria.
- Combined oral contraceptive pills
- It is not clear if the following affect the risk of colorectal cancer:
  - NSAIDs other than aspirin
  - Calcium

Etiology

- **Chromosomal instability pathway in colon cancer:** The adenoma-carcinoma sequence is the progressive accumulation of mutations in oncogenes (e.g., KRAS) and tumor suppressor genes (e.g., APC, TP53) that results in the slow transformation of adenomas into carcinomas.
  - APC gene mutation (loss of cellular adhesion and increased cellular proliferation) → KRAS gene mutation (unregulated cellular signaling and cellular proliferation) → TP53 and DCC gene mutation
  - Most cases of sporadic CRC develop via this pathway.
- **Microsatellite instability pathway in colon cancer:** due to methylation or mutations in mismatch repair genes (MMR genes, e.g., MLH1 or MSH2)

Etiology


85%
Chromosomal instability pathway (e.g., in FAP and most cases of sporadic CRC)
Loss of tumor suppression gene APC → ↑ β-catenin
↓ Intercellular adhesion
↑ Proliferation
Hyperproliferative epithelium
Mutation of proto-oncogene (KRAS)
Abnormal epithelial proliferation
Adenoma
Loss of tumor suppression gene(s) (TP53, DCC)
↑ Risk of carcinogenesis
Carcinoma
Normal epithelium
Epithelium affected by inherited or acquired mutations of mismatch repair genes (e.g., MLH-1, MSH-2)
Somatic mutations resulting in a loss of function of the second allele
Sessile serrated adenoma
Accumulation of mutations in genes involved in cell survival and proliferation
Carcinoma
15%
Microsatellite instability pathway (e.g., in Lynch syndrome and some cases of sporadic CRC)

Intestinal Polyps

- Adenomatous polyps:
  - The most common type (70%).
  - High malignant potential.
- More risk of malignancy in:
  - **Histology**: Villous > tubular
  - **Size**: more size will increase risk
  - **Morphology**: Sessile > Pediculated

Inflammatory	Inflammatory polyps (pseudopolyps in ulcerative colitis)
Hamartomatous	Peutz–Jeghers polyp
	Juvenile polyp
Serrated polyps (serrated lesions)	Hyperplastic polyp
	Sessile serrated lesion
	Sessile serrated lesion with dysplasia
	Traditional serrated adenomas
	Mixed polyp
Adenoma	Tubular
	Tubulovillous
	Villous
Malignant polyp	Adenocarcinoma

Hereditary non-polyposis colorectal cancer (Lynch syndrome)

- caused by an **autosomal dominant** mutation in DNA mismatch repair (MMR) genes.
  - The most affected genes are MLH1 and MSH2.
- increased risk of colorectal cancer and cancers of the endometrium, ovary, stomach and small intestines.
- Colon cancer and lynch syndrome:
  - Most common cause of inherited CRC.
  - Accounts for approx. 3–8% of all new cases of CRC.
  - The lifetime risk of developing colorectal cancer in Lynch syndrome is 80%.
  - The mean age of diagnosis is 45 years.
  - Most cancers develop in the proximal colon.

Hereditary non-polyposis colorectal cancer (Lynch syndrome)

- Diagnosed by Amsterdam criteria II:
  - Presence of at least three relatives with a Lynch syndrome-associated cancer; all the following criteria should be present:
    - One should be a first-degree relative of the other two
    - At least two consecutive generations affected
    - At least one relative with a diagnosis before 50 years of age
    - Exclude cases of familial adenomatous polyposis.
    - Verify tumors with pathological examination.

3-2-1 rule: (3 affected family members, 2 generations, 1 relative under 50 years of age).

- Patients with HNPCC are subjected to regular (every one to two years) colonoscopic surveillance.

Pathology - Macroscopically

1. Annular.
2. Tubular.
3. Ulcerative.
4. Cauliflower.

- The annular variety tends to give rise to **obstructive symptoms**, whereas the others will present more commonly with **bleeding**.

