BENIGN AND MALIGNANT LESIONS OF LARGE INTESTINE

Done by:

Mahmoud Abu Hilal

Farah Bdir

Batool Samara

Saeed Bydoon

Ibrahim Maraqa

Colon polyps

DONE BY
Mahmoud Abu Hilal

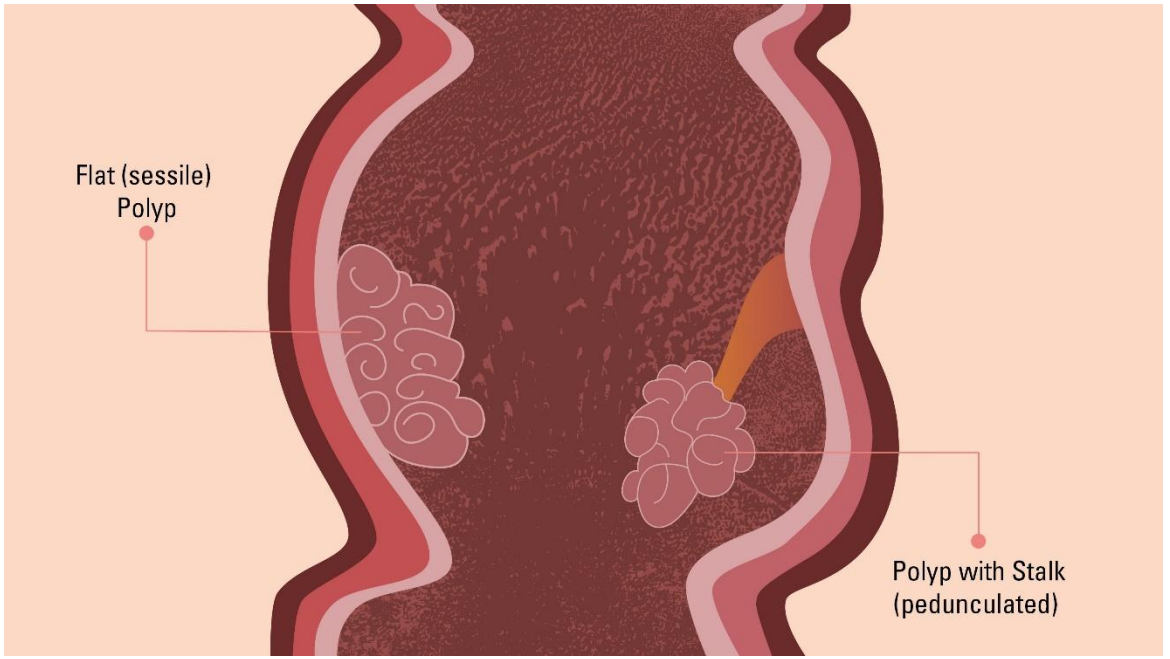
POLYPS

- It is an abnormal growth of tissue projecting from the colonic mucosa regardless the histological nature.
- Can either be **pedunculated** (with a stalk) OR

sessile (broad base attached to colon).

- Almost always asymptomatic
- Large polyps may cause bleeding

Usually not visible in stool (“occult”)



- Screening done for detection
- Basis for screening with fecal occult blood testing
- Most commonly detected during routine endoscopic surveillance

- Removal can prevent colon cancer
- Usually removed for pathology to classify them

CLASSIFICATION OF POLYPS:

- Non-neoplastic Polyps:

✔ Hyperplastic

✔ Hamartomatous (Juvenile polyposis + Peutz-Jeghers + Cronkhite–Canada + Cowden syndrome)

✔ Inflammatory

- Neoplastic Epithelial Lesions:

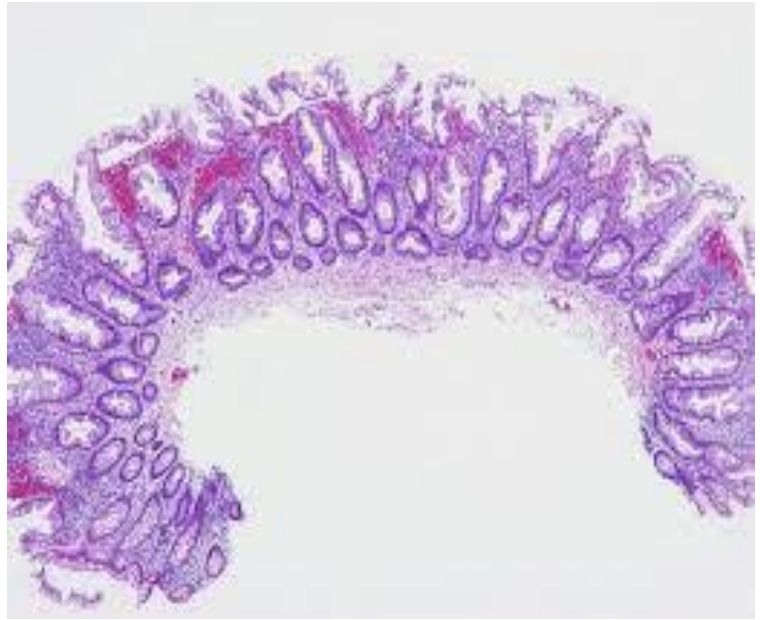
 Benign polyps: Adenomas

 Malignant: Adenocarcinoma

HYPERPLASTIC POLYPS

Benign

- Most common type of non-neoplastic polyp
- Normal cellular structure, no dysplasia
- Common in rectosigmoid colon
- Classically have a "saw-tooth" or serrated pattern
- Usually no special screening required after biopsy
- Exception if large number of big polyps



❑ Small hyperplastic polyps are typically removed (biopsied) because they can be difficult to distinguish

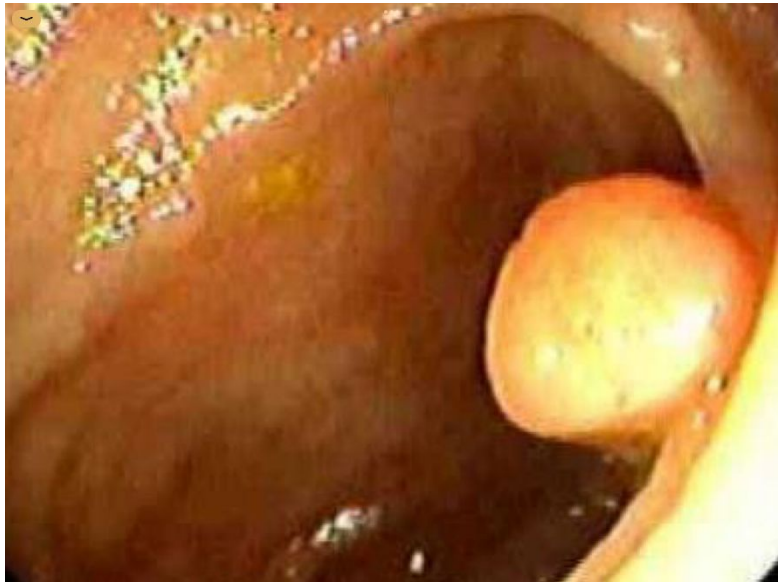
HAMARTOMATOUS POLYPS

Hamartomas (benign tumors)

- ❑ Normal but disorganized tissue masses
  - Usually in rectum
  - Usually pedunculated
  - Often "auto-amputate"
  - Cause painless rectal bleeding
- ✔ Juvenile polyp = sporadic hamartomatous polyp

Common in children

No associated colorectal cancer risk, but it is highly vascular so it should be removed



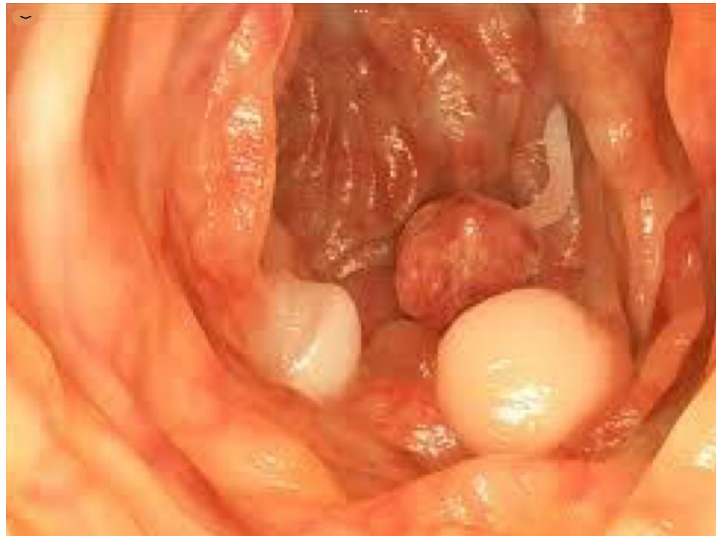
❑Mostly occurs as syndromes:

1. JUVENILE POLYPOSIS SYNDROME

- Rare,Autosomal Dominant mutation
- Multiple polyps(from10 to 100) throughout the

GI tract around age 10 years.

- Increased risk of colon cancer
- 50% lifetime risk of colorectal cancer.
- Colonoscopic surveillance is recommended 1–2 yearly

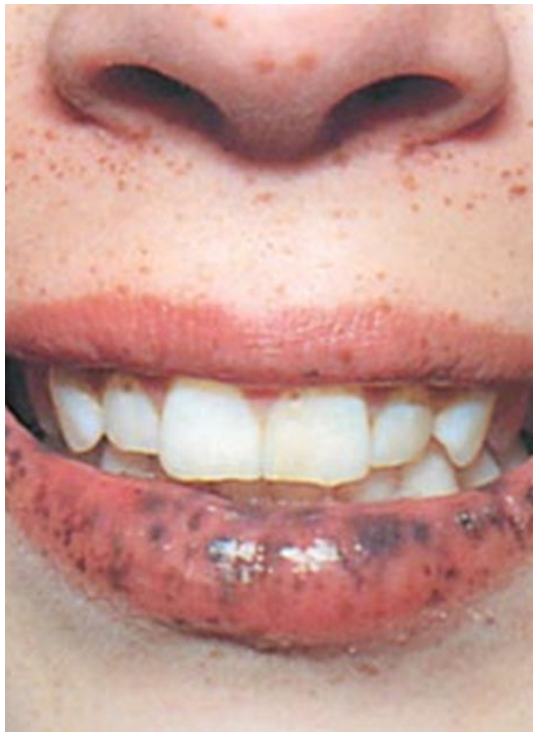


2. PEUTZ-JEGHERS SYNDROME

- Autosomal dominant disorder
  - Multiple hamartomas throughout GI tract "Peutz-Jeghers polyps" *(presented in any part of GI tract mostly on small bowel)*
  - Pigmented spots on lips and buccal mucosa Often presents in childhood with spots around lips

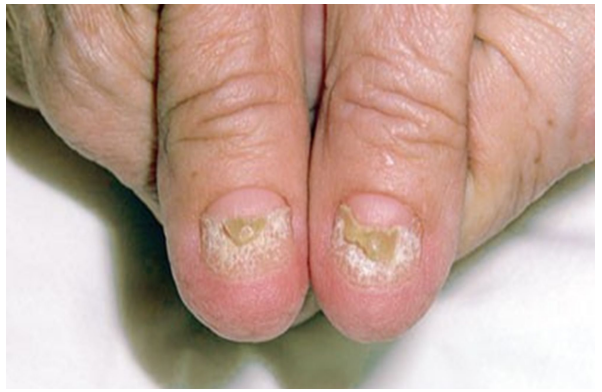
- Risk of gastric, small intestinal, and colon cancer

- Also pancreatic and breast cancer
- Early screening for malignancy



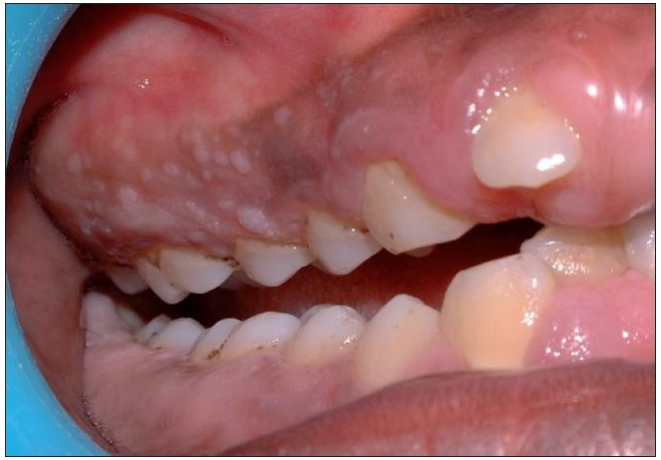
3. CRONKHITE–CANADA SYNDROME

- Rare, nonheritable syndrome
- Intestinal polyposis with alopecia, nail atrophy and brown macular hyperpigmentation



4. COWDEN SYNDROME

- Autosomal Dominant
- results in hamartomatous neoplasms of skin and mucosa, GI tract, bones, central nervous system, and the GU tract. Majority of cases of Cowden Disease involves the skin and in some cases the thyroid is also involved.
- There is a 10% risk of developing colorectal cancer.
- Benign and malignant disease of the breast and thyroid are the main risks.



INFLAMMATORY POLYPS

- Non-Neoplastic
- Occur most commonly in the context of inflammatory bowel disease, but they may also occur after amebic colitis, ischemic colitis.
- Usually smaller than 2 cm
- Management do not require excision unless they cause symptoms (eg, bleeding, obstruction).
- Because they cannot be distinguished from adenomatous polyps based on gross appearance, they should be removed.

