Colorectal Cancer: Diagnosis, Treatment, & Prevention

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Objectives

- Discuss the incidence of colorectal cancer in recent years.
- Identify the etiology and risk factors of colorectal cancer.
- Evaluate the biomarkers and screening tools for the detection of colorectal cancer.

https://youtu.be/oQWcNHQ7TlI

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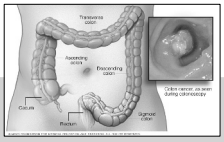
Colorectal Cancer



- Begins in the colon or rectum
  - Usually begins as small benign clump of cells (polyps)
    - Asymptomatic, most of the time
  - Over time, polyps may become malignant
  - Screening tests to detect polyps
- Mostly affects older adults…this is changing
  - Better prevention
  - Early detection

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Colorectal Cancer

- Highly treatable
- Often curable

When localized to bowel

- Primary form of treatment is surgery
  - 50% patients cured
- Recurrence is major problem

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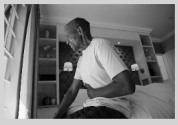
Symptoms of CRC



➢Often asymptomatic

- Change in bowel habits
- Blood in the stool
- Diarrhea, constipation, or feeling that the bowel does not empty completely
- Abdominal pain or cramps
- Weight loss

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Colorectal Cancer Statistics

- Fourth most common type of malignancy in U.S.
- Fourth-leading cause of cancer deaths
- Affects men & women of all racial and ethnic groups
  - 90% of cases are in people over 50

https://www.cdc.gov/cancer/colorectal/statistics/index.htm

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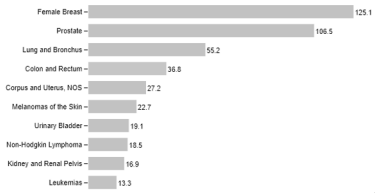
Top 10 Cancers (by rates of new cancer cases)



https://gis.cdc.gov/Cancer/USCS/DataViz.html

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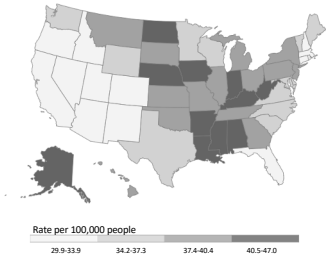
Rate of new CRC diagnoses



https://gis.cdc.gov/Cancer/USCS/DataViz.html

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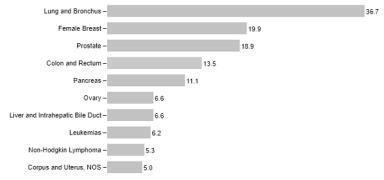
Top 10 Cancers (rates of cancer deaths)



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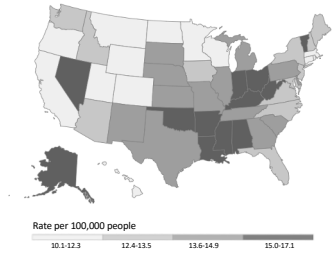
Rate of CRC deaths



https://gis.cdc.gov/Cancer/USCS/DataViz.html

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Incidence & mortality

- Estimated new cases and deaths in U.S. in 2021:
  - New cases of colon cancer: ~104,000
  - New cases of rectal cancer: ~45,000
  - Deaths from both: ~53,000

American Cancer Society. Cancer Facts and Figures 2021. American Cancer Society, 2021.

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Risk factors for CRC

- Smoking
- Unhealthy diet
  - Low fruits and veggies
  - Low fiber
  - High fat
- High alcohol consumption
- Physical inactivity
- Excess body weight

Potentially preventable

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Other risk factors for CRC

- Inflammatory bowel disease
  - Crohn's disease or ulcerative colitis
- Personal or family history (CRC or colorectal polyps)
- Genetic syndrome
  - Familial adenomatous polyposis (FAP)
  - Lynch syndrome

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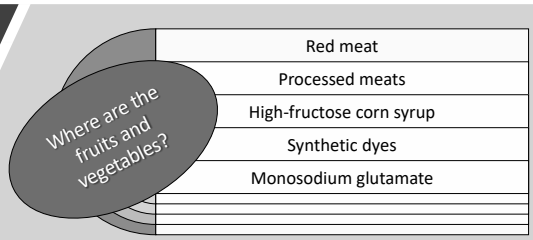
Significance of a Western diet



