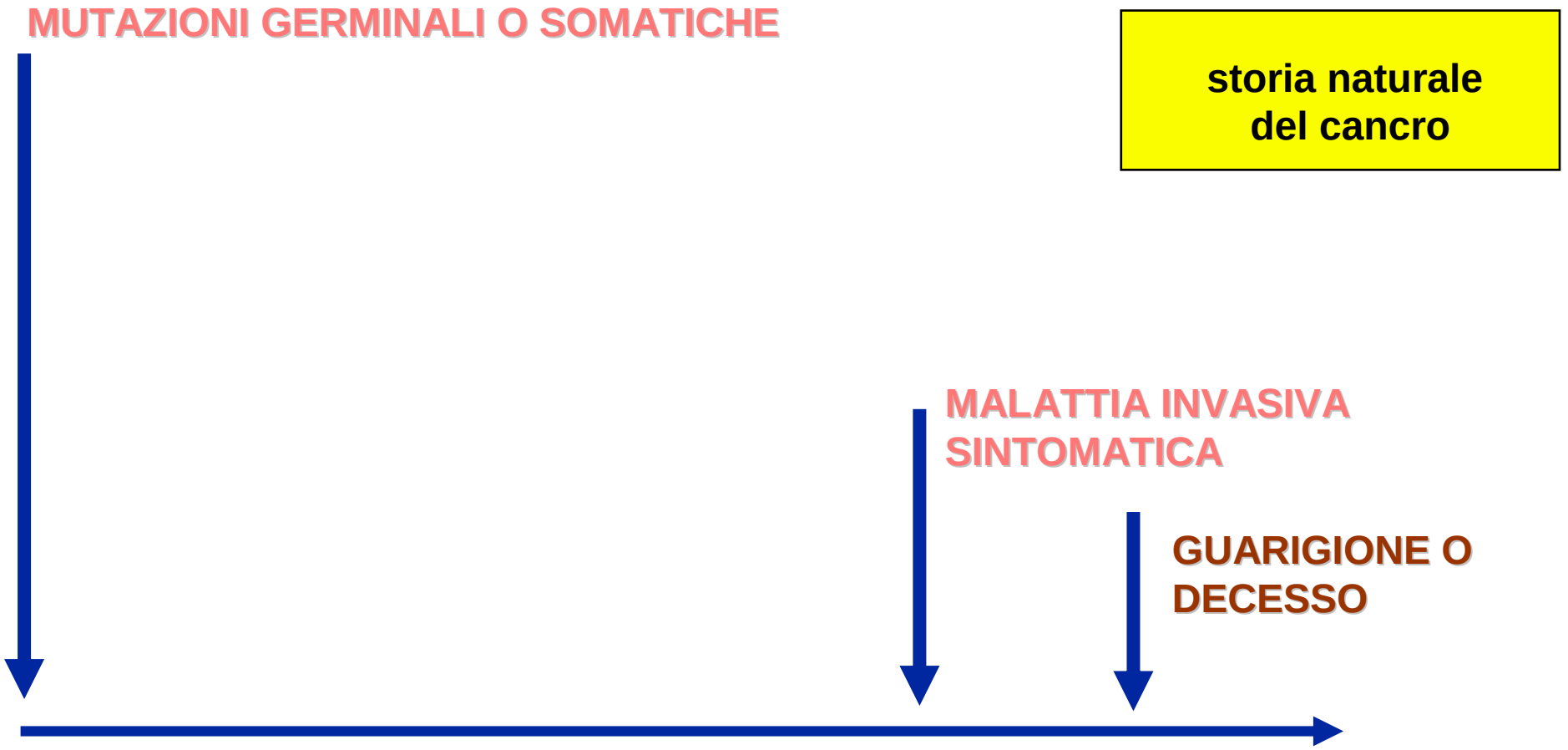
Screening del cancro colorettale e introduzione di nuove tecnologie

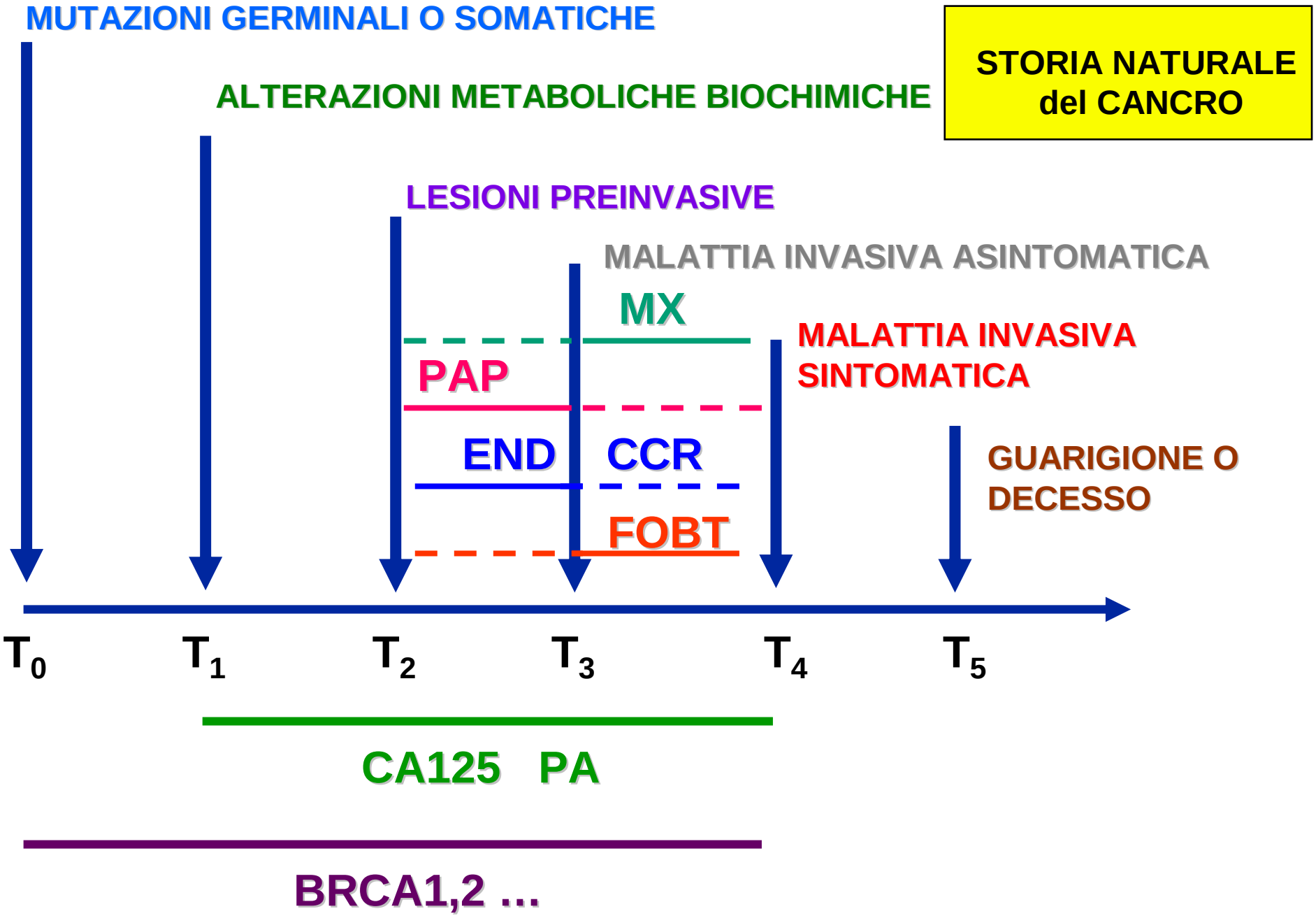
Nereo Segnan

CPO Piemonte e Azienda Ospedaliero Città della Salute e della Scienza - Torino

Torino, 9 0ttobre 2012



Eventi a livello genetico determinano stati (fasi , stadi) nel processo di progressione neoplastica


MUTAZIONI GERMINALI O SOMATICHE
STORIA NATURALE del CANCRO
ALTERAZIONI METABOLICHE BIOCHIMICHE
LESIONI PREINVASIVE
MALATTIA INVASIVA ASINTOMATICA
MX
PAP
END
CCR
FOBT
MALATTIA INVASIVA SINTOMATICA
GUARIGIONE O DECESSO
T0
T1
T2
T3
T4
T5
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.

