

Colon Cancer in the young

Howard K. Gogel, MD, FACP
Southwest Gastroenterology Associates
Albuquerque, NM
November, 2019

Conflicts of interest

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function MM_swapImgRestore() { //v3.0
  var i,x,a=document.MM_sr; for(i=0;a&& i<a.length&&(x=a[i])&&x.oSrc;i++) x.src=x.oSrc;
}function MM_preloadImages() { //v3.0
  var d=document; if(d.images){ if(!d.MM_p) d.MM_p=new Array();
  var i,j=d.MM_p.length,a=MM_preloadImages.arguments; for(i=0; i<a.length; i++)
  if (a[i].indexOf("#")!=0){ d.MM_p[j]=new Image; d.MM_p[j++].src=a[i];}}
}function MM_findObj(n, d) { //v4.01
  var p,i,x; if(!d) d=document; if((p=n.indexOf("?"))>0&&parent.frames.length) {
  d=parent.frames[n.substring(p+1)].document; n=n.substring(0,p);}
  if(!(x=d[n])&&d.all) x=d.all[n]; for (i=0;!x&&i<d.forms.length;i++) x=d.forms[i][n];
  for(i=0;!x&&d.layers&&i<d.layers.length;i++) x=MM_findObj(n,d.layers[i].document);
  if(!x && d.getElementById) x=d.getElementById(n); return x;
}function MM_swapImage() { //v3.0
