

# **Screening del cancro coloretale e introduzione di nuove tecnologie**

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Battista - Torino**

**Biella ,24 Marzo 2012**

MUTAZIONI GERMINALI O SOMATICHE

ALTERAZIONI METABOLICHE BIOCHIMICHE

STORIA NATURALE  
del CANCRO

LESIONI PREINVASIVE

MALATTIA INVASIVA ASINTOMATICA

MX

MALATTIA INVASIVA  
SINTOMATICA

PAP

END

CCR

FOBT

GUARIGIONE O  
DECESSO

T<sub>0</sub>

T<sub>1</sub>

T<sub>2</sub>

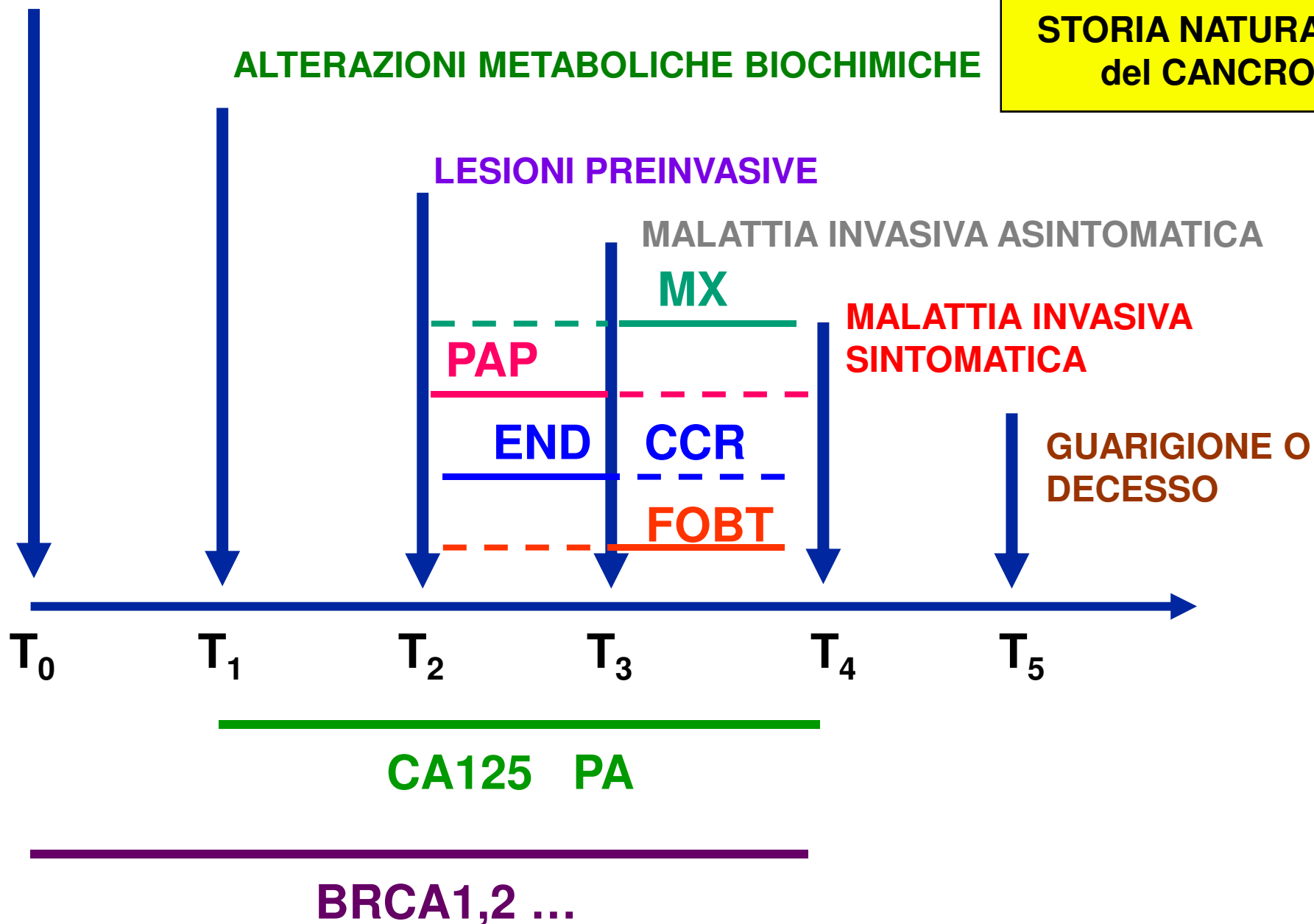
T<sub>3</sub>

T<sub>4</sub>

T<sub>5</sub>

CA125 PA

BRCA1,2 ...



▪

**La diagnosi precoce dei tumori  
e' vista con favore dalla  
popolazione e dai medici  
poiché l'idea che 'curare prima  
significhi curare meglio' e' non  
solo attraente ma  
intuitivamente convincente.**

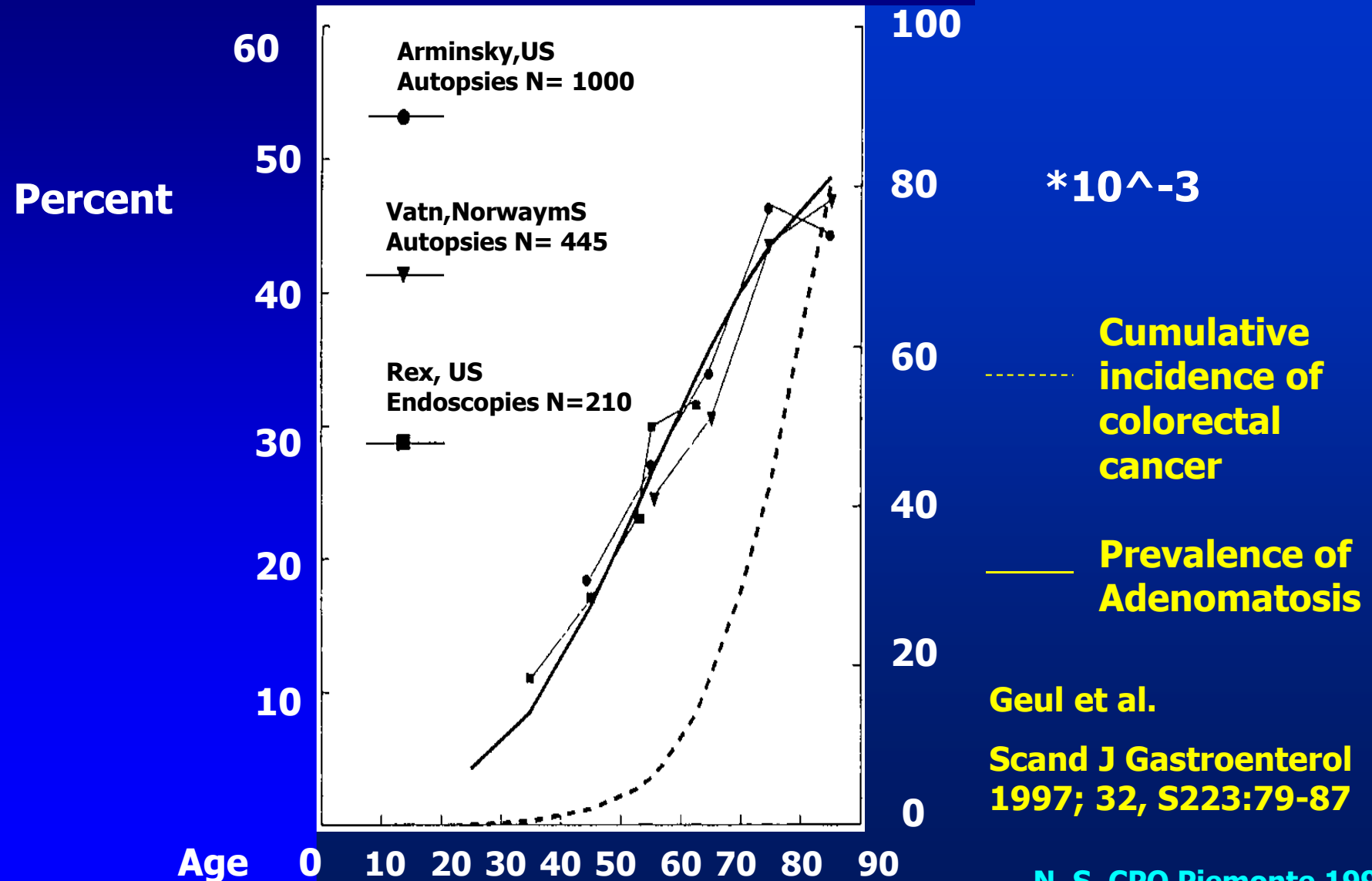
*La diagnosi precoce tende ad individuare  
anche casi che non giungerebbero mai  
all'osservazione clinica.*

# Effect of using clinical and microscopical detection thresholds in three cancers

	PREVALENCE	
	CLINICAL	MICROSCOPICAL
<b>BREAST (women 40-50)</b>	1%	39% (Nielsen et al.)
<b>PROSTATE (men 60-70)</b>	1%	46% (Montie et al.)
<b>THYROID (adults 50-70)</b>	0.1%	100% (Harach et al.)

Black et al. NEJM 1993;328(17):1237-43

# Prevalence of adenomatosis and cumulative incidence of colorectal cancer



# Progression of CRC

Normal tissue																								
Hyperplastic polyp																								
Advanced adenomas																								
symptomatic cancer																								
Cancer death																								

## Dwelling time ADENOMA $\xrightarrow{\quad}$ CARCINOMA

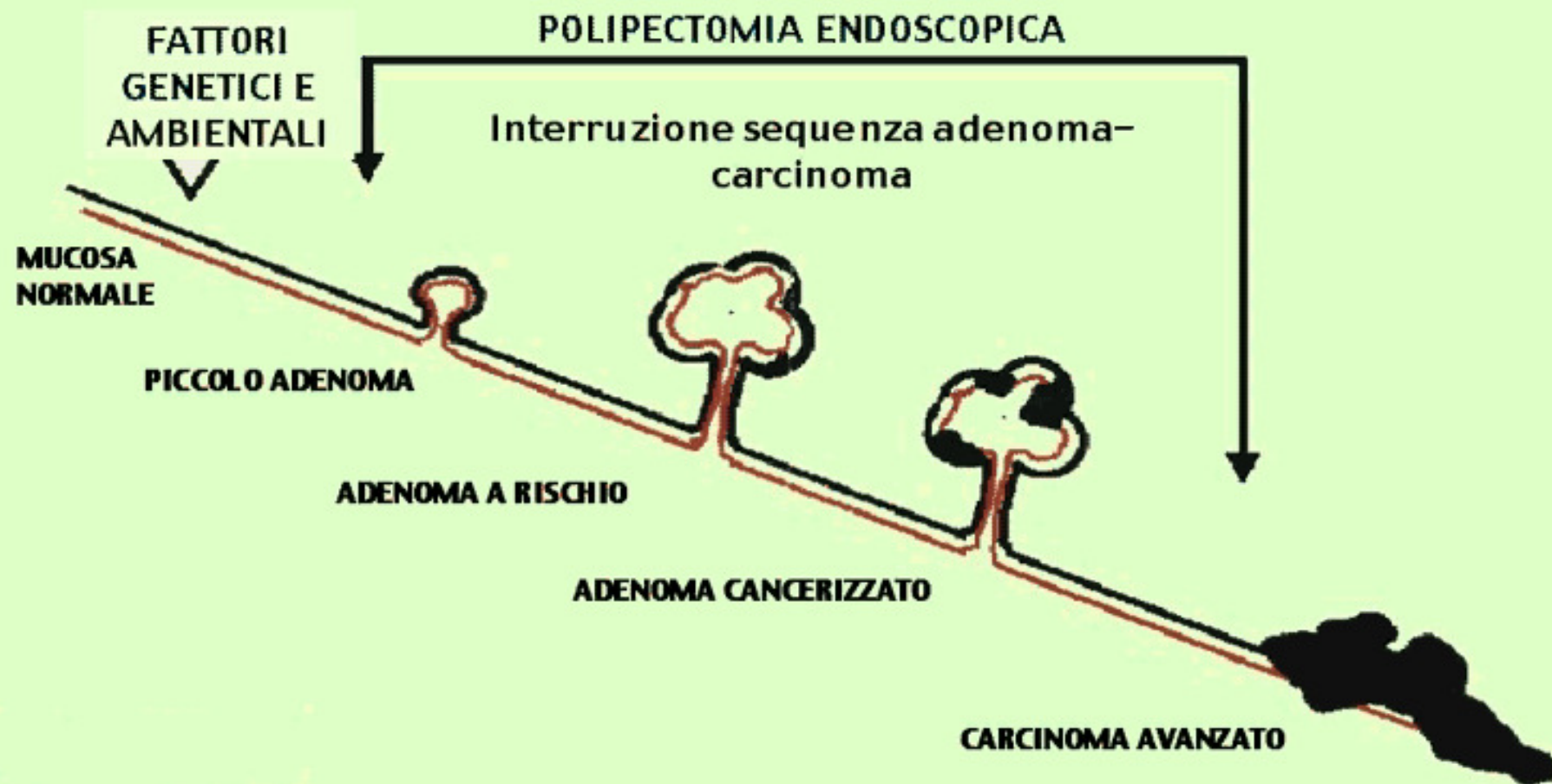
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### Estimate of dwelling time :

- Wagner (1995): 5-10 yrs
- Eddy (1990) from 1cm to CRC: 7 yrs
- Atkin (1993) 10 - 35 yrs
- Knighth (1989) at least 5 yrs, on average 10-15yrs
- Winawer (1997) from < 1cm to CRC :10 yrs
- MISCAN COLON MODEL:16.3 yrs



# Storia naturale CCR: effetto della polipectomia endoscopica



*Non sempre è chiaro se i casi, diagnosticati precocemente, siano da sottoporre a terapia e quale terapia adottare.*

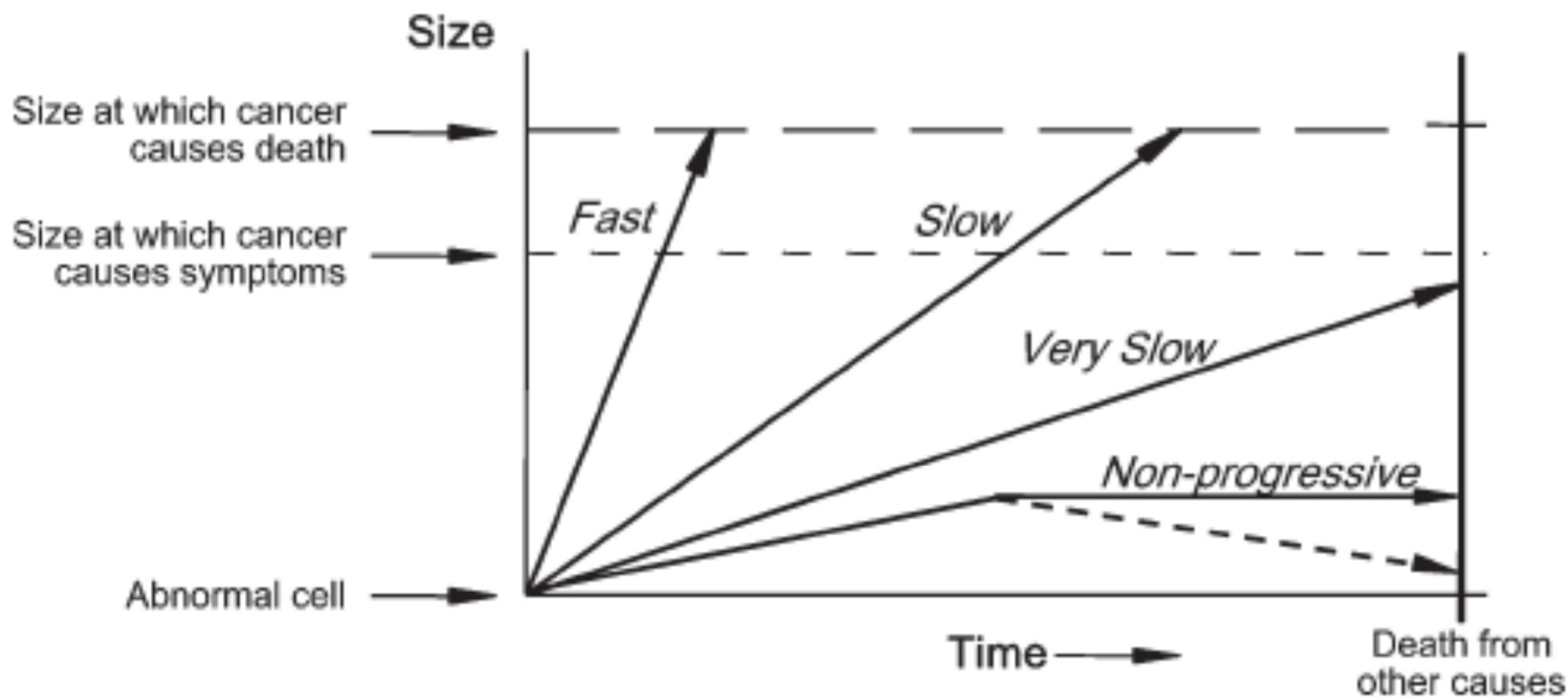
**Sovradiagnosi**

# Overdiagnosis in Cancer

H. Gilbert Welch, William C. Black

Manuscript received September 3, 2009; revised March 1, 2010; accepted March 5, 2010.

**Correspondence to:** H. Gilbert Welch, MD, MPH, Veterans Affairs Outcomes Group (111B), Department of Veterans Affairs Medical Center, White River Junction, VT 05009 (e-mail: h.gilbert.welch@dartmouth.edu).



