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/oQWcNHQ7TI

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

Colorectal Cancer Statitics
• 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

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
• 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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When localized to bowel

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Top 10 Cancers (by rates of new cancer cases)

- Female Breast
- Prostate
- Lung and Bronchus
- Colon and Rectum
- Skin, Melanoma
- Intervening Sites
- Cervix, Uterine
- Non-Hodgkin Lymphoma
- Bladder
- Kidney, Renal Pelvis

Rate per 100,000 people

- 112.0
- 98.2
- 79.8
- 44.2
- 43.1
- 42.7
- 27.9
- 27.3
- 25.3
- 22.4

Top 10 Cancers (rates of cancer deaths)

- Female Breast
- Male Breast
- Prostate
- Lung and Bronchus
- Colon and Rectum
- Intervening Sites
- Cervix, Uterine
- Non-Hodgkin Lymphoma
- Bladder
- Kidney, Renal Pelvis

Rate per 100,000 people

- 144.5
- 59.8
- 42.5
- 42.1
- 41.7
- 40.4
- 37.4
- 31.9
- 27.5
- 26.2

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


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
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

Significance of a Western diet

- Red meat
- Processed meats
- High-fructose corn syrup
- Synthetic dyes
- Monosodium glutamate

Where are the fruits and vegetables?

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

Why the rise in EOCRC cases?

- Stress
- Obesity
- Sedentary lifestyle
- Antibiotics
- Poor diet

Healthier diets had an inverse association with adenomas

Genetic Testing for CRC
Genetic contribution to CRC

- Strong family history of CRC and/or polyp
- 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

Associated genes & syndromes

- Polyposis
  - Familial adenomatous polyposis (FAP)
  - Attenuated FAP (AFAP)
  - MUTYH-associated polyposis
  - Lynch syndrome
    - Referred to as hereditary nonpolyposis CRC

Estimated risk of developing CRC

<table>
<thead>
<tr>
<th>Family history</th>
<th>Absolute risk of CRC by age 79</th>
</tr>
</thead>
<tbody>
<tr>
<td>No family history</td>
<td>4%</td>
</tr>
<tr>
<td>One FDR with CRC</td>
<td>9%</td>
</tr>
<tr>
<td>More than one FDR with CRC</td>
<td>16%</td>
</tr>
<tr>
<td>One affected FDR diagnosis with CRC before age 45</td>
<td>15%</td>
</tr>
<tr>
<td>One FDR with colorectal adenoma</td>
<td>8%</td>
</tr>
</tbody>
</table>
Molecular testing for EOCRC

- Might identify molecular changes in genes already associated with early disease
  - KRAS
  - TP53
  - LINE-1 hypomethylation

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

- Common in non-hereditary cancers
- Potentially serve as EOCRC biomarkers

Other genetic variations:
- BRCA1
- BRCA2
- Other genetic variations can be identified.

Ohio Colorectal Cancer Prevention Initiative

- Higher rate of hereditary cancer

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.

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.

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

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
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

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

CRC Screening

90% of new cases are in people over 50
Recommended for those ages 50-75
Regular screening should begin at age 50

Screen before age 50, if you:
• Diagnosed relative have history of colorectal polyps or CRC
• Have inflammatory bowel disease
• Have genetic condition that puts you at high risk

Screening Tests

• Fecal occult blood test
  • Uses guaiac to detect presence of blood
• Fecal immunochemical test (FIT)
  • Uses Ab to detect presence of blood
• FIT-DNA test (stool DNA test)
  • Combine FIT with a test that detect altered DNA in the stool

• Flexible Sigmoidoscopy
  • Checks for polyps or cancer inside rectum and lower third of colon
• Colonoscopy
  • Checks for polyps or cancer inside rectum and entire colon
  • Polyps may be removed during procedure
  • Follow-up for screening tests
• CT Colonography (Virtual Colonoscopy)
  • Produces images of entire colon
CRC Screening Tests

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

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

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

This means 4.2 million more people were screened for CRC

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

Stages of CRC
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

Determination of CRC Stage – TNM System

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

Staging system

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<tr>
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<tbody>
<tr>
<td>II A</td>
<td>T3 N0 M0</td>
<td>Cancer grown through mucosa into submucosa (T3) and possibly into muscularis propria (T2). Spread to 1-3 nearby lymph nodes (N1) or into areas of fat near lymph nodes (N1a). Not spread to distant sites (M0)</td>
</tr>
<tr>
<td></td>
<td>T4a N0 M0</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>T4b N0 M0</td>
<td>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)</td>
</tr>
<tr>
<td>III A</td>
<td>T3 or T4a N1/N1C M0</td>
<td>Cancer grown through mucosa into muscularis propria (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 (N1a). Not spread to distant sites (M0)</td>
</tr>
<tr>
<td>III B</td>
<td>T2 or T3 N2a M0</td>
<td>Cancer grown through muscularis propria (T2) or outermost layers of colon/rectum (T3). Spread to 4-6 nearby lymph nodes (N2a). Not spread to distant sites (M0)</td>
</tr>
<tr>
<td>III C</td>
<td>T1 N2b M0</td>
<td>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)</td>
</tr>
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### Staging system

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<tbody>
<tr>
<td>IIIC</td>
<td>T4a N2a M0</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>T3 or T4a N2b M0</td>
<td>Cancer grown through outermost layers of colon/rectum (T3) into visceral peritoneum (T4a), but has not reached nearby organs - Spread to 7 or more nearby lymph nodes (N2b) - Not spread to distant sites (M0)</td>
</tr>
<tr>
<td></td>
<td>T4b N1 or N2 M0</td>
<td>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)</td>
</tr>
</tbody>
</table>

### IVB

<table>
<thead>
<tr>
<th>AJCC Stage</th>
<th>Stage Grouping</th>
<th>Stage Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIA</td>
<td>Any T Any N M1a</td>
<td>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 at least 1 distant organ (such as liver or lung) or distant lymph nodes, but not distant parts of peritoneum (M1a)</td>
</tr>
</tbody>
</table>

### IVC

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<th>Stage Description</th>
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</thead>
<tbody>
<tr>
<td>IIIA</td>
<td>Any T Any N M1c</td>
<td>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)</td>
</tr>
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</table>

### CRC Grading

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GX</td>
<td>Tumor grade cannot be identified</td>
</tr>
<tr>
<td>G1</td>
<td>Cells more like healthy cells; called well-differentiated</td>
</tr>
<tr>
<td>G2</td>
<td>Cells somewhat like healthy cells; called moderately differentiated</td>
</tr>
<tr>
<td>G3</td>
<td>Cells look less like healthy cells; called poorly differentiated</td>
</tr>
<tr>
<td>G4</td>
<td>Cells barely look like healthy cells; called undifferentiated</td>
</tr>
</tbody>
</table>

### Management of CRC
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

5-year Survival Rates (Colon Cancer) 2010-2016

<table>
<thead>
<tr>
<th>SEER Stage</th>
<th>5-year relative survival rate</th>
</tr>
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<tbody>
<tr>
<td>Localized</td>
<td>91%</td>
</tr>
<tr>
<td>Regional</td>
<td>72%</td>
</tr>
<tr>
<td>Distant</td>
<td>14%</td>
</tr>
<tr>
<td>All SEER stages combine</td>
<td>63%</td>
</tr>
</tbody>
</table>

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

Localized Treatment for CRC

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

Systemic Treatment for CRC

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

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

So much research...

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

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

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
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

In conclusion

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

References

- https://www.cdc.gov/cancer/colorectal/
- https://www.cancer.gov/types/colorectal/hp