  var i,j=0,x,a=MM_swapImage.arguments; document.MM_sr=new Array; for(i=0;i<(a.length-2);i+=3)
  if ((x=MM_findObj(a[i]))!=null){document.MM_sr[j++]=x; if(!x.oSrc) x.oSrc=x.src; x.src=a[i+2];}
}function MM_swapImgRestore() { //v3.0
  var i,x,a=document.MM_sr; for(i=0;a&& i<a.length&&(x=a[i])&&x.oSrc;i++) x.src=x.oSrc;
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  d=parent.frames[n.substring(p+1)].document; n=n.substring(0,p);}
  if(!(x=d[n])&&d.all) x=d.all[n]; for (i=0;!x&&i<d.forms.length;i++) x=d.forms[i][n];
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  if ((x=MM_findObj(a[i]))!=null){document.MM_sr[j++]=x; if(!x.oSrc) x.oSrc=x.src; x.src=a[i+2];}
```

Conflicts of Interest: Translated

Ironwood Pharmaceuticals: PI Study C3718-301

Allergan Pharmaceuticals: Sub-I Study 3150-201

Allergan Pharmaceuticals: Sub-I Study 3151-201

Typical Conflicts of Interest Statement, Properly Revealed:

Engagement: % of professional compensation:

| | |
|-----------------|--------|
| Ironwood Pharma | < .04% |