ADENOMATOUS POLYI

- •Most common neoplastic polyp dysplastic with malignant potential
- Have 3 types according histological feature:

1. Tubular

- Most common subtype (80%+)
- Adenomatous epithelium forming tubules

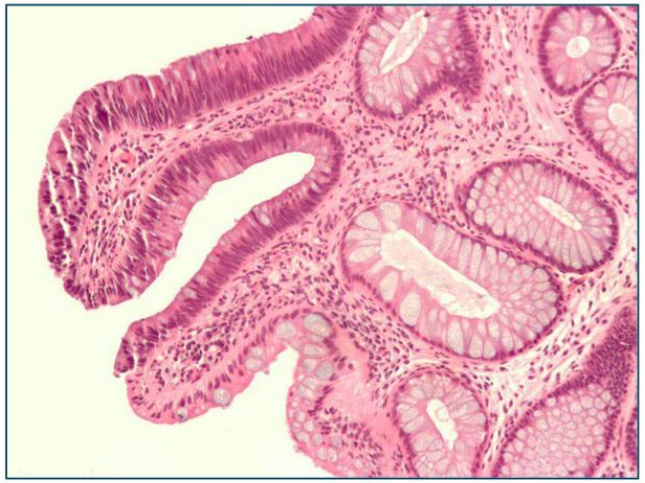
2. Villous

❖ Less common type
❖ Often sessile
❖ Long projections extending from surface
❖ Higher risk of development into colon cancer(villous=villain)

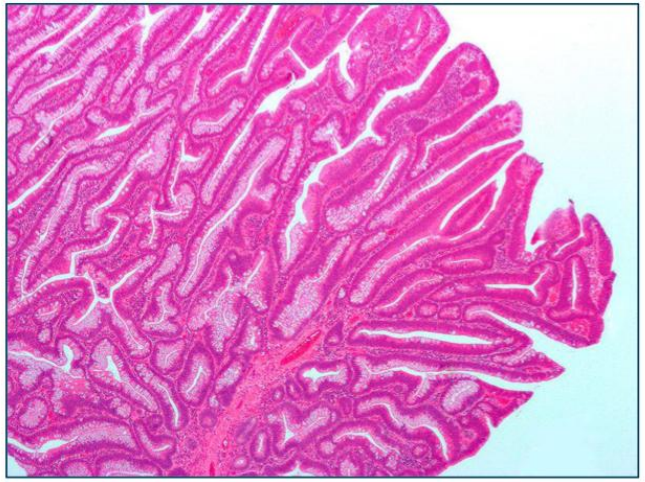
3. Tubulovillous

✔ Moderate risk of development into colon cancer

Tubular Polyp



Villous Polyp



Box 6.10 Factors affecting risk of malignant change in an adenoma

	Higher risk	Lower risk
Size	>1.5 cm	<1 cm
Type	Sessile or flat	Pedunculated
Histology	Severe dysplasia Villous architecture Squamous metaplasia	Mild dysplasia Tubular architecture
Number	Multiple polyps	Single polyp

FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

- Autosomal dominant disorder
- Germline mutation of APC gene
- Always (100%) progresses to colon cancer
- Treatment: colectomy or proctocolectomy

FAP variants

- All have APC gene mutation
- Polyposis plus extra-intestinal signs/symptoms

1. Gardner's Syndrome:osteomas, dental abnormalities, benign soft tissue tumors, desmoid tumors, sebaceous cysts
2. Turcot's Syndrome:cerebellar medulloblastoma or glioblastoma multiforme

HEREDITARY NONPOLYPOSIS COLORECTAL CANCER (HNPCC) OR LYNCH SYNDROME

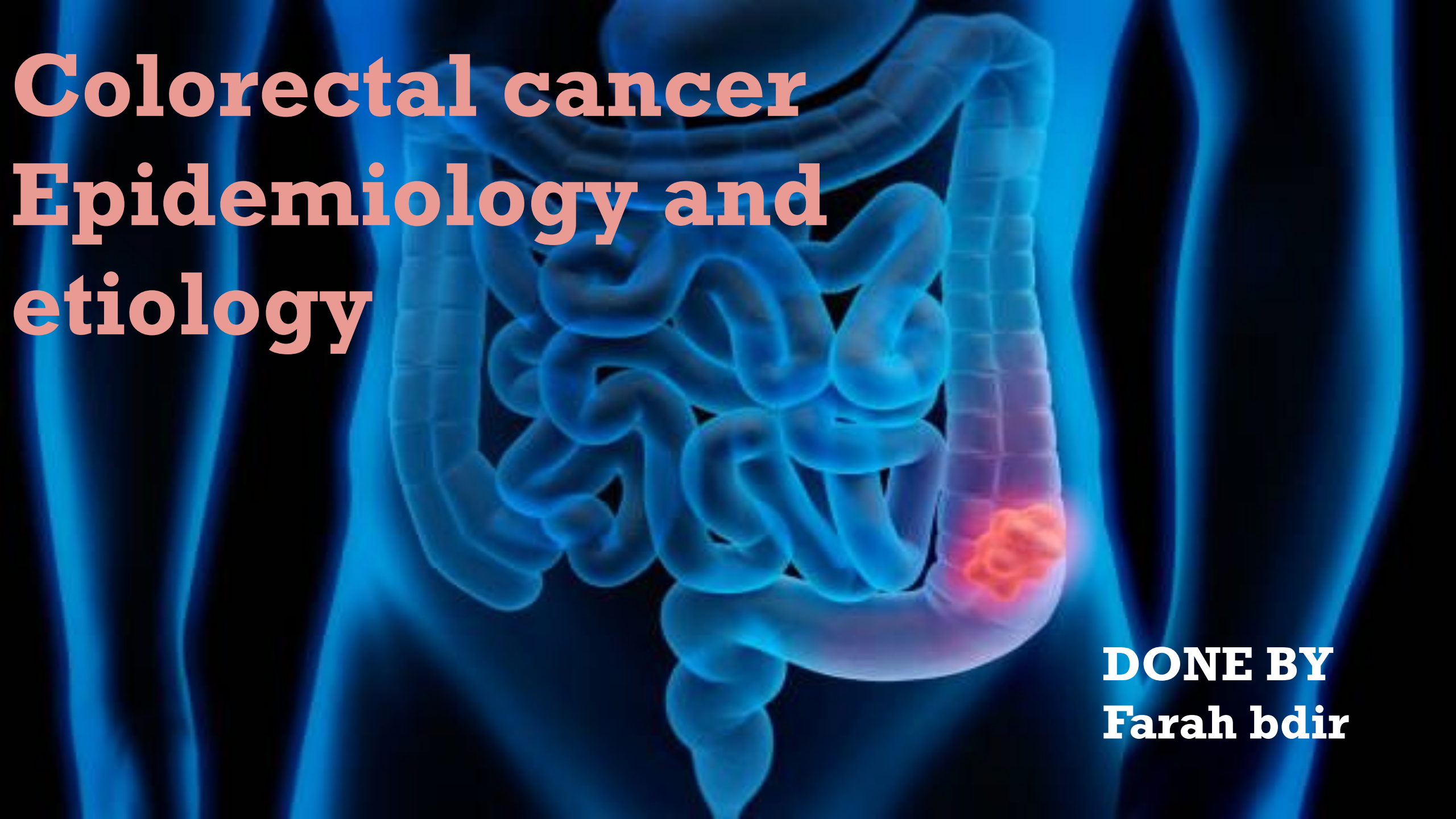
- Autosomal Dominant
- The genetic defects arise from errors in mismatch repair genes.
- Lead to different types of cancers the most common malignancies are colorectal and endometrial.
- **Lynch type 1** results in more colonic cancers, often on the right side and typically in the 4 th decade of life.
- **Lynch type 2** plus extracolonic cancers (e.g., female genital tract, skin, stomach, pancreas, brain, breast, biliary tract).
- Colon cancers associated with HNPCC still arise from adenomas, but the adenomas tend to be flat.
- Also, the adenomas associated with HNPCC are more likely to become malignant.

Table 6.17 Classification of colorectal polyps and polyposis syndromes

Histology	Polyposis syndrome	Defective gene	Inheritance	CRC risk
Hyperplastic	Hyperplastic polyposis	*BRAF*		Yes
Hamartoma	Juvenile polyposis	*MADH4 or BMPR1A*	AD	10–70%
	Peutz–Jeghers syndrome	*STK11*	AD	Yes
	Cowden's syndrome	*PTEN*	AD	10%?
	Lhermitte–Duclos disorder	*PTEN*	AD	
	Bannayan–Riley–Ruvalcaba syndrome	*PTEN*	AD	
Inflammatory	None	None		No
Lymphoid	Benign lymphoid polyposis	Unknown		No
Adenoma	FAP	*APC*	AD	100%
	AFAP			Yes
	Gardner			Yes
	Turcot		AR	Yes
	MYH-AP	*MYH-AP*		
Adenoma	HNPCC (Lynch type I or II)	Mismatch repair genes (*MSH-2*, *MLH-1*)	AD	70–80%

AD, autosomal dominant; AR, autosomal recessive; AFAP, attenuated FAP; FAP, familial adenomatous polyposis; HNPCC, hereditary non-polyposis colorectal cancer; MLH-1, MutL homologue 1; MSH-2, MutS homologue 2; MYH-AP, MUT Y homologue-associated polyposis; PTEN, phosphatase and tensin homologue.

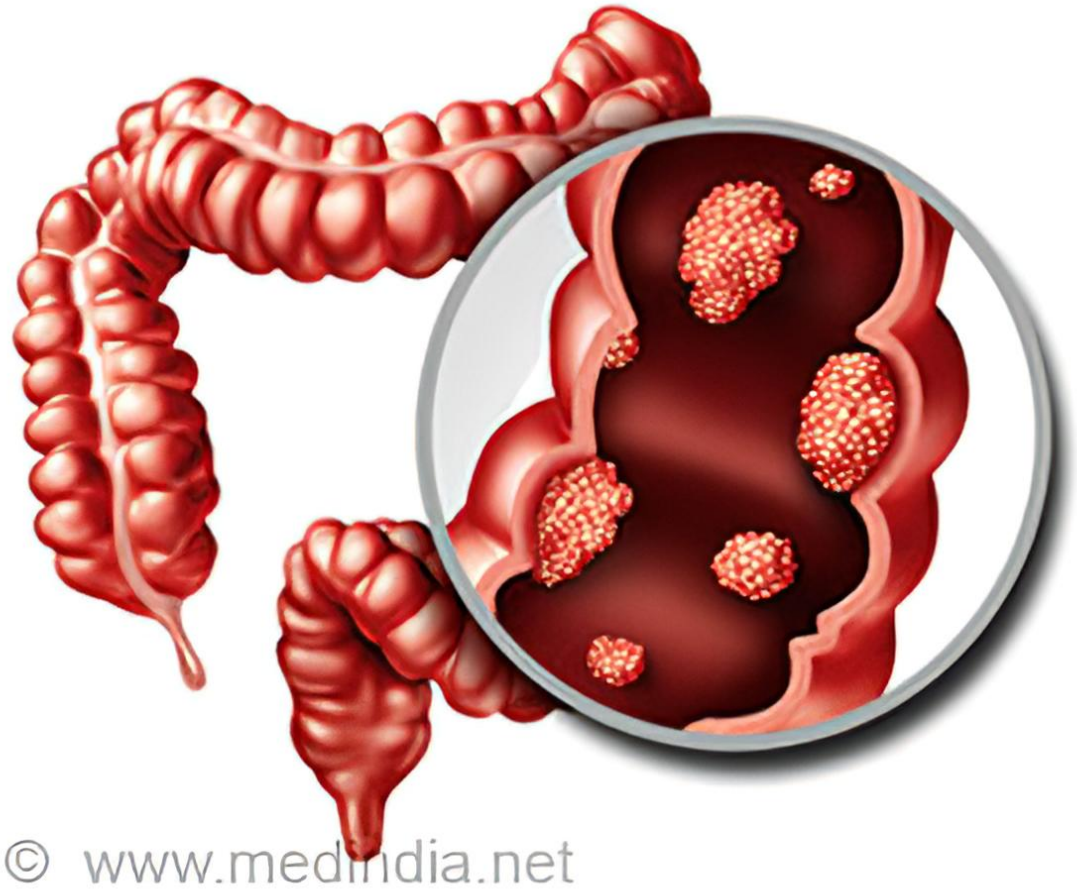
Colorectal cancer Epidemiology and etiology



DONE BY
Farah bdir

DEFINITION OF COLORECTAL CANCER:

- Colorectal cancer is cancer that occurs in the colon (the longest part of the large intestine) or rectum. If it starts in the colon, it may be referred to as colon cancer & if it starts in the rectum, it may be called rectal cancer. Regardless of where they start, however, these cancers share a lot in common, which is why they're together known as colorectal cancer.
- Most colorectal cancers are adenocarcinomas (cancers that begin in cells that make and release mucus and other fluids).
- Rarely, carcinoid tumors, lymphomas, and Kaposi sarcoma may be present but majority are adenocarcinomas.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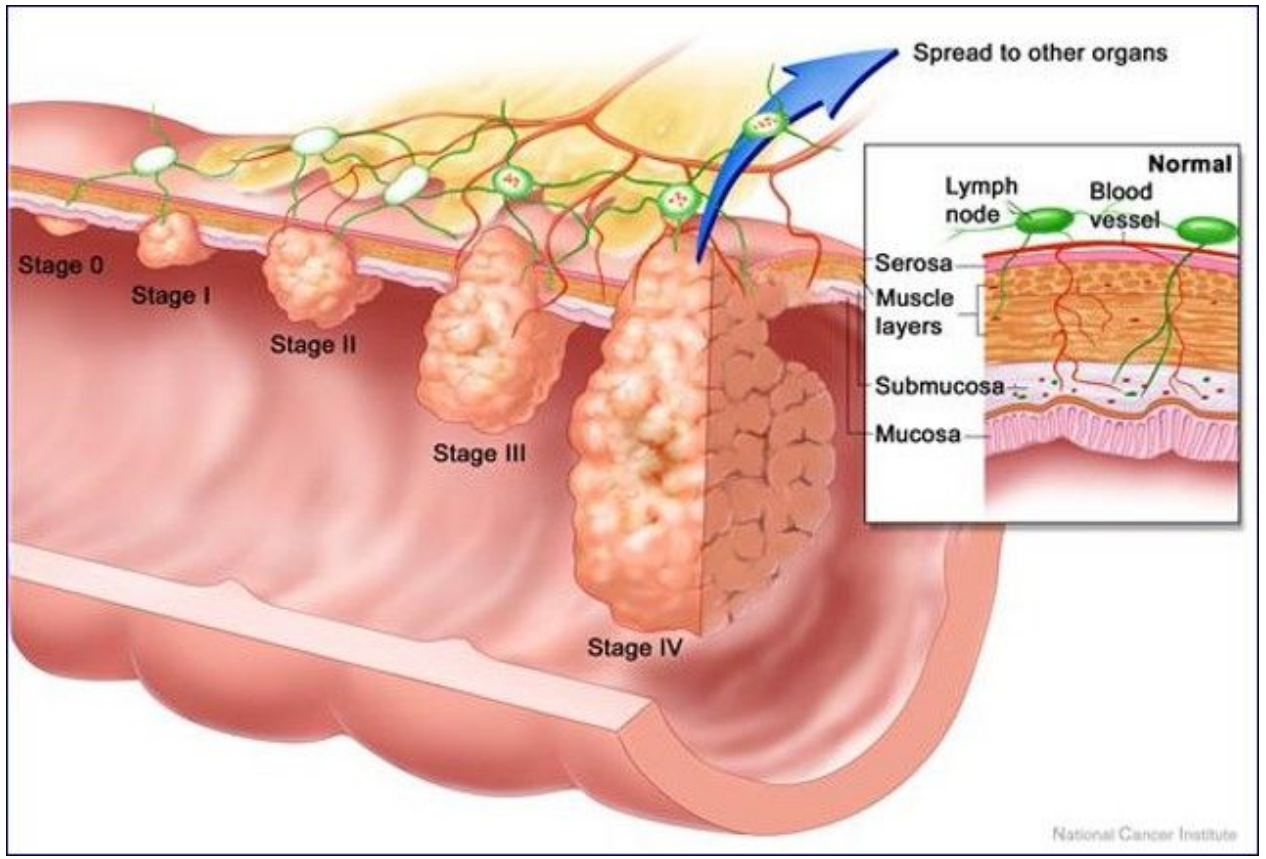
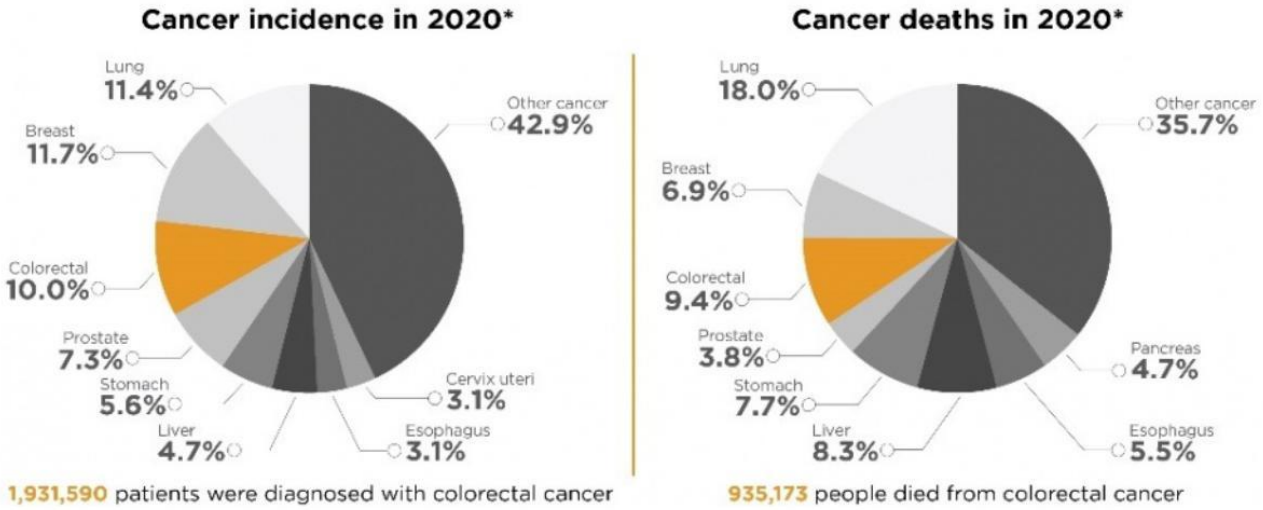

