Natural History and Epidemiology of Colorectal Cancer
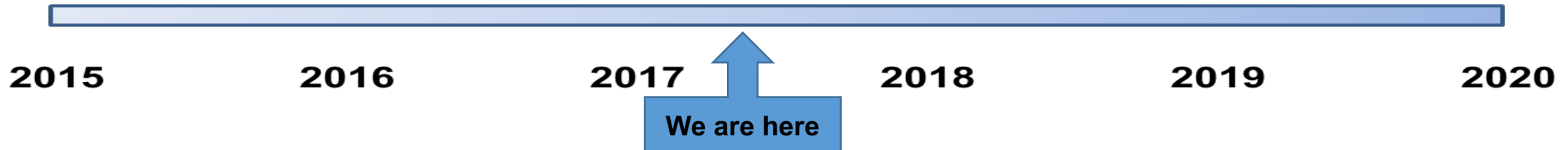
Prevent Cancer Foundation
2017 Dialogue for Action
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2015   2016   2017   2018   2019   2020

We are here

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.

- I am the recipient of a Patient-Centered Outcomes Research Institute (PCORI) Program Award (EA-1148-UMC).

- 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 most common cancer in men + women.
  - 1 in 20 lifetime probability of CRC.

- CRC is 2nd leading cause of cancer death in men + women.

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

- CRC screens are net cost-SAVING.

Sequence of development from polyp to cancer

Take-home lesson:

CRC cancer biology explains why prevention is highly effective, but atypical CRC cancer biology may shed light on future progress

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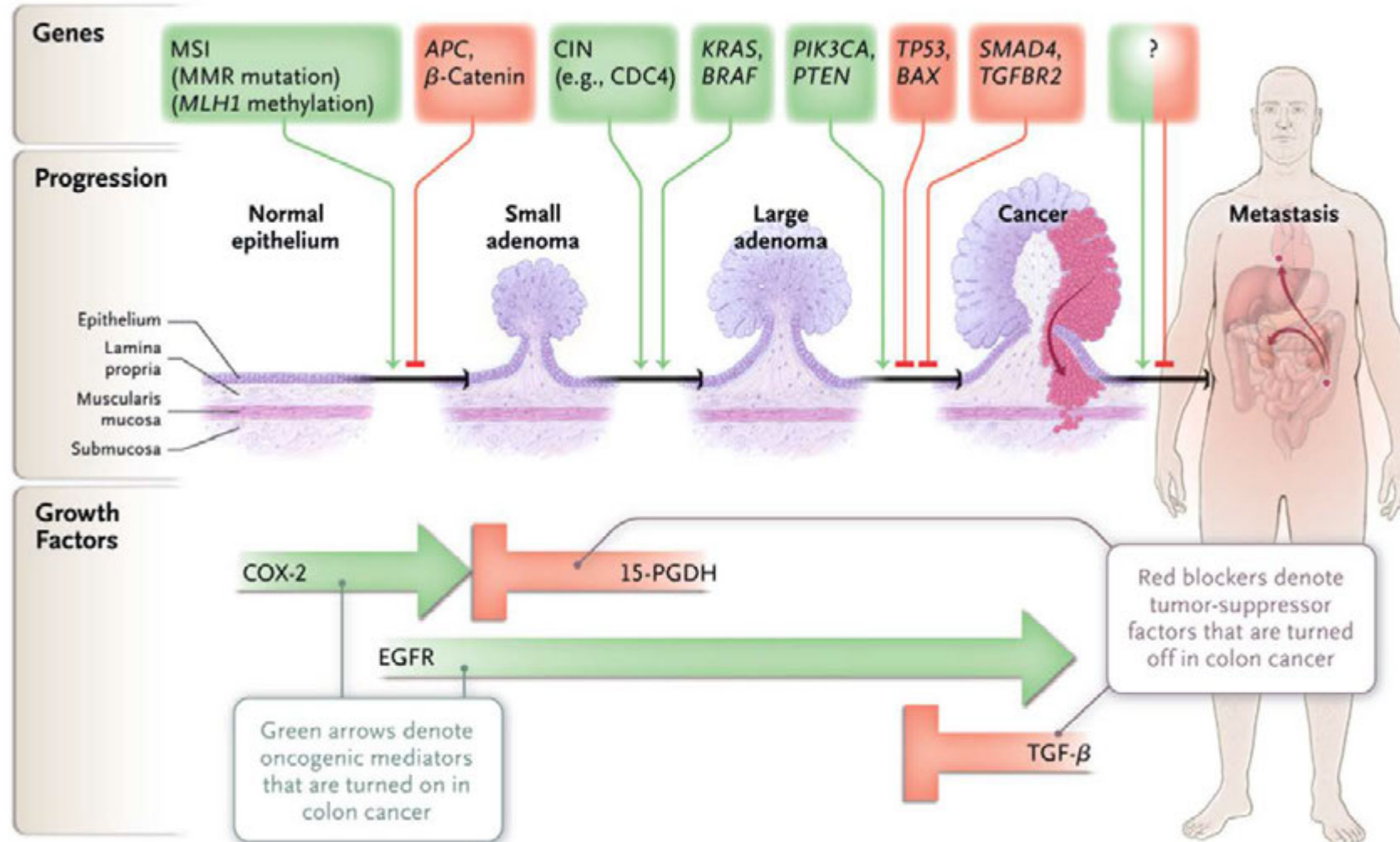
- Adenoma is precursor to CRC, rarely occurs in individuals under 49, adenomas & CRC more prevalent later in life.
- In the 6th, 7th, and 8th decades of life the prevalence of adenomas increases.
- The dwell time of an early to advanced adenoma ~2-5 years.
- Similarly, the dwell time of an advanced adenoma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

IMPORTANT UNANSWERED QUESTION: Do all CRCs follow the generalized model of progression, or are some lesions "primed" to metastasize at earlier stages?
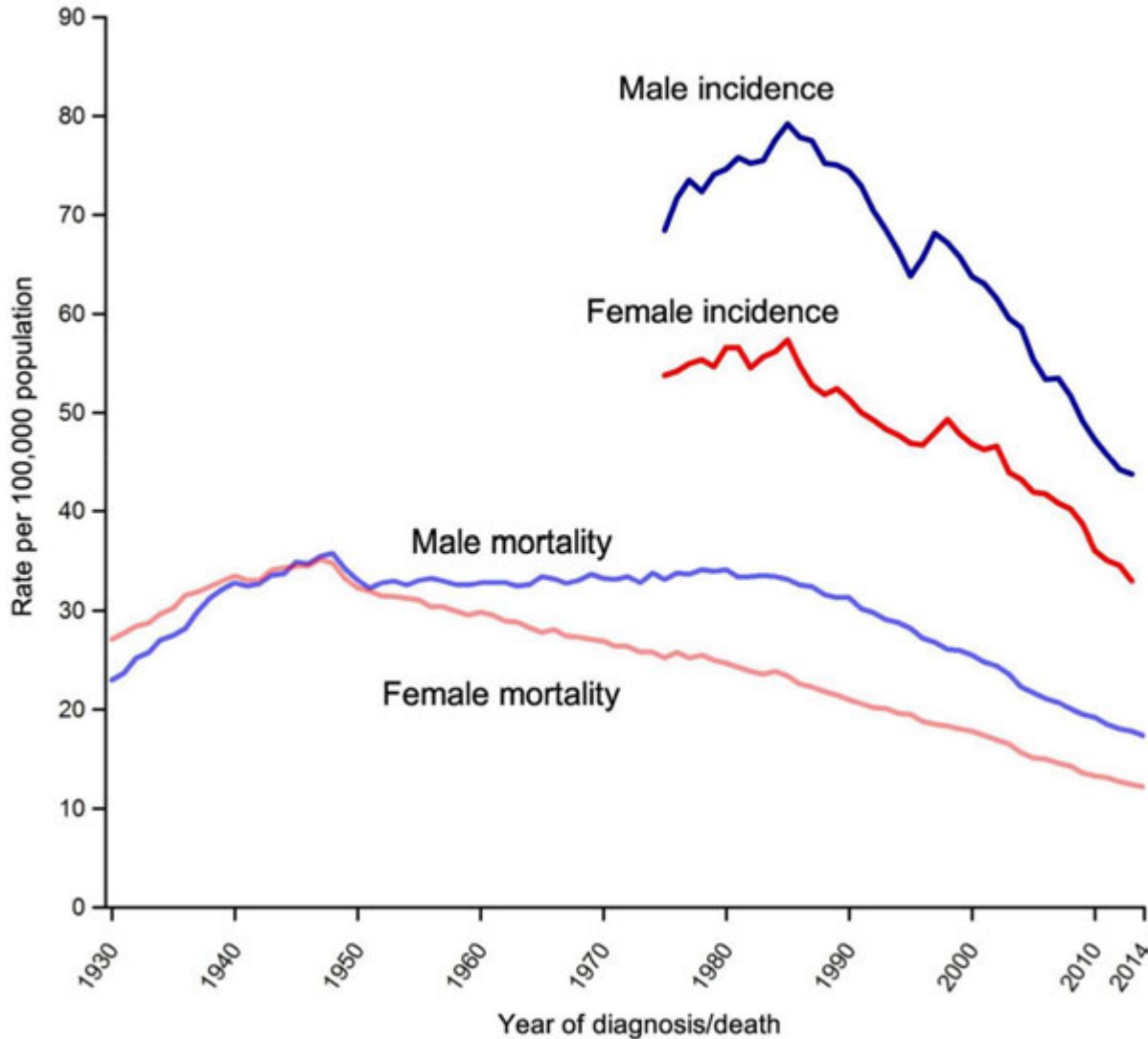