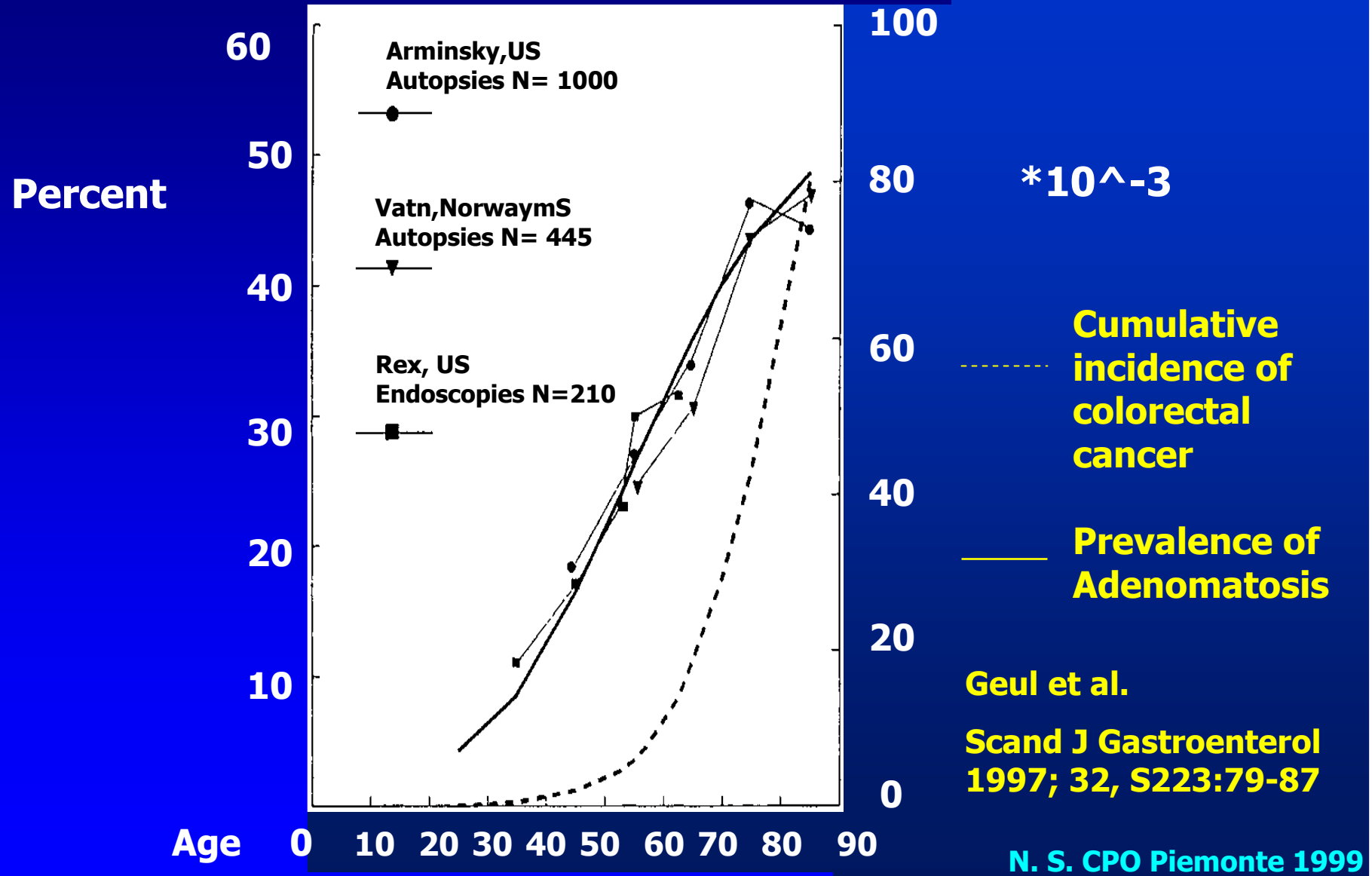
N. Segnan CPO 2001

Effect of using clinical and microscopical detection thresholds in three cancers

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

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

Prevalence of adenomatosis and cumulative incidence of colorectal cancer

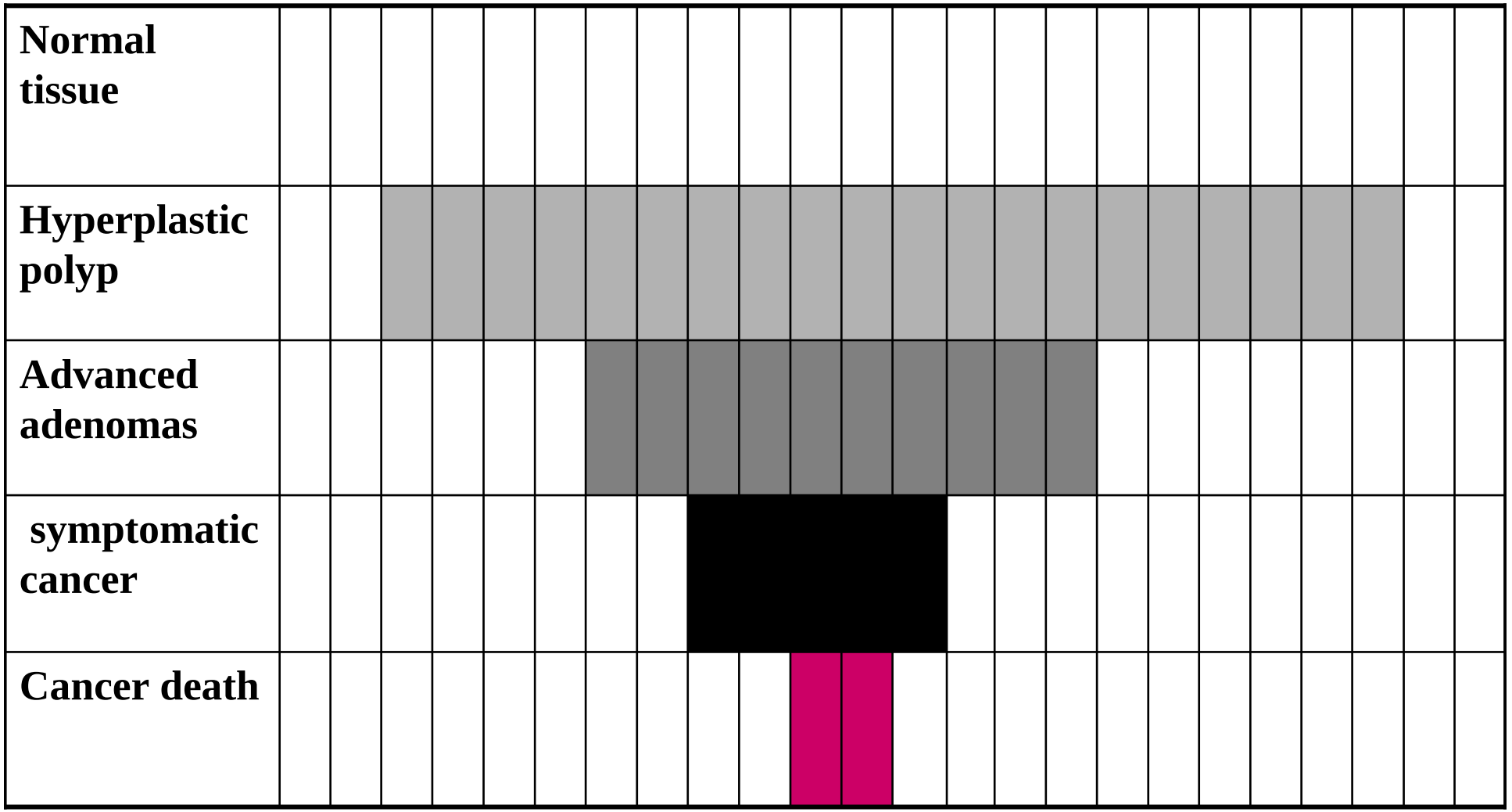


Geul et al.

Scand J Gastroenterol 1997; 32, S223:79-87

N. S. CPO Piemonte 1999

Progression of CRC

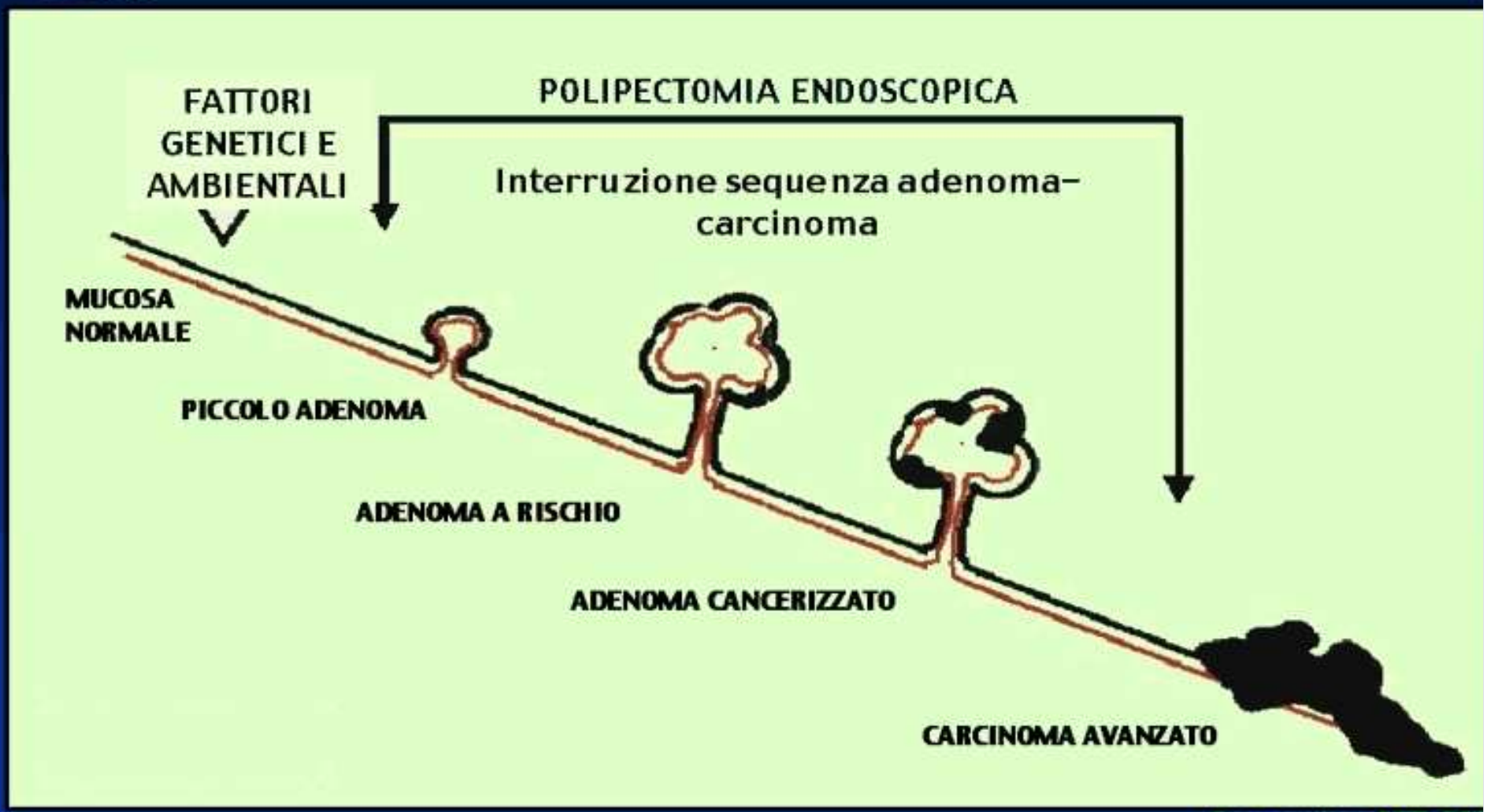


Dwelling time ADENOMA ➔ CARCINOMA

Estimate of dwelling time :

