Natural History and Epidemiology of Colorectal Cancer

Prevent Cancer Foundation
2019 Dialogue For Action® on Cancer Screening and Prevention
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Disclaimers

- I am a member of the Advisory Board of the Mississippi Cancer Registry and the Medical/Research Advisor to the Mississippi Partnership for Comprehensive Cancer Control Executive Board; these are uncompensated voluntary appointments.

- Otherwise, I have no conflicts of interest to disclose.

- ***The statements and views expressed in this presentation are my own*** **and may not reflect the opinions of the University of Mississippi Medical Center or any other organization with which I am associated.**

Learning Objectives

After engaging in this activity, participants will be able to:

1) **Describe the population- and geographic-based epidemiological trends in colorectal cancer (CRC) incidence and mortality rates and the probable causes of CRC disparities.**

2) **List the recommended CRC screening options and their re-screening frequencies.**

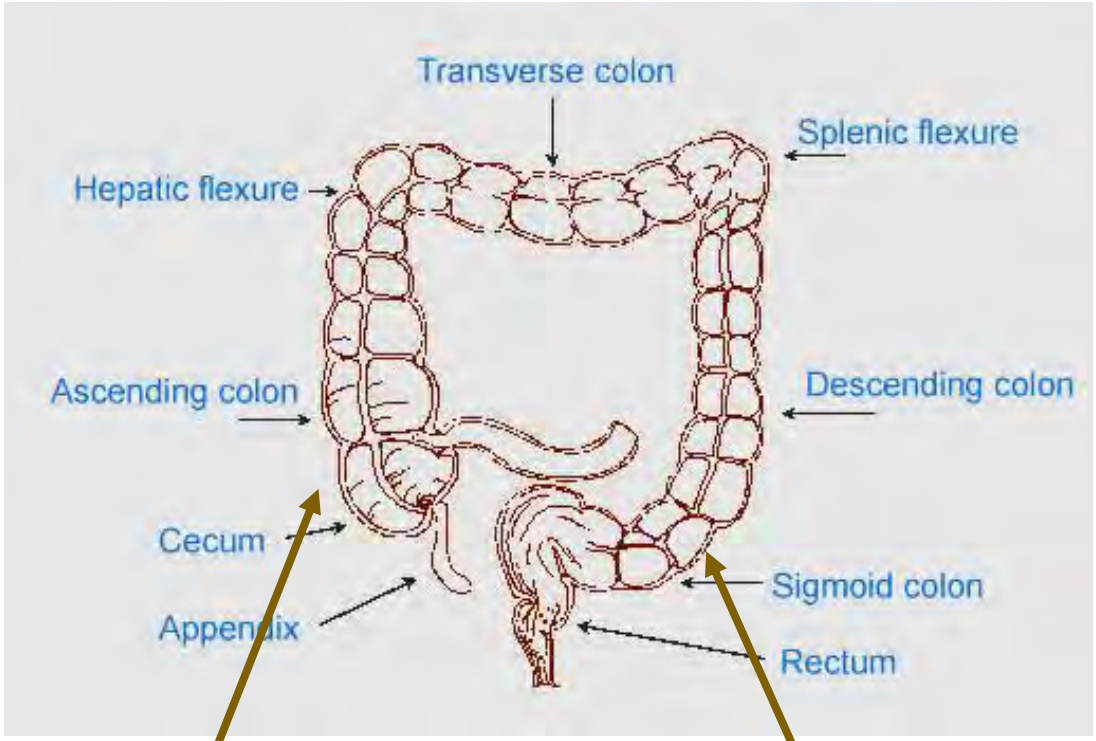
3) **Associate the predominant biological process of colorectal cancer development with the rationale supporting screening strategies for average-risk populations.**

4) **Assess the impact of intrinsic, behavioral, environmental and socio-economic CRC risk factors.**

5) **Recommend CRC screening for family members of patients with colorectal cancer due to Lynch syndrome or other genetic factors indicative of above-average cancer risks.**

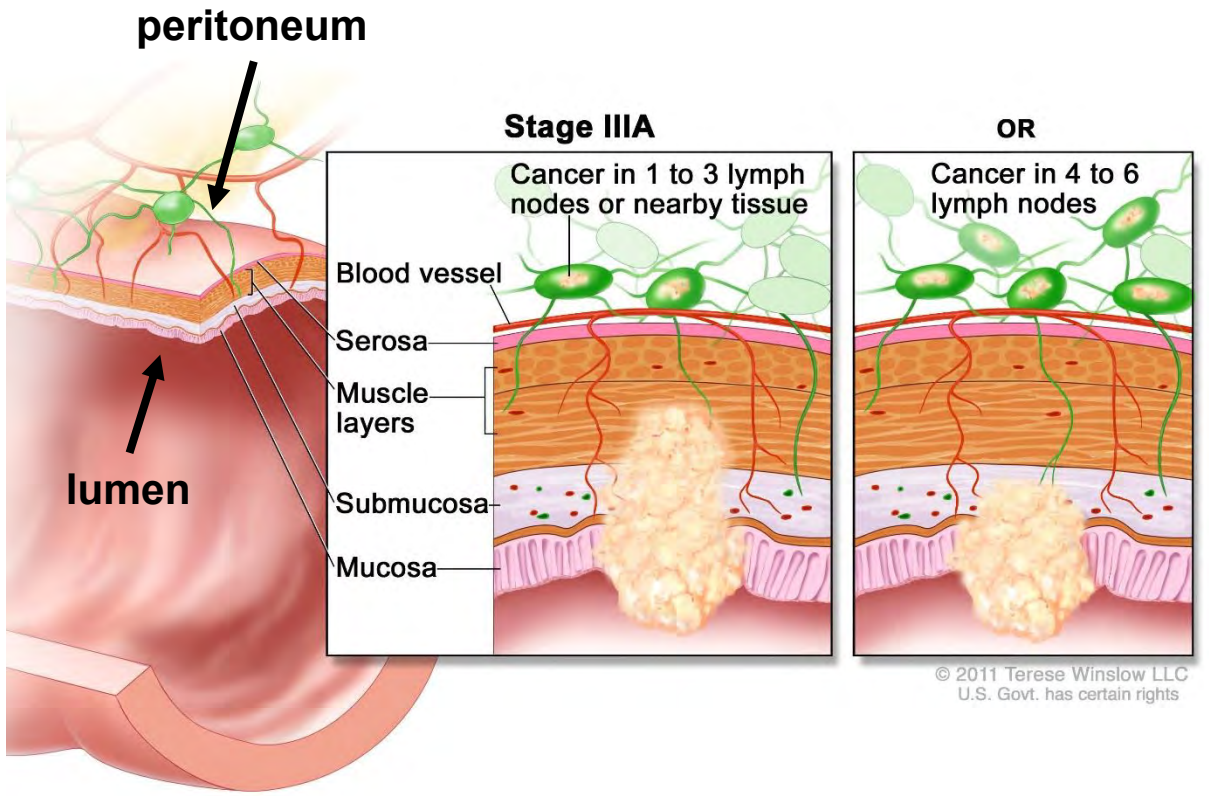
6) **Re-examine young adults who present with symptoms of colon cancer or rectal cancer for these diseases.**

Fundamental Colorectal Anatomy



proximal right colon

distal left colon



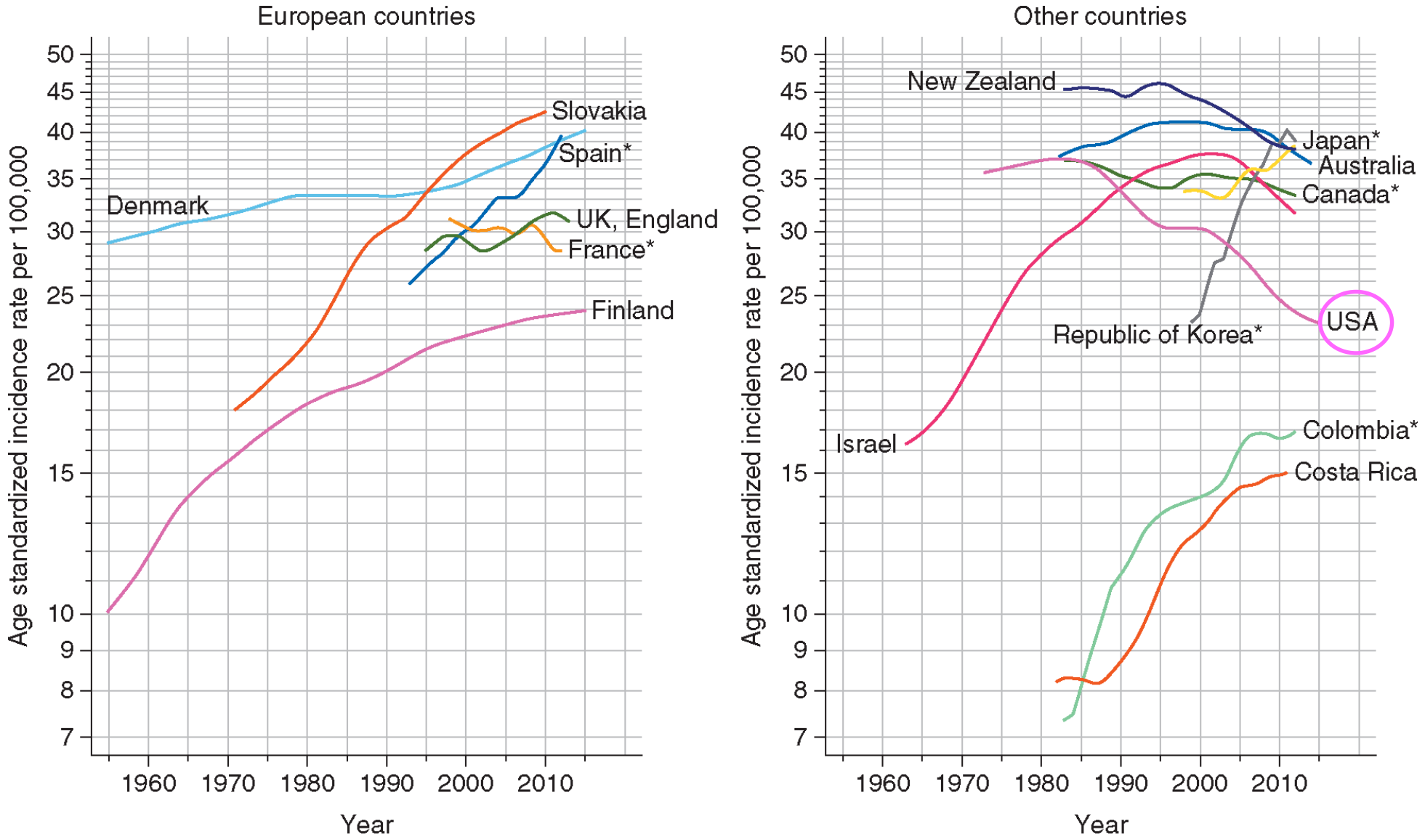
Regional lymph nodes provide CRC staging information

SOURCE: National Cancer Institute

Why focus on colorectal cancer?