Spread to other organs
Normal
Lymph node
Blood vessel
Serosa
Muscle layers
Submucosa
Mucosa
Stage 0
Stage I
Stage II
Stage III
Stage IV
National Cancer Institute

EPIDEMIOLOGY

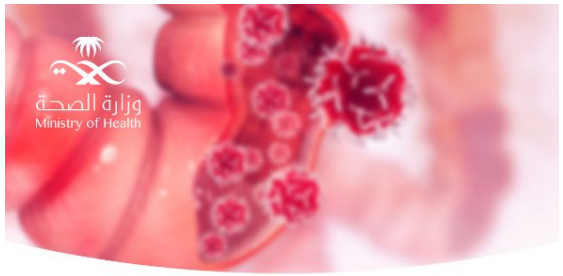
- Colorectal cancer (CRC) is the third most common cancer worldwide, and the second most common cancer among both men and women in Jordan.
- The most common GI cancer.
- The incidence is greatest among males (37.4 per 100.000 vs 29.9 per 100.000)
- Colorectal cancer is the second most common cause of death in Jordan, with approximately 4000 deaths per year.
- The incidence increases with age; the average age at diagnosis is 60–65 years.
- The disease is much more common in westernized countries than in Asia or Africa.

Global CRC incidence and mortality



*Both sexes, all ages.

Reproduced from IARC CRC fact sheet 2020[1] (GLOBOCAN data).
CRC, colorectal cancer; IARC, International Agency for Research on Cancer.



يتسبب سرطان القولون و المستقيم في وفاة حوالي **4,000** شخص سنوياً في المملكة

وهو مسبب الوفاة **01** عند الذكور

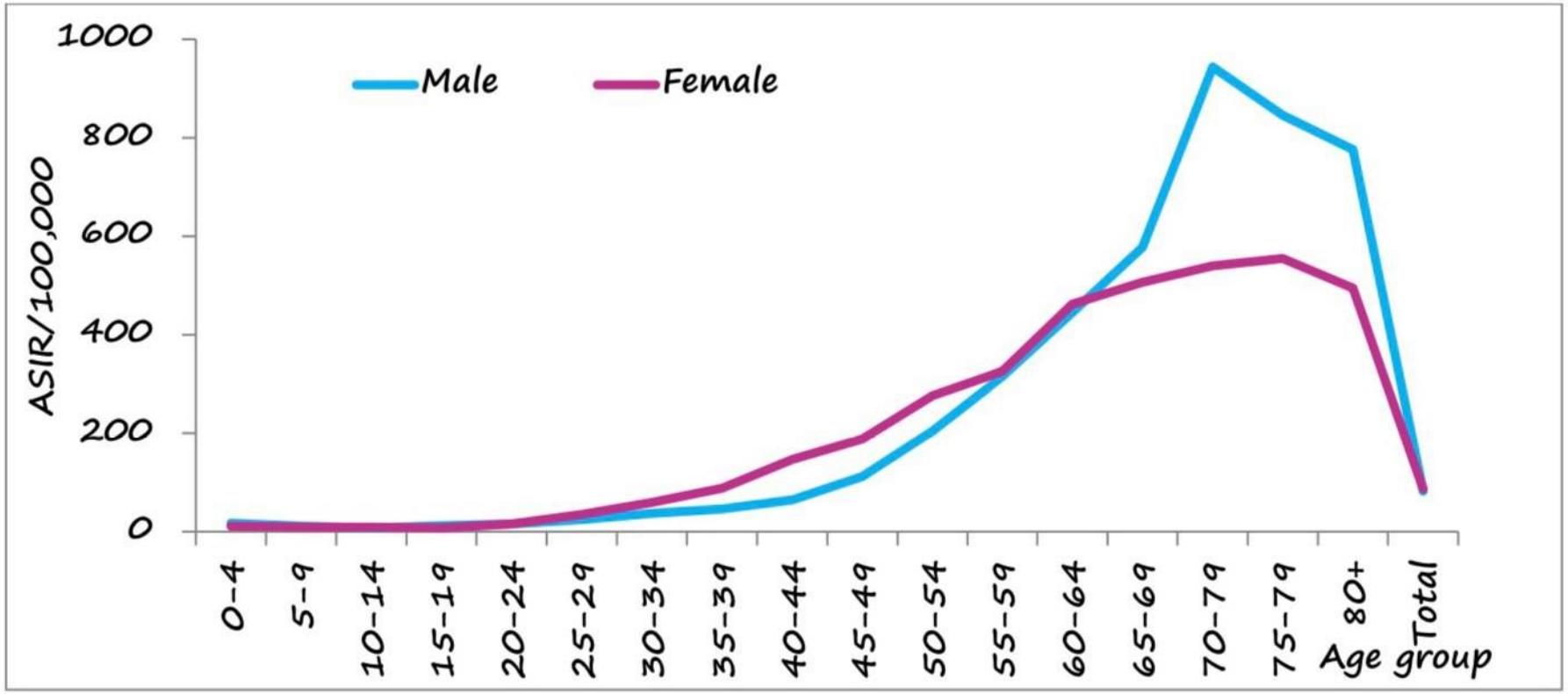
وعند **03** الإناث

بالفحص المبكر
تزيد من فرص الشفاء -بإذن الله-

احجز موعدك عبر تطبيق صحتي

عش بصحة
@LiveWellMOH

ASIR for cancer cases by age group and gender –Jordanian, 2015

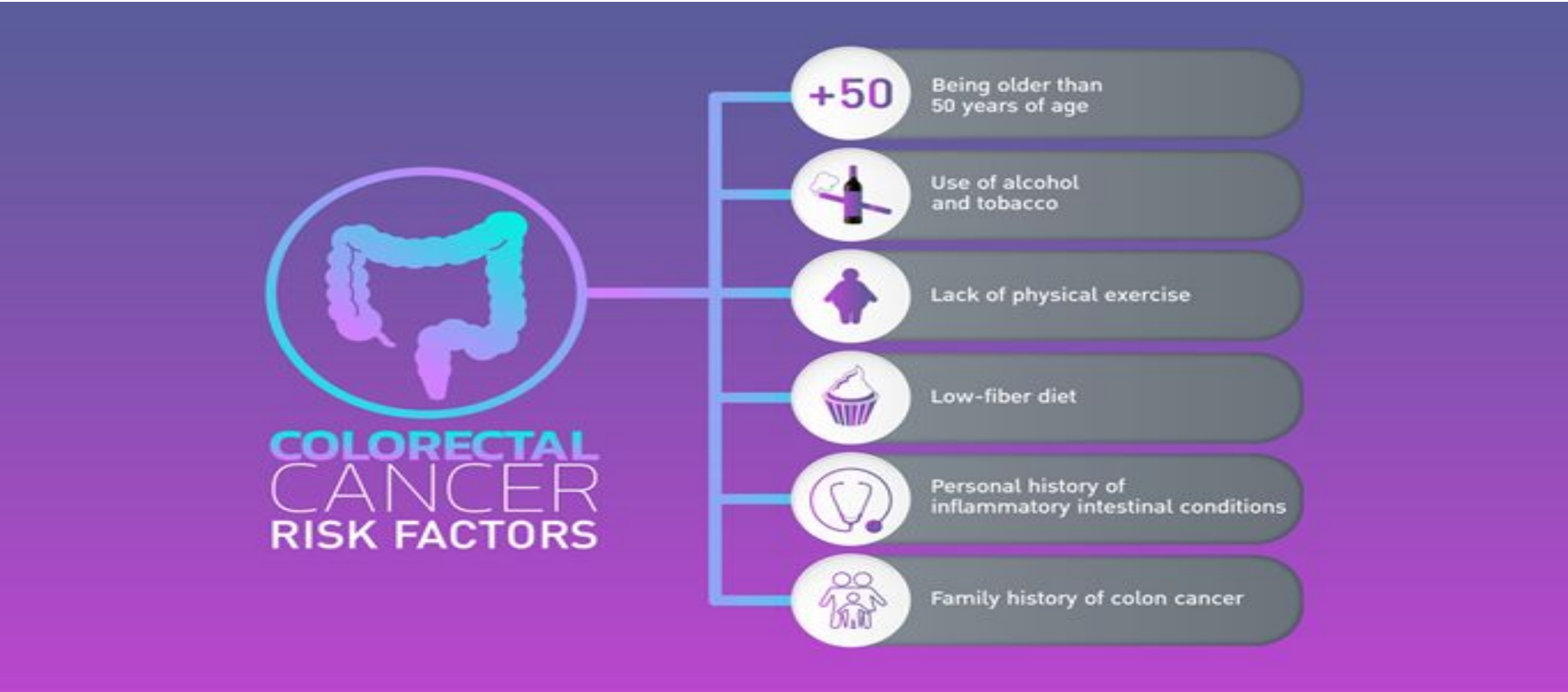


*ASIR: Age-standardized incidence rates

- 5-year survival rate:

Disease Stage	5- Year survival
Early stages (localized/stage I, II) of colon	91 %
Early stages rectal cancer.	88%
Regional disease/Stage III: Colon & rectal cancer after the tumor has spread regionally to adjacent LNs or tissues	70%
Metastatic disease	≤ 12%

RISK FACTORS IN COLORECTAL CANCER



- Increased risk:
  - Increasing age (>50 yrs)
  - Male sex
  - Personal history (history of colorectal polyps):

    Some types of polyps can change into cancer over time (usually many years), but not all polyps become cancer.
  - Modifiable risk factors:
    - Animal fat (saturated) and red meat consumption

      (diets high in fat content can increase bile acid deposition into the colon)
    - Sugar consumption

      A new study has found a link between drinking sugar-sweetened beverages and an increased risk of developing colorectal cancer in women under age 50. The findings suggest that heavy consumption of sugary drinks during adolescence (ages 13 to 18) and adulthood can increase the disease risk.
    - Obesity (body and abdominal)
    - Smoking

- Family history & genetics of colon cancer or colonic polyps

  - Most colorectal cancers are found in people without a family history of colorectal cancer. Still, as many as 1 in 3 people who develop colorectal cancer have other family members who have had it.

  - The risk is even higher if that relative was diagnosed with cancer when they were younger than 50 , or if more than one first-degree relative is affected.

  - The reasons for the increased risk are not clear in all cases. Cancers can “run in the family” because of inherited genes, shared environmental factors, or some combination of these.

  - Most colorectal cancers develop as a result of a stepwise progression from normal mucosa to adenoma to invasive cancer. This progression is controlled by the accumulation of abnormalities in a number of critical growth-regulating genes.

  - These include APC mutation and loss, K-ras mutation,

  Smad2/4 loss, and TP53 mutation and loss, and altered DNA

  methylation with progression to carcinoma.

- The 2 most common forms of hereditary colon cancer are:

1- Familial adenomatous polyposis (FAP):

✔ Increased risk (100%)

✔ Mutations of the adenomatous polyposis coli (APC) gene.

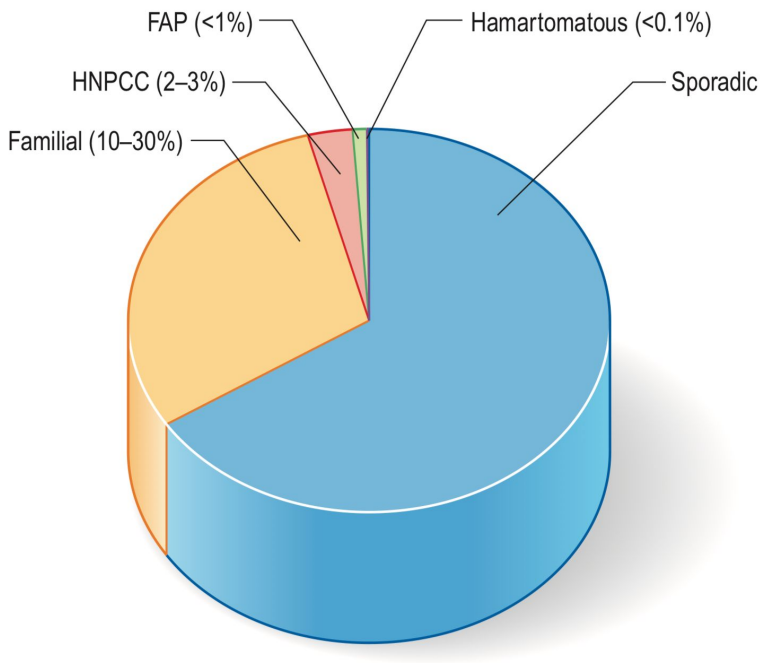
✔ 0.2% to 1% of all colorectal cancers.

✔ Diagnosed by late teens or early 20s.

✔ Total colostomy is recommended when detected.

2- hereditary non-polyposis colon cancer (HNPCC):

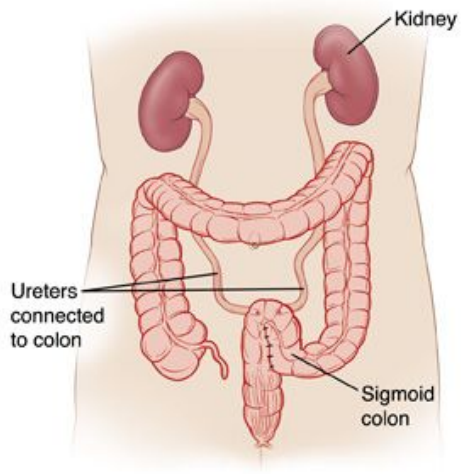
- ✔ Mismatch repair genes mutation in DNA.
- ✔ 2-3% of all colorectal cancers.
- ✔ Diagnosed later in life as compared to FAP.
- ✔ Tend to be located primarily in the right-sided (proximal colon).

