

Definition

Cancer of the **colon** or **rectum**

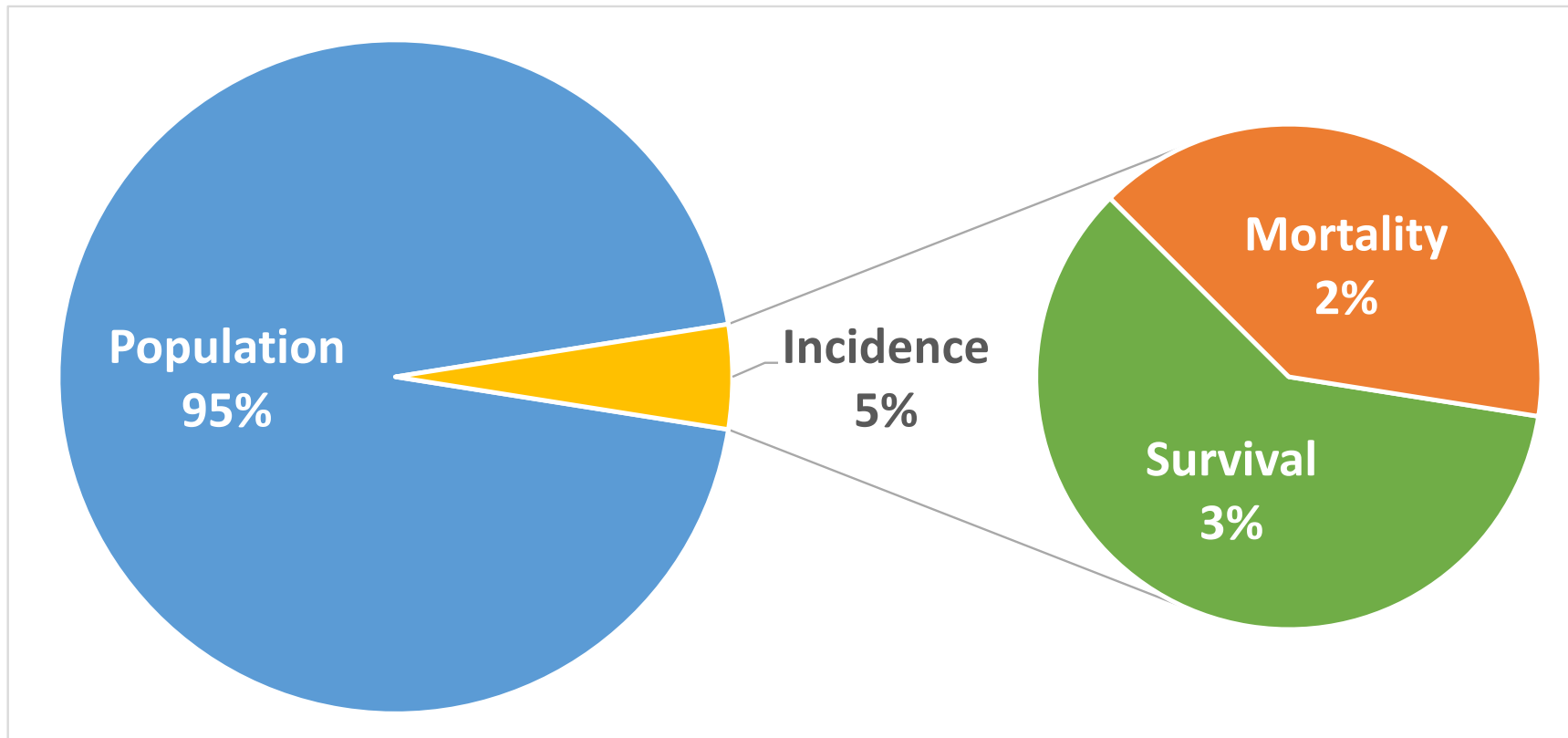
Type	Frequency	Cellular origin
Adenocarcinoma	95%	Glandular epithelium
Lymphoma	1%	Extranodal lymphatic system
Carcinoid	0.5%	Neuroendocrine cells
Sarcoma	0.3%	Blood vessels, muscle, connective tissue
Squamous cell	rare	Squamous cells
Stromal	rare	Interstitial cell of Cajal

Adenocarcinoma

- By far the most common
- ***"Colorectal adenocarcinoma"***
used interchangeably with
"colorectal cancer"

Lifetime Incidence

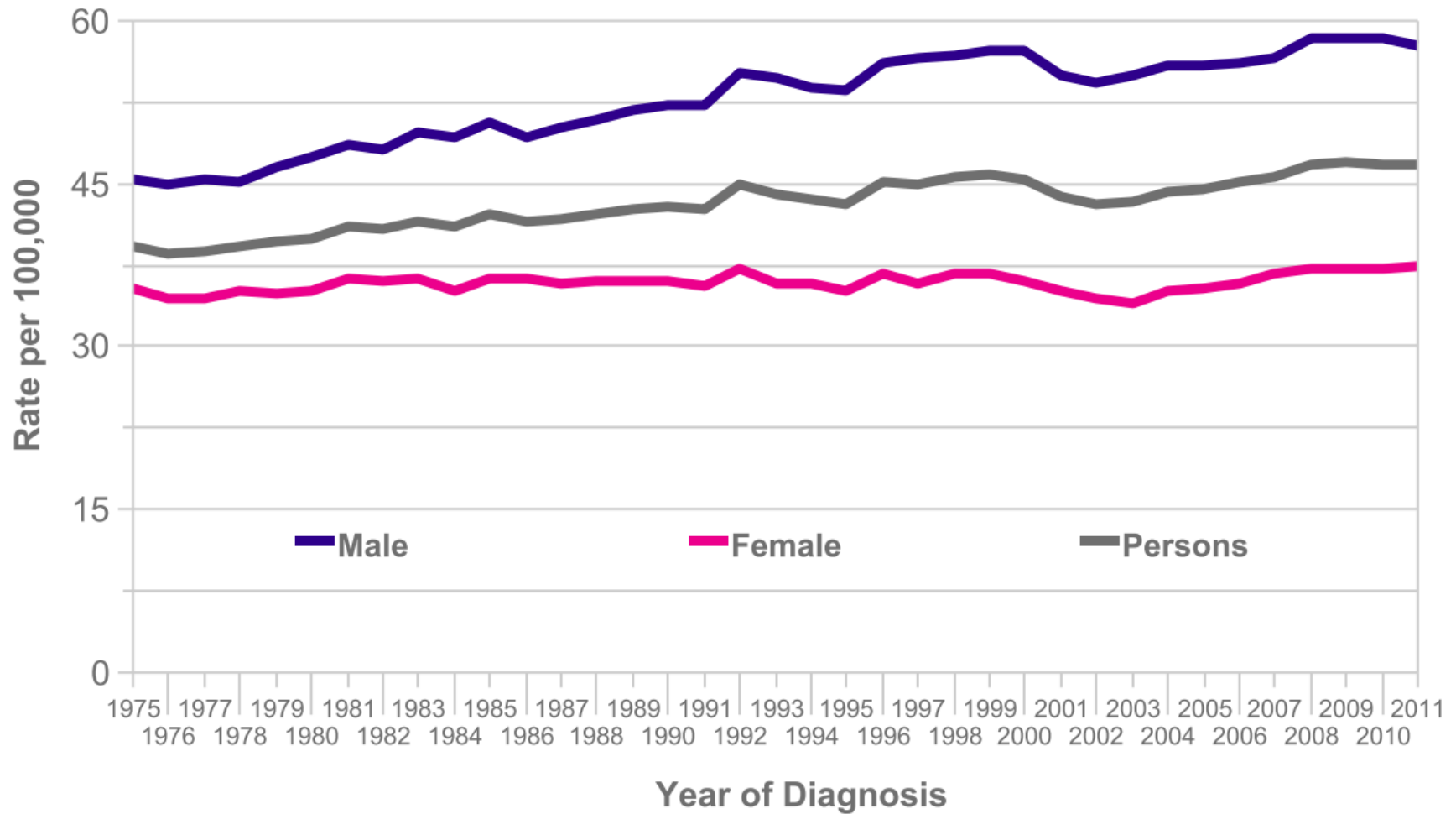
- **1 in 20 will develop** in lifetime
- **1 in 50 will die** from in lifetime