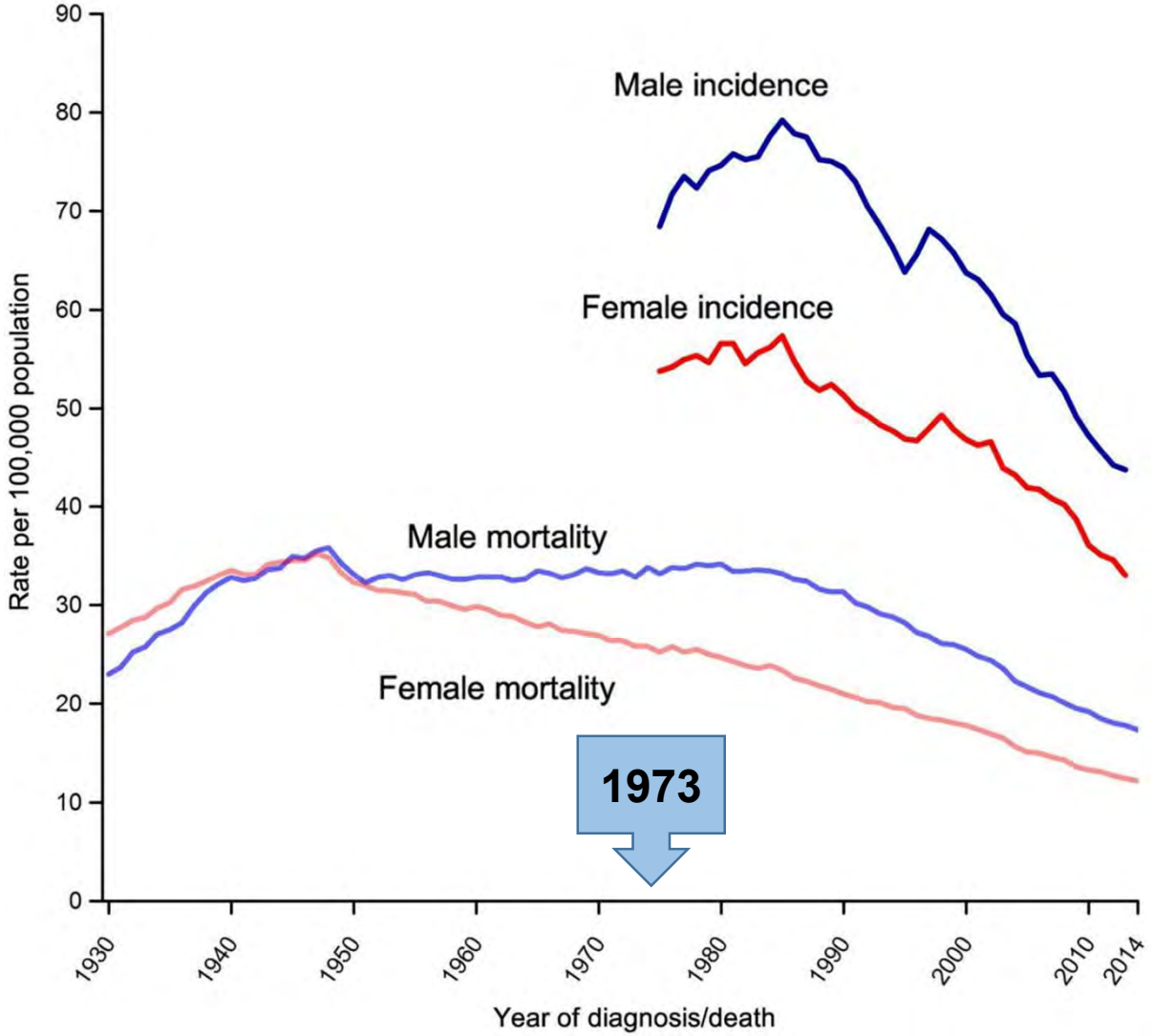
- **CRC is highly preventable & declining in most states.**
- **CRC is ~~2nd~~ 4th most common cancer in men + women (USA).**
  - **1 in 23 American males; 1 in 25 American females**
- **CRC is 2nd leading cause of cancer death in men + women (USA).**
- **CRC treatment costs are 2nd highest of all cancer sites (USA).**
- **CRC screens are net cost-SAVING (USA).**

Global *vs.* U.S.A. trends in colorectal cancer incidence



SOURCE: GLOBOCAN 2018; Gunter, et. al., (2019) *Annals of Oncology* (doi: 10.1093/annonc/mdz044. [Epub ahead of print])

Colorectal Cancer Incidence and Mortality Rates, U.S.A.

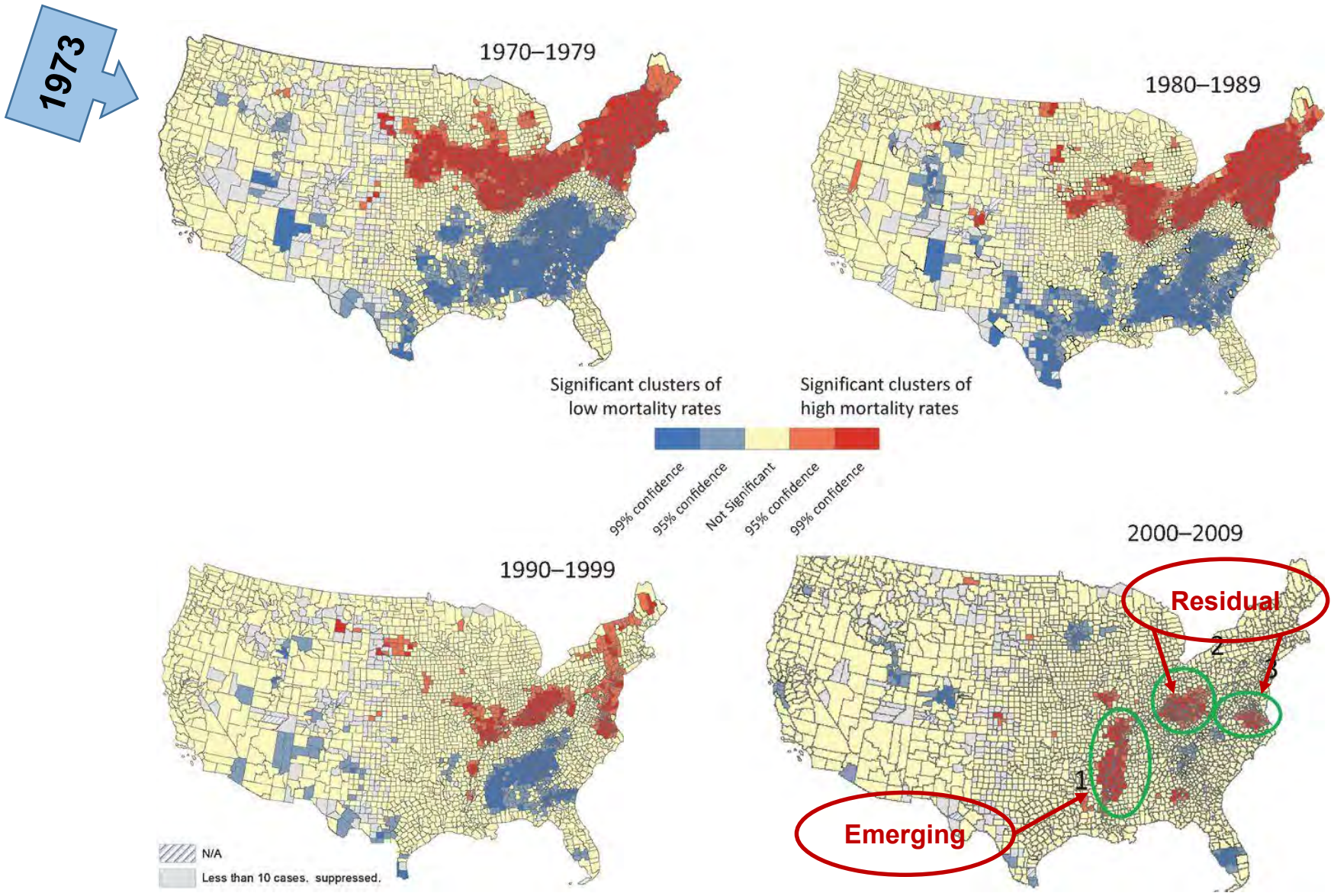


- **145,600 newly diagnosed CRC cases (U.S., 2019, projected)**
- **39.3 per 100,000 (U.S., 2011-2015, age-adjusted incidence)**
- **51,020 deaths from CRC (U.S., 2019, projected)**
- **14.2 per 100,000 (U.S., 2012-2016, age-adjusted mortality)**

Siegel, et. al. (2017) *CA: A Cancer Journal for Clinicians*, doi: 10.3322/caac.21395.

Siegel, et. al. (2019) *CA: A Cancer Journal for Clinicians*, doi: 10.3322/caac.21551.

