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**USING COLONOSCOPY TO SCREENING FOR  
COLORECTAL CANCER.  
DO WE HAVE ALL THE ANSWERS?**

**11TH ANNUAL NYC CITYWIDE COLON CANCER CONTROL COALITION (CC) SUMMIT  
JUNE 9, 2010**

## Objectives

- Provide an overview of trends in colorectal cancer incidence and mortality
- Describe the role of screening in reducing incidence and mortality from colorectal cancer
- Discuss the evolution of screening guidelines with emphasis on the evidence
- Discuss controversies concerning the use of colonoscopy for screening average-risk persons
- Describe future/ongoing studies evaluating the efficacy and effectiveness of screening colonoscopy



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## Clarifications

- No conflicts of interest to declare
- Considerations other than evidence may drive public health programs
- Presentation is about screening asymptomatic average-risk persons, mostly
- “All” current colon cancer screening tests require colonoscopy if positive

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## Background

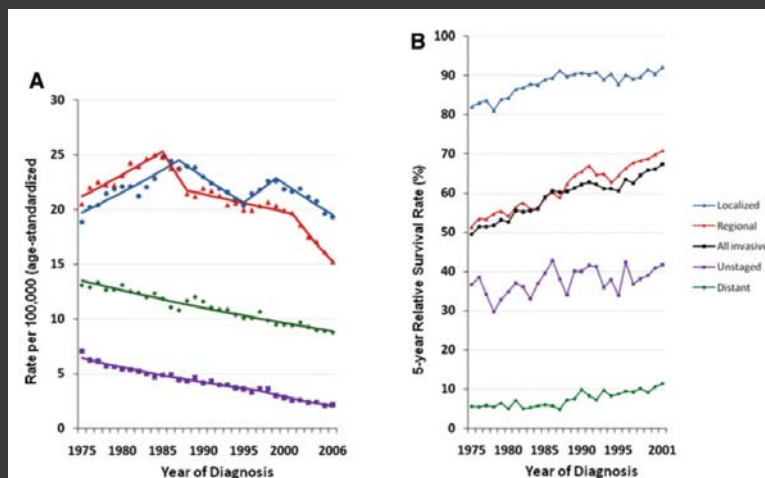
- A good test used in the wrong setting may cause more harm than good
- Screening has been driven by fascination with technology and the “more you can see and do, the better” approach (mostly)
- We need to pause and think about other lessons (d-sotalol, flecainide, etc)
  - Use of antiarrhythmic drugs for potentially fatal arrhythmias post-MI made clinical sense
  - Trials showed excess mortality from these drugs

J Am Coll Cardiol. 2006; Pratt CM. Am J Cardiol. 1998;  
Skanes AC, Can J Cardiol. 1996

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## Colorectal Cancer Trends by Tumor Stage

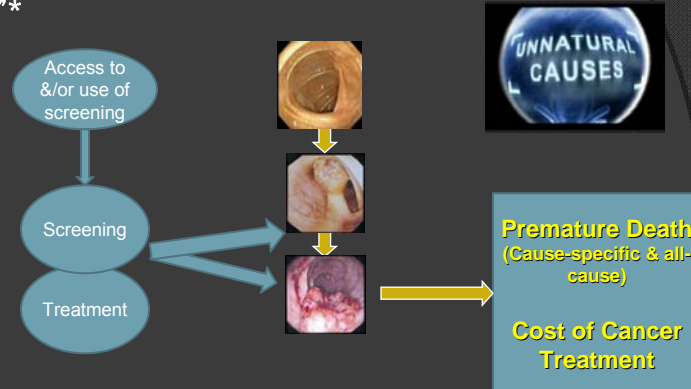


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Edwards et al. Cancer. 2010;116:544-73.