- Wagner (1995): 5-10 yrs
- Eddy (1990) from 1cm to CRC: 7 yrs
- Atkin (1993) 10 - 35 yrs
- Knigth (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

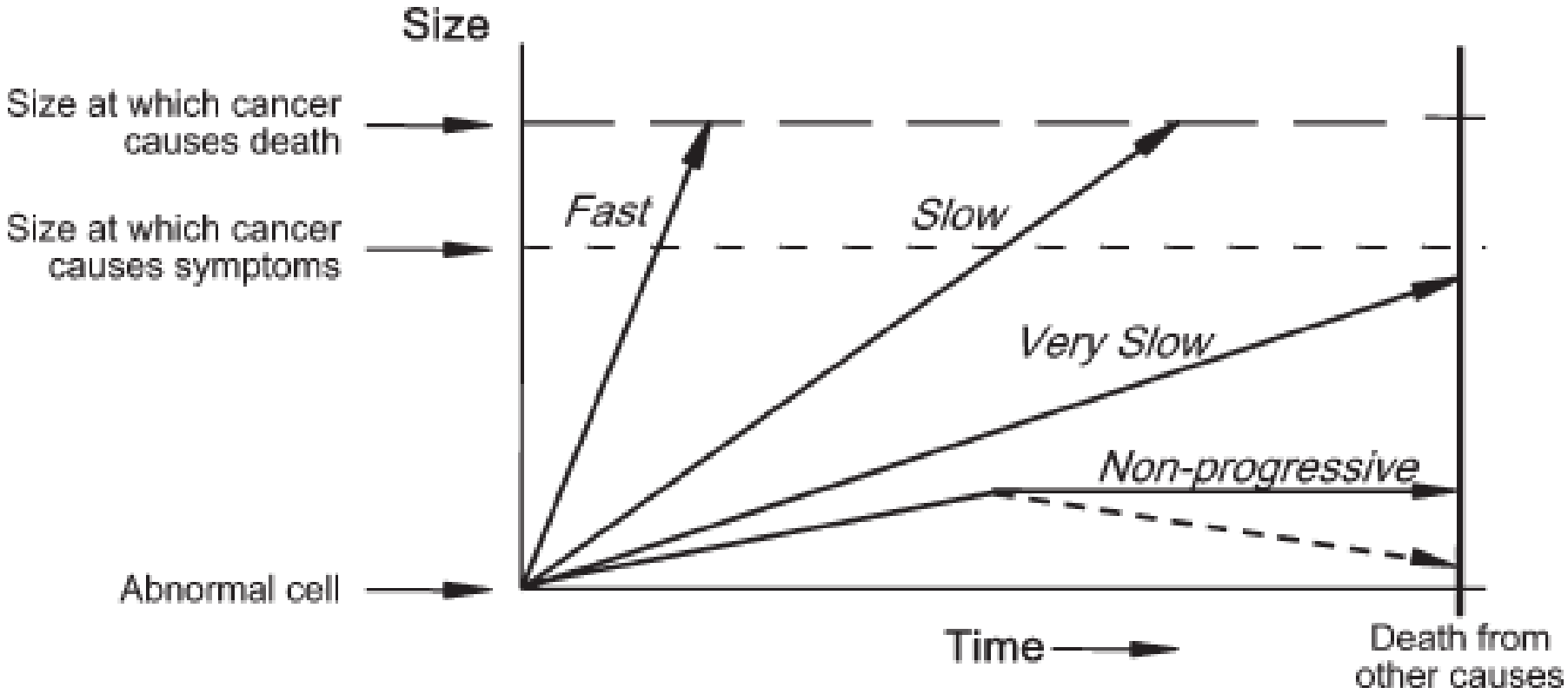
N. Segnan CPO 2001

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).

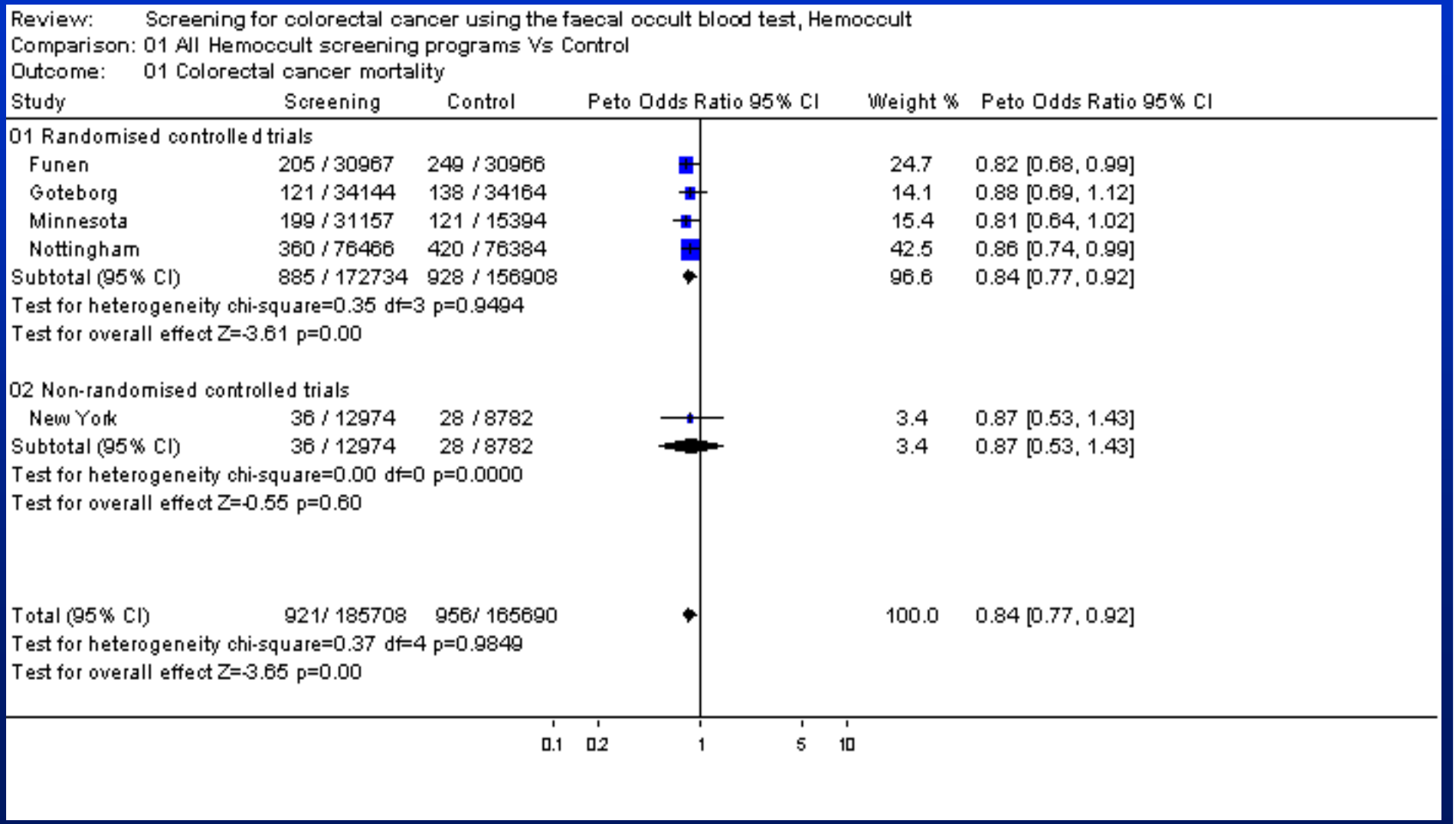


Meta-analisi degli studi sperimentali (RCT) che hanno utilizzato il FOBT (Hemoccult)