# Meta-analisi degli studi sperimentali (RCT) che hanno utilizzato il FOBT (Hemoccult)

	<b>%</b>	<b>RR</b>	<b>CI</b>
<b>Riduzione di mortalita' nei soggetti allocati allo screening</b>	<b>16</b>	<b>0.84</b>	<b>0.77-0.93</b>
<b>Riduzione di mortalita' "corretta" per la partecipazione allo screening</b>	<b>23</b>	<b>0.77</b>	<b>0.57-0.89</b>

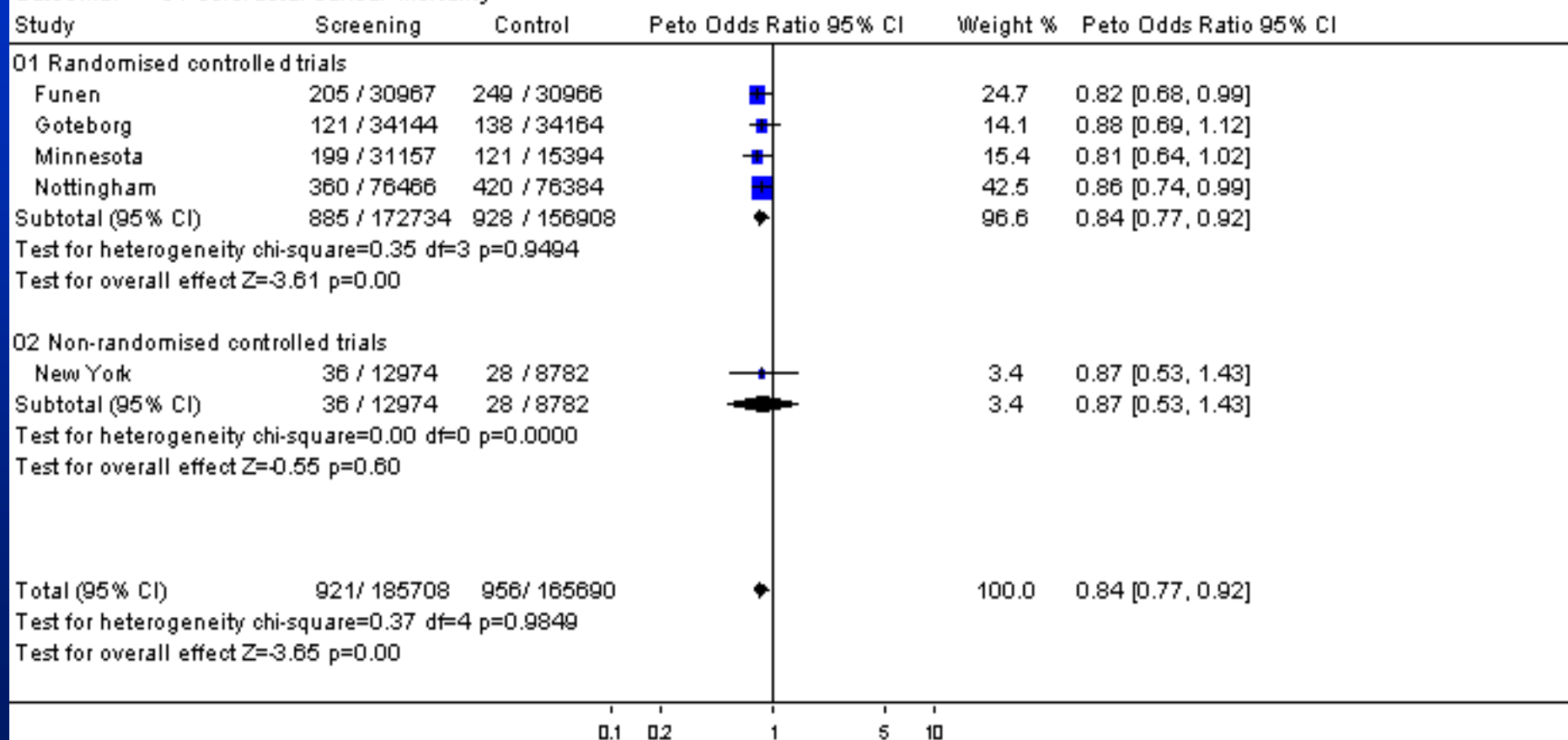
**Towler et al. The Cochrane Lybrary, Issue 4, 1998. Oxford: Update Software**

# Screening for colorectal cancer using the faecal occult blood test, Hemoccult (Review); Towler BP, Irwig L et al

Review: Screening for colorectal cancer using the faecal occult blood test, Hemoccult

Comparison: 01 All Hemoccult screening programs Vs Control

Outcome: 01 Colorectal cancer mortality



**ONCE-ONLY SIGMOIDOSCOPY SCREENING IN  
COLORECTAL CANCER SCREENING:  
FOLLOW UP FINDINGS  
OF THE ITALIAN RANDOMIZED CONTROLLED TRIAL  
SCORE**

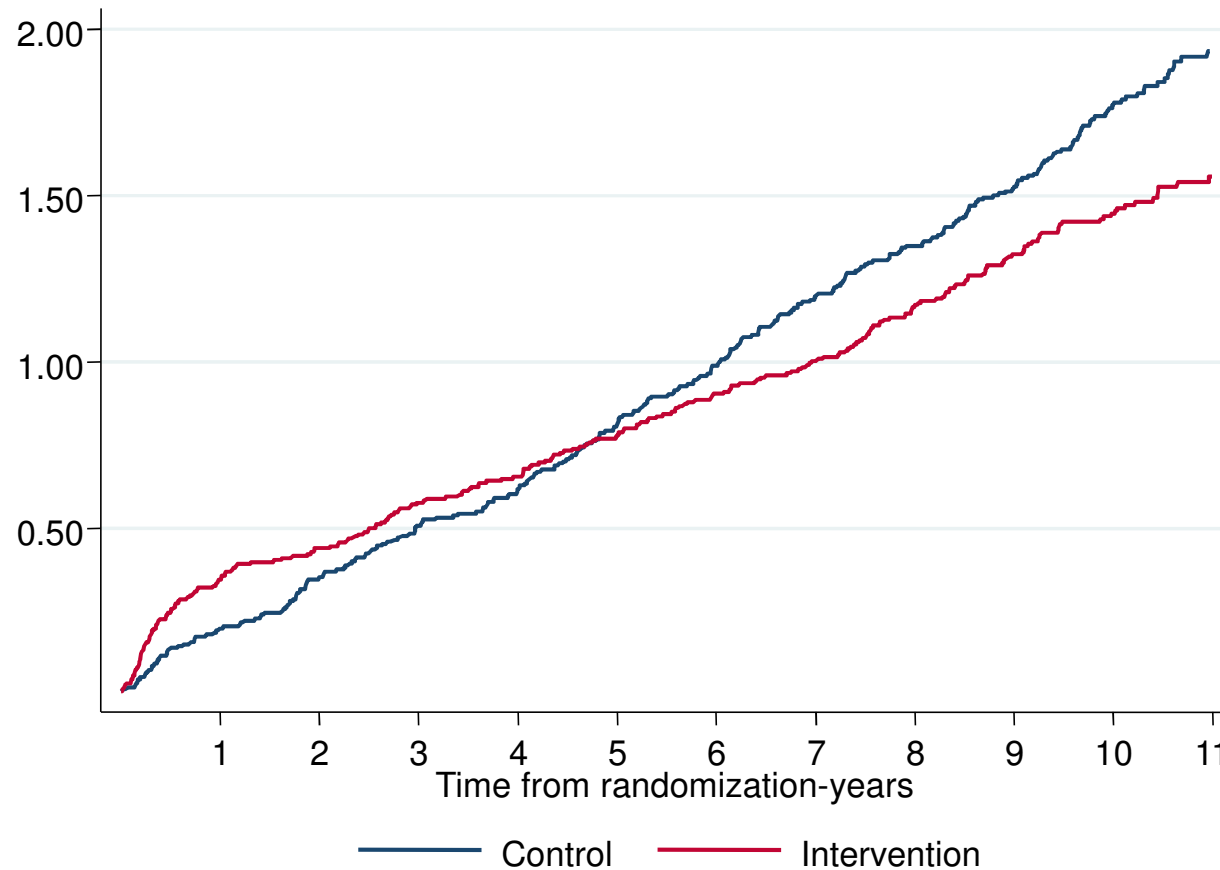
**JNCI 2011 Sep 7;103(17):1310-22. Epub 2011 Aug 18.**

**Nereo Segnan, Paola Armaroli, Luigina Bonelli, Mauro Risio, Stefania Sciallero, Marco Zappa, Bruno Andreoni, Arrigo Arrigoni, Luigi Bisanti, Claudia Casella, Cristiano Crosta, Fabio Falcini, Franco Ferrero, Adriano Giacomini, Orietta Giuliani, Alessandra Santarelli, Carmen Beatriz Visioli, Roberto Zanetti, Wendy S Atkin, Carlo Senore; SCORE working group collaborators**

## Intention to treat analysis - Colorectal cancer

### INCIDENCE, ALL SITES

Nelson Aalen Cumulative Hazard (%) by time from randomization



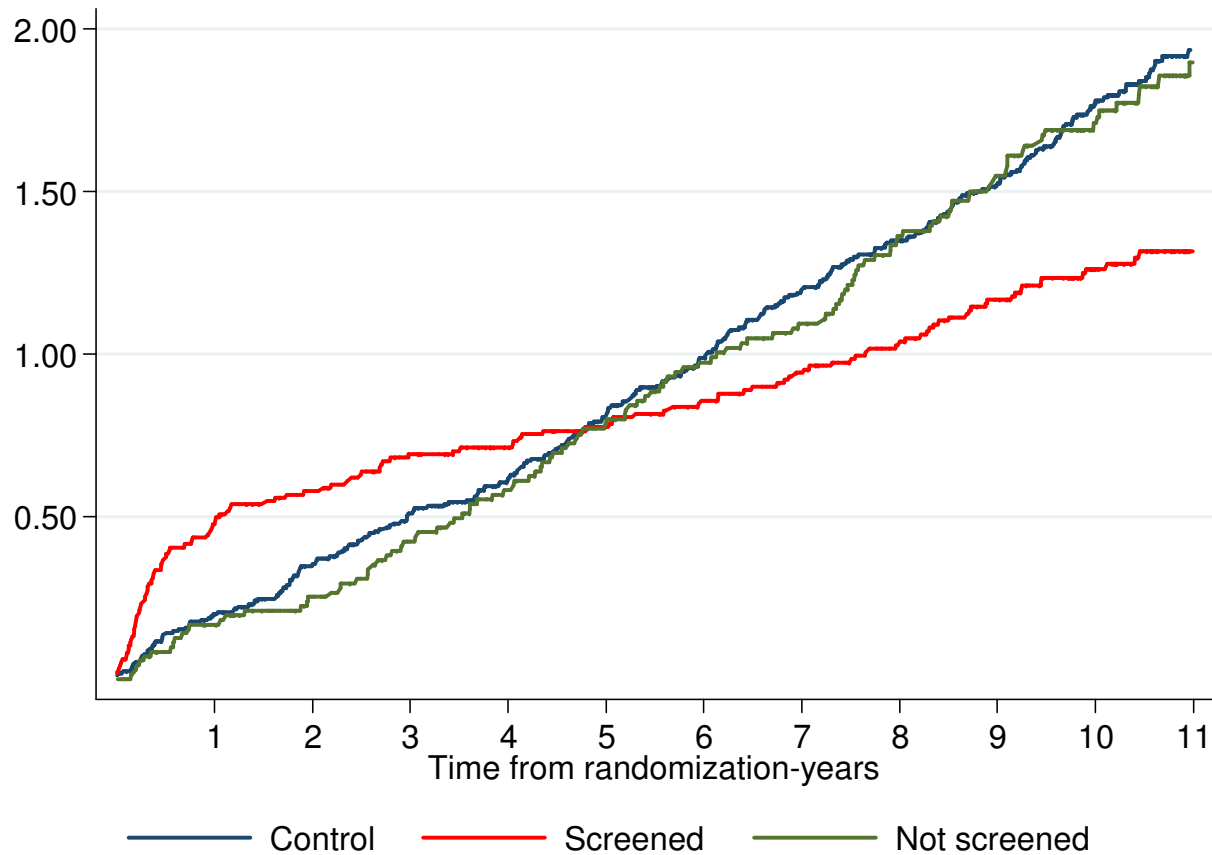
RR (95%CI) =  
0.82 (0.69-0.96)

Cumulative Events by years from randomization						
	≤2	≤4	≤6	≤8	≤10	>10
Control	60	104	165	223	286	306
Intervention	75	111	152	195	237	251

# Per protocol analysis-Colorectal cancer

## INCIDENCE, ALL SITES

Nelson Aalen Cumulative Hazard (%) by time from randomization



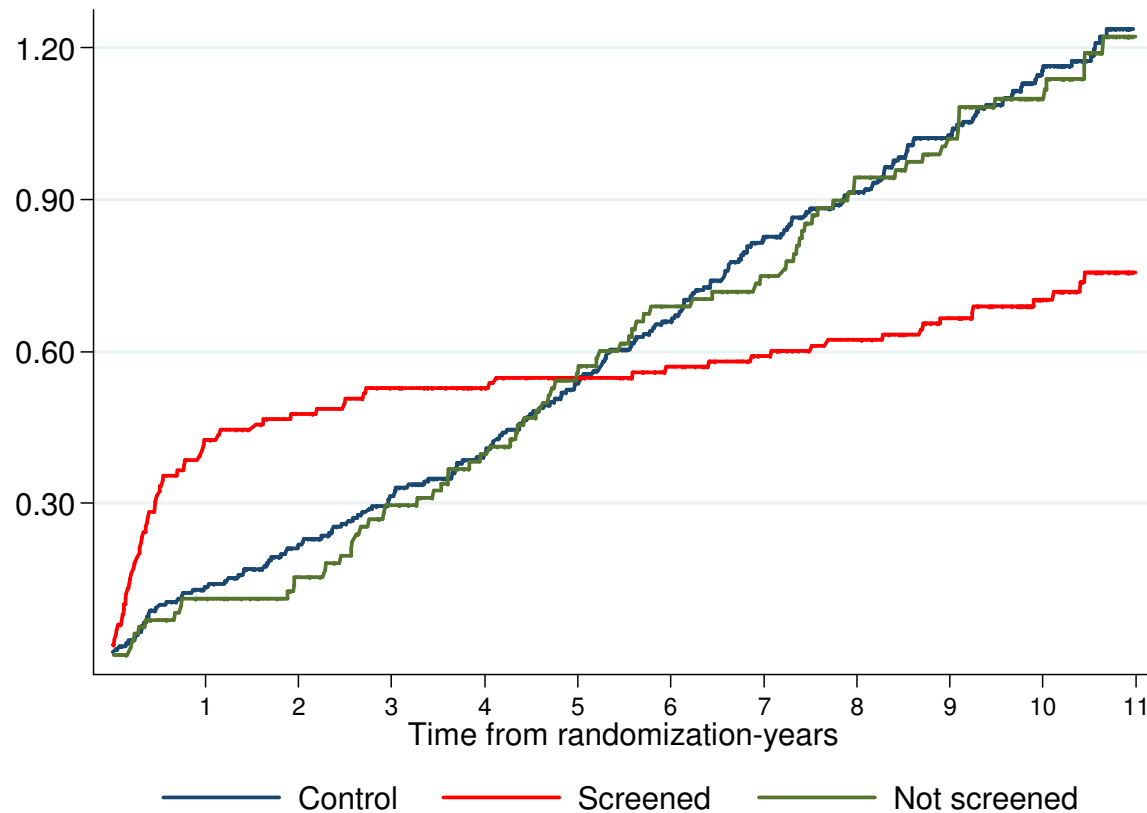
Cumulative Events by years from randomization						
	≤2	≤4	≤6	≤8	≤10	>10
Control	60	104	165	223	286	306
Not Screened	18	41	68	94	116	125
Screened	57	70	84	101	121	126



## Per protocol analysis-Colorectal cancer

### INCIDENCE, Distal&Descendent

Nelson Aalen Cumulative Hazard (%) by time from randomization



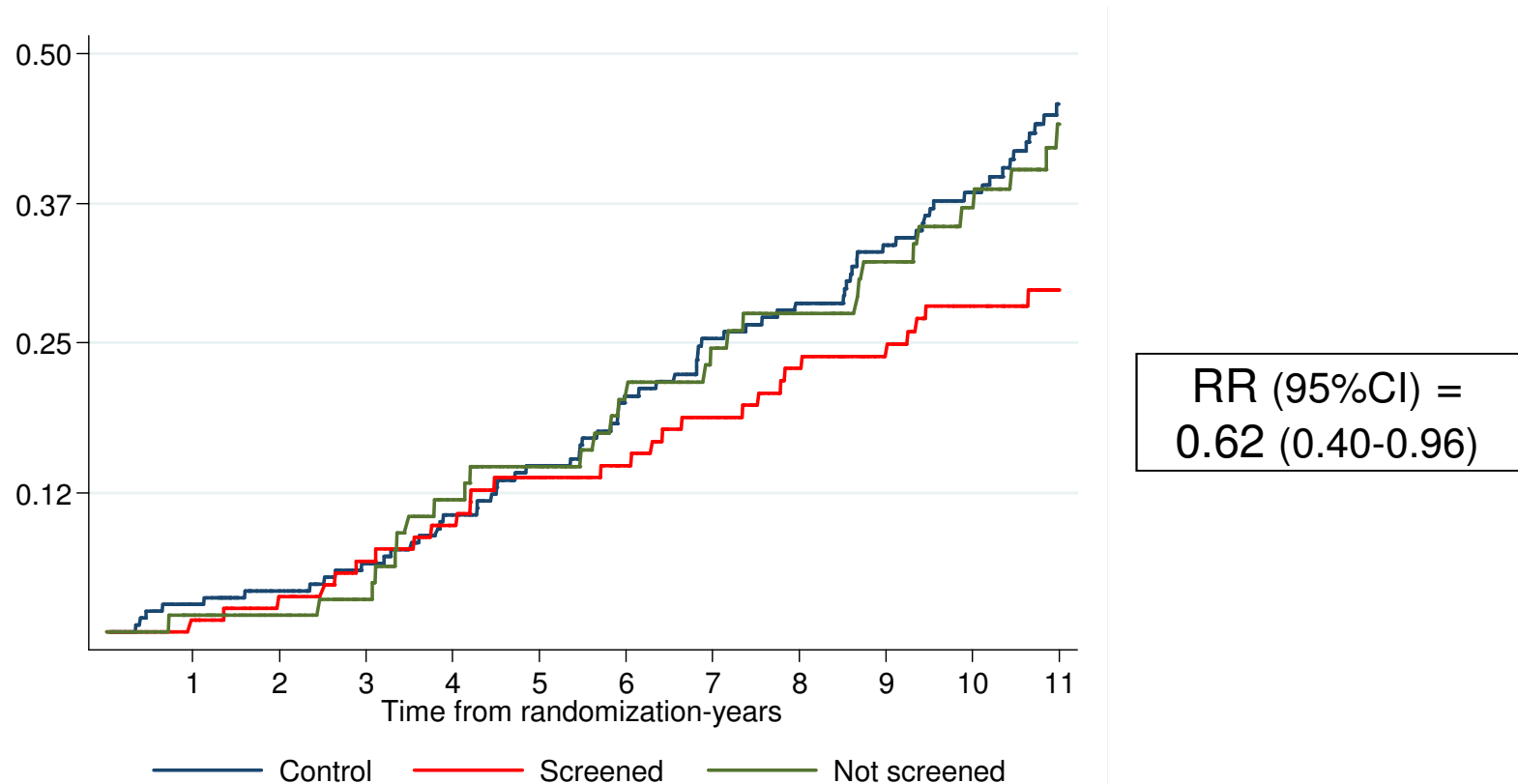
RR (95%CI) =  
0.60 (0.46-0.80)