Prevalence

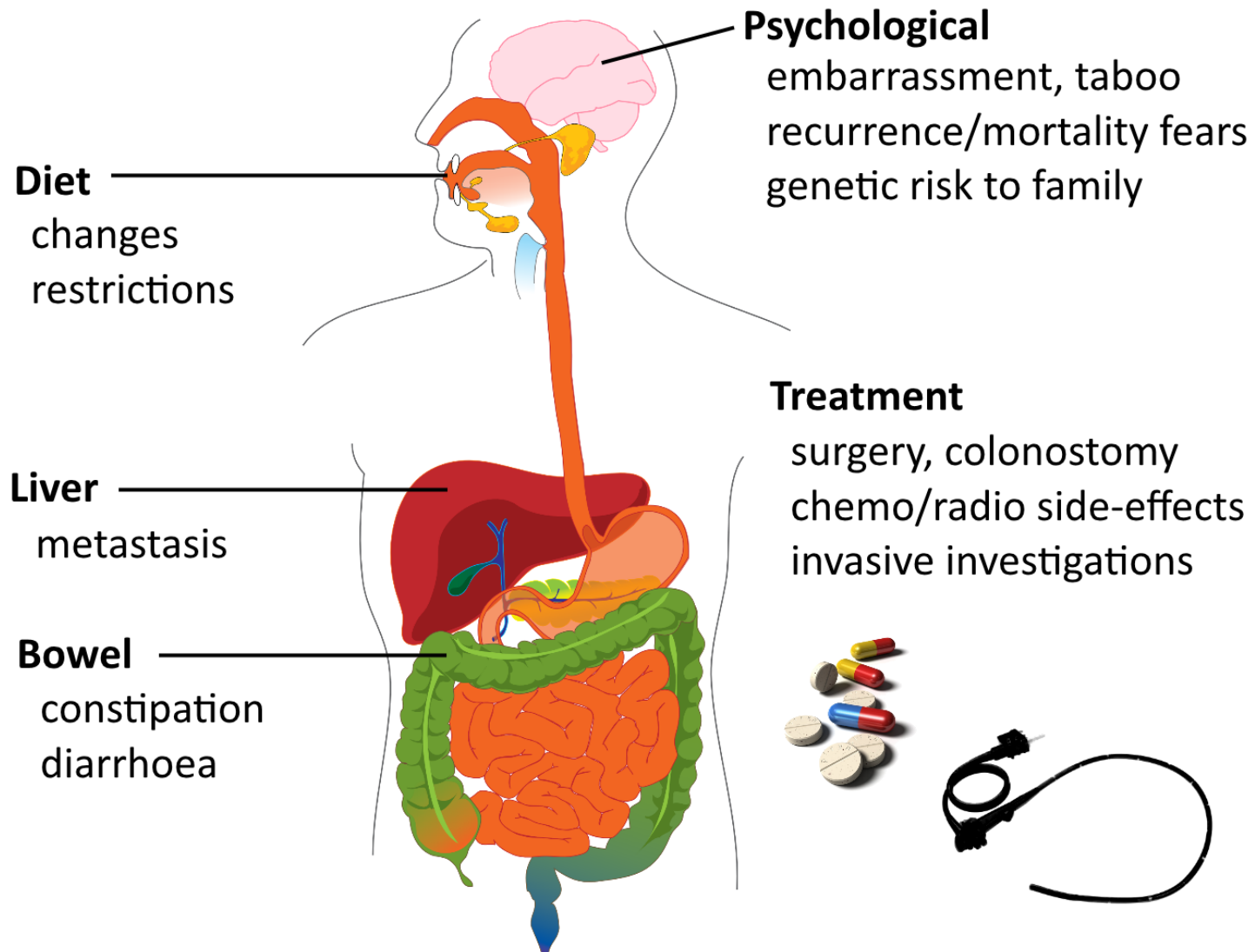
- 3rd most common cancer worldwide (10% of total cancers)
- Steadily increasing incidence
 - ↑ 30% among males since 1975
 - Ageing population?
 - Westernised diet?

**Age-standardised incidence rates per 100,000
(UK, 1975-2011)**



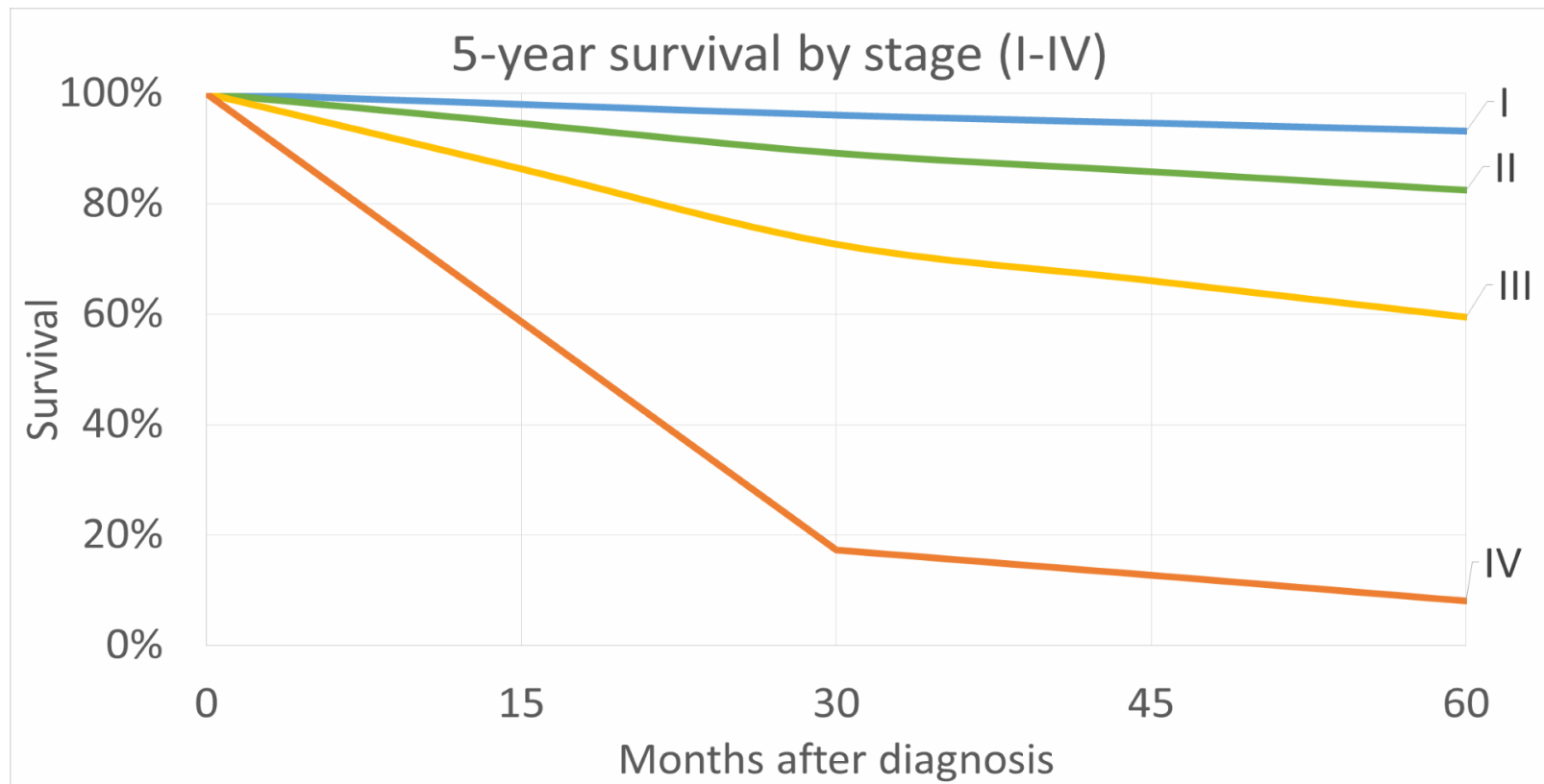
Ref: [Cancer Research UK](#)

Morbidity



Mortality

- **40% overall**
- **2nd-3rd most responsible for cancer-related mortality**



Data: [O'Connell et al.](#)