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

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



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

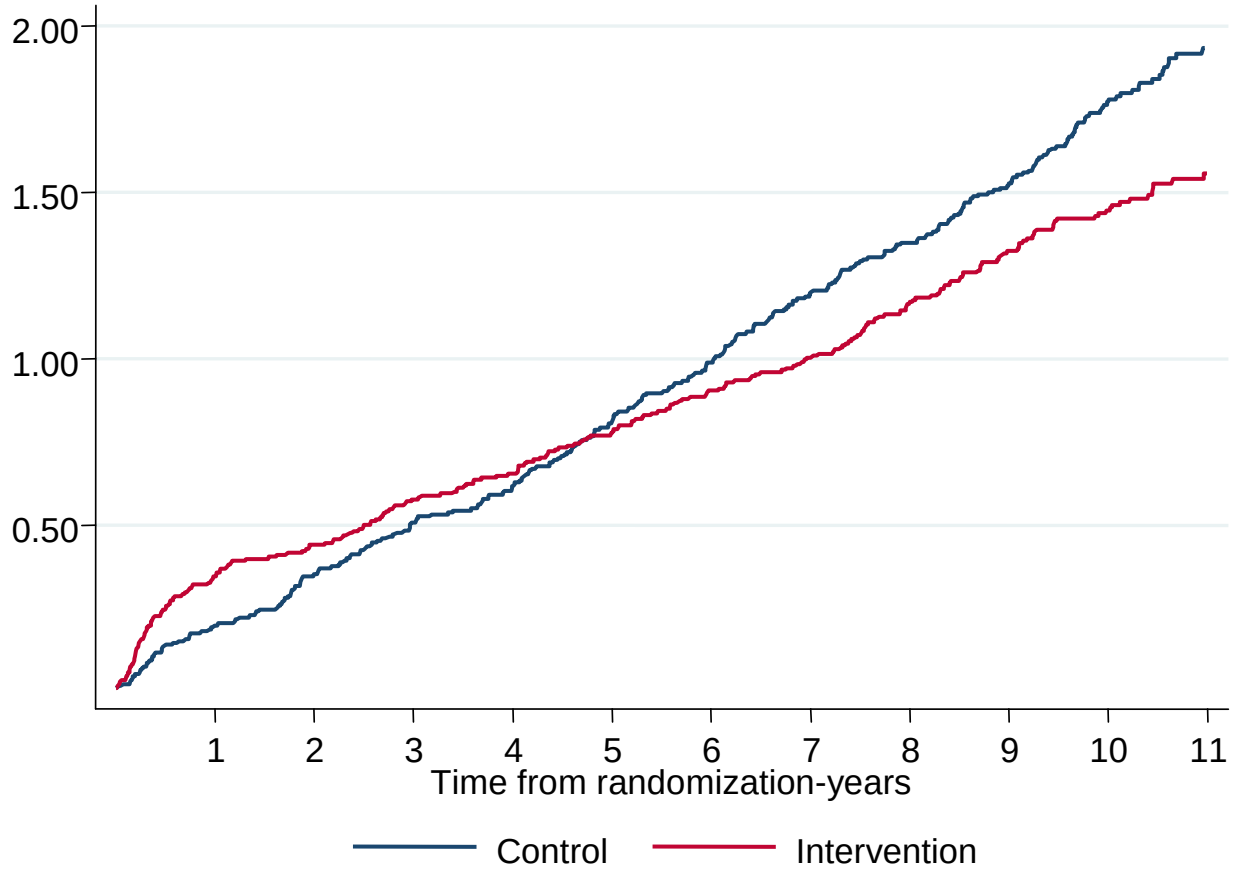
JNCI 2011 Sep 7;103(17):1310-22. Epub 2011 Aug 18.

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 Giacomin, 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



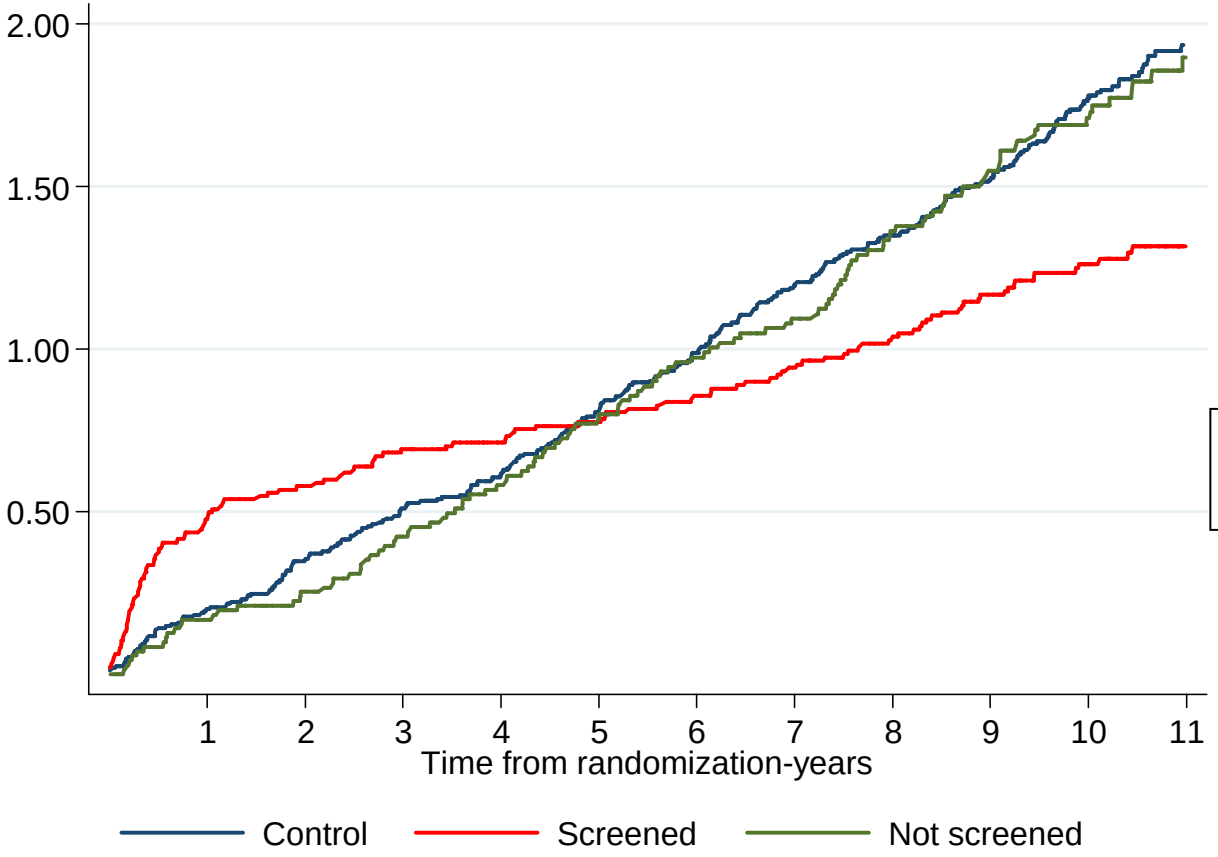
RR (95%CI) = 0.82 (0.69-0.96)

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



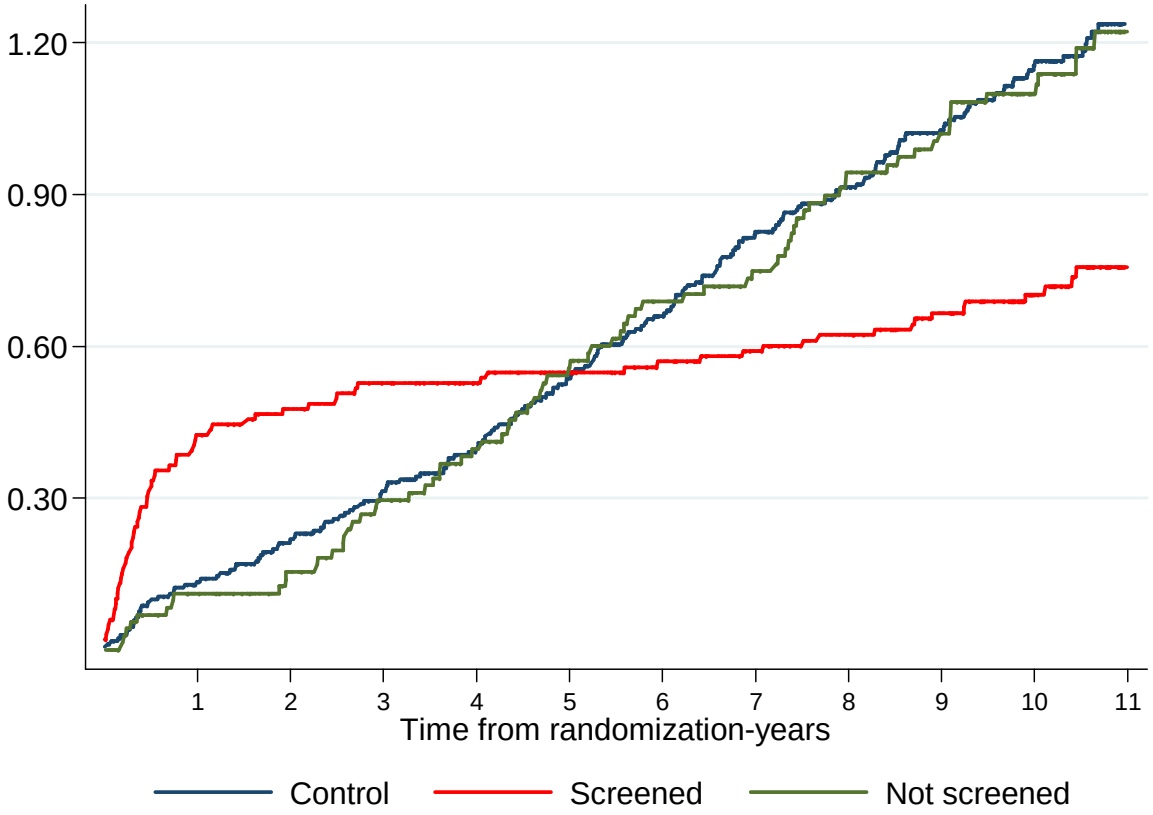
RR (95%CI) = 0.69 (0.56-0.86)

