

# **How to Screen a patient with a Family History of Adenoma(s)**

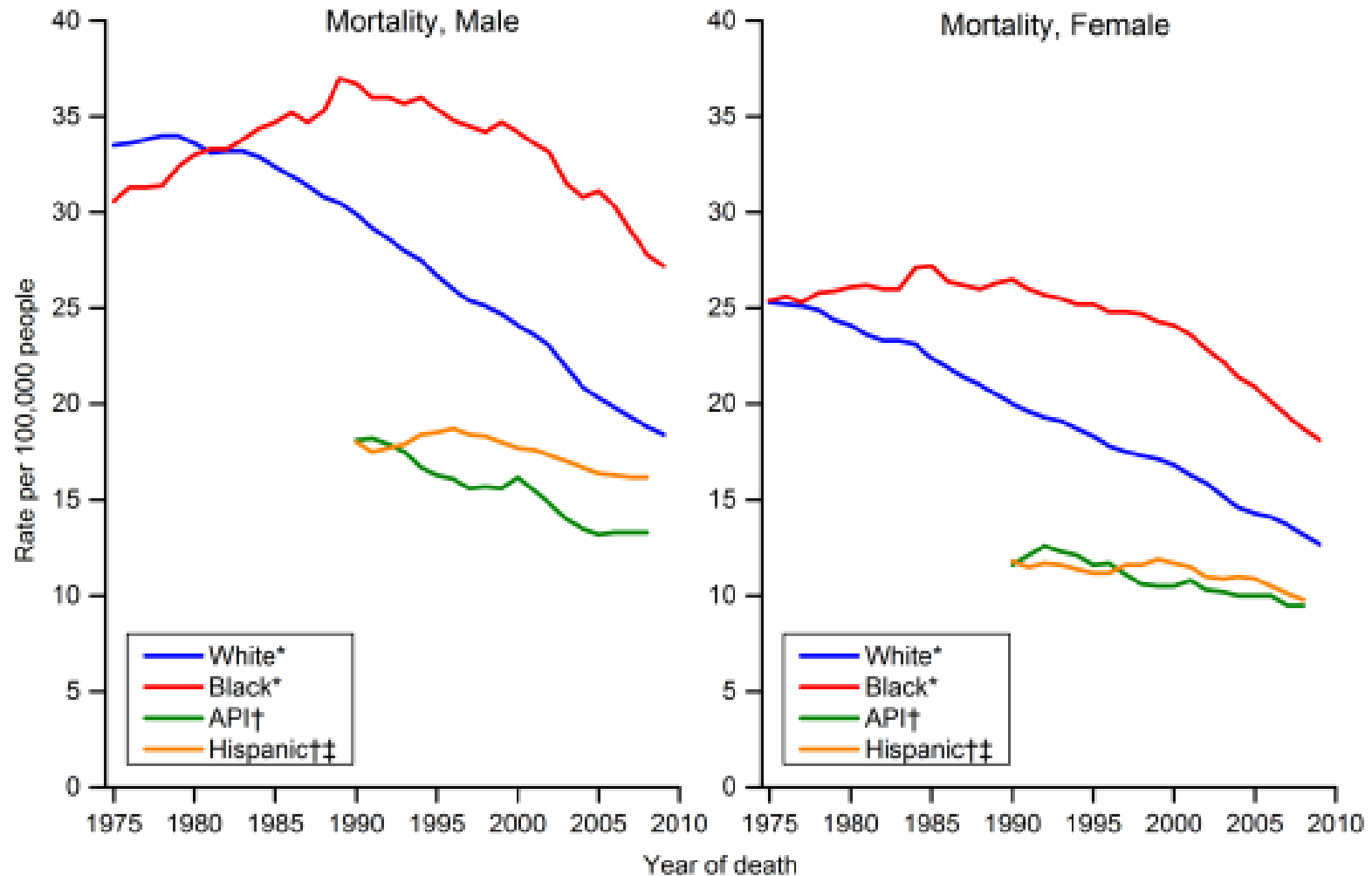
CDDW  
Banff 3-5-17

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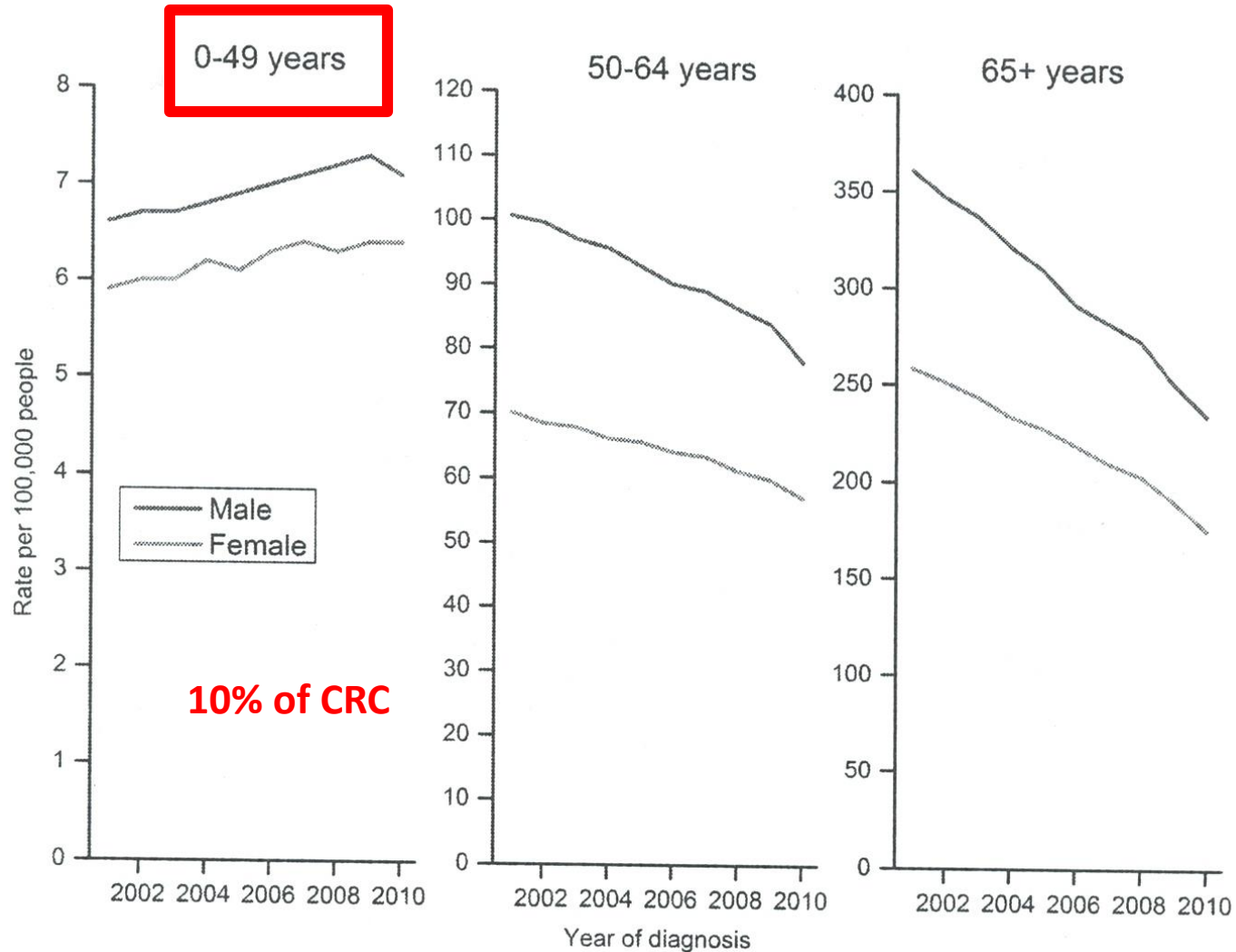
# Disclosures 2016