| Allergan Pharma | < .04% |

Ideal Conflict of Interest Statement:

Engagement: % of professional compensation:

Southwest Gastroenterology 100%

Nature of potential bias: Presenter does clinical care of gastroenterology patients including colonoscopy.

Risk factors for Colon Cancer

Age

Inherited Genetic syndrome

Inflammatory Bowel Disease involving the colon

Abdominal or Pelvic irradiation

Lifestyle and other “choices”

- Diet (red meat, processed meats vs fiber, veges)

- Obesity

- Diabetes

- Physical Activity

- Alcohol

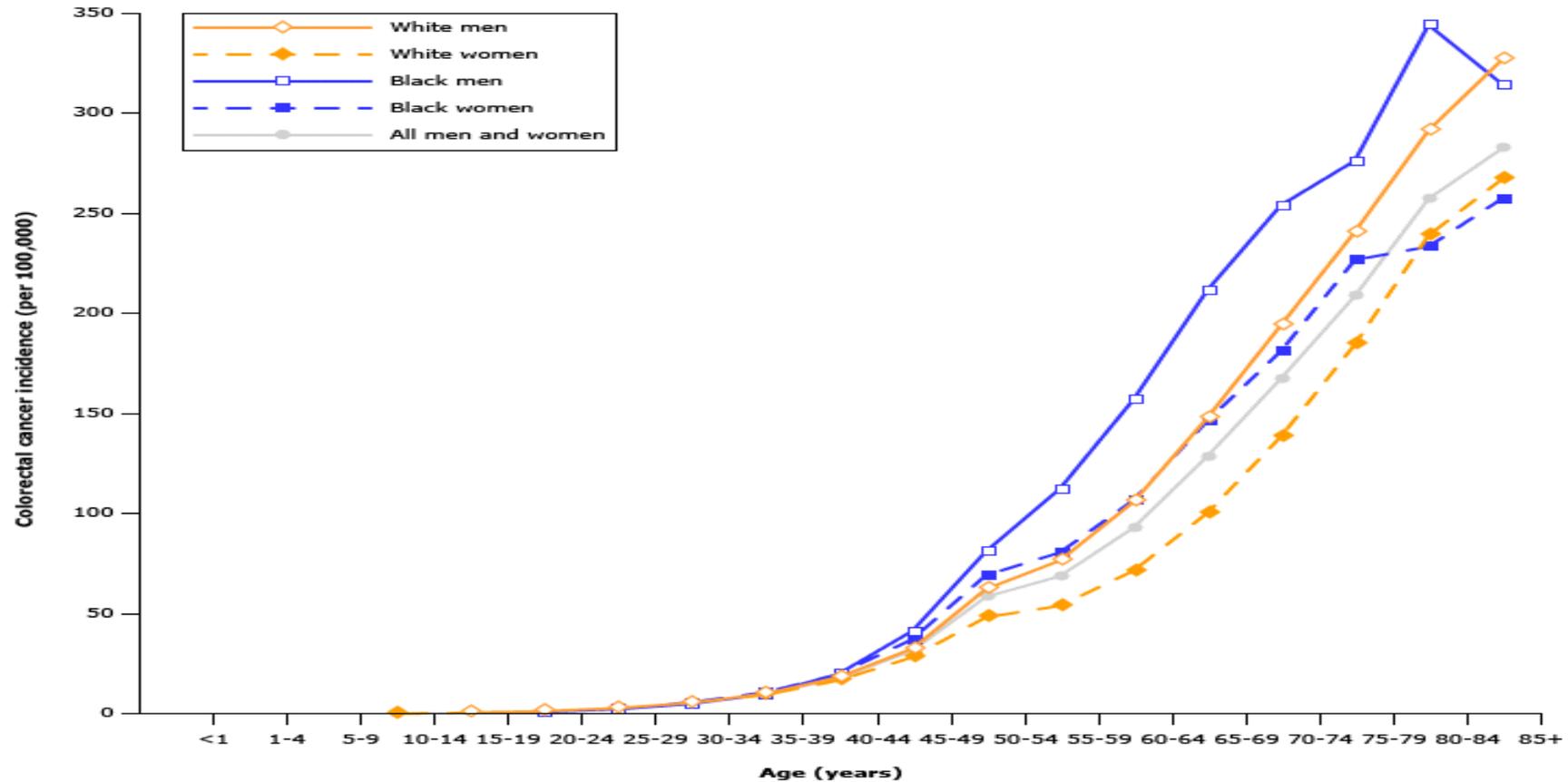
- Smoking

- Estrogen replacement

- NSAID/ASA use

Epidemiology of Colon Cancer

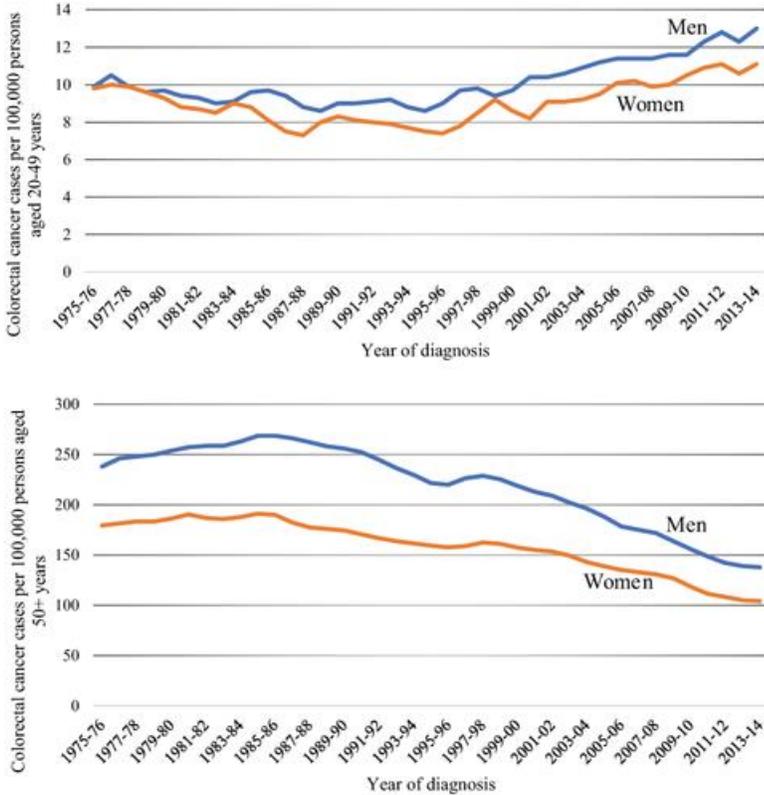
Colorectal cancer incidence: SEER data, 2011 to 2015

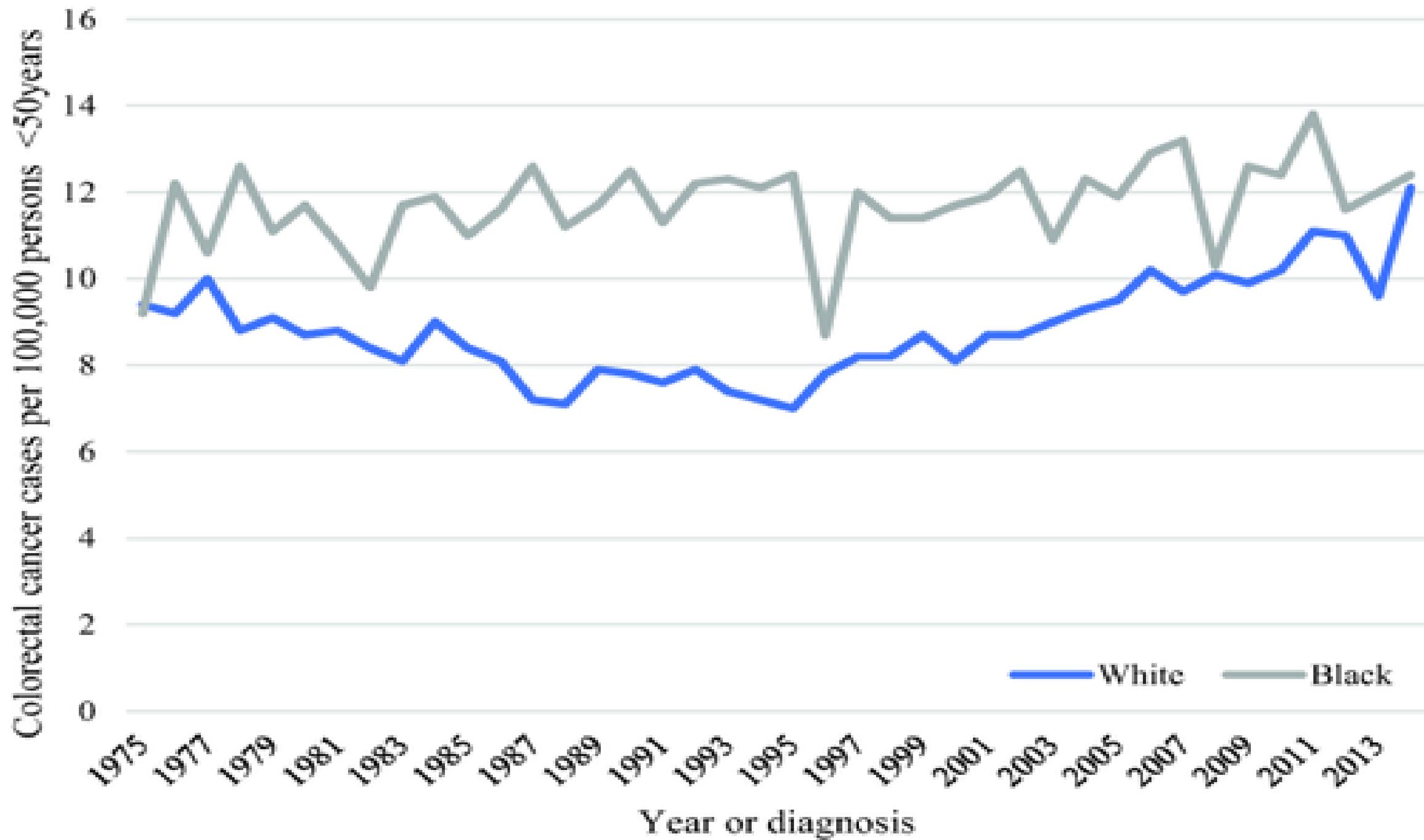


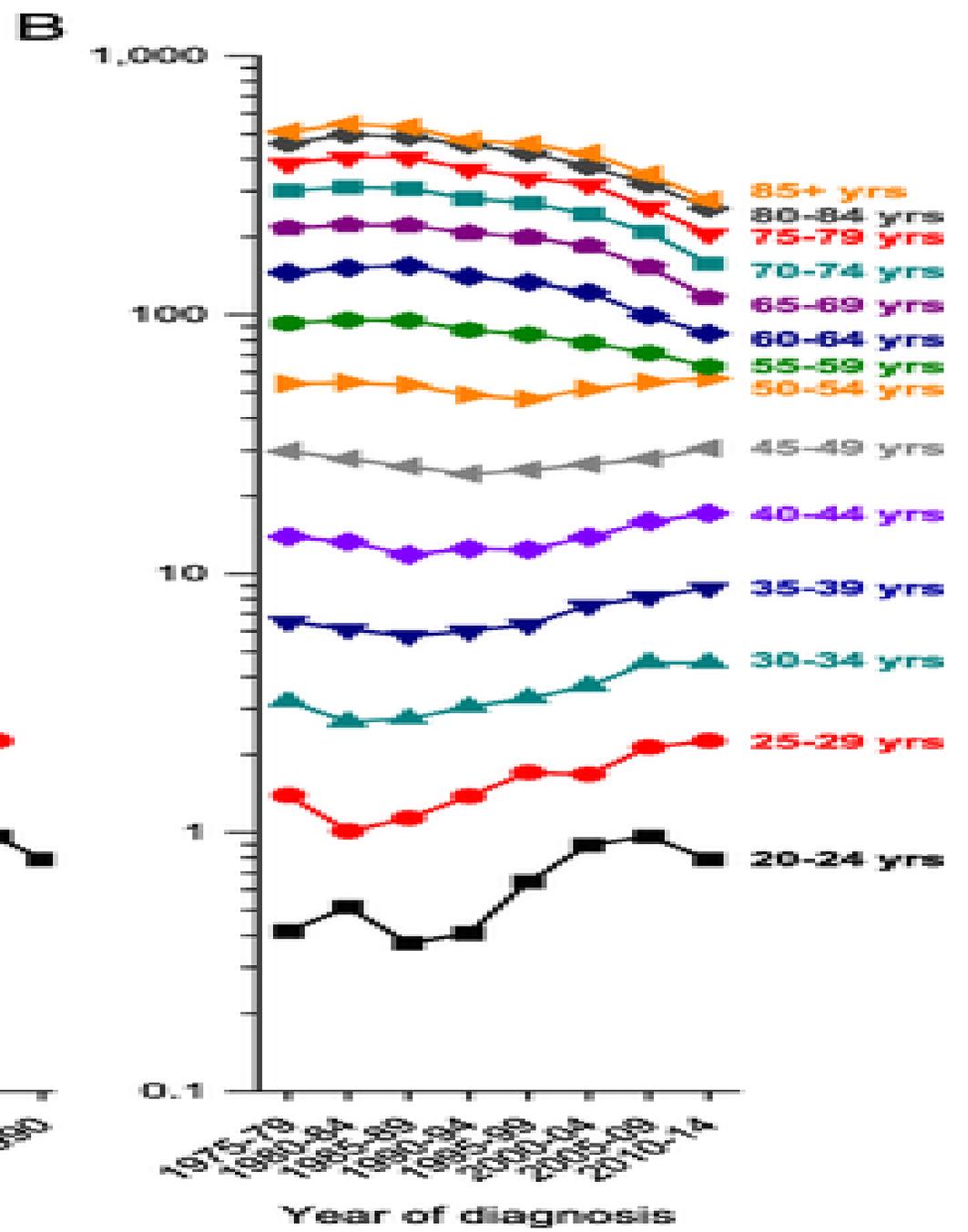
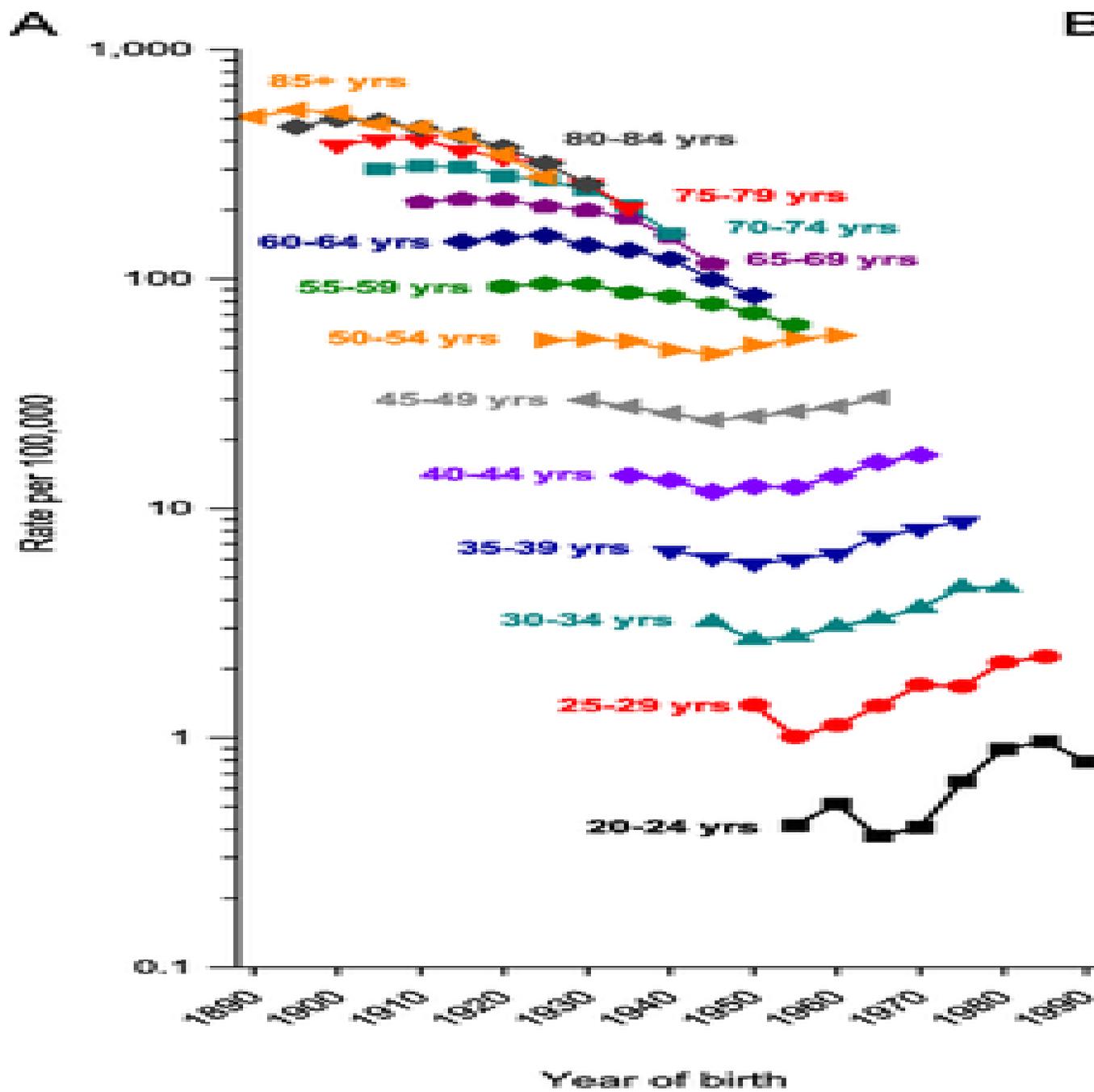
Data from: National Cancer Institute. SEER Data, 2011-2015. Available at: <https://seer.cancer.gov/faststats/selections.php?series=cancer> (Accessed on March 11, 2019).