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Early-onset Colorectal Cancer

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Early-onset colorectal cancer (EOCRC)

- On the rise in adults under 50
- Incidence rates doubled in U.S. since 1990s
- Diagnosed at more advanced stages
- More aggressive than CRC in older people

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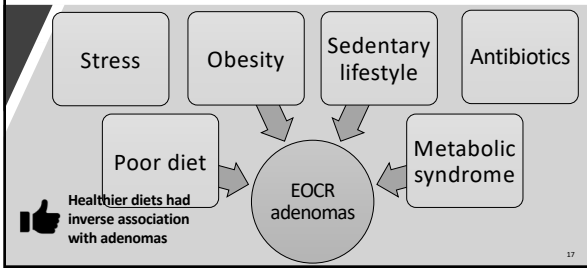
Why the rise in EOCRC cases?



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Genetic Testing for CRC

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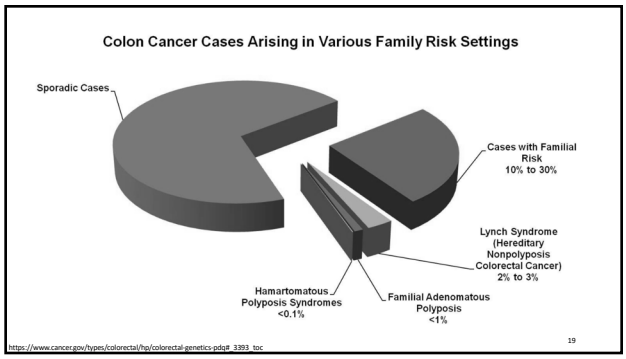

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Genetic contribution to CRC

- Strong family history of CRC and/or polyps
- Multiple primary cancers in patient with CRC
- Presence of other cancers that are related to inherited risk of CRC, such as endometrial cancer
- Diagnosis of CRC at early age

- Usually autosomal dominant

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Associated genes & syndromes

- Polyposis
  - Familial adenomatous polyposis (FAP)
  - Attenuated FAP (AFAP)
  - MUTYH-associated polyposis

Caused by variants in *APC* gene

Caused by variants in *MUTYH* gene

- Lynch syndrome
  - Referred to as hereditary nonpolyposis CRC

Caused by variants in DNA MMR genes (*MLH1, MSH2, MSH6, PMS2*) and *EPCAM*

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Estimated risk of developing CRC

Family history	Absolute risk of CRC by age 79
No family history	4 %
One FDR with CRC	9%
More than one FDR with CRC	16%
One affected FDR diagnosis with CRC before age 45	15%
One FDR with colorectal adenoma	8%

Adapted from: https://www.cancer.gov/types/colorectal/hp/colorectal-genetics-pdq#_3393_toc

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Associated genes & syndromes

- Oligopolyposis
- *NTHL1*
- Juvenile polyposis syndrome
- Cowden syndrome
- Peutz-Jeghers syndrome

- Familial CRC

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Molecular features of EOCRC

Review of over 36,000 CRC patients (2019)

- Early onset:
  - More likely to have microsatellite instability
  - More likely to have primary tumors in distal colon and rectum
  - Fewer BRAF V600 mutations
  - Patients under 40 → CMS1 most common

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Molecular testing for EOCRC

Research suggests greater use of genetic testing and whole genome sequencing (WGS) for high-risk patients and family members of patients with EOCRC

- Might identify molecular changes in genes already associated with early disease
  - *KRAS*
  - *P53*
  - *LINE-1* hypomethylation

Common in nonhereditary cancers

Potentially serve as EOCRC biomarkers

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Molecular testing for EOCRC

- Other genetic variations:
  - *BRCA1*
  - *BRCA2*

  } Higher rate of hereditary cancer
- Ohio Colorectal Cancer Prevention Initiative

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Molecular testing for EOCRC

National Comprehensive Cancer Network guidelines recommend that all CRC patients under age 50 get genetic evaluations

Most people diagnosed with CRC before 50, without family history of cancer, do not have pathogenic variant associated with an inherited cancer syndrome

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Family history – a question of accuracy