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



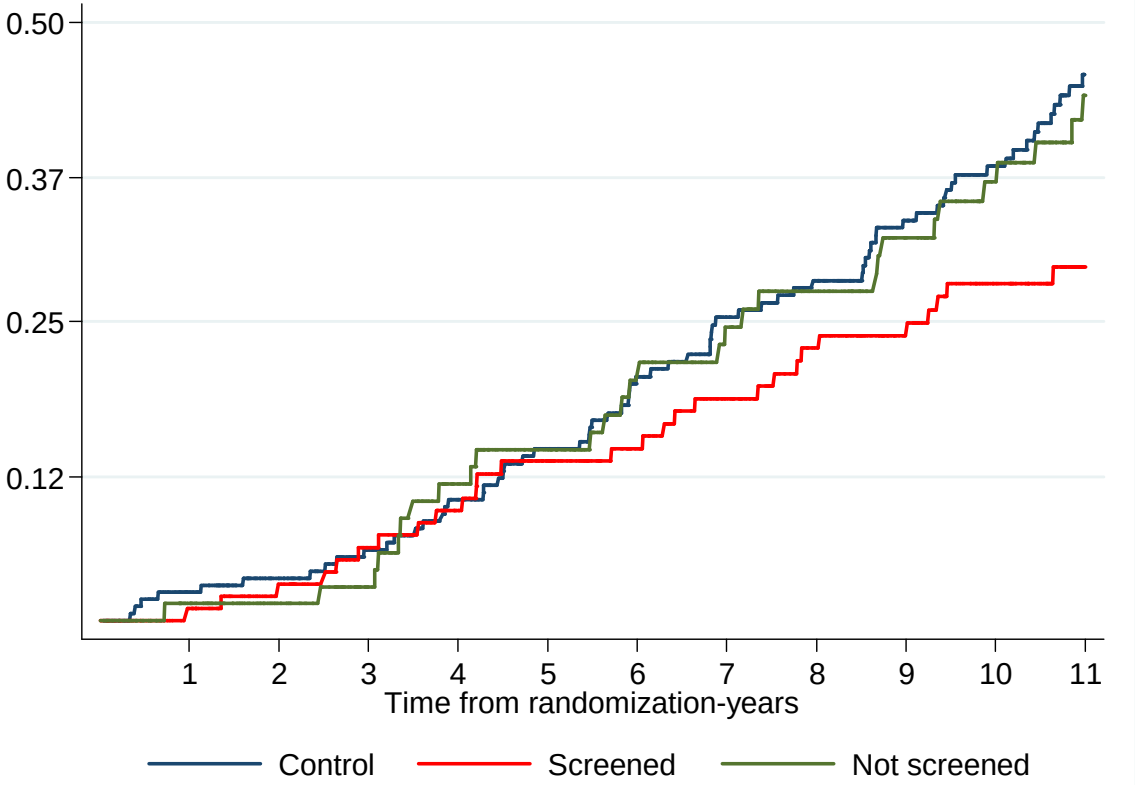
RR (95%CI) = 0.60 (0.46-0.80)

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



RR (95%CI) = 0.62 (0.40-0.96)

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

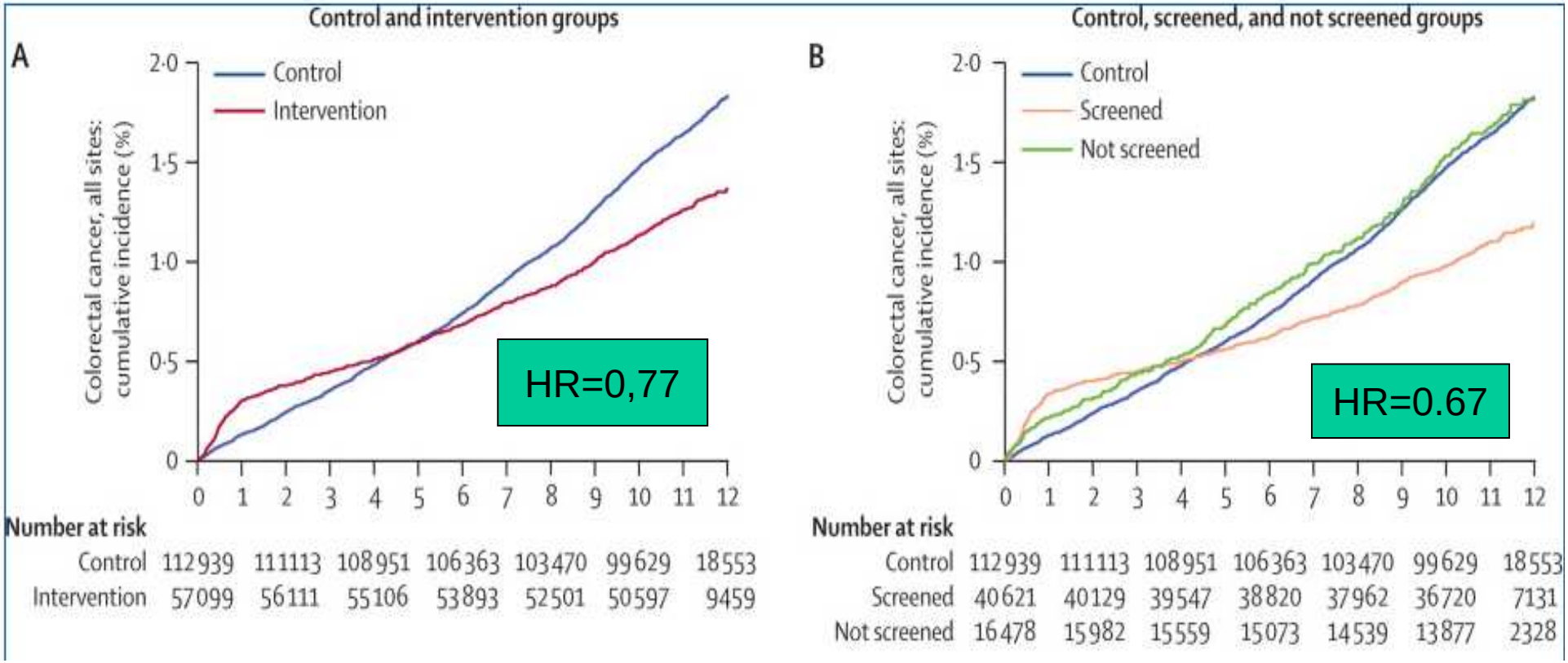
Lancet 2010; 375: 1624-33
Published Online April 28, 2010
DOI:10.1016/S0140-6736(10)60551-X
See Comment page 1582

Summary

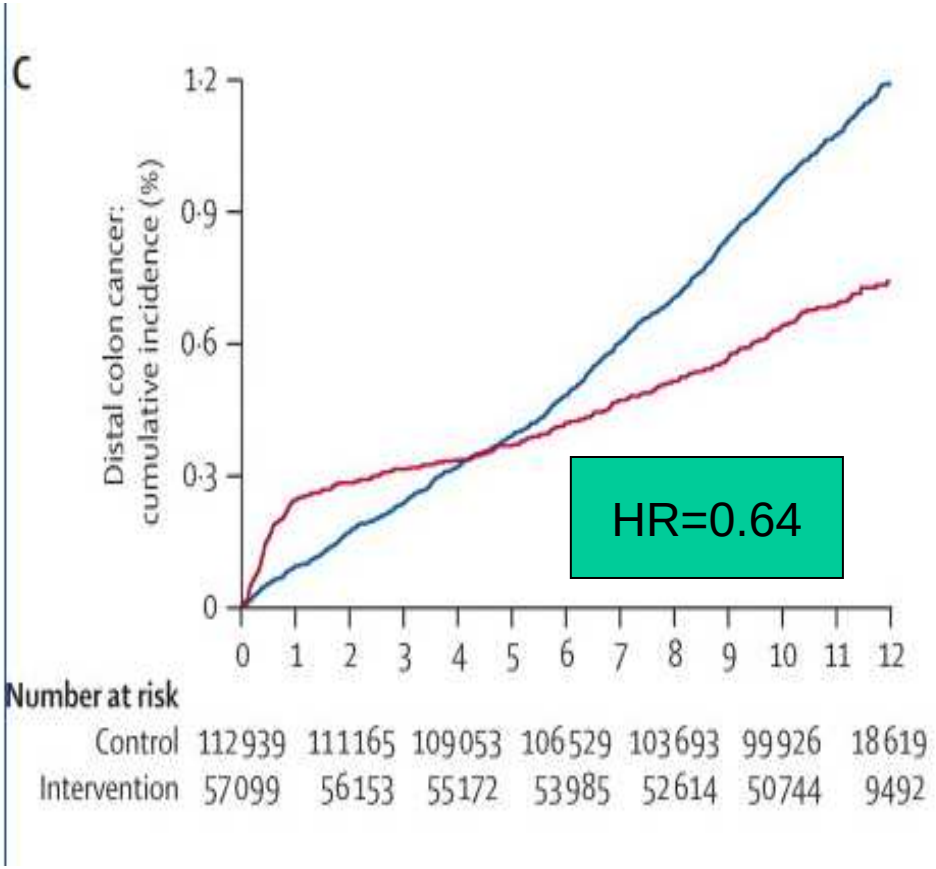
Background Colorectal cancer is the third most common cancer worldwide and has a high mortality rate. We tested the hypothesis that only one flexible sigmoidoscopy screening between 55 and 64 years of age can substantially reduce colorectal cancer incidence and mortality.