UpToDate®

Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society







Why are we talking about this now?

The American Cancer Society has recently recommended decreasing the screening age to 45 y/o:
Wolf et al. Colorectal Cancer Screening for Average-Risk Adults: 2018 Guideline Update from the American Cancer Society. *CA: A Cancer Journal for Clinicians* 2018; 68: 250 (July/August issue)

1 in 10 new colon cancers will be at age < 50

The incidence of colon cancer in younger patients is projected to double by 2030

Colon Cancer Diagnoses at Southwest Gastroenterology

| | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
|---------------------------|------|------|------|------|------|------|------|------|------|
| Total colon cancers (214) | 3 | 30 | 26 | 22 | 0 | 16 | 31 | 38 | 39 |
| 50+ | 3 | 25 | 24 | 21 | | 16 | 24 | 33 | 37 |
| < 50 | 0 | 5 | 2 | 1 | | 0 | 7 | 5 | 2 |
| Average age | 67 | 63 | 64 | 68 | | 66 | 63 | 65 | 67 |

Thus $22/214 = \sim 10\%$ of new diagnoses are in pts < 50 y/o

The data set is too small to see a trend...

Changing Risk factors in the Young

Obesity is on the rise

Inflammatory Bowel disease is on the rise

Diets are evolving (not necessarily in a positive way)

Cohort effect of unclear nature

The identified risk factors do not explain the changing epidemiology.

Obesity

Each 5 unit increase in BMI increased Colon Ca risk by 13-18 % !

Diabetes is associated with an increased risk of up to 38% (20% for rectal cancer)

Regular physical activity is associated with a 24-31% decrease in risk.

(Increased) relative risks are in the range of 1.3-2.0

Magnitude and Likelihood of Risk

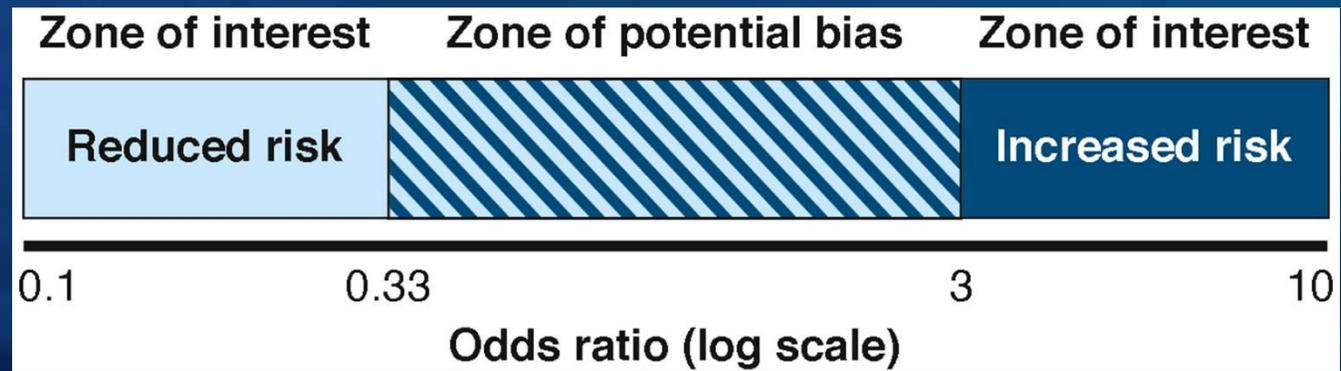
In a case/control observational study, an odds ratio for association can be calculated, but relative risk can only be estimated.

In a cohort study, relative risk can be calculated.

The observed relative risks for several possible PPI side effects are nearly always <2 and often <1.6 .

In this low range, confounding factors may be responsible for “risks” of this magnitude.

Causation is even tougher to prove: dose response and duration effects are inconsistently present

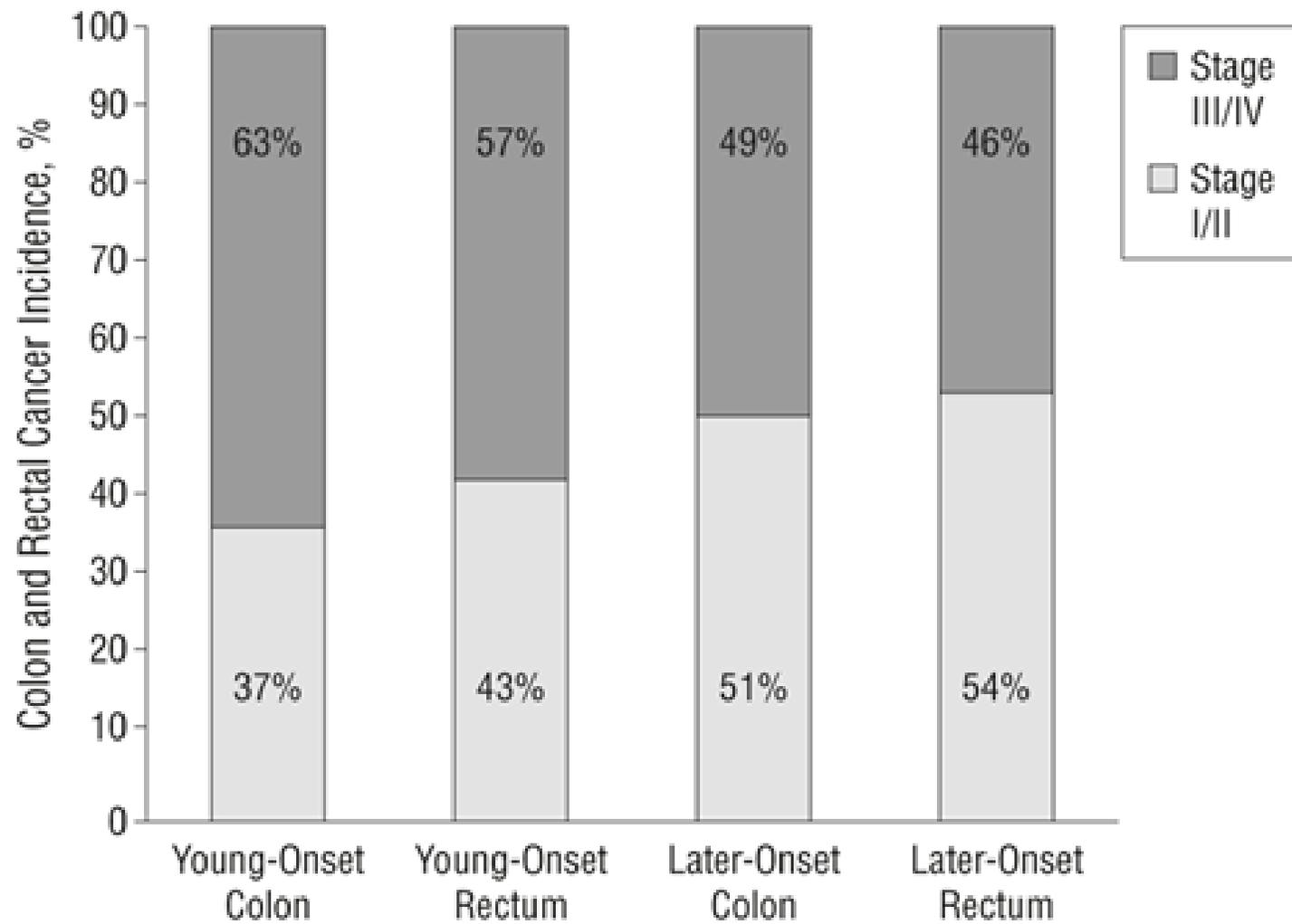


What happens to Younger People when they get Colon cancer?