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“...declines in CRC death rates are consistent with a relatively large contribution from screening and with a smaller but demonstrable impact of risk factor reductions and improved treatments.”\*



“colorectal cancer is one important disease in which racial and socioeconomic disparities in outcomes can most readily be eliminated by ensuring that all eligible adults are effectively screened and abnormal findings are fully treated.”‡

Laiyemo AO, et al. JNCI. 2010; \*Edwards BK, et al. 2010; ‡Ayanian JZ. JNCI. 2010

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There are multiple screening tests

Do we know enough to choose among the tests?

Should we use different approaches for different population groups?

Is colonoscopy appropriate for population-based screening?

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## Evolution of U.S. CRC Screening Guidelines

- 1995 – Guide to Clinical Preventive Services, 2nd edition
  - Options: **FOBT, Flex sig +/- FOBT**
- 1997 - USMSTF & ACS: **Colonoscopy** q10 yrs an option
- 2000 – ACG recommendations: **Colonoscopy preferred**
- 2002 - USPSTF: Evidence **Grade A**
- 2003 - USMSTF: Included **FIT, Sensitive FOBT**
- 2008 - USMSTF: **Prevention vs. Early Detection**
- 2008 – USPSTF: **FOBT, flex sig, or colonoscopy**
  - Against routine screening 76-85 & against screening >85
  - Insufficient evidence for CT colonography
- 2008/9 – ACG: **African Americans begin at age 45**

Byers et al. CA 1997; USPSTF 2002 & 2008; Winawer et al. Gastro 1997, 2003;  
Levin et al. Gastro 2008; ACG, AJG 2009; Agrawal S, et al. AJG 2005  
\*Adapted from Sid Winawer

## Colonoscopy in Screening Guidelines

### American College of Gastroenterology

- 2000 recommendations:
  - Colonoscopy – preferred screening strategy
- 2008 recommendations:
  - If colonoscopy is not available or person unwilling ...
    - Offer alternative **prevention** tests – flex sig q5–10 years, CT colonography q5 years)
    - [May be] **Early detection** tests -- FIT

## Evidence for Efficacy of Screening

- Fecal Occult Blood Testing
  - Minnesota, UK & Danish RCTs
- Sigmoidoscopy
  - RCTs (PLCO, Flexi-Scope, NORCCAP)
  - Case-control studies (Selby, etc)
- Colonoscopy
  - No RCT results (Barcelona & Spanish trials in the field, 2 US trials in planning)
  - Case-control studies

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## FOBT Screening Randomized Controlled Trials

	Mortality Reduction		
	Biennial	Annual	Compliers
Minnesota* 47,000/18 yrs. 90% adherence	21%	33%	45%
Denmark 140,000/10yrs. 67% adherence	18%	—	30%
U.K 153,000/7.8 yrs. 60% adherence	15%	—	—

\*Rehydrated slides

Winawer et al, Gastro 1997

Courtesy: Sydney Winawer

## Sigmoidoscopy Trials with Mortality Outcome

	Setting	Enrollment	
		Sample	Dates
<b>PLCO (NCI)</b>	US	154,910	1993-2009
<b>Flexi-SCOPE</b> †‡	UK†	170,432	1994-2010
<b>SCORE</b> †‡	Italy†	34,292	1995----
<b>NORCCAP</b>	Nordic†	55,736	1999-2017

All studies compared to usual care.  
 Age groups: PLCO 55-74, others 55-64  
 † Compared to no screening \*One-time ‡Same study

## Percentage reduction in occurrence and mortality – UK Sigmoidoscopy Trial

Analysis type	<u>Incidence</u>			<u>Mortality</u>	
	Any CRC	Rectum /sig	Proximal	CRC	All-cause
Assigned group	23%	36%	2% (NS)	31%	3% (0-6)
Per protocol	33%	50%	3% (NS)	43%	5% (0-9)

- Number needed to screen
  - To prevent 1 cancer 191
  - To prevent 1 death 489

Atkin WS, et al. Lancet. 2010  
 6/9/2010 Median follow-up of 11.2 years (range 10.7-11.9)