de Sousa e Melo, et. al., (2013) *Nature Medicine* 19:614–618
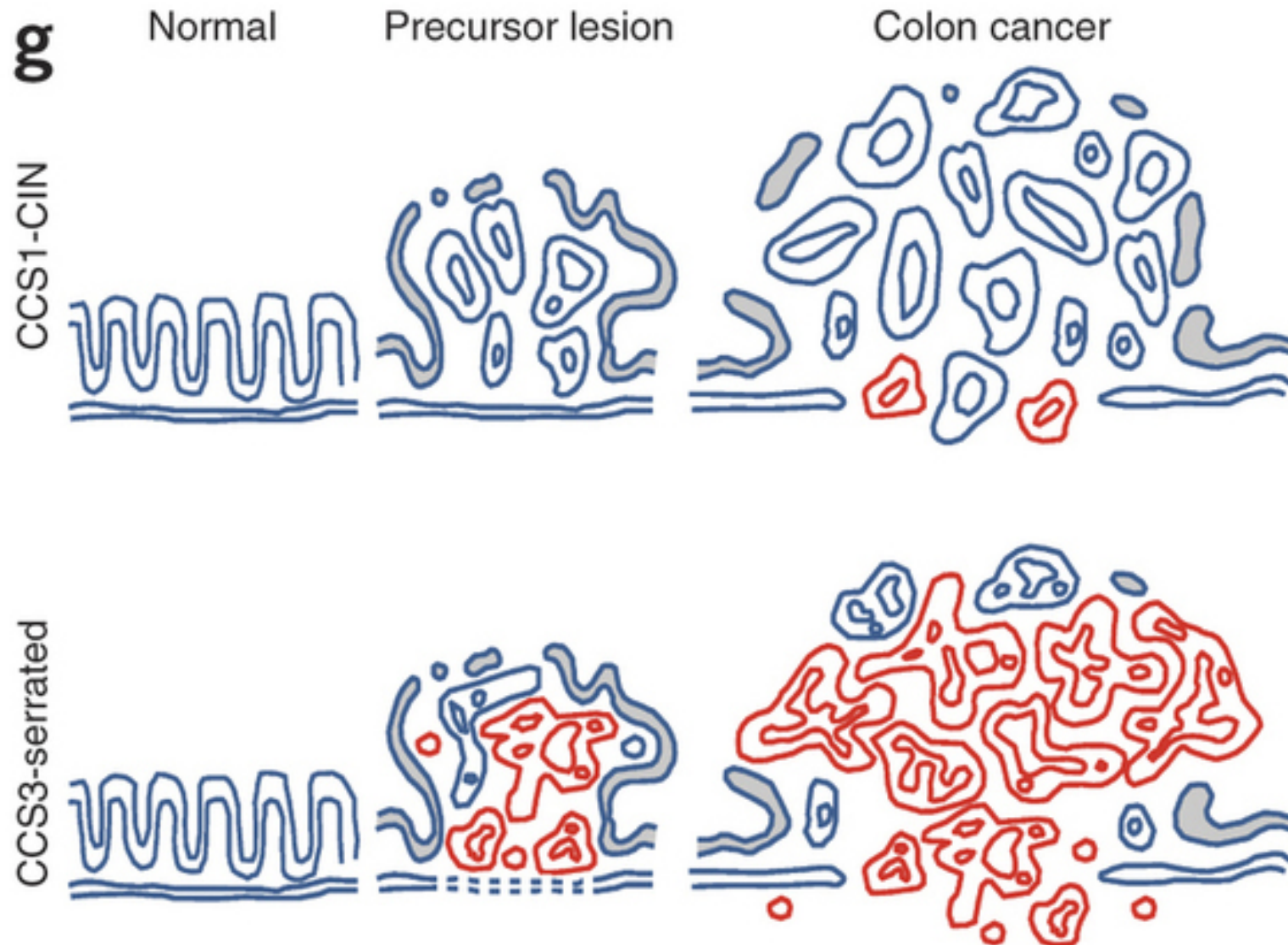
Epidemiology of colorectal cancer

Take-home lesson:

Dynamic changes in CRC epidemiology reflect changing landscape of disparately-distributed positive & negative risk factors

# Colorectal Cancer Incidence and Mortality Rates, United States.

- **135,430 newly diagnosed CRC cases (U.S., 2017, projected)**
- **40.7 per 100,000 (U.S., 2009-2013, age-adjusted incidence)**
- **50,260 deaths from CRC (U.S., 2017, projected)**
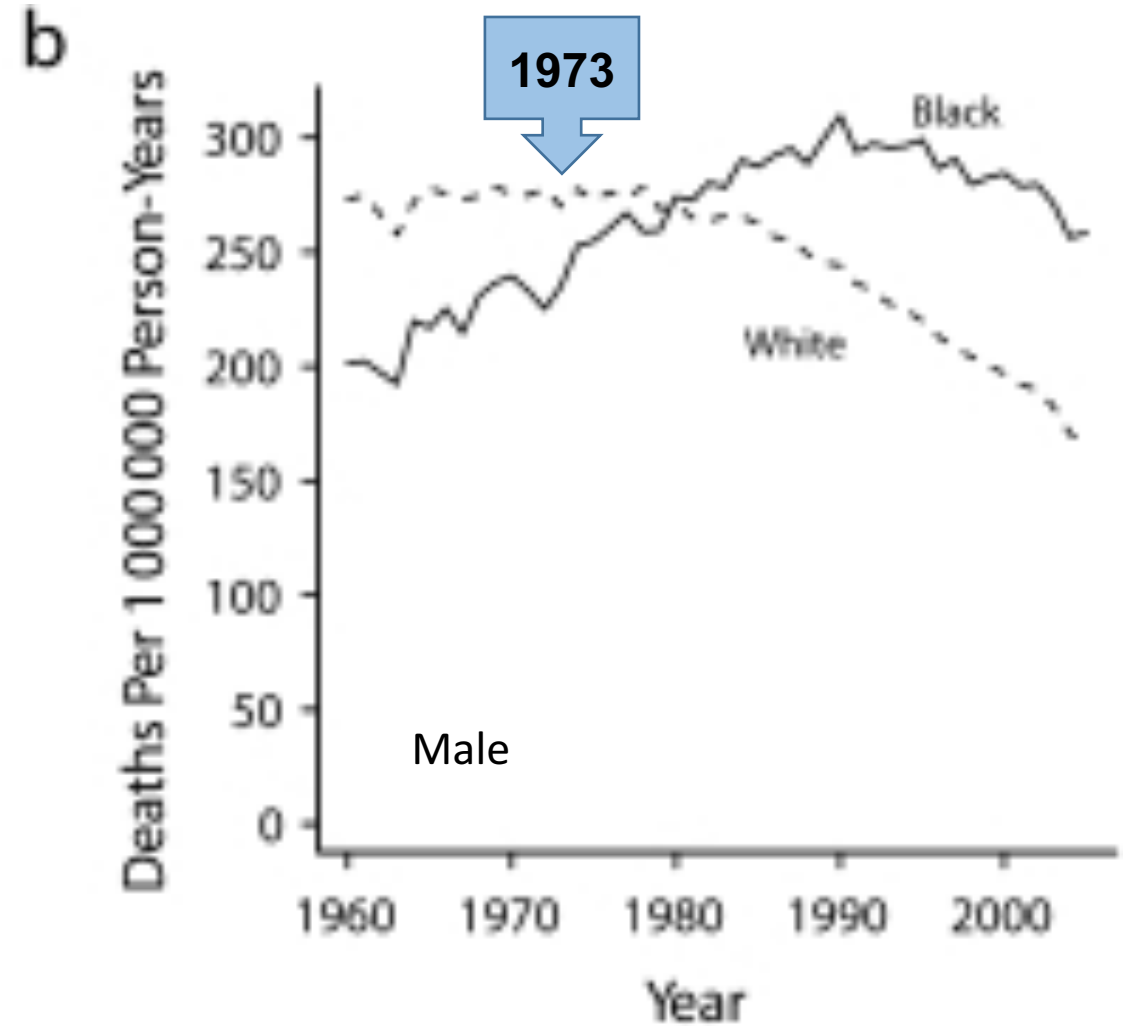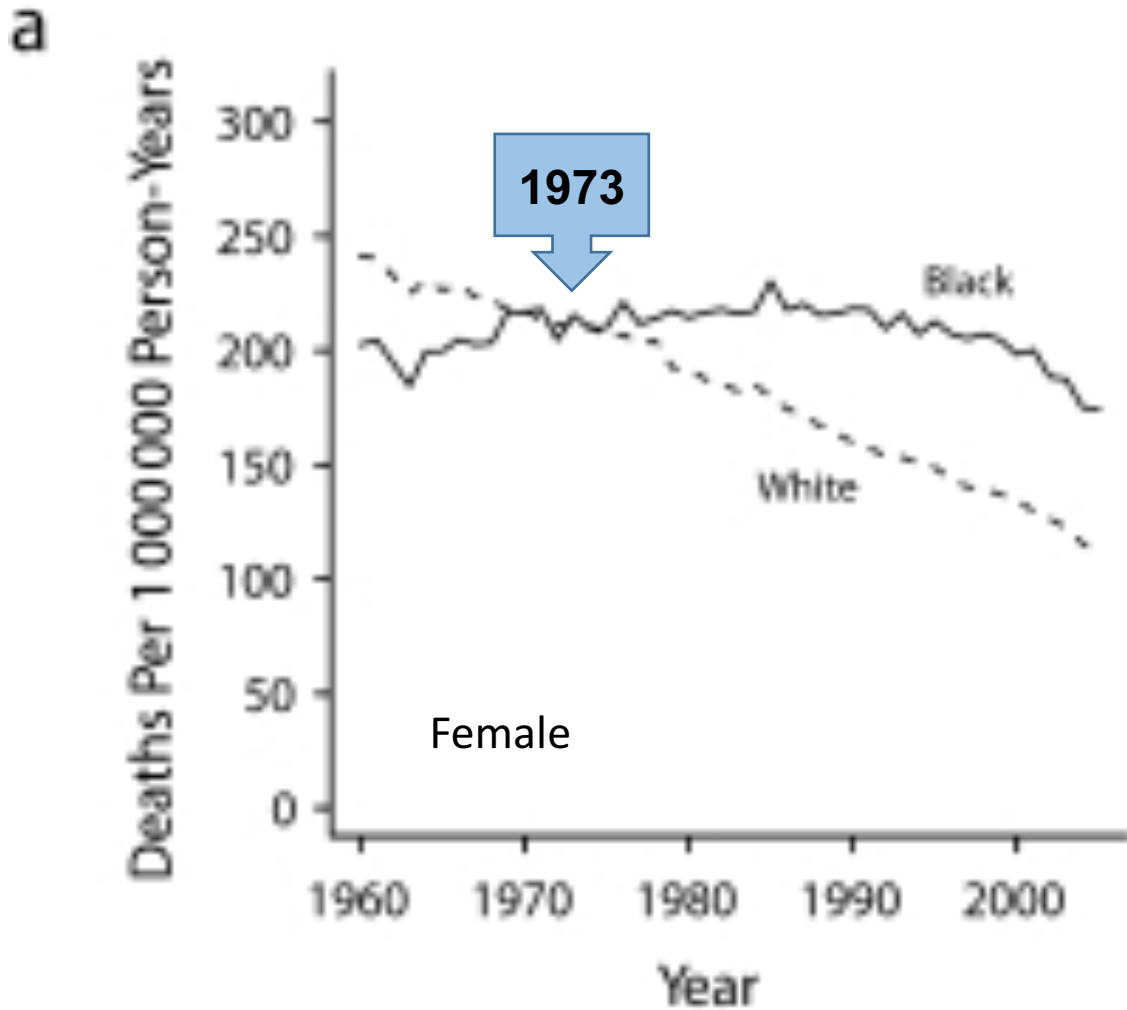- **14.8 per 100,000 (U.S., 2010-2014, age-adjusted mortality)**