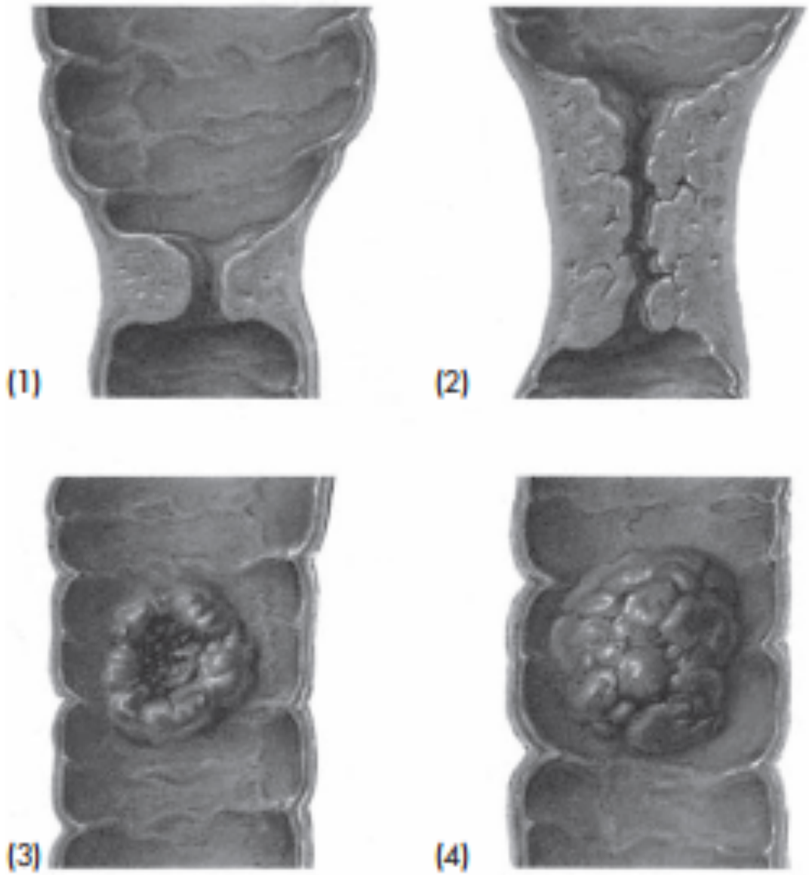
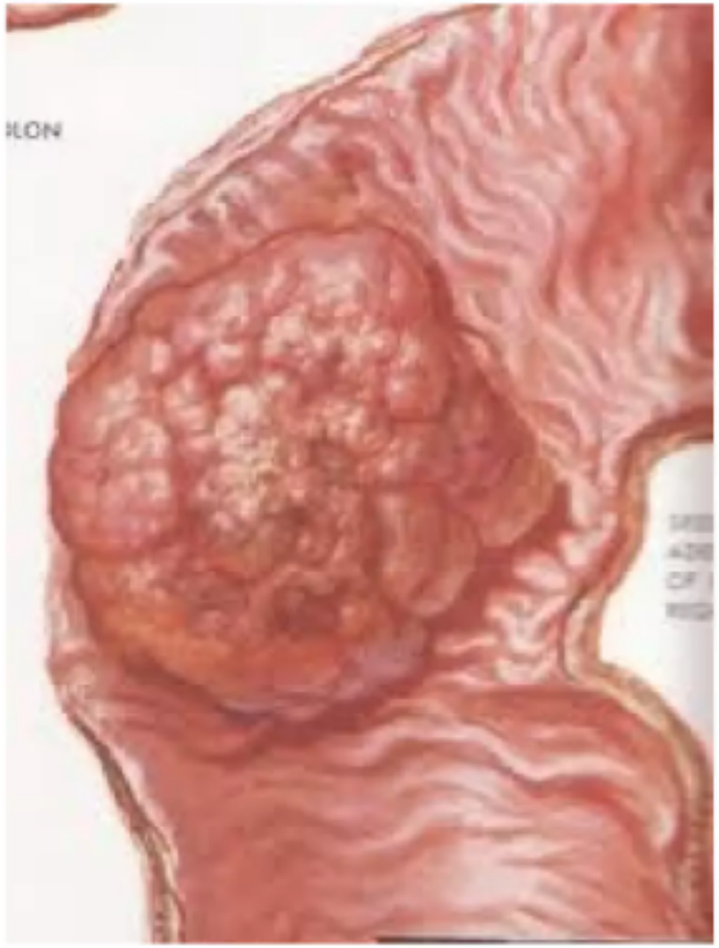


Figure 69.22 The four common macroscopic varieties of carcinoma of the colon. (1) Annular; (2) tubular; (3) ulcer; (4) cauliflower.

