Natural History and Epidemiology of Colorectal Cancer

Prevent Cancer Foundation
2018 Dialogue for Action
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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.**

Why focus on colorectal cancer?

- CRC is highly preventable & declining in most states.

- CRC is ~~2nd~~ 3rd most common cancer in men + women.
  - Estimated 97,220 new cases of colon cancer in 2018 (source: ACS)
  - Estimated 43,030 new cases of rectal cancer in 2018 (source: ACS)

- CRC is 2nd leading cause of cancer death in men + women.
  - Estimated 50,630 deaths during 2018 (source: ACS)

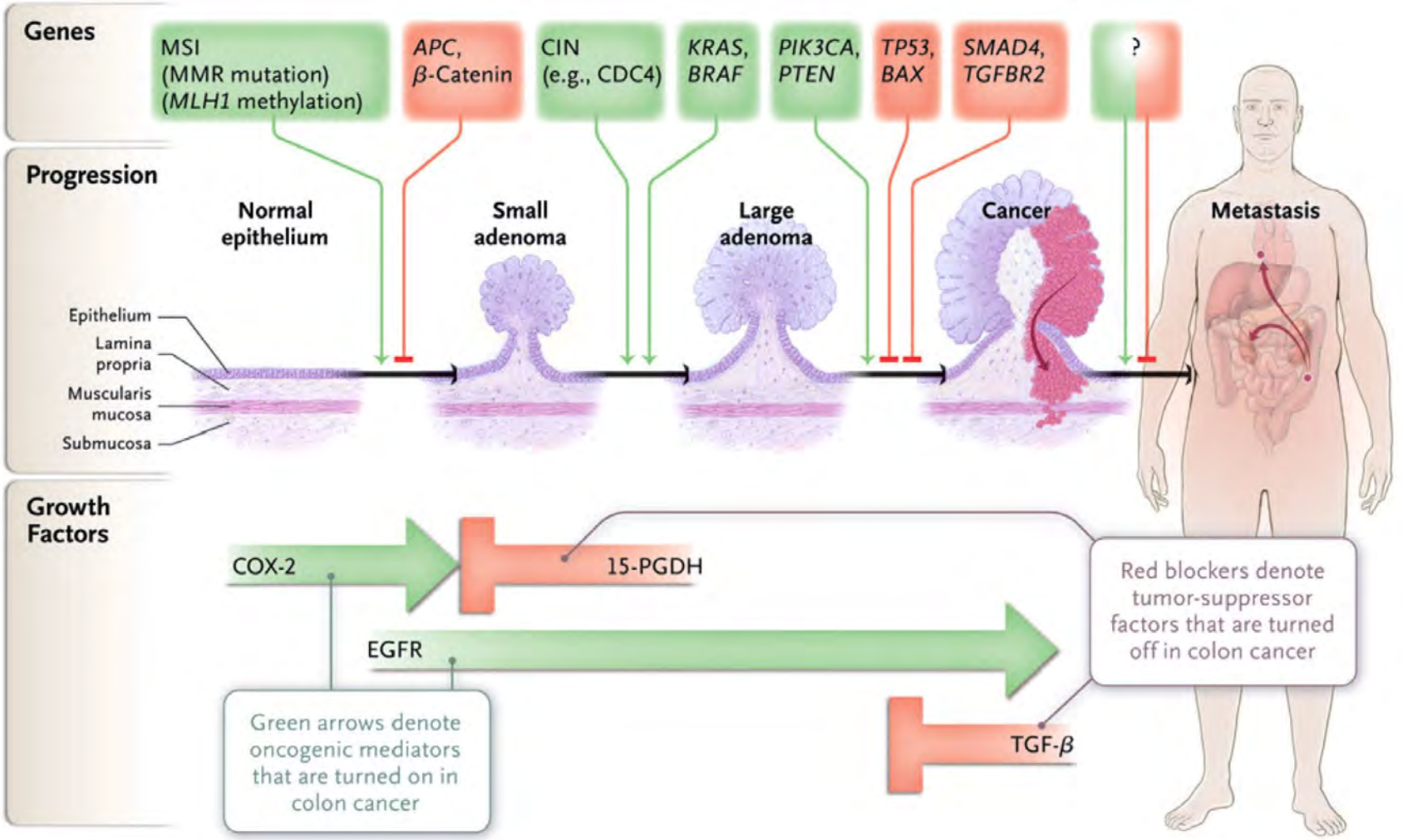
- CRC treatment costs are 2nd highest of all cancer sites.

- CRC screens are net cost-SAVING.

Learning objectives of this presentation

Topic to be covered	Take-home message
Sequence of development from polyp to cancer	CRC cancer biology explains why prevention is highly effective, but atypical CRC cancer biology may shed light on future progress
Screening options	Many choices available for preventive and early-detection screens, which all require colonoscopy for diagnostic confirmation
CRC screening effectiveness requires effective therapy	Early identification of CRC via screening results in optimal outcomes with less toxic, less expensive medical procedures
Epidemiology of colorectal cancer	Dynamic changes in CRC epidemiology reflect changing landscape of disparately-distributed positive & negative risk factors
Increased incidence of colorectal cancer in people younger than 50	Causes of recent trends are unknown; requires physicians' attention to symptoms to avoid delays in diagnosis & treatment
Genetics and colorectal cancer	Genetic factors can identify young high-risk individuals and may be useful in treatment decisions
Risk factors associated with colorectal cancer	CRC risk factors include intrinsic, behavioral, environmental and socio-economic factors.

A generalized (Vogelstein) model of CRC development & progression



- Adenoma is precursor to CRC, rarely occurs in individuals under 49, adenomas & CRC more prevalent later in life.
- In the 6th, 7th, and 8th decades of life the prevalence of adenomas increases.
- The dwell time of an early to advanced adenoma ~2-5 years.
- Similarly, the dwell time of an advanced adenoma to early cancer ~2-5 years.

Flexible fiber optics revolutionized CRC prevention & control in 1973 with the introduction of colonoscopy

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

published in the *New England Journal of Medicine*

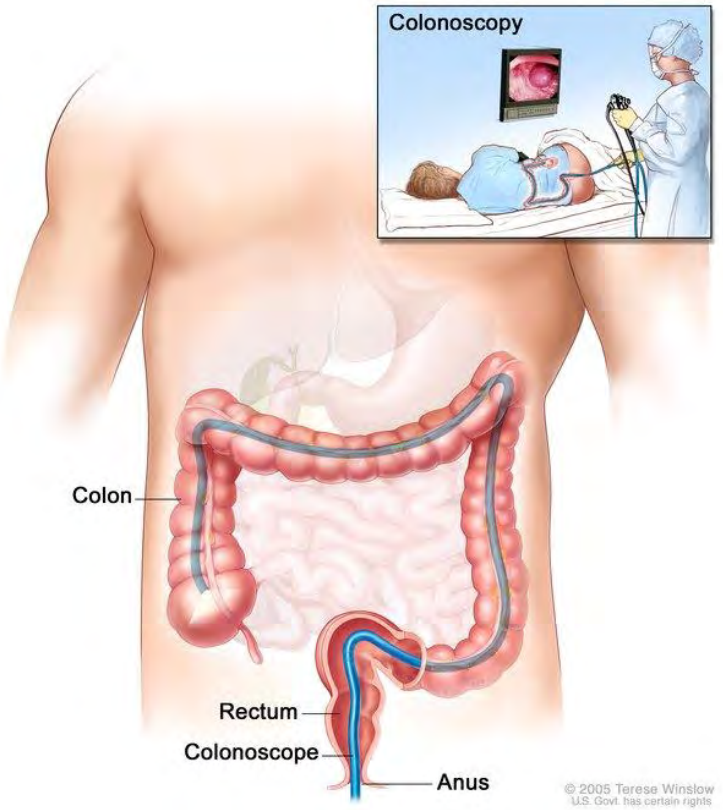
(288:329-332)

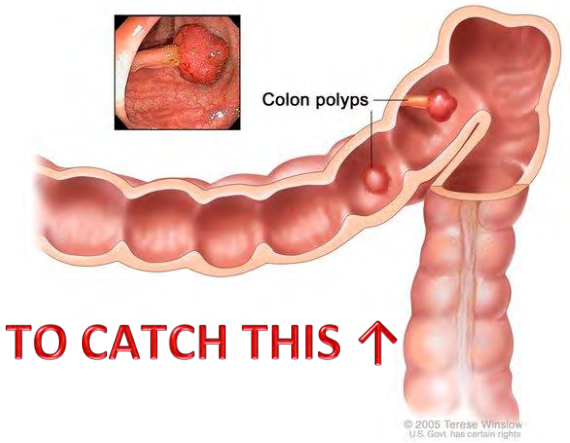
on February 15, 1973

by

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

DO THIS ↓





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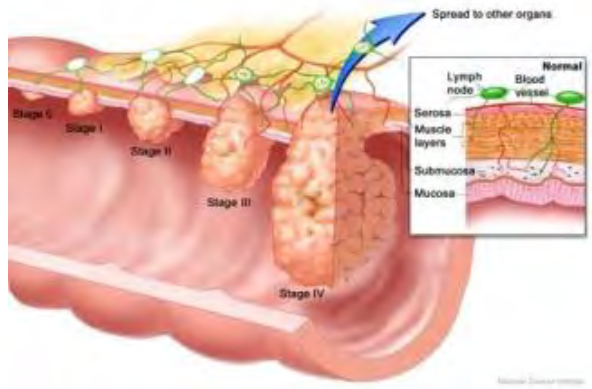
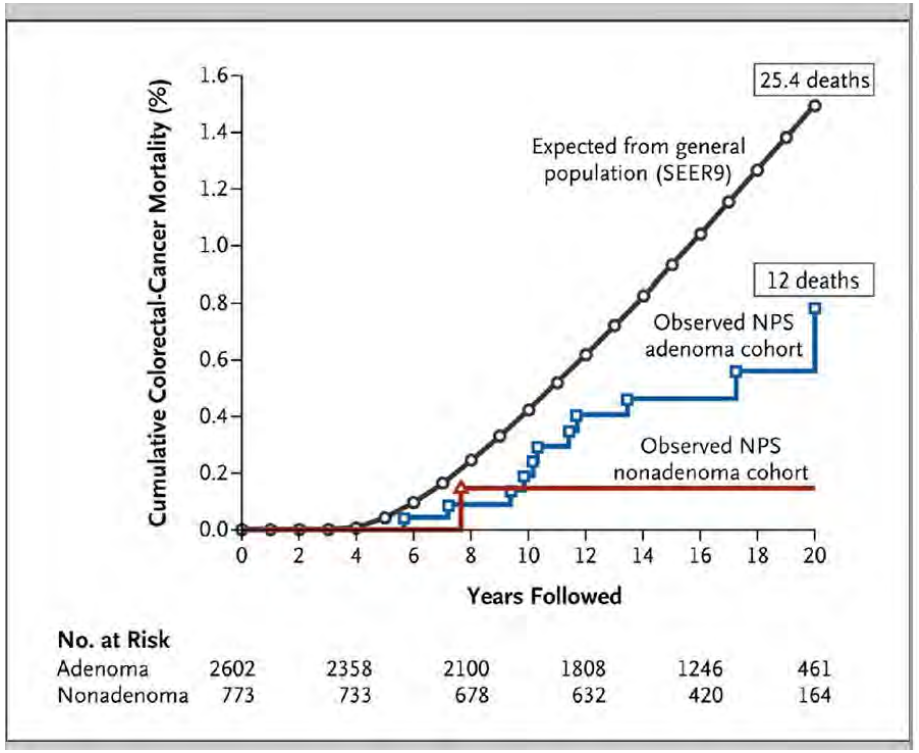


Can colonoscopy / polypectomy *alone* eliminate CRC mortality?