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

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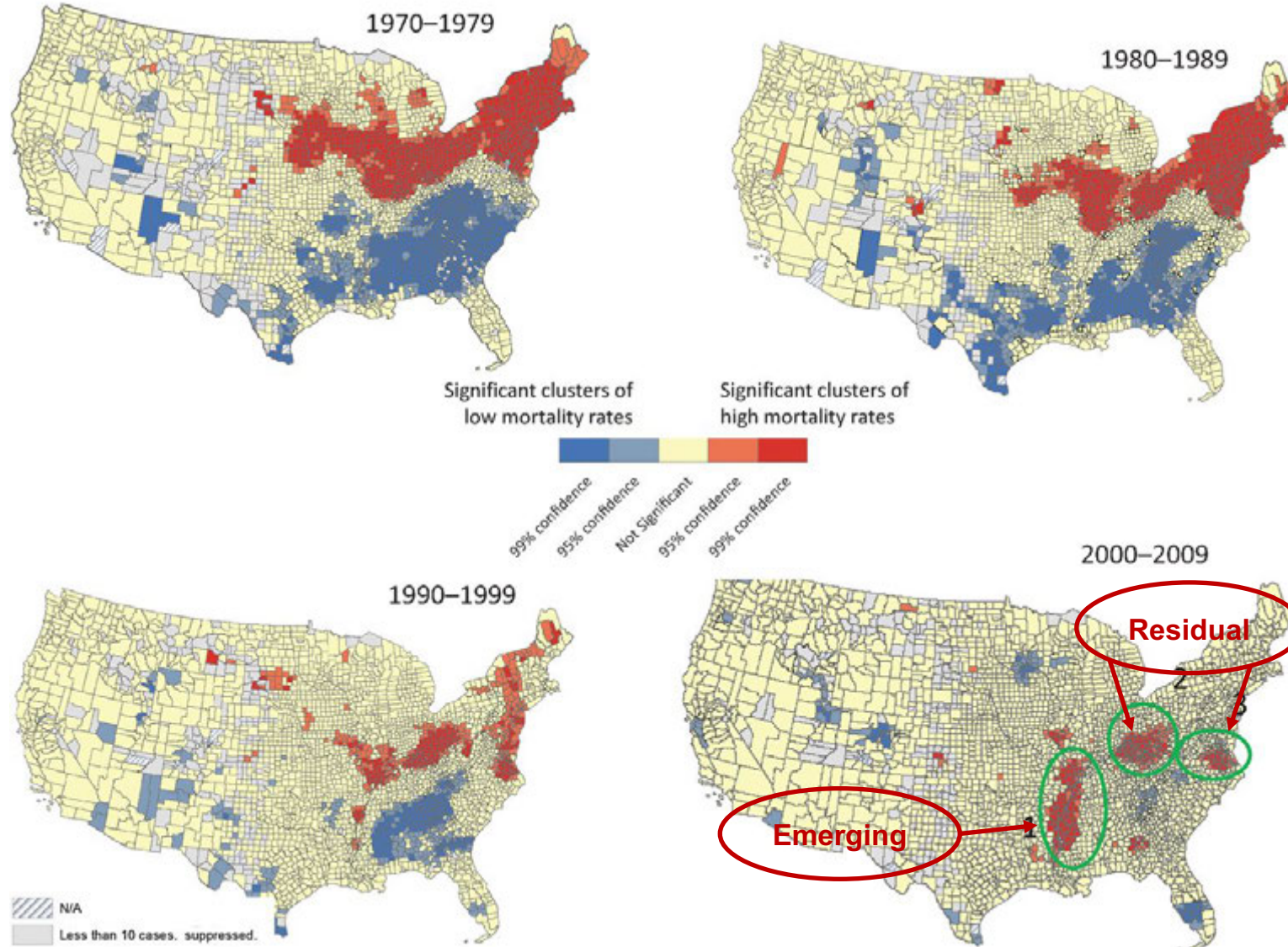

- **Decreasing CRC mortality rates in Midwest & Northeast best explained by increasing CRC screening rates.**

- **Increasing CRC rates (esp. in Mississippi River Delta) may involve other risk factors (e.g., "nutrition transition").**

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

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.
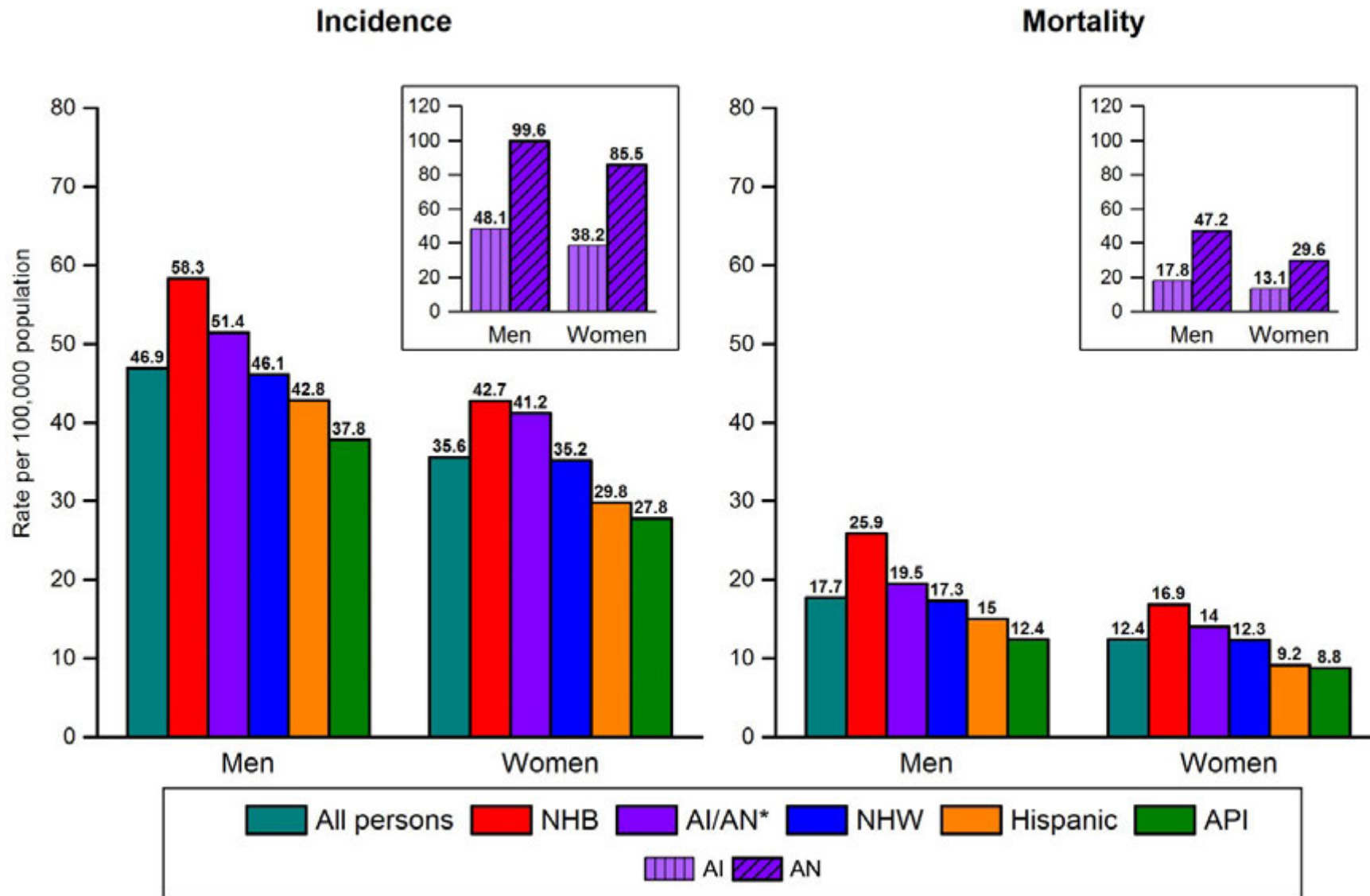
Increased incidence of colorectal cancer in people younger than 50

Take-home lesson:

Causes of recent trends are unknown, but an immediate response requires attention to symptoms to avoid delays in diagnosis

# Colorectal Cancer Incidence and Mortality Trends by Age and Sex, United States, 1975-2014.
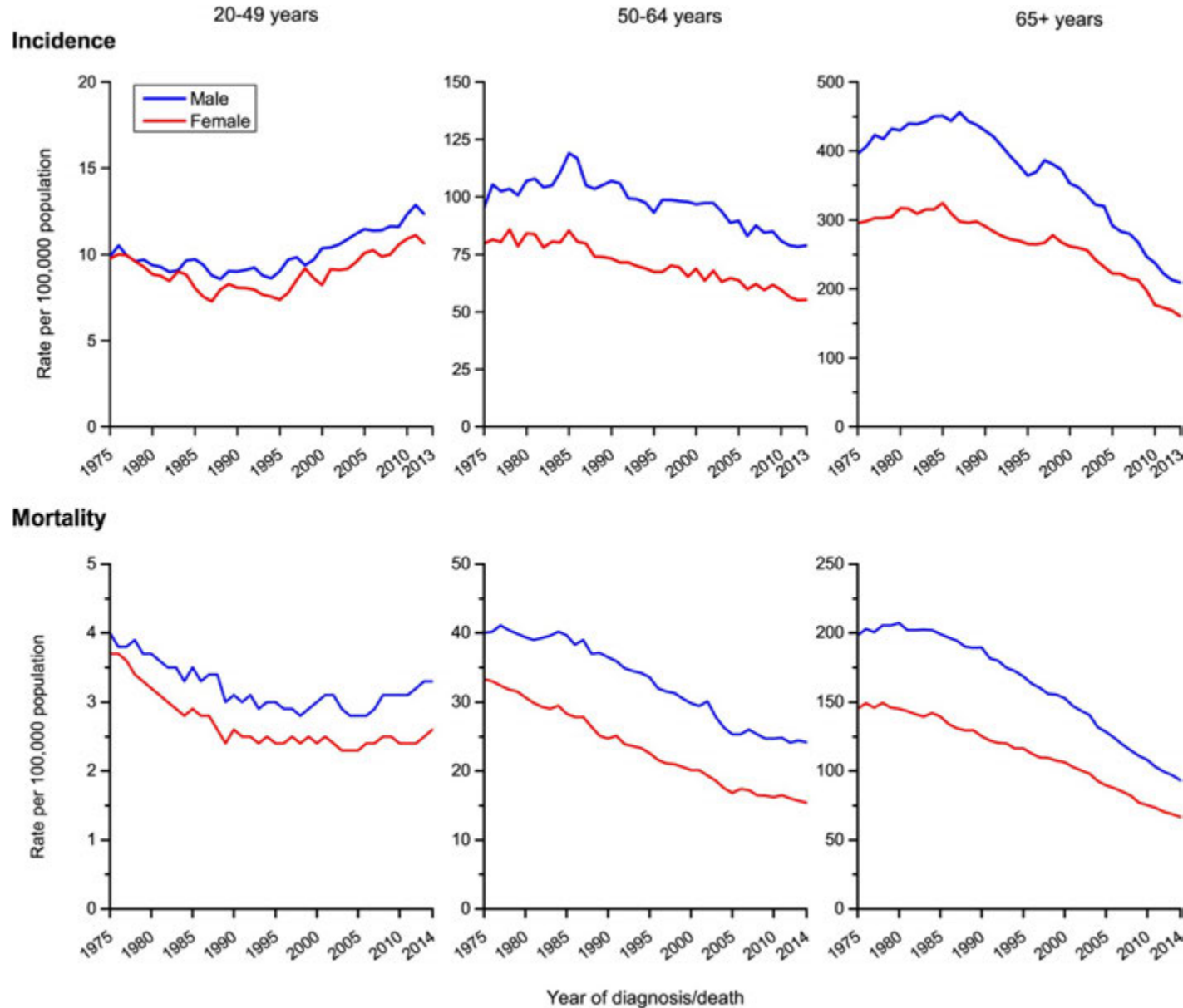