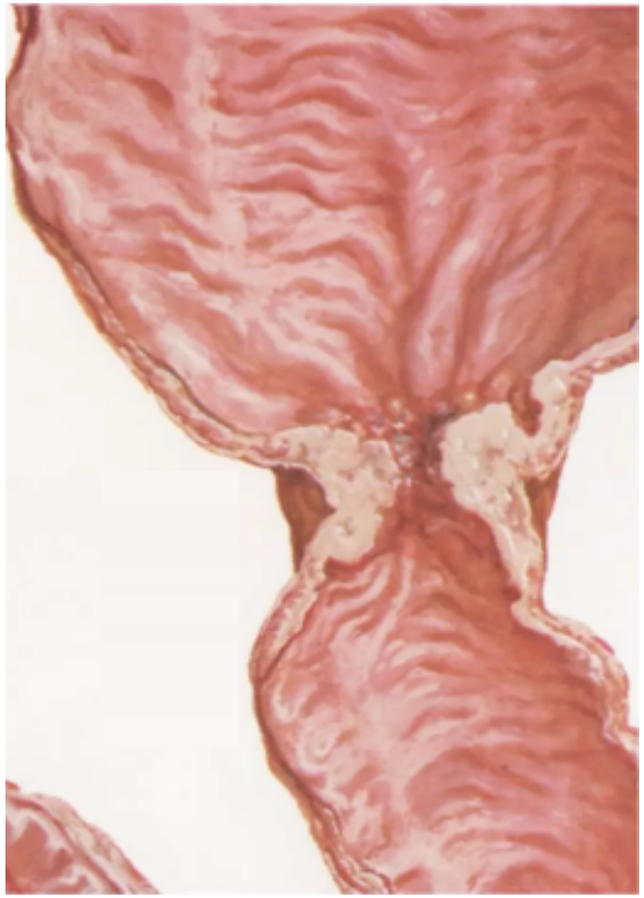
Pathology - Macroscopically

- **Right-sided colon carcinomas**: mostly exophytic mass ; **tend to bleed**.

- **Left-sided colon carcinomas**: mostly infiltrating mass , produce ‘apple-core or napkin-ring’ appearance; **tends to obstructive**.



Exophytic mass



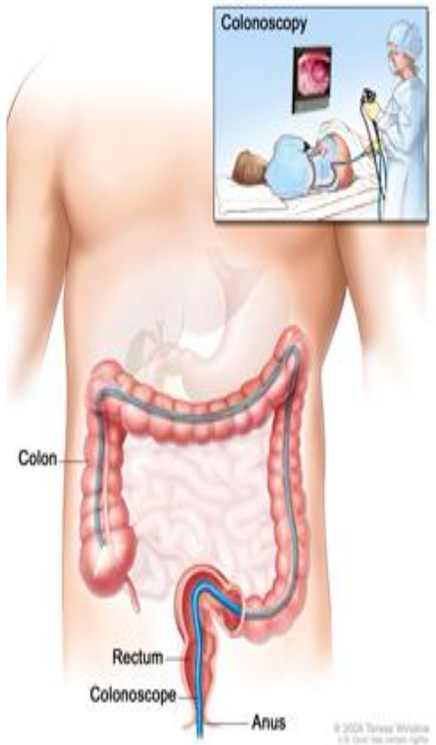
Napkin-ring
mass

Pathology - Microscopically

- Most common: adenocarcinoma (95%)
- Less common (5%)
  - Mucinous adenocarcinoma
  - Signet ring cell carcinoma
  - Small cell carcinoma
  - Adenosquamous carcinoma (rare)

