# Colorectal Cancer

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# INTRODUCTION

- Colorectal cancer(CRC) refers to cancers of the colon and rectum
- The third most common malignancy overall
- The most common gastrointestinal cancer
- Adenocarcinoma is the most common type of colorectal cancer
- Despite evidence that 5-year survival is 90% when CRC is diagnosed at an early stage, less than 40% of cases are diagnosed when the cancer is still localized

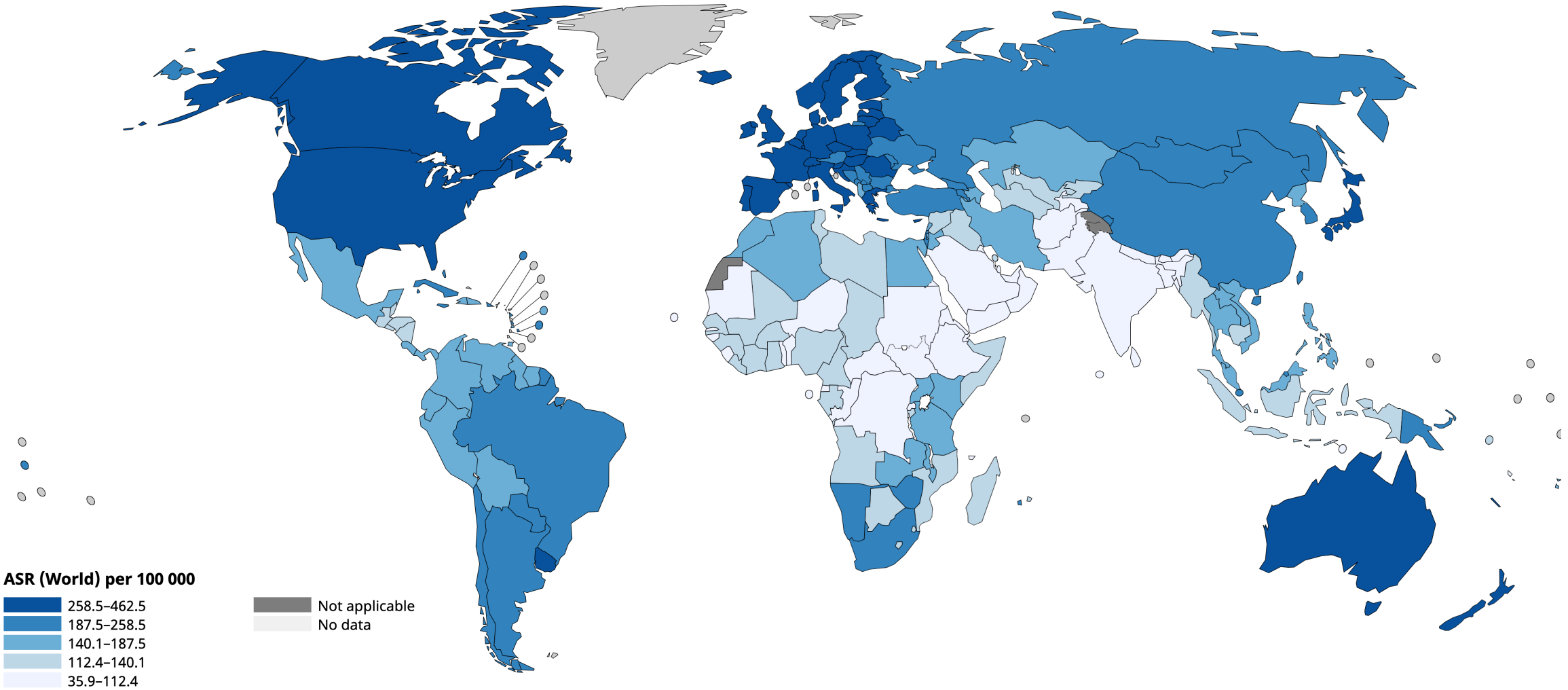
Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. Transl Oncol. 2021;14:101174
Wang S et al. Global, regional, and national lifetime risks of developing and dying from gastrointestinal cancers in 185 countries: a population-based systematic analysis of GLOBOCAN. *Lancet Gastroenterol Hepatol*. 2024;9(3):229-237.

# EPIDEMIOLOGY

- CRC is the third most commonly diagnosed cancer in males and the second in females, according to the World Health Organization GLOBOCAN database
- Incidence and mortality are substantially higher in males than in females
- Incidence increases with age, and the median age of diagnosis is about 70 years
- The incidence and mortality rates of CRC exhibit substantial geographical variation, largely influenced by lifestyle and environmental factors associated with a Western lifestyle, such as diet, obesity, and physical inactivity

# Age-Standardized Rate (World) per 100 000, Incidence, Both sexes, in 2022

All cancers



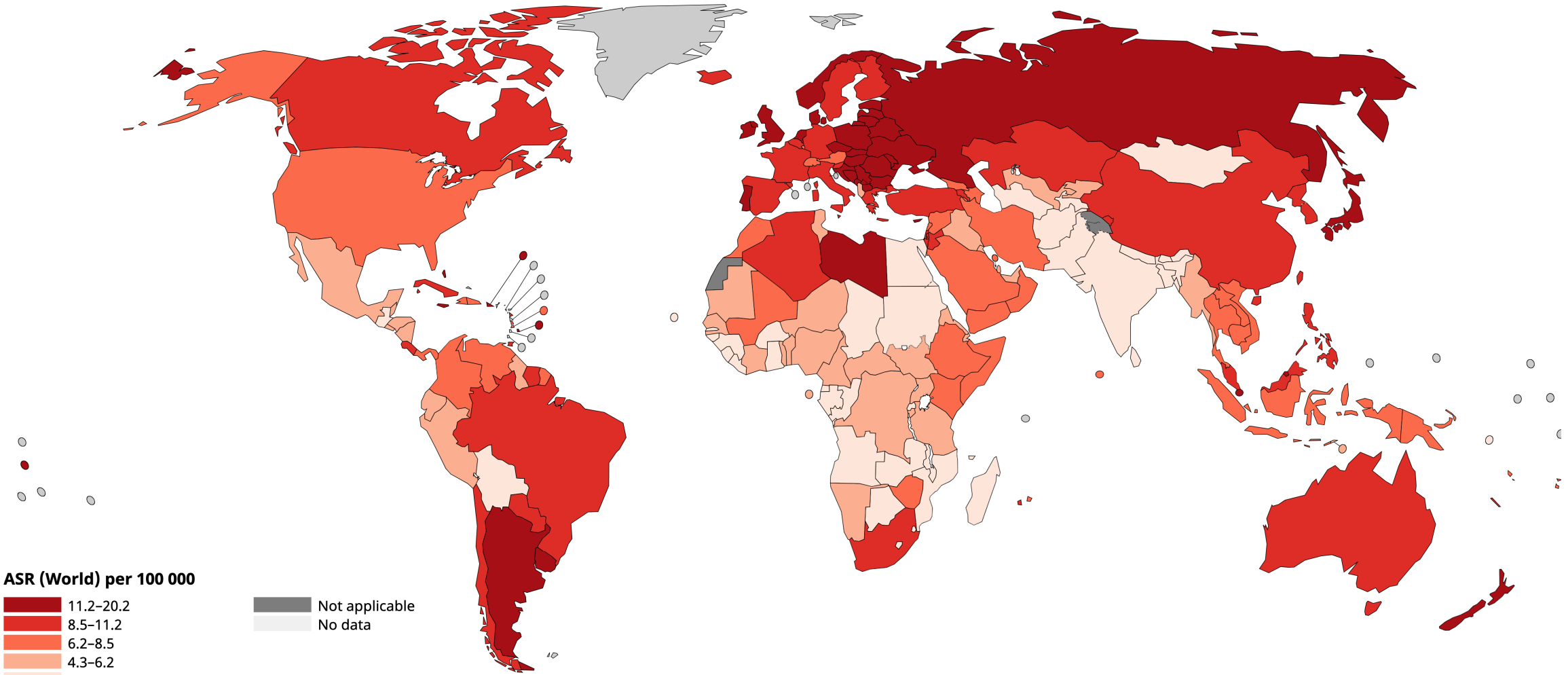



**Cancer TODAY | IARC**
https://gco.iarc.who.int/today
Data version: Globocan 2022 (version 1.1) - 08.02.2024


International Agency for Research on Cancer
World Health Organization

# Age-Standardized Rate (World) per 100 000, Mortality, Both sexes, in 2022

Colorectum



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International Agency for Research on Cancer
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# RISK FACTORS FOR CRC

- In epidemiological studies, male sex and increasing age have consistently shown strong associations with disease incidence.