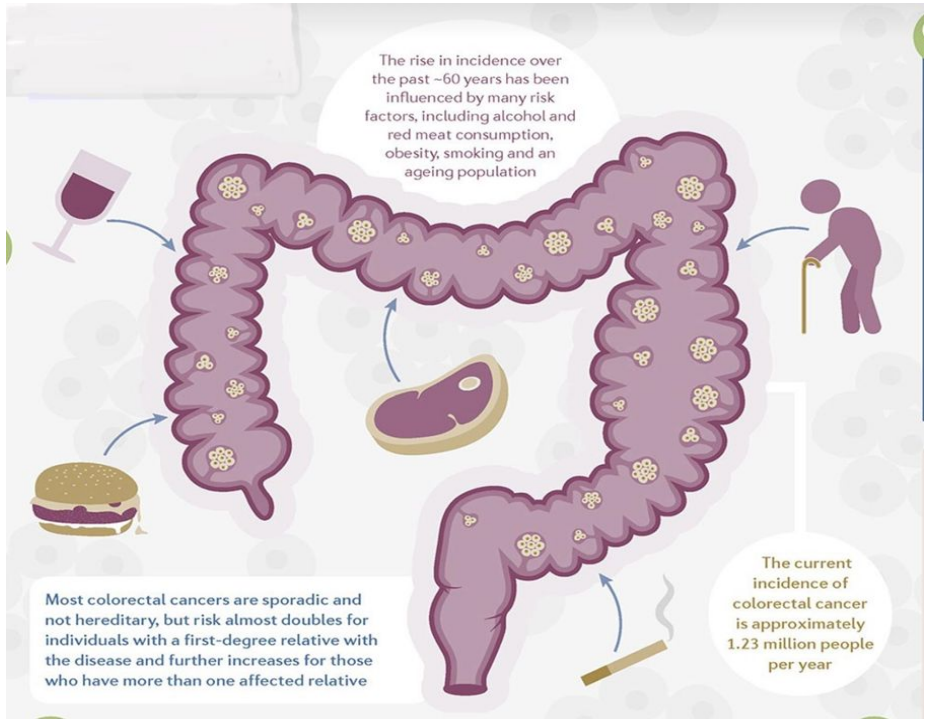


- Other factors can increase risk of colon cancer:
  - DM (type 2)

    In 15 studies, hyperinsulinemia & increased levels of free insulin-like growth factor-1 (IGF-1), promote tumor cell proliferation
  - Chronic inflammatory bowel disease

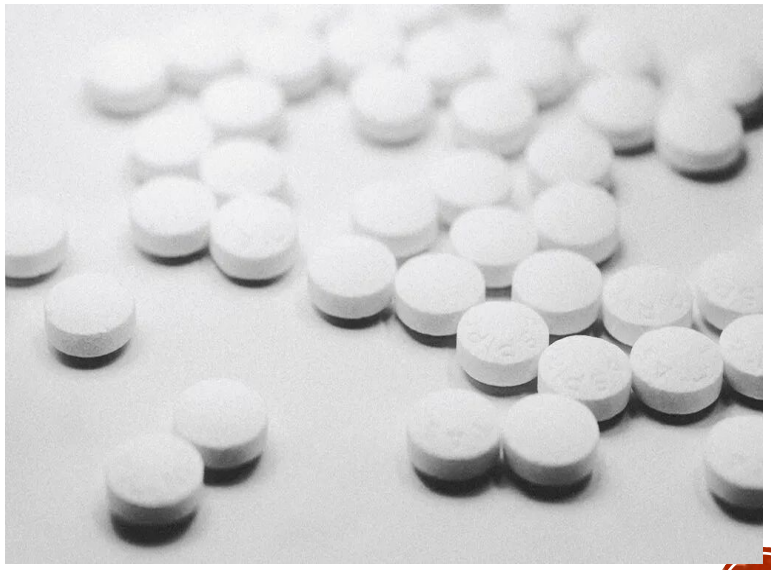
    IBD is a condition in which the colon is inflamed over a long period of time. People who have had IBD for many years, especially if untreated, often develop dysplasia.
  - Acromegaly
  - Abdominal radiotherapy
  - Ureterosigmoidostomy

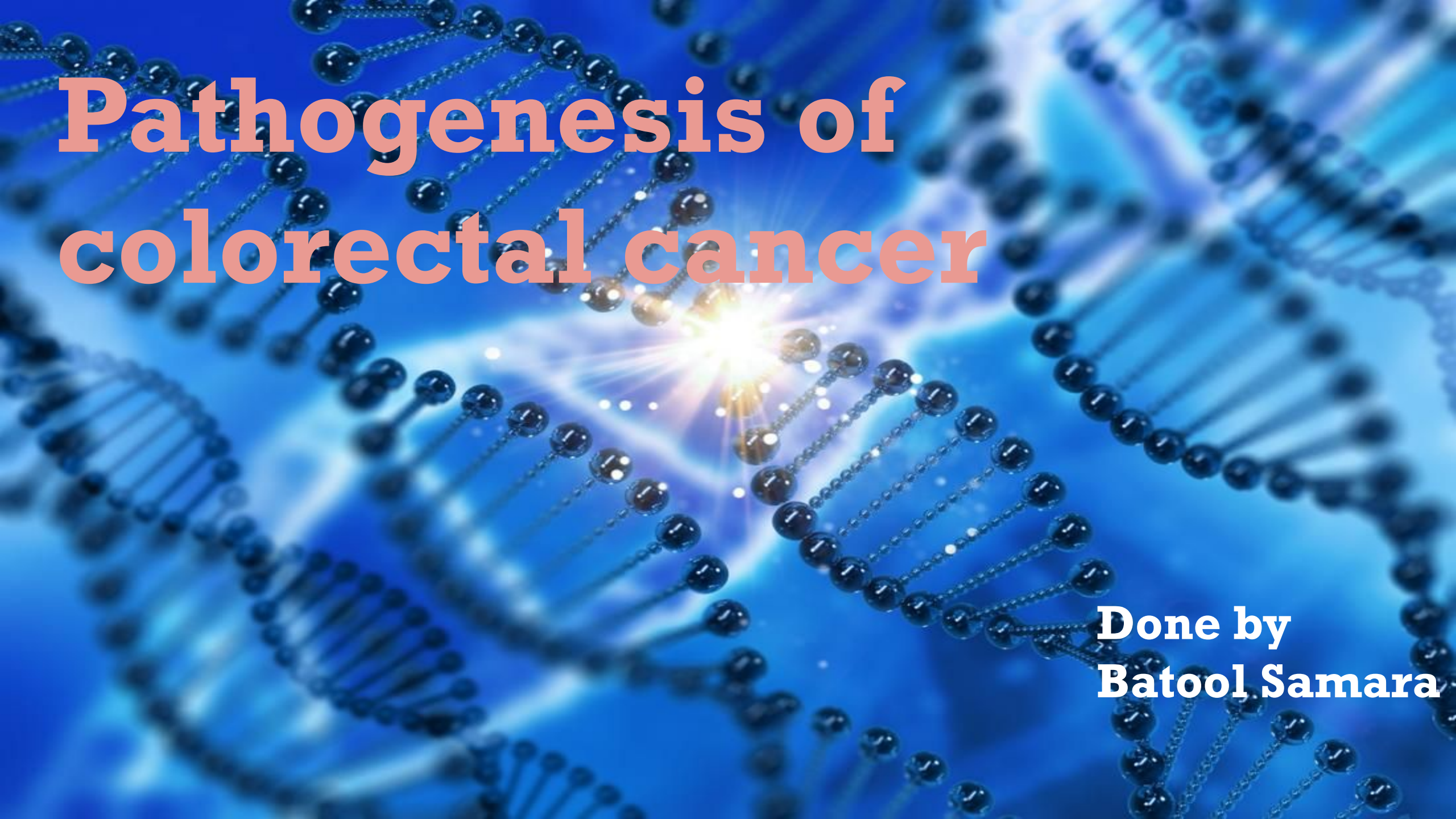




- Decreased risk:

- Fruits, vegetable &garlic consumption
- milk, calcium & vitamin D consumption (may have antiproliferative effects)
- Exercise (colon only)
- Aspirin (including low dose) and other NSAIDs.





Pathogenesis of colorectal cancer

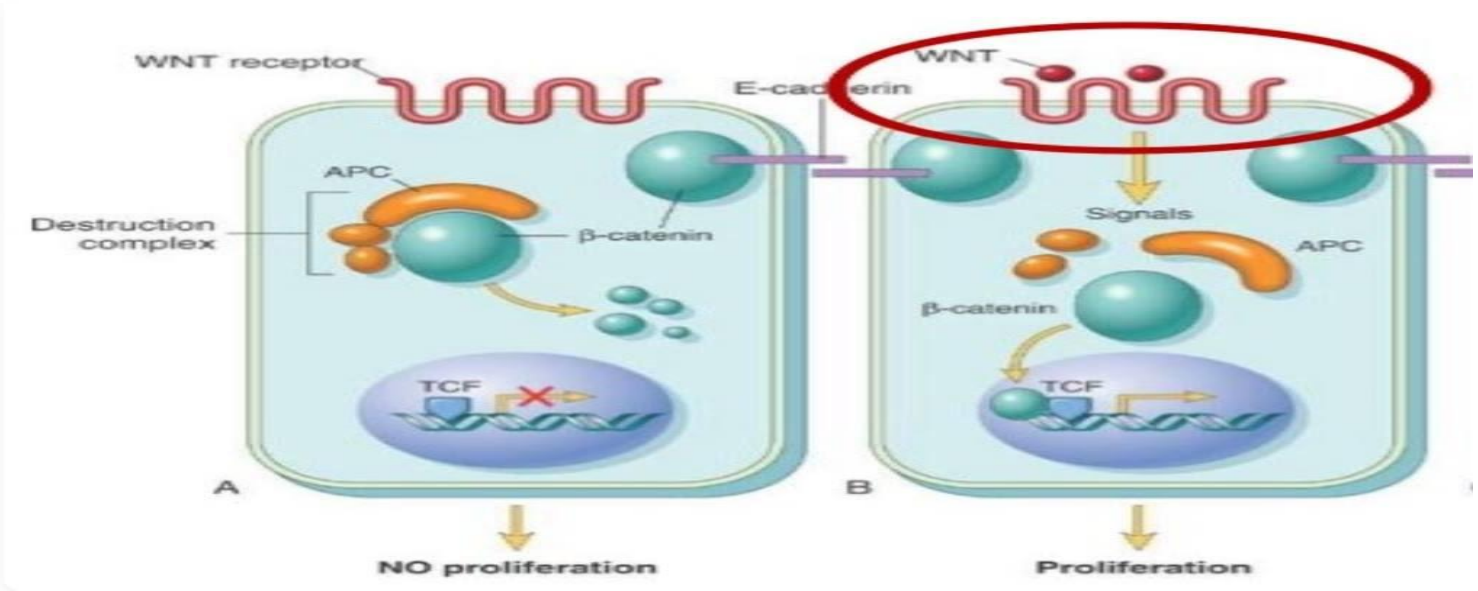
Done by
Batool Samara

PATHWAYS

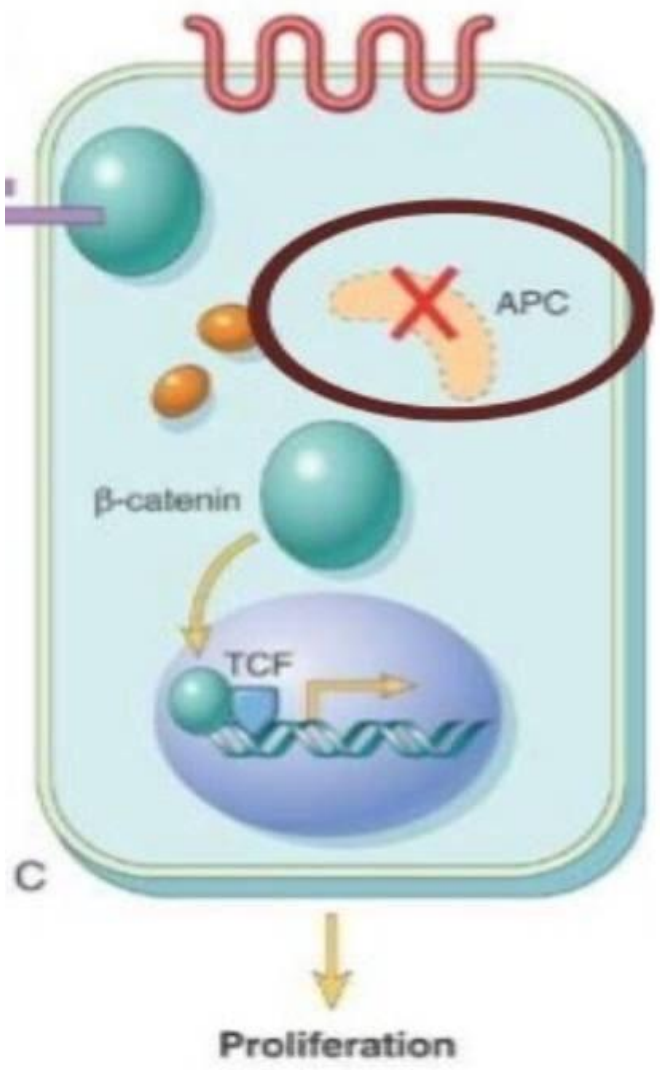
- Colorectal cancer development results from the accumulation of multiple genetic mutations arising from two major pathways:
  - chromosomal instability(adenoma-carcinoma sequence)
  - microsatellite instability

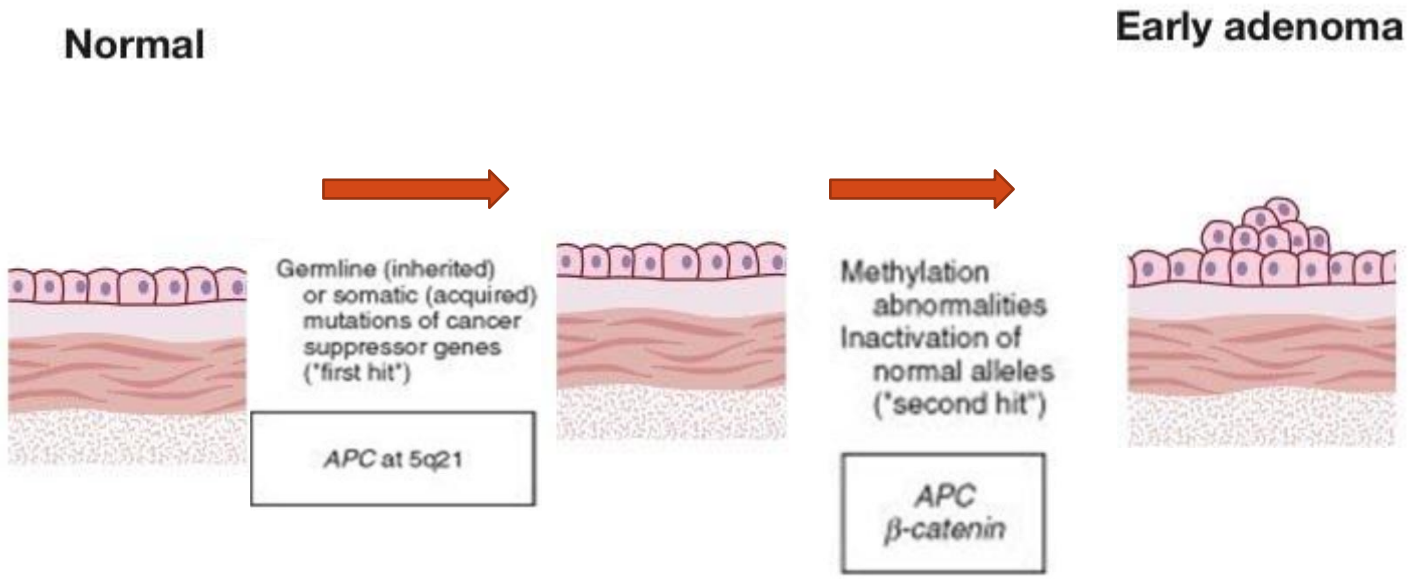
CHROMOSOMAL INSTABILITY(ADENOMA–CARCINOMA SEQUENCE)