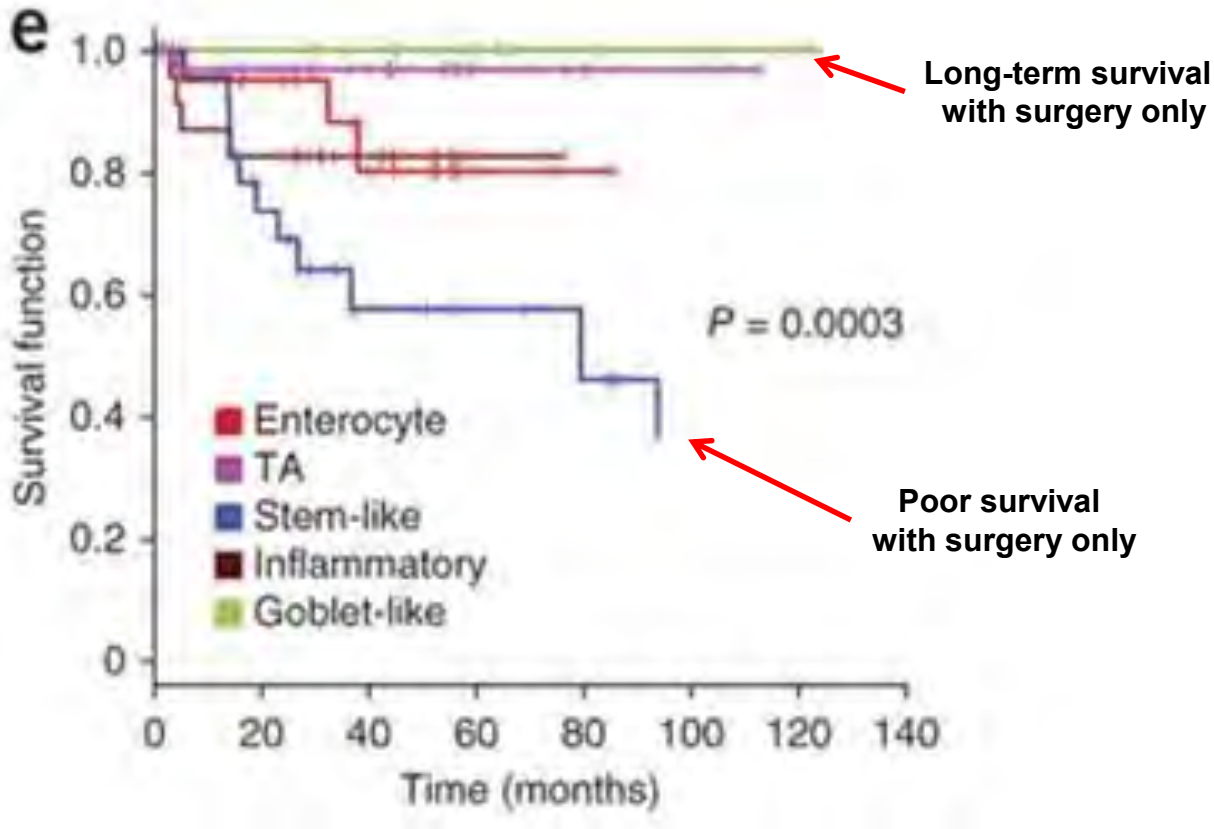
- **<10% of all adenomas become cancerous, but**
- **> 95% of colorectal cancers develop from adenomas.**

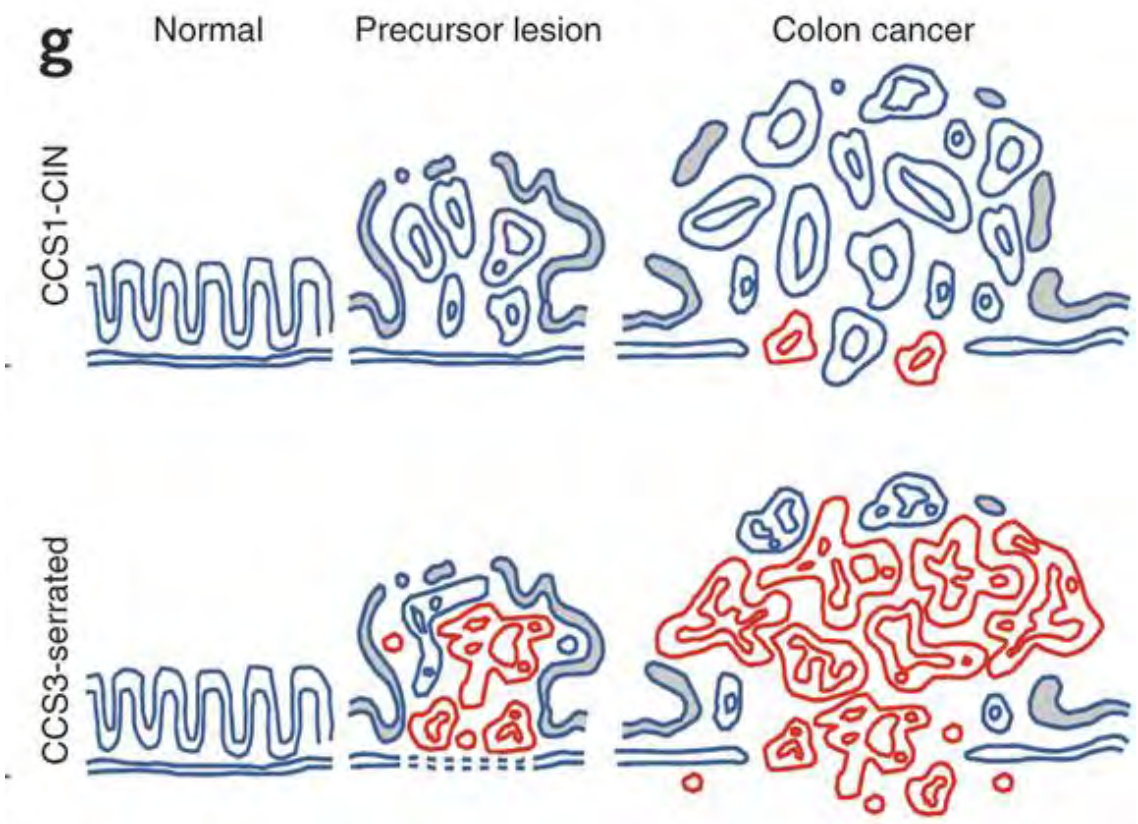
- **1993 National Polyp Study provided proof-of-concept evidence that colonoscopic polypectomy reduced the incidence of colorectal cancer (Winawer, et. al. (1993) *NEJM* 329(27):1977-1981).**



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).

Do atypical CRCs with early metastatic tendencies adversely affect survival outcomes?
Does this signal a need for changing clinical practice guidelines?





Sadanandam, et. al., (2013) *Nature Medicine* 19:619–625

de Sousa e Melo, et. al., (2013) *Nature Medicine* 19:614–618

Why does screening matter?

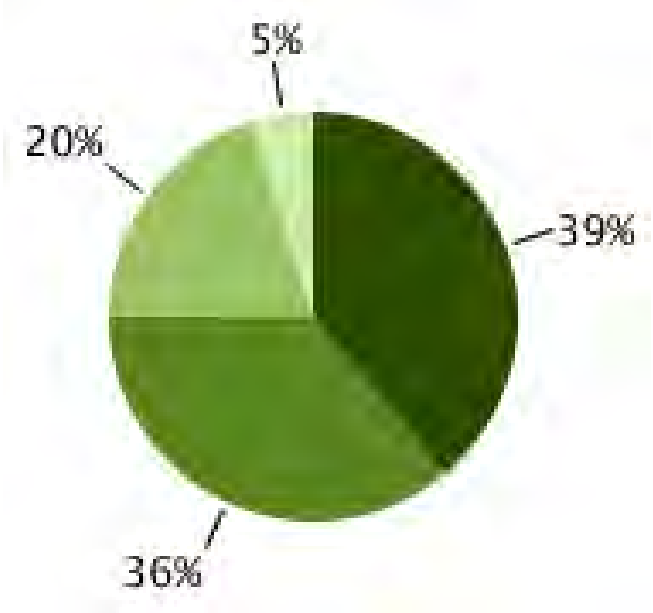
Because survival is tremendously improved by early-stage diagnosis

(SEER 2005-2011 Data, All Races, Both Sexes)