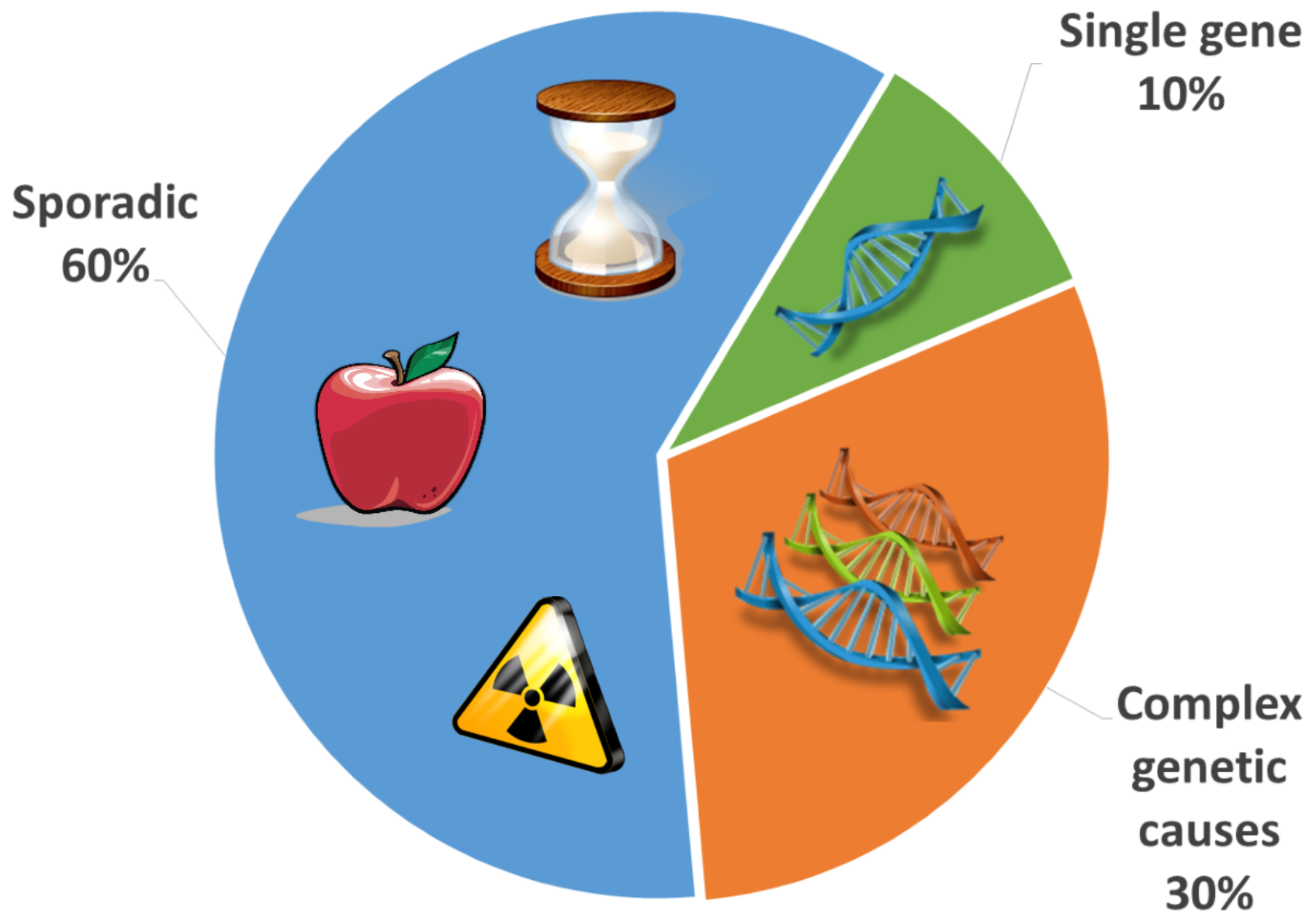
Cost

Ireland, 2008 (Ref: [Tilson et al.](#))

- Average healthcare cost per case = ~€40,000
- More for rectal cancers
- More for advanced stages

Pathogenesis

- **5-10% single gene disorders**
 - **HNPCC** (*MLH1*, *MSH2* genes)
 - **FAP** (*APC* gene)
- **30% complex genetic causes**
- **60% sporadic**
 - age-associated
 - Western diet
 - chronic inflammation
 - abdominal radiation
 - immunosuppression

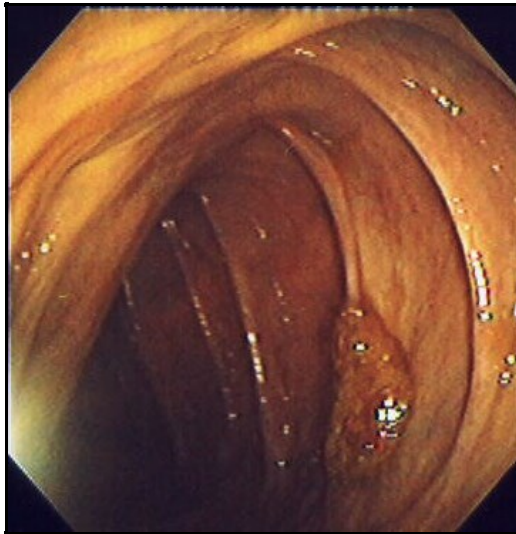


Polyps

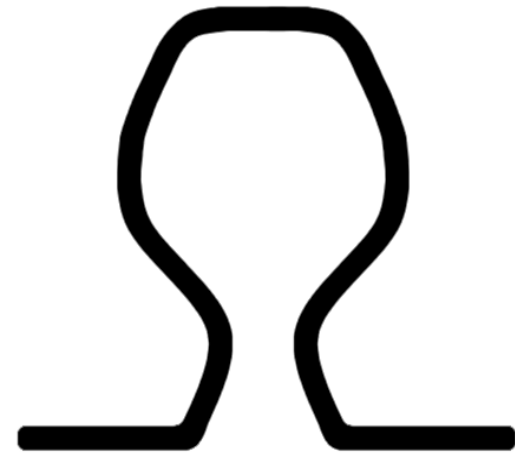
Small growths from mucous membranes



sessile
(flat)



Kd4ttc [CC-BY-2.5], via Wikimedia Commons



pedunculated
(stalked)



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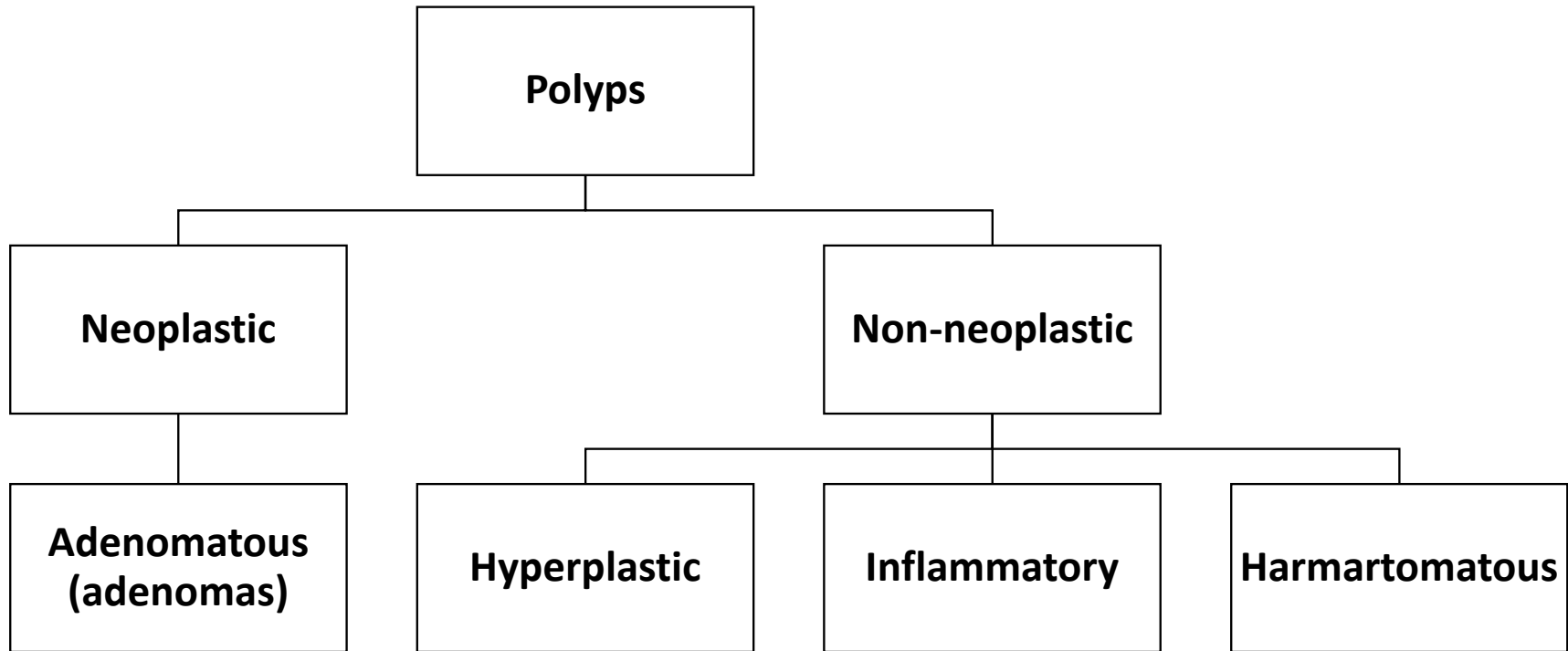
Pedunculated polyp