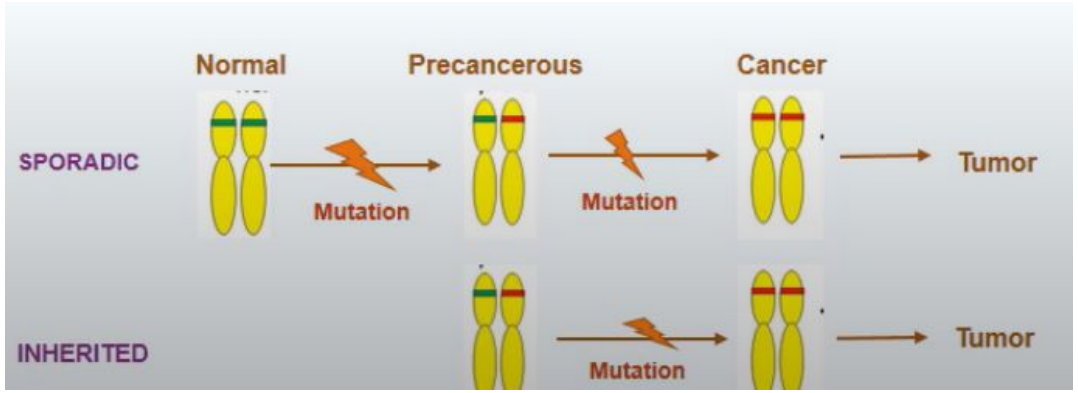
- **Step 1- APC gene loss**
  - Tumor suppressor gene
  - Located on chromosome 5
  - Inhibits translocation of β-catenin to nucleus ⟶ suppress cell growth



- **Loss of APC gene** → **accumulation of** β-catenin and translocation to nucleus → proliferation

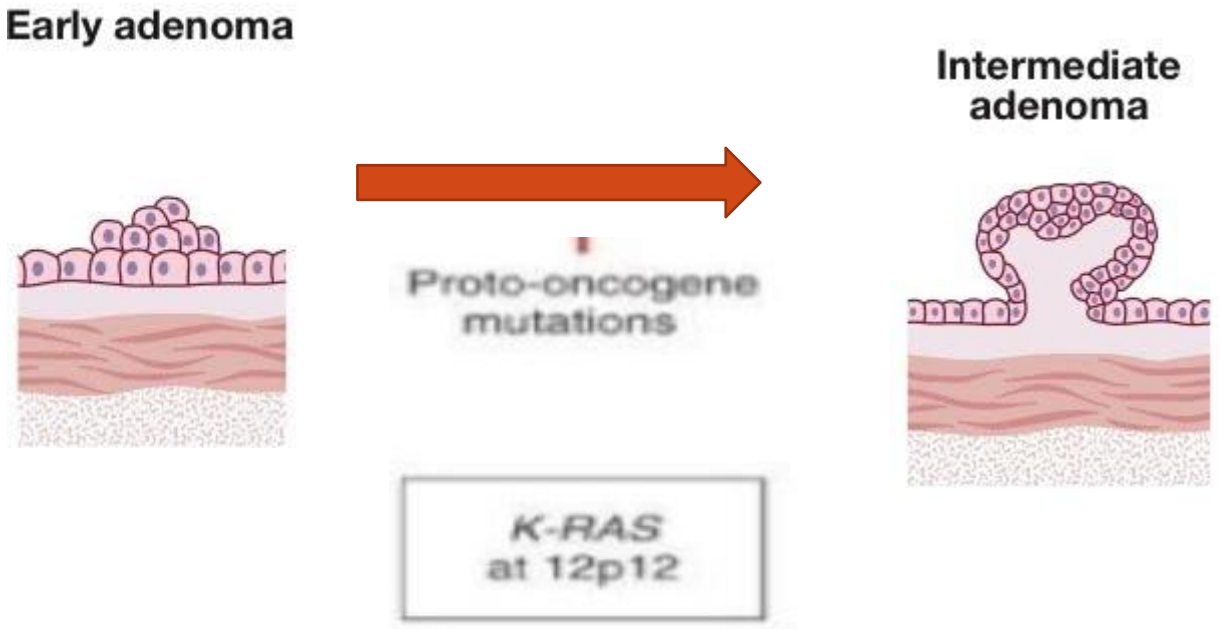


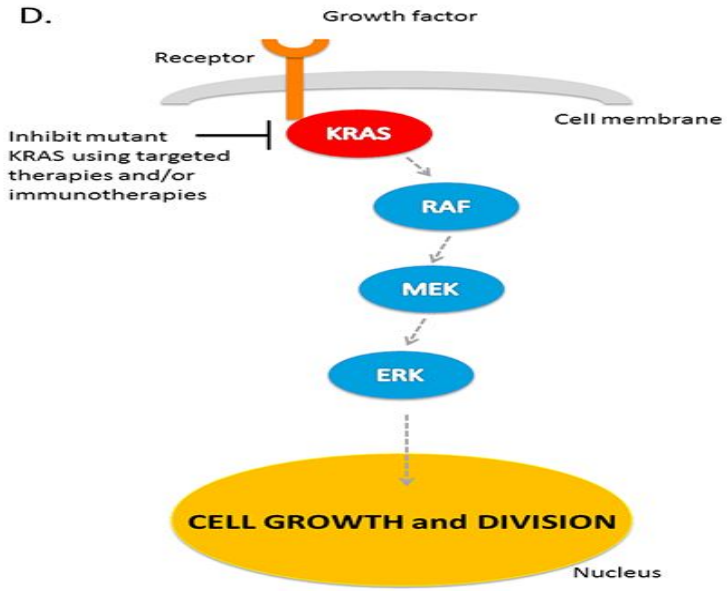




Step 2- K-RAS mutation

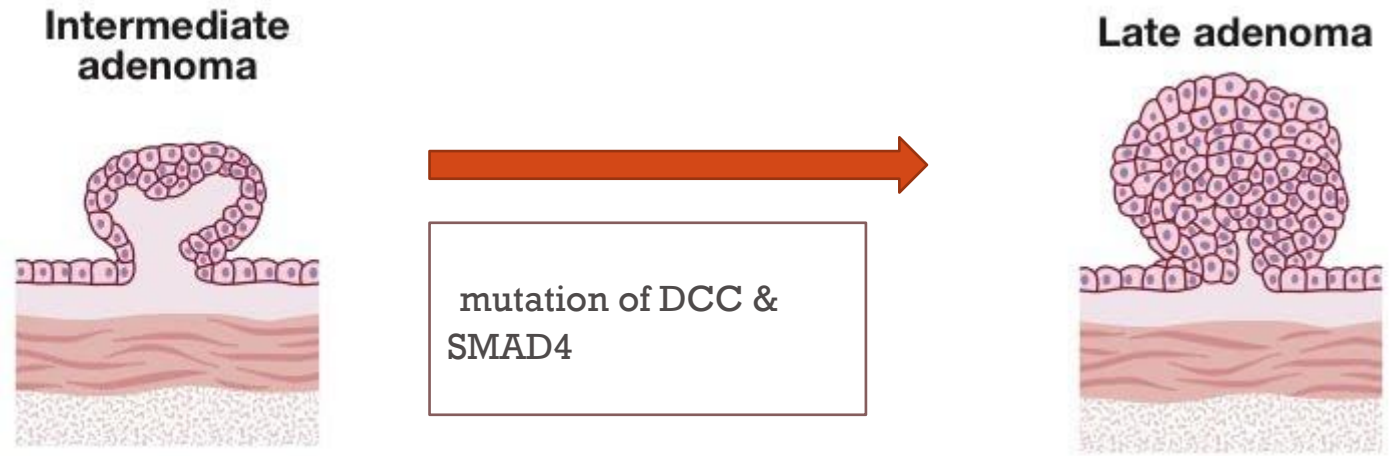
- Proto-oncogene
- Located on chromosome 12
- Transmembrane GTP-binding protein mediating mitogenic signals ⟶ cell proliferation
- K-RAS mutation ⟶ ↑↑ its function(more proliferation)





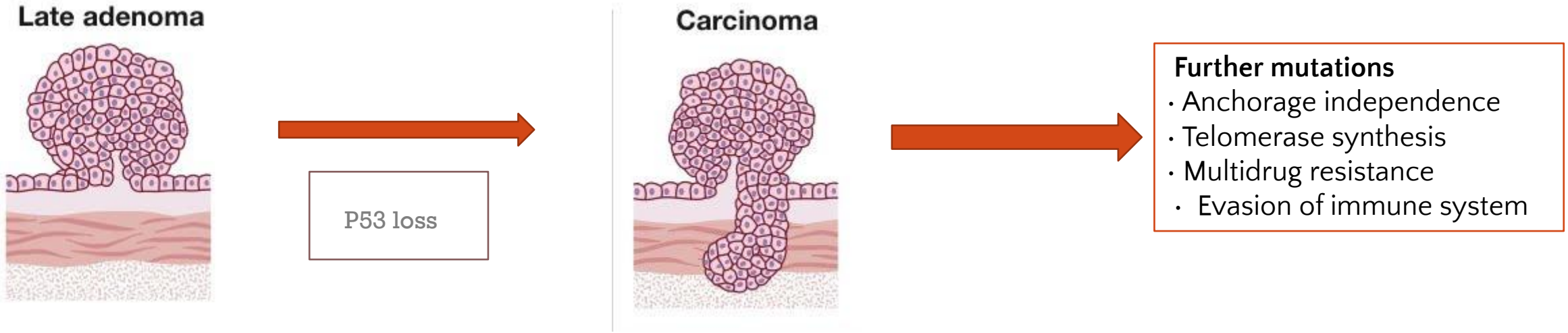
Step 3-DCC(Deleted in colon cancer) & SMAD4 mutation

- Located on chromosome 18
- DCC regulates apoptosis and has a tumor suppressor function
- SMAD4 regulates cell growth
- Deletion of DCC & inc function of SMAD4 ⟶ Proliferation

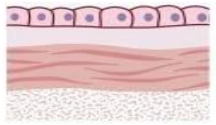
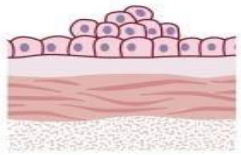
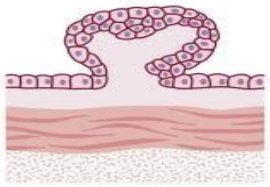
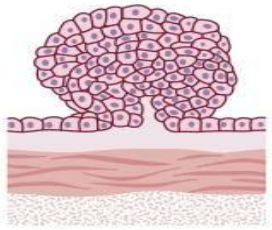
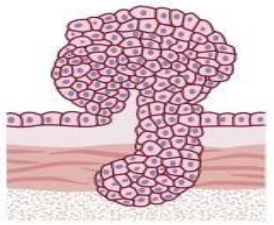


Step 4-p53 mutation

- Tumor suppressor gene
- Located on chromosome 17
- Upregulated during cell damage to arrest cell cycle and allow DNA repair or apoptosis to occur
- Loss of p53 ⟶ Cell proliferation; impaired apoptosis



SUMMARY

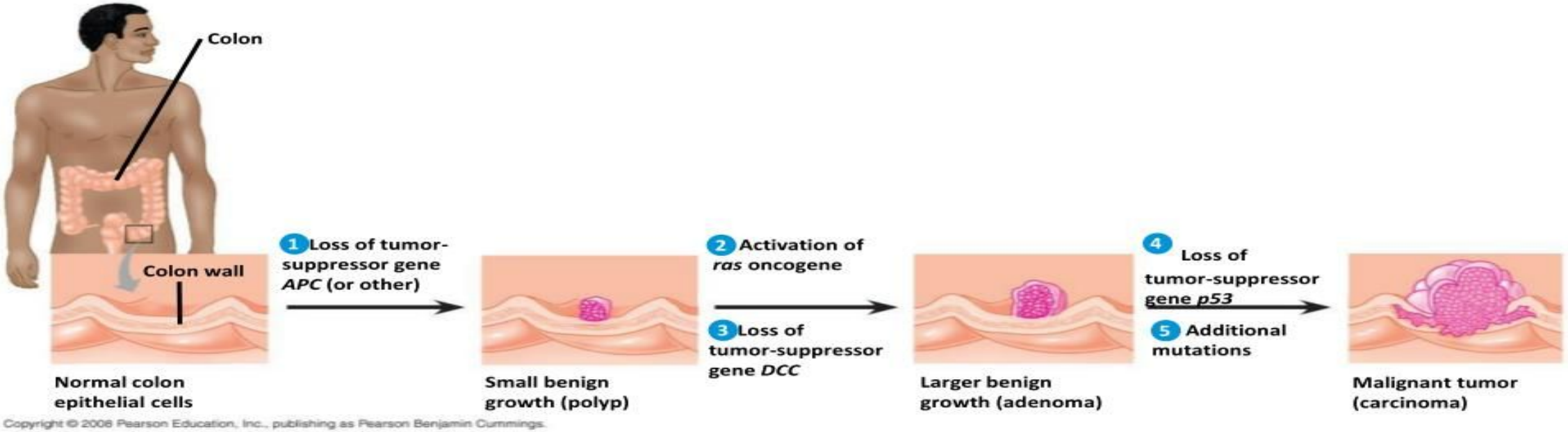
Normal	Early adenoma	Intermediate adenoma	Late adenoma	Carcinoma
				
Key gene(s)	*APC* (adenomatous polyposis coli)	*K-ras*	*DCC* (deleted in colon cancer) *SMAD4*	*p53*
Chromosome	5q	12p	18q	17p
Normal function	Inhibits translocation of β-catenin to nucleus and suppresses cell growth	Transmembrane GTP-binding protein mediating mitogenic signals (p21)	*DCC* regulates apoptosis and has a tumour suppressor function *SMAD4* regulates cell growth	Upregulated during cell damage to arrest cell cycle and allow DNA repair or apoptosis to occur
Alteration	Truncating mutations	Gain-of-function mutations	Allelic deletion or silencing (*DCC*) Gain-of-function mutations (*SMAD4*)	Allelic deletion; gain-of-function mutations
Effect	Progression to early adenoma development	Cell proliferation	Enhanced tumour growth, invasion and metastasis	Cell proliferation; impaired apoptosis

Further mutations
- Anchorage independence
- Protease synthesis
- Telomerase synthesis
- Multidrug resistance
- Evasion of immune system

Fig. 22.62 **The multistep origin of cancer: molecular events implicated in colorectal carcinogenesis.** (GTP = guanine triphosphate)