- **NOTE: Ordinate scales on graphs are not equal; magnitude of CRC incidence & mortality very different in age groups shown.**
- **Greatest decrease in CRC incidence & mortality in population age ≥ 65y**
- **Significant decrease in CRC mortality in 50-64 y.o.**
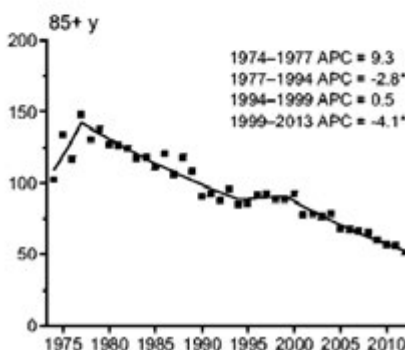- **Significant increase in CRC incidence in 20 – 49 y.o. since 2000**

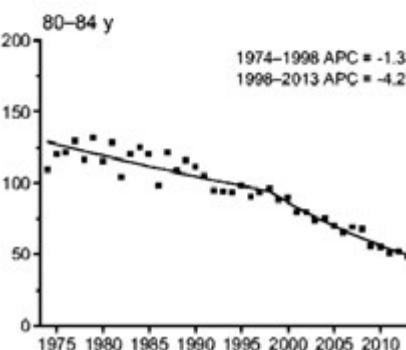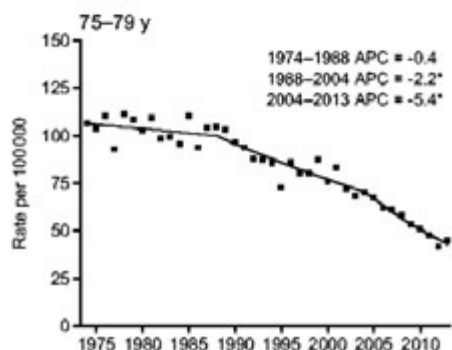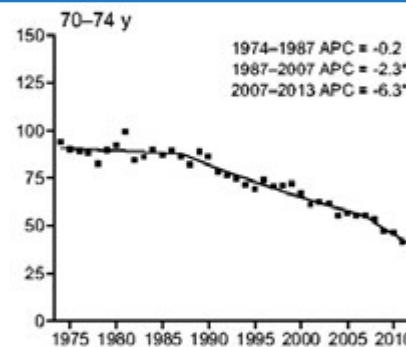**Annual percent change in age-specific rectal cancer incidence rates in the United States, 1974–2013**

Increasing trends in 20-54 y.o.
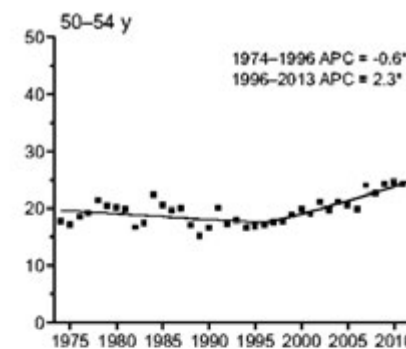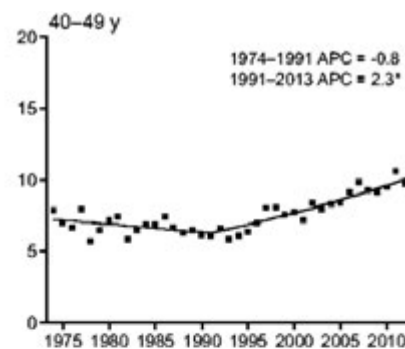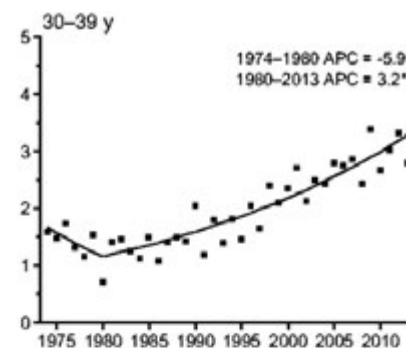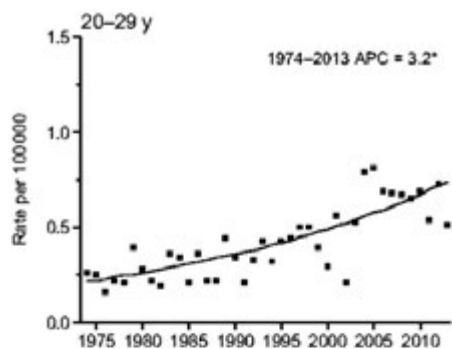
Decreasing trends in age ≥ 55 y.o.

NOTE: Tremendous variation in ordinate scales

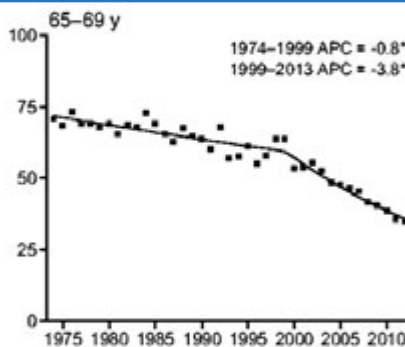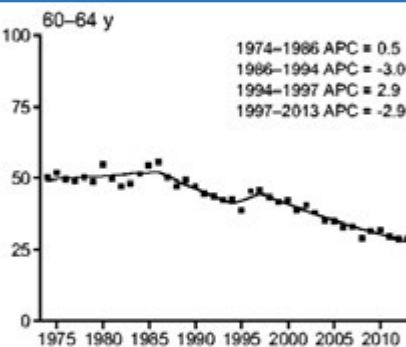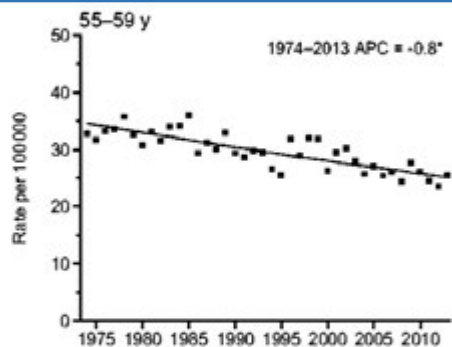Siegel, et. al., *J Natl Cancer Inst.* (2017) 109(8):djw322

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

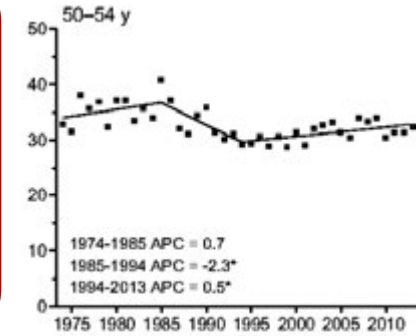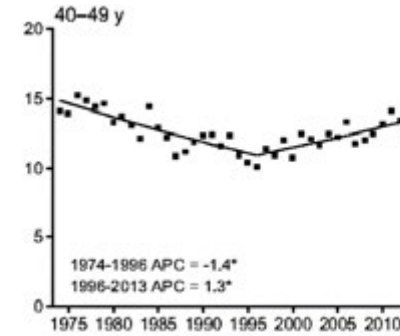**Increasing trends in 20-49 y.o.**

Decreasing trends in age ≥ 55 y.o.

NOTE: Tremendous variation in ordinate scales

20–29 y
1974-1983 APC = -4.9
1983-2013 APC = 2.4*

30–39 y
1974-1988 APC = -2.0*
1988-2013 APC = 1.0*

40–49 y
1974-1996 APC = -1.4*
1996-2013 APC = 1.3*

50–54 y
1974-1985 APC = 0.7
1985-1994 APC = -2.3*
1994-2013 APC = 0.5*

55–59 y
1974–1985 APC = 1.1*
1985–2007 APC = -1.6*
2007–2013 APC = -4.1*

60–64 y
1974–1985 APC = 1.0*
1985–2001 APC = -1.1*
2001–2013 APC = -4.4*

65–69 y
1974–1985 APC = 1.2*
1985–1997 APC = -1.4*
1997–2000 APC = 1.2
2000–2007 APC = -3.5*
2007–2013 APC = -6.0*

70–74 y
1974–1984 APC = 0.9*
1984–2004 APC = -1.1*
2004–2013 APC = -5.2*

75–79 y
1974–1985 APC = 1.4*
1985–1995 APC = -2.0*
1995–2001 APC = -0.1
2001–2013 APC = -4.1*

80–84 y
1974–1984 APC = 2.2*
1984–2002 APC = -1.5*
2002–2013 APC = -3.7*

85+ y
1974–1983 APC = 2.6*
1983–1995 APC = -1.7*
1995–1998 APC = 2.2
1998–2008 APC = -3.3*
2008–2013 APC = -5.2*

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

Genetics and colorectal cancer

Take-home lesson:

Genetic factors can identify young high-risk individuals and may be useful in treatment decisions

Genes with predisposing mutations to inherited colorectal cancer syndromes

Gene	Hereditary syndrome	Age of onset (years)	Pathway/biological function*
APC	FAP, AFAP	34–43	Wnt signalling pathway
MUTYH	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	PJS	65	Tumour suppressor
GREM1,15q13 locus	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