Cumulative Events by years from randomization						
	≤2	≤4	≤6	≤8	≤10	>10
Control	37	67	110	151	187	198
Not Screened	11	28	48	65	75	81
Screened	47	52	56	61	68	71

# Per protocol analysis-Colorectal cancer

## MORTALITY, ALL SITES

Nelson Aalen Cumulative Hazard (%) by time from randomization



Cumulative Events by years from randomization						
	≤2	≤4	≤6	≤8	≤10	>10
Control	6	17	34	47	62	83
Not Screened	1	8	14	19	25	35
Screened	3	9	14	22	27	30

# THE LANCET

Volume 375, Issue 9726, 8 May 2010-14 May 2010, Pages 1624-1633



## Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial

Wendy S Atkin, Rob Edwards, Ines Kralj-Hans, Kate Wooldrage, Andrew R Hart, John M A Northover, D Max Parkin, Jane Wardle, Stephen W Duffy, Jack Cuzick, UK Flexible Sigmoidoscopy Trial Investigators

### Summary

Lancet 2010; 375: 1624-33

Published Online

April 28, 2010

DOI:10.1016/S0140-

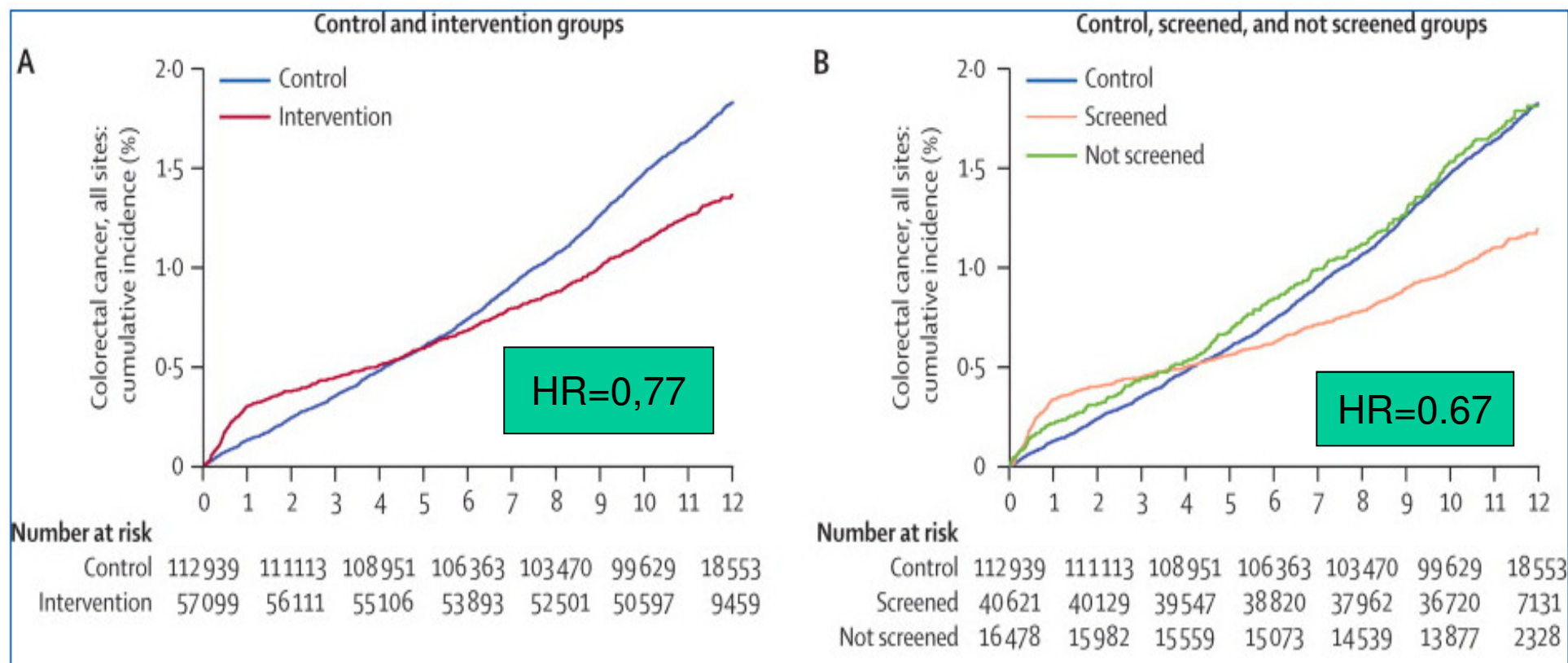
6736(10)60551-X

See Comment page 1582

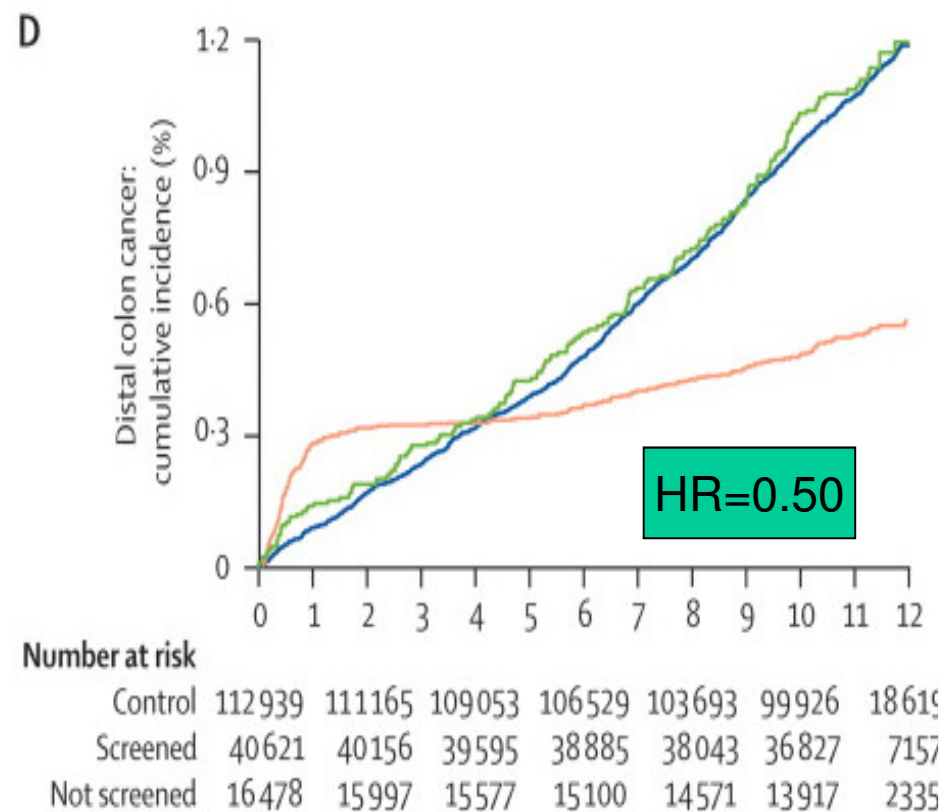
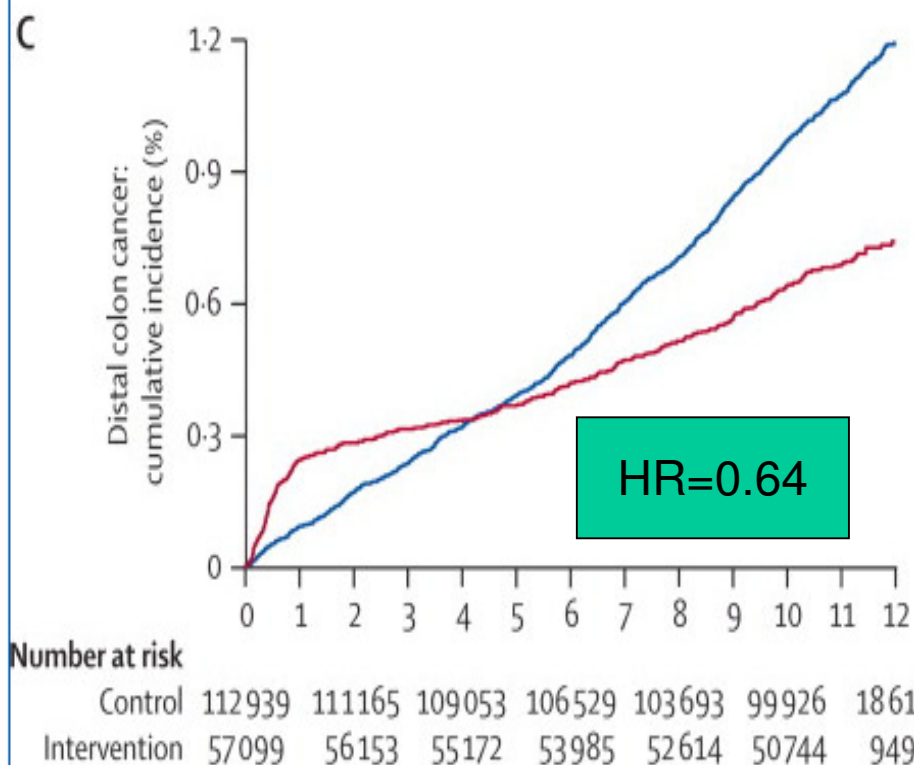
**Background** Colorectal cancer is the third most common cancer worldwide and has a high mortality rate. We tested the hypothesis that only one flexible sigmoidoscopy screening between 55 and 64 years of age can substantially reduce colorectal cancer incidence and mortality.

**Methods** This randomised controlled trial was undertaken in 14 UK centres. 170 432 eligible men and women, who had indicated on a previous questionnaire that they would accept an invitation for screening, were randomly allocated

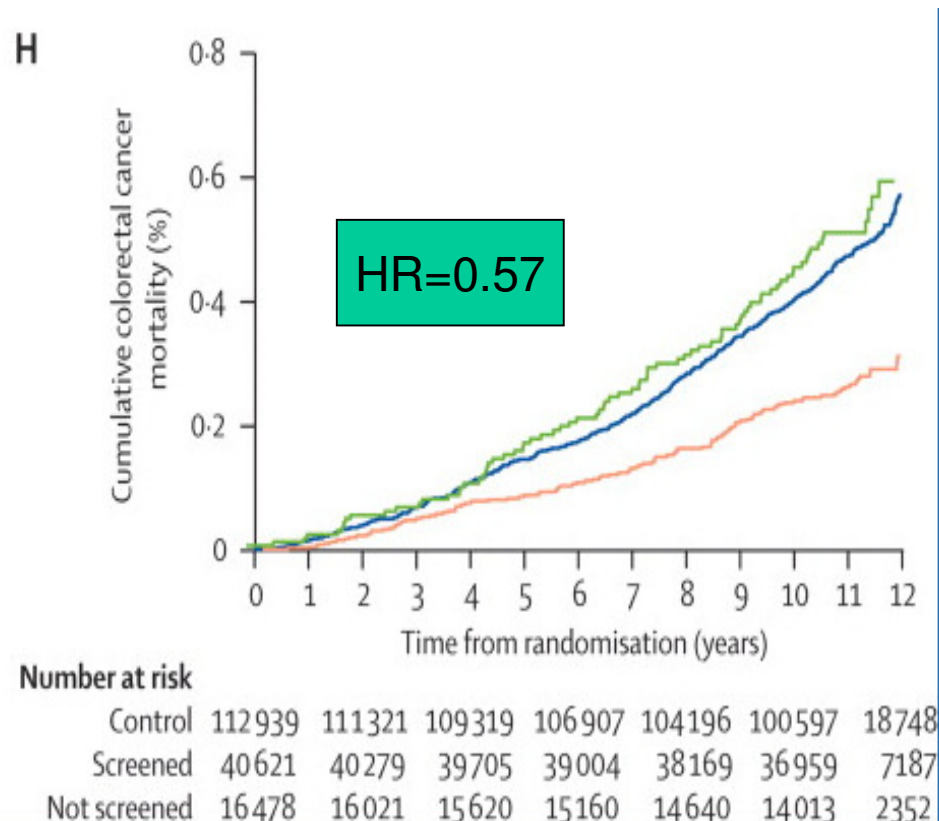
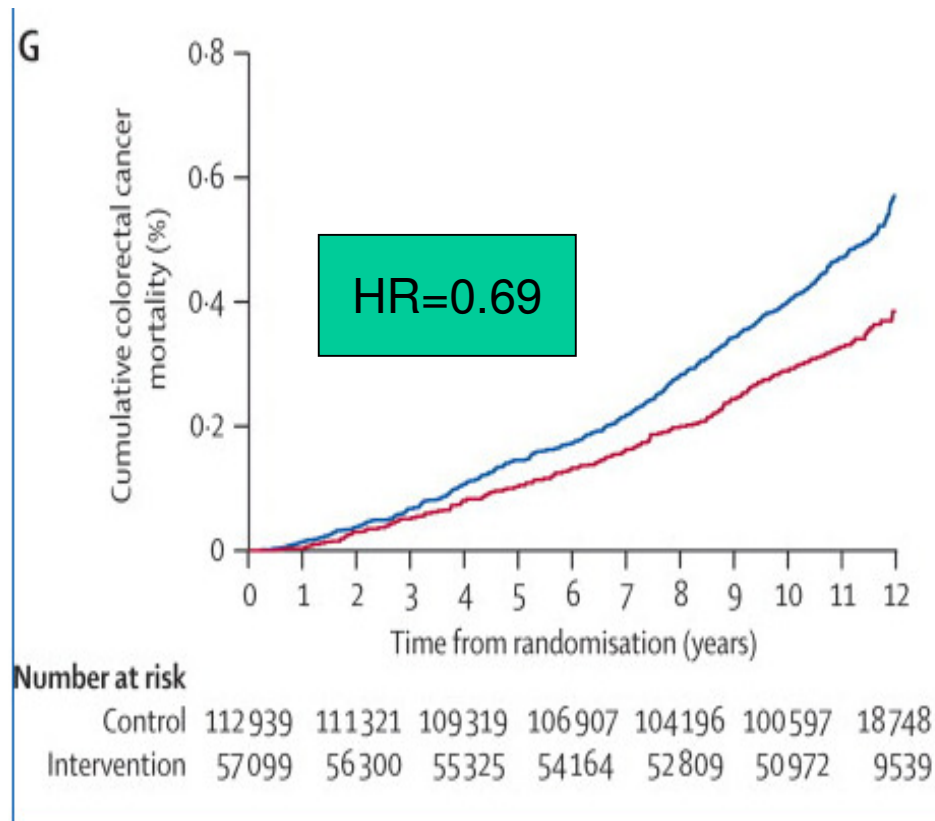
## Colorectal cancer incidence (Kaplan-Meier estimates)