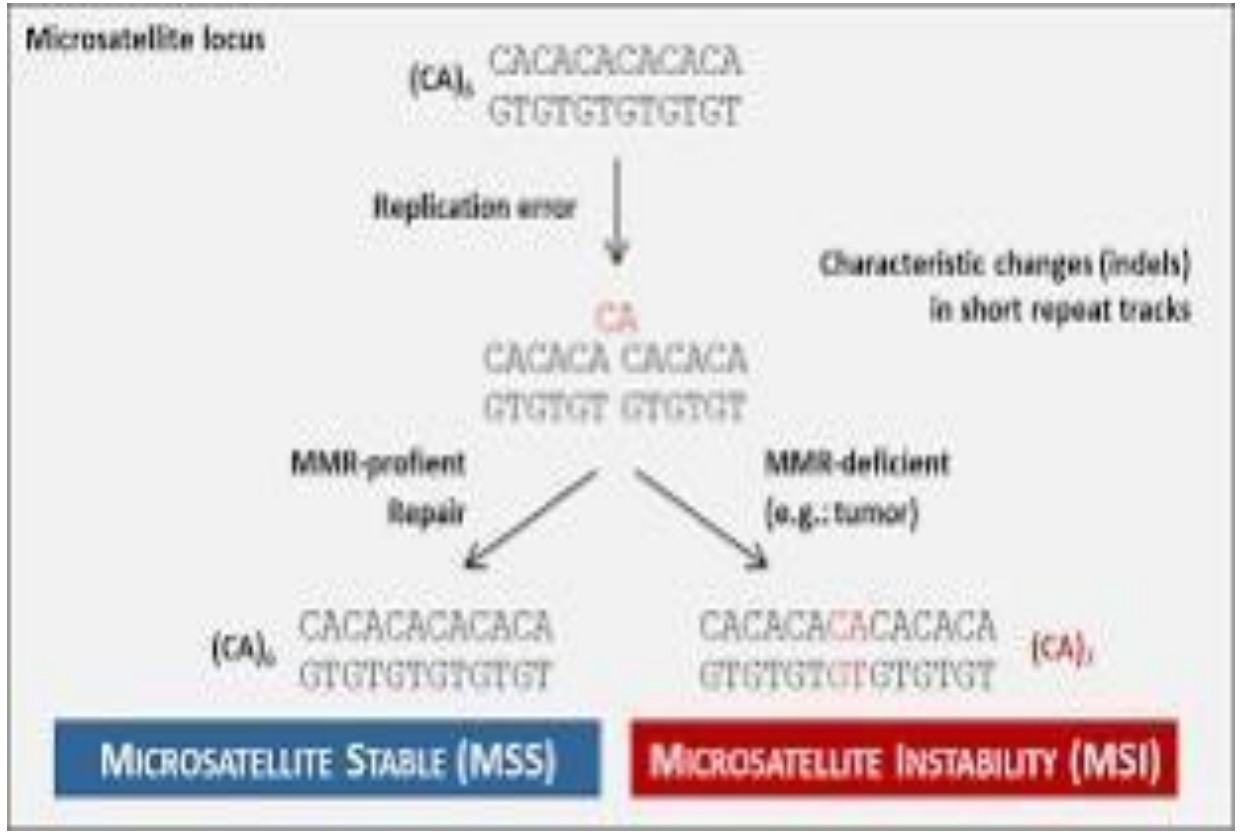
Fig. 18-22

The multiple-mutation model for the progression of cancer

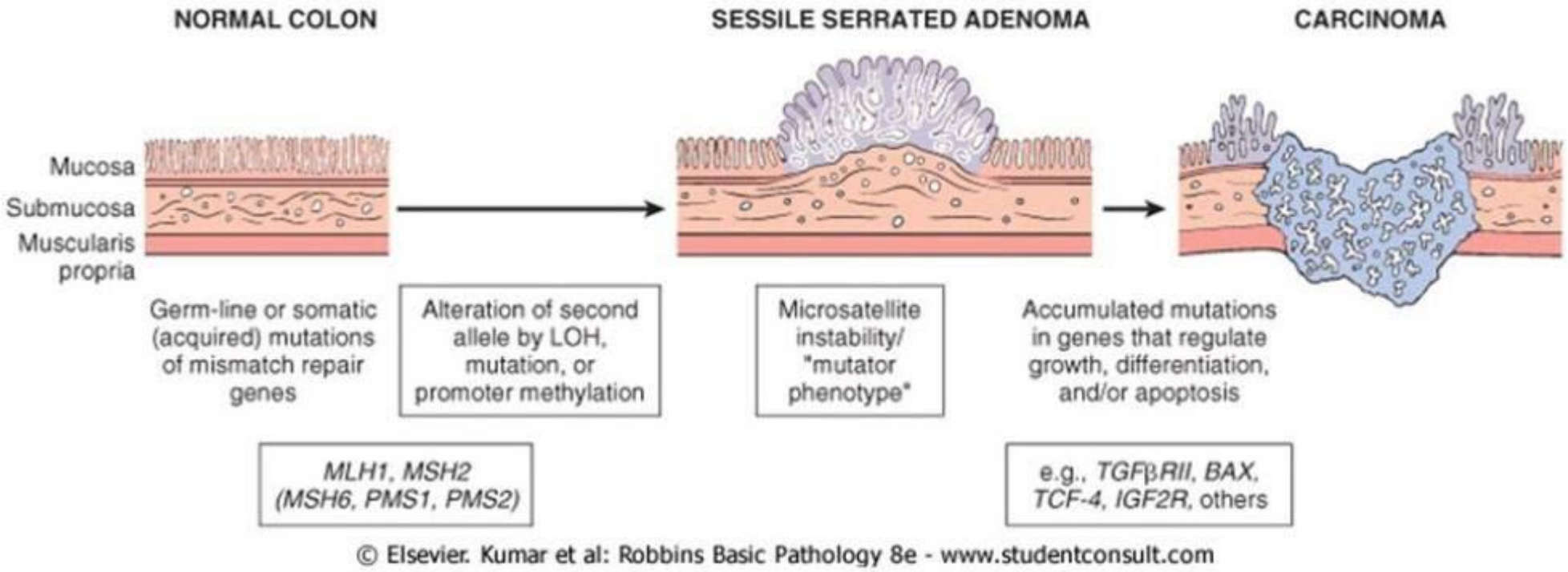


MICROSATELLITE INSTABILITY

- Microsatellite –tandemly repeated sequences of 1-6bp
- Microsatellites are more prone to get unstable compared to other regions of DNA
- instability is due to many errors occur during DNA replication
- Such error is normally repaired by mismatch repair enzymes which are encoded by mismatch repair genes.
- Microsatellite instability- mutations in mismatch repair genes(hMSH2, hMSH6, hMLH1, hMLH3, hPMS1 and hPMS2)

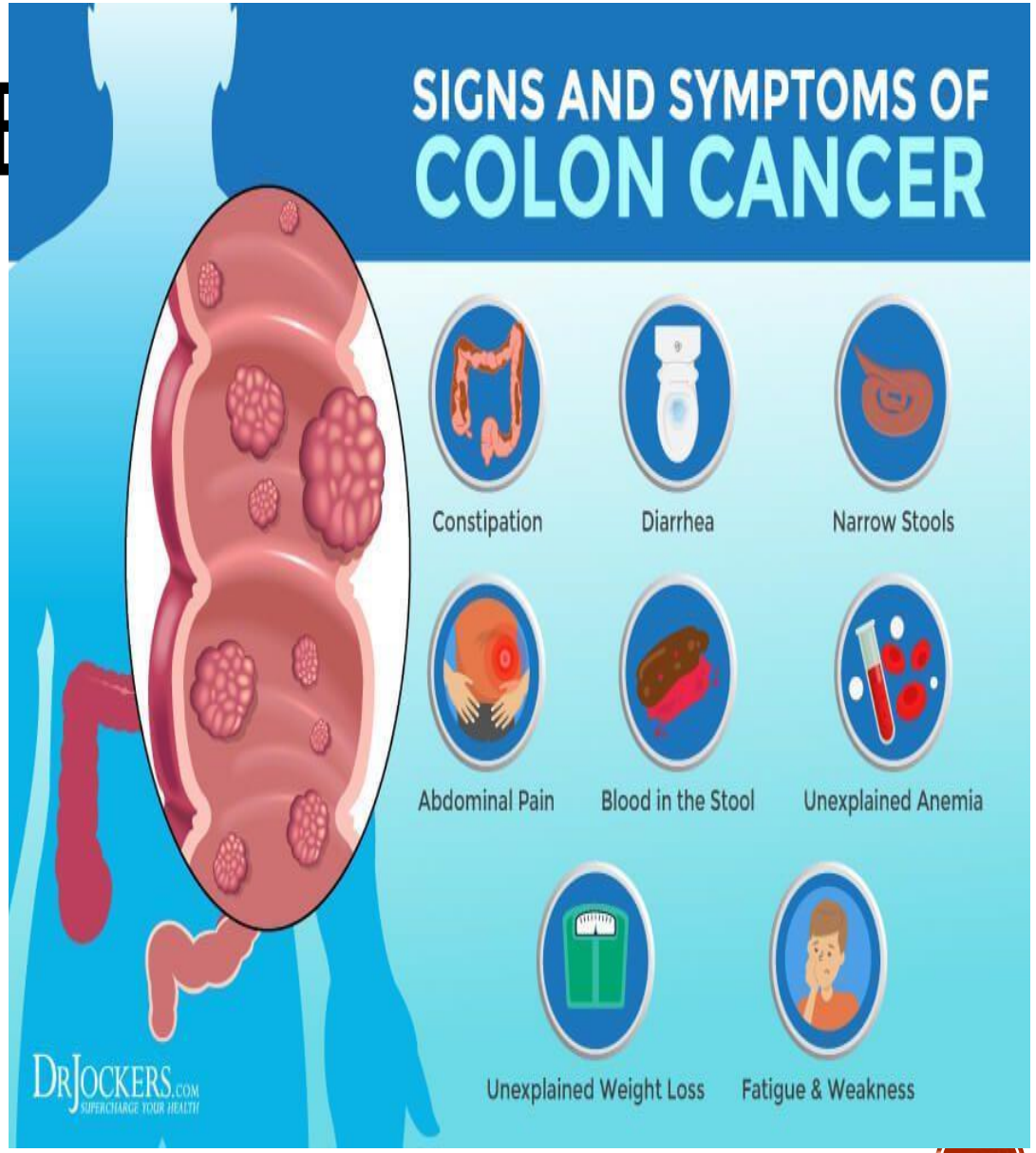


- As majority of microsatellites are located in the non-coding region, these mutations are generally silent.
- • Some microsatellites which are present in the coding region of the gene are involved in the regulation of cell growth.

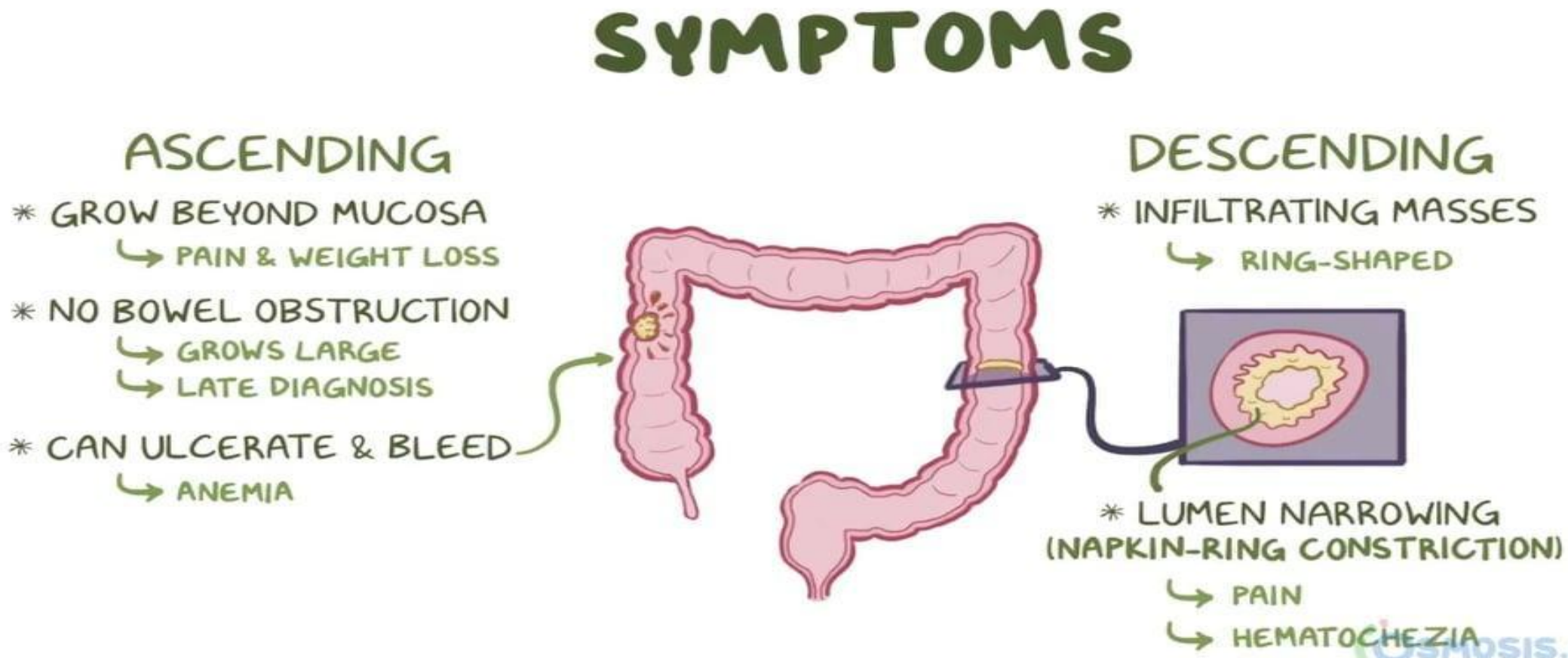


CLINICAL FEATUR

- Asymptomatic
- Abdominal pain
- Blood in stool
- Change in bowel habit
- ……

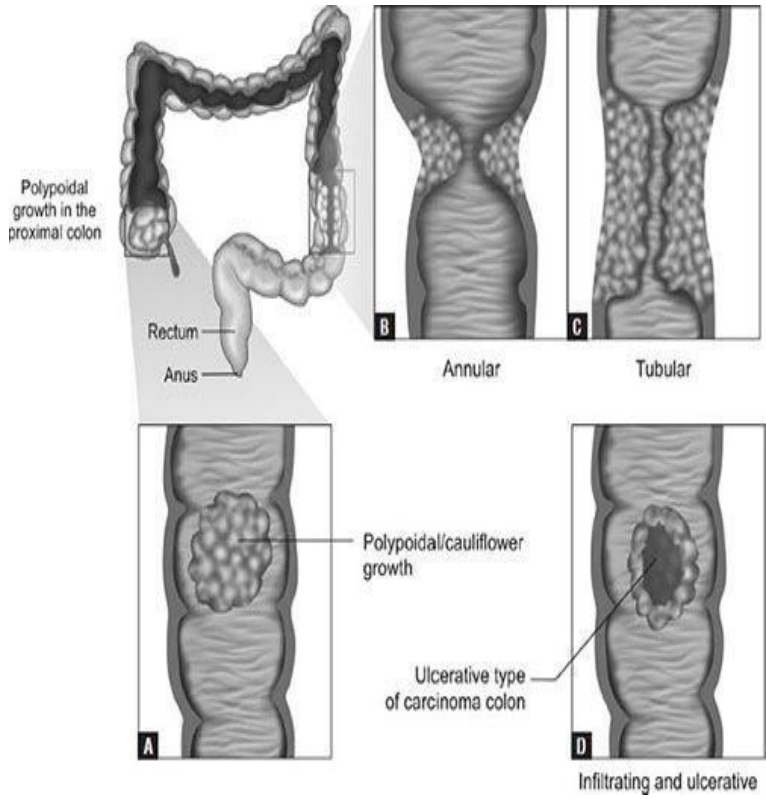


SIGNS AND SYMPTOMS BASED ON LOCATION:



SIGNS AND SYMPTOMS BASED ON LOCATION:

Right colon	Left colon	RECTUM
Exophytic lesions	Annular lesions	Ulcerated lesions
• weakness • Weight loss • Unusual Obstruction • Uncommon Change in bowel habit	• Abdominal pain • Change in bowel habits • Narrowing of stool • obstruction	• Mucus discharge • Feeling of incomplete emptying • ”tenesmus”
• Occult bleeding • Iron deficiency anemia	• Fresh rectal bleeding “hematochezia”	• Fresh bleeding ” hematochezia” • Palpable mass on rectal examination



Investigations and Screening of Colorectal Cancer

DONE BY SAEED BAIDOUN

INVESTIGATIONS OF COLORECTAL CANCER

DIGITAL RECTAL EXAMINATION

- It is the simplest method of colorectal cancer recognition along with the case history
- 70% of rectal cancers and 30% of colorectal cancers are recognized
- The accuracy of the examination increases with the experience of the doctor

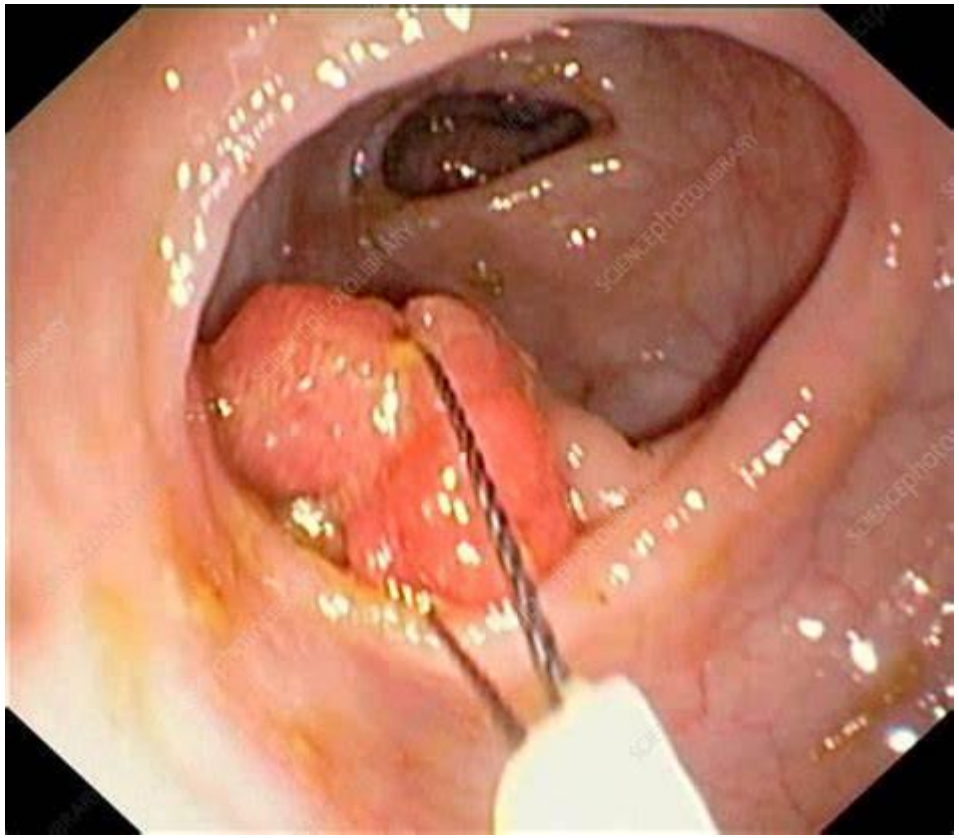
COLONOSCOPY

- Colonoscopy is the investigation of choice
- Allows physician to see inside the large intestine
- Moderate sedation or deep sedation with the anesthetic propofol
- Using a flexible camera called a scope
- Follow a special diet, no solids the day before colonoscopy
- Only fluids such as plain water
- Use laxatives
- Use enema kit

COLONOSCOPY

- The lining of the intestine, colon and rectum can be viewed by a flexible tube inserted through the rectum
- Air or carbon dioxide will be passed into the colon to inflate the colon to provide better view of the lining of the colon
- It has a higher sensitivity and specificity than barium enema,
- A biopsy of the lesion can be obtained
- Polyps can be removed

COLONOSCOPY



COLONOSCOPY

Indications
Inflammatory Bowel Disease (IBD)
Chronic Diarrhoea
Altered bowel habit
Rectal bleeding
Iron deficiency anemia
Assessment of abnormal CT colonogram or barium enema
Colorectal cancer screening
Colorectal adenoma and carcinoma follow up
Endoscopic resection
Stent Insertion
Argon plasma coagulation
Dilatation of strictures

COLONOSCOPY

Contraindications
Acute severe ulcerative colitis (UC) (unprepared flexible sigmoidoscopy is preferred)
Severe shock
Recent Myocardial infarction
Unstable Angina
Cardiac arrythmia
Severe respiratory disease
Atlantoaxial subluxation
Visceral perforation

COLONOSCOPY

Complications
Cardiorespiratory depression due to sedation
Perforation
Bleeding following polypectomy

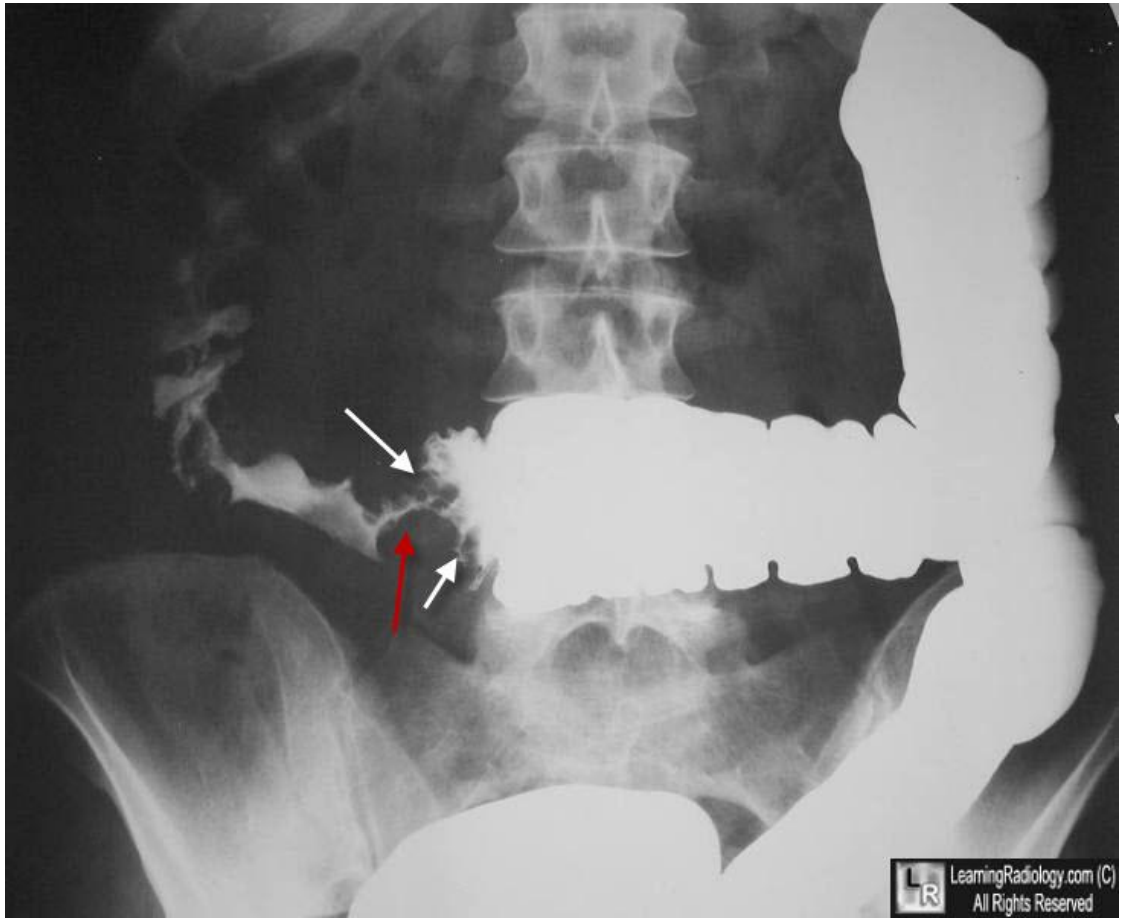
CT COLONOGRAPHY (VIRTUAL COLONOSCOPY)

- Done for patients whom colonoscopy is incomplete or patients at risk of complications of colonoscopy
- It is a sensitive technique
- Non invasive
- Used to diagnose tumors and polyps more than 6mm in diameter
- Used to evaluate the extent of other organ involvement, specially the liver which helps stage the cancer and guide therapy

BARIUM ENEMA

- This procedure is done by inserting a lubricated enema tip into the patient rectum
- It allows liquid barium to flow through the enema tip
- A series of x-ray pictures of the colon are taken
- The exam takes approx. 45 minutes
- A special preparation and only clear liquids are taken the day before the procedure
- Low risk and less expensive than colonoscopy
- Commonly used to diagnose colorectal cancer, inflammatory bowel disease, polyps and diverticula

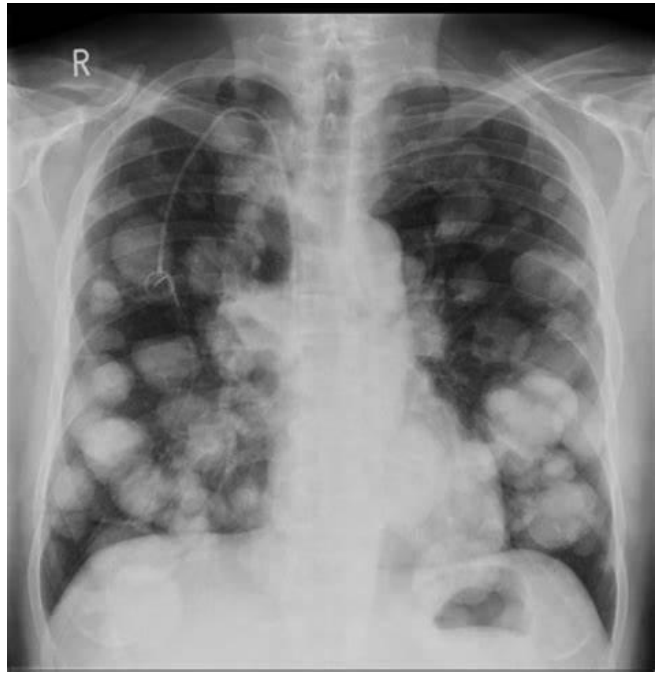
BARIUM ENEMA



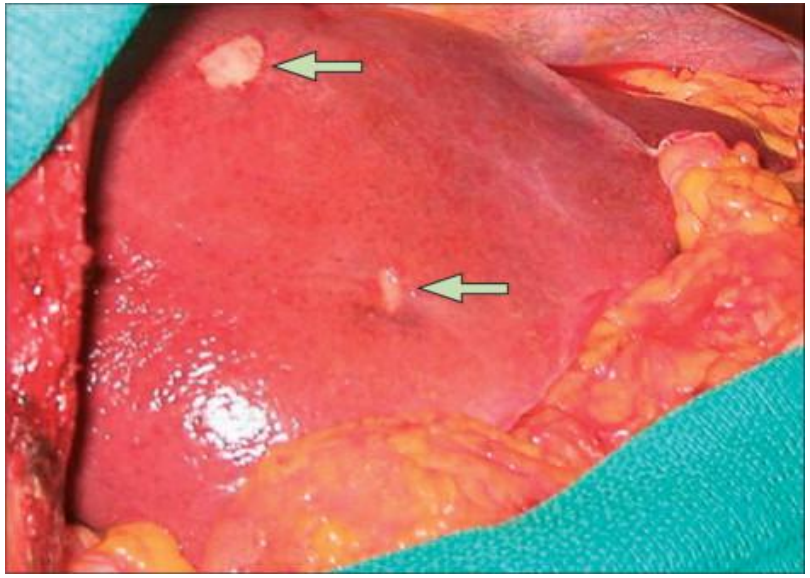
CRC

CT SCAN OF CHEST, ABDOMEN AND PELVIS

- Done as a screening investigation
- To detect hepatic and lung metastasis



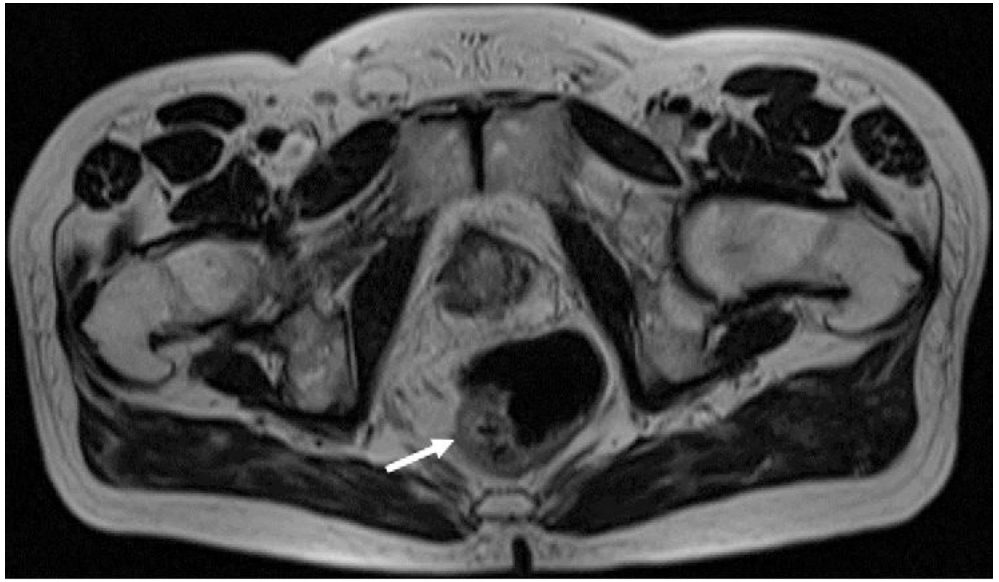
CRC metastasis to lung



CRC metastasis to liver

MRI AND ENDOANAL ULTRASOUND

- Used for local staging of rectal cancer
- MRI accurately assesses the extramural tumor spread and relation to mesorectal fascia and the sphincter complex



MRI of CRC

LAB TESTS
BLOOD TESTS

- CBC test to detect anemia
- Liver function tests to assess spread to the liver
- Stool tests
- Like Stool DNA test, fecal immunochemical test, and fecal occult blood test

MEASUREMENT OF CARCINOEMBRYONIC ANTIGEN LEVELS

- Carcinoembryonic antigen measurement is limited in diagnosis
- Normal values in many patients
- For follow-up for recurrence
- Increased in colorectal cancer as well as breast, lung, pancreatic, stomach, liver and ovarian cancer
- Also associated with non cancerous conditions such as peptic ulcer (PU) , ulcerative colitis, rectal polyps , emphysema, benign breast disease, pancreatitis, cholecystitis and smokers.