- Both hereditary and environmental risk factors play a part in the development of colorectal cancer

# RISK FACTORS FOR CRC

- **Non-Modifiable Risk Factors for Colorectal Cancer (CRC)**
- **Age**
  - Risk increases with age, especially after 50 years.
  - Over 90% of CRC cases occur in individuals aged 50+.
- **Gender**
  - CRC risk higher in men (23.4/100,000) vs. women (16.2/100,000).
  - Male-to-female incidence ratio: 1.4 in high-income and 1.2 in low-income countries

Roshandel G, et al. Colorectal Cancer: Epidemiology, Risk Factors, and Prevention. Cancers (Basel). 2024 Apr 17;16(8):1530.

# RISK FACTORS FOR CRC

- **Non-Modifiable Risk Factors for Colorectal Cancer (CRC)**
- **Genetic Predisposition**
- **Hereditary CRC syndromes**:
  - *Familial Adenomatous Polyposis* (APC mutations).
  - *Lynch Syndrome* (DNA mismatch repair mutations).
- Account for ~5% of CRC cases.
- **Family History**
  - Higher CRC risk in individuals with CRC or adenomatous polyp history in first-degree relatives.
  - Relative risk (RR): 2–4.

Roshandel G, et al. Colorectal Cancer: Epidemiology, Risk Factors, and Prevention. Cancers (Basel). 2024 Apr 17;16(8):1530.

# RISK FACTORS FOR CRC

- **Non-Modifiable Risk Factors for Colorectal Cancer (CRC)**
- **Abdominopelvic Radiation**
  - Cancer survivors with radiation therapy (e.g., prostate cancer) have increased CRC risk.
  - Early screening is recommended for these individuals.
- **Personal History of Diseases**
- **High-risk conditions**:
  - Inflammatory bowel disease (ulcerative colitis, Crohn's disease).
  - Diabetes and insulin resistance stimulate tumor growth.
  - Cystic fibrosis, renal transplantation, coronary heart disease.

Roshandel G, et al. Colorectal Cancer: Epidemiology, Risk Factors, and Prevention. Cancers (Basel). 2024 Apr 17;16(8):1530.

- **Gut Microbiota**
  - Gut microbiome changes and reduced diversity linked to CRC.
  - Dysbiosis and specific microbial species influence CRC risk.
  - *Fusobacterium nucleatum*, *Streptococcus gallolyticus* (formerly known as *S. bovis*)
- **Implications**:
  - Potential for microbiome modulation in CRC prevention.
  - FMT is being explored in patients with MSIH or dMMR mCRC initially resistant to check point inhibitors

Roshandel G, et al. Colorectal Cancer: Epidemiology, Risk Factors, and Prevention. Cancers (Basel). 2024 Apr 17;16(8):1530.

- **Modifiable Risk Factors for Colorectal Cancer (CRC)**
- **Alcohol Consumption**
  - Positive association with CRC risk, especially in heavy drinkers (≥50 g/day).
  - Risk increase partly linked to DNA methylation affecting gene expression.
- **Smoking**
  - Consistent association with CRC risk due to exposure to carcinogens (e.g., nitrosamines, benzene).
  - Long-term exposure causes genetic changes in colorectal cells.
  - Risk decreases after smoking cessation

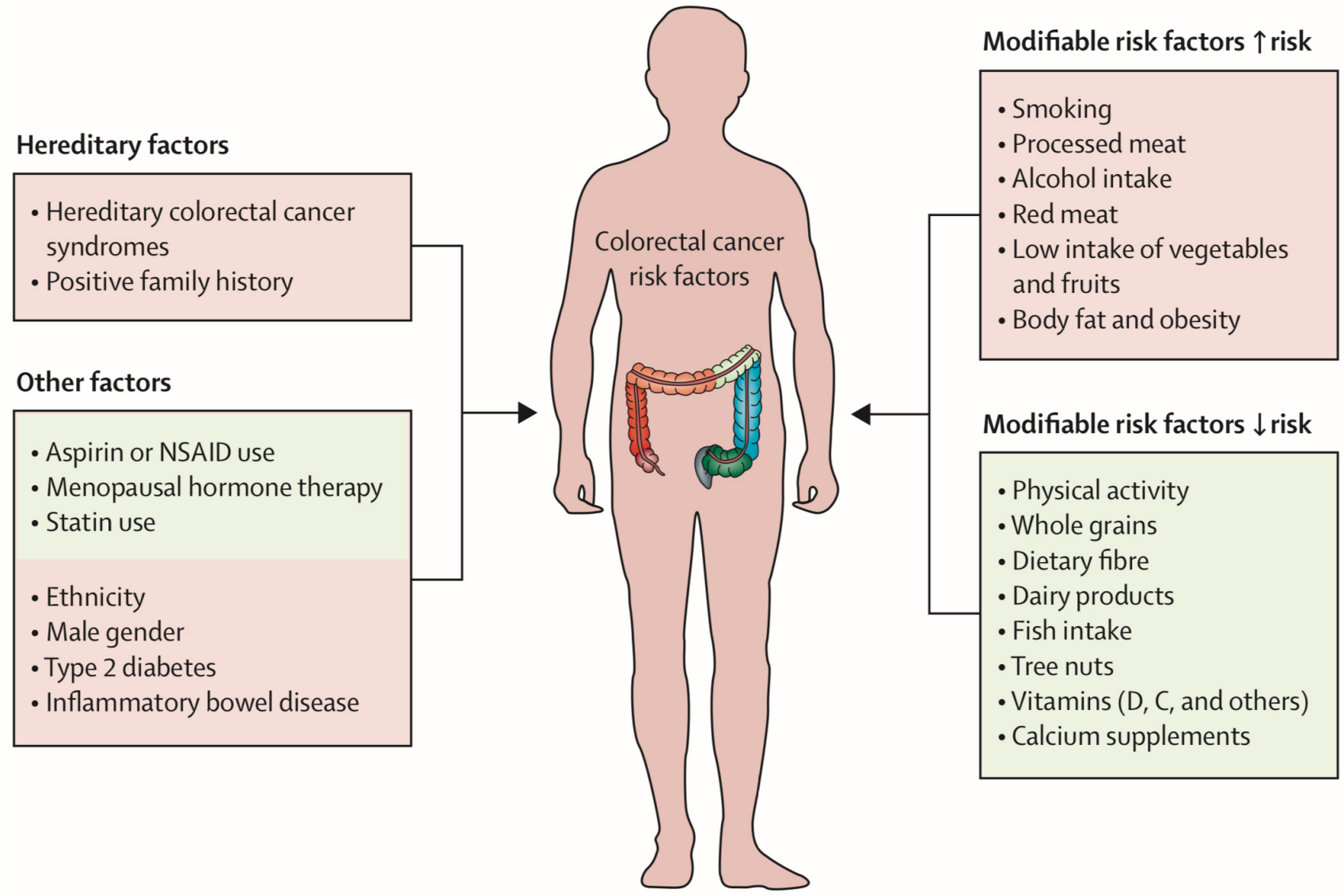
Roshandel G, et al. Colorectal Cancer: Epidemiology, Risk Factors, and Prevention. Cancers (Basel). 2024 Apr 17;16(8):1530.

- **Obesity**
- Direct link between obesity and CRC via:
  - Pro-inflammatory cytokines (e.g., IL-6, TNF-α).
  - Insulin/IGF promoting tumor cell growth.
  - Increased bile acid levels causing inflammation.
- **Sedentary Lifestyle**
  - Low physical activity increases CRC risk; active individuals have a 30–50% reduced risk.
  - Mechanisms: higher obesity rates, glucose levels, insulin resistance, and abnormal intestinal peristalsis.

Roshandel G, et al. Colorectal Cancer: Epidemiology, Risk Factors, and Prevention. Cancers (Basel). 2024 Apr 17;16(8):1530.

- **Unhealthy Diet**
- High intake of **red/processed meat** and **fat** linked to CRC:
  - 100g/day red meat → 10–16% risk increase.
  - 50g/day processed meat → 16–22% risk increase.
  - Cooking at high temperatures produces carcinogens (e.g., heterocyclic amines).
- Mixed evidence on dietary fat and CRC.
- **Psychological Stress**
  - Evidence suggests stress (e.g., work stress) may increase CRC risk (36% in some studies).
  - Mechanism: Overactivation of hypothalamic-pituitary-adrenal axis → immune impairment, abnormal metabolism, and cancer.
  - More research needed due to inconsistent findings.

Roshandel G, et al. Colorectal Cancer: Epidemiology, Risk Factors, and Prevention. Cancers (Basel). 2024 Apr 17;16(8):1530.




Dekker E, et al . Colorectal cancer. The Lancet. 2019 Oct 19;394(10207):1467-80.