## Distal cancer incidence (Kaplan-Meier estimates)



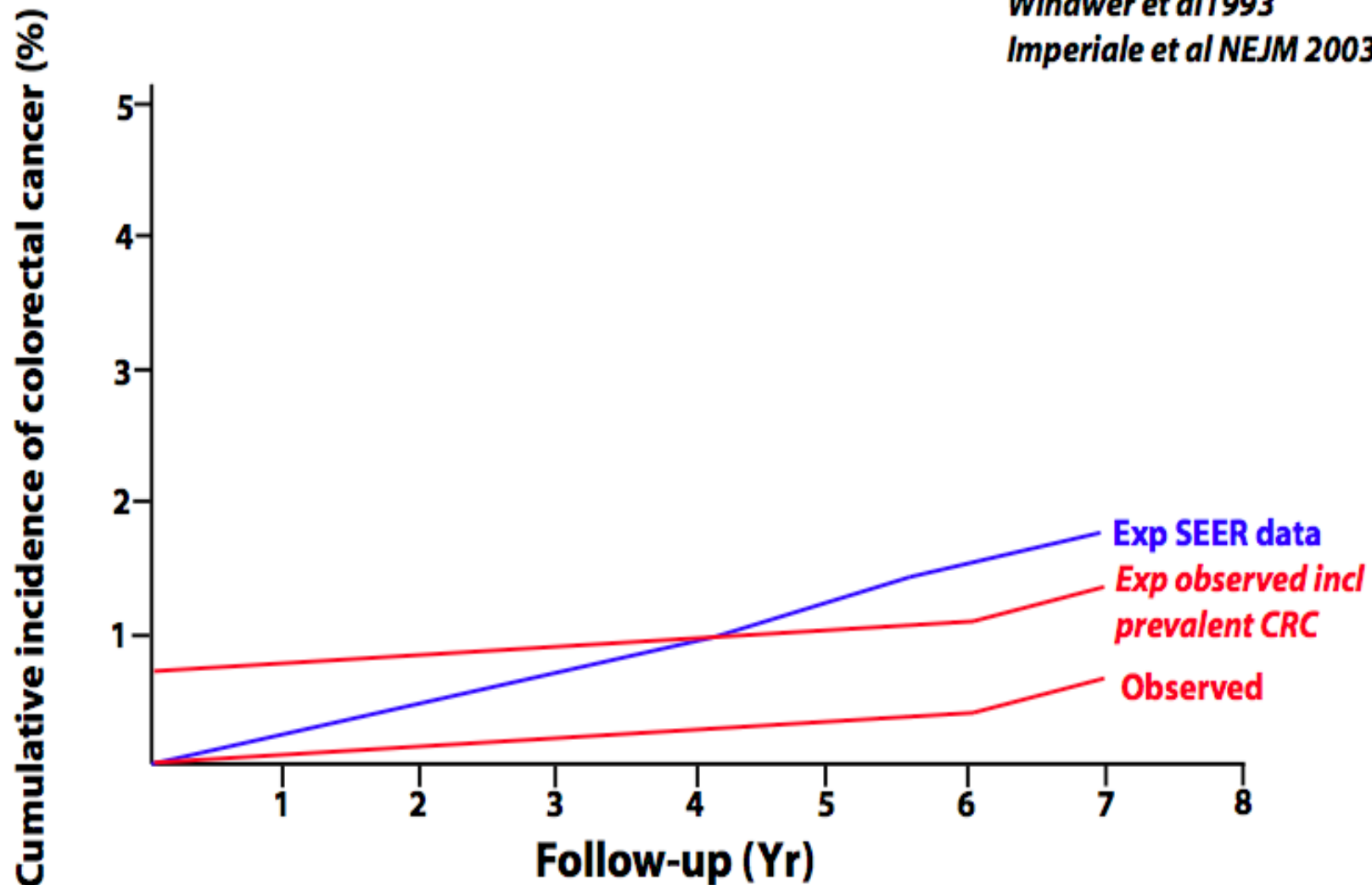
## Colorectal cancer mortality (Kaplan-Meier estimates)



# Cumulative incidence CRC in National Polyp Study ... *adjusting for prevalent cancers*

*Winawer et al 1993*

*Imperiale et al NEJM 2003*



# Evidence of efficacy of colonoscopy

	Year	Outcome	Left side	Right side
Singh	2010	Mortality	0.53	0.95
Baxter	2009	Mortality	0.33	0.99
Brenner	2009	High Risk Adenomas	0.33	1.02
Lakoff	2008	Incidence	0.21	varied by year
Cotterchio	2005	Incidence	0.68	1.02

*Singh et al. Gastroenterology 2010;139:1128–1137*

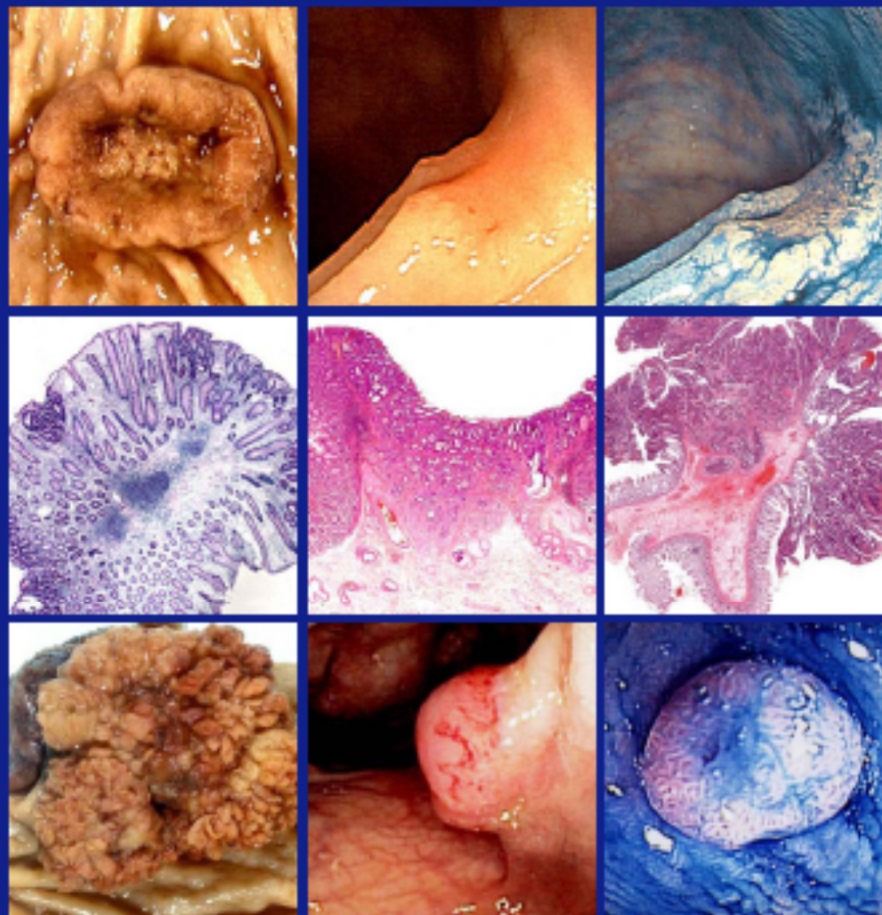
*Baxter et al. Ann Intern Med. 2009;150:1-8.*

*Brenner et al. JNCI. 2010;102(2): 89-95.*

*Lakoff et al. Clin Gastroenterol Hepatol. 2008 Oct;6(10):1117-21*

*Cotterchio et al. Cancer Causes Control. 2005 Sep;16(7):865-75.*





**European guidelines for quality assurance in colorectal  
cancer screening and diagnosis** *First Edition*



European Commission



Directorate-General for  
Health & Consumers



Executive  
Agency for  
Health and  
Consumers



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# **European guidelines for quality assurance in colorectal cancer screening and diagnosis**

*First Edition*

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## **Editors**

N. Segnan

J. Patnick

L. von Karsa

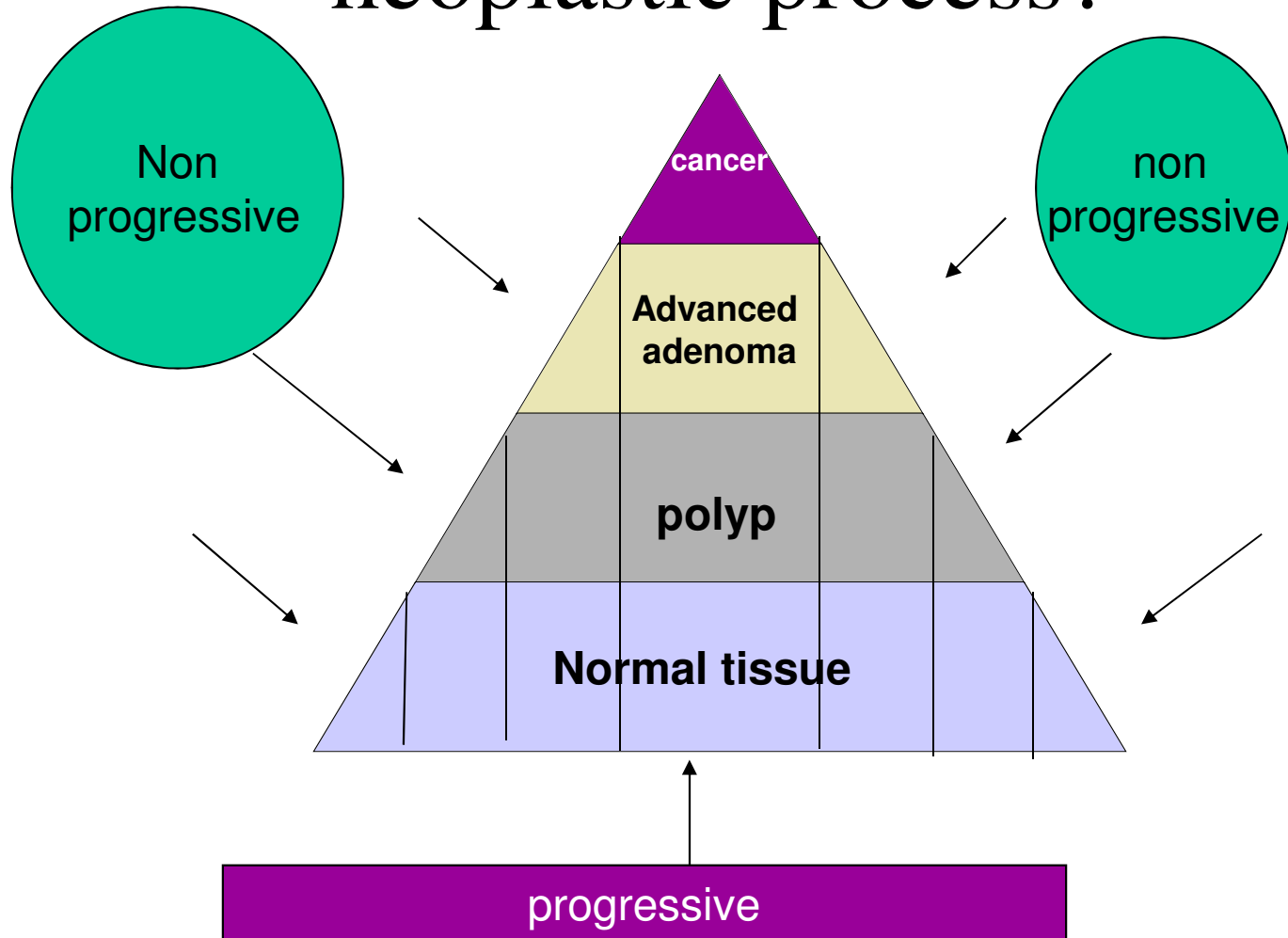
# Livello di evidenza linee guida europee

FOBT I

Sigmoidoscopia II

Colonscopia III

Which event or condition is most informative in understanding the neoplastic process?

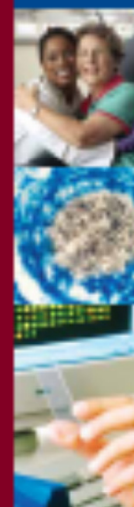


Division of Cancer Prevention

# The Early Detection Research Network

Investing in Translational Research on Biomarkers of Early Cancer and Cancer Risk

FOURTH REPORT • JANUARY 2008



National Cancer Institute

National Cancer Institute

The Early Detection Research Network

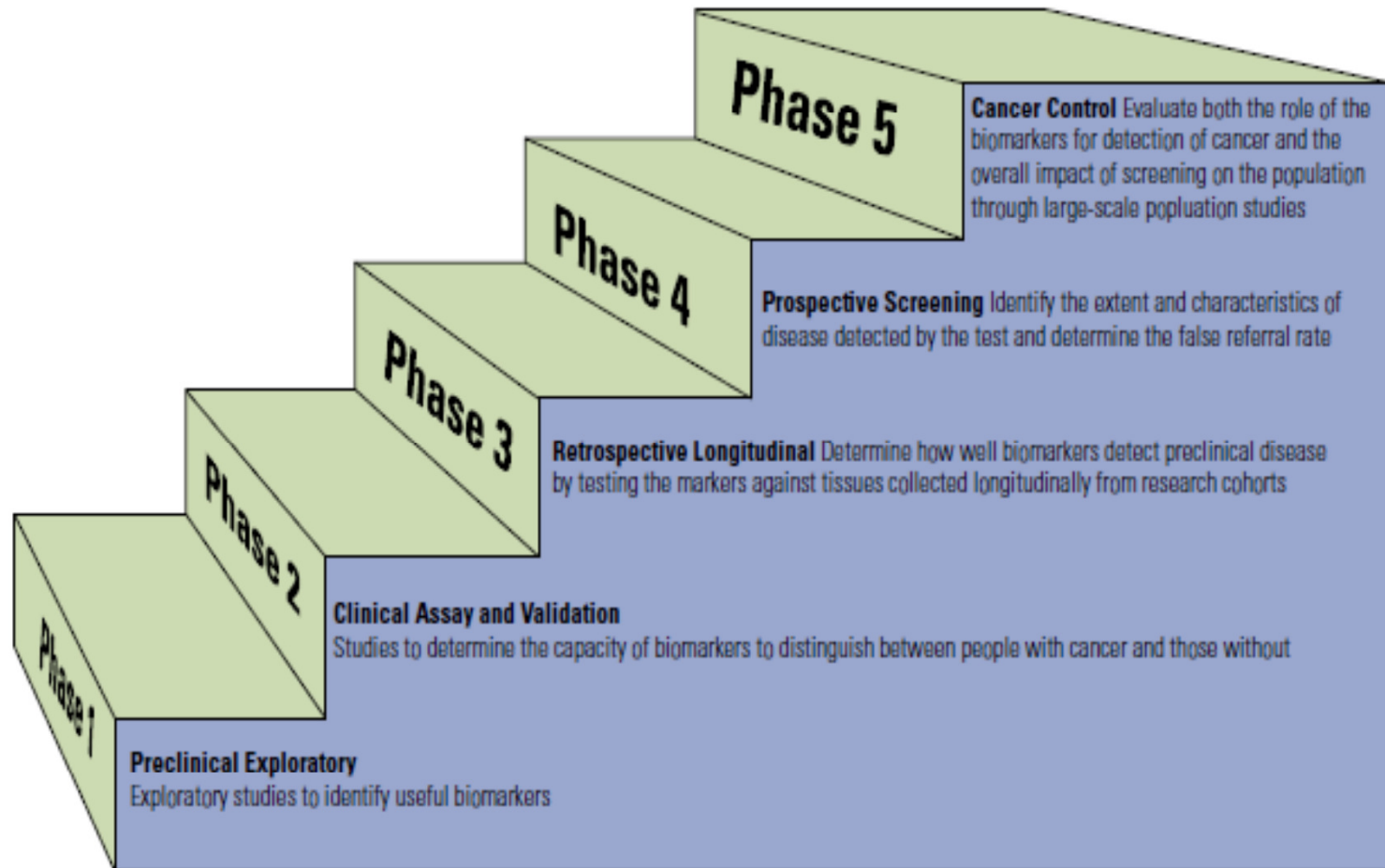


NATIONAL  
CANCER  
INSTITUTE  
NIH Publication No. 02-1728  
Printed January 2008






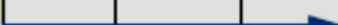
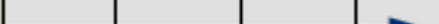
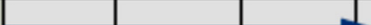



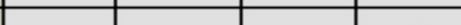
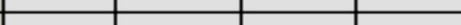
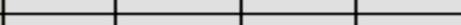


U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
National Institutes of Health

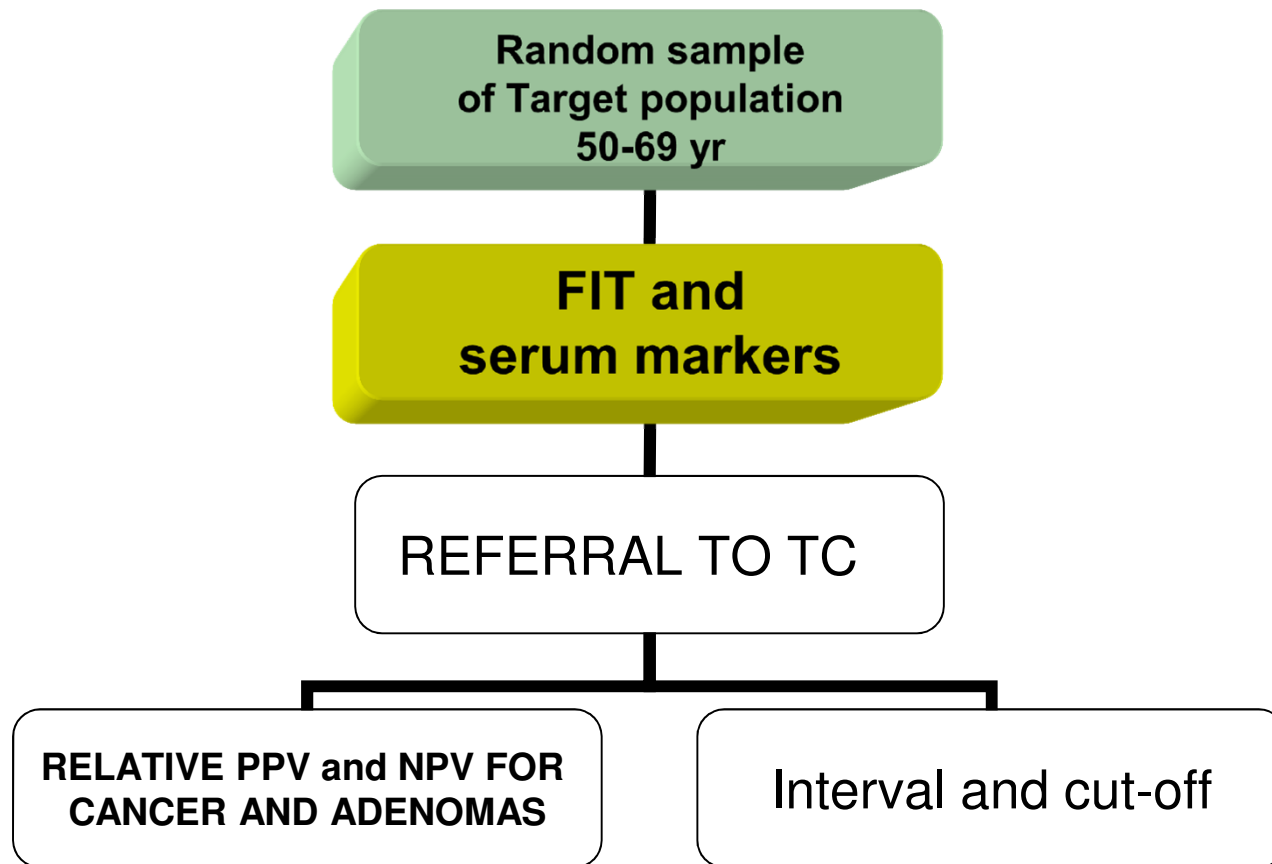
**Figure 6-1. Five Phase Approach to Biomarker Translational Research**