More often present with advanced disease:
Symptomatic young patients wait 6 months before seeking care!

More often have left sided disease, particularly rectal.
But for a given stage, survival is better than older folks.

18% of patients < 50 y/o have a germline mutation
35% of patients < 35 y/o have a germline mutation



5 Year survival by CRC Stage

| AJCC stage | Survival rate (%) | | P value |
|------------|----------------------------|----------------------------|---------|
| | Younger (20-40 y) (n=1196) | Older (60-80 y) (n=35,837) | |
| All | 61.5 | 64.9 | .02 |
| I | 93.3 | 94.9 | NS |
| II | 88.6 | 82.7 | .01 |
| III | 58.9 | 57.2 | NS |
| IV | 18.1 | 6.2 | <.001 |

? Screening for younger patients ?

None of the current screening strategies have been properly studied in younger age groups

Participation in screening strategies is as important as test characteristics and cost for long term outcomes

Symptoms associated with colorectal cancer

| Symptom | DOR* (95% CI*) | AUC† | Sensitivity (95% CI) | 1- specificity (95% CI) | LR+ (95% CI) | LR- (95% CI) |
|------------------------------|-------------------------------|------|-------------------------|----------------------------------|--------------------|--------------------|
| Rectal bleeding ^Δ | 2.6 (1.9-3.6) p<0.001 | 0.66 | 0.46 (0.38-0.55) | 0.25 (0.19-0.31) | 1.9 (1.5-2.3) | 0.7 (0.6-0.8) |
| Blood mixed with stool | 3.1 (2.0-4.8) p<0.001 | 0.68 | 0.49 (0.30-0.69) | 0.24 (0.13-0.40) | 2.1 (1.5-2.8) | 0.7 (0.5-0.9) |
| Blood: dark red | 3.9 (1.7-9.2) p = 0.004 | 0.71 | 0.29 (0.09-0.65) | 0.10 (0.03-0.28) | 3.1 (1.6-6.0) | 0.8 (0.6-1.1) |
| Change in bowel habit | 1.5 (0.8-2.8) p = 0.16 | 0.57 | 0.32 (0.21-0.46) | 0.24 (0.15-0.35) | 1.4 (0.9-2.1) | 0.9 (0.7-1.1) |
| Constipation | 1.1 (0.8-1.5) p = 0.48 | 0.52 | 0.12 (0.08-0.18) | 0.11 (0.07-0.16) | 1.1 (0.8-1.5) | 1.0 (1.0-1.0) |
| Diarrhea | 0.9 (0.4-1.7) p = 0.65 | 0.47 | 0.15 (0.07-0.28) | 0.17 (0.09-0.29) | 0.9 (0.5-1.6) | 1.0 (0.9-1.1) |
| Abdominal pain | 0.7 (0.5-1.1) p = 0.12 | 0.45 | 0.19 (0.13-0.28) | 0.24 (0.17-0.33) | 0.8 (0.6-1.1) | 1.1 (1.0-1.2) |
| Weight loss | 2.9 (1.6-5.0) p = 0.001 | 0.67 | 0.20 (0.12-0.31) | 0.08 (0.05-0.13) | 2.5 (1.5-4.0) | 0.9 (0.8-1.0) |

LR+: the likelihood ratio of having colorectal cancer in the presence of the symptom; LR-: the likelihood ratio of having colorectal cancer in the absence of the symptom.

* DOR: diagnostic odds ratio. No association between symptom and cancer if DOR = 1.

† AUC: Area Under the receiver operating characteristic Curve. No association between symptom and cancer if AUC = 0.5.

Δ Bleeding of any type.

Reproduced from: Adelstein B, Macaskill P, Chan SF, et al. Most bowel cancer symptoms do not indicate colorectal cancer and polyps: a systematic review. *BMC Gastroenterology* 2011; 11:65.

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Cost of Current Screening Strategies

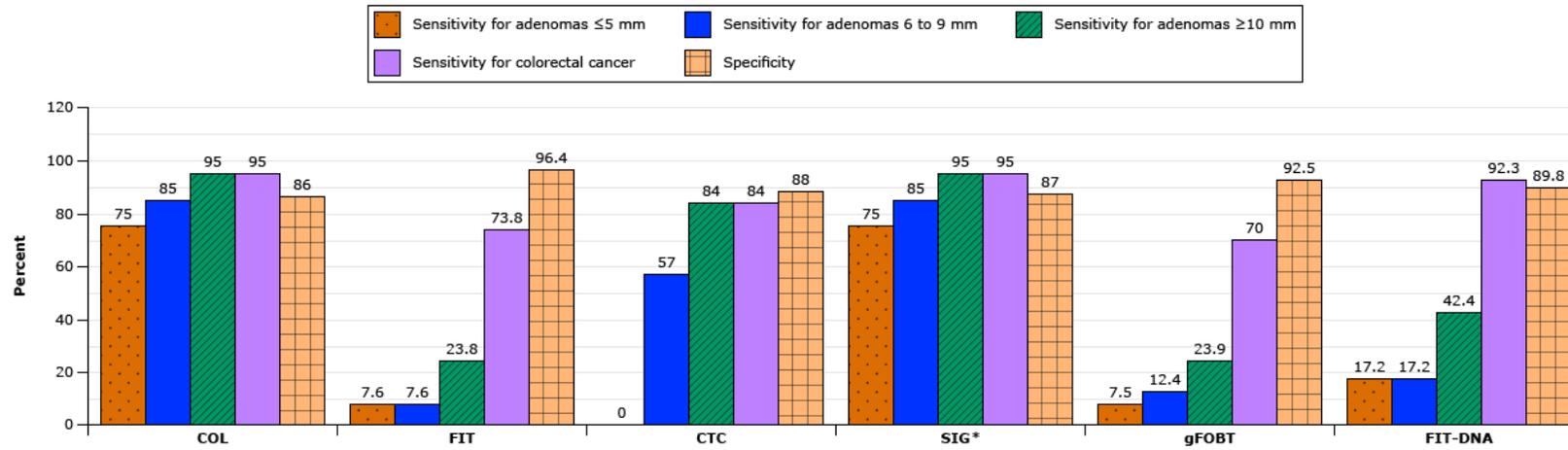
About \$ 15,000 per QALY

Compares favorably with a “standard” threshold of \$ 50 – 100K/ QALY

But the best screening strategy is the one that is acceptable to the individual patient – as any screening modality is much better than no screening.