# EARLY ONSET COLORECTAL CANCER

- Early onset colorectal cancer (EOCRC) refers to the diagnosis of CRC in people under the age of 50 years.
- EOCRC now accounts for approximately 10% of all new diagnoses of this cancer, and
- An accompanying increase in CRC–related mortality during the past decade has also been observed among younger patients
- In the next 10 years, it is estimated that 25% of rectal cancers and 10 to 12% of colon cancers will be diagnosed in persons younger than 50 years of age

Sinicrope FA. Increasing incidence of early-onset colorectal cancer. New England Journal of Medicine. 2022 Apr 21;386(16):1547-58.

# EARLY ONSET COLORECTAL CANCER

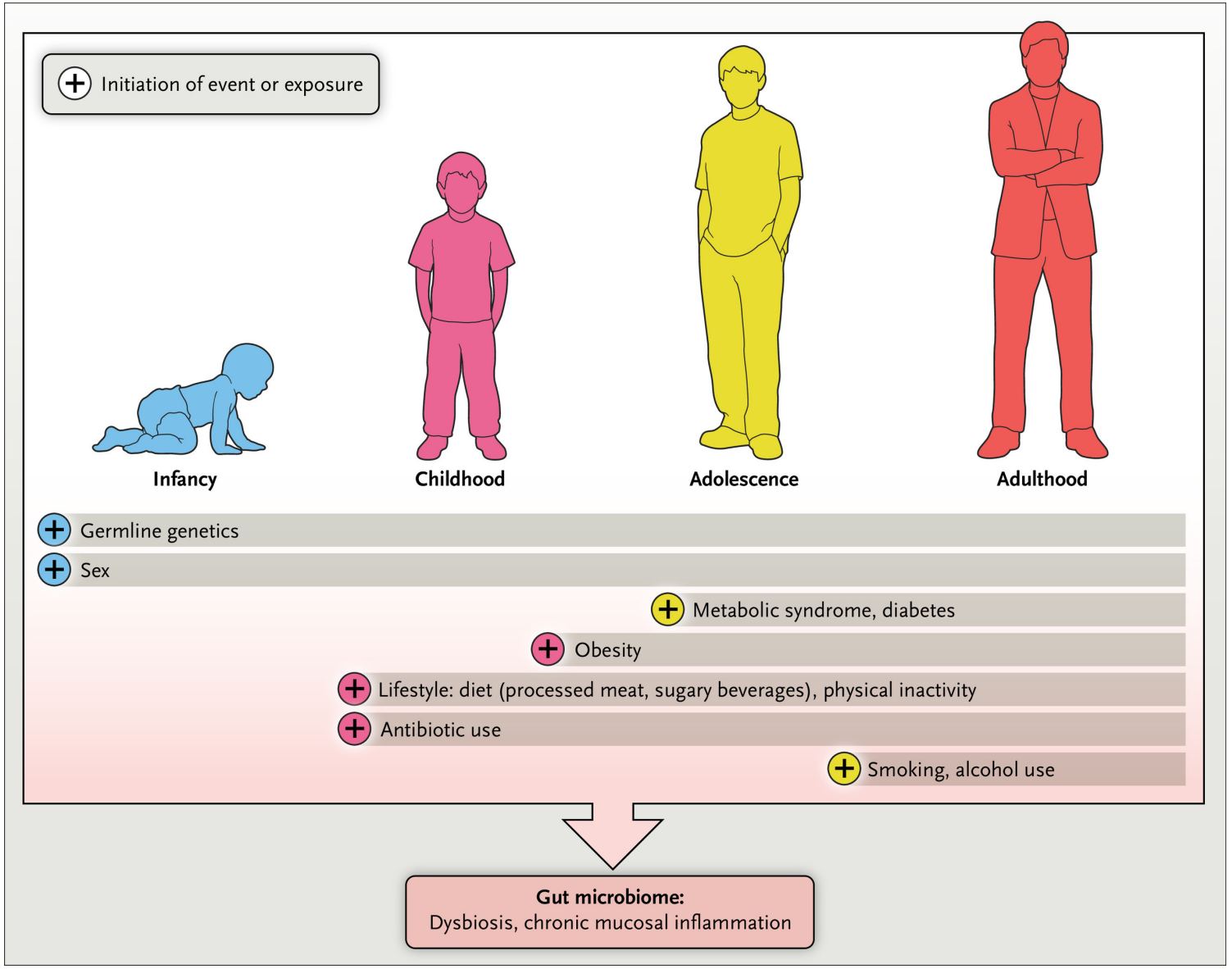
- **Clinical Phenotype**
- Clinical features of EOCRC differ from those of later-onset disease
- EOCRC are most commonly detected in the rectum, followed by the distal colon (> 70% of early-onset colorectal cancers are in the left colon at presentationa)
- Later-onset colorectal cancers (those diagnosed in patients ≥50 years of age) occur at similar frequencies in the proximal colon and distal colorectum.
- Early studies, suggested higher rates of poorly differentiated cancers and those with signet-ring cells among patients with EOCRC (particularly among patients <40 years of age) than among patients with later- onset disease

Sinicrope FA. Increasing incidence of early-onset colorectal cancer. New England Journal of Medicine. 2022 Apr 21;386(16):1547-58.

**Figure .**

**Factors Influencing the Risk of Colorectal Cancer**

Germline genetics, sex, diet and other lifestyle exposures, and health conditions interact with the gut microbiome over a patient's lifetime and influence the risk of colorectal cancer

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# Pathogenesis of CRC

- CRC is caused by the colon's aberrant proliferation of glandular epithelial cells.
- A complex multistep process involving genetic and epigenetic alterations that leads to transformation of normal colonic epithelium to malignant tumors
- Three principal types of CRC: Sporadic, hereditary, and colitis-associated
- These rapidly developing cells form a benign adenoma which can advance to cancer and metastasize via several distinct pathways

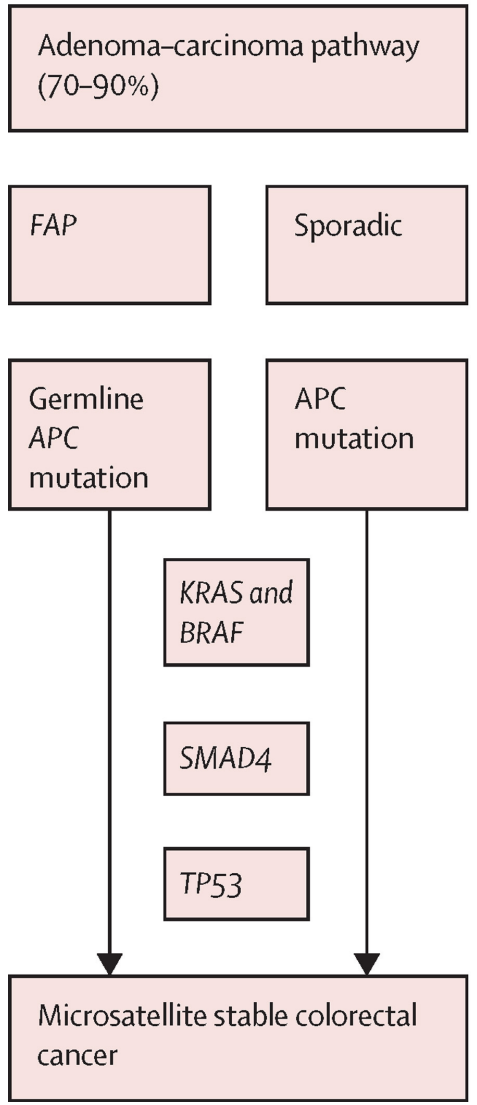
Dekker E, et al . Colorectal cancer. The Lancet. 2019 Oct 19;394(10207):1467-80.
Hossain, M.S.; et al. Colorectal Cancer: A Review of Carcinogenesis, Global Epidemiology, Current Challenges, Risk Factors, Preventive and Treatment Strategies. Cancers2022,14,1732.

# Pathogenesis of CRC

- There are two major  pathways:
  - the traditional adenoma–carcinoma pathway (also referred to as the chromosomal instability sequence) leading to 70–90% of colorectal cancers, and
  - the serrated neoplasia pathway (10–20% of colorectal cancers)
- These pathways represent distinct multiple genetic and epigenetic events in a rather sequential order

Dekker E, et al . Colorectal cancer. The Lancet. 2019 Oct 19;394(10207):1467-80.
Hossain, M.S.; et al. Colorectal Cancer: A Review of Carcinogenesis, Global Epidemiology, Current Challenges, Risk Factors, Preventive and Treatment Strategies. Cancers2022,14,1732.

- **Chromosomal instability phenotypes** typically develop following genomic events initiated by an APC mutation, followed by RAS activation or function loss of TP53.