Genetic architecture of known colorectal cancer genetic susceptibility loci
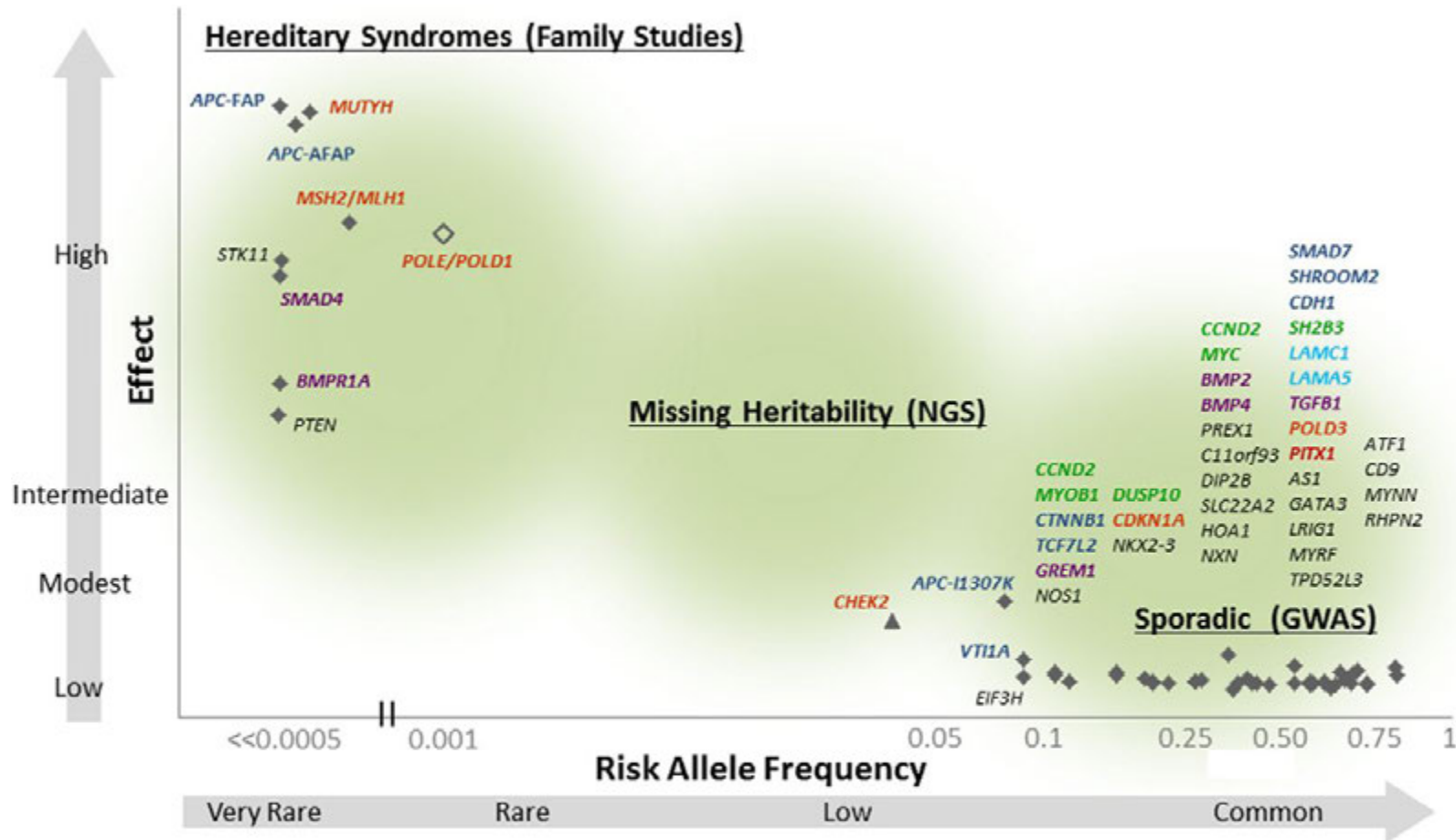
Epigenomics:

- **Chromosomal Instability (CIN) Pathway**

- **CpG Island Methylator Phenotype (CIMP) Pathway**

- **MicroSatellite Instability (MSI) Pathway**

- **Effect of microenvironment (including gut microbiome) on epigenomics & phenotype**

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

Risk factors associated with colorectal cancer

Take-home lesson:

CRC risk factors include intrinsic, behavioral, environmental and socio-economic factors.

Factors increasing risk for CRC

Intrinsic (Most Non-Modifiable)	Environmental / Socio-economic	Behavioral (Modifiable)
Age	Community-level poverty	Non-compliant with screening recommendations
Ethnicity	Lack of Insurance	Red meat consumption
Family History	Lack of Access to Medical Care	Processed meat consumption
History of Polyps		Low vegetable, low fiber diets
History of Inflammatory Bowel Disease		
Central Obesity		
Type II Diabetes		
Specific Genetic Conditions		

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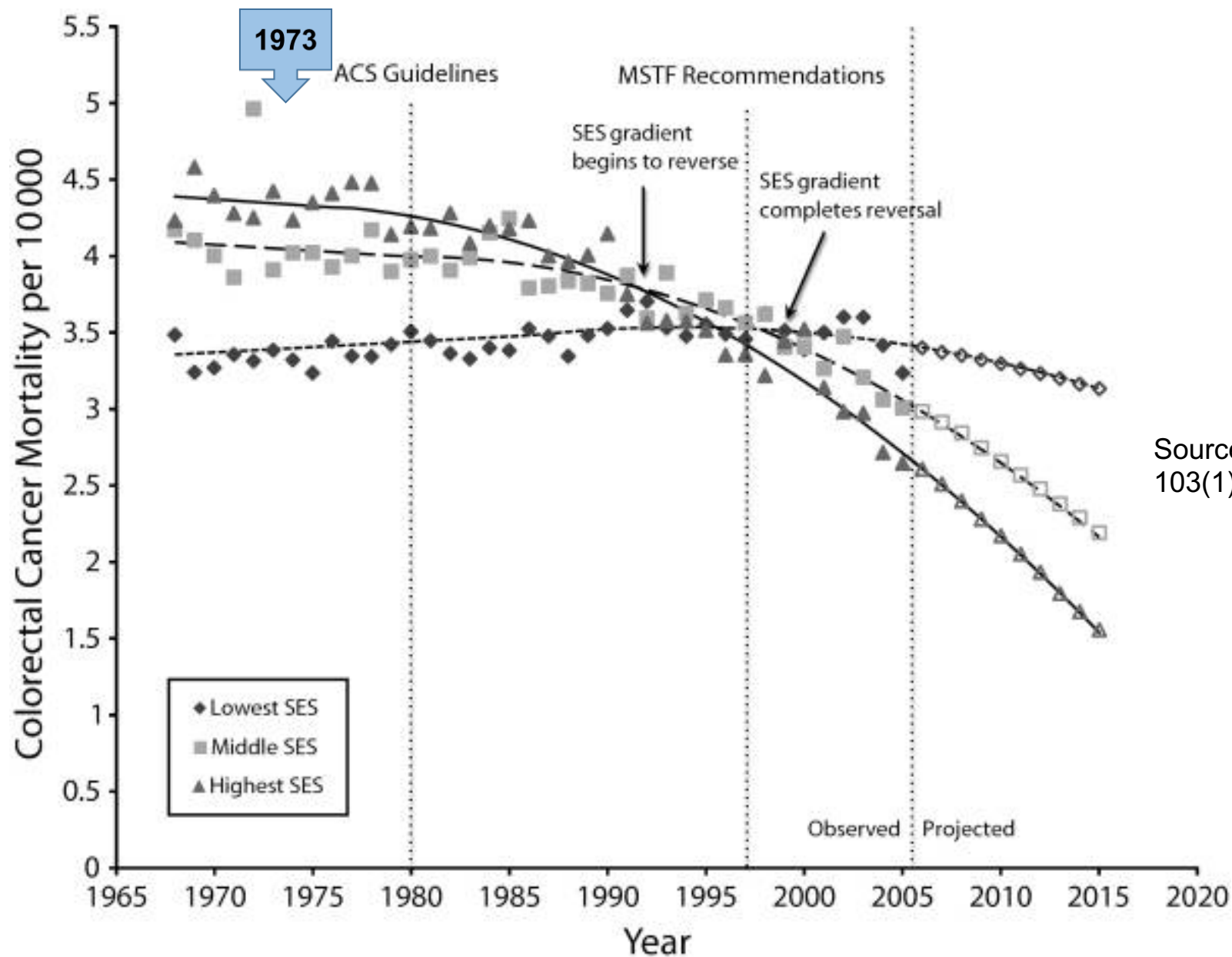
Source: Am J Public Health (2013) 103(1): 99–104.

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

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

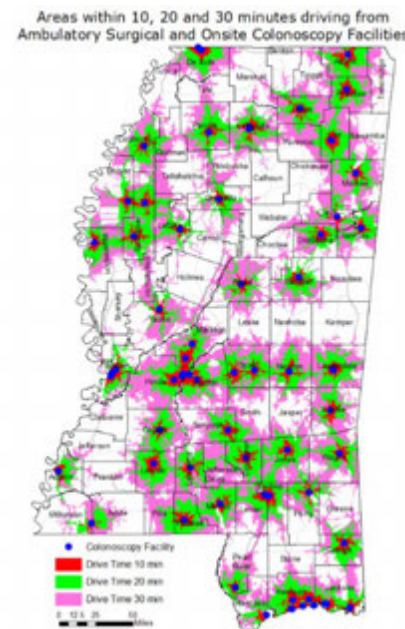| Variable	Within 30-min drives	Beyond 30-min drives	P value
Median household income	33,607	33,953	0.597
Mean household income	46,291	45,279	0.194
Per capital income	17,797	17,141	0.049

Areas within 10, 20 and 30 minutes driving from Ambulatory Surgical and Onsite Colonoscopy Facilities

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

Areas within 10, 20 and 30 Minutes Driving from Primary Practice Sites of Gastroenterologists