## Candidate Colorectal Cancer Biomarkers

Candidate Biomarker	Discovery			Pre-validation	Validation
	Discovery	Predictive Analysis	Assay Refinement	Blinded Limited Cross-Sectional	Large Cross-Sectional
CCSA-2, 3 and 4 (Serum)					
Spectral Markers (Tissue)					
ColoUp 1 and 2 (Serum)					
2D Mass Map (Serum)					
K-Ras (Urine)					
Methylation Marker Panel (Stool)					
TIMP-3 Methylation (Tissue)					
SELDI Profile (Serum)					
MALDI Profile (Serum)					
K-Ras (Stool Gujac)					
Flat adenoma (Tissue)					
GOS (Stool)					
Galectin-3 Lig (Serum)					
TIMP-1 (Serum)					

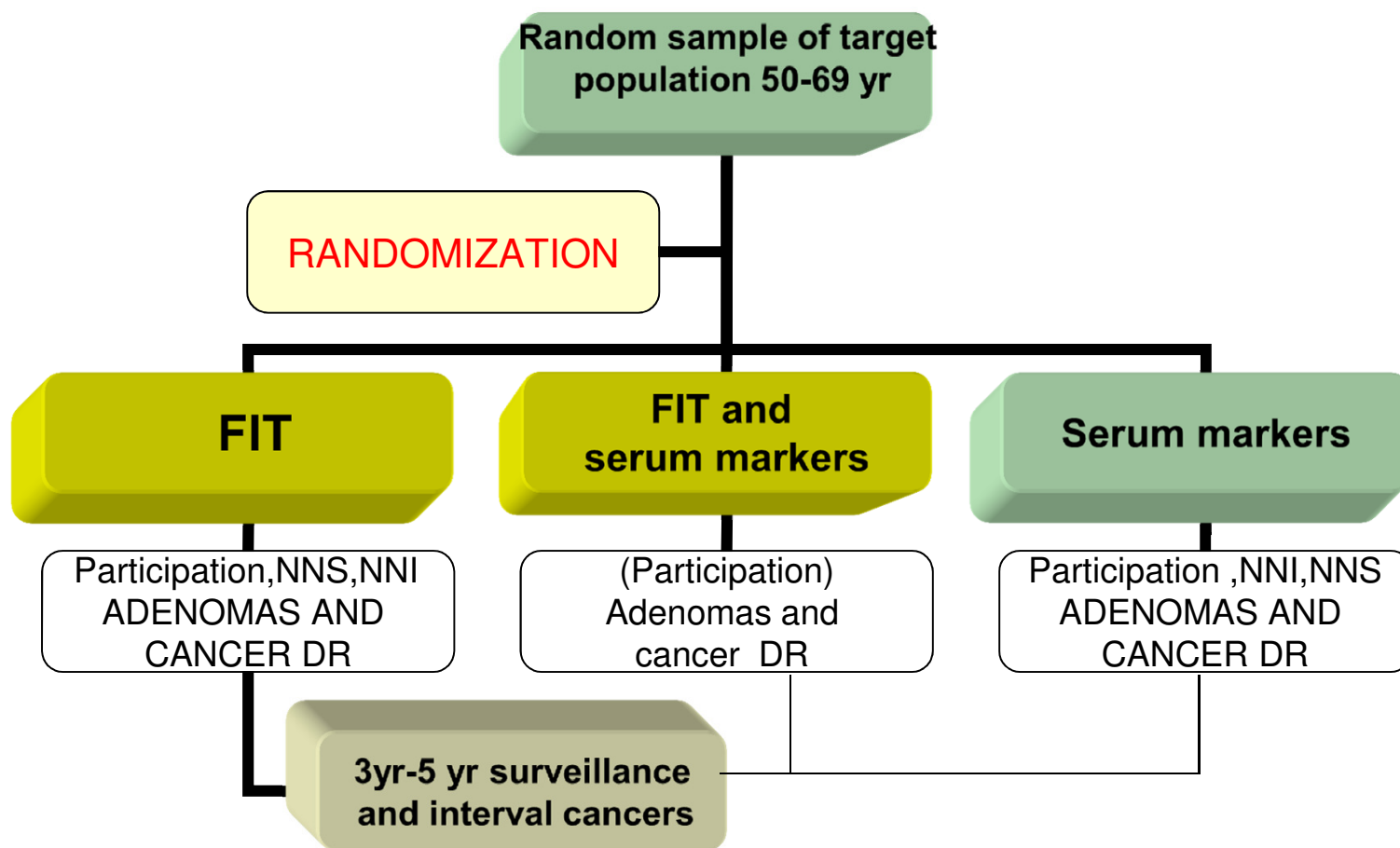
# Comparative effectiveness Phase 2





# Comparative effectiveness

## Phase 4



## Rotterdam screening trial in 15.013 average risk screening-naïve individuals aged 50 – 74 years

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	% Adherence	% positive test	% true positives*	True positives per 1000 invited
gFOBT	50	2.8	45	6
FIT <sup>50</sup>	62	8.1	42	21
Sigmoidoscopy	32	10.2	100	33
2-step: Sigmo + FIT <sup>50</sup>	57	16.8		43

*\* of those with positive test*

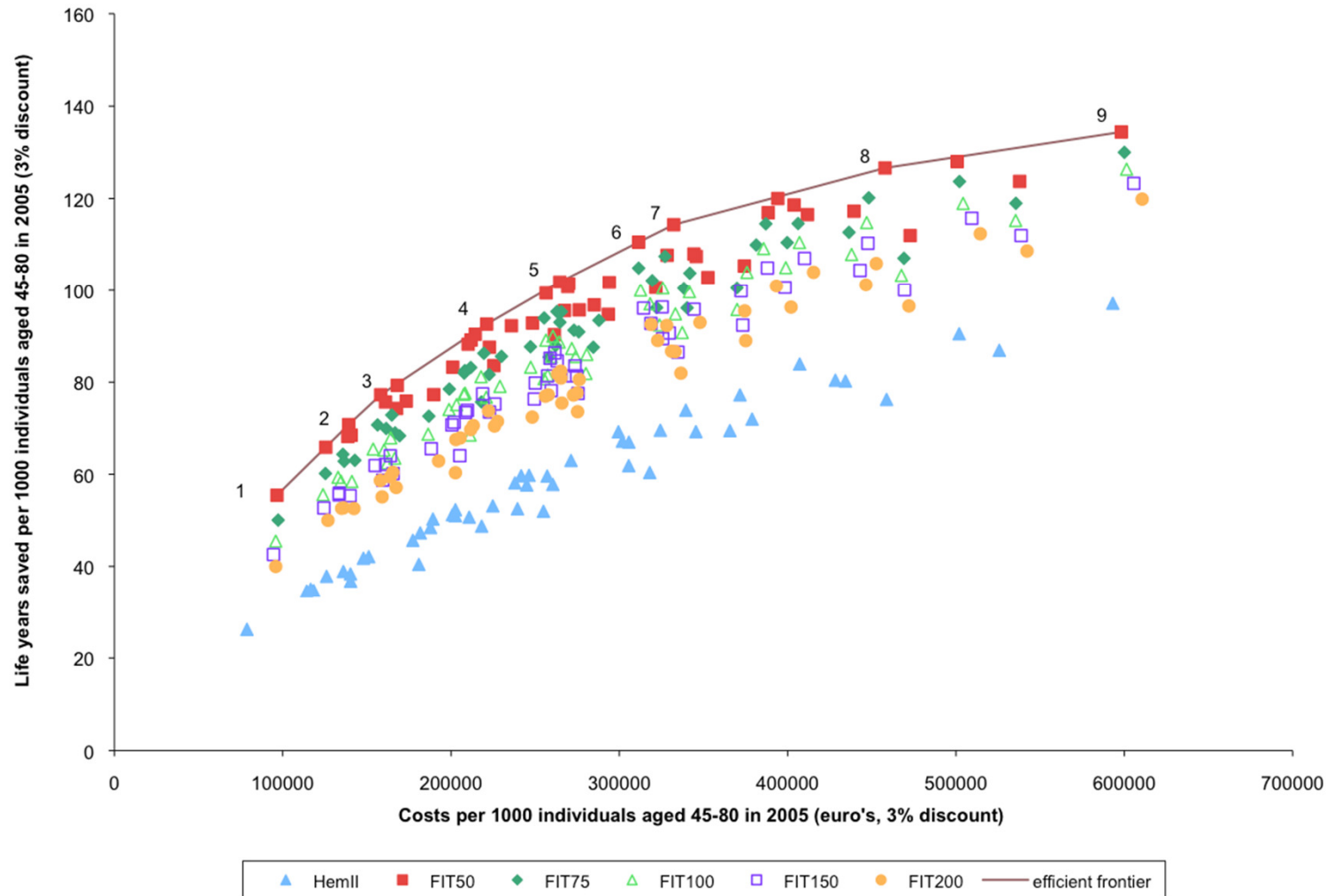
Hol L, et al. Gut 2010, **Int J Cancer** 2011;

## CRC prevented cases

	FS 58 YRS	4 FIT 50-69 YRS	5FIT 50-69 YRS	6 FIT 58-69 YRS
UPTAKE	% N	% N	% N	% N
30%	10.3%	8.9%	11.0%	9.2%
	349	480	595	312
40%	13,7%	9.9%	12.1%	12.3%
	466	538	654	417
50%	16,5%	10.9%	13.1%	15.4%
	582	595	713	523
65%	22.3%	12.5%	14.7%	20.0%
	757	680	801	681

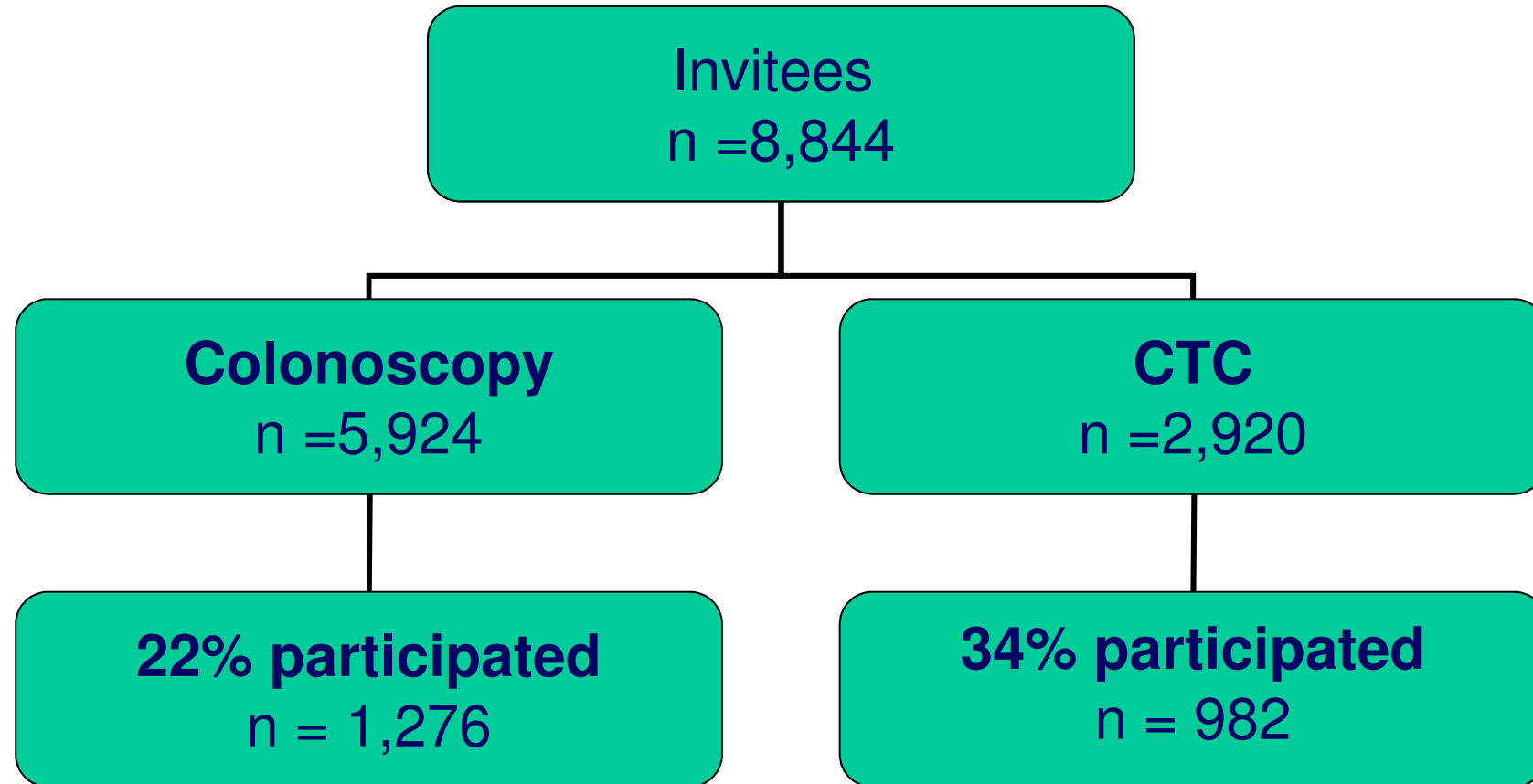
# Cost – performance modelling of gFOBt and FIT

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Van Wilschut JA, van Ballegooijen M, et al. Gastroenterology 2011;

# Primary screening with colonoscopy vs CT colonography; a randomized trial



**RR 1.56**

(1.46-1.68;  $p < 0.001$ )

# Diagnostic yield CTC vs Colo

(number of subjects with advanced neoplasia)

	CC	CTC	P-value	RR (95%CI)
n/100 participants	8.7	6.1	0.02	1.46 (1.06-2.03)
n/100 invitees	1.9	2.1	0.56	0.91 (0.66-2.03)

# The Protèus project

Randomized trial comparing detection and participation rate of Sigmoidoscopy and CT Colonography screening program.

- Target population: subjects aged 58 years
- 26000 invitations by letter
- 10 centers performing CTC (8 in Piedmont, 2 in the province of Verona)
- CTC scans sent to a screening center for reporting
- CTC reading assisted by Computer Aided Detection

# Computer-aided detection in CT Colonography: which CAD paradigm is best in a screening population?

G. Iussich<sup>1</sup>, MD; L. Correale<sup>2</sup>, PhD; C. Senore<sup>3</sup>, MD;  
D. Campanella<sup>1</sup>, MD; G. Galatola<sup>1</sup>, MD; C. Laudi<sup>1</sup>, MD;  
P. Falco<sup>2</sup>, PhD; N. Segnan<sup>3</sup>, MD; D. Regge<sup>1</sup>, MD

<sup>1</sup>Institute for Cancer Research and Treatment (IRCC),  
Candiolo, Italy

<sup>2</sup>im3D S.P.A - Medical Imaging Lab, Torino, Italy

<sup>3</sup>Unit of Cancer Epidemiology CPO Piemonte, Italy



## Results: per patient analysis

### Reading Paradigm

	Second Reader		Double Reading FR	
	Radiologist	Radiologist + CAD	FR CAD	CAD+ Radiologist
Sensitivity (%)	80 (74/93) (70,87)	86 (80/93) (77,92)	85 (79/93) (75,91)	89 (83/93) (81,95)
Specificity (%)	92 (82/93) (82,97)	90 (80/89) (82,95)	93 (83/93) (86,97)	91 (81/93) (83,96)
PPV (%)	91 (74/81) (83,96)	90 (80/89) (82,95)	92 (78/84) (85,97)	91 (83/91) (83,96)
AUC	0.86 ± 0.04	0.90 ± 0.03	0.92 ± 0.02	0.94 ± 0.02

The difference in sensitivity between SR and DR with FR CAD was not statistically significant (P=0.5)  
Compared to the Unassisted reading, CAD increased sensitivity for both reading paradigm (P=0.03)

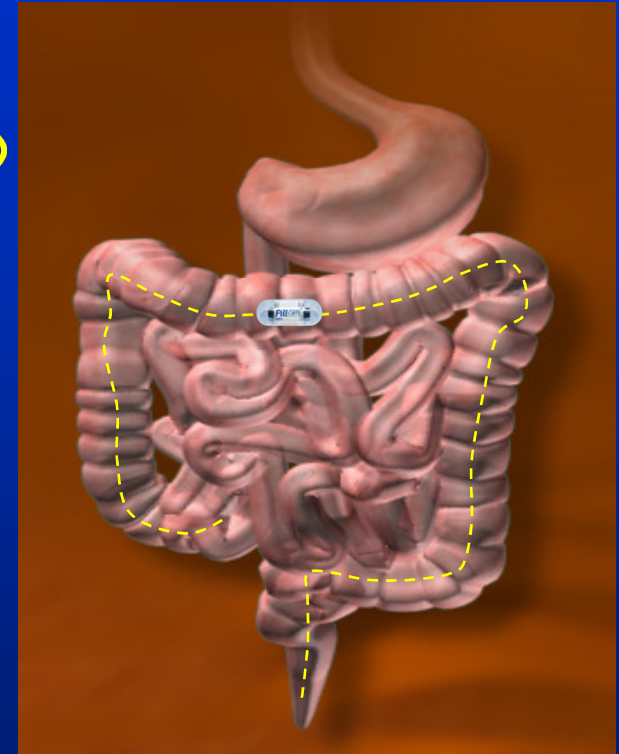
# Methods: PillCam® COLON Capsule

- New PillCam Design
- 2-sided video cameras; 4 images per second, 2 fps per camera
- Dimensions:
  - Diameter: Same as PillCam SB
  - Length: 5 mm longer than PillCam SB
- Optimized optics and automatic light control, with each camera providing more than double the area coverage and depth of view of PillCam SB
- 9-10 hours operating time