- Scientific advisory board
  - MOTUS-GI

# CRC Mortality Trends

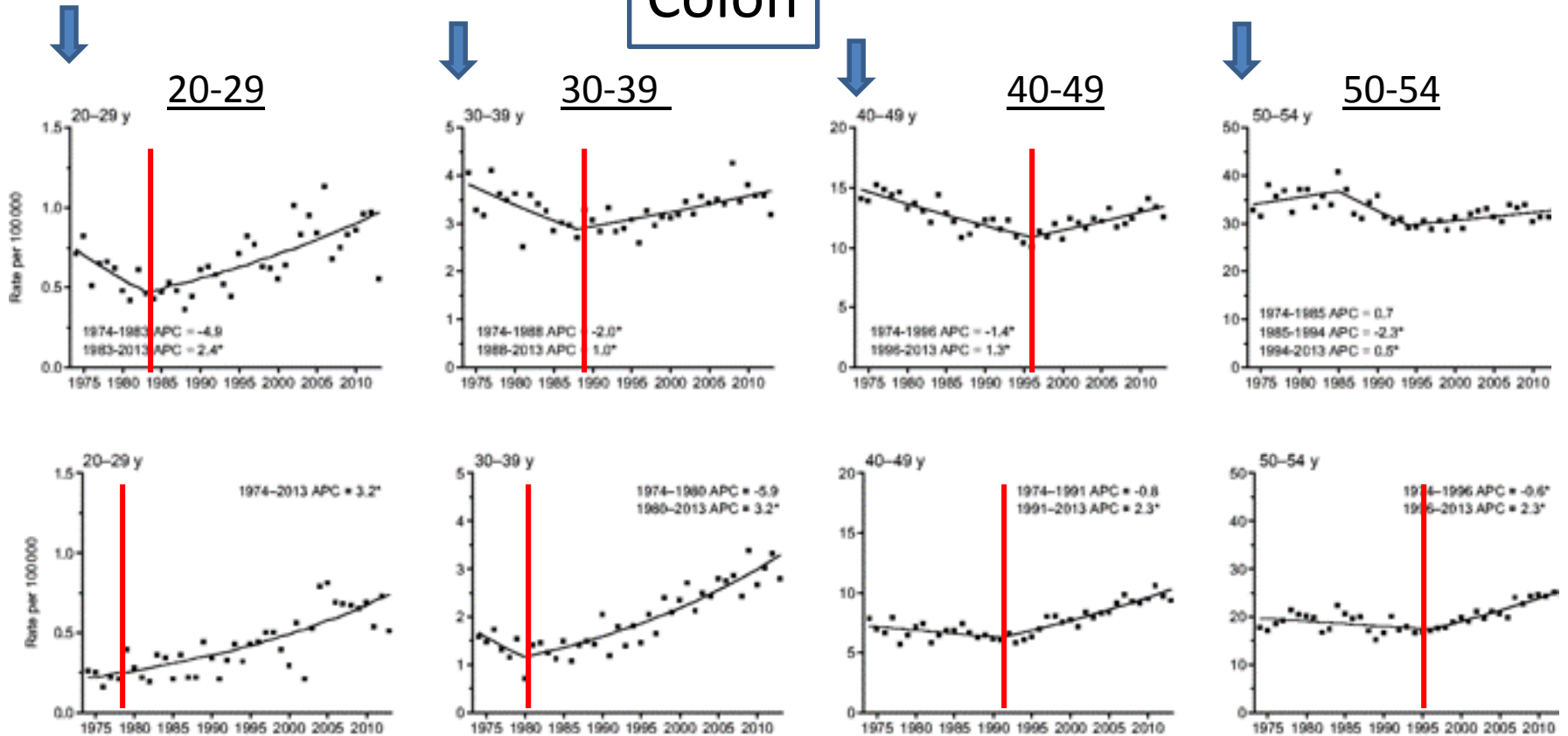


# Incidence Trends by Age



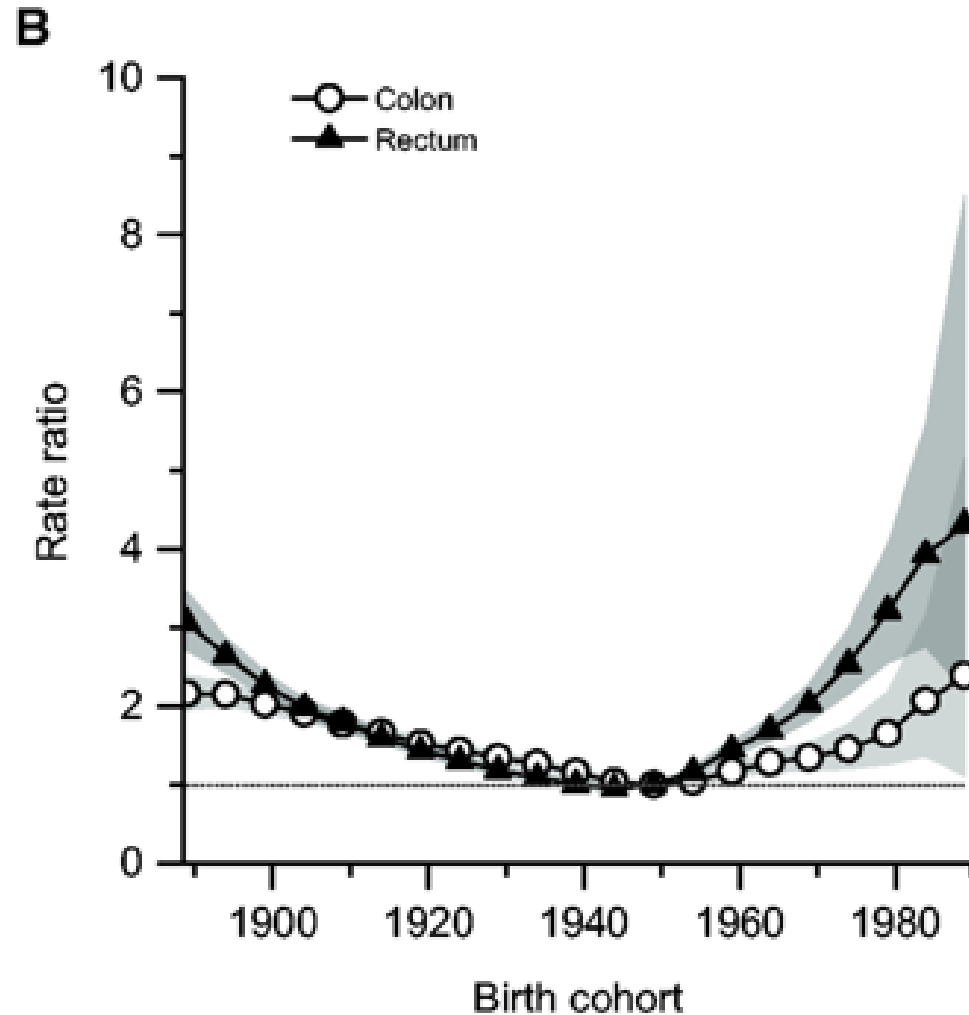
# CRC Incidence < age 54 years

Colon



Rectum

# CRC <54 years



# Familial Risk and Age of CRC

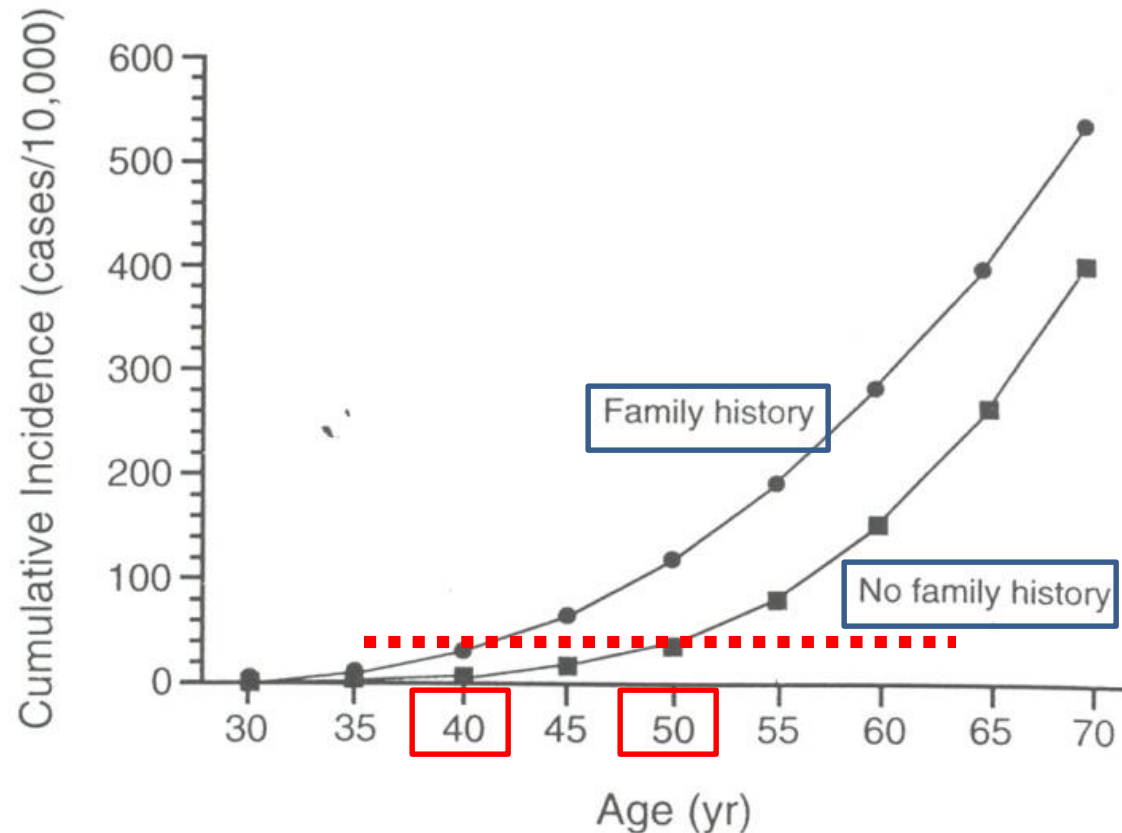
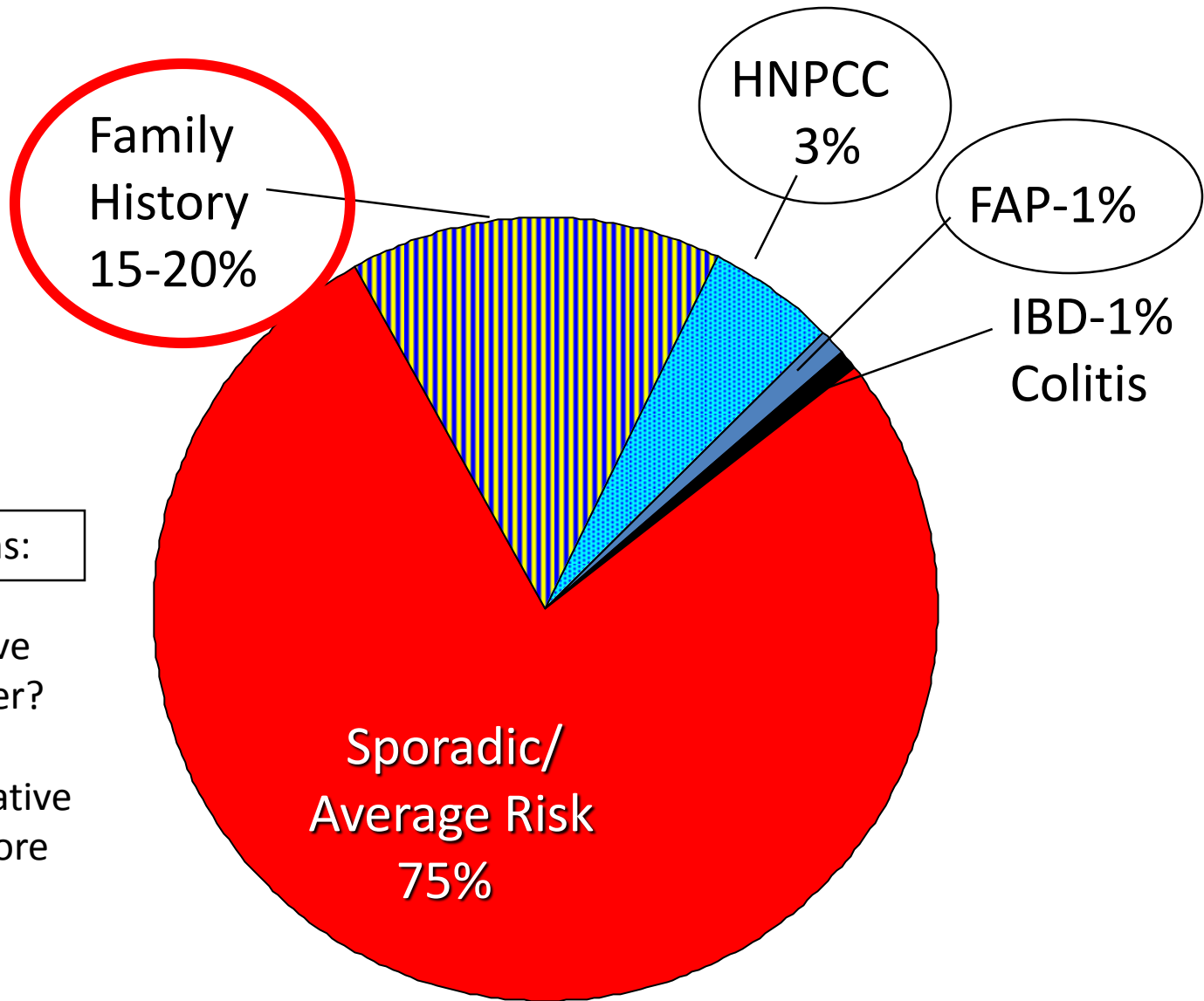


Figure 1. Cumulative Incidence of Colorectal Cancer According to Age and the Presence or Absence of a Family History of the Disease.

# Risk Factors for CRC



## Simple Questions:

Do you have a  
1<sup>st</sup> degree relative  
with colon cancer?

If so, did the relative  
have cancer before  
age 50 yrs