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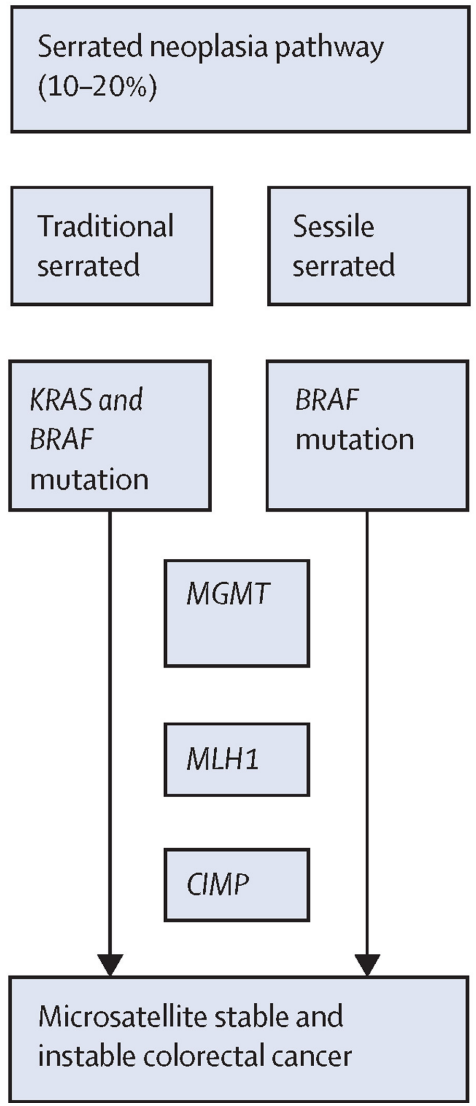
Hossain, M.S.; et al. Colorectal Cancer: A Review of Carcinogenesis, Global Epidemiology, Current Challenges, Risk Factors, Preventive and Treatment Strategies. Cancers2022,14,1732.

- The **serrated neoplasia pathway** is associated with RAS and RAF mutations, and epigenetic instability, characterised by the CpG island methylation phenotype, leading to microsatellite stable and instable cancers

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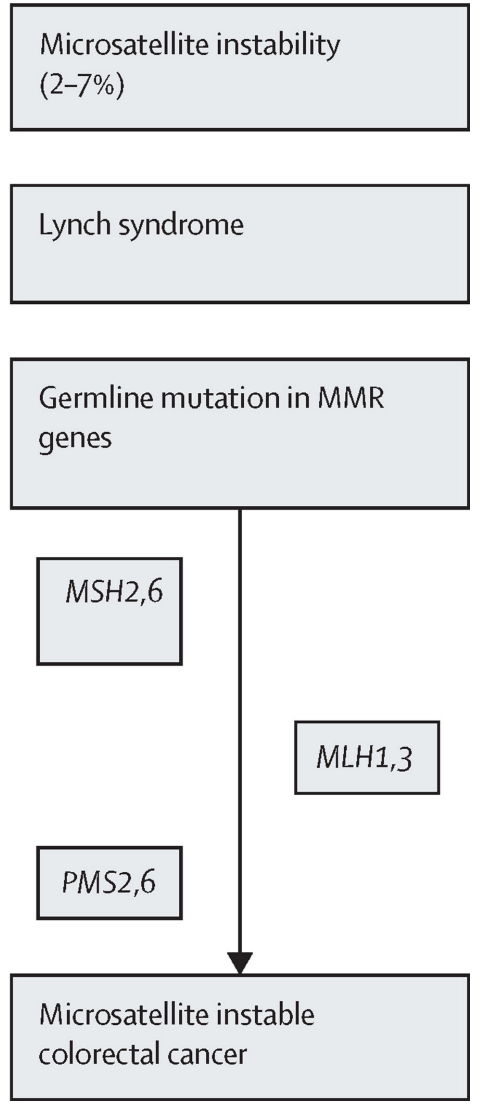
Hossain, M.S.; et al. Colorectal Cancer: A Review of Carcinogenesis, Global Epidemiology, Current Challenges, Risk Factors, Preventive and Treatment Strategies. Cancers2022,14,1732.

- **Microsatellite instability (MSI),** which is caused by the disruption of DNA repair genes.
- MSI can result in uneven replication of repetitive DNA sequences in short, noncoding regions (microsatellites) and increased susceptibility to additional genetic mutations
- can occur in both adenomatous and serrated polyps and is associated with germline mutations in DNA mismatch repair genes




Dekker E, et al . Colorectal cancer. The Lancet. 2019 Oct 19;394(10207):1467-80.
Simon K. Colorectal cancer development and advances in screening. Clin Interv Aging. 2016 Jul 19;11:967-76
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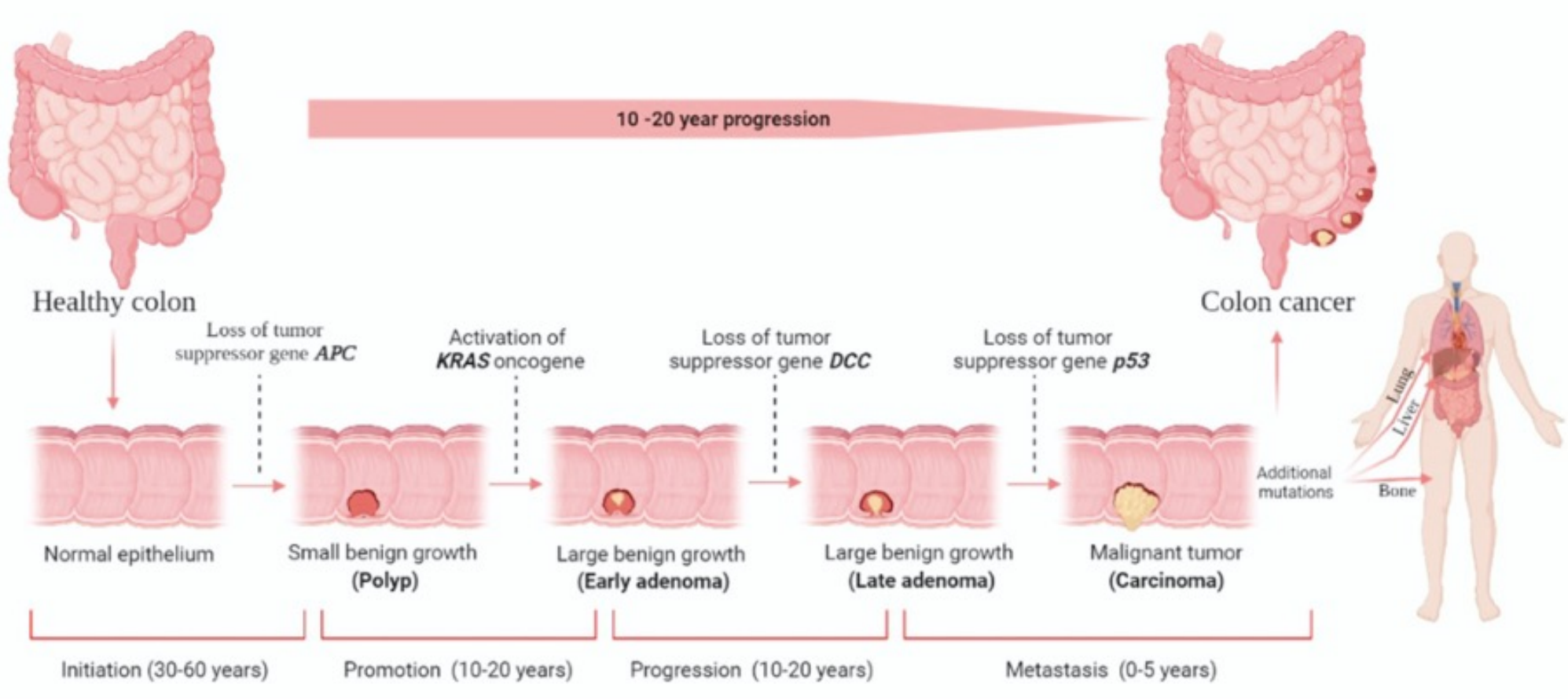
# Colorectal cancer (CRC) stages and development




Hossain, M.S.; et al. Colorectal Cancer: A Review of Carcinogenesis, Global Epidemiology, Current Challenges, Risk Factors, Preventive and Treatment Strategies. Cancers2022,14,1732.