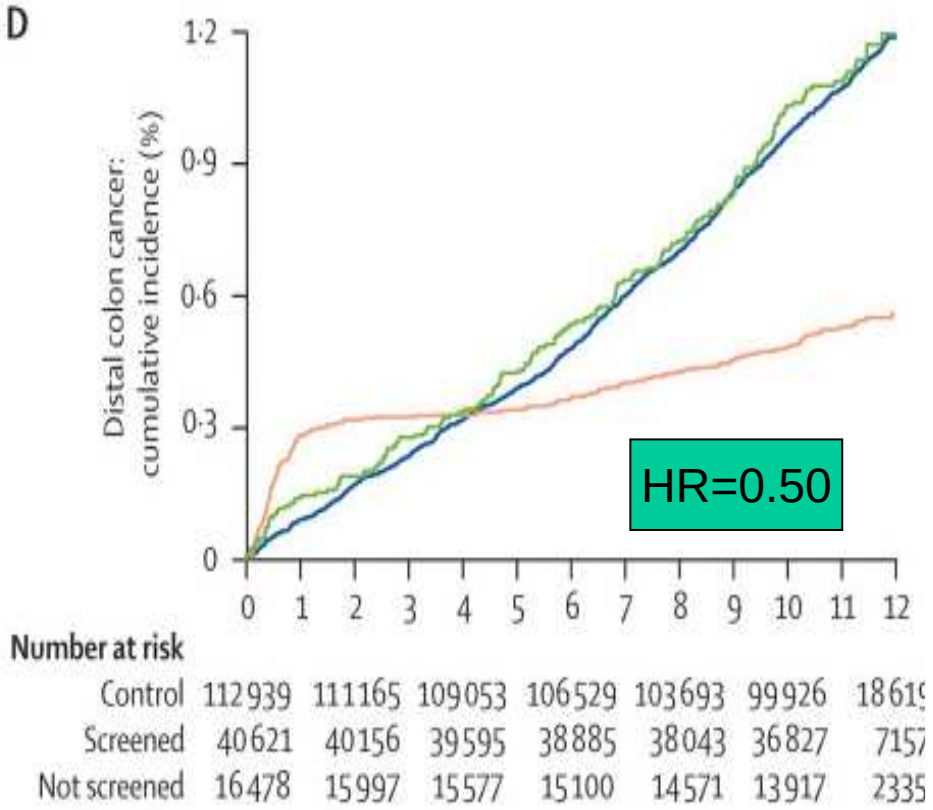
Methods This randomised controlled trial was undertaken in 14 UK centres. 170 432 eligible men and women, who had indicated on a previous questionnaire that they would accept an invitation for screening, were randomly allocated

Colorectal cancer incidence (Kaplan-Meier estimates)

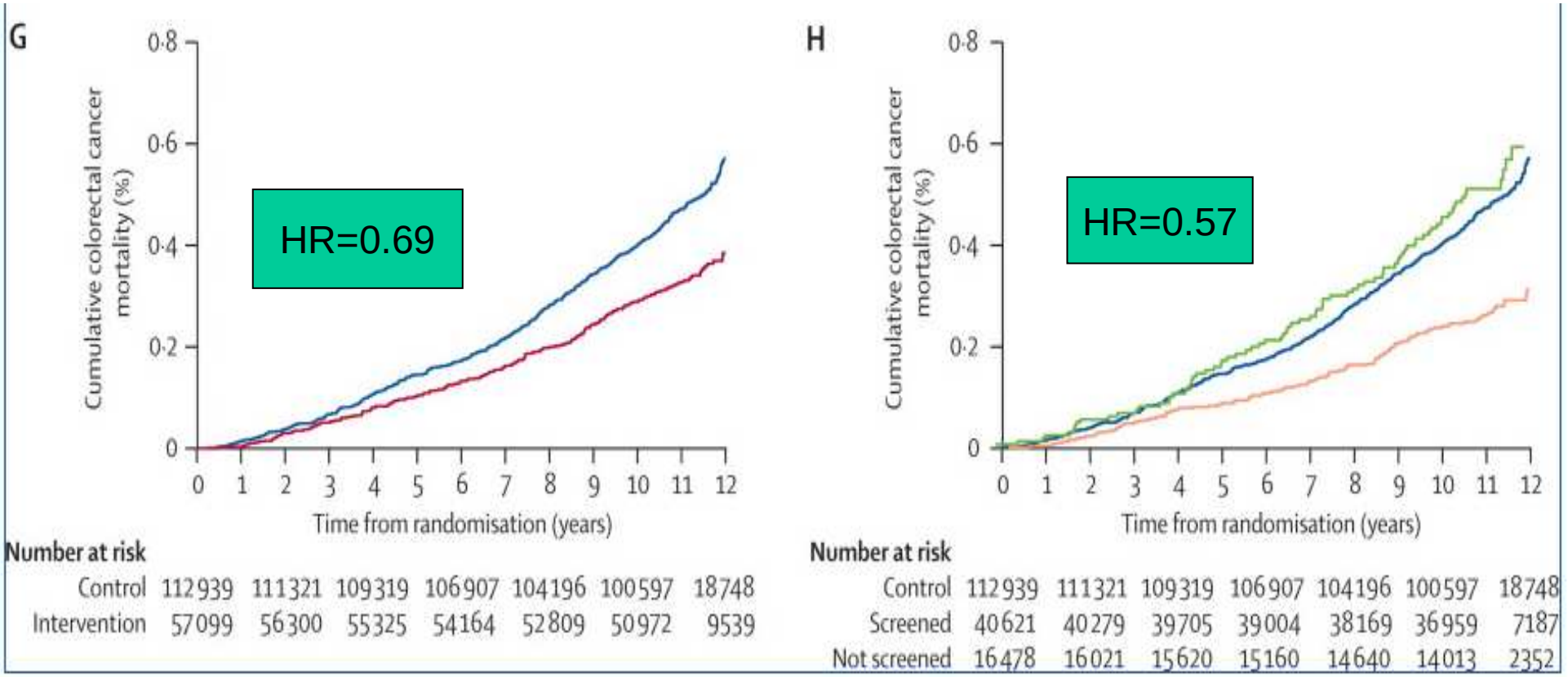


Distal cancer incidence (Kaplan-Meier estimates)



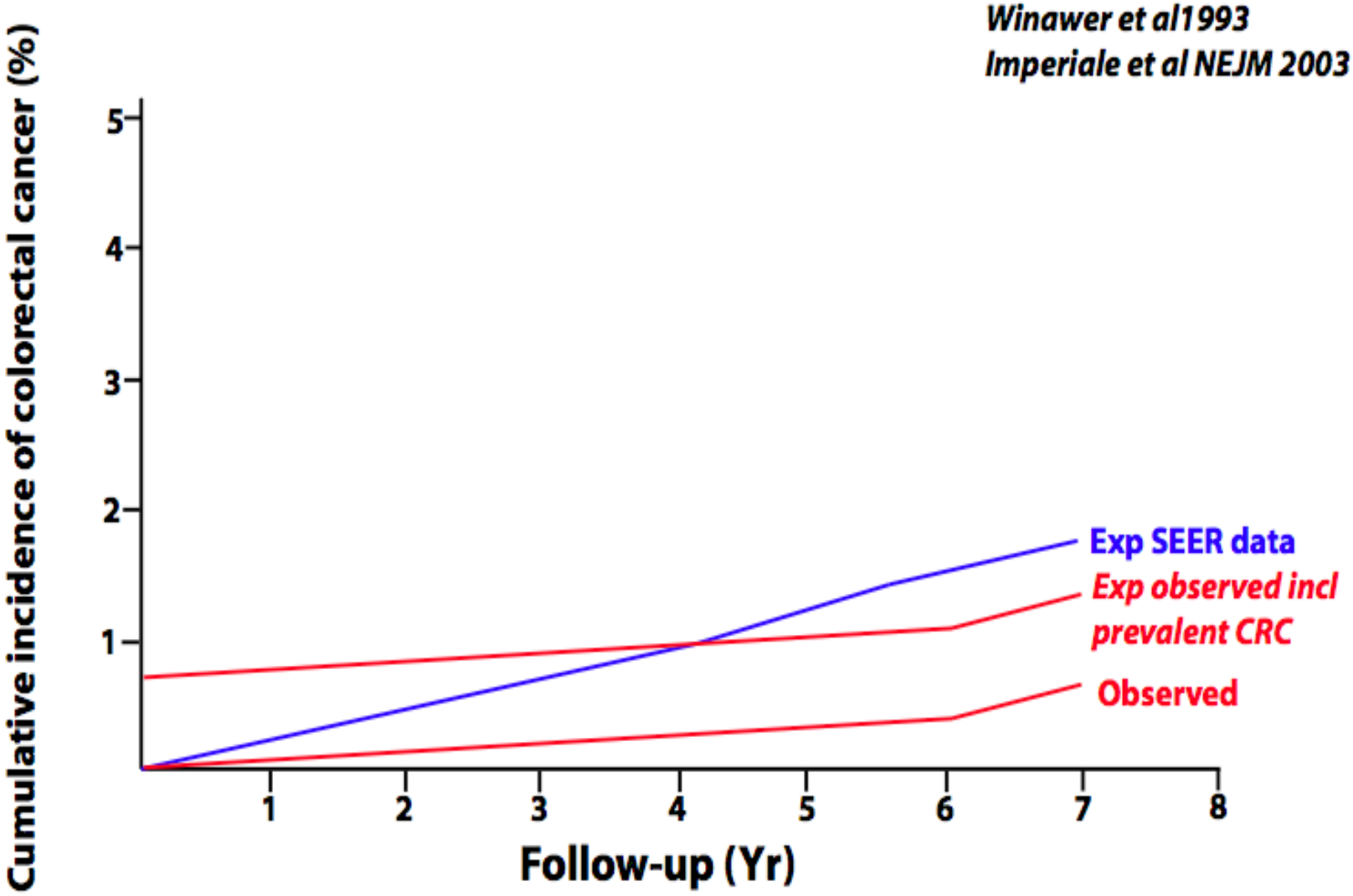


Colorectal cancer mortality (Kaplan-Meier estimates)