Percent of Cases by Stage

Distant (20%)
Cancer Has Metastasized

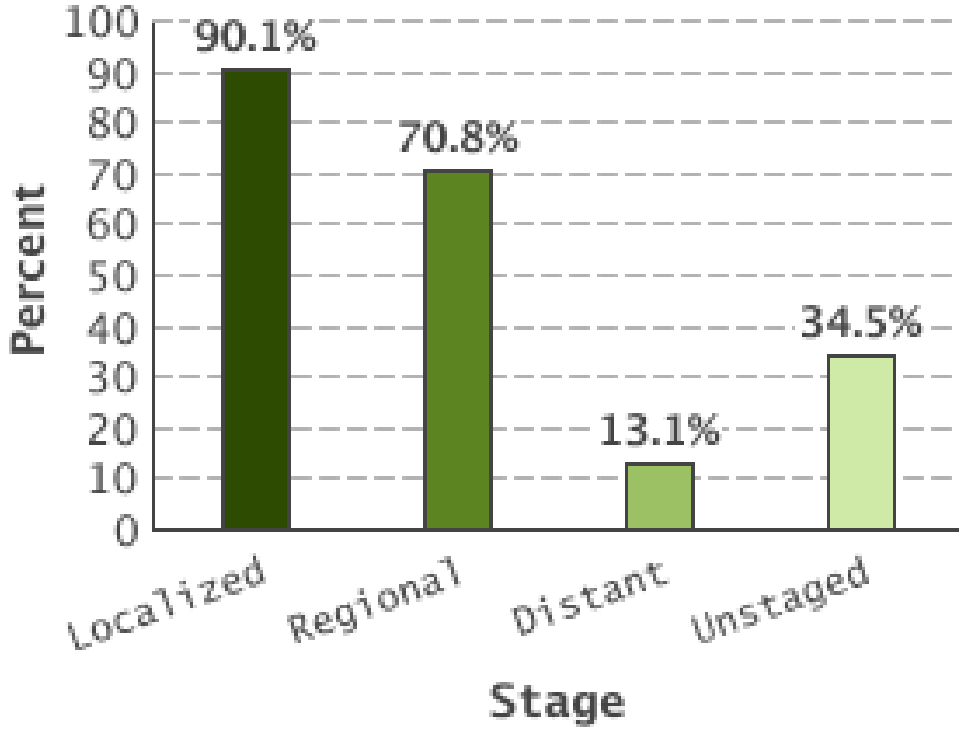
Unknown (5%)
Unstaged



Localized (39%)
Confined to Primary Site

Regional (36%)
Spread to Regional Lymph Nodes

5-Year Relative Survival



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

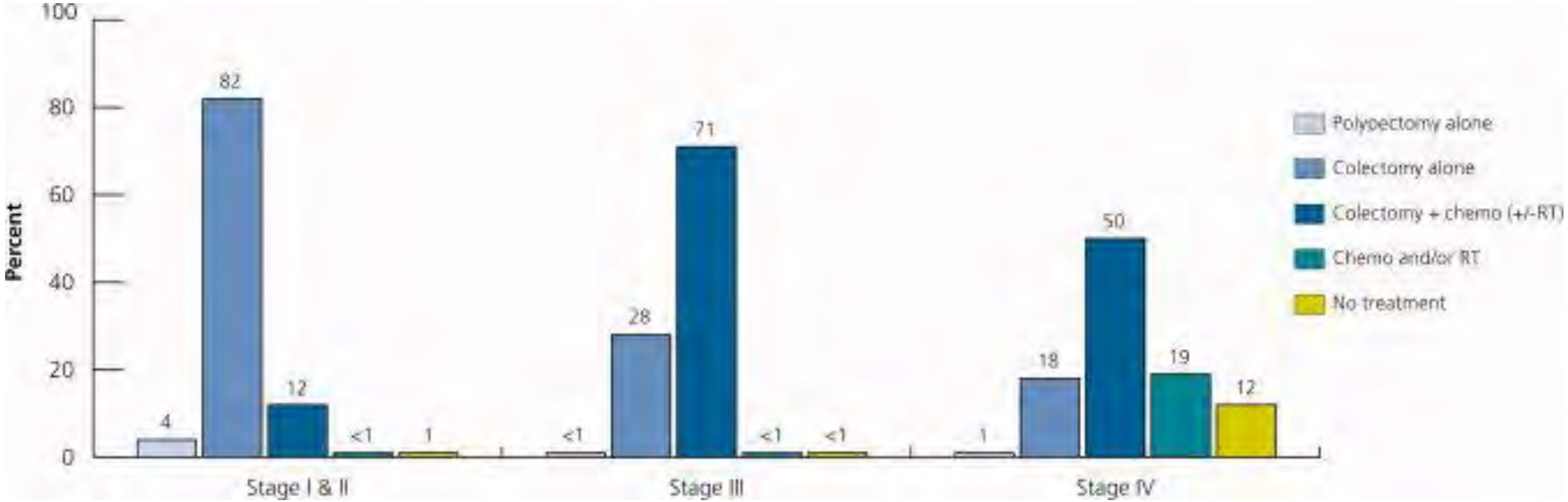
Screening Test	Description	United States Preventive Services Task Force (USPSTF)	American Cancer Society–U.S. Multi-Society Task Force (ACS-USMSTF)
Fecal occult blood test (FOBT)* and fecal immunochemical test (FIT)*	Examination of the stool for traces of blood not visible to the naked eye	Recommends 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 **Positive findings require follow-up 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

Implementing colonoscopy navigation improves practice-centered outcomes

	Intervention Group N = 131	Control Group N = 75	Intervention Group Versus Control Group	
Outcome	**%**	**%**	**Odds Ratio**	**p (Fisher exact test)**
Colonoscopy completed (w/in 12 m)	96.2	69.3	11.2	<0.001
Adequate bowel preparation quality	97.6	87.5	5.9	0.010
Missed appointment / no show	0.0	15.6	48.4	<0.001
Cancellation <24 h before appointment	0.8	16.0	24.8	<0.001
Results communicated to patient	100.0	96.2	10.1	0.084
Results communicated to PCP	100.0	48.1	272.2	<0.001
Final recommended rescreening interval consistent with clinical guidelines	100.0	82.4	54.0	<0.001

Rice, et. al. (2017) *Cancer* 123:3356-3366.

Treatment of most CRCs is based on stage of disease



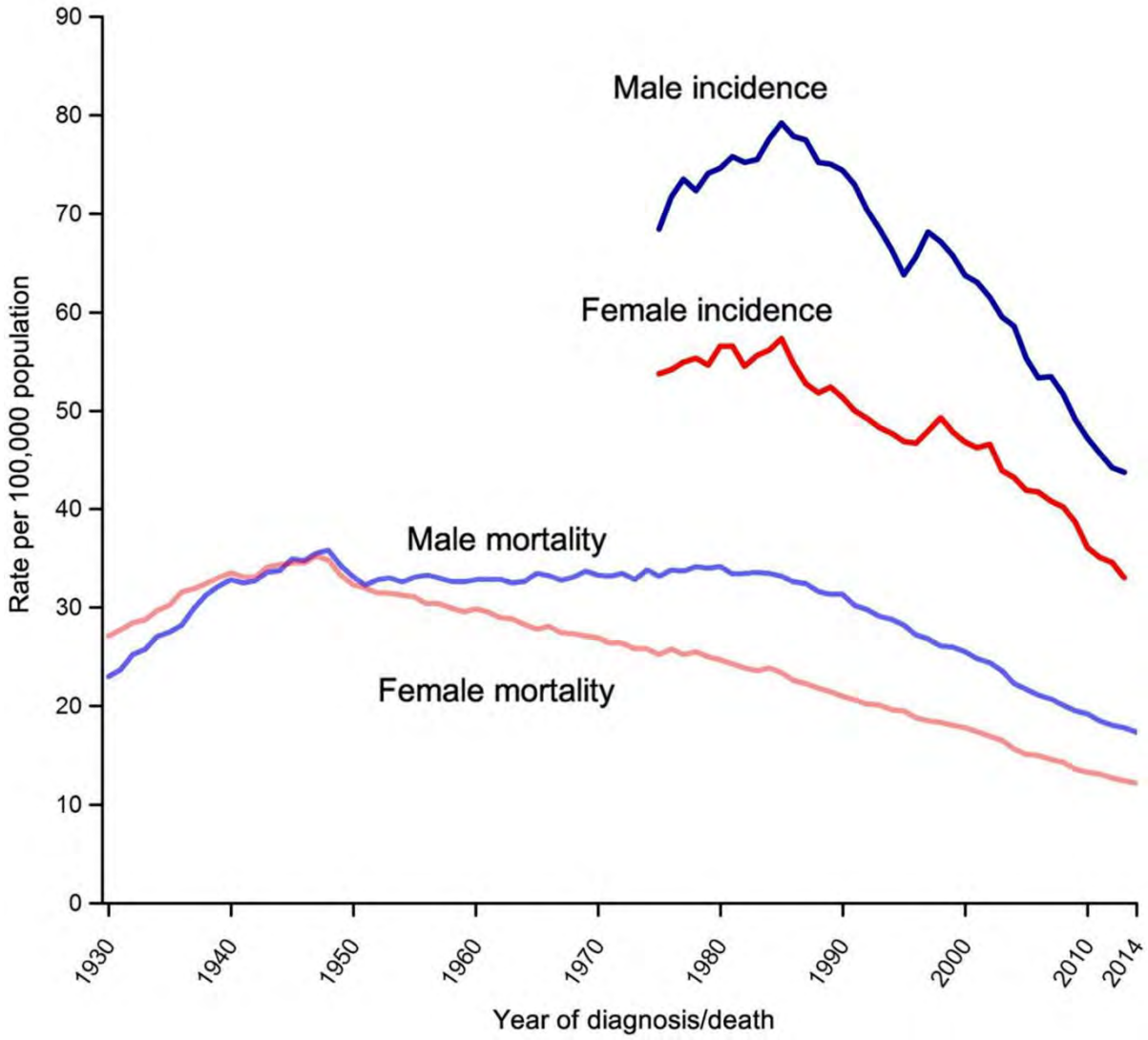
86% of all stage I & II CRCs treated with surgery alone

Siegel, et. al. (2012) *CA: A Cancer Journal for Clinicians*, 62: 220–241.