# Questions posed

- Does FHx of adenoma change screening approach?
- Does age of patient change approach
- What type of screening – FIT or colonoscopy?

# The questions behind the questions

- Is lifetime risk of CRC increased in individuals with a family history of CRC ?
  - If index family member < 60 yrs
  - If index family member >60 yrs


# FDR with CRC – What we know

Family History Category	Pooled Risk Measure (95% CI)
<b>1 FDR</b>	<b>2.24</b> (2.06-2.43)
1 FDR <50	3.55 (1.84-6.83)
1 FDR 45-59 years	2.25 (1.85-2.72)
1 FDR >60	1.83 (1.347-2.25)
1 FDR >70	1.97 (1.86-2.08)
<b><u>≥2 FDRs</u></b>	<b>3.97</b> (2.60-6.06)

# FHX of CRC

- Question posed: does age of index case make a difference in CRC risk in family?

Age of Index Case	HR FDR	HR FDR <50	HR FDR >50
<40	2.53 (1.7-3.79)	2.28 (1.86-2.80)	1.81 (1.71-1.92)
40-49	2.26	2.93	2.03
50-59	2.35	2.91	2.29
60-69	1.85	2.09	1.82
70-79	1.69	2.19	1.67
>79	1.76	1.61	1.76



Younger Index Case = Younger age of onset

# FDR with CRC: # of FDRs

**Table 1.** Selected Familial Relative Risk (FRR) Estimates for Probands Considering Only First-Degree Relative (FDR) Family History

No. of affected FDRs	No. of probands	FRR (95% CI)
0	2,232,396	0.89 (0.87–0.91)
1	87,089	1.91 (1.82–2.00)
≥1	94,931	2.05 (1.96–2.14)
2	6966	3.01 (2.66–3.38)
3	762	4.43 (3.24–5.90)
4	92	7.74 (3.71–14.24)
≥5	22	19.86 (7.29–43.24)