Test for Colon Cancer Screening.

Estimated sensitivity, specificity, and cancer-specific deaths averted for each colorectal cancer screening strategy



| Colorectal cancer deaths averted per 1000 40-year-olds (n)¶ | 22 to 24 | 20 to 23 | 16 to 24 | 16 to 21 | 20 to 23 | 21 to 24 |
|---|----------|----------|----------|----------|----------|----------|
| | | | | | | |

Sensitivity, specificity, and cancer-specific deaths averted for each screening strategy.

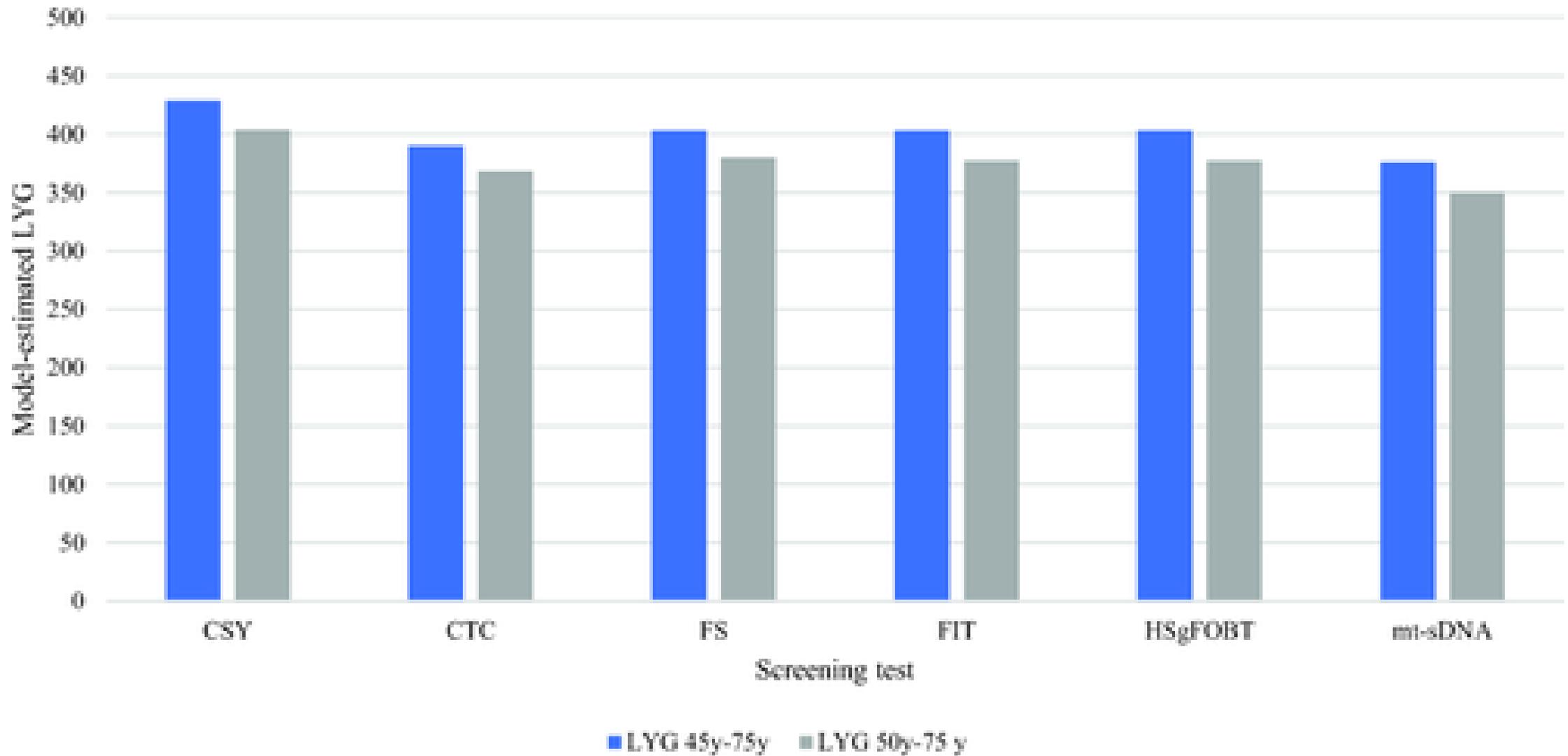
COL: colonoscopy; FIT: fecal immunochemical test; CTC: computed tomography colonography; SIG: sigmoidoscopy; gFOBT: guaiac-based fecal occult blood test; FIT-DNA: multitargeted stool DNA test.

* The sensitivity is only for the part of the colon that is within the reach of the sigmoidoscope.

¶ Assumes screening from ages 50 to 75 years, including 100% adherence, complete follow-up without delay, and appropriate surveillance. Ranges reflect results from 3 models. Stool tests assume yearly testing, sigmoidoscopy assumes testing every 5 years, CTC assumes testing every 5 years, colonoscopy assumes testing every 10 years.

Data from:

1. Zauber A, Knudsen A, Rutter CM, et al. Evaluating the Benefits and Harms of Colorectal Cancer Screening Strategies: A Collaborative Modeling Approach. AHRQ Publication No. 14-05203-EF-2. Rockville, MD: Agency for Healthcare Research and Quality; October 2015.
2. Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force. JAMA 2016; 315:2595.