- May be erroneous or person unaware of complete history
- People are less likely to know about history of polyps
- Small family size and premature deaths may limit information about family history
- Some people may carry genetic predisposition for CRC, but do not develop cancer → gives impression of skipped generation

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Approach to new CRC diagnosis

- Guidelines from The American College of Medical Genetics and Genomics
- Identify people whose clinical features warrant genetic counseling
- Multiple polyps (>20) → gene-directed testing
- Possible Lynch syndrome → germline genetic testing
- Challenge when clinical picture is not clear
  - Tumor screening for Lynch syndrome
  - Panels for somatic mutations

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Psychosocial aspect of genetic testing

- Influences decisions regarding genetic testing for CRC & potential risk-management
- Factors associated with genetic counseling:
  - Number of children
  - Number of affected relatives
  - Perceived risk of developing CRC
  - Frequency of thoughts about CRC

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Psychosocial aspect of genetic testing

- Research indicated LOW LEVELS OF DISTRESS after genetic testing for Lynch syndrome in both carriers and non-carriers
- Other studies demonstrated INCREASED DISTRESS after genetic testing for FAP

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Psychosocial aspect of genetic testing

- Colon & gynecologic cancer screening rates are increased or maintained in carriers of MMR variants
- However, screening rates decrease in those that are non-carriers of the genetic marker

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CRC Screening

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CDC's Screening Guidelines

Regular screening should begin at age 50	• 90% of new cases are in people over 50 • Recommended for those ages 50-75
Screen before age 50, if you…	• Or a close relative have history of colorectal polyps or CRC • Have inflammatory bowel disease • Have genetic condition that puts you at high risk

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CRC Screening Tests

Once per year
- Fecal occult blood test
  - Uses guaiac to detect presence of blood
- Fecal immunochemical test (FIT)
  - Uses Ab to detect presence of blood

Once every 3 years
- FIT-DNA test (stool DNA test)
  - Combine FIT with a test that detect altered DNA in the stool

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CRC Screening Tests

Every 5-10 years
- Flexible Sigmoidoscopy
  - Checks for polyps or cancer inside rectum and lower third of colon

Every 10 years (low-risk)
- Colonoscopy
  - Checks for polyps or cancer inside rectum and entire colon
  - Polyps may be removed during procedure
  - Follow-up for screening tests

Every 5 years
- CT Colonography (Virtual Colonoscopy)
  - Produces images of entire colon

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CRC Screening Tests

- Circulating tumor cell DNA (ctDNA)
- Fecal samples for genome or microbiome changes
- Downside → Less sensitive than colonoscopy

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CRC Screening

- Newly diagnosed CRC → evaluate for Lynch syndrome
  - Look for MMR deficiency
- Start with:
  - Immunohistochemistry testing for expression of MMR proteins
  - MSI testing
  - *BRAF* testing
  - *MLH1* hypermethylation analyses

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Who is getting screened?

The percentage of adults in the U.S. who are up-to-date with colorectal cancer screening is increasing

67.4% **2016** → **68.8%** **2018**

The percentage of adults aged 50-75 who were up-to-date with CRC screening increased by **1.4%** from 2016 to 2018

https://www.cdc.gov/cancer/colorectal/statistics/use-screening-tests-BRFSS.htm

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This means **4.2 million** more people were screened for CRC

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However…

21.7 million adults ages 50-75 have never been screened for CRC

81% of adults that have never been screened are ages 50-64

About **one-quarter** of adults have not been screened as recommended

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Stages of CRC

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CRC Stages

- Describes how much cancer is in body
- Helps determine prognosis & proper treatment
- Ranges from Stage 0 through Stage IV

- Each person's experience is unique
- However, cancer with similar stages tend to have similar prognosis and treatment

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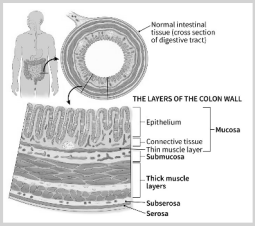
Determination of CRC Stage – TNM System

Extent/size of tumor (T)

Spread to nearby lymph nodes (N)

Spread to distant site (metastasis) (M)