Cumulative incidence CRC in National Polyp Study

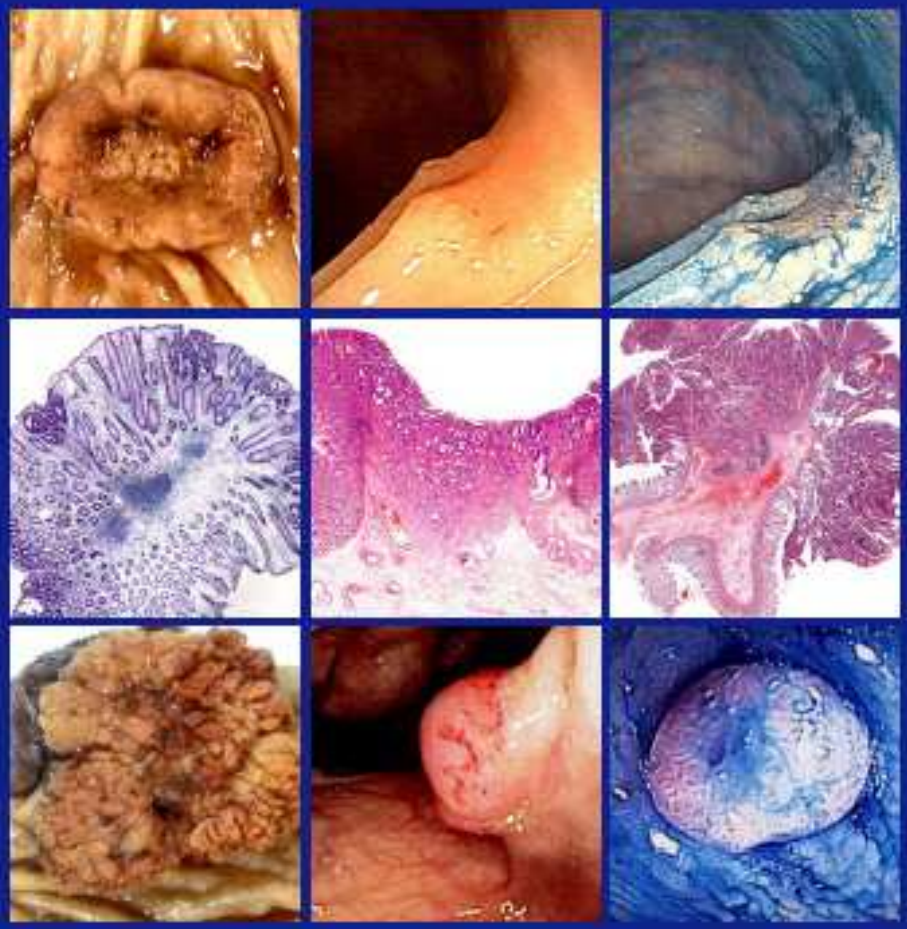
… *adjusting for prevalent cancers*



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

European Partnership Action Against Cancer

European guidelines for quality assurance in colorectal cancer screening and diagnosis