Screening

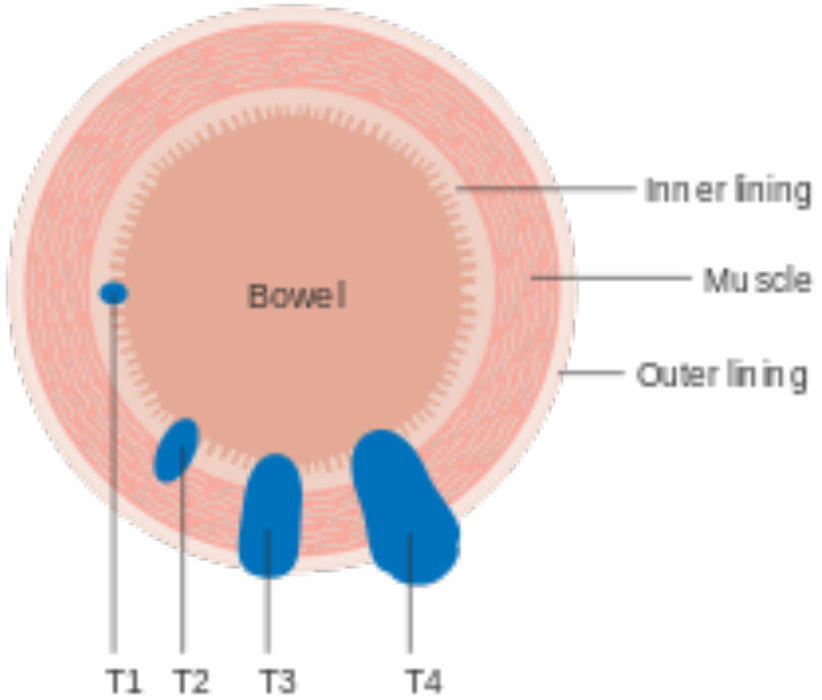
- **Criteria for average risk of CRC include**:
  - No history of CRC, IBD, or adenomatous polyps
  - No family history of hereditary colon cancer syndromes (e.g., HNPCC, familial adenomatous polyposis).
- **Recommended screening age**:
  - All individuals aged > 50 years; recent guidelines at 45 years of age.
- **With risk factors (family history):**
  - At age 40 or 10 years earlier than the index patients age of diagnosis.
- **Screening modalities:** Consider individual risk factors and patient preference when choosing a screening method.
  - Direct visualization
    - Gold standard: Complete colonoscopy every 10 years if no polyps or carcinomas are detected
    - Alternative: FSIG every 5 years, CT colonography every 5 years.
  - Stool-based testing
    - Annual fecal occult blood test



Staging

- Once the diagnosis of CRC is established the local and distant extent of disease is determined via staging to provide a framework for discussing therapy and prognosis.
- **The most important prognostic factor is Lymph node status.**
- The American Joint committee for cancer (AJCC) TNM classification is the standard staging system and the Dukes classification is a simplified approach to staging for academic purposes

TNM classification for colorectal cancer		
T	T1	Tumor invades into submucosa
	T2	Tumor invades into musculars propria
	T3	Tumor invades into subserosa
	T4a	Tumor breach visceral peritoneum
	T4b	Tumor directly invades adjacent tissue or organs
N	N0	No nodes involved
	N1	N1a: 1 regional LN involved N1b: 2-3 regional LNs involved
	N2	N2a:4-6 LNs involved N2b: 7 or more LNs involved
M	M0	No metastases
	M1a	Confined to one organ
	M1b	More than one organ
	M1c	Metastasis to the peritoneum



Dukes' staging for colorectal cancer

- A: Invasion of but not breaching the muscularis propria
- B: Breaching the muscularis propria but not involving lymph nodes
- C: Lymph nodes involved

Dukes himself never described a stage D, but this is often used to describe metastatic disease

Source: Bailey And Love's Short Practice of Surgery 28th Ed

Staging - AJCC staging 8th edition (simplified)