## Percentage reduction in occurrence and mortality - NORCCAP Trial

- Follow-up:
  - 6 years for mortality and 7 years for incidence
- No difference in incidence
- Non-significant 23% reduction in mortality from any CRC
- For those who complied:
  - 59% reduction for any CRC
  - **76% for rectum/sigmoid cancers**

## Sigmoidoscopy Trials & Case Control Studies Percentage reduction in mortality

	All	Distal	Proximal	Distal (compliers)
UK trial (Atkin) 170,432 /11.2 yrs	31%	36%	2% (NS)	-
NORCCAP (Hoff) 55,736/ 6 yrs	27% (NS)	-	-	76%
Selby 1993 (Case-control)	-	-	-	70%

All-cause mortality reduction (UK trial) = 3% (ultimate test)

Selby vs. NORCCAP/Flexi-Scope

SCORE, PLCO, More to come from Flexi-Scope and NORCCAP

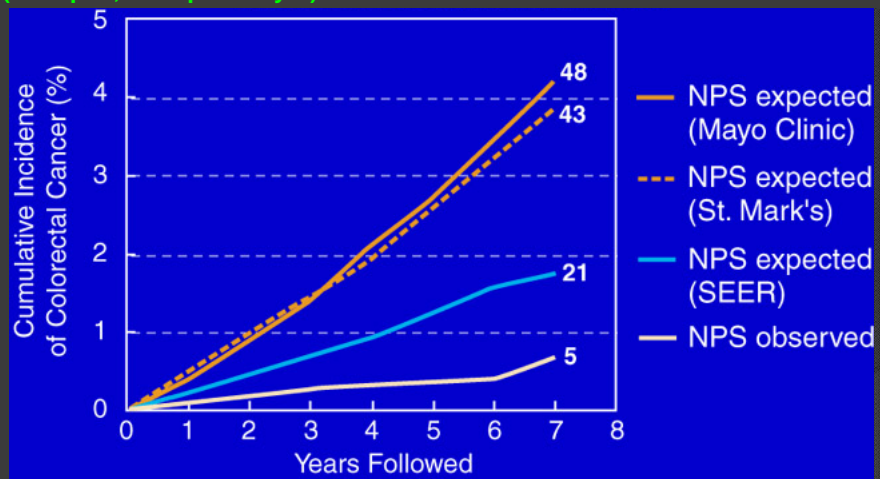
# How about colonoscopy?

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## Colorectal Cancer Incidence in NPS Following Colonoscopic Polypectomy

(1418 pts ; 8401 person yrs)



Winawer et al. 1993. NEJM 329:1977-81

Courtesy Sid Winawer

## Colonoscopy - Population-based Case-Control Study

- Setting: Ontario, Canada
- Data source: Administrative Data
- Subjects: 52-90 yrs
  - Cases: CRC diagnosed 1996-2001
    - Death (n=10,292) assessed through 2003
  - Controls: 1:5 match

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Baxter. Ann Intern Med 2009;150:1-8

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## Colonoscopy - Population-based Case-Control Study

Colonoscopy definition	Any CRC	Left	Right
Any attempted	0.69	0.39	1.07*
Completed	0.63	0.33	0.90
Incomplete	0.91*	0.63	1.35*

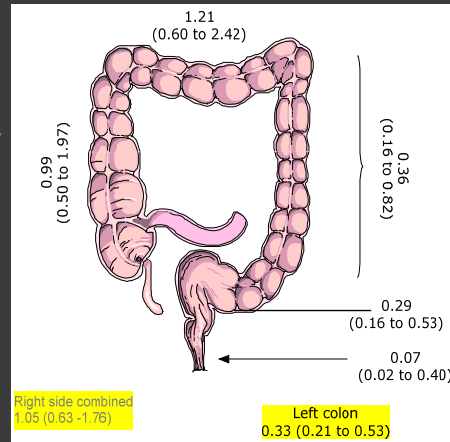
Numbers are odds. \*Not significant.  
Baxter. Ann Intern Med 2009;150:1-8