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Staging system

AJCC Stage	Stage Grouping	Stage Description
0	Tis N0 M0	- Earliest stage - Also known as carcinoma in situ or intramucosal carcinoma (Tis) - Has not grown beyond inner layer (mucosa) of colon or rectum.
I	T1 or T2 N0 M0	- Cancer grown through muscularis mucosa into submucosa (T1) or into muscularis propria (T2). - Not spread to lymph nodes (N0) or distant sites (M0)

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Staging system

AJCC Stage	Stage Grouping	Stage Description
IIA	T3 N0 M0	- Cancer grown into outermost layers of colon or rectum, but has not gone through them (T3) - Not spread to lymph nodes (N0) or distant sites (M0)
IIB	T4a N0 M0	- Cancer grown through wall of colon or rectum but has not spread to nearby tissues or organs (T4a) - Not spread to lymph nodes (N0) or distant sites (M0)
IIC	T4b N0 M0	- Cancer grown through wall of colon or rectum and is attached to or has grown into nearby tissues or organs (T4b) - Not spread to lymph nodes (N0) or distant sites (M0)

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Staging system

AJCC Stage	Stage Grouping	Stage Description
IIIA	T1 or T2 N1/N1C M0	- Cancer grown through mucosa into submucosa (T1) and possibly into muscularis propria (T2) - Spread to 1-3 nearby lymph nodes (N1) or into areas of fat near lymph nodes (N1c) - Not spread to distant sites (M0)
	T1 N2a M0	- Cancer grown through mucosa into submucosa (T1) - Spread to 4-6 nearby lymph nodes (N2a) - Not spread to distant sites (M0)

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Staging system

AJCC Stage	Stage Grouping	Stage Description
IIIB	T3 or T4a N1/N1C M0	- Cancer grown into outermost layers of colon/rectum (T3) or through visceral peritoneum (T4a); has not reached nearby organs - Spread to 1-3 nearby lymph nodes (N1) or into areas of fat near lymph nodes (N1c) - Not spread to distant sites (M0)
	T2 or T3 N2a M0	- Cancer grown through mucosa into muscularis propria (T2) or outermost layers of colon/rectum (T3) - Spread to 4-6 nearby lymph nodes (N2a) - Not spread to distant sites (M0)
	T1 or T2 N2b M0	- Cancer grown through mucosa into submucosa (T1) and possibly into muscularis propria (T2) - Spread to 7 or more nearby lymph nodes (N2b) - Not spread to distant sites (M0)

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Staging system

AJCC Stage	Stage Grouping	Stage Description
IIIC	T4a N2a M0	- Cancer grown through wall of colon/rectum into visceral peritoneum, but has not reached nearby organs (T4a) - Spread to 4-6 nearby lymph nodes (N2a) - Not spread to distant sites (M0)
	T3 or T4a N2b M0	- Cancer grown through outermost layers of colon/rectum (T3) into visceral peritoneum (T4a), but has not reached nearby organs - Spread to 7 ore more nearby lymph nodes (N2b) - Not spread to distant sites (M0)
	T4b N1 or N2 M0	- Cancer grown through wall of colon or rectum and is attached to or has grown into nearby tissues or organs (T4b) - Spread to at least 1 nearby lymph node or into areas of fat near lymph nodes (N1 or N2) - Not spread to distant sites (M0)

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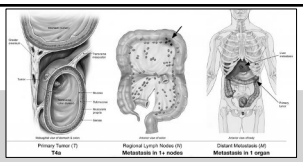
Staging system



AJCC Stage	Stage Grouping	Stage Description
IVA	Any T Any N M1a	- Cancer may or may not have grown through wall of colon or rectum (Any T) - It may or may not have spread to nearby lymph nodes (Any N) - Spread to 1 distant part of body, but not distant part of peritoneum

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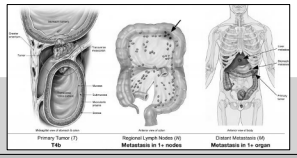
Staging system



AJCC Stage	Stage Grouping	Stage Description
IVB	Any T Any N M1b	- Cancer may or may not have grown through wall of colon or rectum (Any T) - It may or may not have spread to nearby lymph nodes (Any N) - Spread to more than 1 distant organ (such as liver or lung) or distant lymph nodes, but not distant parts of peritoneum (M1b)