Current ACP Guidance:

Qaseem et al. Screening for Colorectal Cancer in Asymptomatic Average-Risk Adults: A guidance statement from the ACP. Ann Int Med 2019;171:643
11/5/2019

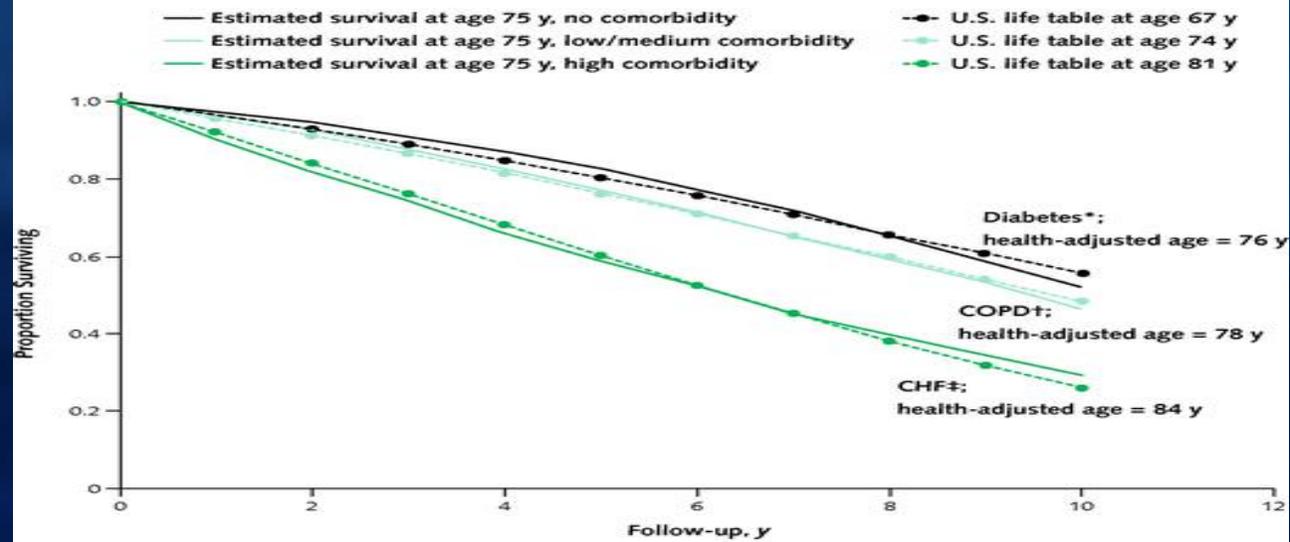
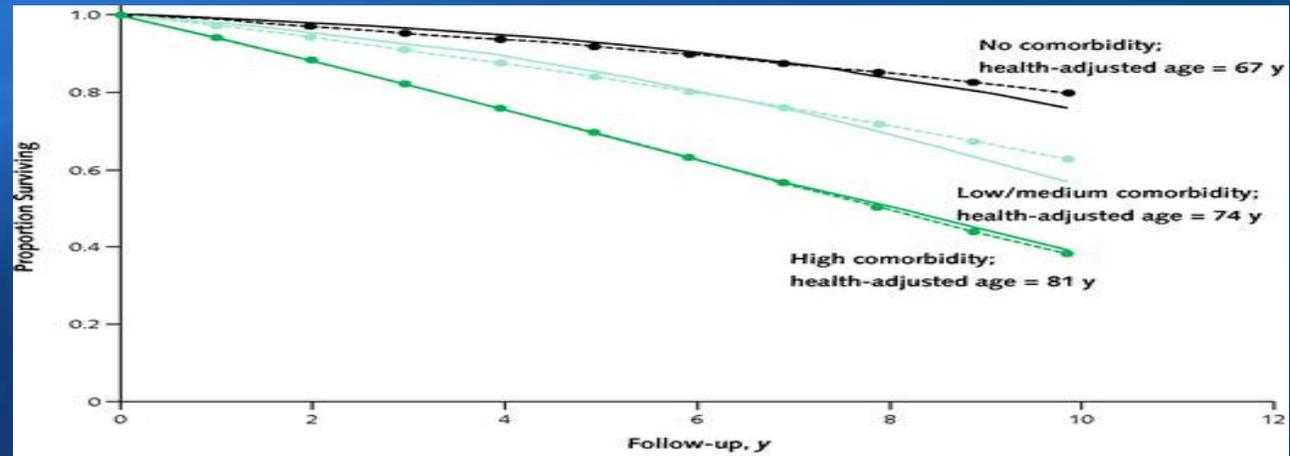
Screen in average risk adults 50-75 y/o

FIT or gFOBT q 2 yrs OR colonoscopy q 10 yrs OR Flex sig q 10 plus
FIT q2yrs

Stop at age 75 or with life expectancy < 10 yrs

What we really need to make good decisions about (any) screening:

- 1) A good way to estimate general prognosis
- 2) A good way to estimate risk of disease



- Estimated survival at age 75 y, no comorbidity
- Estimated survival at age 75 y, low/medium comorbidity
- Estimated survival at age 75 y, high comorbidity
- U.S. life table at age 67 y
- U.S. life table at age 74 y
- U.S. life table at age 81 y

- Estimated survival at age 75 y, diabetes*
- Estimated survival at age 75 y, COPD†
- Estimated survival at age 75 y, CHF‡
- U.S. life table at age 76 y
- U.S. life table at age 78 y
- U.S. life table at age 84 y

Can we be more selective about screening?

<http://magicproject.org/19022dist>

About you

Clinical information

Do you have a family history of ...

Women only: have you had any of these cancers?

Men only: have you had any of these cancers?

(These cancers did not pass our statistical test for significance for women.)

Do you currently have...

Leave blank if unknown Body mass index

Calculate risk over years.

15

About you

Age (25-84):

Sex: Male Female

Ethnicity:

UK postcode: leave blank if unknown

Postcode:

Clinical information

Smoking status:

Alcohol status:

Do you have a family history of ...

gastro-intestinal cancer?

Women only: have you had any of these cancers?

breast cancer?

uterine cancer?

ovarian cancer?

cervical cancer?

Men only: have you had any of these cancers?

(These cancers did not pass our statistical test for significance for women.)

oral cancer?

lung cancer?

cancer of the blood?

Do you currently have...

Diabetes:

ulcerative colitis?