Regional differences in CRC mortality rates may reflect decreasing & increasing trends



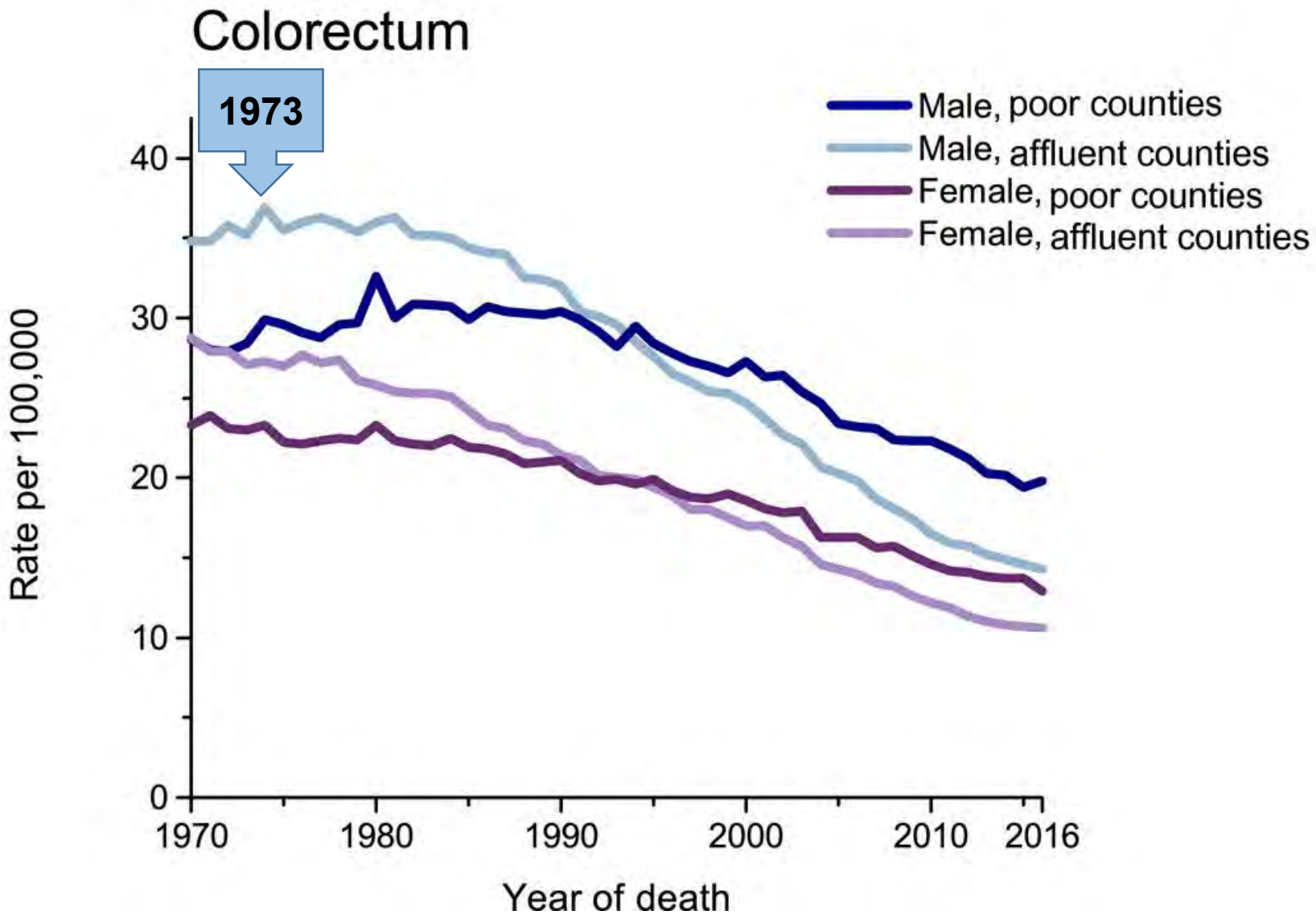
- Decreasing CRC mortality rates in Midwest & Northeast best explained by increasing CRC screening rates.
- Increasing CRC rates (esp. in Mississippi River Delta) may involve other risk factors (e.g., “nutrition transition”).

©2015 by American Association for Cancer Research

Rebecca L. Siegel et al. Cancer Epidemiol Biomarkers Prev 2015;24:1151-1156

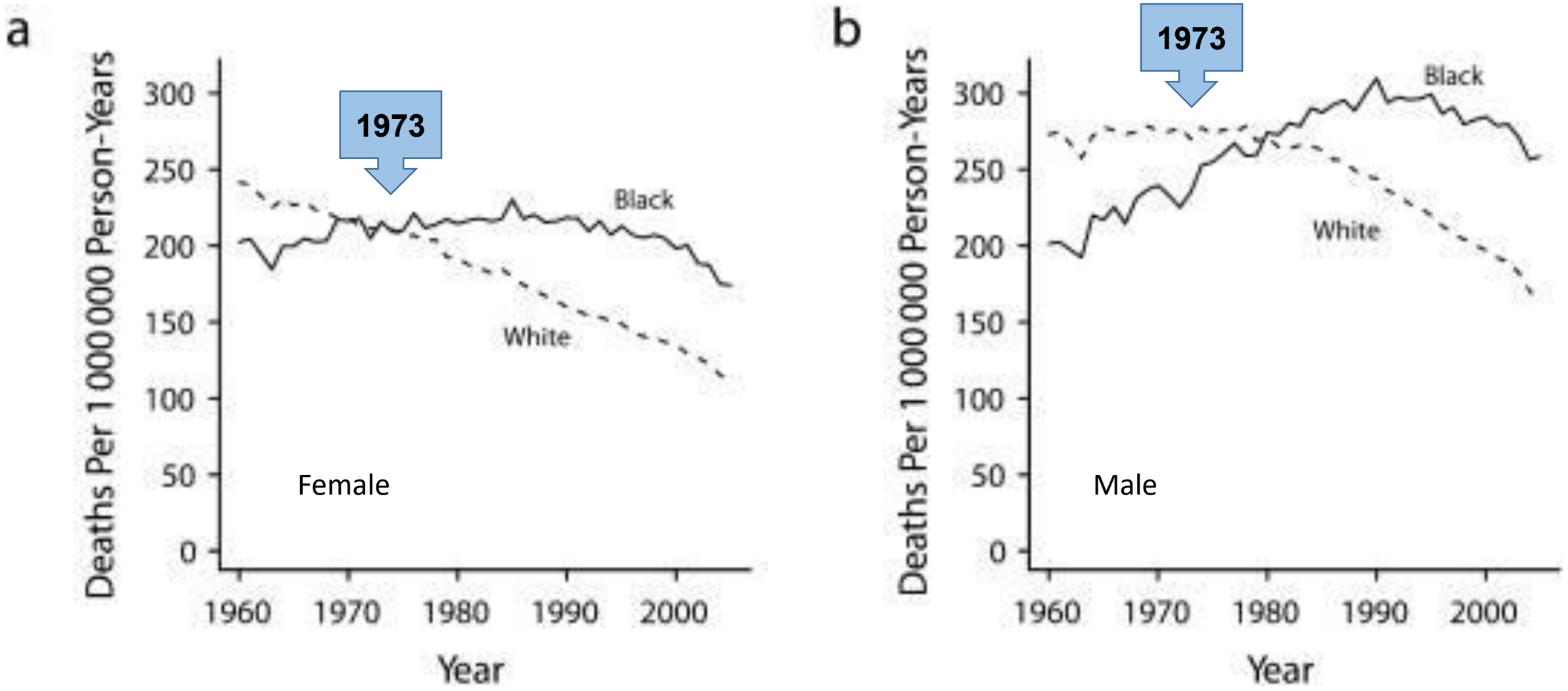
AACR American Association for Cancer Research
Cancer Epidemiology, Biomarkers & Prevention

Colorectal Cancer Mortality Rates by County-Level Poverty, U.S.A. (1970 – 2016)



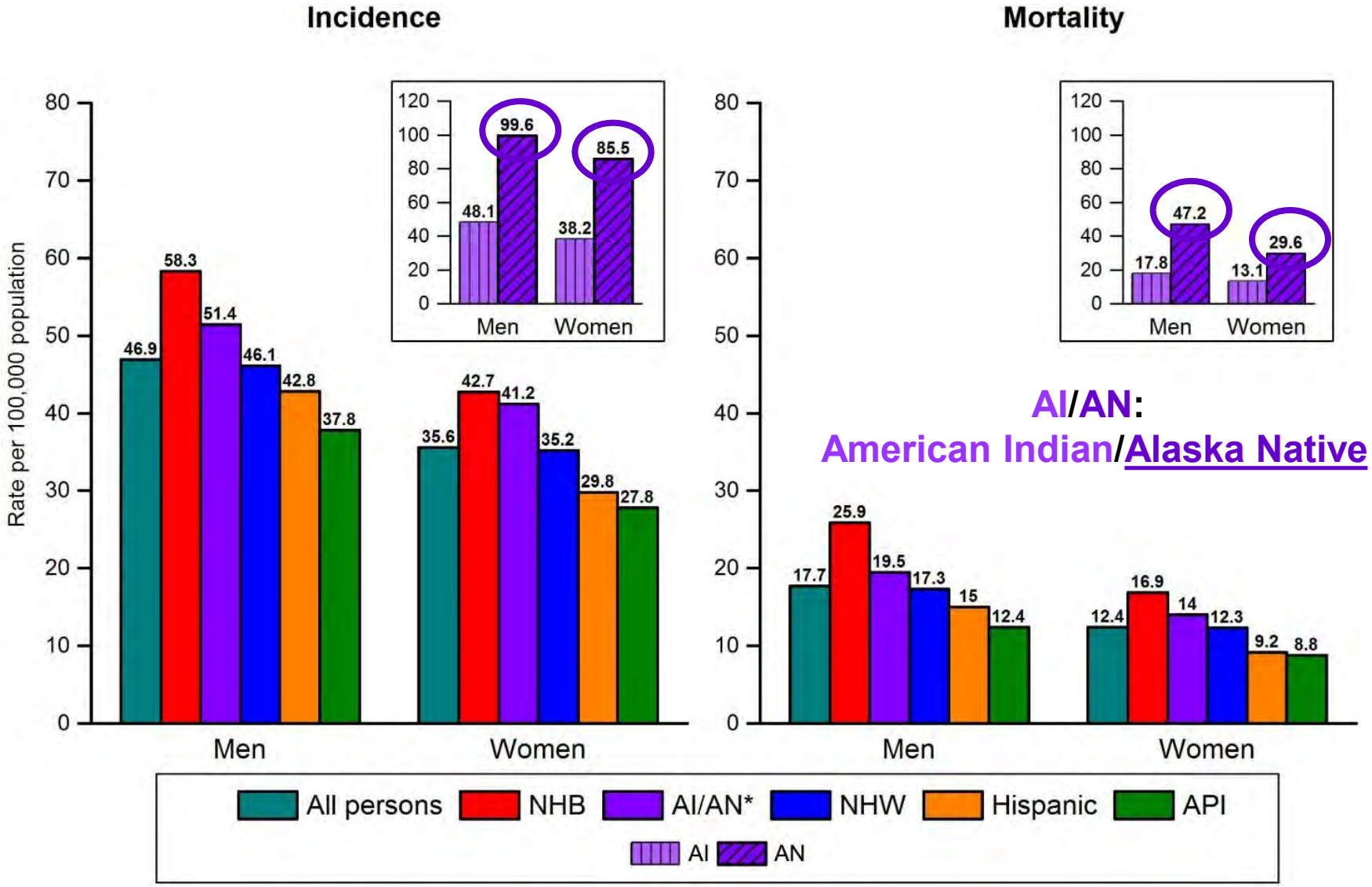
Siegel, et. al. (2019) *CA: A Cancer Journal for Clinicians*, doi: 10.3322/caac.21551.

Population-based disparities have significant adverse effect on overall CRC mortality rates in U.S.



Soneji, et. al. (2010) *Am J Public Health*, 100(10): 1912–1916.