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

Self-reported colonoscopy rates in Mississippi's Public Health Districts are strongly correlated with CRC incidence rates and mortality rates
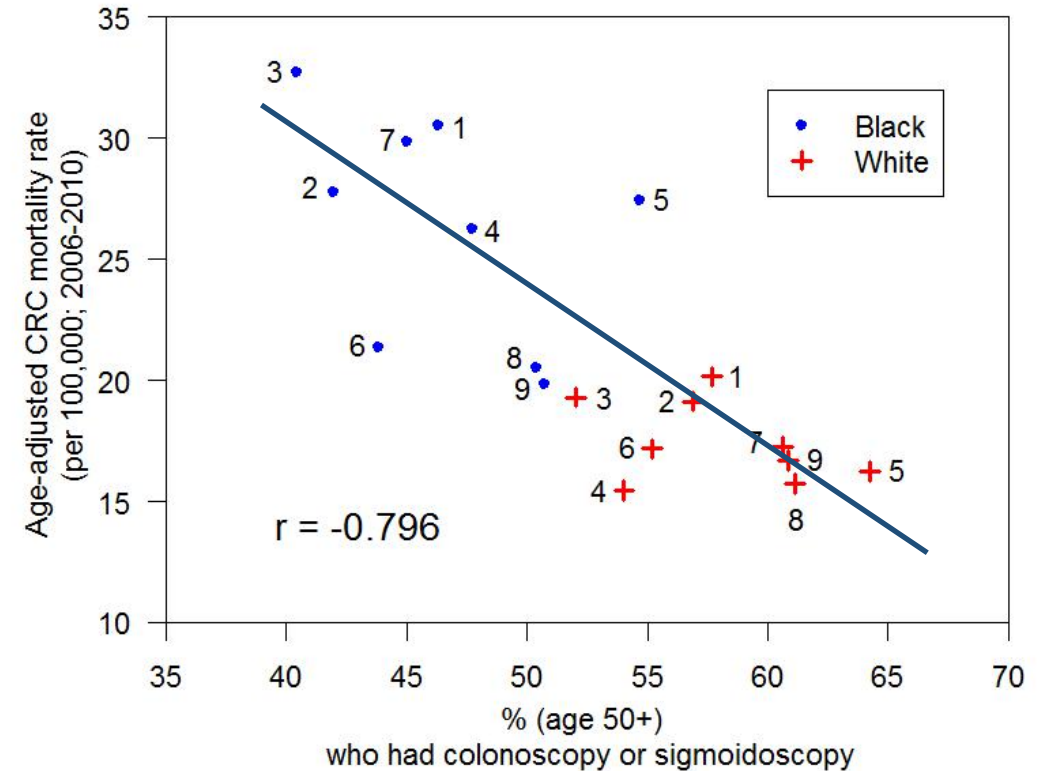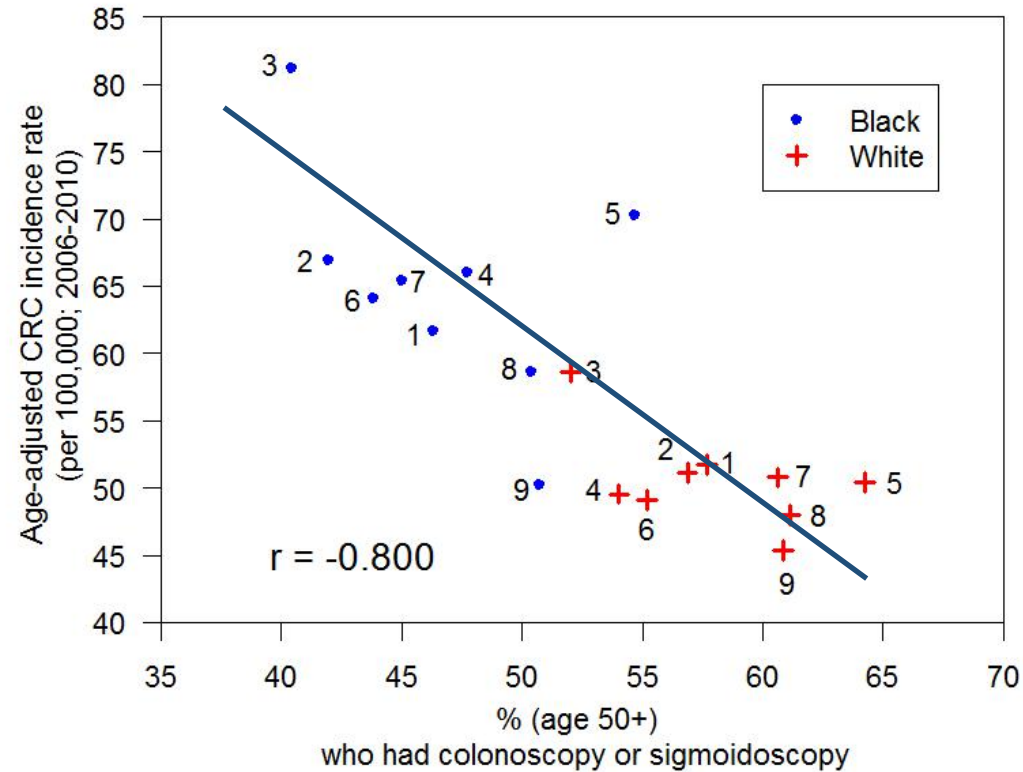
Dietary risks for colorectal cancer

- Processed meat **INCREASES** CRC risk (WHO Group 1, carcinogenic to humans)
- Red meat **INCREASES** CRC risk (WHO Group 2A, probably carcinogenic to humans)
- Fruits, vegetables and dietary fiber **DECREASE** CRC risk

Figueiredo, et al. (2014) *PLoS Genetics* 10(4): e1004228.
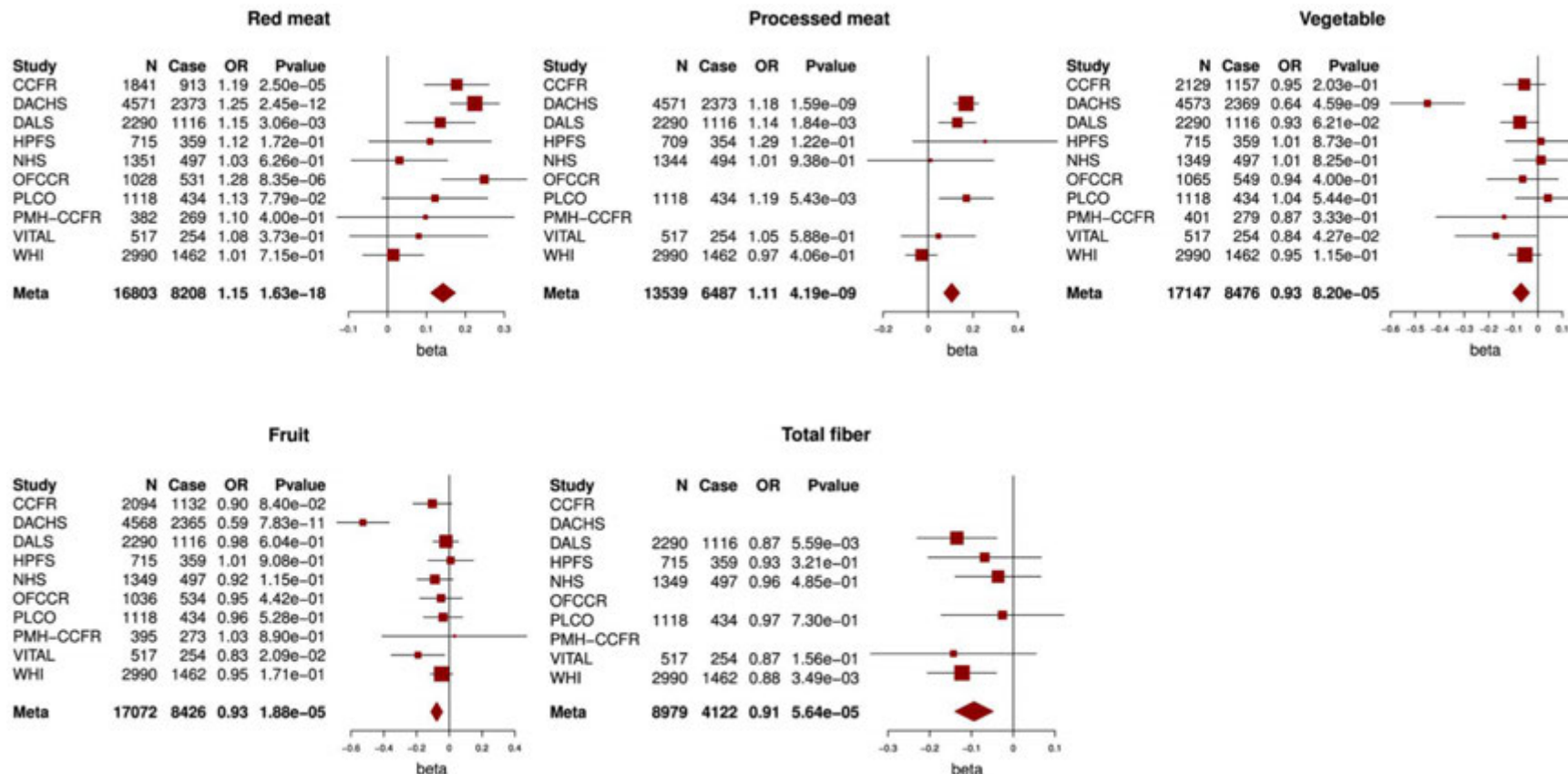
Screening options

Take-home lesson:

Many choices available for preventive and early-detection screens, which all require colonoscopy for diagnostic confirmation

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.

All CRC screens require confirmation via colonoscopy

Flexible fiber optics revolutionized CRC prevention & control in 1973:

"Polypectomy Via the Fiberoptic Colonoscope — Removal of Neoplasms beyond Reach of the Sigmoidoscope"
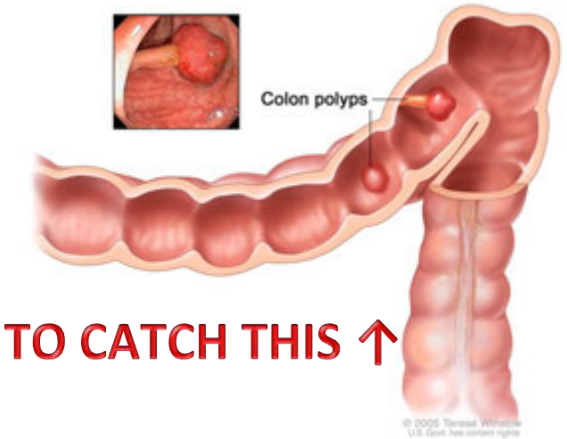
published in the *New England Journal of Medicine* (288:329-332)