Ed Uthman [Public domain], [via Wikimedia Commons](#)

Polyps

- **Neoplastic polyps**
 - **Adenomatous polyps (adenomas)**
 - **10% of all polyps**
 - **Potential for malignant change, but most do not**
- **Non-neoplastic polyps**
 - **Inflammatory, hamartomatous, hyperplastic**
 - **90% of all polyps**
 - **Generally no malignant change**
 - **A sign of greater risk of adenoma (carcinoma)**



Adenomas

- **0.3 to 10 cm** diameter
- Velvety, raspberry-like texture of irregular epithelium
- Sessile or pedunculated

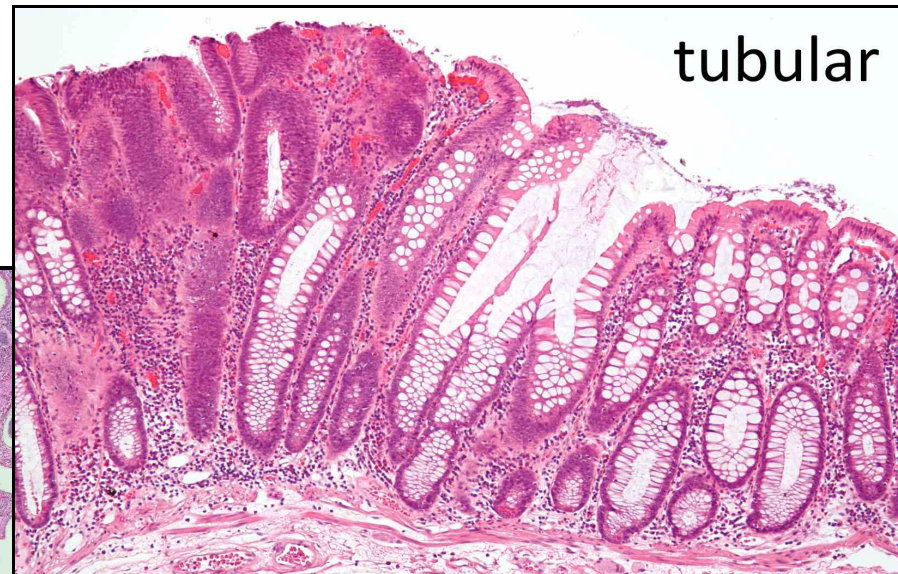
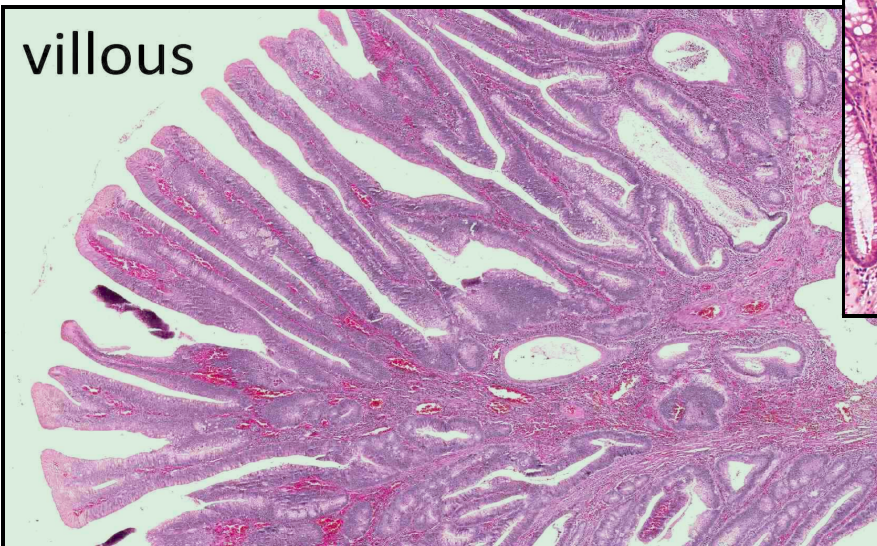


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Adenoma Architectures

1. **Tubular:** small, peduncular, tubular glands
2. **Tubulovillous**
3. **Villous:** larger, sessile, villous surface

The Juan Rosai Collection [CC0], via Wikimedia Commons



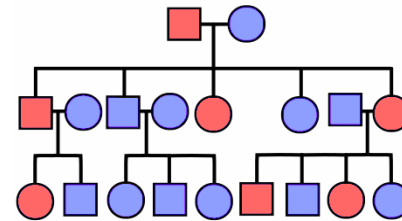
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Malignant Transformation

- Risk factors:
 - **Large** size
 - **Sessile** shape
 - **Villous** architecture
 - **Multiple** adenomas
- **90%** of malignancies develop from **pedunculated** adenomas
 - 33% of Western people have benign adenomas
 - 1% of adenomas undergo malignant change
- **10%** of malignancies develop from **sessile** adenomas
 - more difficult to detect

Familial Colorectal Cancer Syndromes

- **Heritable** genetic syndromes **predisposing to polyps**
- Greatly increased **lifetime risks of colorectal carcinoma**
- Both **autosomal dominant**



Syndrome	Gene	Gene type
Familial Adenomatous Polyposis (FAP)	APC	Tumour suppressor
Hereditary Non-Polyposis Colorectal Cancer (HNPCC)	MLH1, MSH2	Mismatch repair

Familial Adenomatous Polyposis (FAP)

- 3% of all colorectal carcinoma
- Develop **100s-1000s of polyps by teens**
- 100% risk of carcinoma <30y if not treated by **prophylactic colectomy**



Samir [[GFDL](#) or [CC-BY-SA-3.0](#)], from Wikimedia Commons

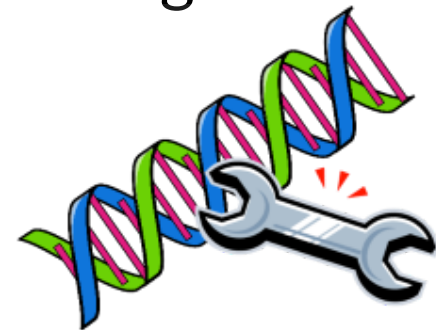
Familial Adenomatous Polyposis (FAP)

- Adenomatous polyposis coli (**APC**) gene
 - **Tumour suppressor gene**
 - Two-hit mutation/silencing
- Specific mutation variants :
 - **Gardner** syndrome
 - **Osteomas** of skull and long bones
 - Epidermal cysts
 - Desmoid, thyroid tumours
 - Supernumerary and unerupted teeth
 - **Turcot** syndrome
 - CNS **medulloblastomas** and **glioblastomas**



Hereditary Non-Polyposis Colorectal Cancer (HNPCC)