Colorectal Cancer Incidence (2009-2013) and Mortality (2010-2014) Rates by Race/Ethnicity and Sex, United States



Siegel, et. al. (2017) *CA: A Cancer Journal for Clinicians*, doi: 10.3322/caac.21395.

The CRC screening revolution occurred in 1973

Flexible fiber optics revolutionized CRC prevention & control in 1973

"Polypectomy Via the Fiberoptic Colonoscope — Removal of Neoplasms beyond Reach of the Sigmoidoscope"

published in the *New England Journal of Medicine*

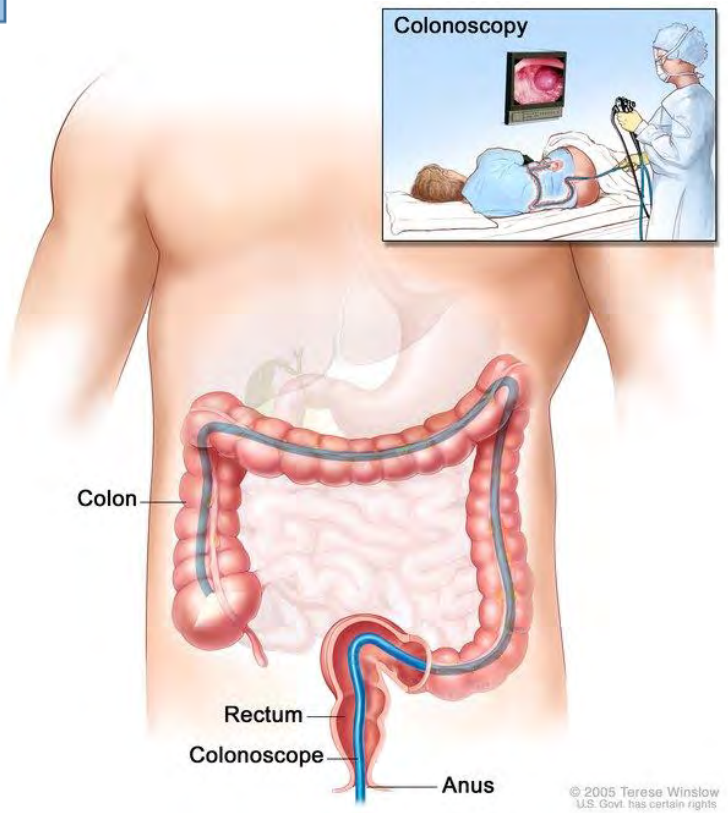
(288:329-332)

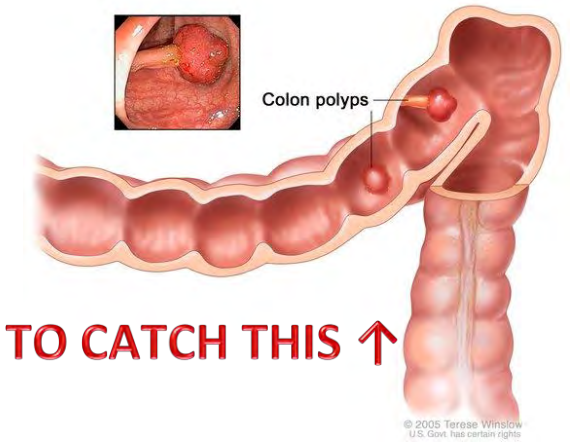
on February 15, 1973

by

William I. Wolff, M.D. and Hiromi Shinya, M.D.

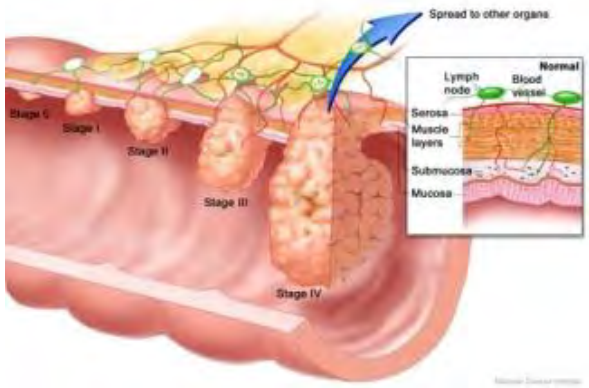
DO THIS ↓



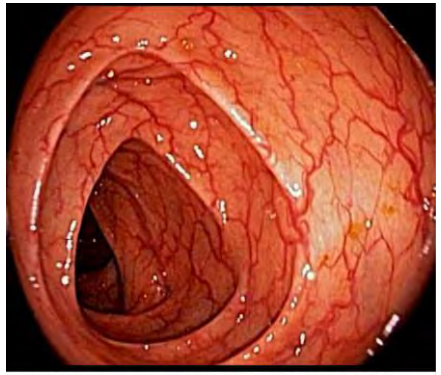


TO CATCH THIS ↑

BEFORE IT BECOMES THIS ↓



If you look inside a colon, what might you see?



Source: The University of Chicago, curated by Ira M. Hanan, MD, Professor of Medicine, The University of Chicago Medicine, Chicago, IL. In: *Atlas of Colon Pathology*. Chicago, IL: McGraw-Hill; 2015. http://www.accesssurgery.com
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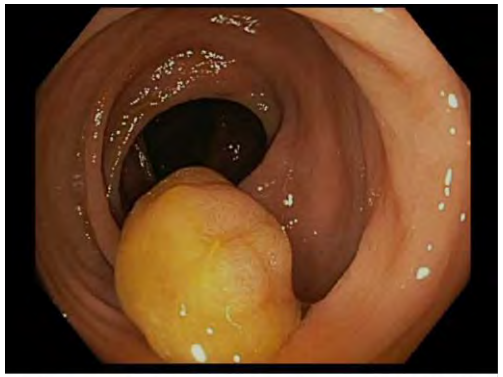
Normal appearance



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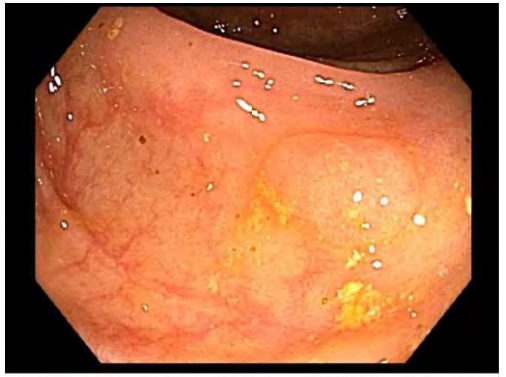
Semi-pedunculated polyp



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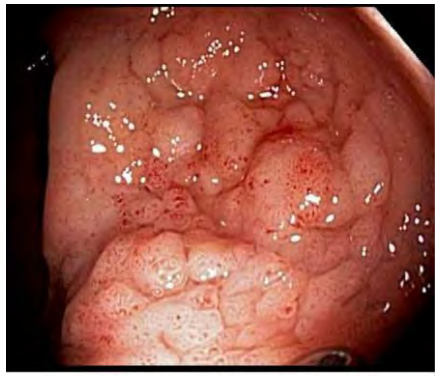
Sessile polyp



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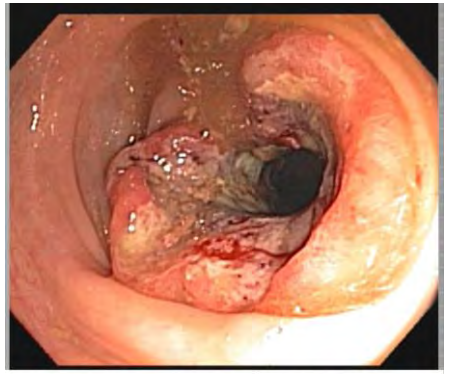
Villous polyp



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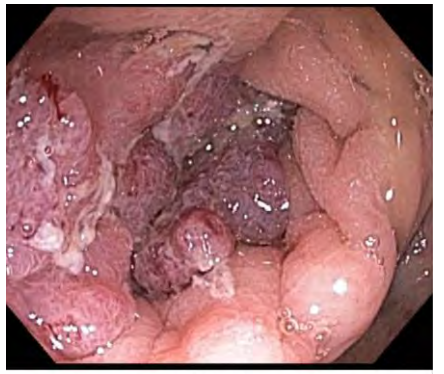
Colon carcinoma



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Obstructing colon mass

Image Source: Malignant Lesions of Colon, by Ira M. Hanan, *Atlas of Colon Pathology;* 2015

Nearly 70 years of progress needed to reach our current understanding of colon and rectal cancers … and to recognize that an even better understanding is forthcoming

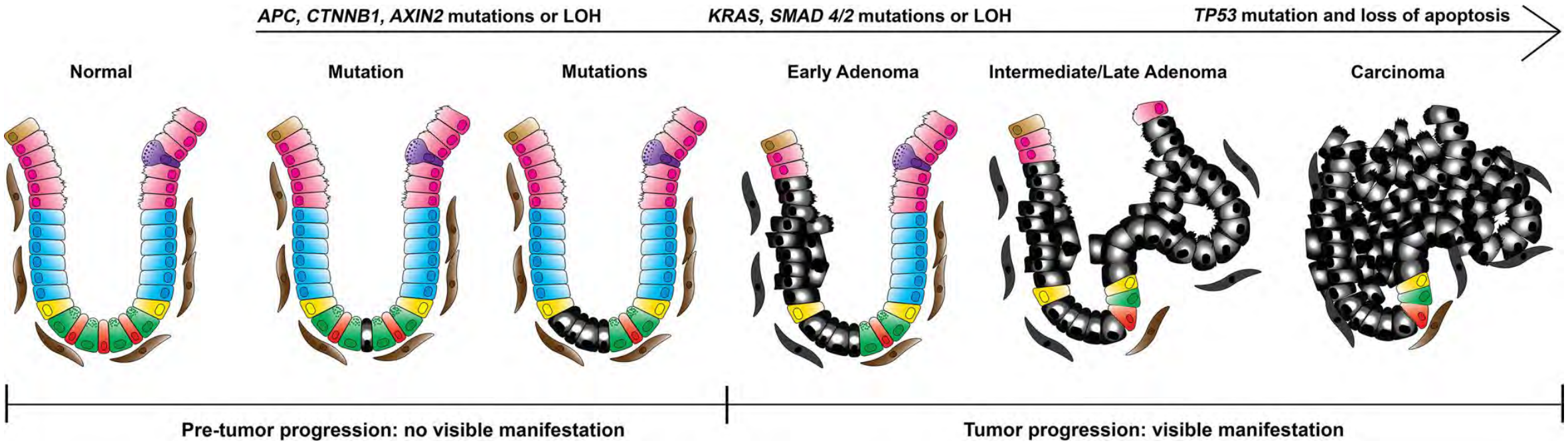
- **Early 1950s: Malignant potential of villous adenomas generally recognized, but the adenoma – carcinoma sequence greatly debated.**