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## Colonoscopy - Cross-Sectional Study

- **Setting:** Screening center, Germany
- **Data source:** Questionnaire/pathology
- **Subjects:** n=3,287, 55+ yrs Having screening colonoscopy 2005-2007
- **Outcome:** Advanced neoplasia
- **Exposure:** colonoscopy previous 10-year period



Prevalence ratios (95% CI)

Brenner JNCI 2010;102:89

## CISNET Microsimulation Studies

All tests may be equally cost-effective

- Compared 4 strategies:
  - Colonoscopy q10 years
  - Flex sig q5 years + FOBT
  - Annual sensitive FOBT
  - Annual FIT
- Assumes high adherence rates
- Yielded similar life-years gained (except colonography)

A consistent evidence is emerging that colonoscopy appears to be no more effective than sigmoidoscopy!!

- Are the studies wrong or is something else...?
- Inadequate visualization
  - Quality of procedure
    - Operator skills (adenoma detection rates, cecal intubation\*)
    - Bowel prep may be poorer in right colon
  - Less adequate detection of flat and depressed lesions
- Differences in biology
  - Gene-specific methylation profiles and molecular characteristics
  - Serrated polyps more prevalent in proximal colon

\*Rex DK, Eid E. Clin Gastroenterol Hepatol 2008; Deng G, et al. Eur J Cancer 2008;  
\*Ferracin M, et al. J Pathol 2008; Freeman HJ. World J Gastro 2008;  
\*Kaminski. NEJM. 2010  
\*Modified from Bob Fletcher

## A Major Scientific and Policy Challenge

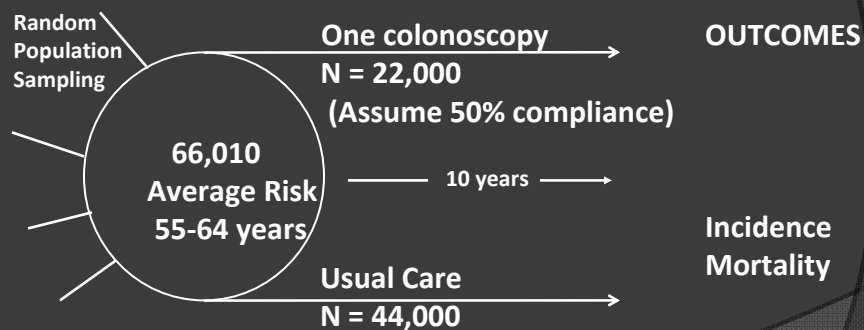
- ◉ No randomized trials exist to quantify the possible benefit of colonoscopy screening
- ◉ Growing evidence that screening colonoscopy is not protective in the right colon
- ◉ Inconsistent evidence: how else could FOBT be efficacious except by colonoscopy?

## Colonoscopy Trials with Mortality Outcome

	Enrollment (Age)	Dates	Control
NordICC (Nordic countries)	66,000 (55-64 yrs)	2009-2029	† Usual care
Barcelona, Spain	55,498 (50-69 yrs)	2008-2021	FIT

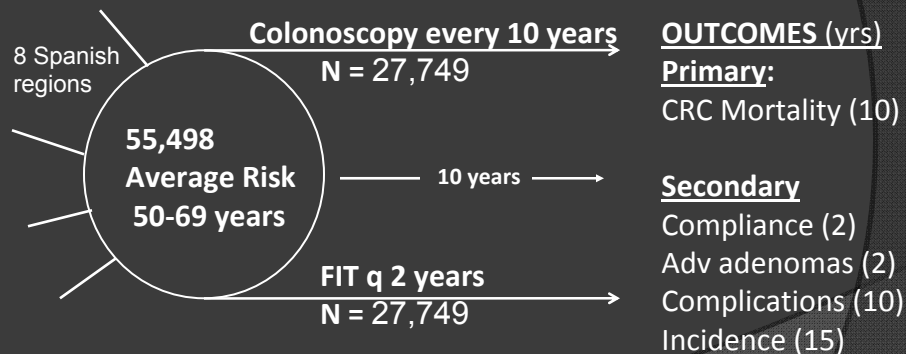
† One-time testing compared to no screening