on February 15, 1973

by

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

DO THIS ↓

Colonoscopy

Colon polyps

TO CATCH THIS ↑

Colon

Rectum

Colonoscope

Anus

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BEFORE IT BECOMES THIS ↓

Spread to other organs

Lymph node | Blood vessel | Normal

Serosa
Muscle layers
Submucosa
Mucosa

Stage 0
Stage I
Stage II
Stage III
Stage IV

National Cancer Institute
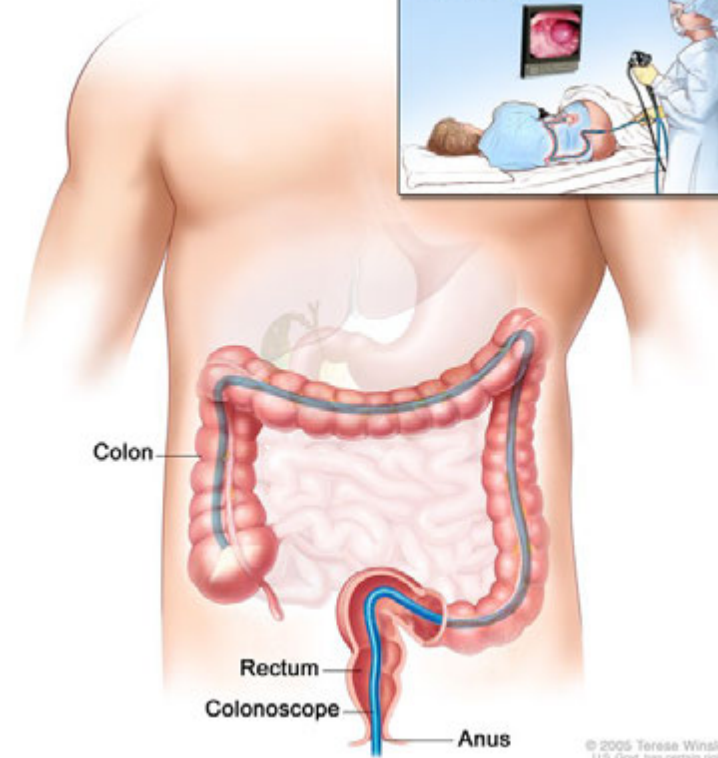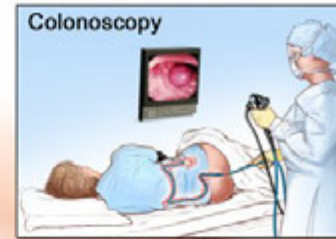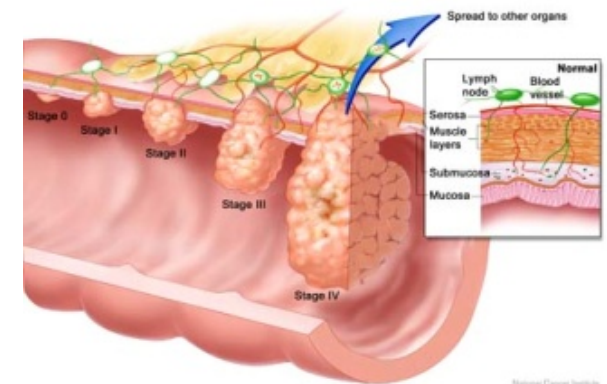
Can colonoscopy / polypectomy *alone* eliminate CRC mortality?

- **<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).**
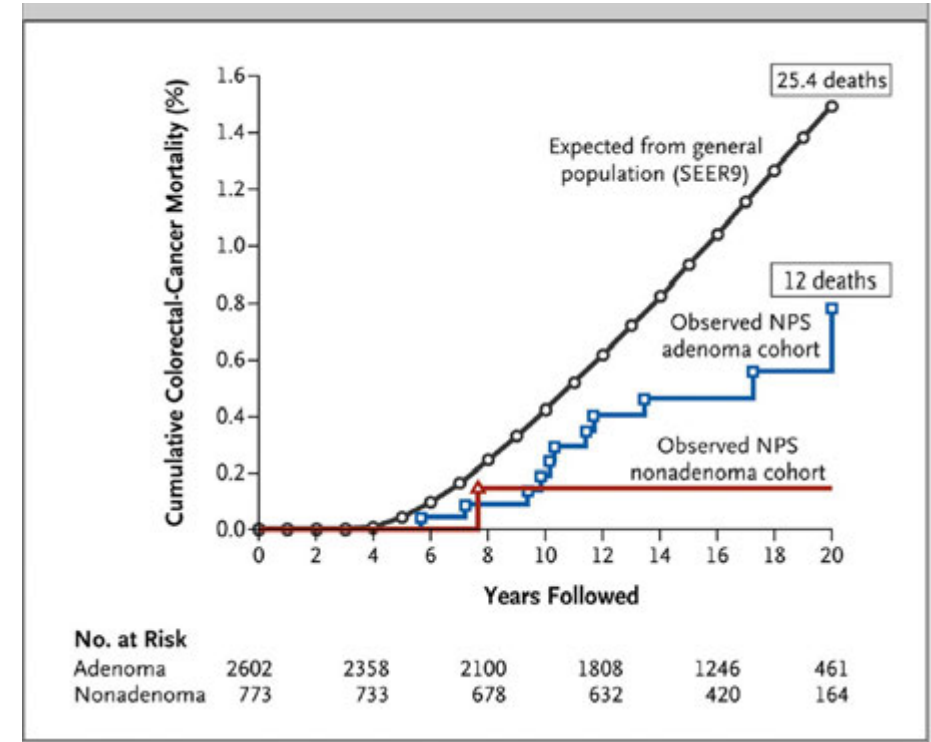

2012 NPS follow-up study indicates that colonoscopic removal of adenomatous polyps reduces death from colorectal cancer by 53%. (Zauber, et. al., (2012) *NEJM*; 366:687-696).

Colorectal cancer screening as part of preventive care

Take-home lesson:

Pro-active CRC screening policies can yield maximum benefit to health care system & reduce expensive medical procedures
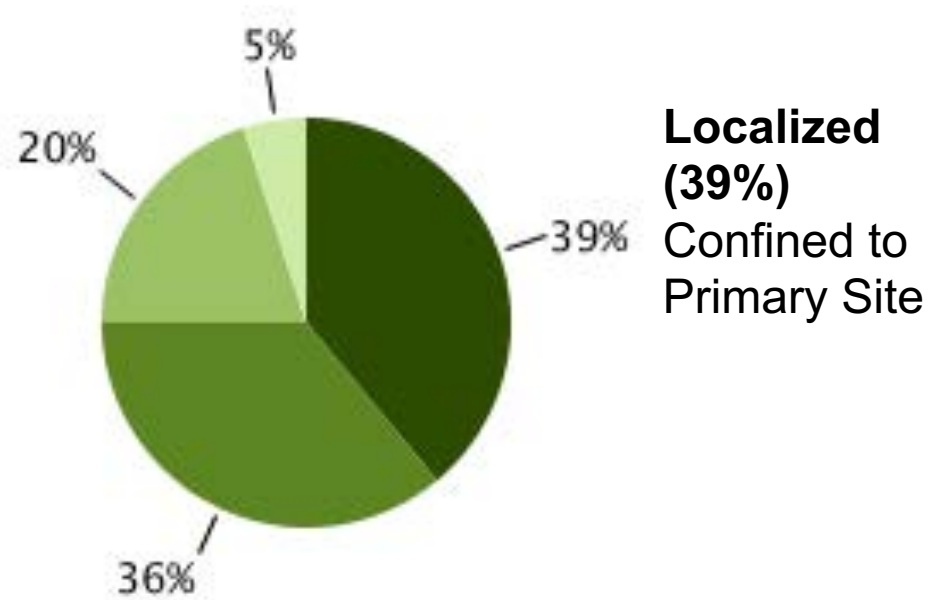
Why does screening matter?
Because survival is tremendously improved by early-stage diagnosis
(SEER 2005-2011 Data, All Races, Both Sexes)
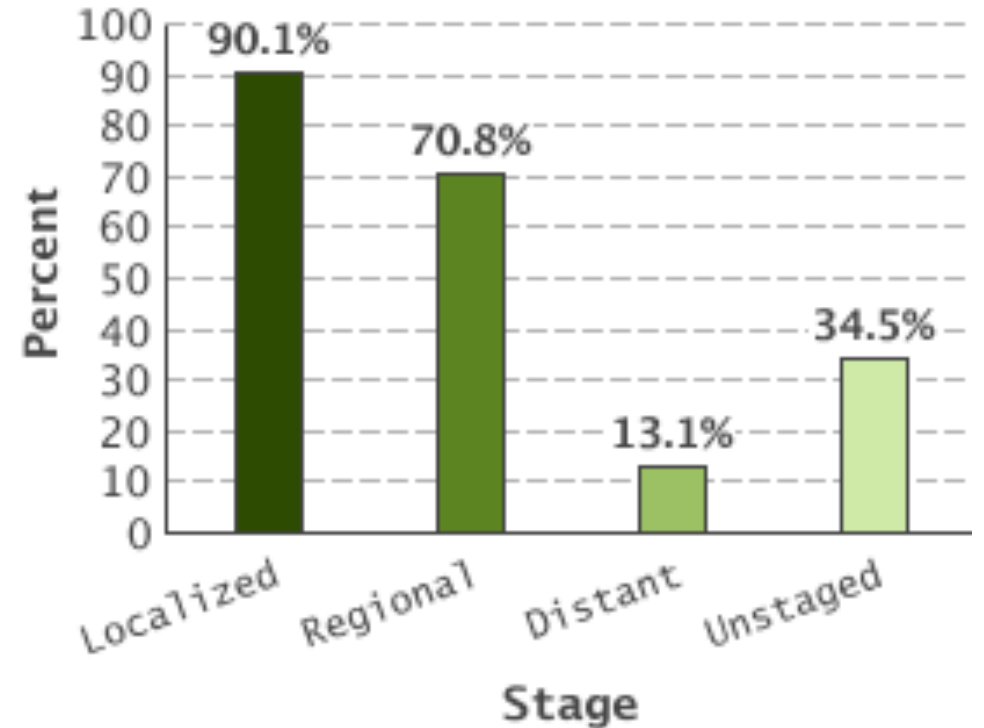
Percent of Cases by Stage