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 CapeOx (capecitibine + oxaliplatin)
III	Surgery w/ lymph node dissection + adjuvant chemotherapy (FOLFOX or CapeOx) 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

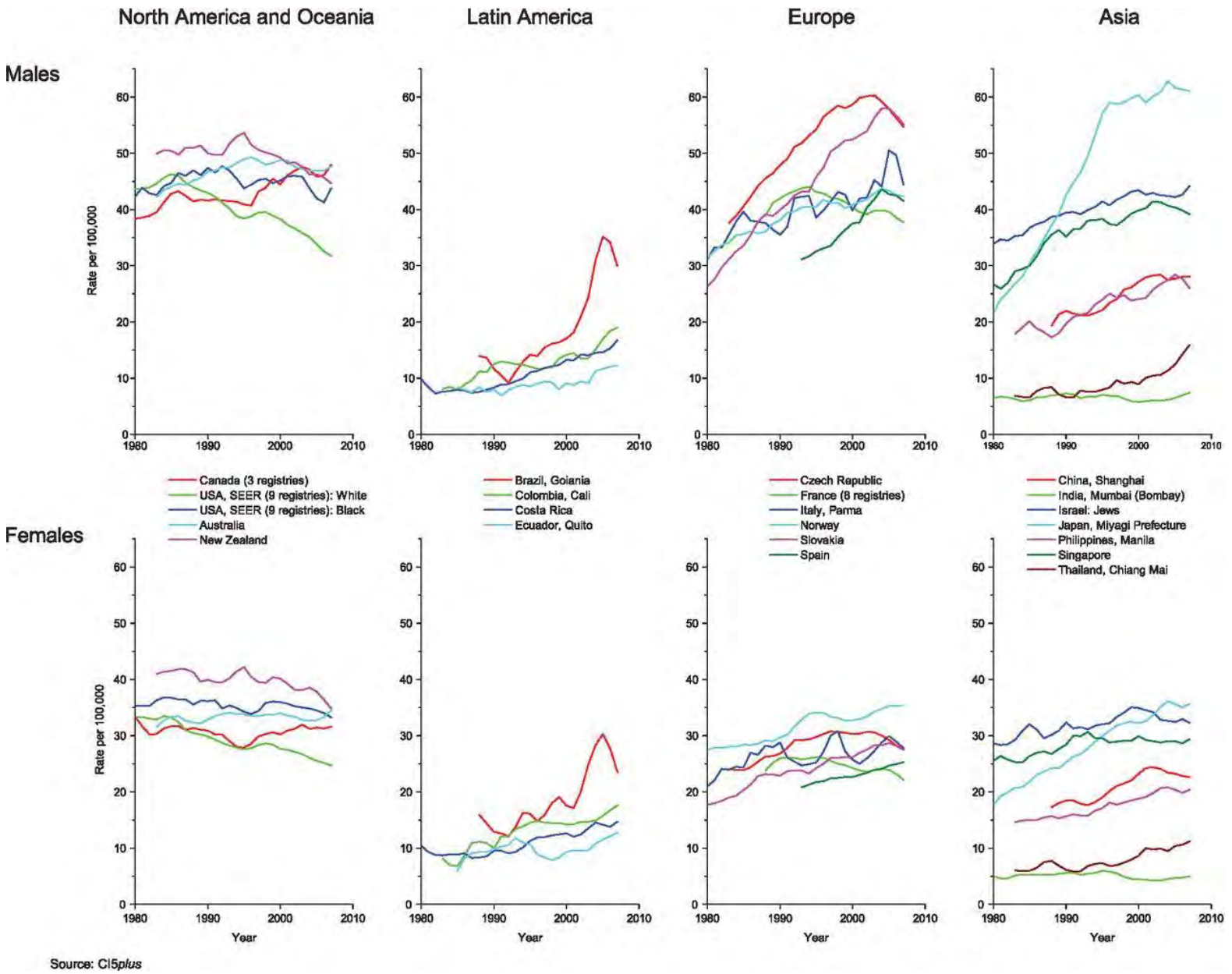
Colorectal Cancer Incidence and Mortality Rates, United States.



- 140,250 newly diagnosed CRC cases (U.S., 2018, projected)
- 34.8 ♀ to 45.9 ♂ per 100,000 (U.S., 2010-2014, age-adjusted incidence)
- 50,630 deaths from CRC (U.S., 2018, projected)
- 12.2 ♀ to 17.3 ♂ per 100,000 (U.S., 2011-2015, age-adjusted mortality)

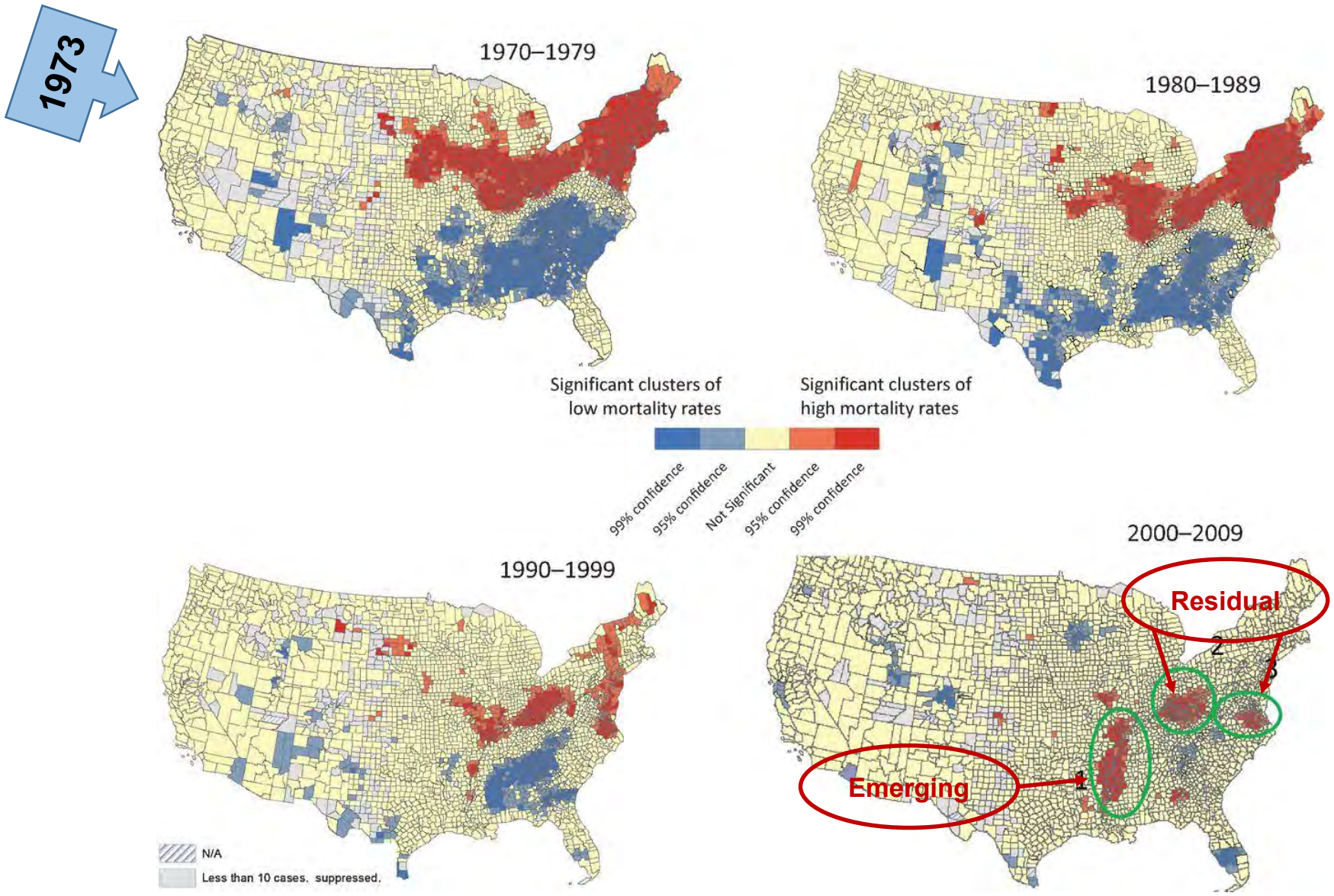
Siegel, et. al. (2018) *CA: A Cancer Journal for Clinicians*, doi: 10.3322/caac.21442.

Declining U.S. CRC incidence trends contrasts with increasing trends elsewhere (1980–2007)



Torre, et. al., (2016)
Cancer Epidemiol Biomarkers Prev.
25(1):16-27. doi: 10.1158/1055-9965.

Regional differences in U.S.CRC mortality rates: Decreasing *vs.* increasing trends