# The Colon Challenge

- **Image** the entire colon
- **Clean** the colon
- **Propel** the Capsule



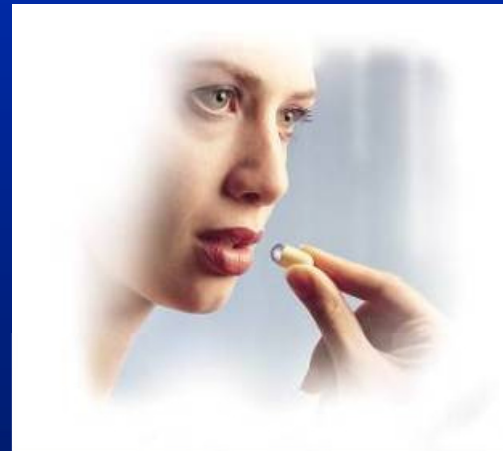
# **Methods: PillCam® COLON Capsule**

## **Sleep mode**

- Capsule shuts off 3 minutes post activation to preserve battery energy
- Capsule automatically turns back on after 1:45 hours before enters the colon

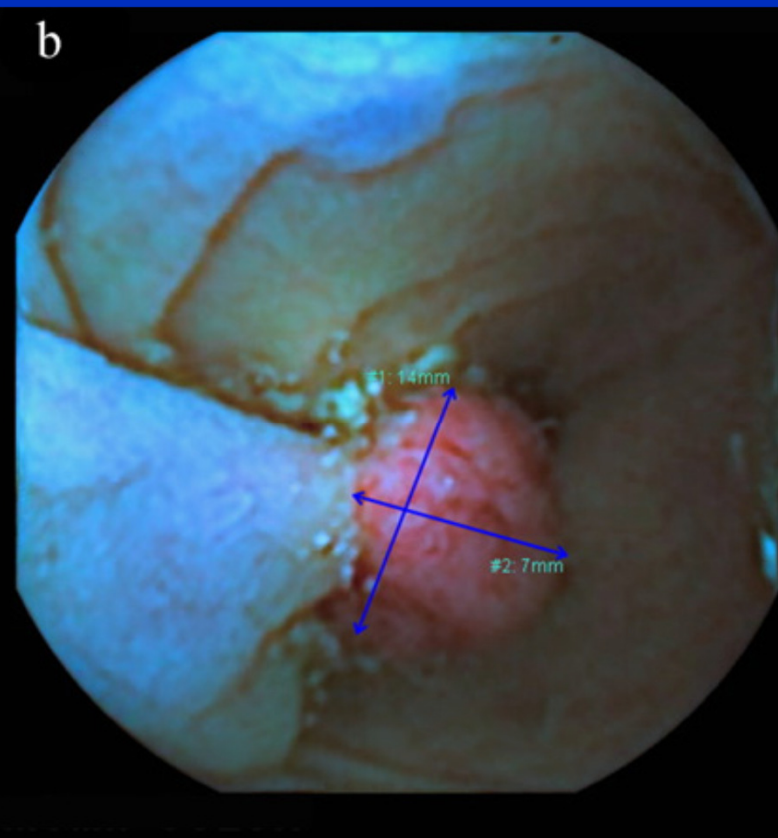
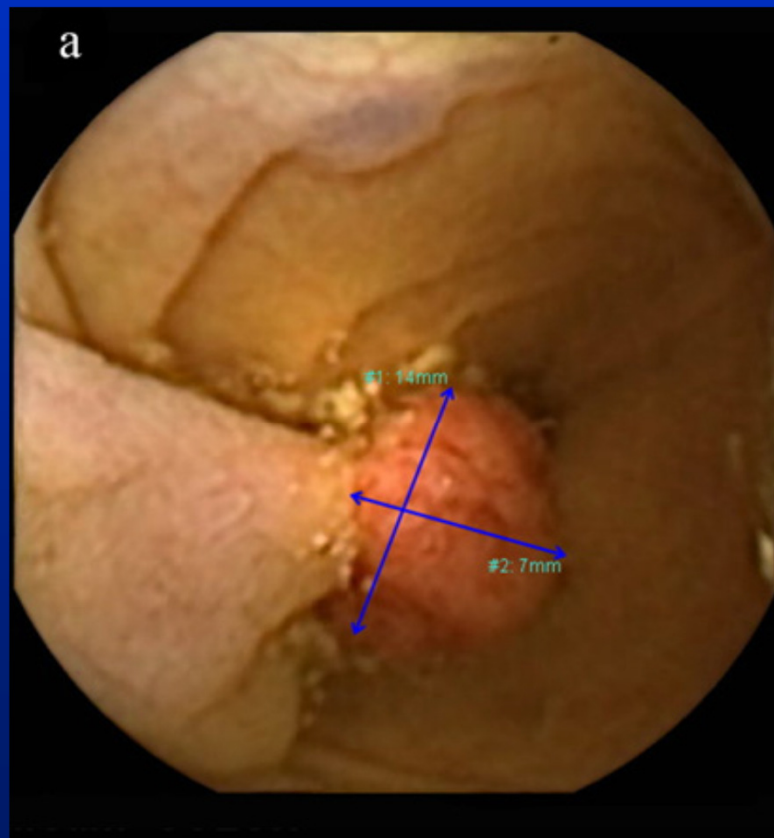
# PillCam® COLON Capsule: the optimistic view

- Direct visualization of colon mucosa
- No sedation
- No intubation
- No insufflation
- No radiation



# **PillCam® COLON Capsule: the pessimistic view**

- Preparation is a concern
- No insufflation/aspiration → no visualization
- Batteries lifetime
- Colon transit time
- Competing technologies



## **Second-generation colon capsule endoscopy compared with colonoscopy**

**Cristiano Spada, MD, Cesare Hassan, MD, PhD, Miguel Munoz-Navas, MD, PhD, Horst Neuhaus, MD, Jacques Deviere, MD, PhD, Paul Fockens, MD, PhD, FASGE, Emmanuel Coron, MD, PhD, Gerard Gay, MD, Ervin Toth, MD, PhD, Maria Elena Riccioni, MD, PhD, Cristina Carretero, MD, Jean P. Charton, MD, Andr  Van Gossum, MD, PhD, Carolien A. Wientjes, MD, Sylvie Sacher-Huvelin, MD, Michel Delvaux, MD, PhD, Artur Nemeth, MD, Lucio Petruzzello, MD, Cesar Prieto de Frias, MD, Rupert Mayershofer, MD, Leila Aminejab, MD, Evelien Dekker, MD, PhD, Jean-Paul Galmiche, MD, FRCP, Muriel Frederic, MD, Gabriele Wurm Johansson, MD, PhD, Paola Cesaro, MD, Guido Costamagna, MD, FACG**

Rome, Italy; Pamplona, Spain; D sseldorf, Germany; Brussels, Belgium; Amsterdam, The Netherlands; Nancy, France; Malm , Sweden



**TABLE 2. Accuracy characteristics for detection of patients with at least one lesion  $\geq 6$  mm or  $\geq 10$  mm**

	Colonoscopy	PillCam Colon 2	
Polyp size, mm	Prevalence, no. (%)	Sensitivity, % (95% CI)	Specificity, % (95% CI)
$\geq 6$ mm	45 (41)	84 (74-95)	64 (52-76)
$\geq 10$ mm	32 (29)	88 (76-99)	95 (90-100)

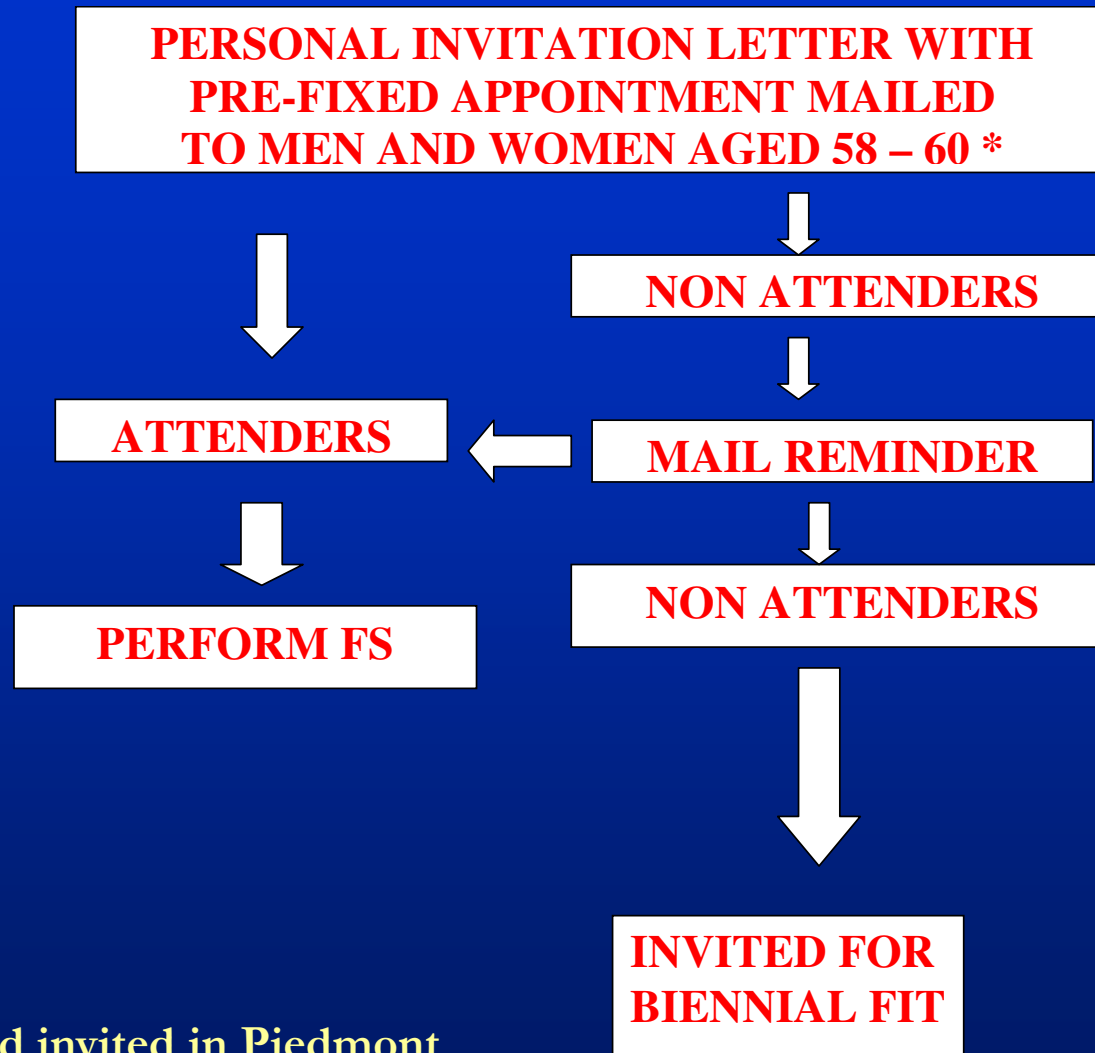
CI, Confidence interval.

# ATTENDANCE RATE

		Invited	FS performed	Attendance rate	Invited to FIT	FIT performed	Attendance rate	Overall coverage
<b>Verona</b>	<b>MEN</b>	9662	4152	<b>43.0%</b>	5040	1201	<b>23.8%</b>	<b>55,4%</b>
	<b>WOMEN</b>	10308	3705	<b>35.9%</b>	6139	1974	<b>32.2%</b>	<b>55,1%</b>
<b>Torino</b>	<b>MEN</b>	20947	7019	<b>33.5%</b>	12183	1518	<b>12.5%</b>	<b>40.8%</b>
	<b>WOMEN</b>	22801	6068	<b>26.6%</b>	14329	2588	<b>18.1%</b>	<b>38.0%</b>