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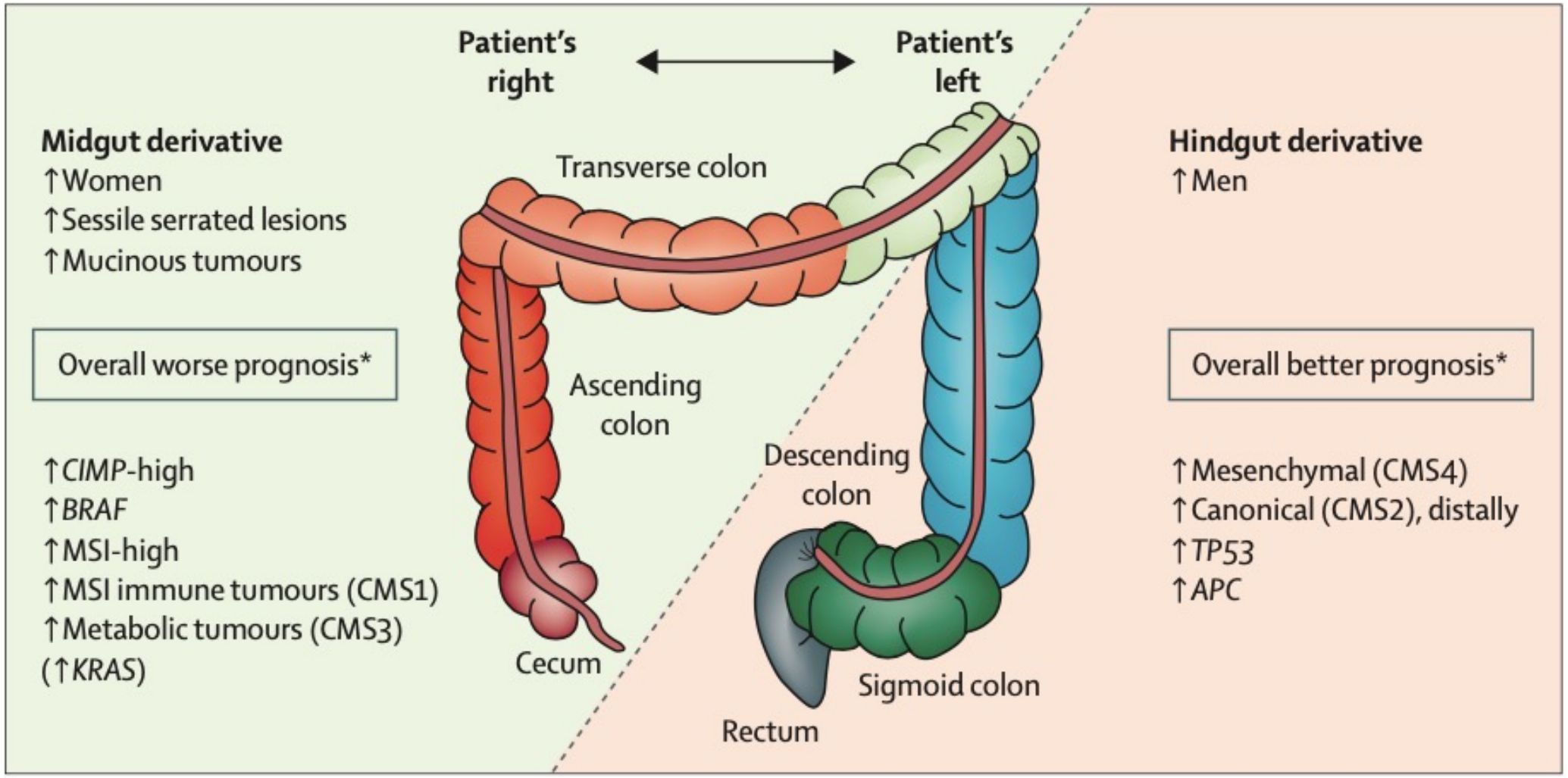
# Left-sided Versus Right-sided Disease

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# Consensus Molecular Subtypes (CMS)

- Prognostic classification beyond standard histology has been characterised by the creation of consensus molecular subtypes (CMSs)
- Derived from transcriptome-wide analysis of CRC tumors.
- Incorporates tumor microenvironment, metabolic signatures, genomic, and epigenomic, molecular aberrations, and other carcinogenesis pathways

Cathy Eng et al Colorectal cancer, Lancet. 2024;404:294-310.

- Four subtypes identified:
  - **CMS1:** Microsatellite instability-immune (MSI-immune).
  - **CMS2:** Canonical (WNT/MYC activation).
  - **CMS3:** Metabolic deregulation.
  - **CMS4:** Mesenchymal (stromal invasion, angiogenesis).
- **Prognostic Role:** linked to overall survival (OS) in metastatic CRC
- Recent data emphasize CMS1 benefits from immune checkpoint inhibitors (ICIs).

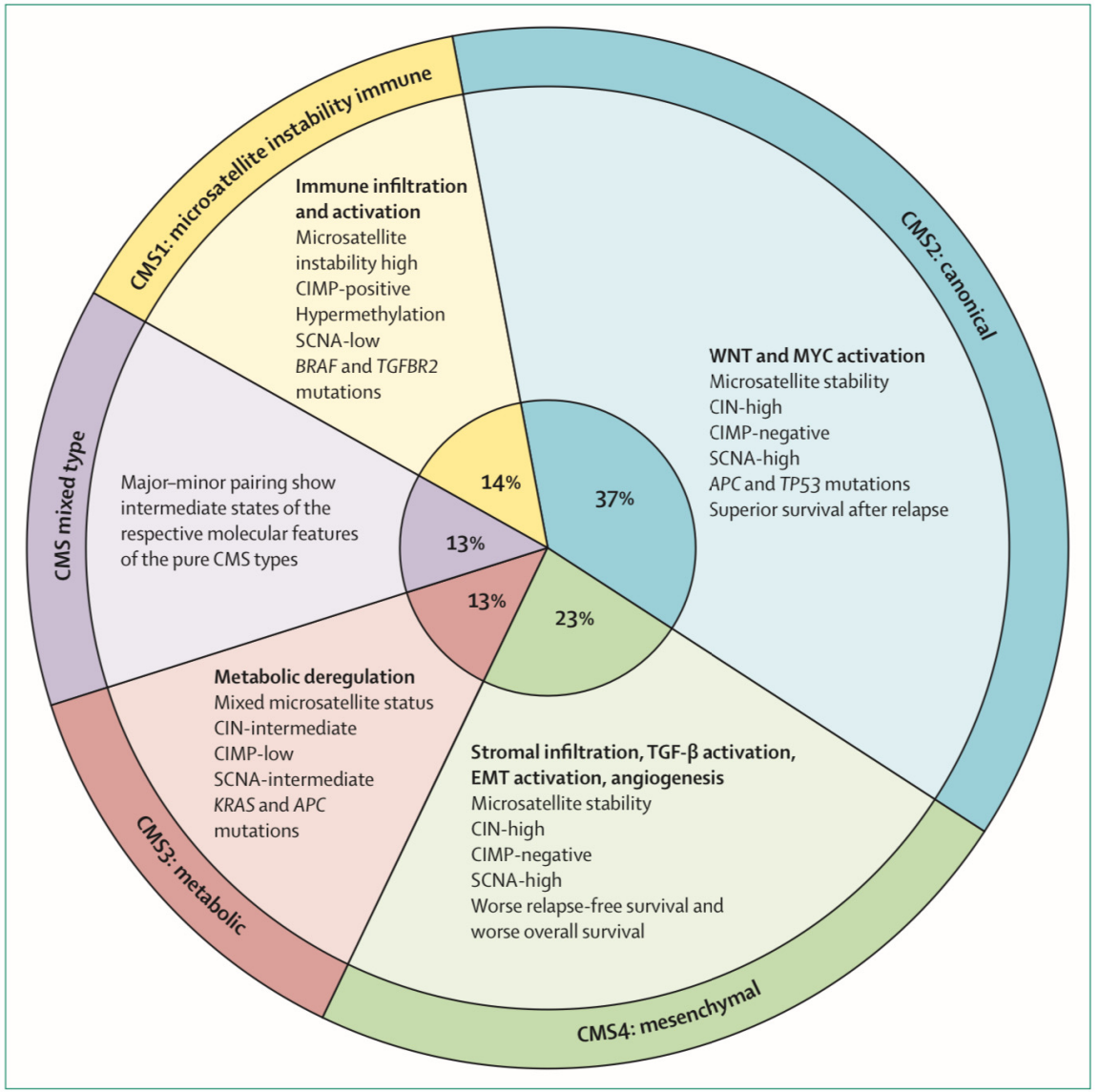



***Figure 1:*** **CMS of colorectal cancer**
CIMP=CpG island methylator phenotype. CMS=consensus molecular subtypes. CIN=chromosomal instability.

Cathy Eng et al Colorectal cancer, Lancet. 2024;404:294-310.

- **Immunescore in CRC Prognosis**
- Immune score quantifies CD3 and CD8-positive T cells in tumor center and margin
- Higher immunoscore correlates with lower recurrence risk.
- Current Challenges:
  - Limited adoption of CMS and immunoscore in clinical settings.