## NordICC: The Northern-European Initiative on Colorectal Cancer Colonoscopy Trial



Norway, The Netherlands, Sweden, Latvia, Memorial Sloan-Kettering Cancer Center, Harvard School of Public Health  
Michael Bretthauer & Geir Hoff  
Modified from Bob Fletcher

## Barcelona (Spanish) Colonoscopy Trial 2008-2021



ClinicalTrials.gov/ct2/NCT00906997  
Antoni Castells & Enrique Quintero  
Modified from Bob Fletcher

## Randomized Comparison of Virtual Colonoscopy, Optical Colonoscopy, and Fecal Occult Blood Testing for Colorectal Cancer Screening: a **Pilot Study**

- Setting: McMaster University
- Estimated Enrollment: 600
- Ages : 50-70 years
- Primary Outcome: % who attend for their assigned screening test

## A US Randomized Trials of Colonoscopy?

- Different settings and practice standards
- Extensive experience with colonoscopy in US
- Current studies are underpowered plus may not be amenable to being pooled

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## Obstacles to Colonoscopy Trials

- Colonoscopy viewed as standard or superior
  - What will be the comparison group?
  - Will patients consent and remain in randomized groups over 10+ years?
  - Accounting for previous screening
- What about the cost and wait for answer
  - Power for right-sided lesions
  - Trial under ideal or ordinary circumstances?

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Courtesy: Bob Fletcher

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Observational Studies and Why do them?  
“real-world” & lessons from sigmoidoscopy studies

**While we wait for trial results...**

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## SEARCH: Cancer Screening Effectiveness Research in Community-based Healthcare – RC2

A comparative effectiveness research project

### Specific Aim(s):

- Among average-risk adults, is screening colonoscopy more effective than sigmoidoscopy &/or fecal occult blood in preventing late-stage colorectal cancers?

\*An ARRA-Funded NCI Collaborative CER Project  
(Co-PIs: Buist & Doubeni; 1 RC2 CA148576-01)

## *Effectiveness of Colonoscopy in Reducing Deaths from Colorectal Cancer*

- Specific aim: estimate the effectiveness of screening colonoscopy in reducing CRC death among **average-risk adults** when compared to no screening
  - Any CRC
  - **Right-** and left-sided cancers
- Secondary aims:
  - 1) determine the impact of the **completeness** of colonoscopy examinations on its effectiveness
  - 2) compare the effectiveness of screening colonoscopy relative to **sigmoidoscopy**.

Effectiveness of Colonoscopy in Reducing Deaths from Colorectal Cancer (Co-PIs: Doubeni & Fletcher)

## *Effectiveness of Colonoscopy in Reducing Deaths from Colorectal Cancer*

- **Nested Case-Control Study**
- **Setting: Cancer Research Network**
  - Fallon Clinic, Kaiser Permanentes (GA & CA)
- **Cases: CRC diagnosis 2007-2013 and CRC death by 2014**
- **Controls: age, sex, site, enrollment**
- **Exposures: colonoscopy, flex sig & FIT**
  - Confirm indication for screening
- **Independent confirmation of cause of death**

(Co-PIs: Doubeni & Fletcher)

## Effectiveness of Colonoscopy in Real-World

What we do in clinical practice should be guided by evidence

- Evidence on Efficacy – randomized trials
- Effectiveness in real-world settings depends on efficacy and:
  - Quality of testing
  - Adherence to a regimen of regular screening and rescreening
  - Acceptance and access to screening
  - Complete diagnostic testing and treatment for positive tests
- Current Evidence does not support use of colonoscopy as the standard for screening average-risk persons
- Should we dust off old sigmoidoscopes?
  - We need better evidence

## Acknowledgements

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