- **Vogelstein et. al. (PNAS, 1988) provide evidence for a progressive model of sporadic colorectal tumorigenesis based on the accumulation of genetic alterations from small adenomas to large adenomas to invasive cancers.**
  - **These account for the majority of sporadic CRCs which have both structural and numerical chromosomal instability (CIN), and are typically aneuploid.**

- **Lynch, et. al. (Gastroenterology, 1993) recognized that colon cancers in hereditary nonpolyposis colorectal cancer (HNPCC, a.k.a., Lynch syndrome) were clinically-, genetically-, and histologically-distinct from sporadic CRCs.**
  - **These are associated with defects in DNA mismatch repair (MMR), resulting in microsatellite instability (MSI), and are typically diploid. While Lynch syndrome accounts for only ~3% of CRCs, ~15% of CRCs show MSI.**

- **Toyota, et. al. (PNAS, 1999) recognized the CpG island methylator phenotype (CIMP) of CRCs.**

A progressive model of sporadic colorectal tumorigenesis: From normal epithelium to adenomatous polyp to colon/rectal cancer



Foundations / Observations / Assumptions

- **Adenoma rare in individuals under 49**
- **Adenomas & CRC more prevalent in individuals 50 & older.**
- **Adenoma prevalence increases in the 6th, 7th, and 8th decades of life.**
- **~2-5 years from early to advanced adenoma.**
- **~2-5 years from advanced adenoma to early cancer.**

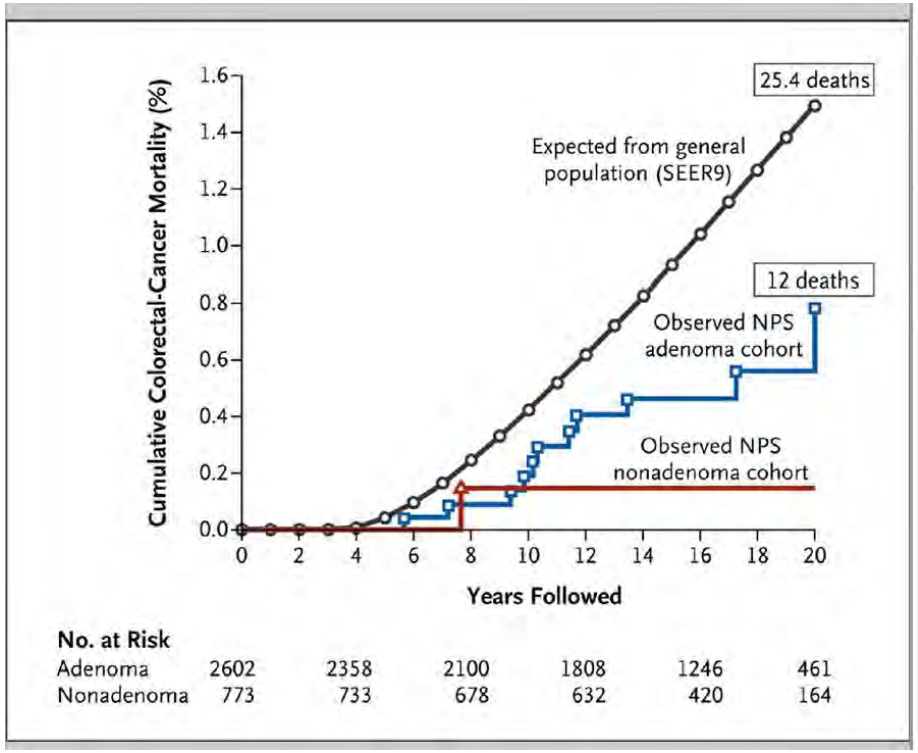
Ma, et. al. (2016) *J Gastroenterol* 51:841–852

Preventive CRC screening via colonoscopy & polypectomy:

Predicated on sporadic occurrence & progression of adenoma to carcinoma in "average risk" individuals

- **<10% of all adenomas become cancerous, but the vast majority of colorectal cancers develop from adenomas.**

- **1993 National Polyp Study provided proof-of-concept evidence that colonoscopic polypectomy reduced the incidence of colorectal cancer (Winawer, et. al. (1993) *NEJM* 329(27):1977-1981).**



2012 NPS follow-up study indicates that colonoscopic removal of adenomatous polyps reduces death from colorectal cancer by 53%. (Zauber, et. al., (2012) *NEJM*; 366:687-696).

Summary of Colorectal Cancer Risk Factors and Preventive Factors		
	Adverse Risk Factor	Beneficial Preventive Factor
Sociodemographic factors		
Older age	↑↑↑	
Male sex	↑↑	
Medical factors		
Family history	↑↑	
Inflammatory bowel disease	↑↑	
Diabetes	↑	
Helicobacter pylori infection	(↑)	
Other infections	(↑)	
Large bowel endoscopy		↓↓
Hormone replacement therapy		↓
Aspirin		↓
Statins		(↓)
Lifestyle factors		
Smoking	↑	
Excess alcohol consumption	↑	
Obesity	↑	
Physical activity		↓
Dietary factors		
High consumption of red and processed meat	↑	
Fruit and vegetables		(↓)
Cereal fiber and whole grain		(↓)
Fish		(↓)
Dairy Products		(↓)

Brenner, et. al. (2014) *Lancet* 383:1490-1502

2016 U.S. Preventive Services Task Force recommended CRC screening tests

Screening Test	Description	United States Preventive Services Task Force (USPSTF)	American Cancer Society–U.S. Multi-Society Task Force (ACS-USMSTF)
Fecal occult blood test (FOBT)* and fecal immunochemical test (FIT)*	Examination of the stool for traces of blood not visible to the naked eye	Recommends high- sensitivity FOBT and FIT annually for ages 50-75	Recommends high-sensitivity FOBT and FIT annually for ages ≥ 50
Sigmoidoscopy*	Internal examination of the lower part of the large intestine	Recommends every 5 years with high- sensitivity FOBT every 3 years for ages 50-75	Age ≥ 50, every 5 years
Double-contrast barium enema*	X-ray examination of the colon	--	Age ≥ 50, every 5 years
Colonoscopy	Internal examination of the entire large intestine	Recommends every 10 years for ages 50-75	Age ≥ 50, every 10 years
Computed tomography colonography*	Examination of the colon and rectum using pictures obtained using a computed tomography scanner	Age ≥ 50, every 5 years	Age ≥ 50, every 5 years
Fecal DNA*	Examination of the stool for traces of colorectal cancer DNA	Age ≥ 50, every 1 or 3 years	Age ≥ 50, every 3 years

**Positive findings require follow-up colonoscopy.*

Will USPSTF recommend CRC screening to begin at age 45 for average-risk Americans?

CA CANCER J CLIN 2018;68:250-281

Colorectal Cancer Screening for Average-Risk Adults: 2018 Guideline Update From the American Cancer Society

Andrew M.D. Wolf, MD[1]; Elizabeth T.H. Fontham, MPH, DrPH[2]; Timothy R. Church, PhD[3]; Christopher R. Flowers, MD, MS[4]; Carmen E. Guerra, MD[5]; Samuel J. LaMonte, MD[6]; Ruth Etzioni, PhD[7]; Matthew T. McKenna, MD[8]; Kevin C. Oeffinger, MD[9]; Ya-Chen Tina Shih, PhD[10]; Louise C. Walter, MD[11]; Kimberly S. Andrews, BA[12]; Otis W. Brawley, MD[13]; Durado Brooks, MD, MPH[14]; Stacey A. Fedewa, PhD, MPH[15]; Deana Manassaram-Baptiste, PhD, MPH[16]; Rebecca L. Siegel, MPH[17]; Richard C. Wender, MD[18]; Robert A. Smith, PhD[19]

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Additional supporting information may be found online in the Supporting Information section at the end of the article.

Abstract: In the United States, colorectal cancer (CRC) is the fourth most common cancer diagnosed among adults and the second leading cause of death from cancer. For this guideline update, the American Cancer Society (ACS) used an existing systematic evidence review of the CRC screening literature and microsimulation modeling analyses, including a new evaluation of the age to begin screening by race and sex and additional modeling that incorporates changes in US CRC incidence. Screening with any one of multiple options is associated with a significant reduction in CRC incidence through the detection and removal of adenomatous polyps and other precancerous lesions and with a reduction in mortality through incidence reduction and early detection of CRC. Results from modeling analyses identified efficient and model-recommendable strategies that started screening at age 45 years. The ACS Guideline Development Group applied the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria in developing and rating the recommendations. The ACS recommends that adults aged 45 years and older with an average risk of CRC undergo regular screening with either a high-sensitivity stool-based test or a structural (visual) examination, depending on patient preference and test availability. As a part of the screening process, all positive results on noncolonoscopy screening tests should be followed up with timely colonoscopy. The recommendation to begin screening at age 45 years is a *qualified recommendation*. The recommendation for regular screening in adults aged 50 years and older is a *strong recommendation*. The ACS recommends (*qualified recommendations*) that: 1) average-risk adults in good health with a life expectancy of more than 10 years continue CRC screening through the age of 75 years; 2) clinicians individualize CRC screening decisions for individuals aged 76 through 85 years based on patient preferences, life expectancy, health status, and prior screening history; and 3) clinicians discourage individuals older than 85 years from continuing CRC screening. The options for CRC screening are: fecal immunochemical test annually; high-sensitivity, guaiac-based fecal occult blood test annually; multitarget stool DNA test every 3 years; colonoscopy every 10 years; computed tomography colonography every 5 years; and flexible sigmoidoscopy every 5 years. CA Cancer J Clin 2018;68:250-281.
© 2018 American Cancer Society.