# FHX of CRC

- Question posed: do asymptomatic family members of patients with CRC have increased risk of CRC and advanced neoplasia?
- Colonoscopy : 3804 index cases with CRC

Risk of CRC	Hazard Rate Ratio
<b>FDRs</b>	<b>1.79 (1.59-2.03)</b>
FDR <60	2.11 (1.70-2.63)
FDR >60	1.77 (1.58-1.99)
SDRs	1.32 (1.19-1.47)
Cousins	1.15 (1.07-1.25)
Risk of Adenomas	
Any adenoma	1.82
Adenoma with villous histology	2.43

# FHX of CRC

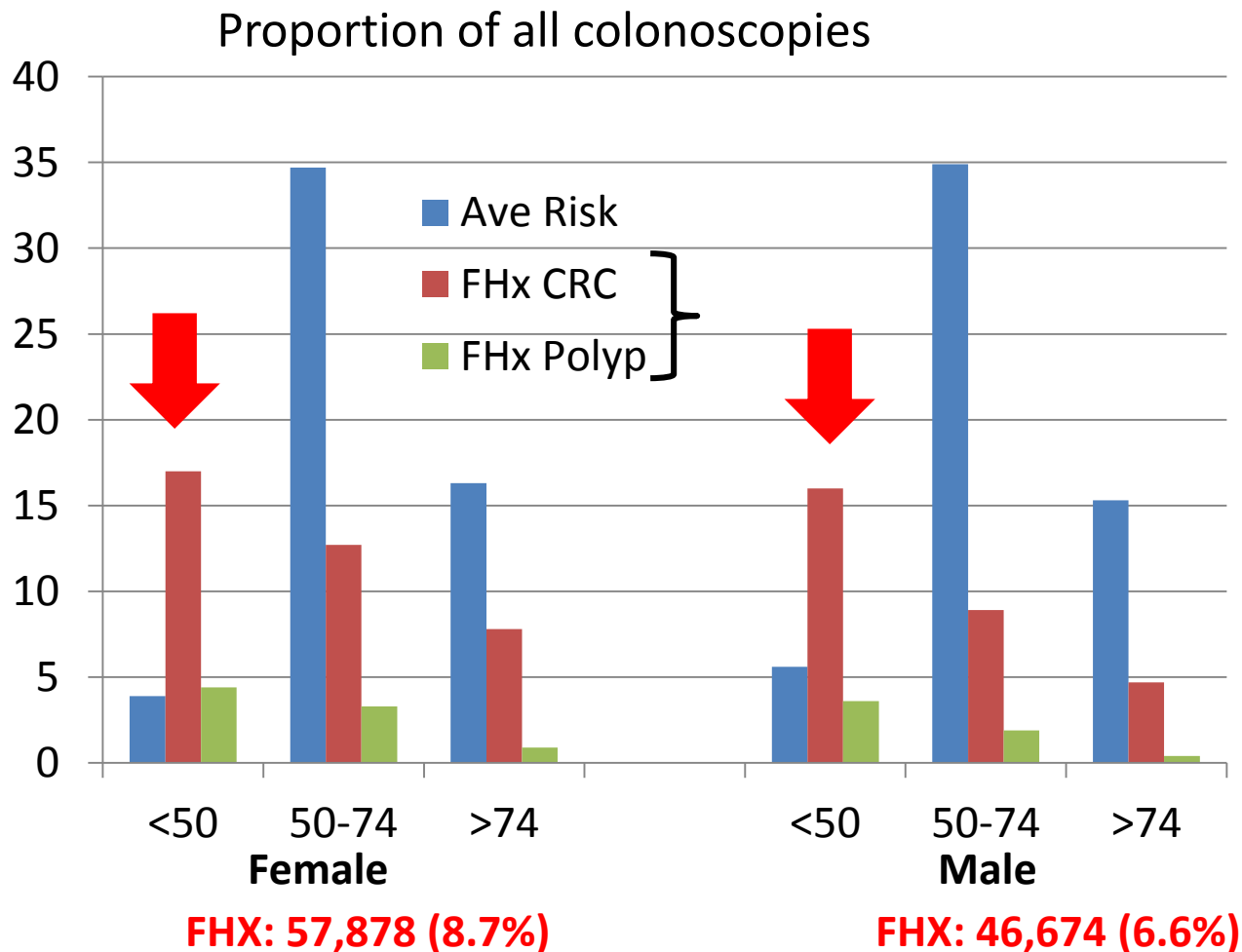
- Question posed: do asymptomatic siblings of patients with CRC have increased risk of advanced neoplasia?
- Colonoscopy
  - 374 Siblings (36% < 50 yrs) with CRC FDR
  - Age: 52.7 yrs vs controls with no FHX
  - Prevalence of Advanced Neoplasia:  
**7.5%** (in FDRs) vs **2.9%** (in controls)
  - 6 cancers
- Suggests high-yield for screening at young age