- Normal range is 0-2.5 ng/ml and 0-5 ng/ml in smokers.

SCREENING OF COLORECTAL CANCER

- Regular screening beginning at age 45 is the key to preventing CRC and finding it early
- Recommended to be done in adults between 45-75 years
- CRC almost develops from precancerous polyps in the colon or rectum,screening of these polyps can find CRC early
- Screening must be done in the following conditions (presence of close relative having CRC or colorectal polyps,in patients with inflammatory bowel disease (IBD) such as Crohn's disease or Ulcerative colitis (UC) and in patients having genetic syndrome such as familial adenomatous polyposis or hereditary non poplyposis CRC (Lynch syndrome))

Staging and treatment

DONE BY Ibrahim Maraqa

ANATOMY

- ● The wall of the colon and rectum comprise five distinct layers:

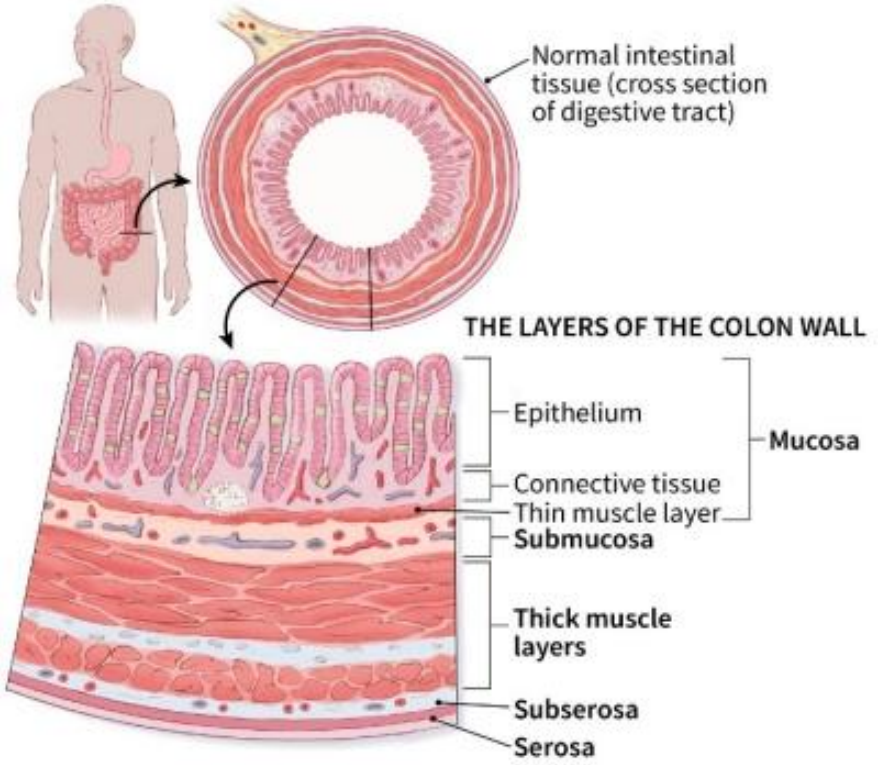
1.Mucosa

2. Submucosa

3. inner circular muscle

4.outer longitudinal muscle

5.serosa.

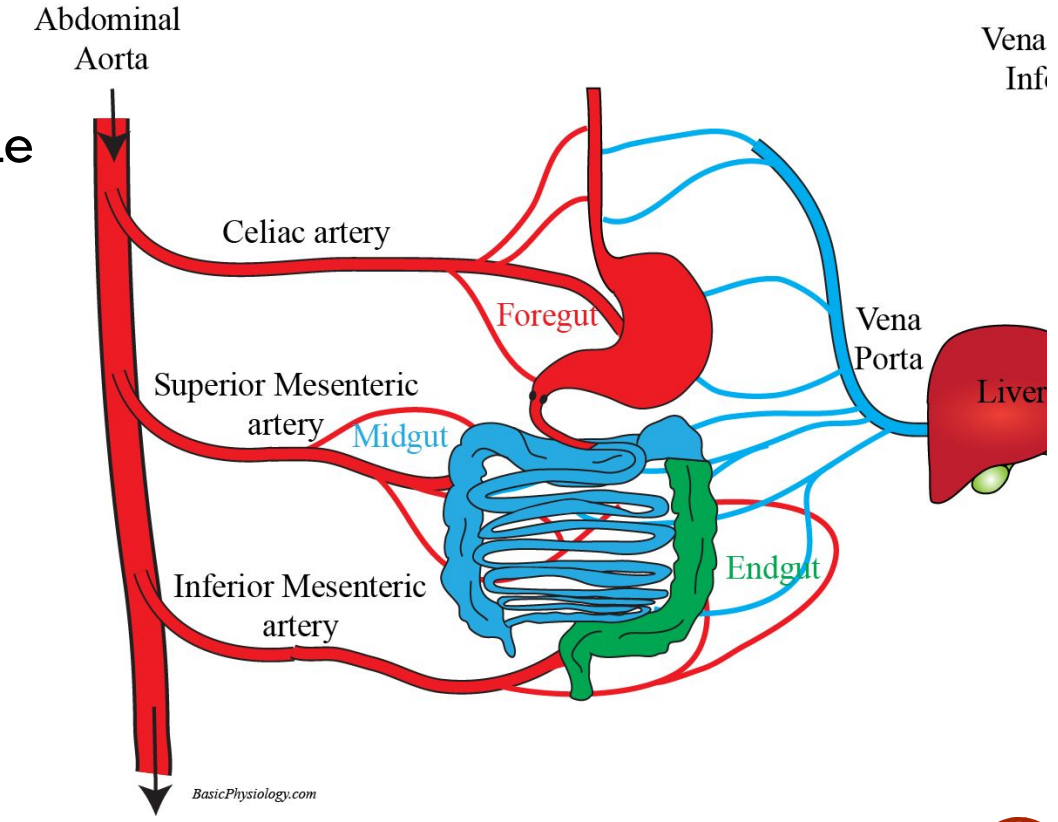


- ● In the colon, the outer longitudinal muscle is separated into three teniae coli , which converge proximally at the appendix and distally at the rectum.

BLOOD SUPPLY

Till the distal transverse colon (midgut) is supplied by superior mesenteric artery.
Distal to it (hindgut), it is supplied by inferior mesenteric artery.

It follows the arterial supply and as for the small intestine system, venous drainage is into **the portal vein** to the liver



STAGING

- There are two classification systems;TNM and Dukes,but there has been a gradual move from using Dukes system to using the TNM classification system.
- The two most important prognostic factors are depth of invasion and the presence or absence of lymph node metastasis, therefore these factors form the basis of the TNM(tumor-node-metastasis) staging system.

TNM

- T-depth of invasion
- N-spread to regional lymph nodes
- M-distant spread

TNM classification			Modified Dukes' classification	5-year survival (%)
Stage I (N0, M0)	Tumours invade submucosa	T1	A	90
	Tumours invade muscularis propria	T2		
Stage IIA (N0, M0)	Tumours invade into subserosa	T3	B	70
IIB	Tumours invade directly into other organs	T4		65
Stage III (M0)	T1, T2 + 1–3 regional lymph nodes involved	N1	C	60
IIIB	T3, T4 + 1–3 regional lymph nodes involved	N1		35
IIIC	Any T + 4 or more regional lymph nodes	N2		25
Stage IV	Any T, any N + distant metastases	M1	D	7

There are different patterns of spread:

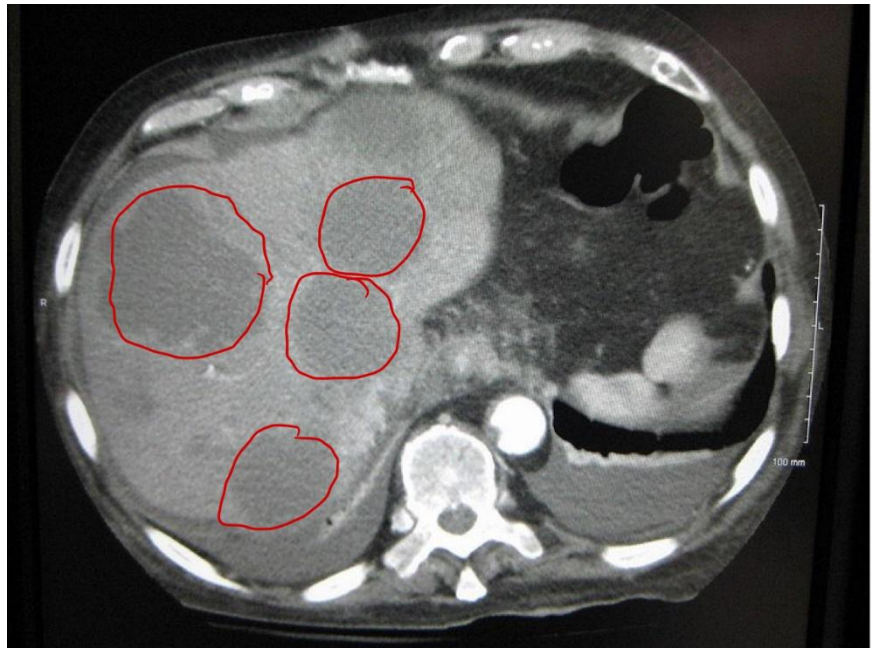
1.Direct extension-through the bowel wall to later invade other abdominoperineal organs

2.lymphatic-regionally

3.Transperitoneal

4.Hematogenous-through portal circulation to liver, which is the most common site of distant spread

Or through lumbar/vertebral veins to lungs



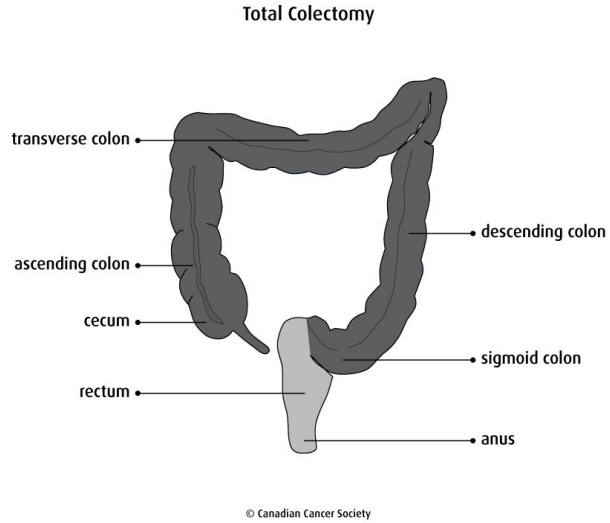
Hepatic metastasis ct scan

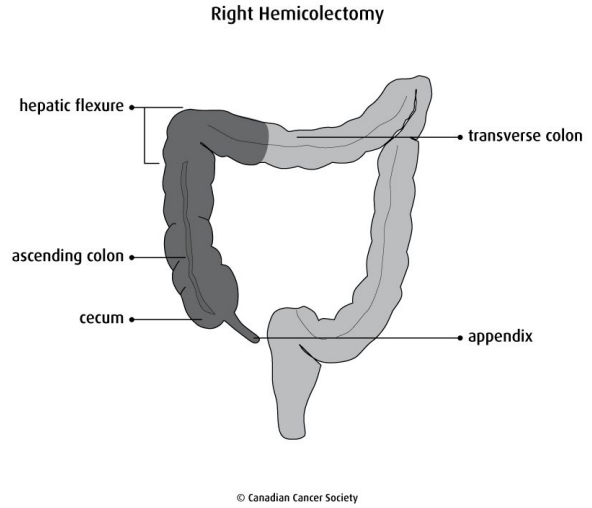
TREATMENT

1.Surgery is the only curative treatment, there is a resection of tumor containing bowel as well as the regional lymphatics

2.CEA level should be obtained before surgery

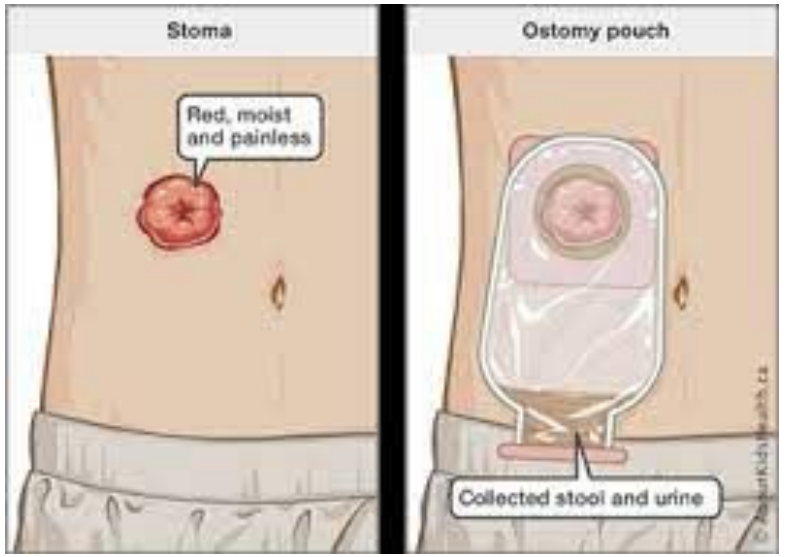
3.Types of surgeries:
A.Total mesorectal excision
B.segmental resiction
C.Local transanal surgery
D.Surgical treatment of lung and liver metastases
E.Total colectomy





STOMA

- A stoma is an opening in your belly's wall that a surgeon makes in order for waste to leave your body if you can't have a bowel movement through your rectum.



- The patient might get one if he have surgery to remove or bypass part of your large intestine (colon and rectum) like in colostomy and can't have bowel movements the usual way.
- The surgeon will attach the end of your colon to the stoma. Bowel movements will leave your body through it and collect in a special pouch that you'll empty out on a bag called colostomy bag.

4.Chemotherapy could be used as an adjuvant therapy, and that depends on the stage of tumor :

- Lymph node-positive disease: Adjuvant chemotherapy(curative).
- Metastatic disease: palliative chemotherapy(don't cure the cancer but it can prolong life).

5.However, radiation therapy is not indicated in the treatment of colon cancer

Follow-up

1.Colonoscopy at 1 year and then every 3 years but patients with stage 2 or 3,colonoscopy should be performed regularly.

2.Annual CT scan of abdomen/pelvis and CXR for up to 5 years

3.CEA levels are checked periodically, every 3 to 6 months
-subsequent increase in CEA could be an indicator of recurrence
-very high elevations suggest liver involvement

Thank you

Any question??

references

- Kumar and Clark's Clinical Medicine, International Edition, 9th Edition
- Davidson's Principles and Practice of Medicine 22nd Edition