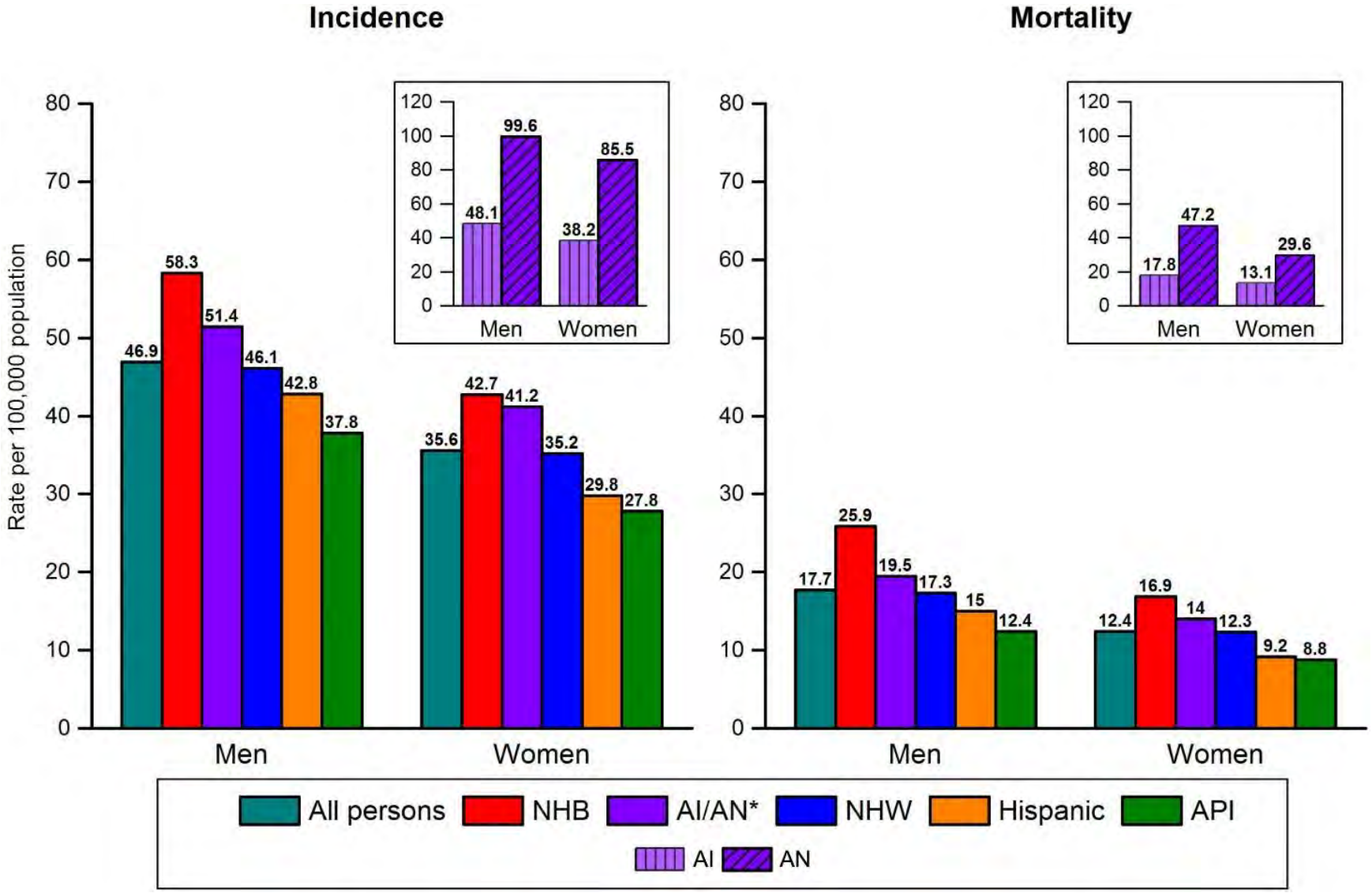


- **Decreasing CRC mortality rates in Midwest & Northeast best explained by increasing CRC screening rates.**
- **Increasing CRC rates (esp. in Mississippi River Delta) may involve other risk factors (e.g., "nutrition transition").**

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

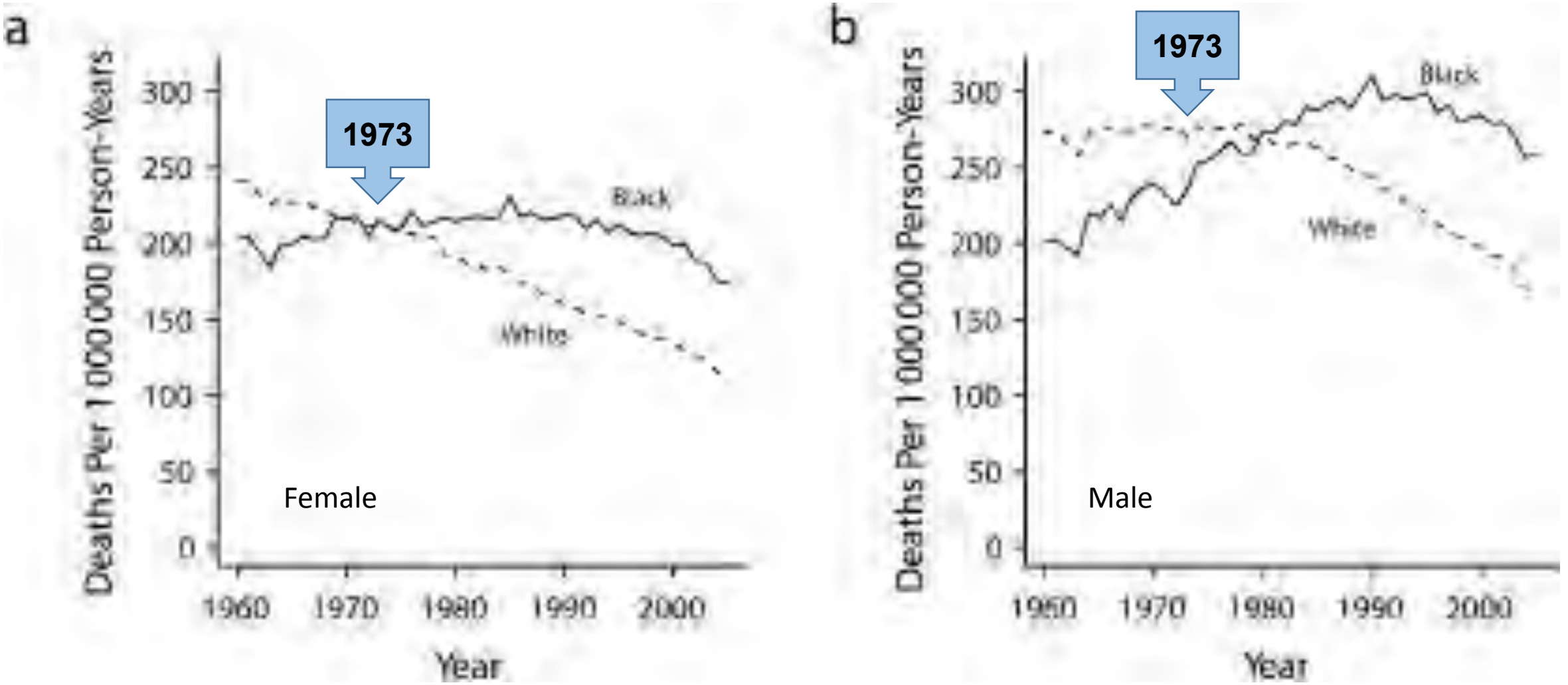
AACR American Association for Cancer Research
Cancer Epidemiology, Biomarkers & Prevention

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



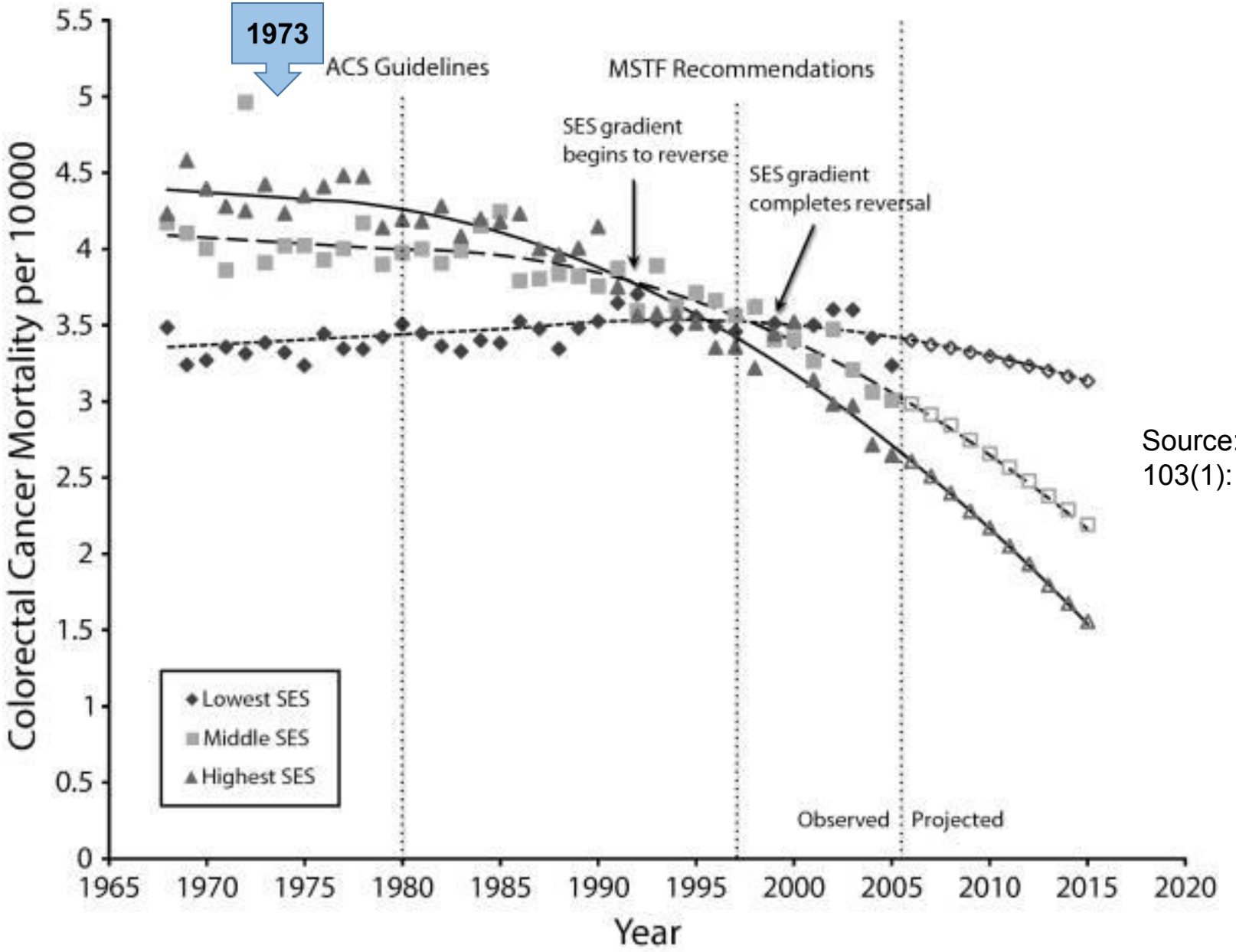
Siegel, et. al. (2017) *CA: A Cancer Journal for Clinicians*, doi: 10.3322/caac.21395.