- Also called ***Lynch*** syndrome
- Cancers: **colorectal, gastric, endometrial, ovarian, uterine**
- Colorectal carcinoma in the young
- Inherited mutations in **DNA mismatch repair genes**:
 - **MLH1, MSH2**, others (rarer)
 - Two-hit mutation/silencing
 - Accumulation of mutations in short, repeating **microsatellite regions**



Gatekeeper/Caretaker Genes

- 'Gatekeeper' genes **'control the gate'** to tumour mutation
- 'Caretaker' genes **'weed the garden'** of tumours

Gatekeeper



Control
cell
growth

Tumour
suppressor
genes

Many
tumours,
but less
aggressive

FAP

Caretaker



Stabilise
genome,
prevent
mutations

Mismatch
repair
genes

Few
tumours,
but more
aggressive

HNPCC

Molecular Pathways

- Identified pathways of colorectal carcinoma development
- **Genetic** and **epigenetic** abnormalities
- Stepwise accumulation of mutations

Pathway	Gene	Gene type	Downstream effects
APC/β-catenin	APC	Tumour suppressor	WNT, KRAS, p53, LOH, SMAD2/4
Microsatellite instability	MLH1, MSH2	Mismatch repair	TGF- β , BAX, BRAF

APC/ β -catenin pathway

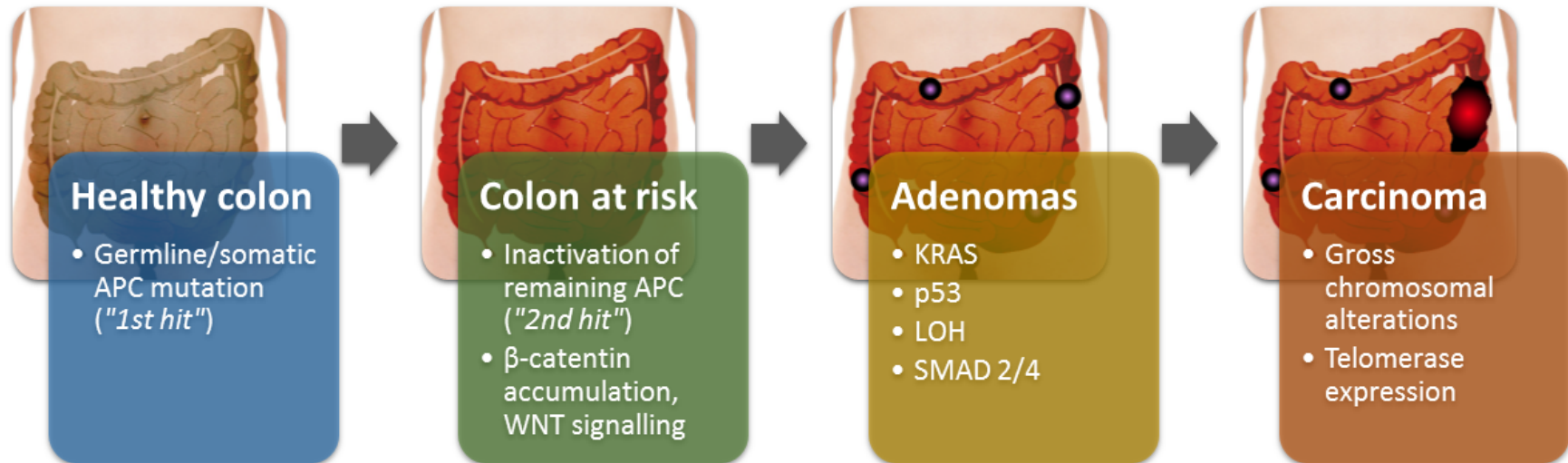
Normal APC function:

- APC binds β -catenin, marks for degradation

Loss of APC function:

- APC cannot bind, β -catenin accumulates
- β -catenin upregulates gene transcription in nucleus:
 - WNT signalling pathway
 - genes promoting proliferation (e.g. MYC, cyclin D1)
- Activating mutations in **KRAS**:
 - promote growth, prevent apoptosis
- **Chromosomal instability**, further mutations:
 - p53, LOH, SMAD2, SMAD4, gross chromosomal alterations, telomerase expansions