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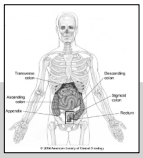
Staging system



AJCC Stage	Stage Grouping	Stage Description
IVC	Any T Any N M1c	- Cancer may or may not have grown through wall of colon or rectum (Any T) - It may or may not have spread to nearby lymph nodes (Any N) - Spread to distant parts of peritoneum and may or may not have spread to distant organs or lymph nodes (M1c)

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CRC Grading

GX	Tumor grade cannot be identified
G1	Cells more like healthy cells; called well-differentiated
G2	Cells somewhat like healthy cells; called moderately differentiated
G3	Cells look less like healthy cells; called poorly differentiated
G4	Cells barely look like healthy cells; called undifferentiated

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Management of CRC

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Prognostic factors for colon cancer

- Degree of penetration of tumor through bowel wall
- Presence or absence of nodal involvement
- Presence of absence of distant metastasis
- Bowel obstruction & perforation
- Elevated pretreatment CEA levels

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5-year Survival Rates (Colon Cancer)

2010-2016

SEER Stage	5-year relative survival rate
Localized	91%
Regional	72%
Distant	14%
All SEER stages combine	63%

https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/survival-rates.html

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5-year Survival Rates (Rectal Cancer)

2010-2016

SEER Stage	5-year relative survival rate
Localized	89%
Regional	72%
Distant	16%
All SEER stages combine	67%

https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/survival-rates.html

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Management following surgery

- Periodic evaluations may lead to earlier identification/management of recurrence
- CEA (carcinoembryonic antigen)
  - Not valuable screening tool
  - Postoperative CEA restricted to patients who would be candidates for lung or liver resection
  - Routine CEA levels alone to monitor treatment is not recommended
- No large-scale research have documented overall survival benefit for standard, postoperative monitoring programs

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Localized Treatment for CRC

- Typically, useful for earlier stages
- Surgery (for colon or rectal cancer)
- Ablation & embolization for CRC
- Radiation therapy

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Systemic Treatment for CRC

- Medications given by mouth or IV
- Reach malignant cells throughout body
- Chemotherapy
- Targeted therapy
- Immunotherapy

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Prophylactic surgery

- Improves survival in patients with FAP
  - Extent of surgery depends on number of polyps, their size, histology, & symptoms
- Patients with Lynch syndrome and diagnosis of CRC
  - Resection associated with fewer metachronous CRCs and additional surgical procedures
- Depends on patient's age, comorbidities, clinical stage of tumor, sphincter function

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Chemopreventive agents

- Manage FAP and Lynch syndrome
- FAP → celecoxib and sulindac are associated with decrease polyp size and number
- Daily aspirin (600 mg/day) shown to prevent incidence of cancer in patients with Lynch syndrome

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So much research…

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Future research

- Epidemiologic shifts in CRC incidence & mortality across different age groups
  - Differences between treatment, molecular, and survival characteristics
- More studies of the microbiome might elucidate bacterial causes of CRC in younger patients

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Future research

- Immune system stimulation
  - Evaluated in MMR-deficient tumors (including those related to Lynch syndrome)
  - Cytokine-rich environment may improve clinical outcomes
  - Study is currently in Phase 2 – using anti-PD-1 immune checkpoint inhibitors → favorable outcomes

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Future research

- Current study evaluating the effects of low doses of aspirin preventing CRC in patients with Lynch syndrome
- Ongoing research to address psychosocial and behavioral issues in high-risk families

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Colorectal Cancer Pooling Project (C2P2)

- International effort
- Examine potential risk factors and biomarkers for CRC in various age groups
- Study potential biomarkers that may be intermediates of lifestyle risk factors related to metabolic health and gut dysbiosis, or microbial imbalance

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In conclusion

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How do I reduce my risk of CRC?

- Most effective way to reduce risk → GET SCREENED beginning at age 50
  - Detect and remove polyps
- Healthy diet
  - Low in animal fats
  - High in fruits, vegetables, whole grains
- Aspirin
  - Current research suggests low-dose aspirin can help prevent CRC in some adults, depending on age and risk factors
- Healthy choices:
  - Exercise
  - Limit alcohol consumption
  - Avoid tobacco products

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