# FHX of CRC

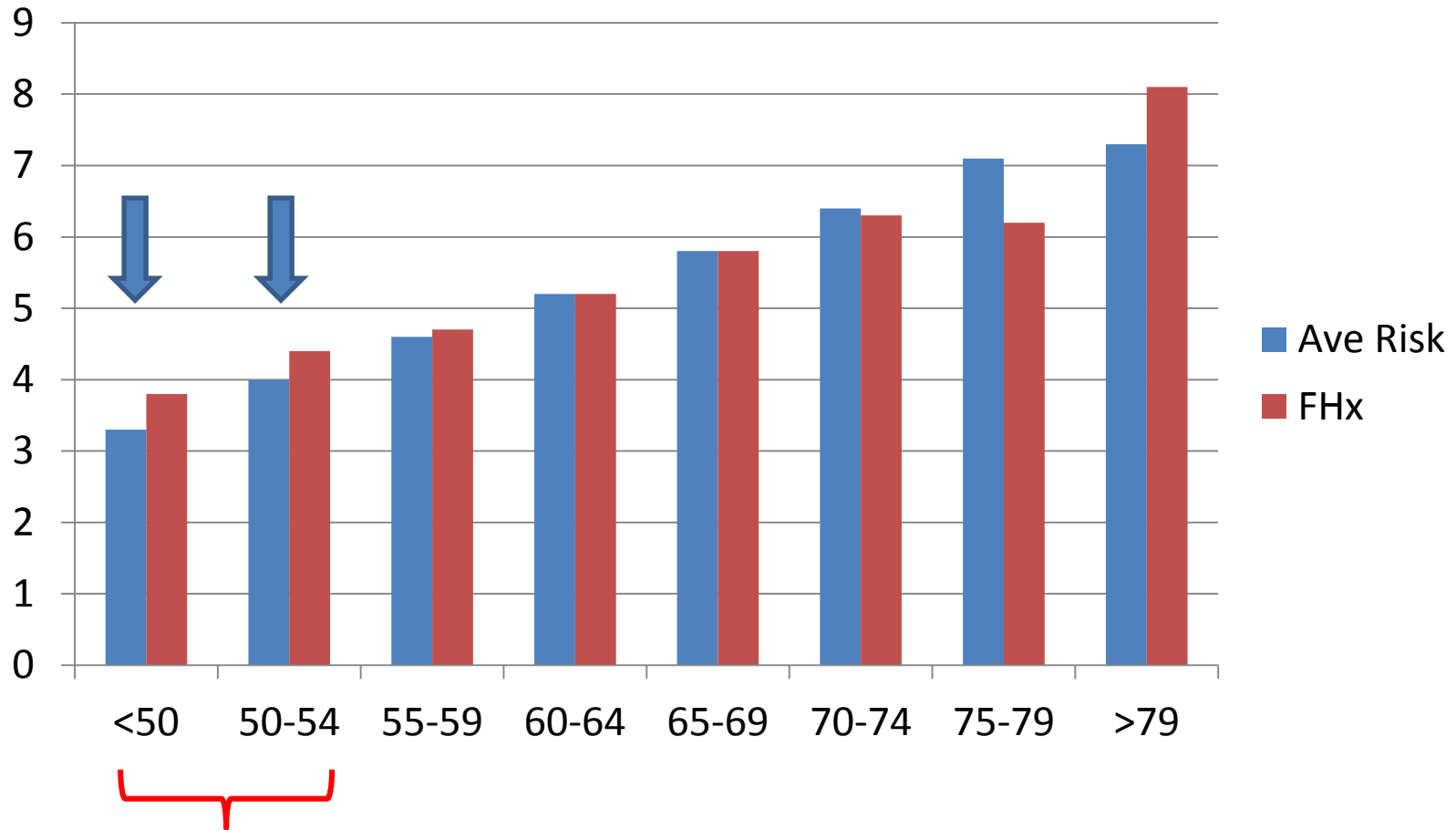
- Questions posed:
  - What proportion of colonoscopy in USA is performed for FHX of CRC or adenoma?
  - Do patients who have colonoscopy performed for this reason have higher likelihood of advanced neoplasia?
- CORI database
  - 70+ practices in USA in diverse settings