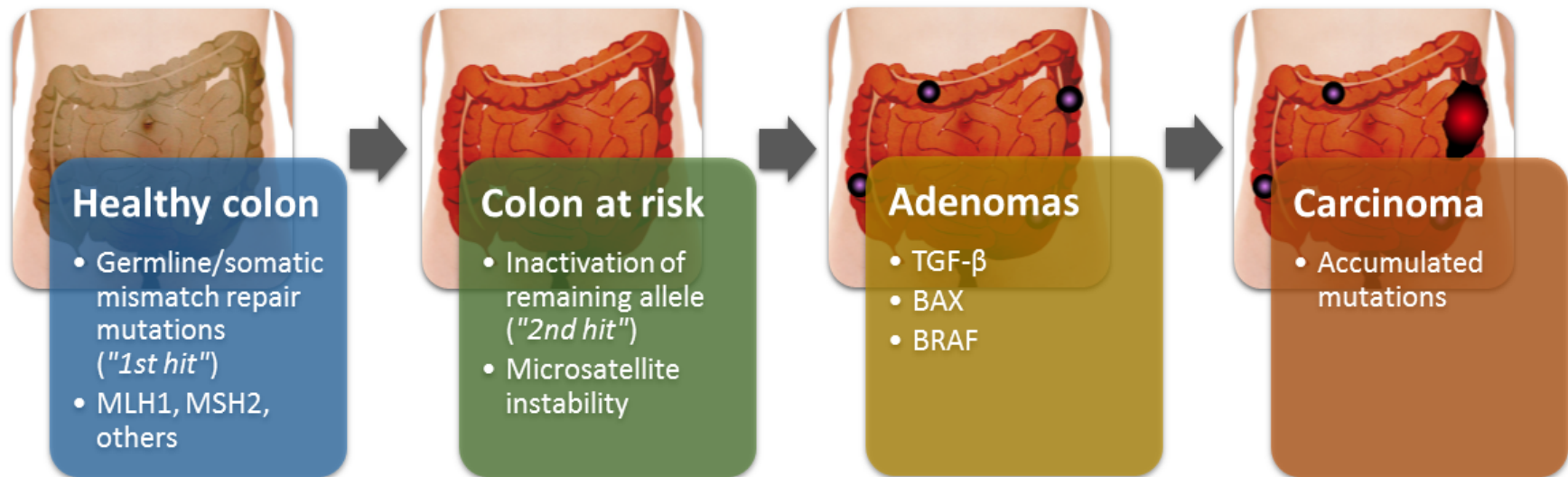
APC/ β -catenin pathway



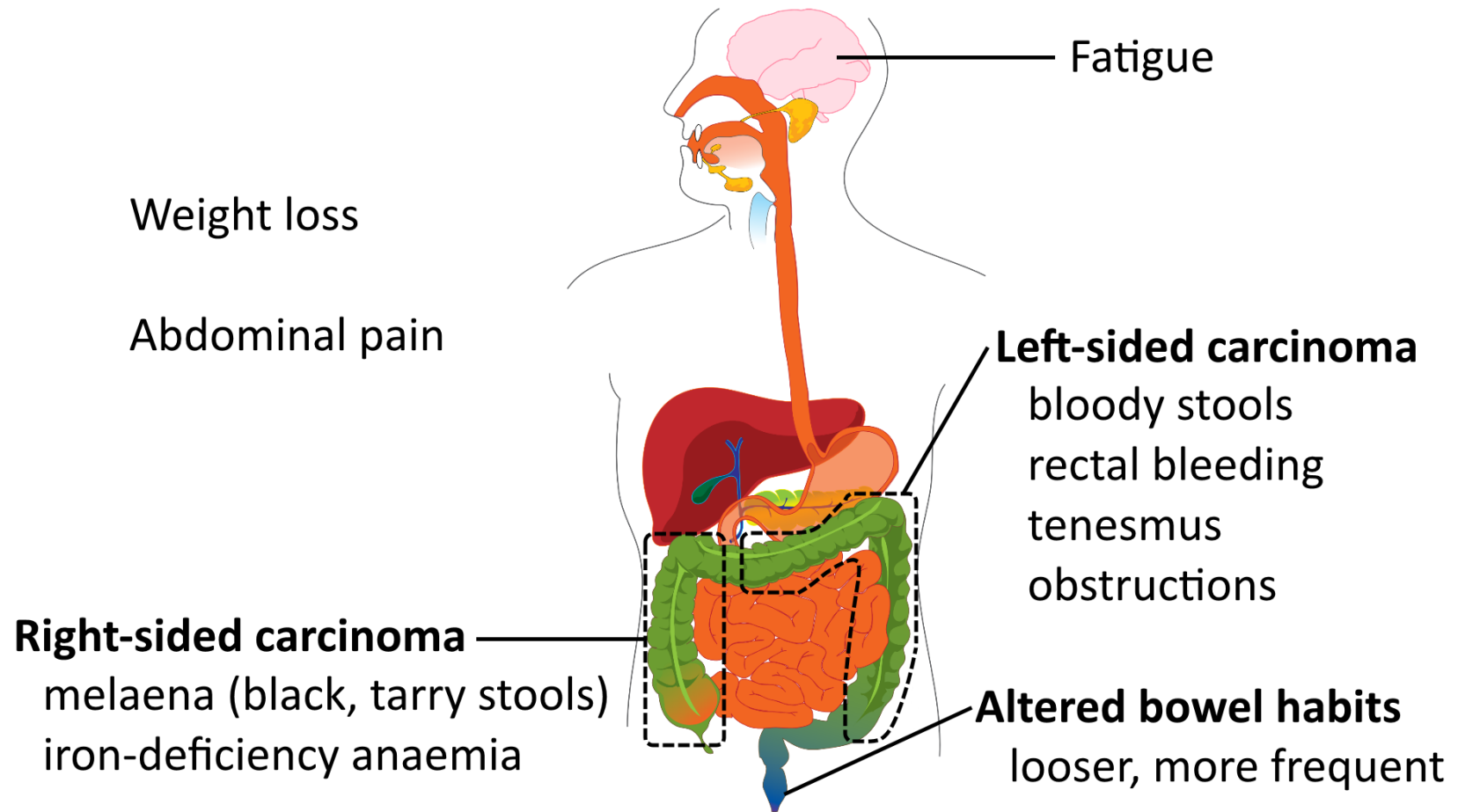
Microsatellite Instability Pathway

- Defects in **mismatch repair genes**
 - **MLH1, MSH2**, others (rarer)
- Mutations accumulate in short, repeating **microsatellite regions**
- Regions are mostly **non-coding**, but contain some **promoters for genes of cell growth regulation**
 - **TGF- β** : inhibits colonic epithelial cell proliferation
 - **BAX**: pro-apoptotic for abnormal clones
 - **BRAF**: oncogene