Cathy Eng et al Colorectal cancer, Lancet. 2024;404:294-310.

# DIAGNOSIS
## Clinical presentation

- Largely asymptomatic  disease until  it reaches an advanced stage
- Typical signs and symptoms include:
  - haematochezia or melena,
  - abdominal pain,
  - otherwise unexplained iron deficiency anaemia, or
  - a change in bowel habits, or a combination thereof
- Less common presenting symptoms include:
  - abdominal distention,
  - nausea, or
  - vomiting, or a combination of these, which could indicate obstruction.
- Iron deficiency anaemia from unrecognised blood loss is common in right sided colorectal cancers

Cathy Eng et al Colorectal cancer, Lancet. 2024;404:294-310.

# Diagnosis

- Diagnosis of CRC is made by histological examination of a biopsy that is usually obtained through a lower GI endoscopy or from a surgical specimen
- A colonoscopy is the most accurate diagnostic test to localise and biopsy lesions, detect synchronous neoplasms, and extract polyps
- Synchronous colorectal cancers, defined as two or more distinct primary tumours diagnosed within 6 months, separated by normal bowel occurs in 3–5% of patients, raising the suspicion for Lynch syndrome or MUTYH associated polyposis

Cathy Eng et al Colorectal cancer, Lancet. 2024;404:294-310.

- **Imaging**
- Imaging methods are mostly used for accurate locoregional and distant staging
- MRI
  - In rectal cancer: loco-regional staging to delineate the tumor, mesorectal fascia, and the circumferential resection margin
  - Guides further treatment decisions
  - MRI is also used for further evaluation of liver lesions
- CT
  - CT chest, abdomen, and pelvis for complete staging before surgical resection or initiation of treatment
  - CT colonography is used as a complementary imaging method for the diagnosis of polyps and colorectal cancer (eg, after incomplete or inadequate colonoscopy)

- **Laboratory**
- **Complete blood count (CBC)**,
- All guidelines recommend checking **carcinoembryonic antigen (CEA)** concentrations at diagnosis
- Elevated CEA is associated with a worse prognosis
- Postoperative monitoring: persistent elevation may indicate residual disease.
- Normalization suggests effective treatment

- **Pathology**
- Histology is still the basis for pathological staging and subsequent management.
- Besides the classic TNM staging, histological subtyping, grading, and histological assessment of lymphatic, perineural, and venous invasion
- Mismatch–repair (MMR) testing and immunescore is increasingly being used
- Universal MMR testing
  - Identification of Lynch syndrome
  - Therapy implications: adjuvant fluoropyrimidine-based therapy and to identify patients with metastatic colorectal cancer who would benefit from immunotherapy.

# Natural History and Staging

- CRCs begin as intramucosal epithelial lesions, usually arising in adenomatous polyps or glands.
- As cancers grow they become invasive, penetrate the muscularis mucosae, and invade lymphatic and vascular channels to involve regional lymph nodes, adjacent structures, and distant sites
- Most often have long periods of silent growth before producing bowel symptoms
- it can take approximately 17 years for a large benign tumor to evolve to advanced cancer but less than 2 years for cells within that cancer to acquire the ability to metastasize
- Patterns of spread depend on the anatomy of the individual bowel segment as well as its lymph and blood supplies

Beaugerie L et. al.: Risk of colorectal high grade dysplasia and cancer in a prospective observational cohort of pateints with inflammatory bowel disease. Gastroenterology 2013; 145: pp. 166-175

- Cancers of the rectum advance locally by progressive penetration of the bowel wall
- Extension of the primary tumor intramurally and parallel to the long axis of the bowel most often is limited
- Lymphatic and hematogenous spread is unusual before penetration of the muscularis mucosae
- Poorly differentiated tumors however can metastasize via lymphatics or hematogenously before completely penetrating the bowel
- Because the rectum is relatively immobile and lacks a serosal covering, rectal cancers tend to spread contiguously to progressively involve local structures
- The lower third of the rectum (dual blood supply)
  - via the superior hemorrhoidal vein and portal system to the liver or
  - middle hemorrhoidal vein and inferior vena cava to the lungs.
- Upper and middle thirds of the rectum (veins drain into the portal system)
  - Via portal system to the liver

Sleisenger and Fordtran's Gastroenterlogy and Liver Disease , Elsevier 2021

- Colon cancers can invade transmurally and involve regional lymphatics and then distant lymph nodes
- Lymphatic drainage generally parallels the arterial supply to a given bowel segment.
- The liver is the most common site of hematogenous spread (via the portal venous system) from colon tumors, and pulmonary metastases from colon cancer usually result from hepatic metastases

# TNM Staging

- The American Joint Committee on Cancer's (AJCC) TNM classification for CRC classifies the extent of the primary tumor (T), the status of regional lymph nodes (N), and the presence or absence of distant metastases (M)

| Stage | Criteria |
|---|---|
| 0 | Carcinoma in-situ: intraepithelial tumor or invasion of the lamina propria (Tis N0 M0) |
| I | Tumor invades submucosa (T1 N0 M0) [Dukes A] |
| | Tumor invades muscularis propria (T2 N0 M0) [Dukes A] |
| II | Tumor invades through the muscularis propria into pericolorectal tissues (T3 N0 M0) [Dukes B] |
| | Tumor penetrates the surface of the visceral peritoneum (T4a N0 M0) [Dukes B] |
| | Tumor directly invades or is adherent to other organs and structures (T4b N0 M0) [Dukes B] |

# TNM Staging

| Stage | Criteria |
|---|---|
| III | **Any degree of bowel wall penetration with regional lymph node metastasis** |
| | N1: metastasis in 1-3 regional lymph nodes |
| | N1a: metastasis in 1 regional lymph node |
| | N1b: metastasis in 2-3 regional lymph nodes |
| | N1c: tumor deposit(s) in the subserosa, mesentery, or non- peritonealized pericolic or perirectal tissues without regional nodal metastases |
| | N2: metastasis in ≥4 regional lymph nodes |
| | N2a: metastasis in 4-6 regional lymph nodes |
| | N2b: metastasis in 7 or more regional lymph nodes |
| | Any T N1 M0 [Dukes C] |
| | Any T N2 M0 [Dukes C] |

# TNM Staging

| Stage | Criteria |
|---|---|
| IV | **Any invasion of the bowel wall with or without lymph node metastasis, but with evidence of distant metastasis** |
| | Any T Any N M1a: metastasis confined to 1 organ or site (liver, lung, ovary, non-regional node) |
| | Any T Any N M1b: metastasis in more than 1 organ/site or the peritoneum |