Population-based disparities in U.S. CRC mortality rates are based on divergent trend lines



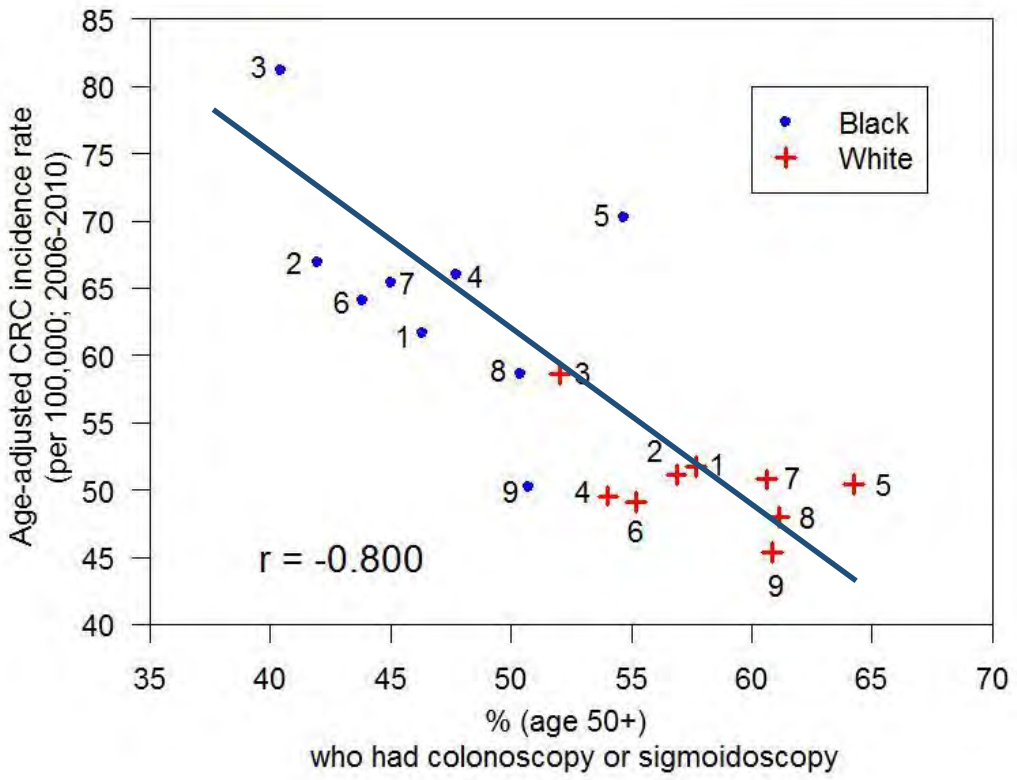
Soneji, et. al. (2010) *Am J Public Health*, 100(10): 1912–1916.

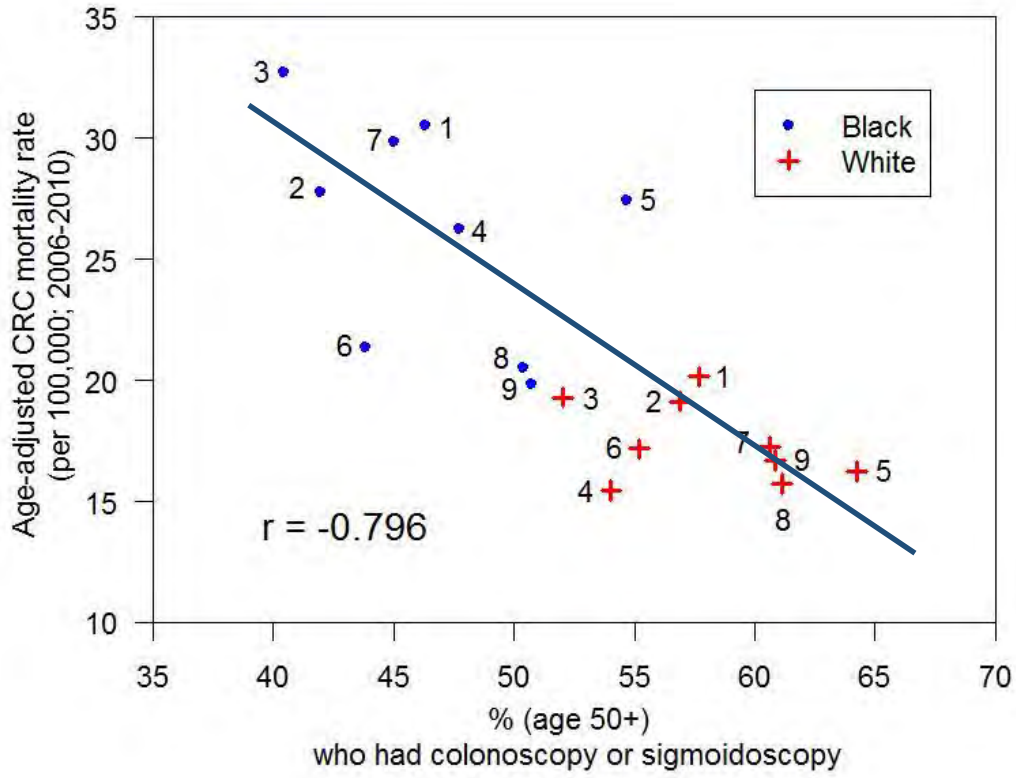
Trends in Average Yearly Age-, Race-, and Sex-Adjusted Colorectal Cancer Mortality Rates, Separated into Tertiles of High, Middle, and Low Socioeconomic Status at the County Level, 1968–2008.



Source: Am J Public Health (2013) 103(1): 99–104.

Regional CRC incidence rates and mortality rates in Mississippi are strongly correlated with colonoscopy rates



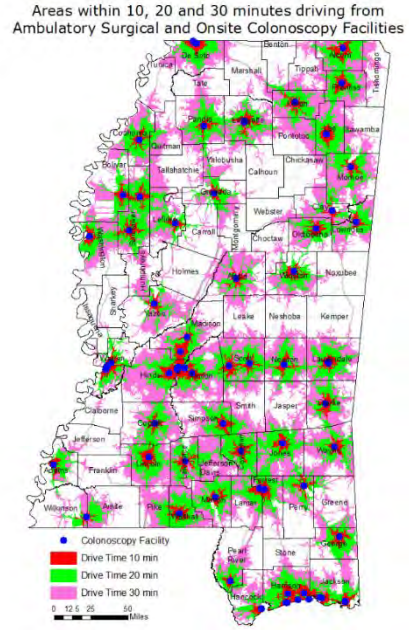


Faruque *et al. BMC Res Notes (2015) 8:423*

Community-level wealth & per-capita income affects resource distribution

Table 4 Incomes within and beyond 30-min drives to colonoscopy facilities

Variable	Within 30-min drives	Beyond 30-min drives	P value
Median household income	33,607	33,953	0.597
Mean household income	46,291	45,279	0.194
Per capital income	17,797	17,141	0.049



52% of the state (17% of the population) is beyond a 30-minute drive to a colonoscopy facility

79% of the state (38% of the population) is beyond a 30-minute drive to gastroenterologist

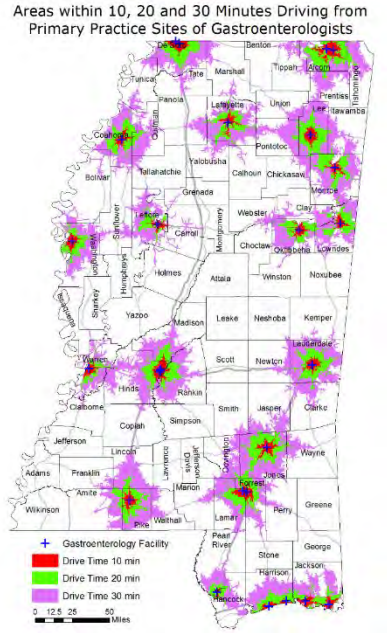
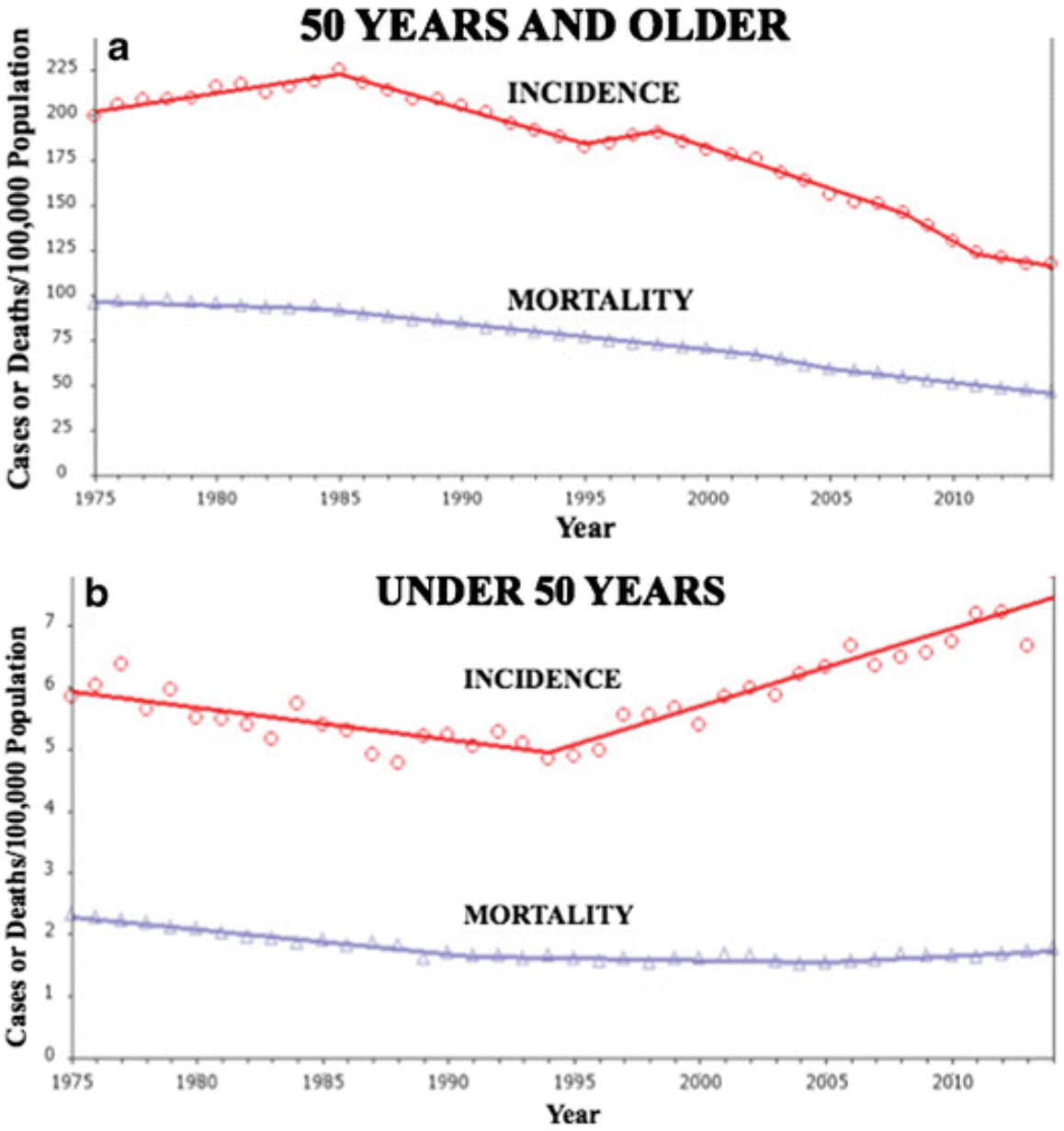