Microsatellite Instability Pathway

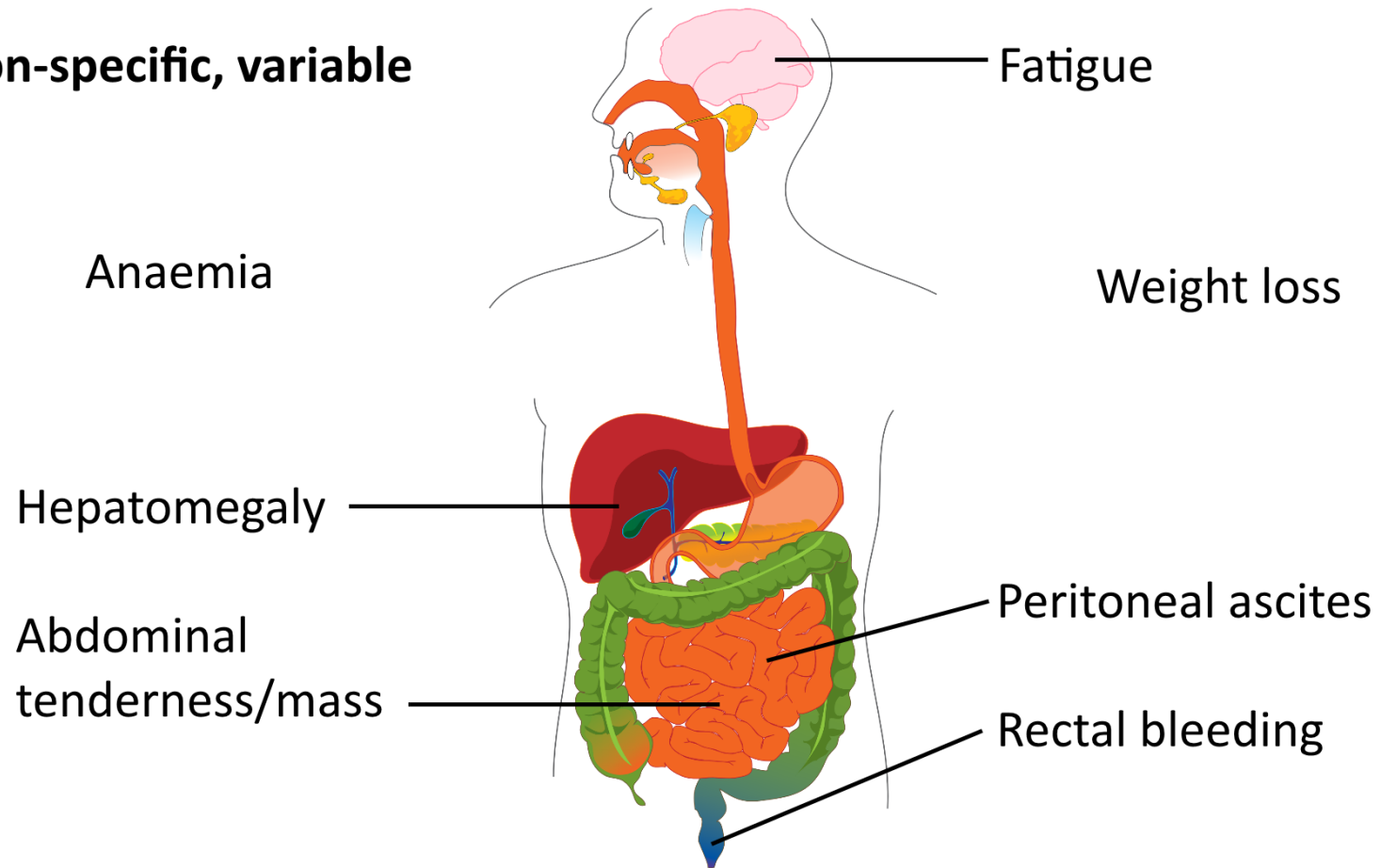


Symptoms



Signs

Non-specific, variable



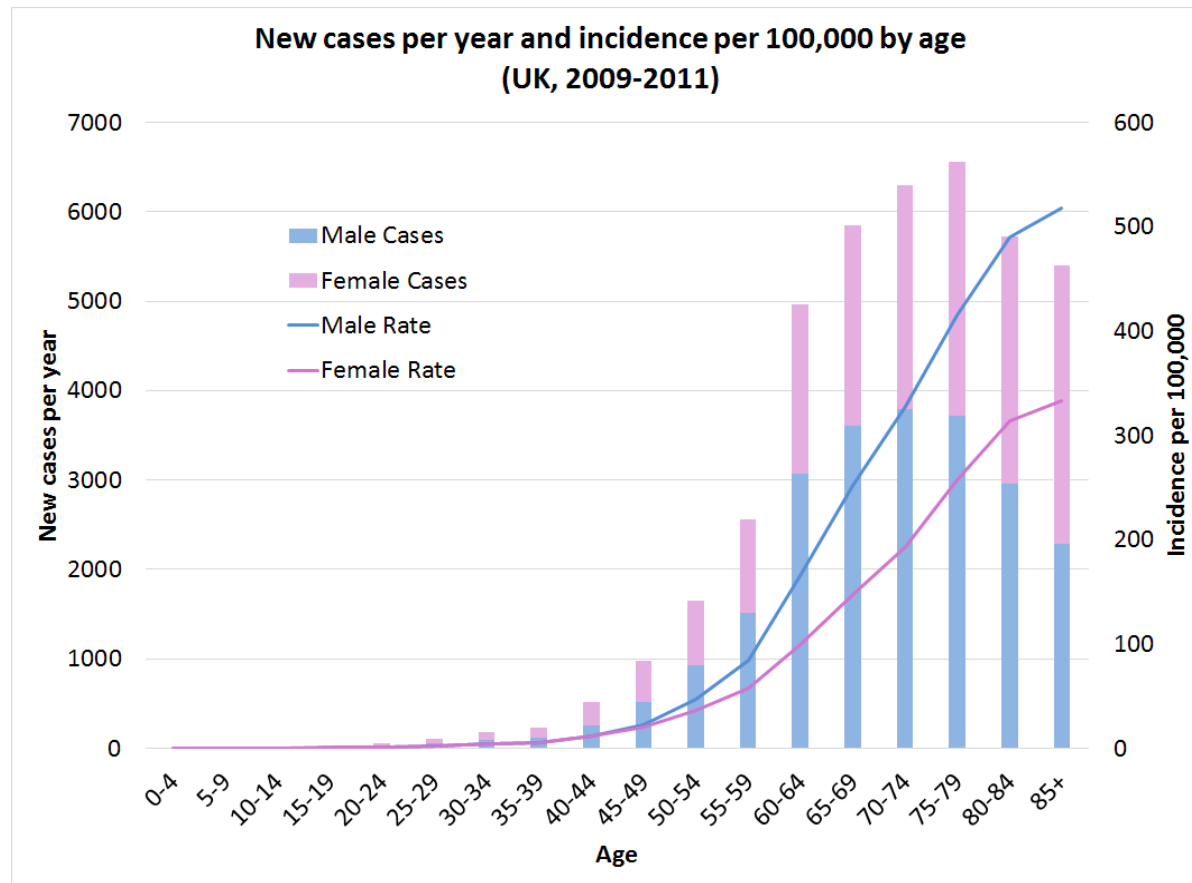
Risk Factors

- History, genes:
 - Family or personal history
 - Polyps, adenomas, cancers, FAP, HNPCC
- Chronic inflammation: ulcerative colitis, Crohn's disease
- Lifestyle: **obesity, sedentary, smoking**
- Diet:
 - risk: fat, red meat, alcohol, refined carbs
 - protective: fibre, antioxidants, NSAIDs



Age

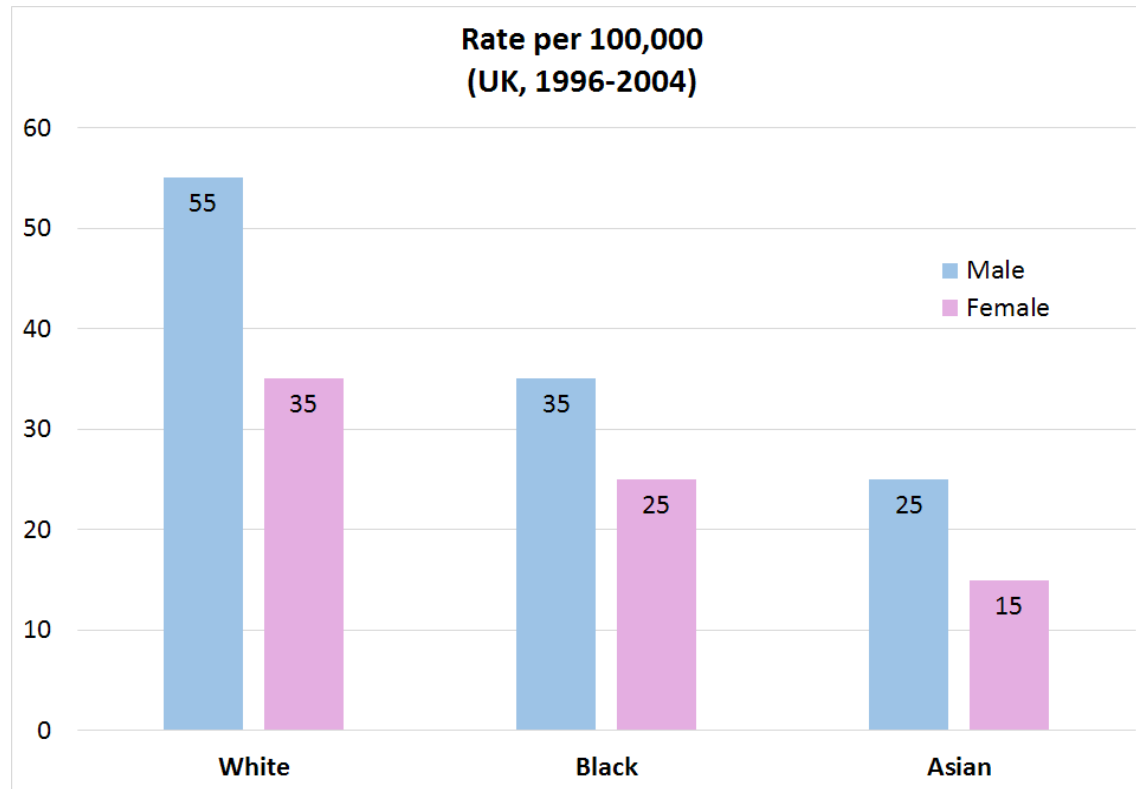
- Strongly related, 95% of cases are >50y



Data: [Cancer Research UK](#)

Ethnicity

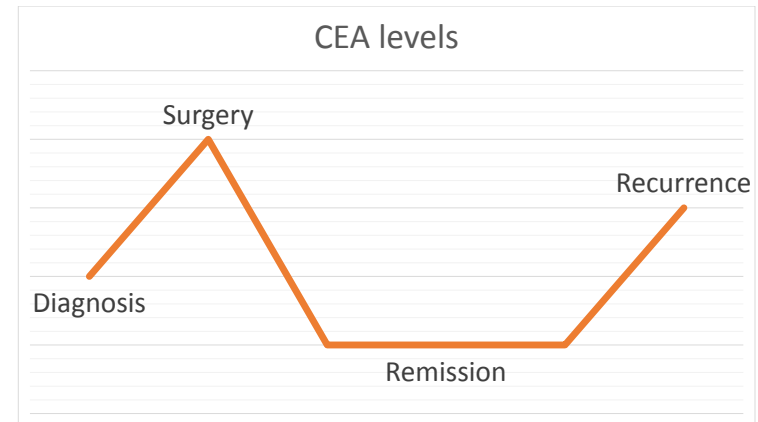
- Higher incidence in West than Africa/Asia
- Increasing incidence in Asia with Westernising diet



Data: [Cancer Research UK](#)

Labs

- Carcinoembryonic antigen (**CEA**)
 - **Serial** measurements for **follow-up**
 - **Rising = recurrence**
 - Not useful for primary Dx
- **Faecal occult blood**
 - Can detect in early stages
 - Populations screening, GP, hospital
- **Liver function tests (mets)**
- **Haemoglobin (blood loss)**



Histology

- Indicators of malignant change:
 - **large** size
 - **villous** architecture
 - severe **dysplasia**
- '**Signet ring**' cells (pictured →)
 - Glandular cells producing **mucin**
 - Mucin displaces **nucleus to edge**
 - Poorer prognosis



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Colonoscopy

- 'Gold-standard' diagnosis
- 70% of carcinomas in **distal 1/3 of colon**, easily visualised
- Can **biopsy** and **remove** polyps