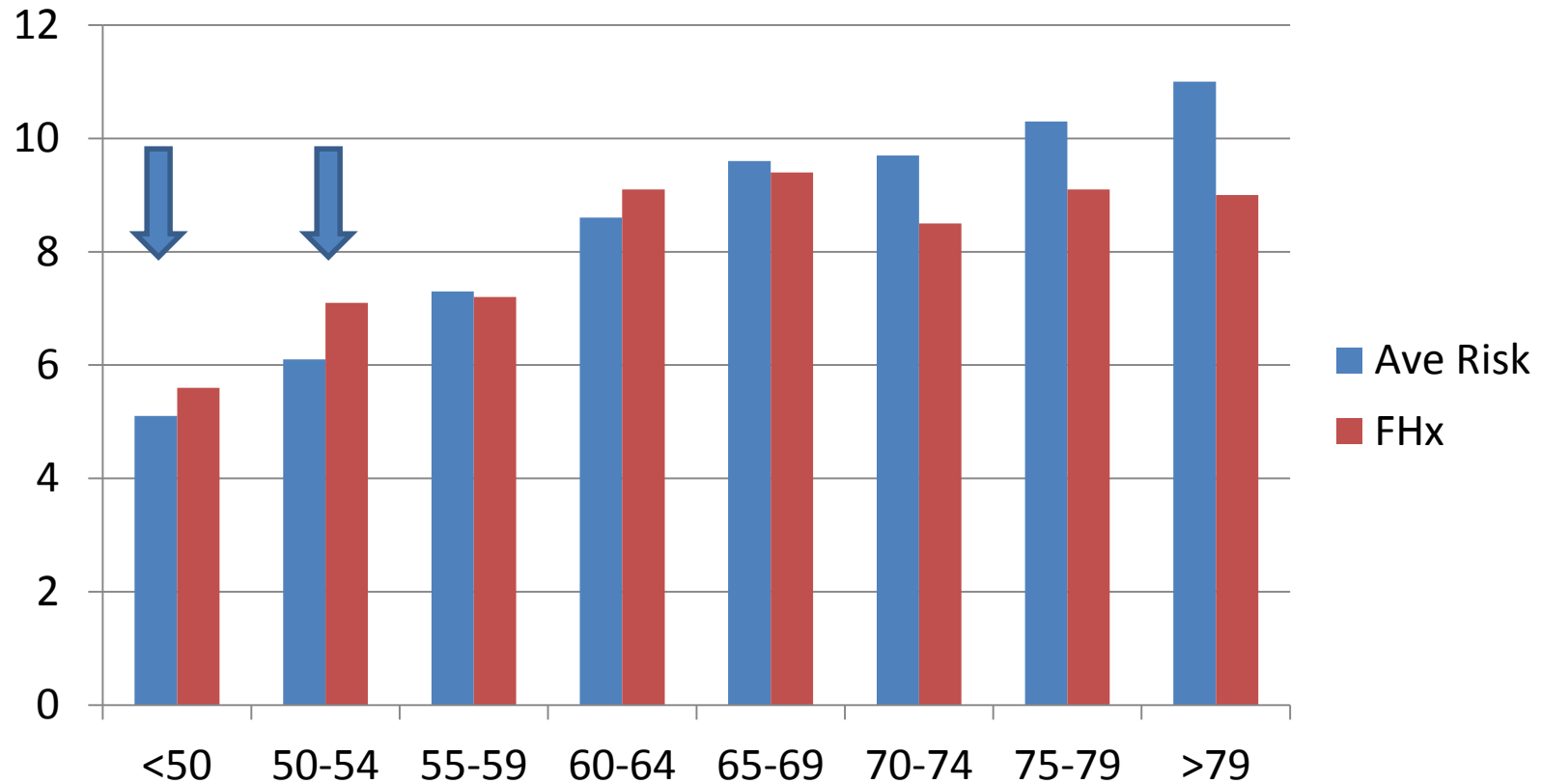
# CORI DATA 2000-2011



# Women polyps >9mm



# Men polyps >9mm



Evidence suggests:  
higher risk of advanced adenomas  
at age <54 with +FHx

# FHX of CRC

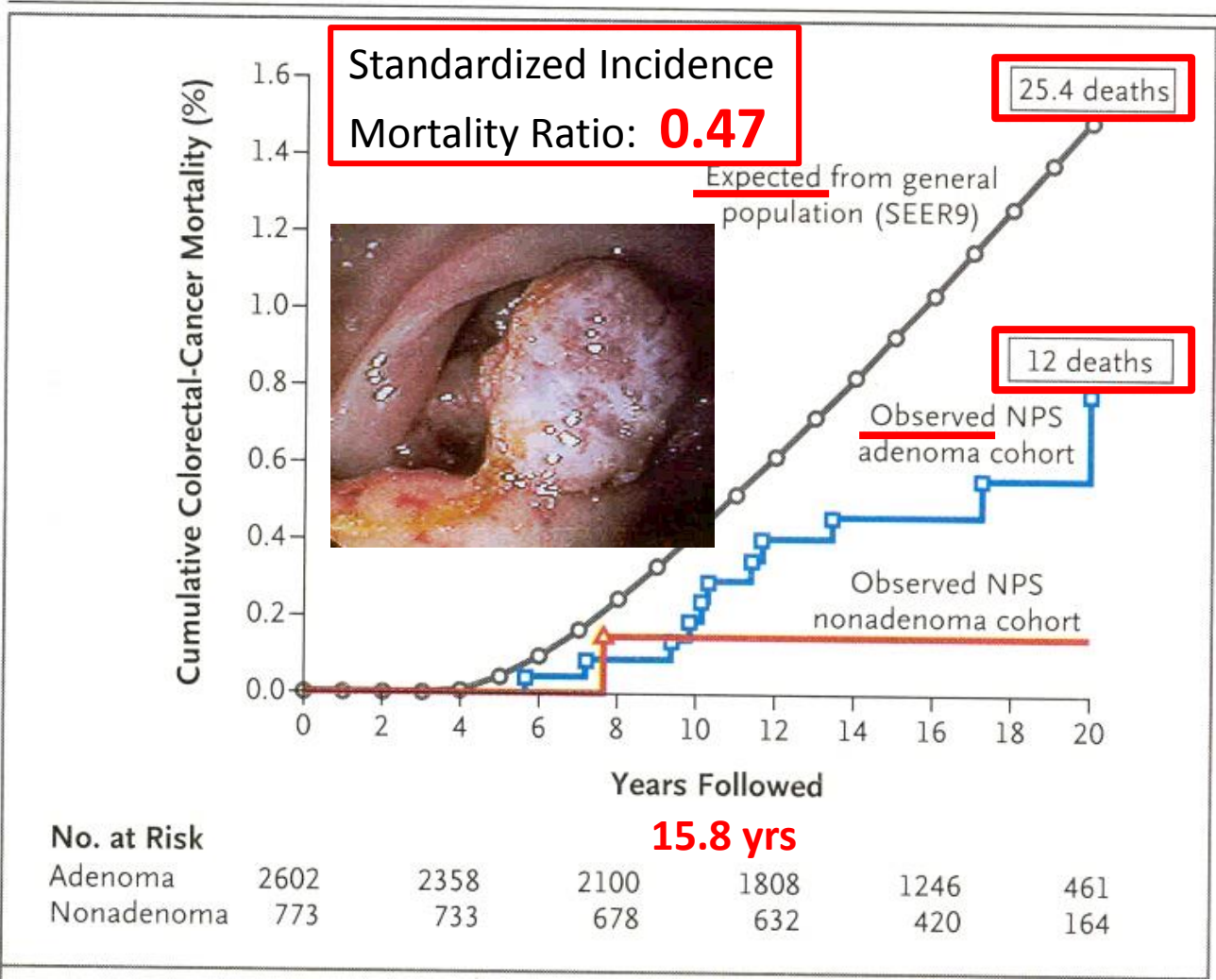
- Question posed: what is the effect of FHX of CRC on CRC incidence AFTER age 55 years (when risk of early onset CRC has passed)?

Index FHX	HR for CRC incidence
No FHX	1.00
$\geq 2$ FDRs	2.04 (1.44-2.86)
1 FDR <60	1.27 (0.97-1.63)
1 FDR 60-70	1.33 (1.06-1.62)
1 FDR > 70	1.14 (0.93-1.45)

# FDR with CRC: What we do NOT know

- Does early screening reduce CRC incidence/mortality
  - It may if cancer precursors are detected and removed (NPS)
- Is one form of screening necessarily better than another?
  - If aim is to **prevent** CRC by detecting cancer precursors, then colonoscopy might be preferred

# Polypectomy reduces Mortality



# Questions posed

- Does FHx of adenoma change screening approach?
- Does age of patient change approach
- What type of screening – FIT or colonoscopy?

# The questions behind the questions

- Is lifetime risk of CRC increased in individuals with family history of adenoma?
  - If index family member had advanced adenoma and is <60 years?
  - If index family member had advanced adenoma and is >60 years?
  - If index family member had LRA before or after age 60 years?