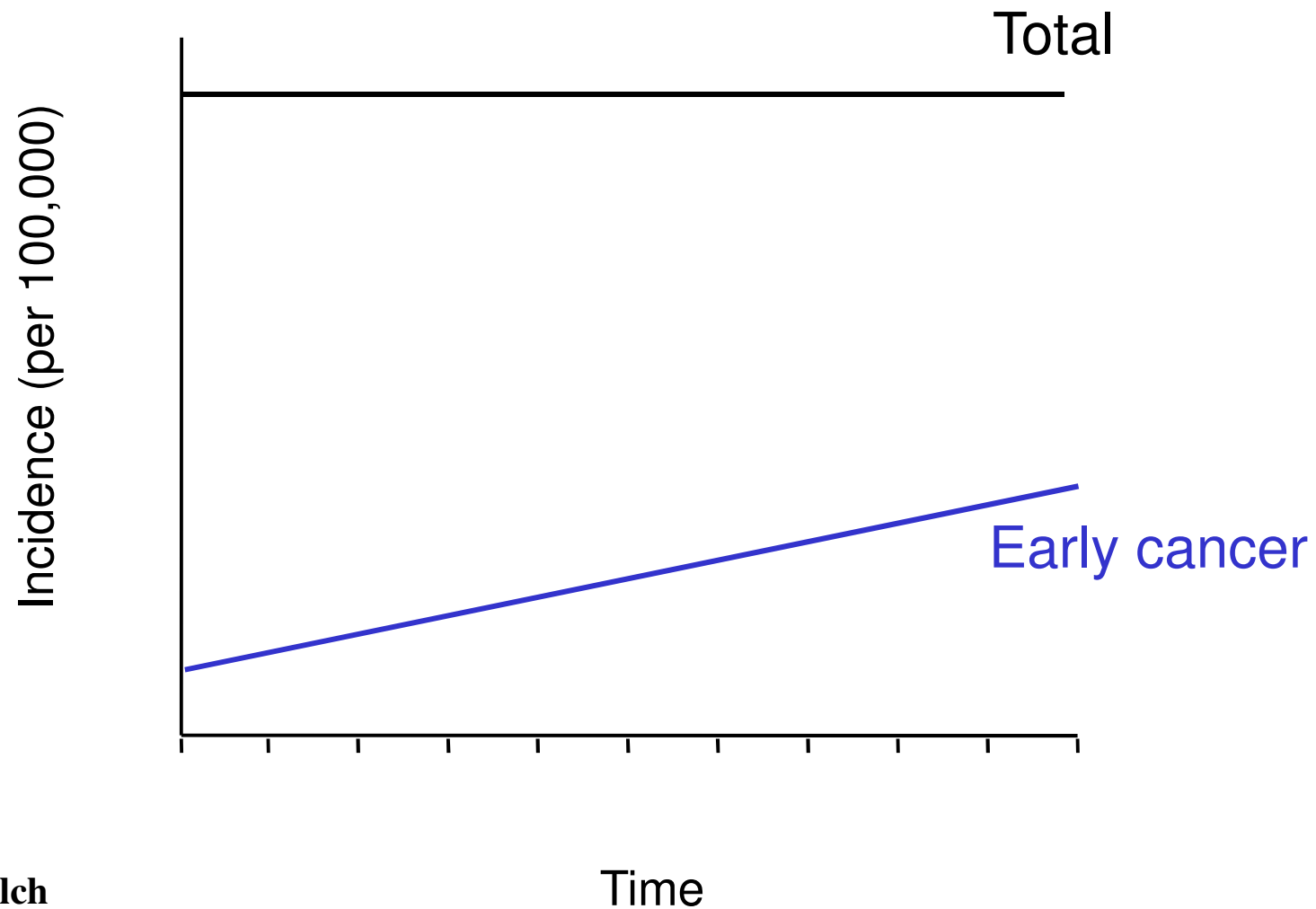
# SCREENING FLOW

*FS*



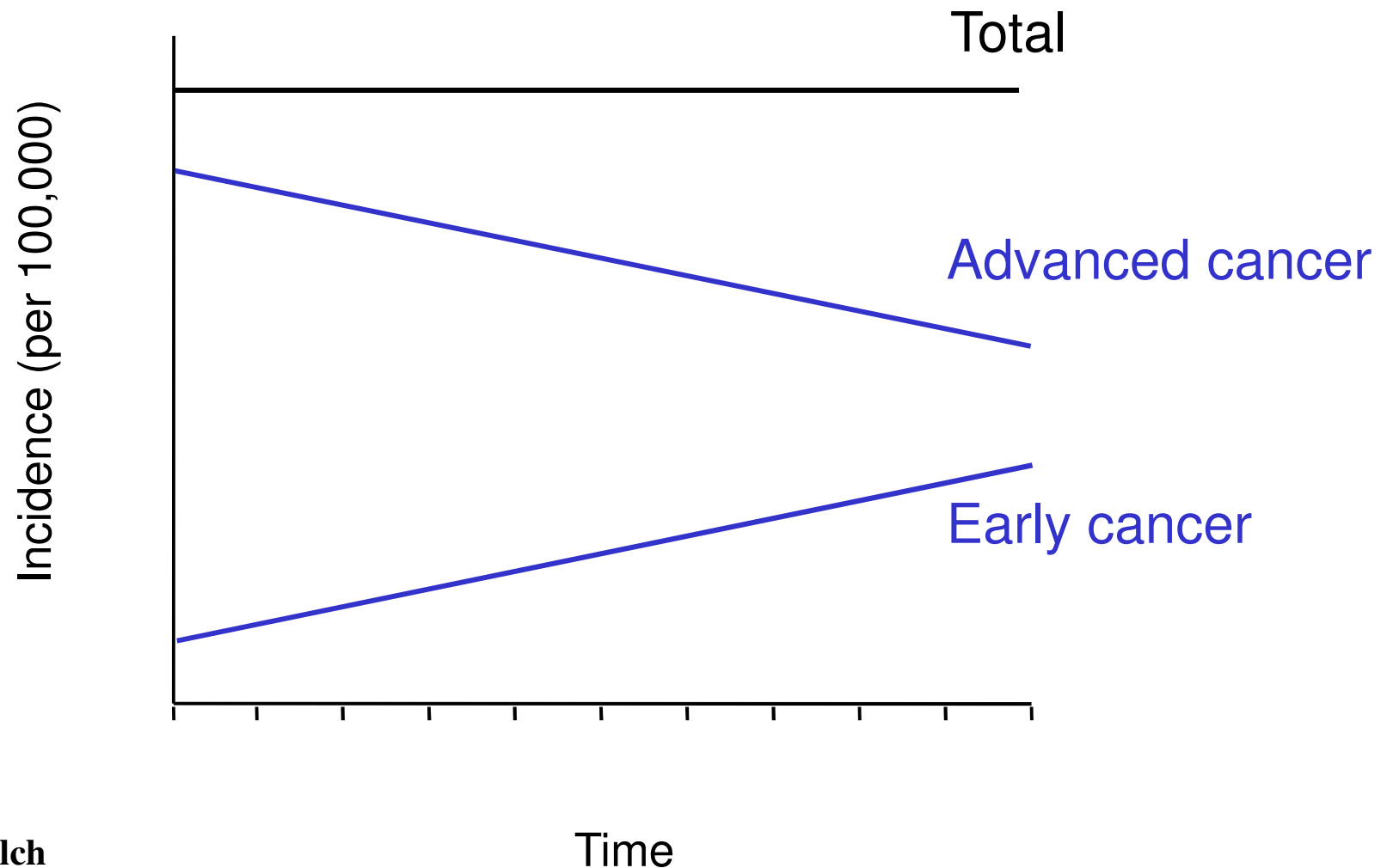
\* 58 years old invited in Piedmont

# Classic model of early detection

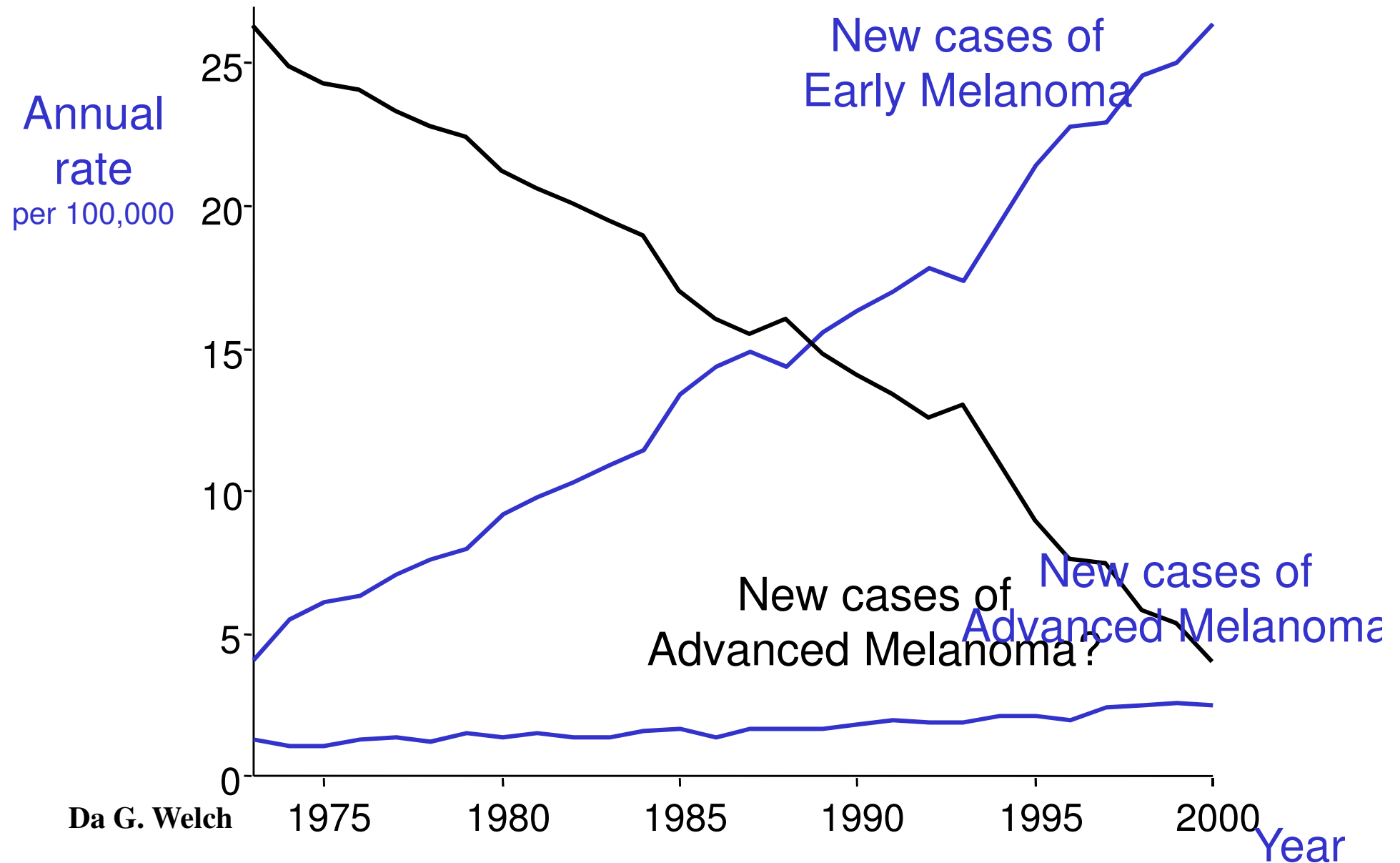


# Classic Model:

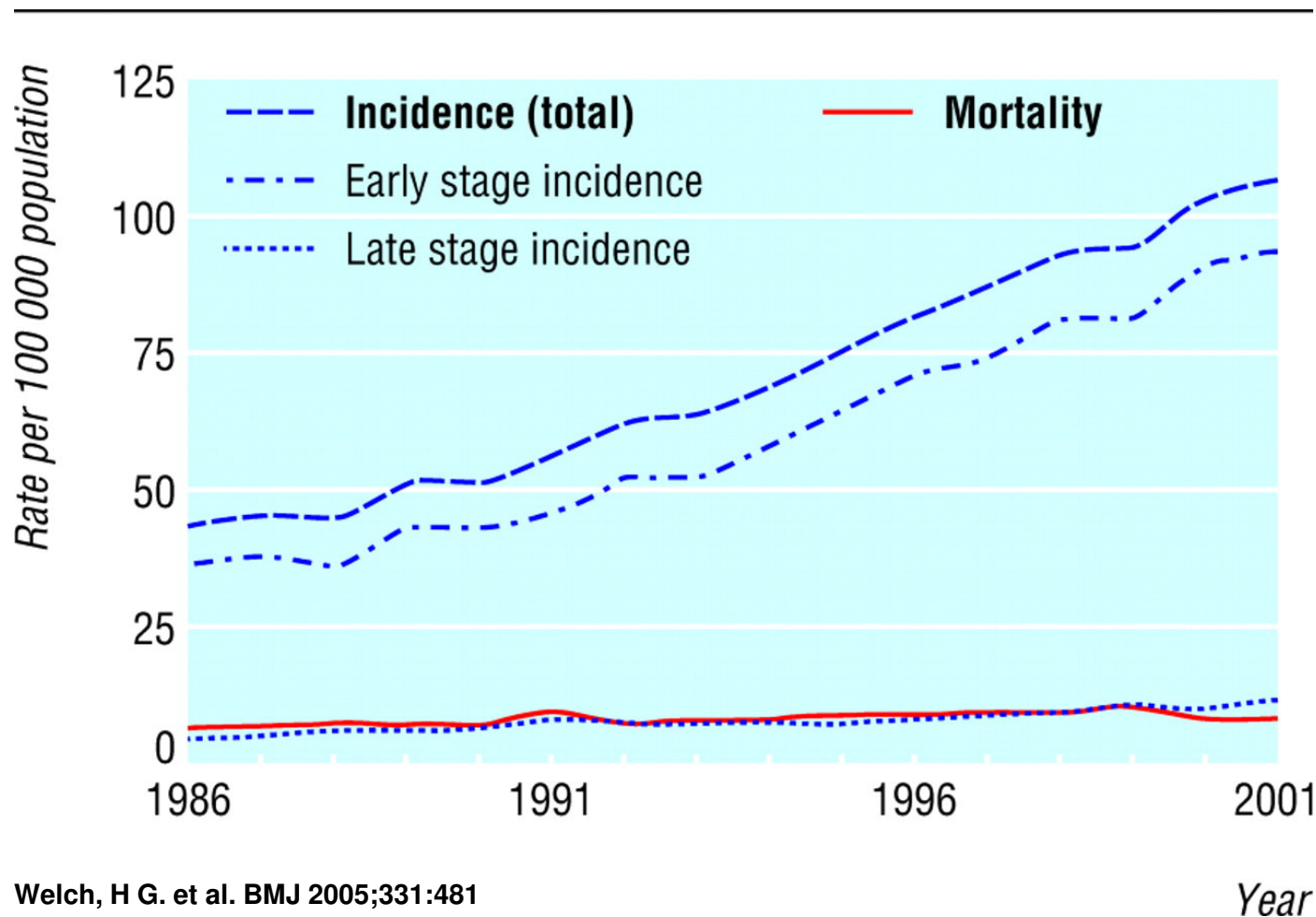
early detection reduces the number  
of advanced cases



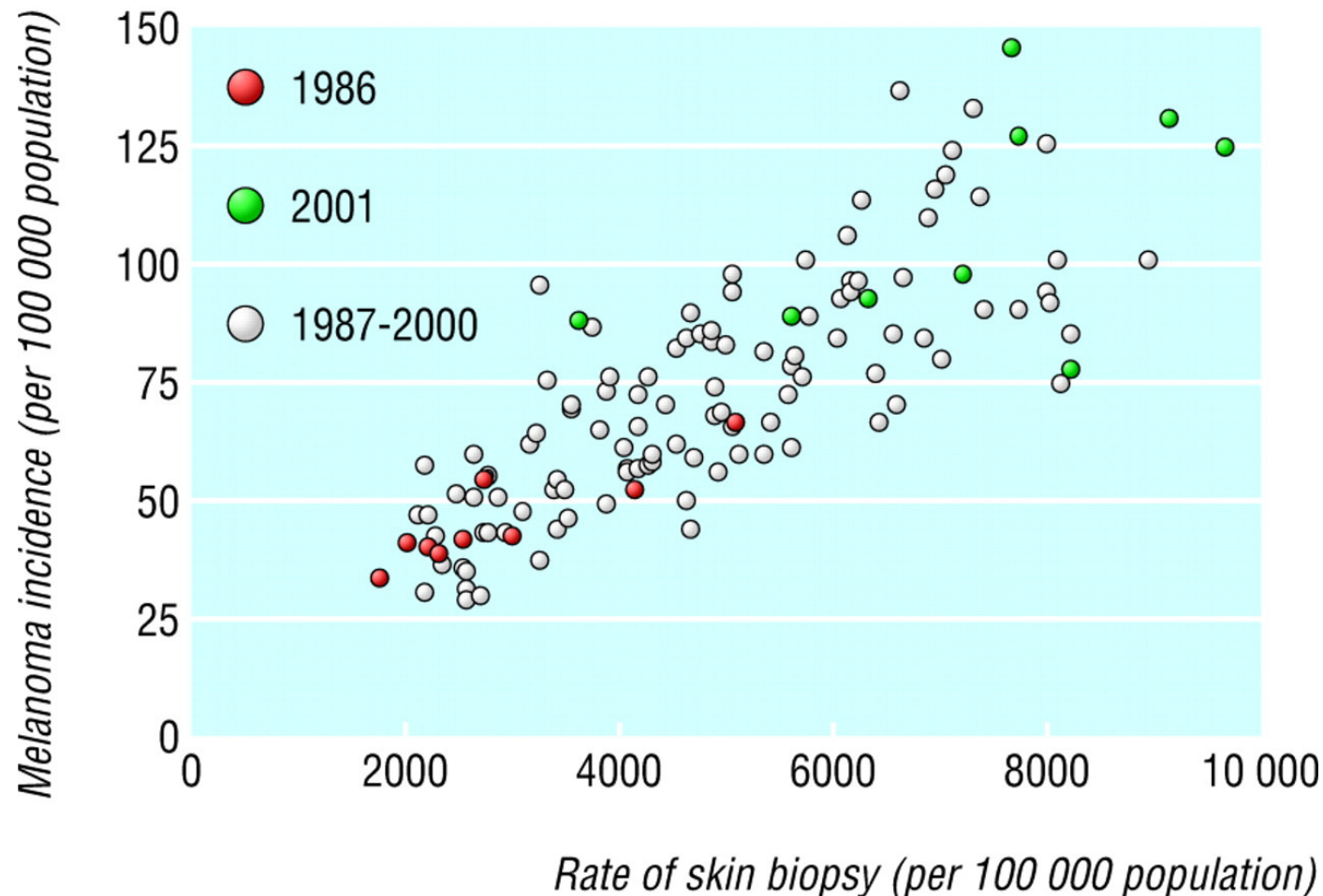
# Does overdiagnosis really happen?



**Fig 1 Incidence of melanoma and mortality in population aged 65 and older residing in one of nine US areas participating in Surveillance Epidemiology and End Results programme, 1986-2001. Early stage refers to in situ and local disease; late stage refers to regional and distant disease**



**Fig 2 Scatterplot of annual rate of skin biopsy and incidence of melanoma for residents age 65 and older in each of nine US areas participating in Surveillance Epidemiology and End Results programme, 1986-2001**



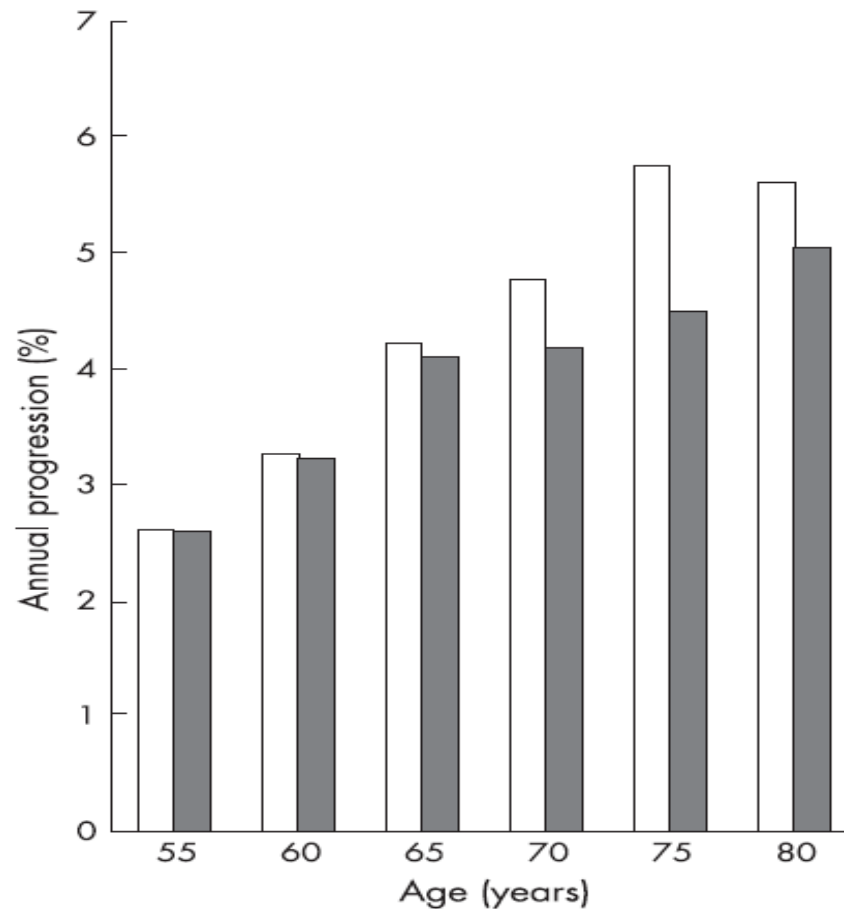
Welch, H G. et al. BMJ 2005;331:481

N. Segnan – CPO 2005



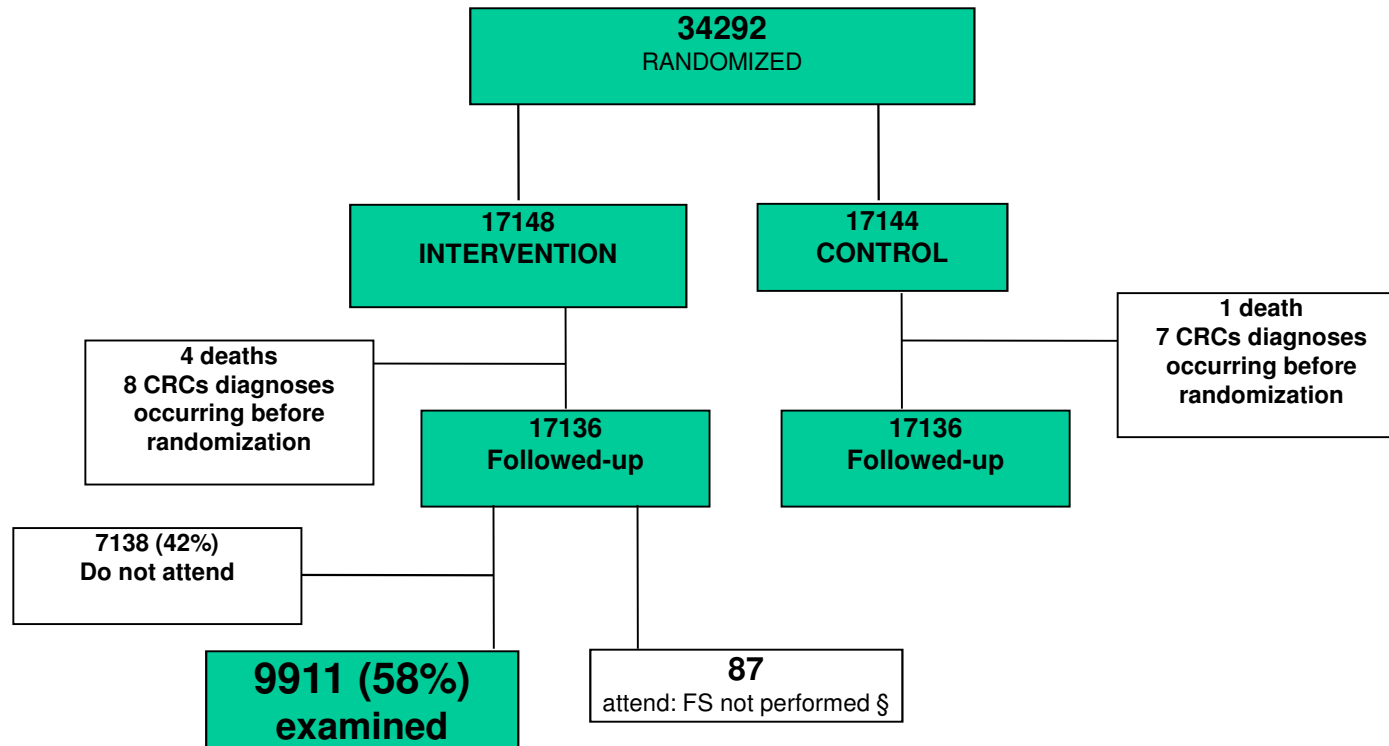
# Projected annual progression of advanced adenomas