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

Simplified summary of CRC treatment plans

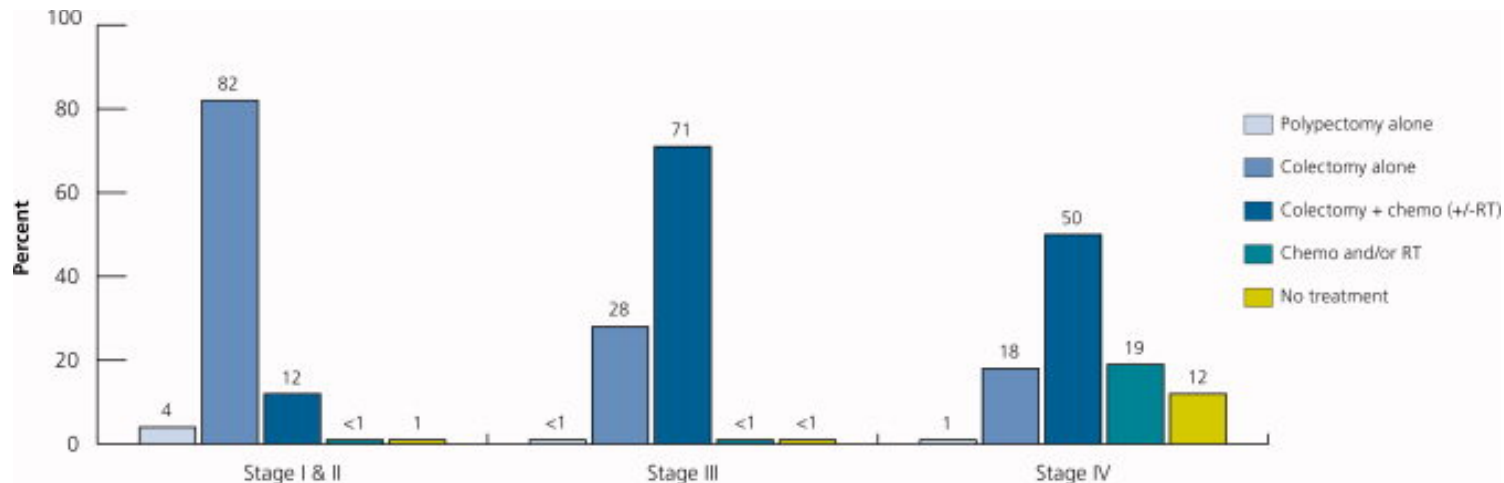| Stage	Colon Cancer	Rectal Cancer
0	Surgery only (polypectomy or partial colectomy)	Surgery only (polypectomy, local excision or transanal resection)
I	Surgery only (polypectomy or partial colectomy with lymph node dissection)	Surgery (above or proctectomy w/ colo-anal anastomosis, other surgical options) 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

In contrast to breast cancer clinical practices, physicians routinely treat CRC based on stage, not subtype.
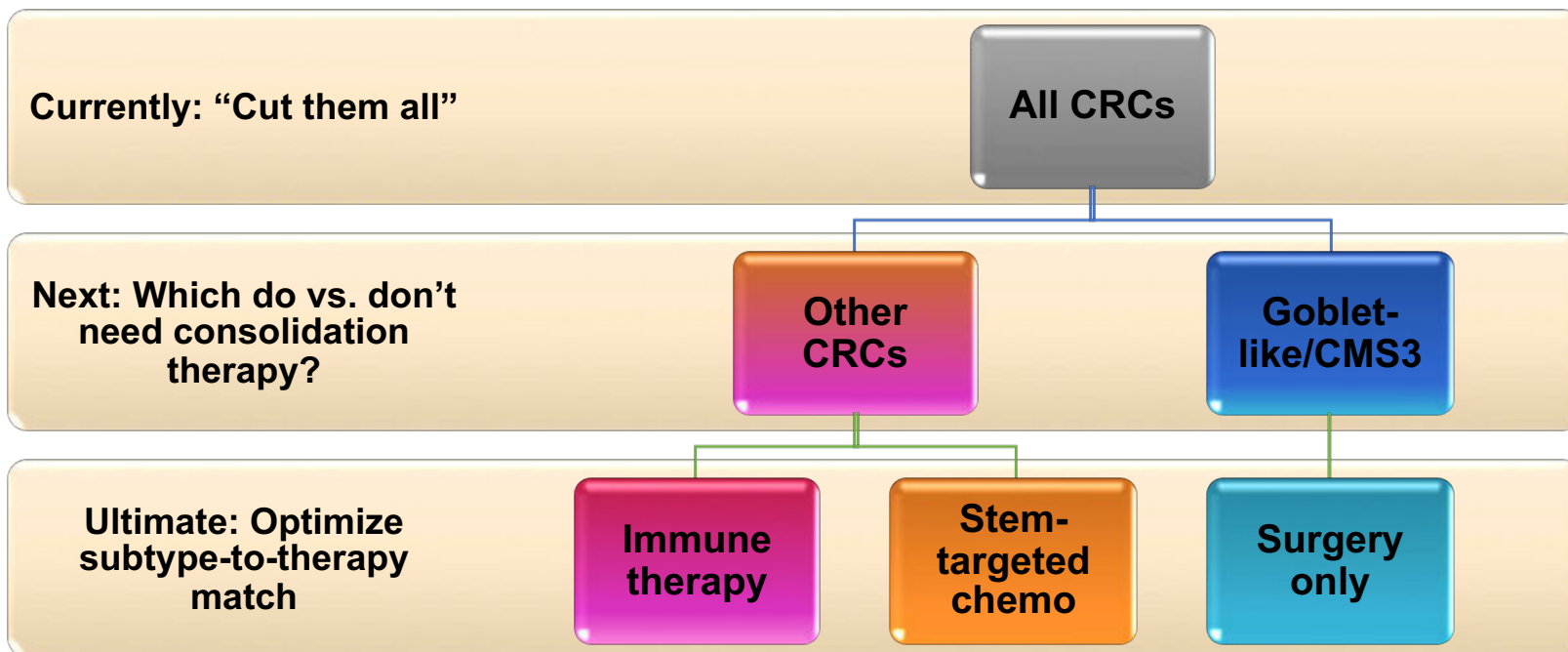

Siegel, et. al. (2012) *CA: A Cancer Journal for Clinicians*, 62: 220–241.
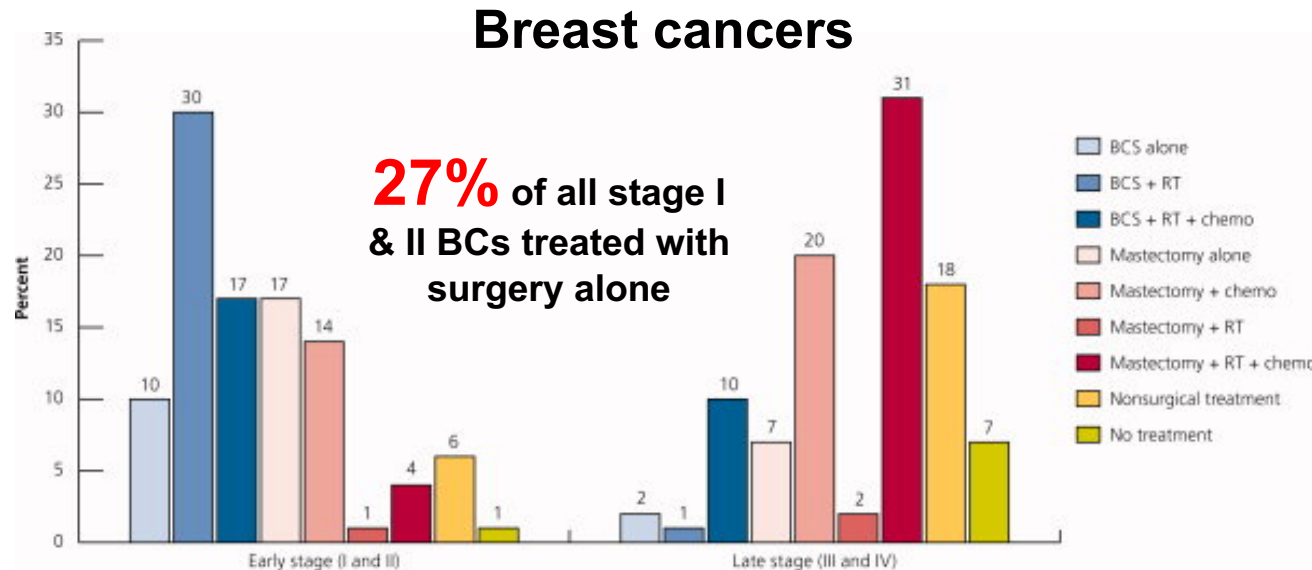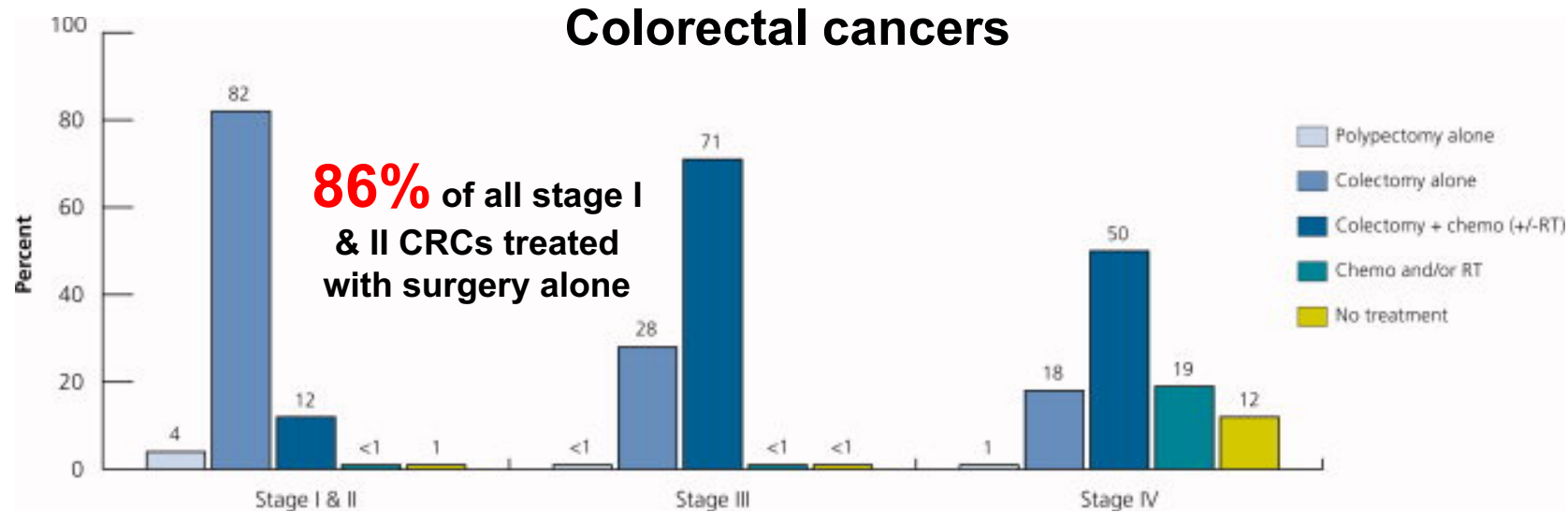
What is my challenge to this audience?
Change early-stage CRC treatment paradigms based on molecular subtype.

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

How do we get there from here?

Currently: "Cut them all"

Next: Which do vs. don't need consolidation therapy?

Ultimate: Optimize subtype-to-therapy match

All CRCs

Other CRCs

Goblet-like/CMS3

Immune therapy

Stem-targeted chemo

Surgery only

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.