# Management

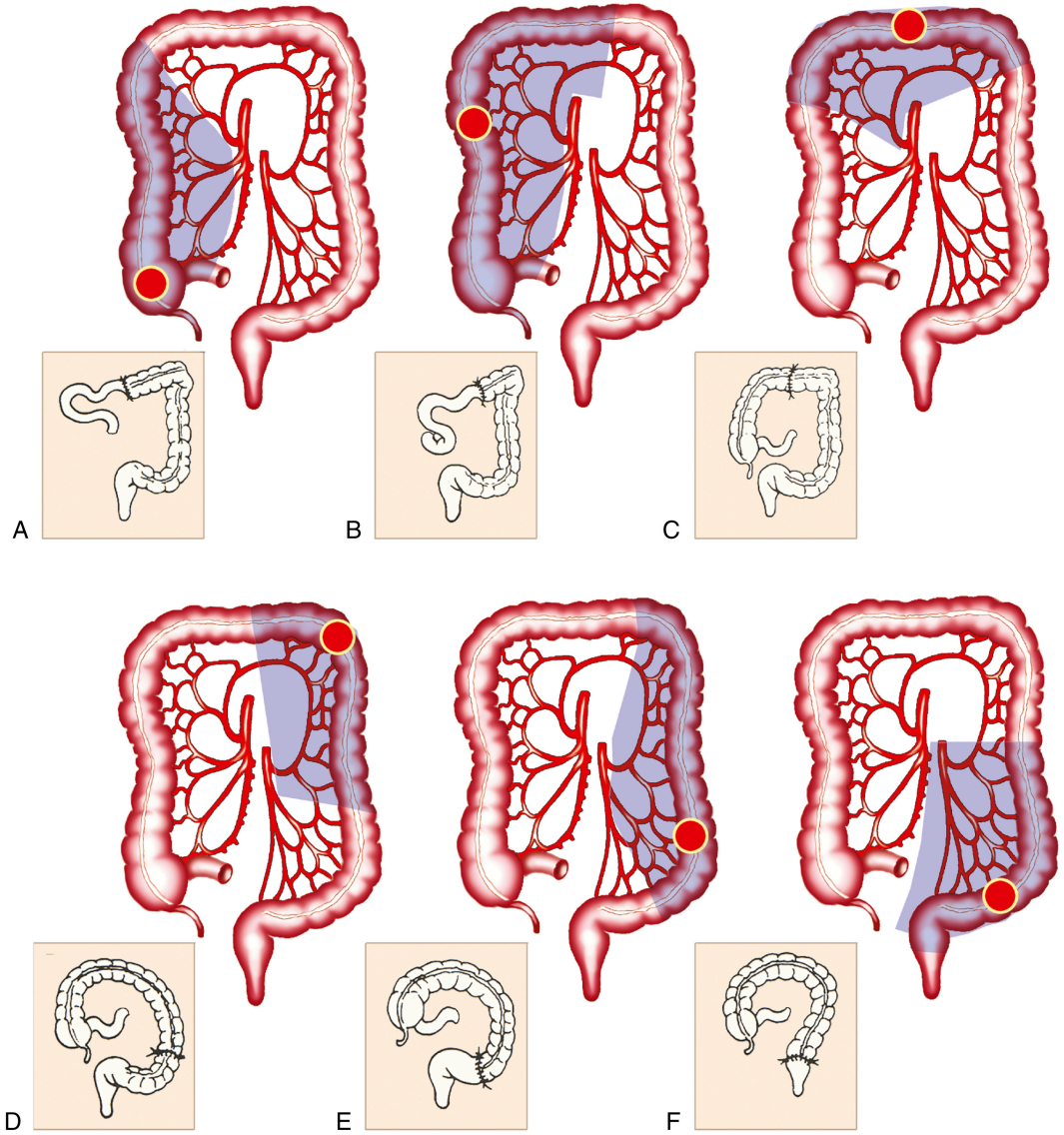
- **Endoscopic management**
- Some early cancers are amenable to local treatment only.
- Malignant polyps can be resected endoscopically in an en-bloc manner
- Depending on its size, appropriate endoscopic resection techniques for T1 cancers are
  - en-bloc endoscopic mucosal resection,
  - endoscopic submucosal dissection, and
  - endoscopic full-thickness resection
- These resection techniques require substantial technical skills and should be done in centres with such expertise.

Dekker E, et al . Colorectal cancer. The Lancet. 2019 Oct 19;394(10207):1467-80.

- **Surgical treatment**
- Complete mesocolic excision: sharp dissection along the embryological planes within the mesofascial interface
- Laparoscopy has become the standard technique worldwide, with proven short-term benefits in randomised trials and population studies
- Surgery for rectal cancer is more complex related to the accessibility and intricate anatomy of the pelvis
- Total mesorectal excision is the standard oncological approach, and extent of resection further depends on involvement of the sphincter complex and other surrounding structures

Dekker E, et al . Colorectal cancer. The Lancet. 2019 Oct 19;394(10207):1467-80.

**Figure:**
Surgical resection of colorectal cancer based on location of primary tumor



- CRC may present as an emergency with obstruction or perforation.
- In obstruction: decompressing colostomy or endoscopic stenting can be used to relieve colonic obstruction and subsequent staging, and patient status can be optimised
- Stenting should be a multi- disciplinary decision since it can limit the later use of anti-VEGF drugs due to risk of perforation

Dekker E, et al . Colorectal cancer. The Lancet. 2019 Oct 19;394(10207):1467-80.

- **Radiotherapy for rectal cancers**
- Preoperative Radiotherapy:
  - Proven to reduce local recurrence risk (better than postoperative radiotherapy)
  - Tailored based on MRI staging, reserved for intermediate-to-high-risk cancers
- Chemoradiotherapy is the most used therapy:
  - Standard dose: 45–50 gray in 25–28 fractions, with a fluoropyrimidine as a radiosensitizer.
  - Achieves downsizing in most patients; complete response in 15–20%
- Timing to Surgery:
  - Debate on optimal interval; common practice is 8–10 weeks

Dekker E, et al . Colorectal cancer. The Lancet. 2019 Oct 19;394(10207):1467-80.

## Rectal Preserving Treatment: Watch-and-Wait Strategy

- Concept:
  - Aims to omit radical surgery in patients with complete clinical response (cCR) after chemoradiotherapy.
  - Focuses on close surveillance instead of immediate surgery.
- Supported by data in selected patients with sustained cCR, but concerns remain about recurrence risks.
- Increasing demand for rectal-preserving options from patients.
- Challenges in conducting randomized trials due to patient preferences.
- If regrowth is detected in a timely way with an intensive surveillance programme with rectal examination, endoscopy, and MRI, salvage surgery is often achievable

Dekker E, et al . Colorectal cancer. The Lancet. 2019 Oct 19;394(10207):1467-80.

- **Systemic Treatment Overview**
- **Adjuvant Therapy**:
- Fluoropyrimidine-based chemotherapy improves survival in:
  - Stage III colon cancer.
  - High-risk stage II (e.g., T4, poorly differentiated).
- Addition of **oxaliplatin** (MOSAIC study): Standard in combination with fluoropyrimidines.
  - *Main side effect*: Cumulative sensory neuropathy.
- Stage II tumors: presence of **dMMR** is good prognosis; no benefit from adjuvant therapy.

- **Systemic Therapy for Metastatic Colorectal Cancer**
- **Treatment Goals**:
  - **Curative**: For oligo-metastases (resectable after therapy).
  - **Palliative**: For widespread metastatic disease.
- **Conversion Therapy**:
  - Down-sizing tumors to make them suitable for local treatment is increasingly used

- **Systemic Therapy Regimens**
- **Chemotherapy Backbone**:
  - Fluoropyrimidines, oxaliplatin, irinotecan (two- or three-drug combinations).
- **Biologics**:
  - Anti-VEGF or anti-EGFR antibodies added based on tumor and patient factors.
- **Multidisciplinary Care**:
  - Input from specialist tertiary care centers is essential.

# Surveillance After Curative Surgery in Colorectal Cancer

- **Stage I Disease**:
  - **Colonoscopy**: Years 1, 3, 5 post-surgery.
- **Stage II & III Disease**:
  - **Clinical Assessments & CEA Levels**: Every 3–6 months for 2–3 years, then biannually until 5 years.
  - **Colonoscopy**: 1 year, then every 3–5 years.
  - **CT Scans (Chest, Abdomen, Pelvis)**: Every 6–12 months for 5 years.
- **Stage IV Disease (Post-Metastatic Resection)**:
  - Close surveillance with regular imaging due to high recurrence risk

Cathy Eng et al Colorectal cancer, Lancet. 2024;404:294-310.

# Prevention

- **Primary Prevention:**
- refers to identifying genetic, biologic, and environmental factors that are etiologic or pathogenetic and subsequently altering their effects on tumor development
- **Lifestyle Changes**:
  - Quit smoking, daily exercise (30+ minutes), and a healthy diet rich in calcium, fiber, fruits, vegetables, nuts, and whole grains.
- **Chemoprevention**:
  - Mixed evidence for vitamin D, calcium supplements, and hormone replacement therapy.
  - Low-dose aspirin/NSAIDs
- **Challenges**:
  - Tailoring prevention to high-risk individuals.
  - Need for personalized risk models incorporating genetics, environment, and family history

Dekker E, et al . Colorectal cancer. The Lancet. 2019 Oct 19;394(10207):1467-80.

# Prevention

- **Secondary Prevention**
- Early detection and treatment of pre-cancerous and cancerous lesions to improve prognosis.
- **Screening Methods**:

**1.Colonoscopy**:

1. Gold standard for detection and removal of lesions.
2. Recommended for high-risk individuals (e.g., hereditary risk, prior adenomas, or CRC, those with long-standing ulcerative colitis are recommended to undergo regular surveillance by colonoscopy. ).

**2.Stool Tests**:

1. **FIT (Fecal Immunochemical Test)**:
    1. More effective than guaiac tests, widely used in Europe.
    2. Reduces mortality by 22% with higher participation (up to 73%).
2. **DNA-based Tests**:
    1. Higher sensitivity than FIT but costly and complex logistics.