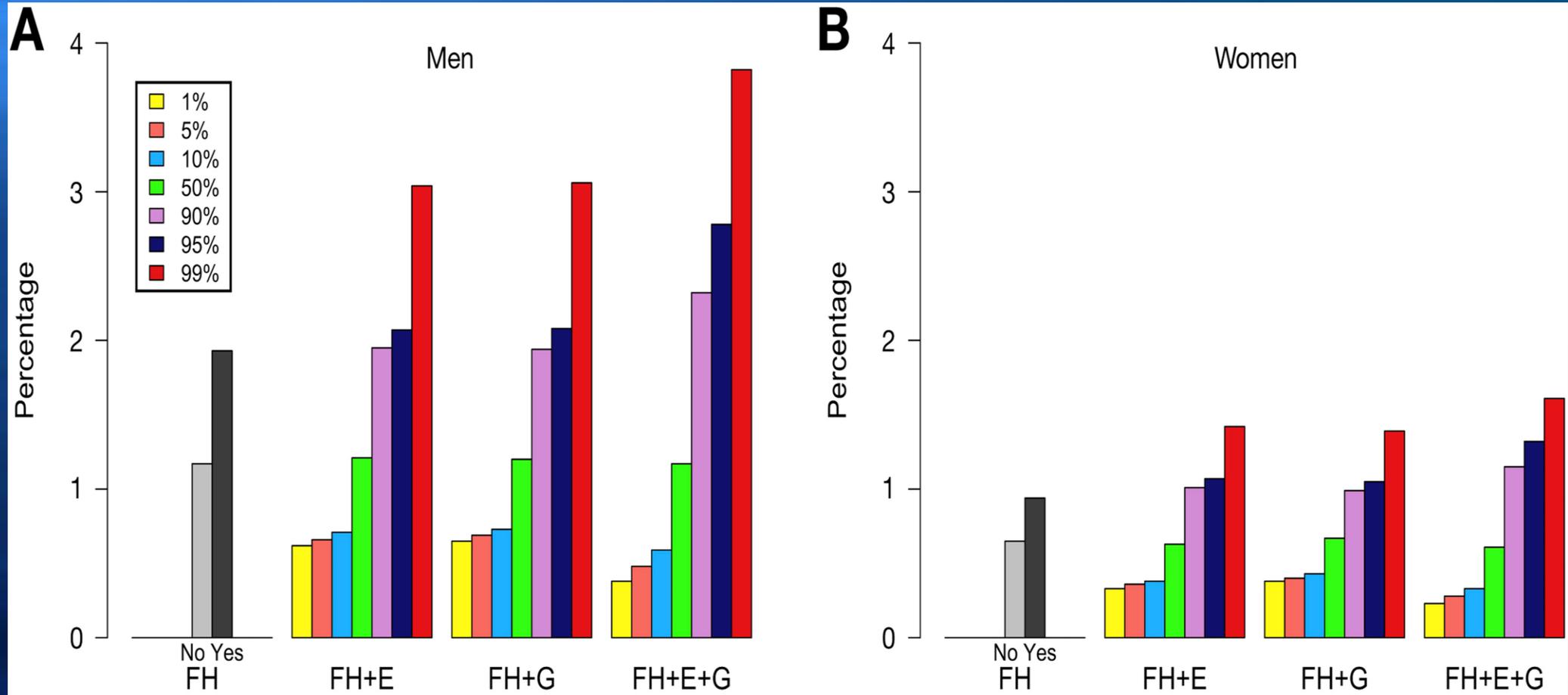
colonic polyps?

Leave blank if unknown Body mass index

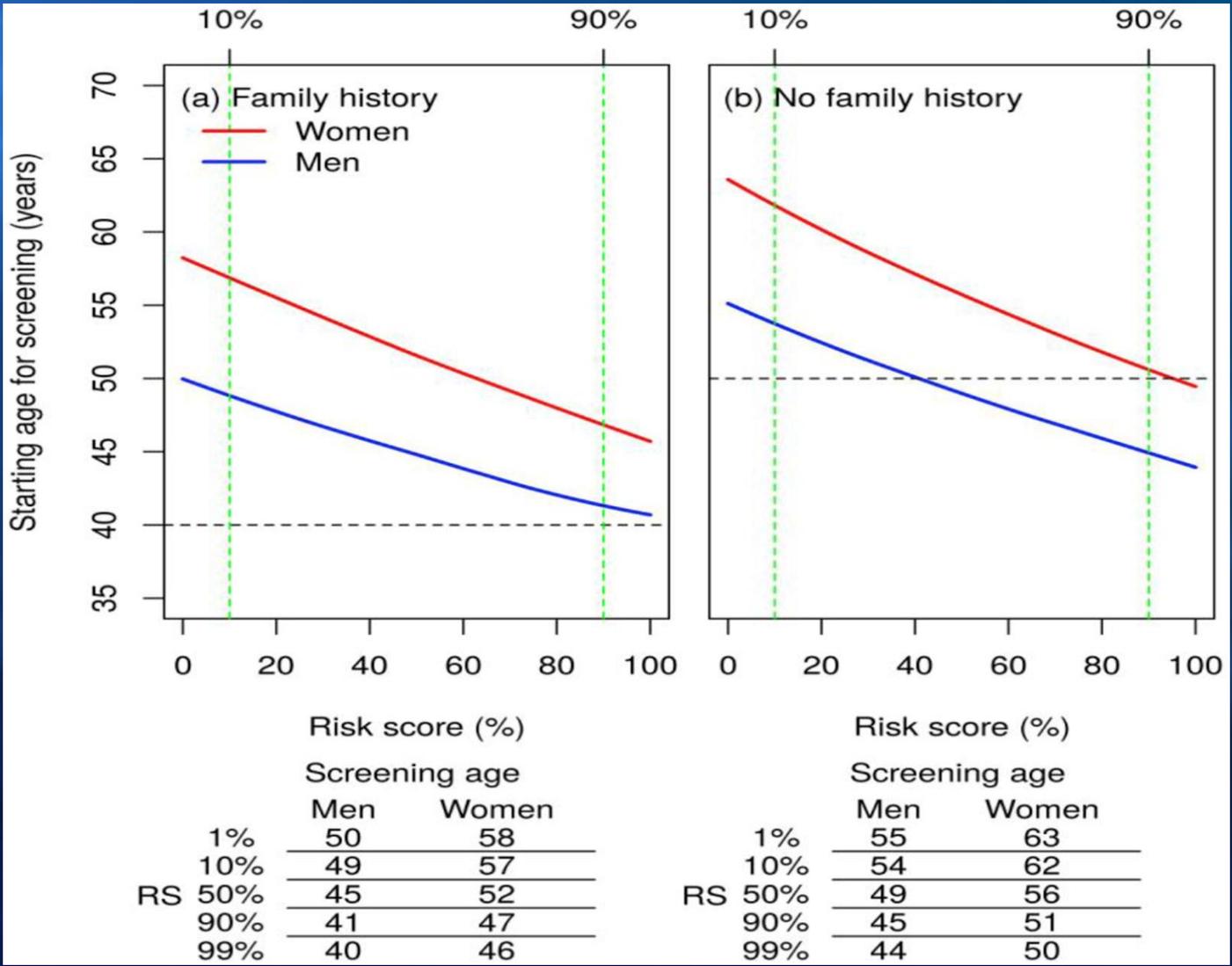
Height (cm):

Weight (kg):

Calculate risk over years.



From Jeon et al. Gastroenterology 2018; 154: 2152



Hypothesis: If we could be more selective, would the uptake of CRC screening by better defined at risk population be better than the current approx. 2/3?

Complex algorithms are not how most folks make decisions!

What about Cologuard?

Sensitivity of 84-97% (median 92%), specificity 84%

Heavily advertized

Numerous publications, but: All original data generated by the manufacturer !

What about Cologuard?

This is a hybrid test: FIT plus abnormal DNA fragments – with no ability to learn which component is “positive”

What to do with a patient with positive Cologuard and negative colonoscopy (which will happen half the time):

- a) nothing – Cotter et al. Cancer Epi Biomark Prev 2007: no increase risk in 1000 patients over 4 years
- b) “more aggressive short-term surveillance”: ACP Guidance 2019

Summary

Get a good family history (review every 3 years)

Take colonic symptoms seriously in younger patients

Consider engaging in screening at age 45 – perhaps most importantly in African Americans

Encourage healthy lifestyle

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