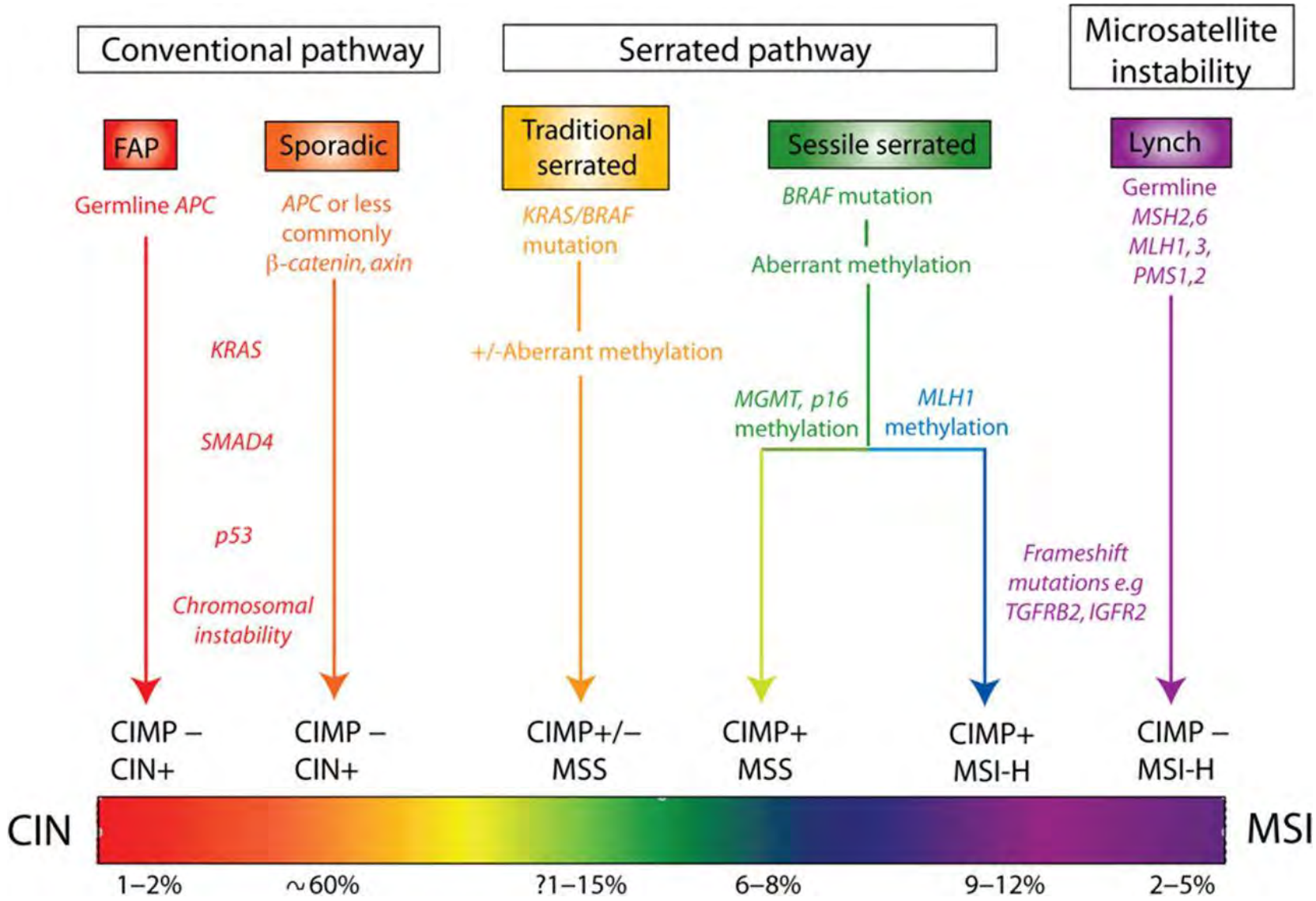
Keywords: adenoma, colonoscopy, computed tomography colonoscopy, colorectal and rectal neoplasms, mass screening and early detection, mortality, occult blood, radiography, sigmoidoscopy, stool testing

Wolf, et. al., (2018)
CA: A Cancer Journal for Clinicians
68:250-281

Simplified summary of CRC treatment plans

Stage	Colon Cancer	Rectal Cancer
0	Surgery only (polypectomy or partial colectomy)	Surgery only (polypectomy, local excision or transanal resection)
I	Surgery only (polypectomy or partial colectomy with lymph node dissection)	Surgery (above or proctectomy w/ colo-anal anastomosis, other surgical options) Possible radiotherapy if patient not suitable for surgery
II	Surgery (partial colectomy with lymph node dissection) Possible chemotherapy (typically (5-FU + leucovorin) or capecitibine) Possible radiotherapy	Combination modality (surgery + (neoadjuvant & adjuvant) chemotherapy ± radiation) Chemo options include FOLFOX (Oxaliplatin + 5-FU + leucovorin) or CAPOX (capecitibine + oxaliplatin)
III	Surgery w/ lymph node dissection + adjuvant chemotherapy (FOLFOX or CAPOX) Possible adjuvant radiotherapy	Combination modality (neoadjuvant chemotherapy + radiation, then surgery + adjuvant/consolidation chemotherapy)
IV (Clinical trials offered)	Systemic chemotherapy (above or FOLFIRI (5-FU + leucovorin + irinotecan) or FOLFOXIRI) ± targeted biologic therapies (e.g., bevacizumab or cetuximab) Possible surgery (diverting colostomy + excise metastases)	Systemic chemotherapy (above or FOLFIRI or FOLFOXIRI) or via hepatic artery infusion) ± targeted biologic therapies + radiation + possible surgery Possible ablation or embolization
Recurrent	Clinical trials frequently offered Options & treatment goals dictated by local vs. distant recurrence	Clinical trials frequently offered Options & treatment goals dictated by local vs. distant recurrence

Not all CRCs develop through the conventional sporadic route: The spectrum of CRC subtypes is evolving.



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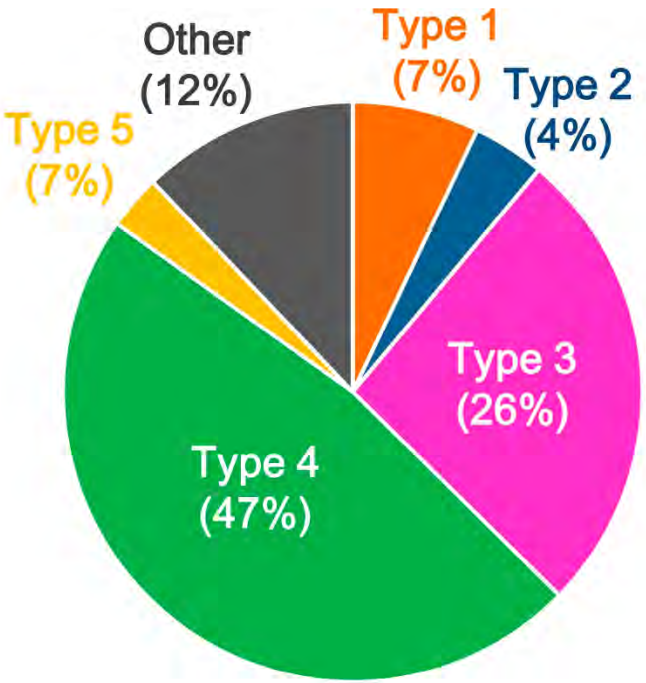
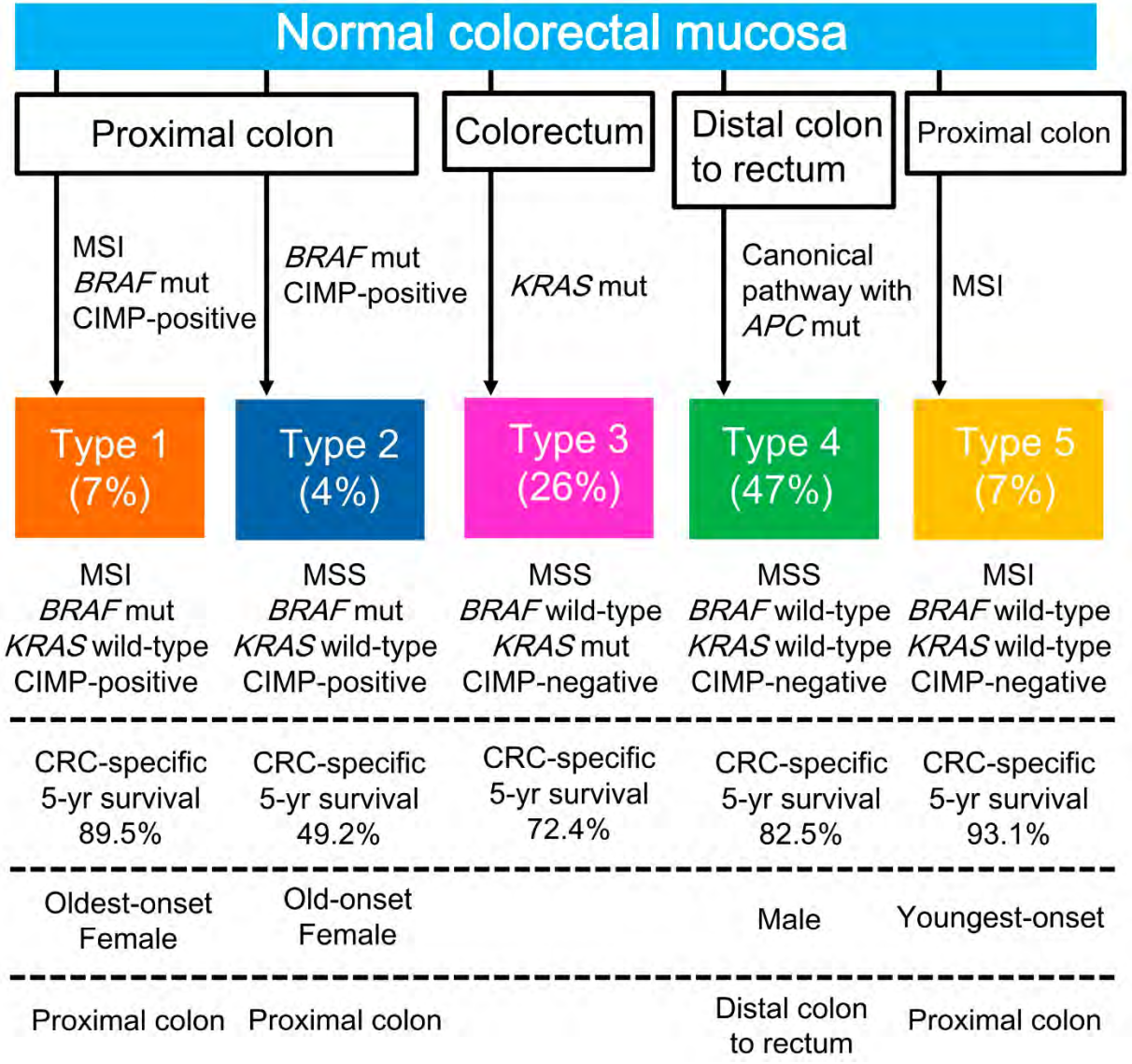
East et al. Gut 2017;66:1181-1196

GUT

Different CRC subtypes are associated with varying prognoses





Inamura (2018) *Cancers* 10:26 (after Phipps, et. al. (2015) *Gastroenterology* 148:77-87).

Multiple classification systems describe the heterogeneity of CRC subtypes. We NEED to transform this into clinically actionable information.