# In the beginning....



- Common inheritance of susceptibility to adenomas and CRC (1988)
- National Polyp Study (1996)  
1031 patients with adenomas
  - 1865 parents
  - 2381 siblings
  - 1411 spouse controls

Cannon-Albright et al; NEJM 1988; 319: 533-7 (Burt)

Winawer et al; Risk of Colorectal cancer in families of patients with adenomatous polyps NEJM 1996; 334: 82-7

# In the beginning....



- National Polyp Study
  - RR CRC (adjusted for age/sex): **1.78** (1.18-2.67) for parents/sibs c/w spouse controls
  - Adenoma <60 (vs >60): RR in sibs **2.59** (1.46-4.58)
  - Index sib with adenoma + parent with CRC:  
RR in sibs **3.25** (1.92-5.52)
- Conclusion:
  - Siblings and parents of patients with adenomas are at increased risk for CRC, especially if index <60 years

# Sniff test:

## Does this make sense?

- We now know that 50%+ of patients having screening colonoscopy have adenomas
  - This means that many, if not most people will have a FDR with adenoma
- 5-10% have advanced adenomas (>1cm; villous or HGD)



# Sniff test:

## Does this make sense?

- 3121 patients enrolled for screening colonoscopy



Finding at Screening Colonoscopy	OR for CRC in FDR
Adenoma-bearing vs patients with no adenomas	1.36 (1.09-1.70)
Small (<1cm Tub Ad)	1.26 (0.99-1.61)
<b>Advanced adenoma</b>	<b>1.62 (1.16-2.26)</b>

Lynch KL, Ahnen DJ, Byers T, Weiss DG, Lieberman DA and VACSP 380  
CGH 2003; 1:96-102

# Sniff test:

## Does this make sense?



- Question posed: does having a FDR with adenoma associated with increased risk of CRC?  
Only 2 relevant studies in 2012

Finding at Screening Colonoscopy	Absolute risk for CRC in FDR	RR	Study
Adenoma	2.31% vs 0.53%	4.38 (2.25-8.43)	Nakama;Eur J Cancer; 2000
Large adenoma	8.3% vs 4.2% (for CRC + Large adenoma)	1.97 (0.89-4.36)	Cottet; Gastroenterol 2007

Imperiale TF, Ransohoff DF; Systematic review  
Ann Intern Med 2012; 156: 703-9

## FDR with Adenoma

	Risk Measure (range): CRC
FHX Adenoma vs no FHX of adenoma	1.35-1.78
FDR with <b>advanced adenoma or large adenoma (&gt;1cm)</b>	1.68-3.90
FDR <60 years	1.41 (1.27-1.56)

# Family History: Current Guidelines

- Screening – Family History (non-hereditary)

Index	Initiation	Interval
<b>FDR &lt;60 CRC</b>	<b>Age 40 - colonoscopy</b>	<b>5 yrs</b>
FDR >60 CRC	Age 40 – any screen	10 yrs
FDR < 60 with known <b>advanced adenoma</b>	Age 40 – colonoscopy	???
<i>FDR: Non-advanced adenoma</i>	50	<i>routine</i>

Evidence : Weak

# What we think we know

- If there is  $\geq 1$  FDR with **CRC**
  - Risk of CRC higher especially if index case <60 yrs
  - Risk of advanced neoplasia higher....at a younger age
    - suggests there could be benefit of early screening
- If there is  $\geq 1$  FDR with **advanced adenoma**
  - Risk of CRC is higher
  - Uncertain if CRC occurs at young age (i.e. <50)
- If there is  $\geq 1$  FDR with **low-risk adenoma**
  - Risk of CRC could be increased, but uncertain



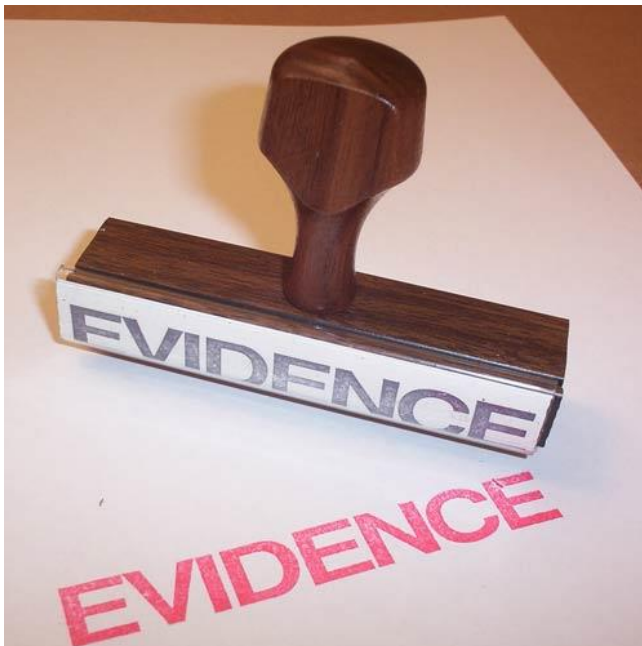
# What we would like to know

- FDR with **CRC and Advanced Adenoma**
  - Does early screening (before age 50 years) reduce incidence/mortality?
  - Is a shorter interval (q 5 years) between screenings associated with reduced incidence/mortality?
  - Should initiation and interval be customized based on age of index family member (i.e. > or < 60 years)?
- FDR with **low-risk adenoma**
  - Is the risk of CRC increased in family members?
  - Should screening be initiated at younger age?
  - Should screening with colonoscopy be preferred?

# FHX and CRC: Summary

A riddle  
Wrapped in a mystery  
Inside an enigma...

Winston Churchill



# New Practice Guideline 2017

- Sponsored by CAG
- Goals: Determine
  - Risk of CRC in families with Index member with CRC, and relationship of age and risk
  - Risk of CRC in families with Index member with adenoma, and relationship of type of adenoma, age, and risk
  - Use these data to understand
    - Age to initiate screening
    - Interval for screening if initial exam negative