Table 5 Incomes within and beyond 30-min drives to gastroenterologists' primary practice sites

Variable	Within 30-min drives	Beyond 30-min drives	P value
Median household income	35,058	33,889	0.279
Mean household income	47,370	45,572	0.083
Per capital income	18,334	17,294	0.016

Faruque *et al. BMC Res Notes (2015) 8:423*

Divergent CRC incidence trends in post-50 vs. pre-50 y.o. since 1994

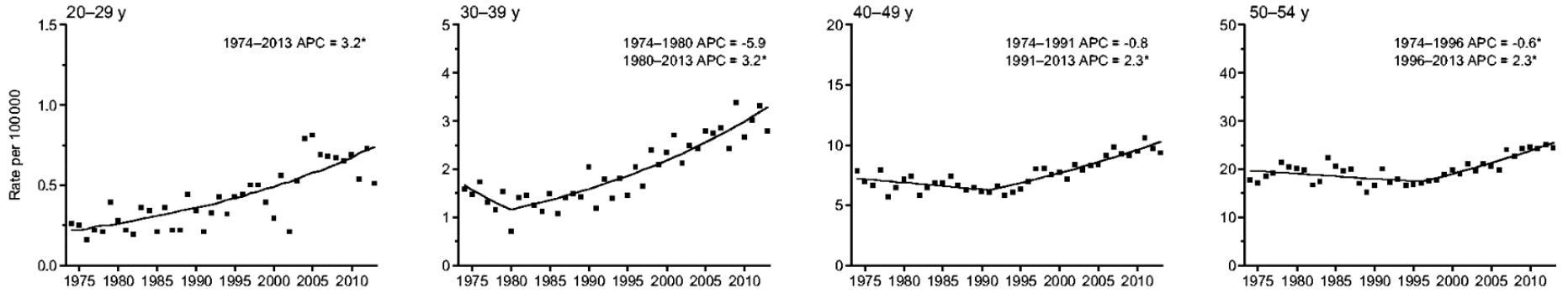


Patel & Ahnen, *Current Gastroenterology Reports* (2018) 20:15
doi: 10.1007/s11894-018-0618-9.

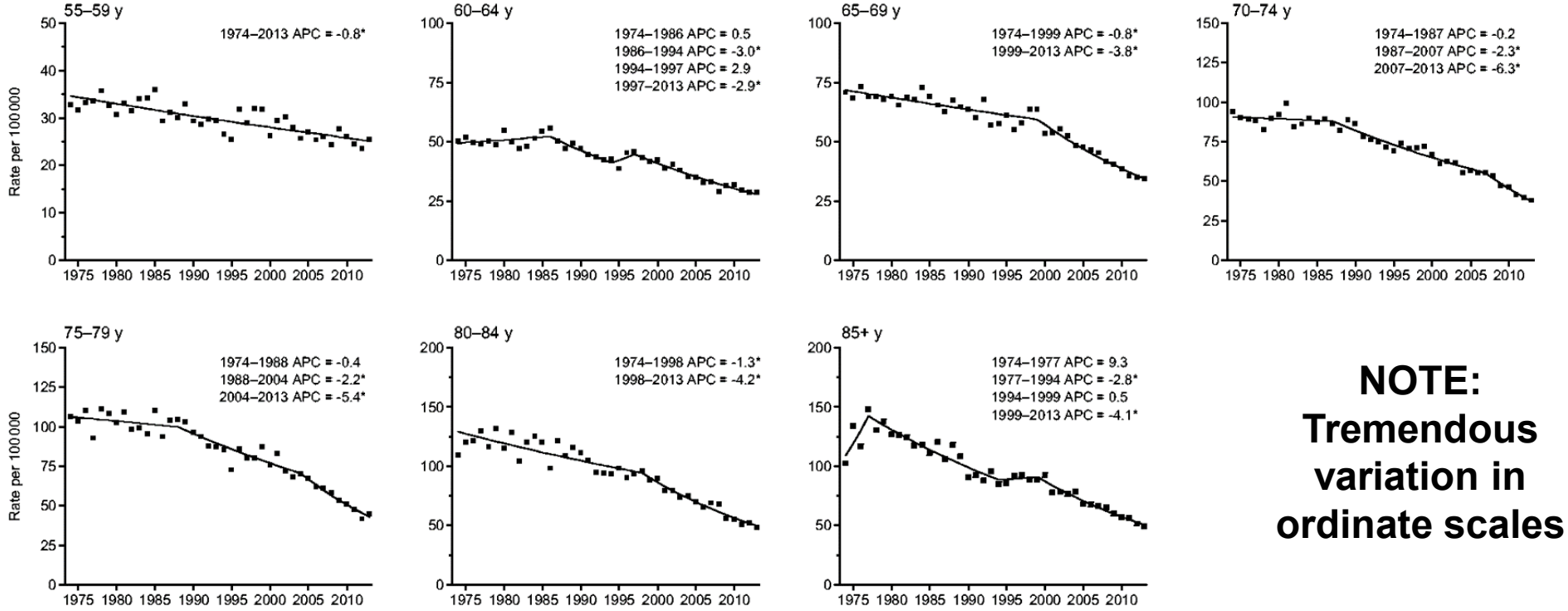
NOTE: Ordinate scales on graphs are not equal; magnitude of CRC incidence & mortality very different in age groups shown.

Annual percent change in age-specific rectal cancer incidence rates in the United States, 1974–2013

Increasing trends in 20-54 y.o.



Decreasing trends in age ≥ 55 y.o.

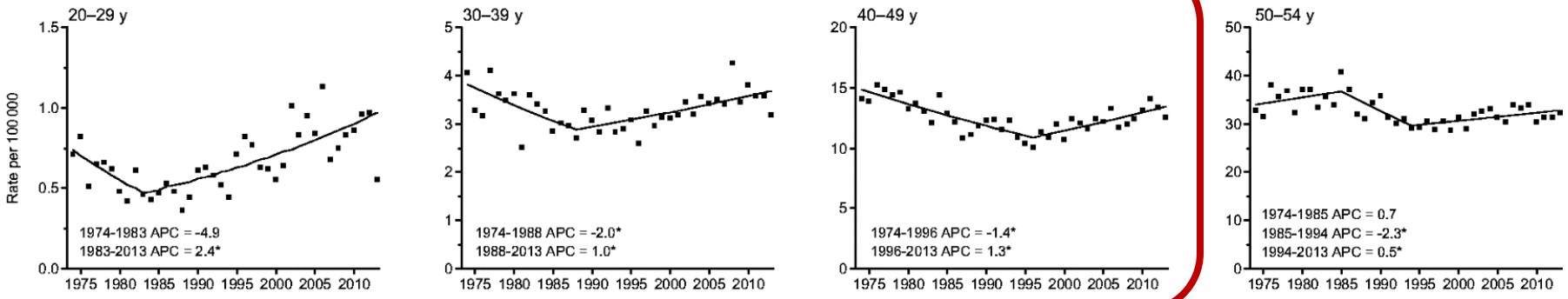


NOTE: Tremendous variation in ordinate scales

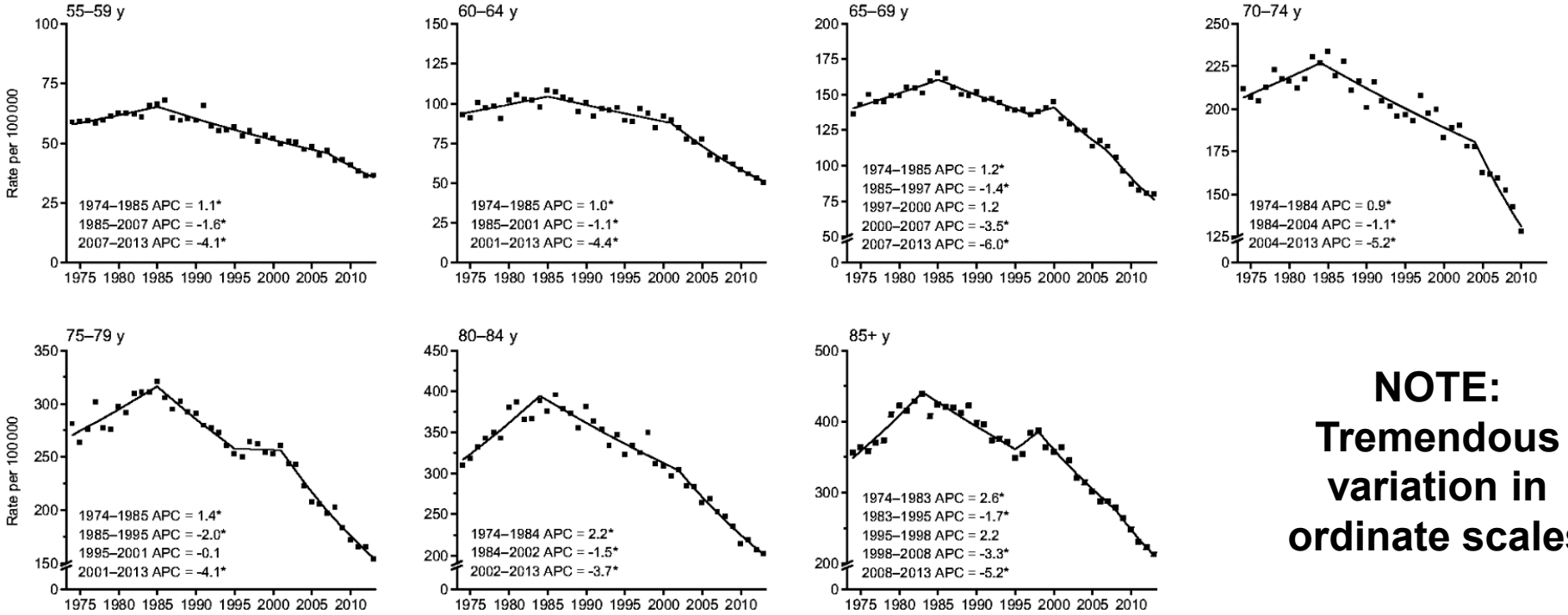
Siegel, et. al., *J Natl Cancer Inst.* (2017) 109(8):djw322

Annual percent change in age-specific colon cancer incidence rates in the United States, 1974–2013

Increasing trends in 20-49 y.o.