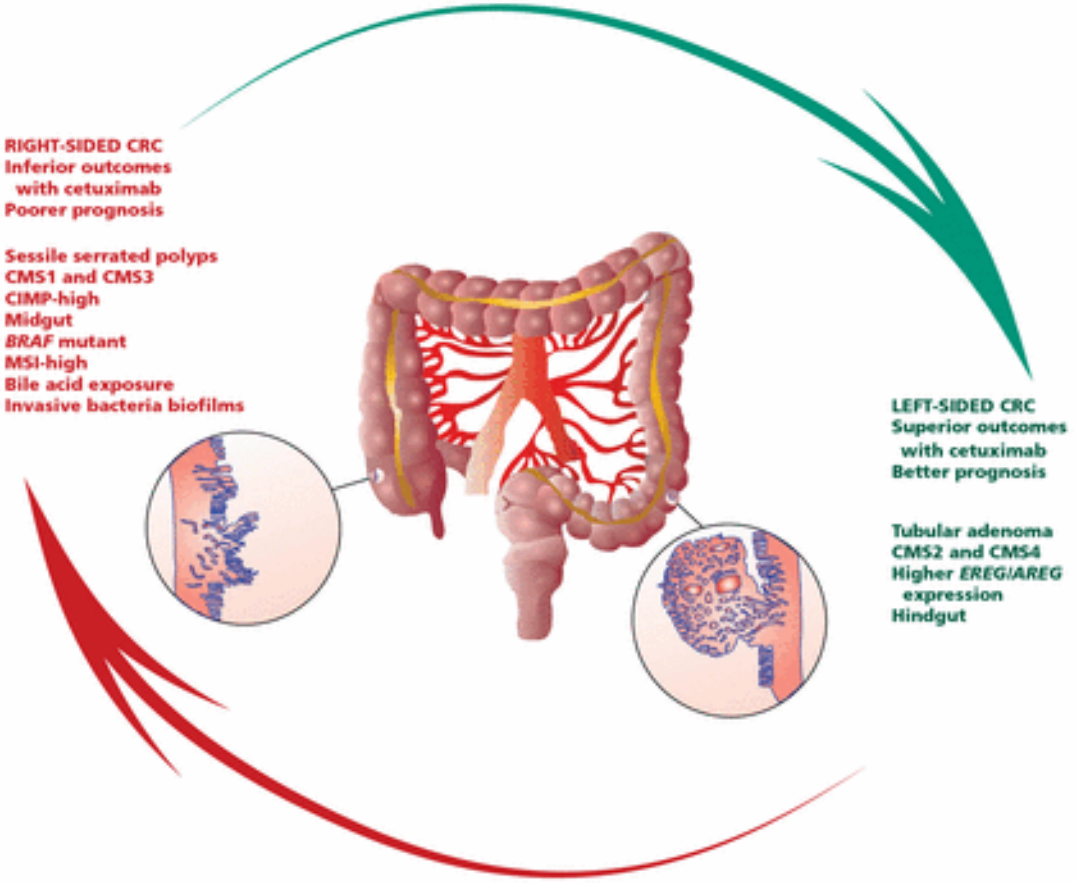


Figure 2. Summary of key biologic differences between right- and left-sided CRCs.
Abbreviations: AREG, amphiregulin; CIMP, CpG island methylator phenotype; CMS, consensus molecular subtype; CRCs, colorectal cancers; EREG, epiregulin; MSI, microsatellite instability.

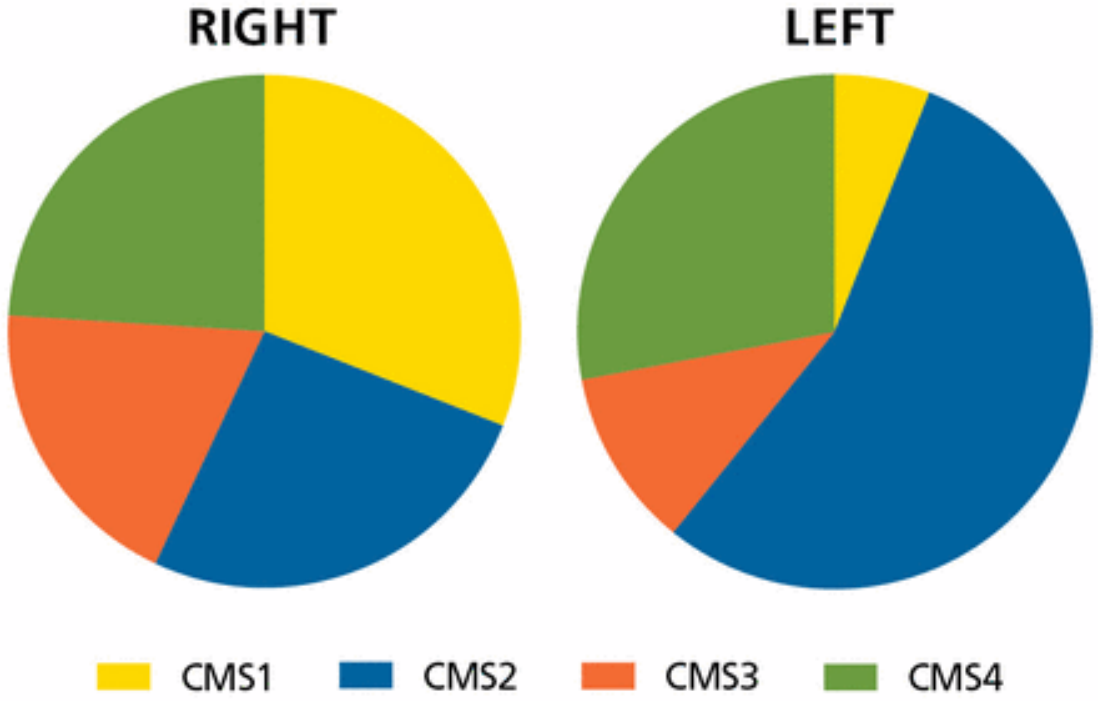


Figure 1. Distribution of CMS by right- and left-sided CRC.[65] Right-side CRC was defined as the cecum through transverse colon, and left-side CRC was defined as the splenic flexure through rectum.
Abbreviations: CMS, consensus molecular subtype; CRC, colorectal cancer.

Lee, et. al. (2017) *J Natl Compr Canc Netw;* 15(3):411–419

Revised Bethesda Guidelines for Testing Colorectal Tumors for MSI

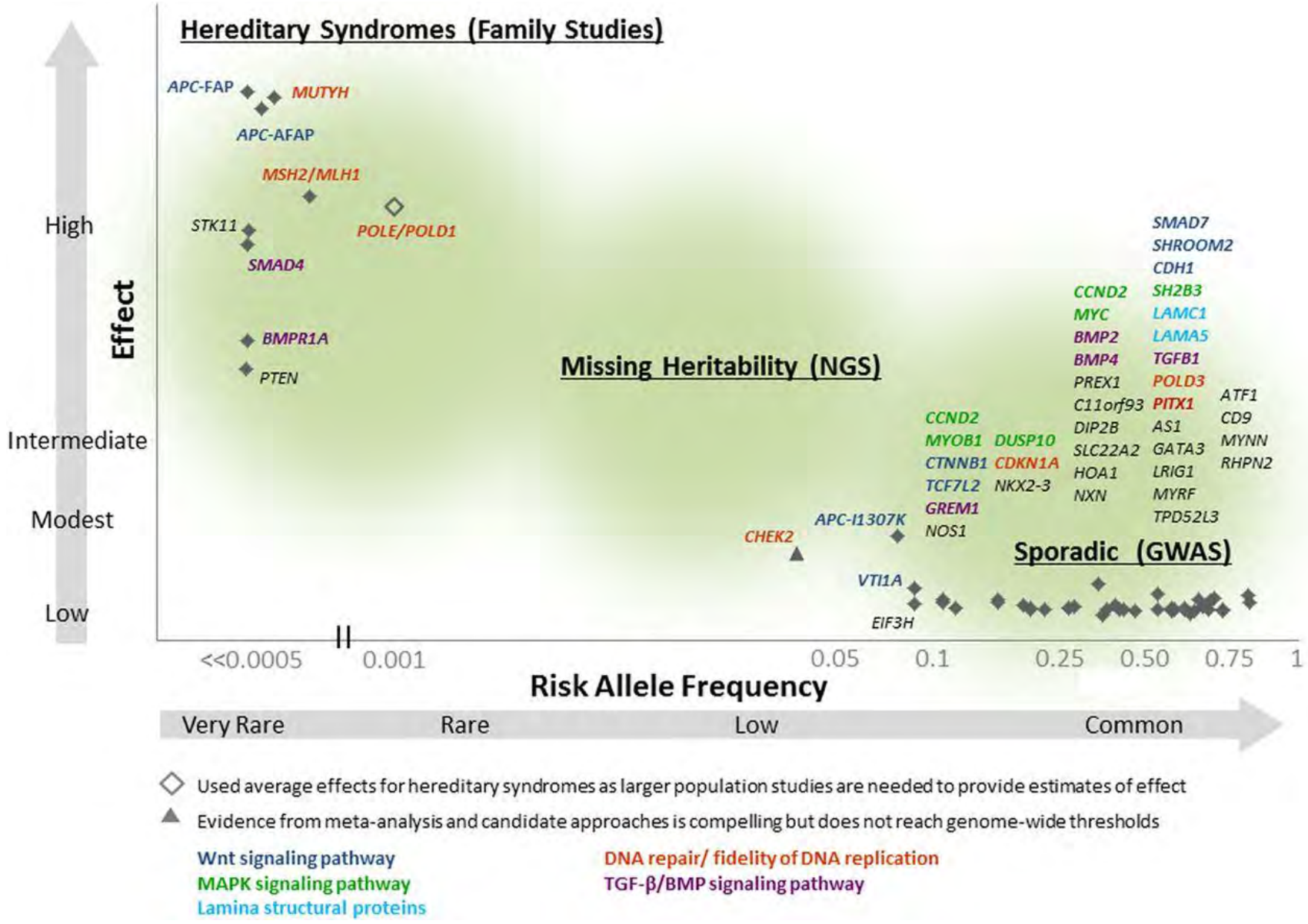
(Pembrolizumab, an Immune Checkpoint Inhibitor, is now indicated for Lynch syndrome CRCs and other MSI-H / dMMR (defective DNA Mismatch Repair) CRCs)

- **Tumors from individuals should be tested for MSI (microsatellite instability) in the following situations:**
- **Colorectal cancer diagnosed in a patient who is < 50 years of age**
- **Presence of synchronous, metachronous colorectal or other Lynch-associated tumors,* regardless of age**
- **Colorectal cancer with the MSI-H histology diagnosed in a patient who is < 60 years of age**
- **Colorectal cancer diagnosed in one or more first-degree relatives with a Lynch-related tumor, with one of the cancers being diagnosed under age 50 years**
- **Colorectal cancer diagnosed in two or more first- or second-degree relatives with Lynch-related tumors, regardless of age**