AJCC staging	TNM classification	Dukes stage
I	Up to **T2**, N0, M0	A
II	Up to **T4**, N0, M0	B
III	Any T, **N1/N2**, M0	C
IV	Any T, any N, **M1**	D

Clinical presentation

- Patients with CRC may present in three ways:

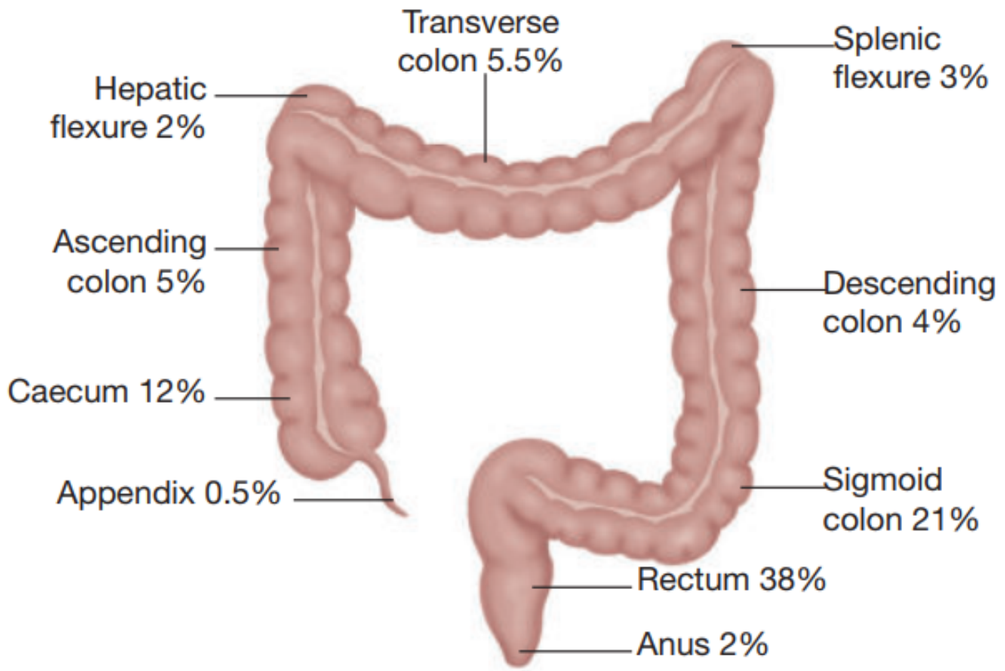
1. Those with suspicious symptoms and signs
2. Asymptomatic patients discovered by routine screening which account for 10%
3. Emergency admission with intestinal obstruction, perforation or an acute GI bleed which account for 20-30% of CRC diagnosis

Signs and symptoms

- Change in bowel habits (the most common symptom)
- Rectal bleeding
- Iron deficiency anemia
- Rectal or abdominal mass
- Abdominal pain
- Constitutional symptoms like: weight loss, fever, night sweats, fatigue and abdominal discomfort

Distribution of colorectal cancer by site

- Based on sites of onset, rectal cancer approximately accounts for 38% and colon cancer approximately accounts for 62%, and both sites combined account for 1.25%. Among colon cancers, the most common sites are the sigmoid colon (21%), followed by the ascending colon (5%), transverse colon (5.5%), descending colon (4%) and the cecum (12%)



Right-sided colon cancer

- Large bowel malignancies arising in cecum, ascending colon or transverse colon.
- Clinical features include:
  - Occult bleeding or melena
  - Iron deficiency anemia
  - Diarrhea

Left-sided colon cancer

- Arising from the splenic flexure, descending colon, sigmoid colon or the rectosigmoid junction.
- Clinical features include:
  - Change in bowel habits (size, consistency and frequency)
  - Blood-streaked stool
  - Colicky abdominal pain (due to obstruction)

Rectal carcinoma

- Large bowel malignancies located within 15 cm from the anal verge.
- Clinical features include:
  - Hematochezia
  - Decrease in stool caliber (pencil shaped stool)
  - Rectal pain
  - Tenesmus
  - Fecal incontinence