H. Brenner *et al.* Gut 2007



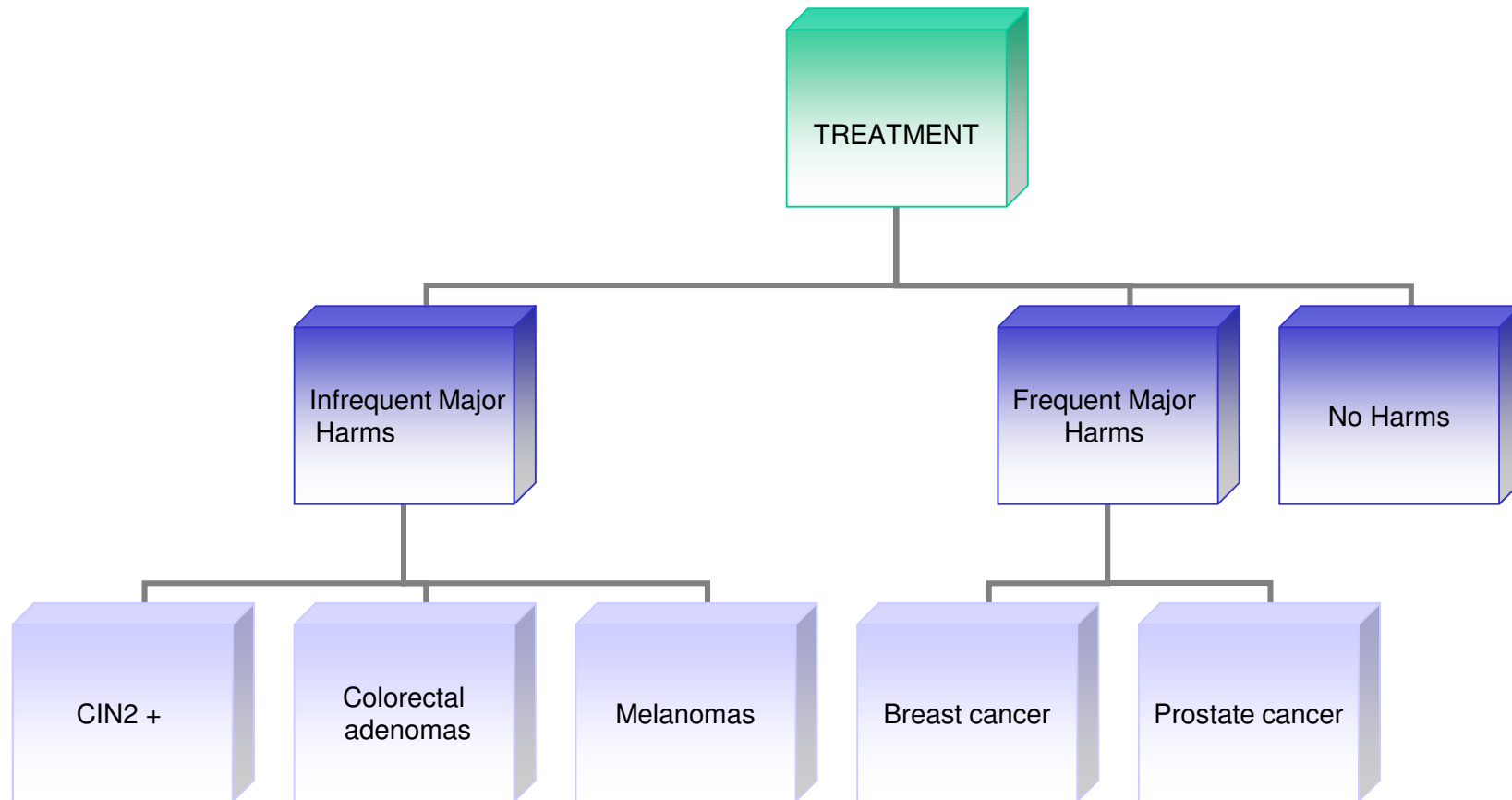
- Advanced adenoma:
  - size: >10mm
  - morphology: tubulovillous or villous
  - pathology: high grade dysplasia
- Women: left, white columns
- Men: right, grey columns

## SCORE Trial profile-2



§ 1 patient who refused to repeat the FS following inadequate preparation, had been diagnosed with a CRC prior to randomization. He was therefore excluded from the follow-up analysis.

# Overdiagnosis and treatment



# **FOLLOW-UP**

Participants were followed-up until

31/12/2007 for incidence

31/12/2008 for mortality

Median follow-up time to death, emigration, or end of follow-up:

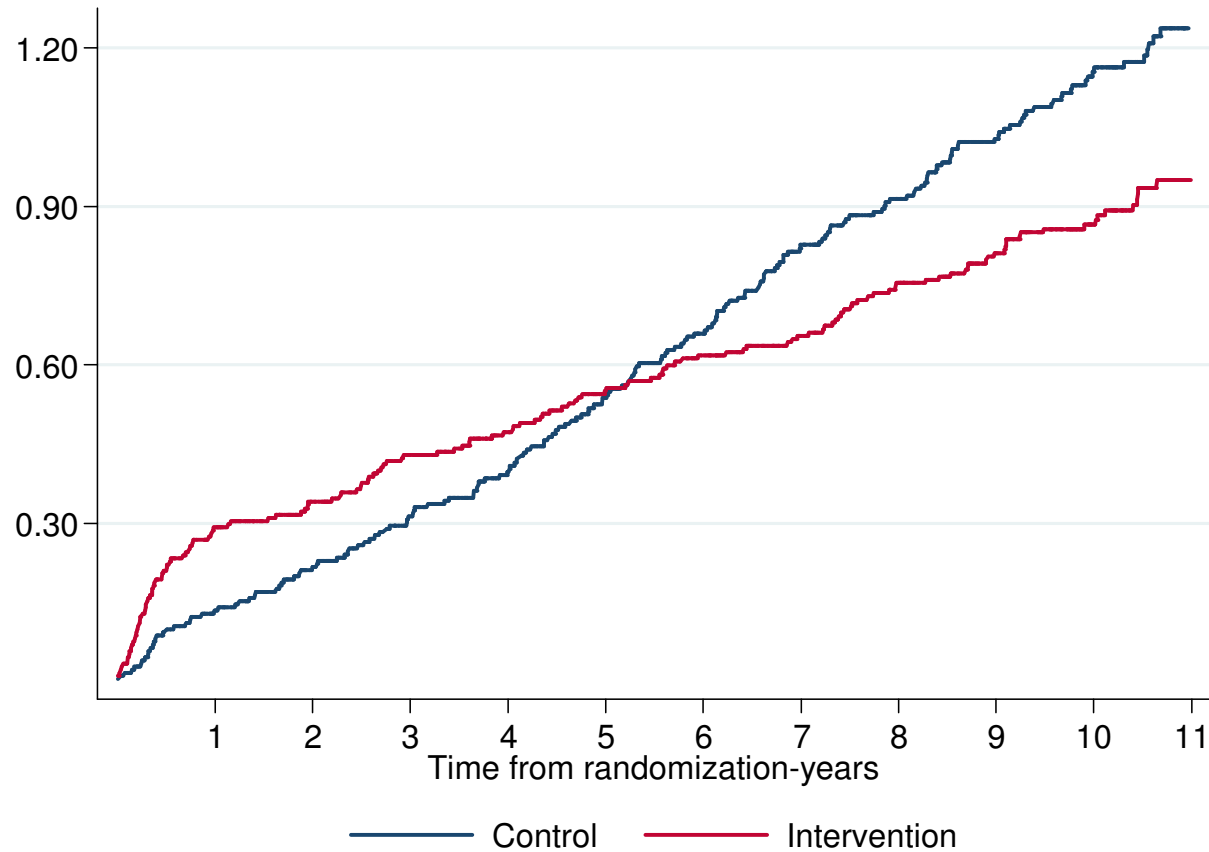
**10.5 years (IQR=9.9-11.3) for incidence**

**11.4 years (IQR=10.8-11.9) for mortality**

## Intention to treat analysis-Colorectal cancer

### INCIDENCE, Distal&Descendent

Nelson Aalen Cumulative Hazard (%) by time from randomization

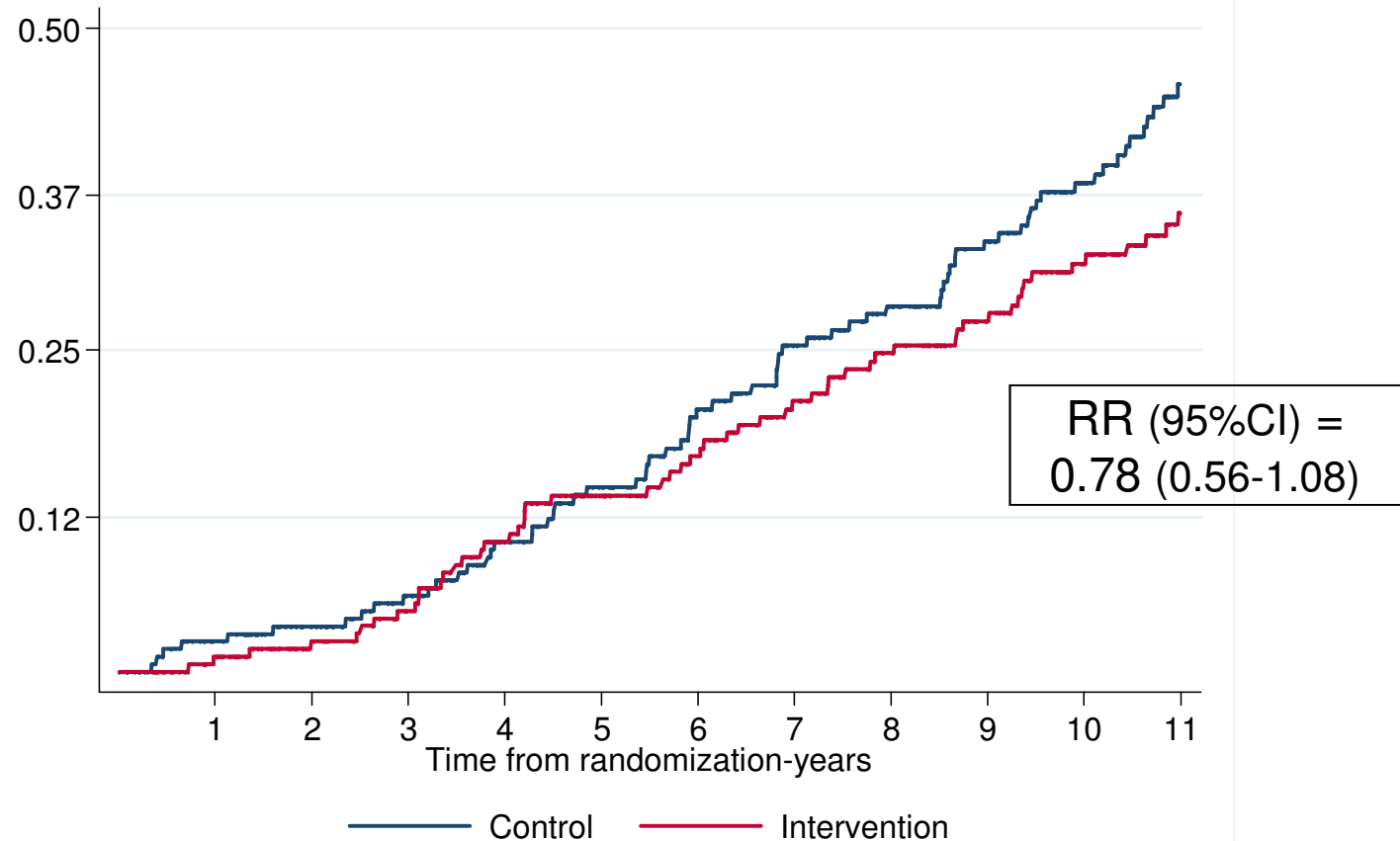


Cumulative Events by years from randomization						
	≤2	≤4	≤6	≤8	≤10	>10
Control	37	67	110	151	187	198
Intervention	58	80	104	126	143	152

# Intention to treat analysis-Colorectal cancer

## MORTALITY, ALL SITES

Nelson Aalen Cumulative Hazard (%) by time from randomization



Cumulative Events by years from randomization						
	≤2	≤4	≤6	≤8	≤10	>10
Control	6	17	34	47	62	83
Intervention	4	17	28	41	52	65

## **Contributing members of the SCORE Working Group:**

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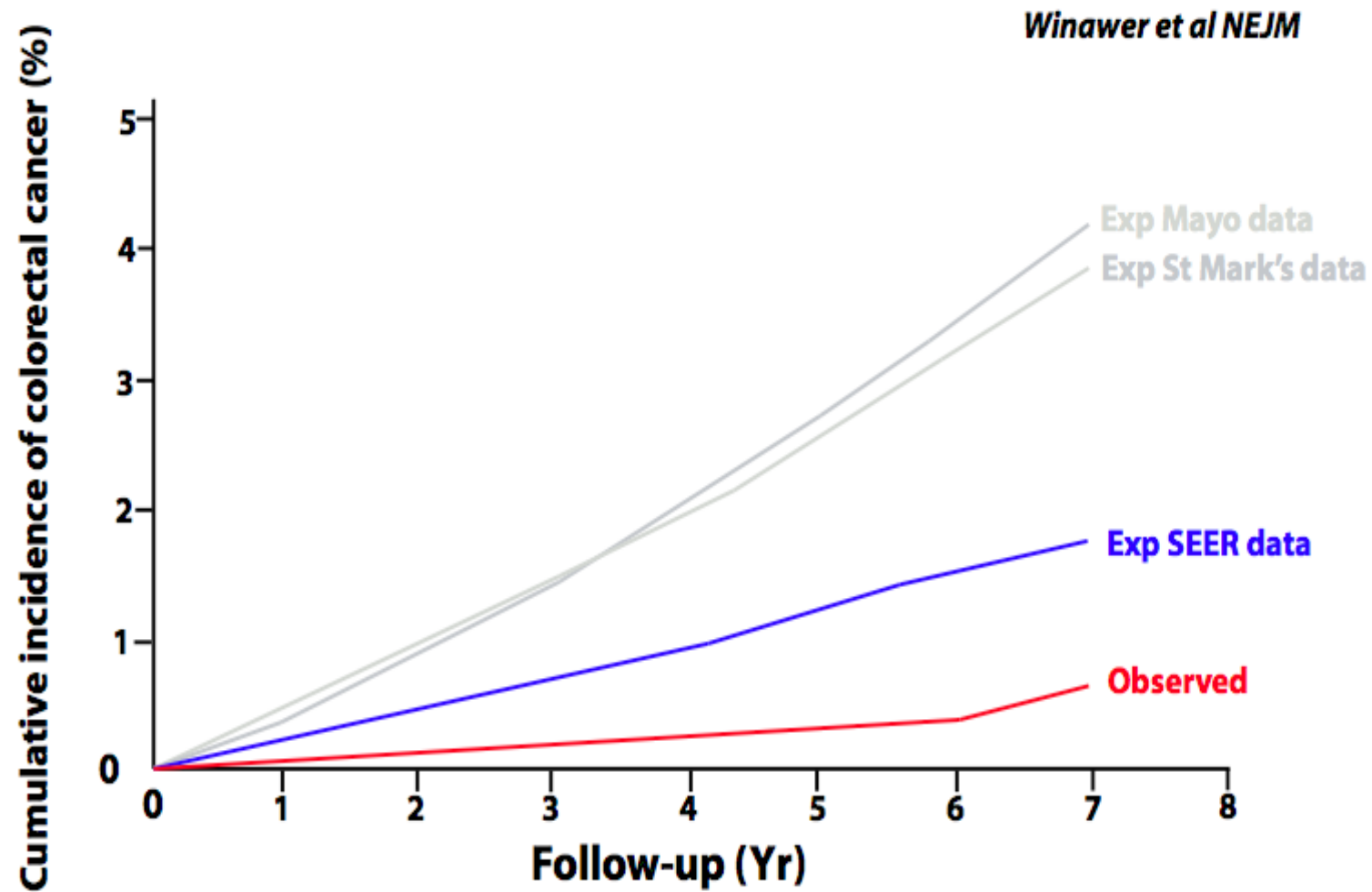
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# National Polyp Study





# Limitations of current biomarker studies

- Some markers are not very reliable (e.g. high interlaboratory variation)
- Biological meaning not always clear (e.g. mutations in plasma DNA)
- Long gap between marker development and its validation
- Time relationships between exposure, marker measurement, disease
- Usually only one spot biosample available (little is known on intra-individual variation)
- Little is known on potential confounders