***Lynch syndrome–related tumors include**

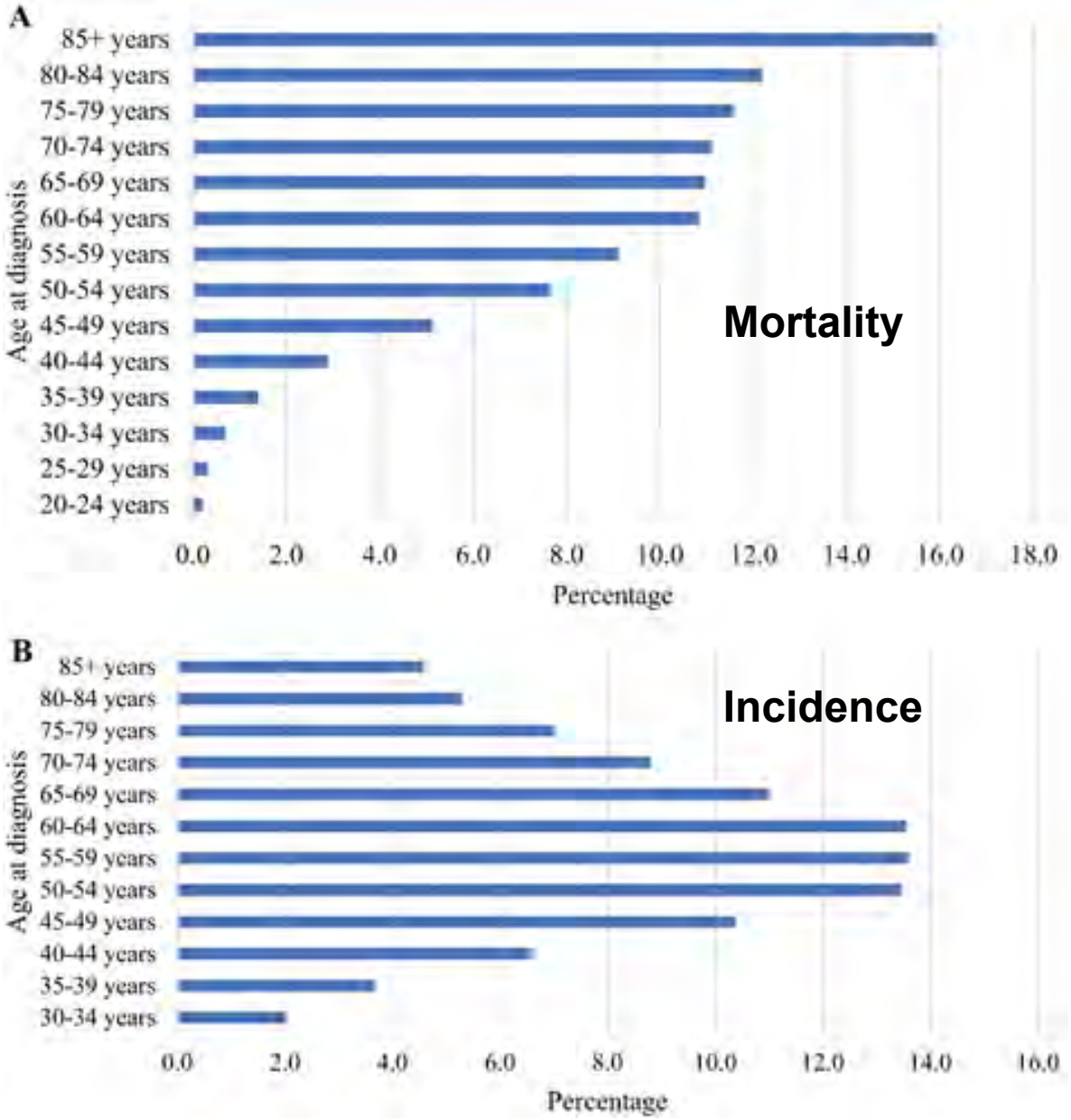
- **Colorectal tumors**
- **Endometrial tumors**
- **Stomach tumors**
- **Ovarian tumors**
- **Pancreatic tumors**
- **Ureter and renal pelvic tumors**
- **Biliary tract tumors**
- **Brain (usually glioblastoma, as seen in Turcot syndrome) tumors**
- **Sebaceous gland adenomas**
- **Keratoacanthomas in Muir-Torre syndrome**
- **Carcinomas of the small bowel**

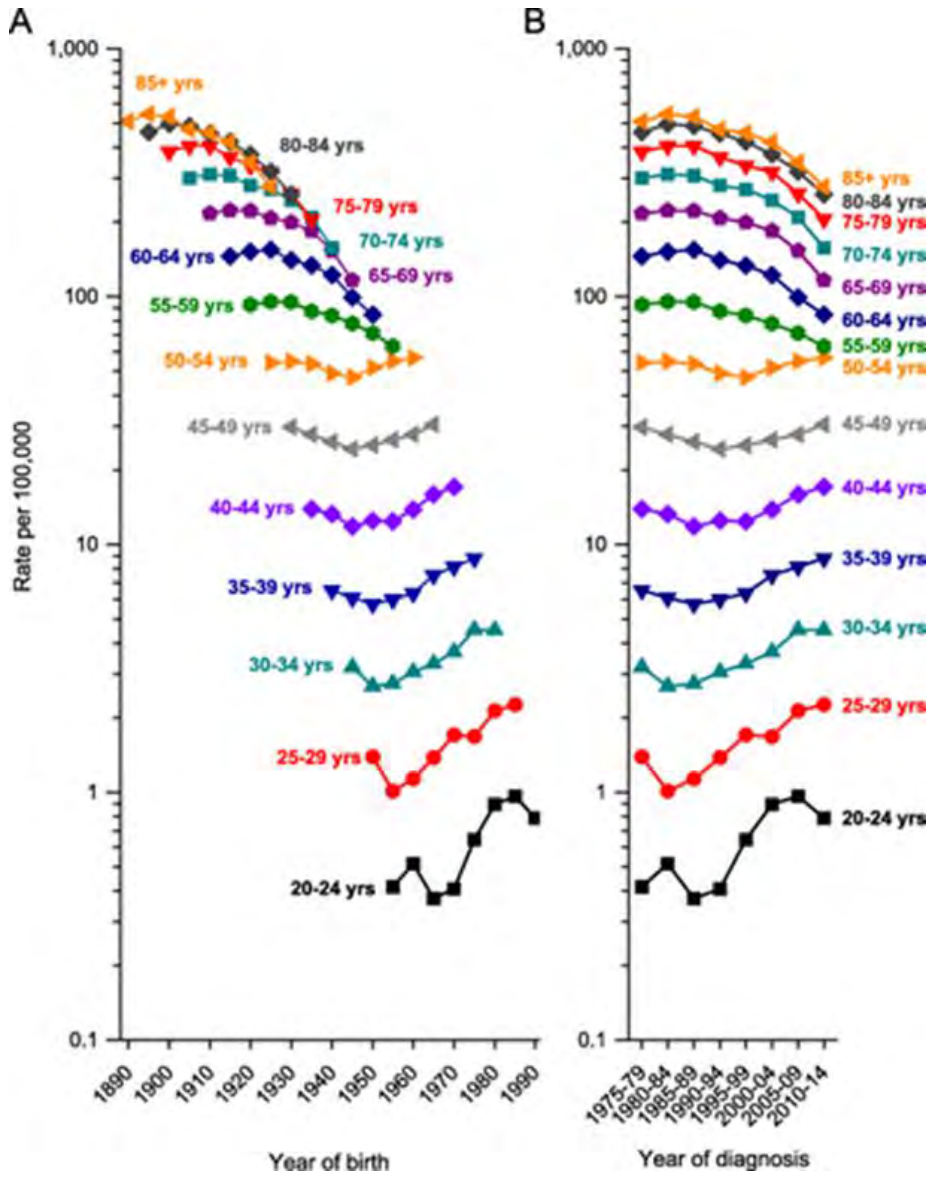
Distribution of known colorectal cancer genetic susceptibility loci



Peters, et. al., *Gut* (2015) 64:1623-1636.

Distribution of Colorectal Cancer Burden by Age at Diagnosis (U.S.A.)





Wolf, et. al. (2018) *CA Cancer J Clin*; 68:250–281

Early-onset colorectal cancers:
An urgent need for improved primary-care provider awareness

Characteristic (relative to >50 y.o.)	Cohort size	Statistical confidence	SOURCE
Primary tumors in the distal colon or rectum	4 cohorts totaling 36,000 pts. w/ CRC	P < .0001	Willauer, et. al., (2019)
Primary tumor site increases in a step-wise fashion from the ascending colon to rectum	369,796 pts. w/ CRC from 2000-2011 SEER	$P < 2.2e^{-16}$	Yeo, et. al., (2017)
Synchronous metastatic disease	4 cohorts totaling 36,000 pts. w/ CRC	P = .009	Willauer, et. al., (2019)
Associated with distant disease	369,796 pts. w/ CRC from 2000-2011 SEER	P < .001	Yeo, et. al., (2017)
Traditional risk factors (obesity, diabetes, smoking, excess alcohol consumption) NOT associated with early-onset CRC	369,796 pts. w/ CRC from 2000-2011 SEER	P = 0.006, 0.5812, 0.6465, and 0.6649, respectively	Yeo, et. al., (2017)
Difference in Consensus Molecular Subtype (CMS) distribution, with markedly higher prevalence of CMS1 in early-onset CRCs	626 patients	P = 0.0003	Willauer, et. al., (2019)

Sources:
Willauer, et. Al., (2019): *Cancer* (doi: 10.1002/cncr.31994. [Epub ahead of print])
Yeo, et. Al., (2017): *Clinical Colorectal Cancer*, 16(4): 293-299 (doi: 10.1016/j.clcc.2017.06.002)

Summary

- **CRC epidemiology reveals changing landscape of disease.**
- **CRC screening options are varied & require colonoscopy for confirmation.**
- **CRC cancer biology explains why prevention is highly effective for average-risk individuals.**
- **CRC risk factors include intrinsic, behavioral, environmental and socio-economic factors.**
- **CRC genetic factors can identify high-risk individuals in affected families and may be useful in treatment decisions.**
- **CRC in young adults requires attention to symptoms to avoid delays in diagnosis.**
- **The elimination of deaths caused by CRC will require additional translational and clinical research, and improvements in health care systems and policies.**


Thank you for your attention.
Any questions?