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CT Colonography

- 'Virtual colonoscopy'
- Assess size, spread, metastasis

Video: YouTube

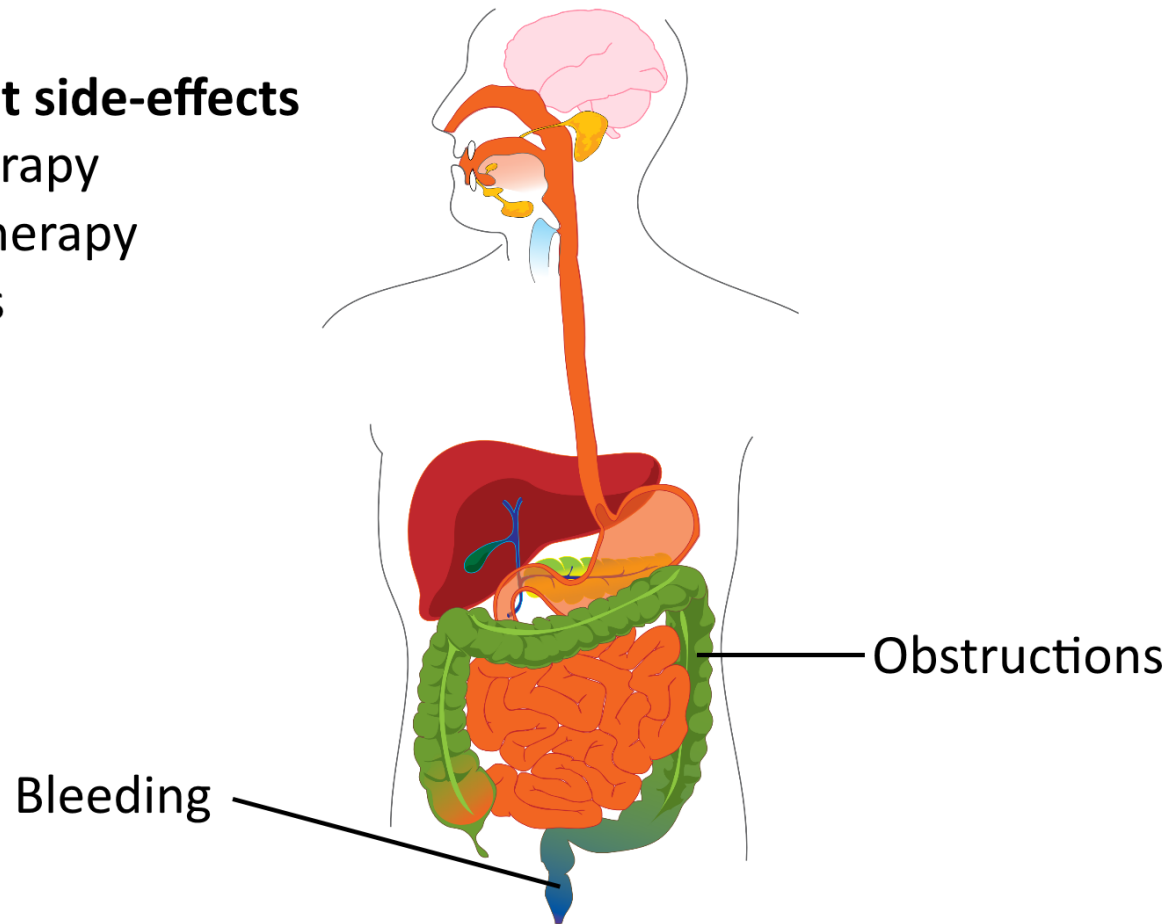
Imaging

- **Ultrasound**
 - staging
- **PET**
 - suspicious small lesions not confirmed by CT
- **MRI**
 - staging, suspicious small lesions
- **Double-contrast barium enema**
 - when CT or colonoscopy not possible

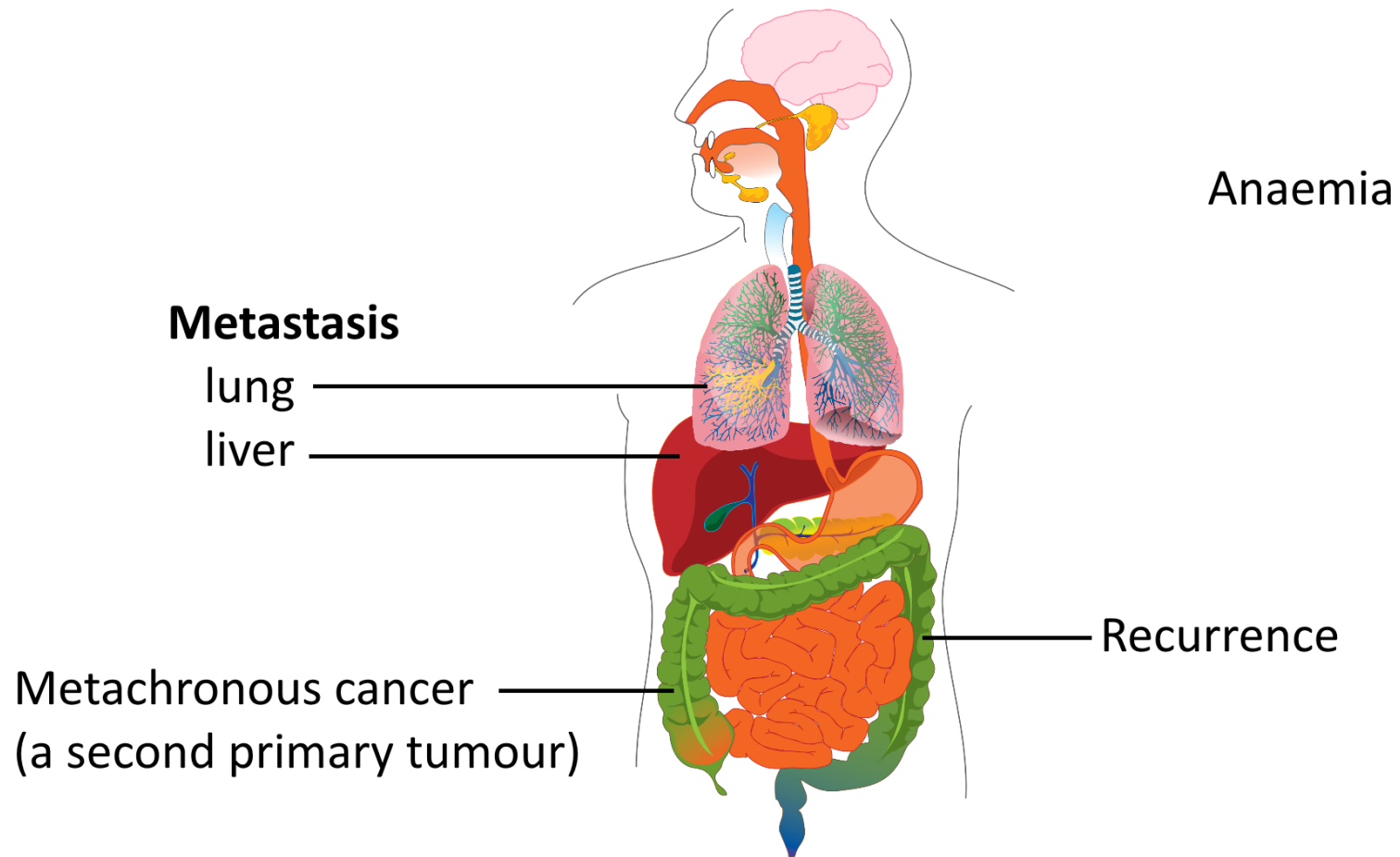
Acute Complications

Treatment side-effects

radiotherapy
chemotherapy
biologics

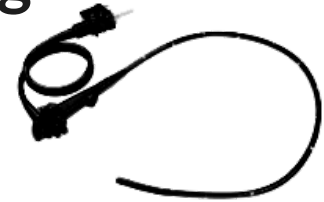


Chronic Complications



Treated

- Potential for early **detection with screening**
- **Removal of adenomas during endoscopy**
- Most have surgery, <50% survive 5yr
 - variable type, depending site
 - most: **resection with restorative anastomosis**

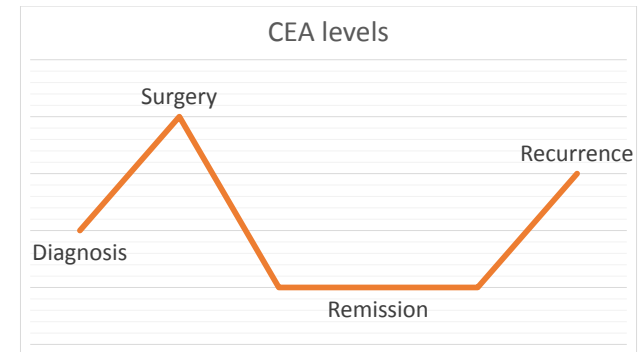


- Adjuvant **chemotherapy**
- **Biologics:**
 - *Bevacizumab*: anti-VEGF
 - *Cetuximab*: anti-EGFR, KRAS mutation resistance



Follow-Up

- Regular **colonoscopy**
- **Annual CT** for liver metastases
- Serial **CEA**, rise = recurrence



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Untreated