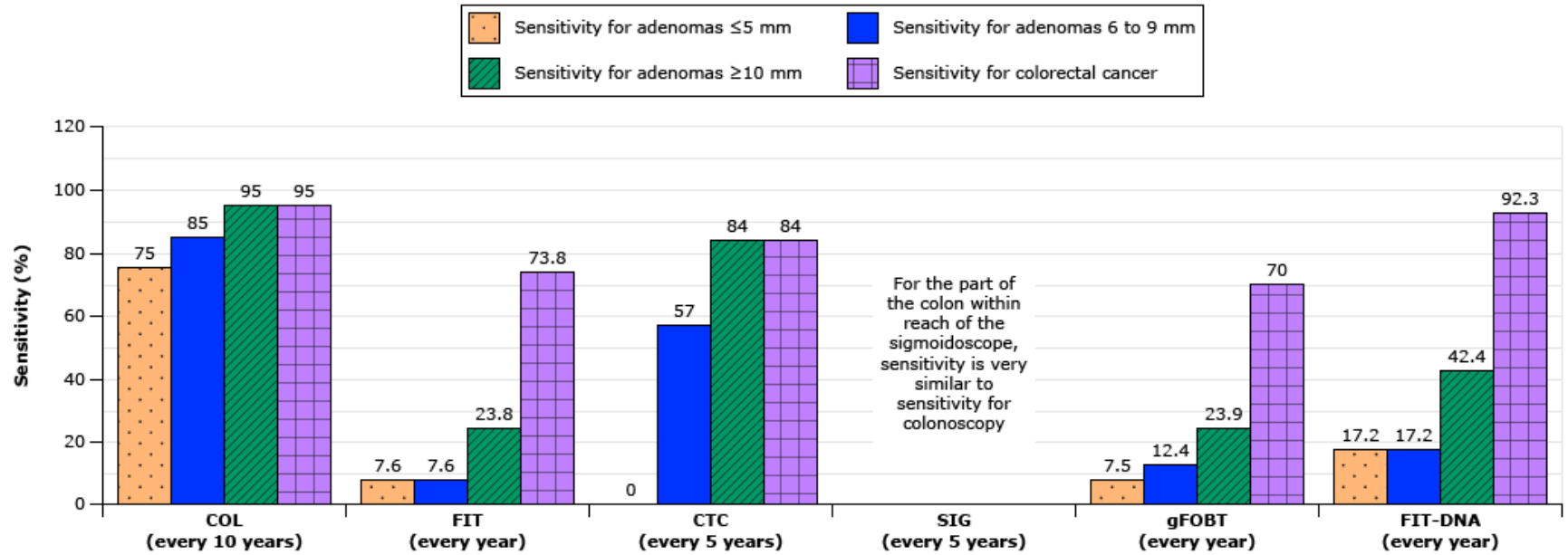
Dekker E, et al . Colorectal cancer. The Lancet. 2019 Oct 19;394(10207):1467-80.

# Prevention

- Screening Alternatives and Challenges
- **Other Screening Methods**:
- **Sigmoidoscopy**:
  - Reduces incidence (18–26%) and mortality (22–31%) but with lower participation rates.
- **CT Colonography**:
  - Similar cancer detection rates to colonoscopy but lower for advanced adenomas.
  - high costs, radiation exposure, and need for follow-up colonoscopy of all CT positive results, CT colonography is not currently used in population screening
- **Challenges**
  - Low participation in invasive methods.
  - Cost-efficiency and logistical issues in large-scale programs
- **Role for circulating tumour DNA**
  - moderate sensitivity (83.1%) and specificity (89.9%) for detecting colorectal cancer but performs poorly for advanced precancerous lesions (13.2%) and early-stage cancer (55%)

Dekker E, et al . Colorectal cancer. The Lancet. 2019 Oct 19;394(10207):1467-80.

## Estimated sensitivity, specificity, and cancer-specific deaths averted for each colorectal cancer screening strategy




| | COL (every 10 years) | FIT (every year) | CTC (every 5 years) | SIG (every 5 years) | gFOBT (every year) | FIT-DNA (every year) |
|---|---|---|---|---|---|---|
| **Test specificity** | 86 | 96.4 | 88 | 87 | 92.5 | 89.8 |
| **Colorectal cancer deaths averted per 1000 40-year-olds (n)*** | 22 to 24 | 20 to 23 | 16 to 24 | 16 to 21 | 20 to 23 | 21 to 24 |

Sensitivity, specificity, and cancer-specific deaths averted for each screening strategy.

COL: colonoscopy; CTC: computed tomography colonography; FIT: fecal immunochemical test; FIT-DNA: multitargeted stool deoxyribonucleic acid test; gFOBT: guaiac-based fecal occult blood test; SIG: sigmoidoscopy.

* Assumes screening from ages 50 to 75 years, including 100% adherence, complete follow-up without delay, and appropriate surveillance. Ranges reflect results from 3 models.

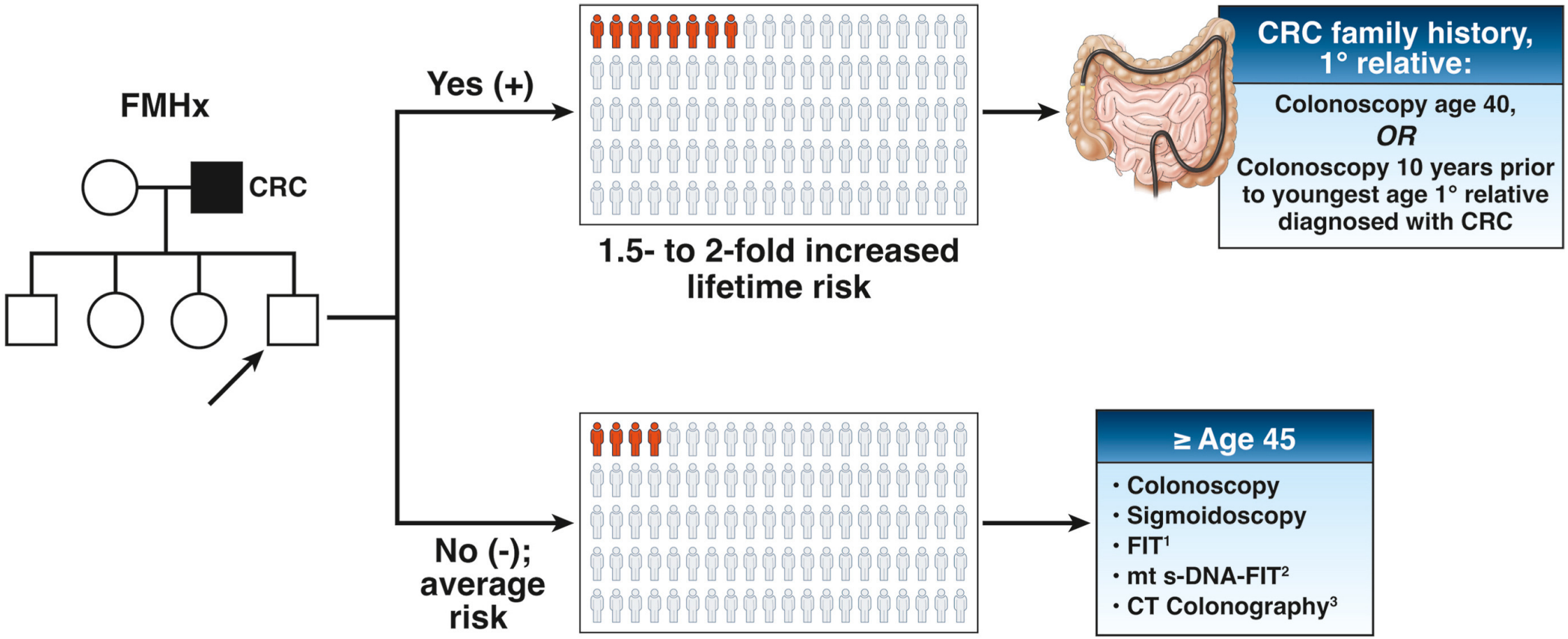
*Data from:*


1. *Zauber A, Knudsen A, Rutter CM, et al. Evaluating the Benefits and Harms of Colorectal Cancer Screening Strategies: A Collaborative Modeling Approach. AHRQ Publication No. 14-05203-EF-2. Rockville, MD: Agency for Healthcare Research and Quality; October 2015.*
2. *Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force. JAMA 2016; 315:2595.*

# Risk stratification

- Increased risk
- All individuals with a first-degree relative (defined as a parent, sibling, or child) who was diagnosed with CRC, particularly before the age of 50 years, should be considered at increased risk for CRC.
- Average risk
- All individuals without a personal history of CRC, inflammatory bowel disease, hereditary CRC syndromes, other CRC predisposing conditions, or a family history of CRC should be considered at average risk for CRC.

Issaka RB, et al. AGA Clinical Practice Update on Risk Stratification for Colorectal Cancer Screening and Post-Polypectomy Surveillance: Expert Review. *Gastroenterology*. 2023;165(5):1280-1291




[1]Fecal Immunochemical Test (FIT)
[2]Multi-target stool DNA-FIT
[3]Computed Tomography (CT) Colonography

Issaka RB, et al. AGA Clinical Practice Update on Risk Stratification for Colorectal Cancer Screening and Post-Polypectomy Surveillance: Expert Review. *Gastroenterology*. 2023;165(5):1280-1291

# THANK YOU