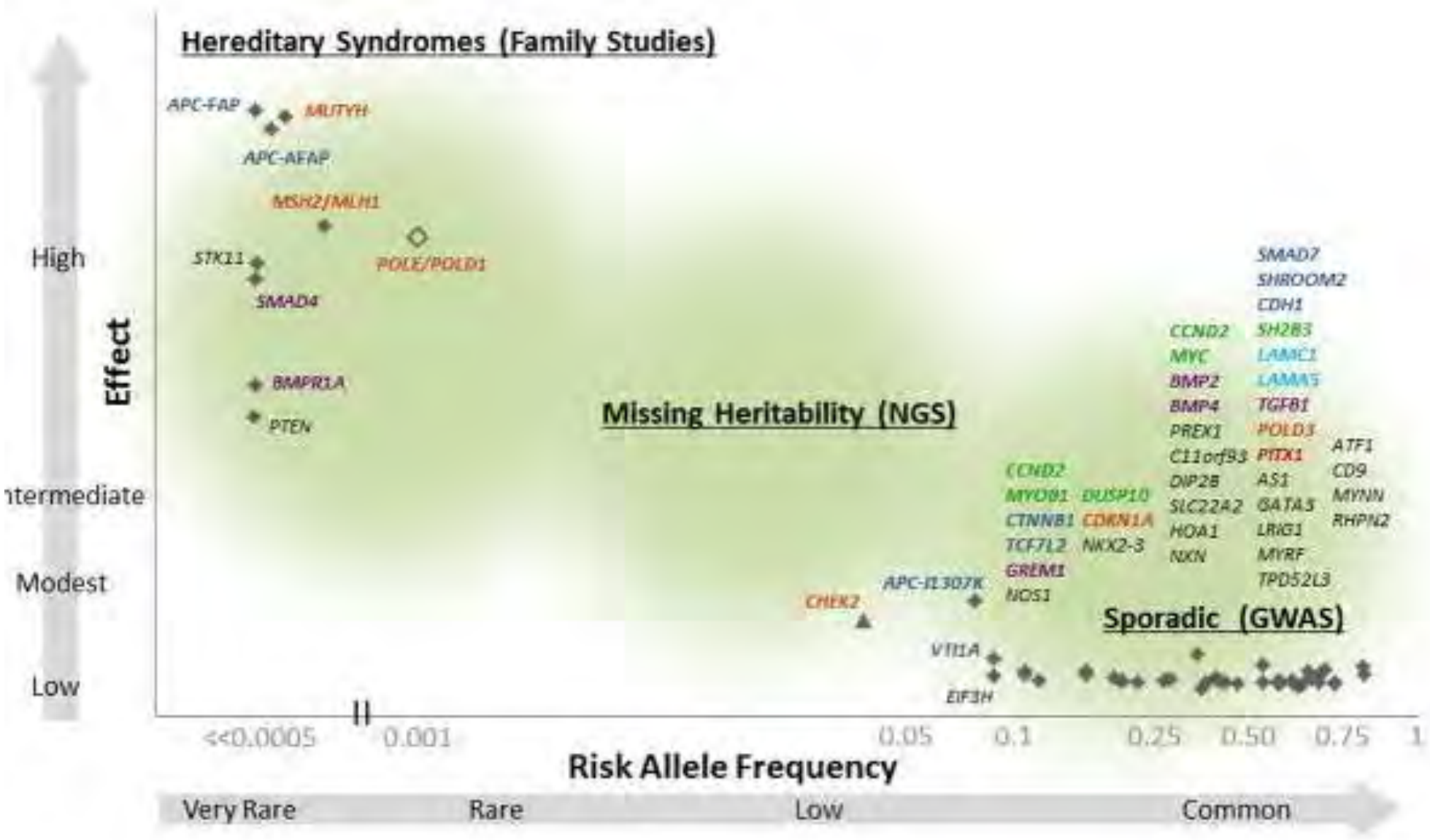
Decreasing trends in age ≥ 55 y.o.



NOTE: Tremendous variation in ordinate scales

Siegel, et. al., *J Natl Cancer Inst.* (2017) 109(8):djw322

Most sporadic CRCs are driven by accumulation of common mutations with low individual impact; most known familial CRCs driven by rare mutations with high impact.



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

Genes with predisposing mutations to inherited colorectal cancer syndromes

Gene	Hereditary syndrome	Age of onset (years)	Pathway/biological function*
APC	Familial adenomatous polyposis (FAP), attenuated FAP (AFAP), Gardner syndrome	34–43	Wnt signalling pathway
MUTYH	MYH-associated polyposis (MAP)	48–56	Base excision repair
MLH1, MSH2,MSH6, PMS2,EPCAM	Lynch syndrome	44–56	Mismatch repair
PTEN	Cowden syndrome (includes BRR syndrome)	<50 (BRR paediatric onset)	Negative regulator of metabolic signalling
STK11	Peutz-Jeghers syndrome (PJS)	65	Tumour suppressor
GREM1,15q13 locus	Hereditary mixed polyposis syndrome (HMPS)	48	TGFβ/BMP signalling pathway
BMPR1A	HMPS, juvenile polyposis syndrome	48, 42	TGFβ/BMP signalling pathway
MADH4/SMAD4	Juvenile polyposis syndrome	42	TGFβ/BMP signalling pathway
POLE, POLD1	Oligopolyposis or polymerase proofreading associated polyposis	23–80	DNA repair

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

Factors increasing risk for CRC

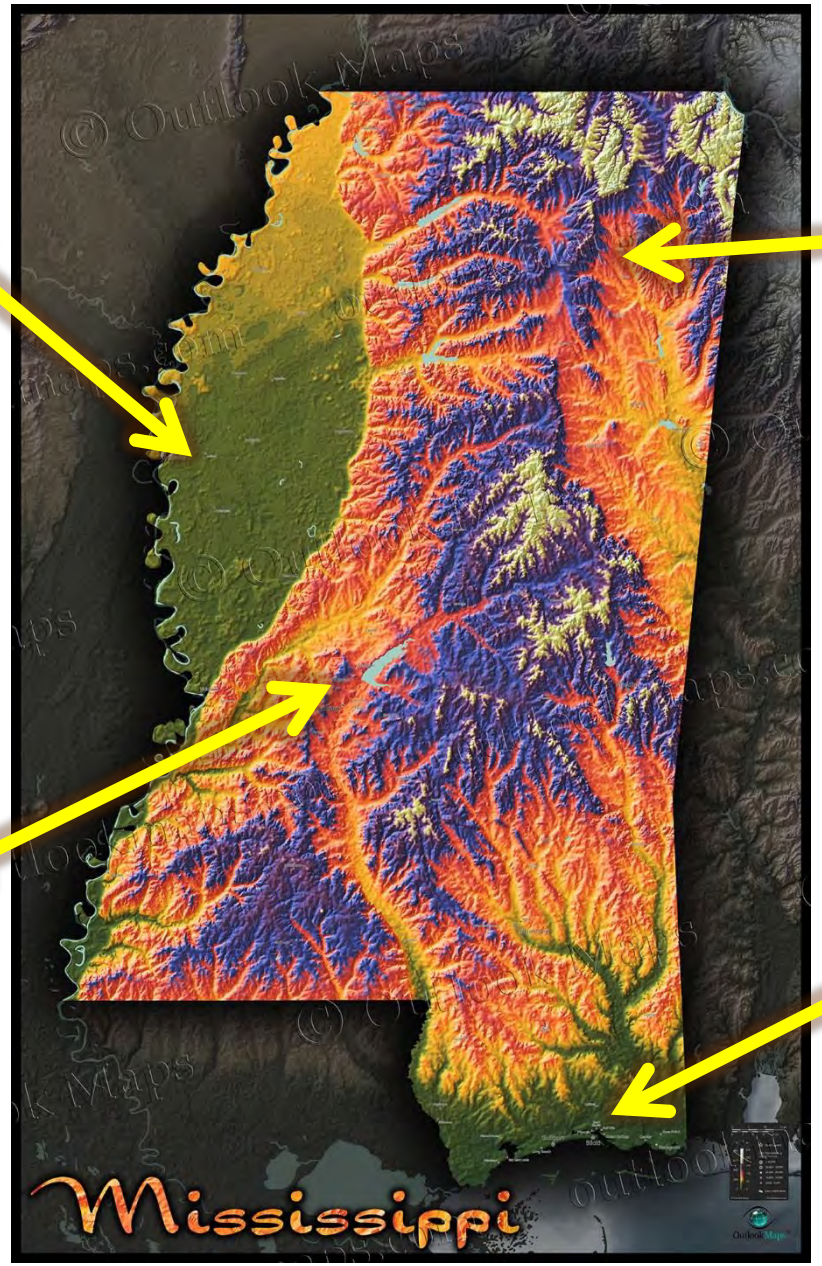
- **Intrinsic Risk Factors (Non-Modifiable)**
  - Age
  - Ethnicity
  - Family History
  - History of Polyps
  - History of Inflammatory Bowel Disease
  - Central Obesity*
  - Type II Diabetes
  - Specific Genetic Conditions

- **Environmental / Socio-economic Risk Factors**
  - Community-level poverty
  - Lack of Insurance
  - Lack of Access to Medical Care

- **Behavioral Risk Factors (Modifiable)**
  - Non-compliant with screening recommendations
  - Red meat consumption
  - Processed meat consumption
  - Low vegetable, low fiber diets

Thanks to the 70x2020 Colorectal Cancer Screening Partnership for raising awareness throughout Mississipp!

Greenville (4-10-2018)



Tupelo (4-3-2018)

Jackson (4-31-2018)

Biloxi (4-22-2018)

Summary

- CRC cancer biology explains why prevention is highly effective & identifies areas for improvement.
- CRC epidemiology reveals changing landscape of disease.
- CRC in young adults requires attention to symptoms to avoid delays in diagnosis.
- CRC genetic factors can identify young high-risk individuals.
- CRC risk factors include intrinsic, behavioral, environmental and socio-economic factors.
- CRC screening options are varied & require colonoscopy for confirmation.
- CRC screening policies benefit to health care system by reducing expensive medical procedures & saving lives.