First Edition

Editors
N. Segnan
J. Patnick
L. von Karsa

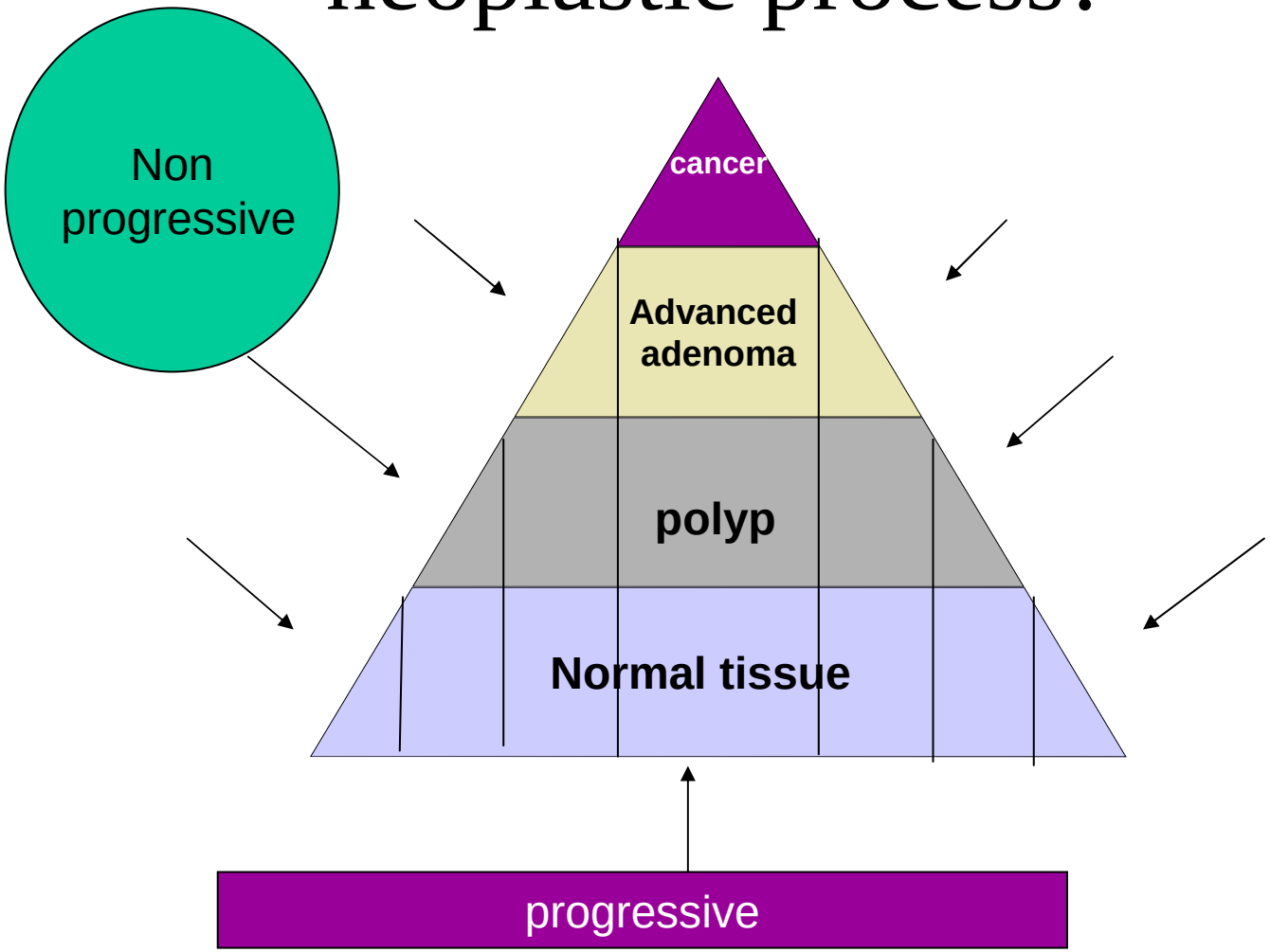
Livello di evidenza linee guida europee

FOBT I

Sigmoidoscopia II

Colonscopia III

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



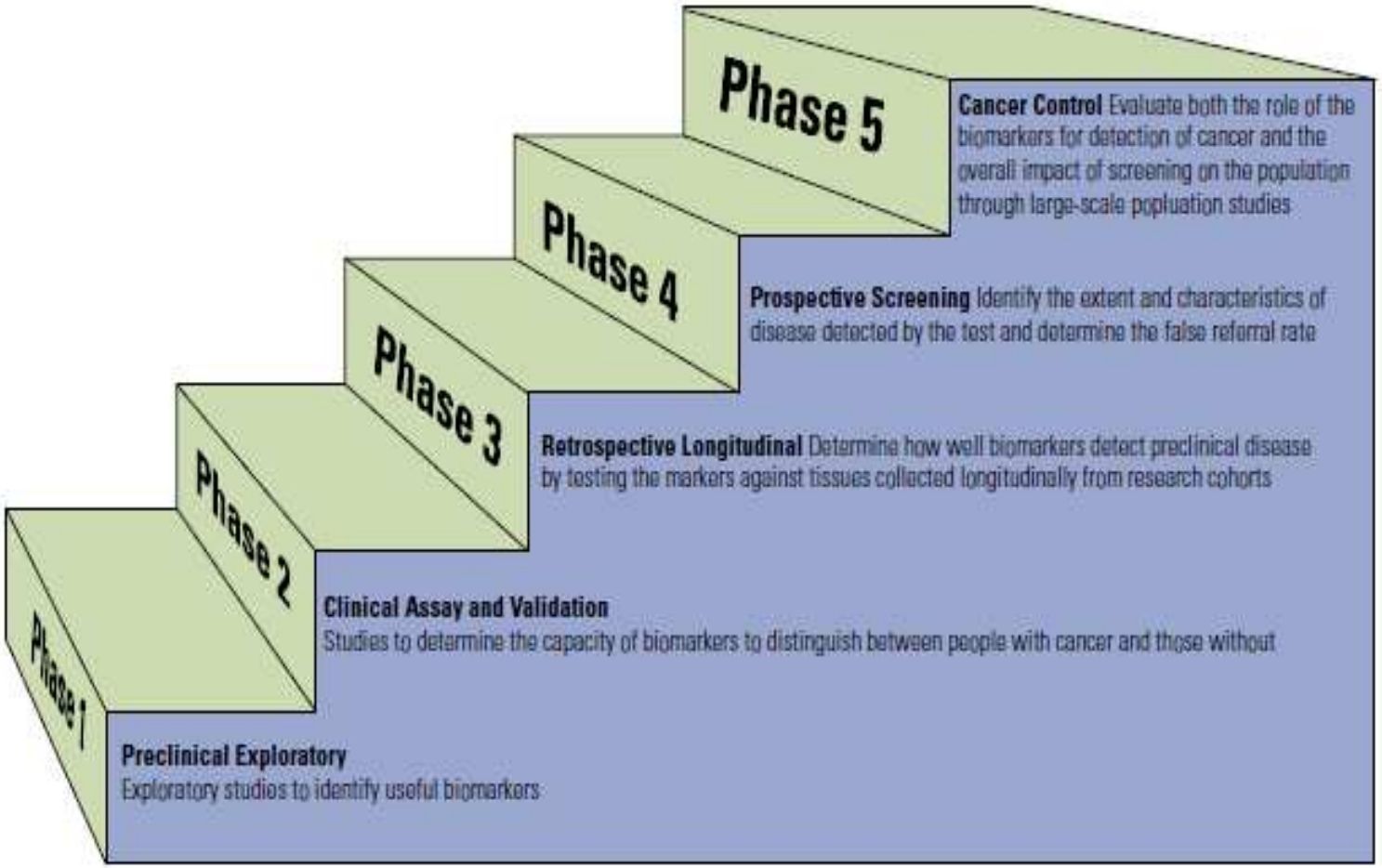
National Cancer Institute

Division of Cancer Prevention

The Early Detection Research Network

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

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



Source: *Journal of the National Cancer Institute* 93, 1054-1061, 2001

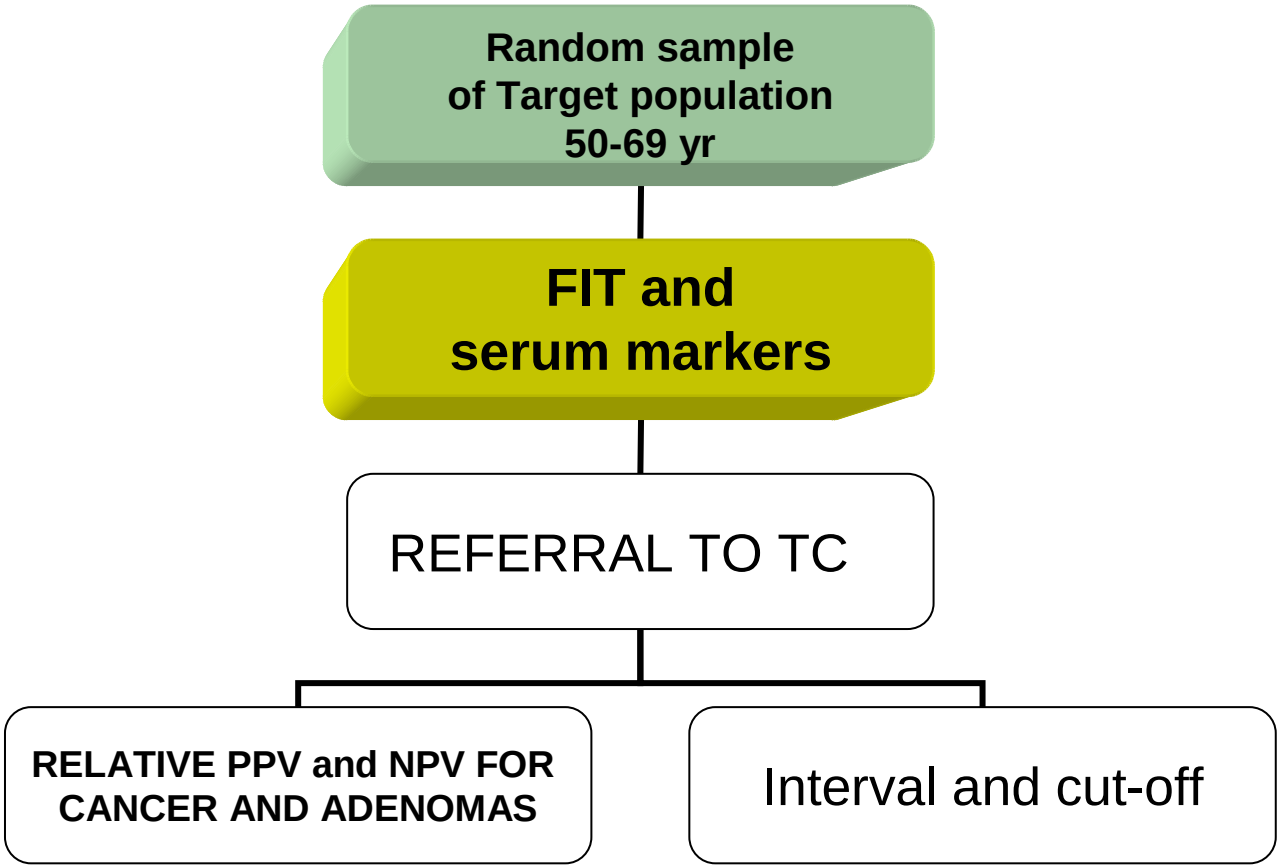
Candidate Colorectal Cancer Biomarkers

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 Guiac)	→	→	→	→	
Flat adenoma (Tissue)	→	→			
GOS (Stool)	→	→	→	→	
Galectin-3 Lig (Serum)	→	→	→	→	
TIMP-1 (Serum)	→	→	→	→	

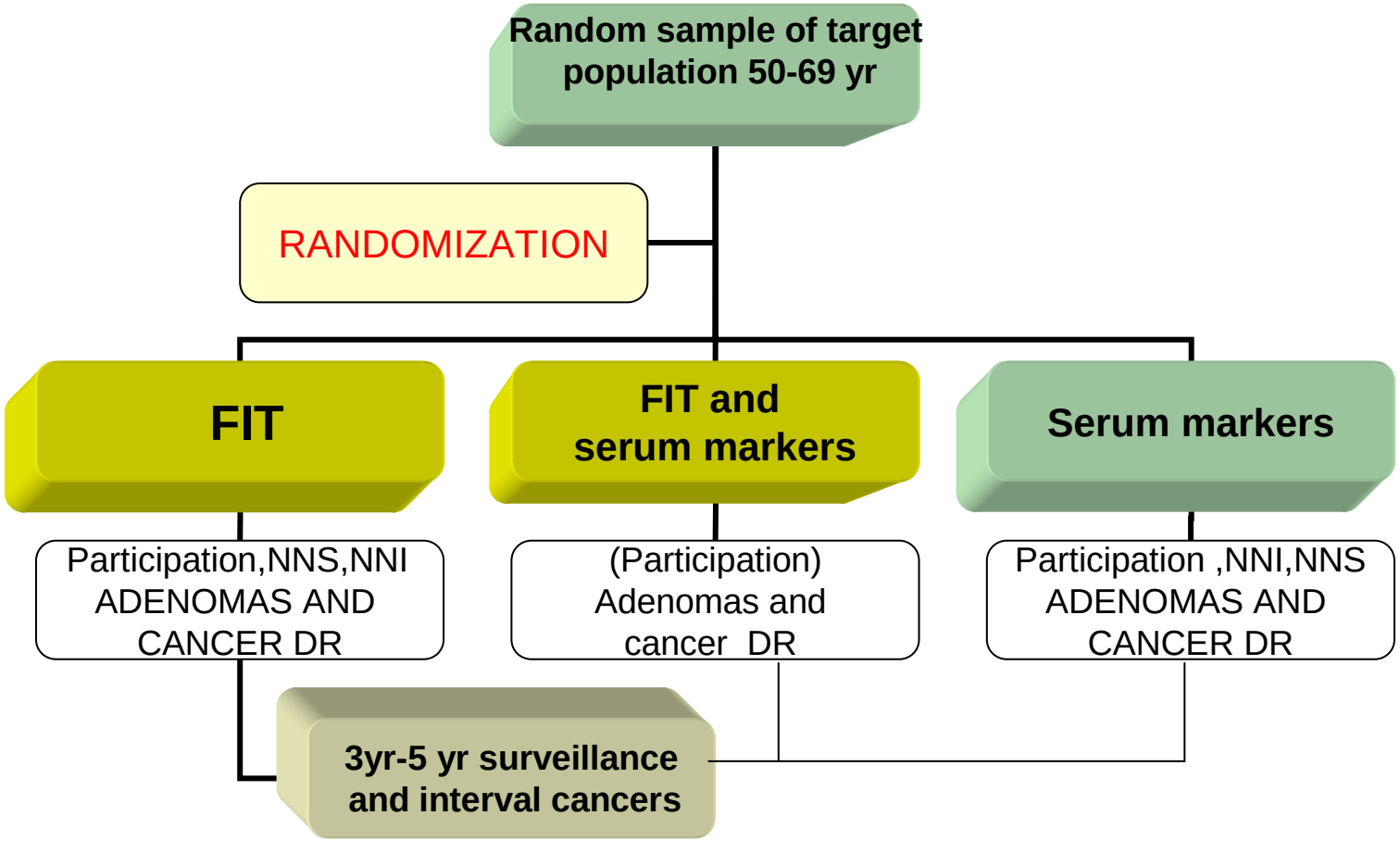
Table 1. Noninvasive molecular biomarkers for the detection of CRC

Analyte	Subject
Fecal hemoglobin	Stool
K-*ras*	Stool
APC	Stool
L-DNA	Stool
p53	Stool
CEA	Serum
CA19.9	Serum
TIMP-1	Serum
Spondin-2, DcR3, Trail-R2, Reg IV, MIC 1	Serum
PSME3	Serum
NNMT	Serum
CRMP-2	Serum
SELDI (apolipoprotein C1, C3a-desArg, alpha1-antitrypsin, transferrin)	Serum
HNP 1-3	Serum
MIF	Serum
M-CSF	Serum
M2-PK	Serum
Prolactin	Serum
Septin 9	Plasma

Comparative effectiveness Phase 2



Comparative effectiveness Phase 4



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

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

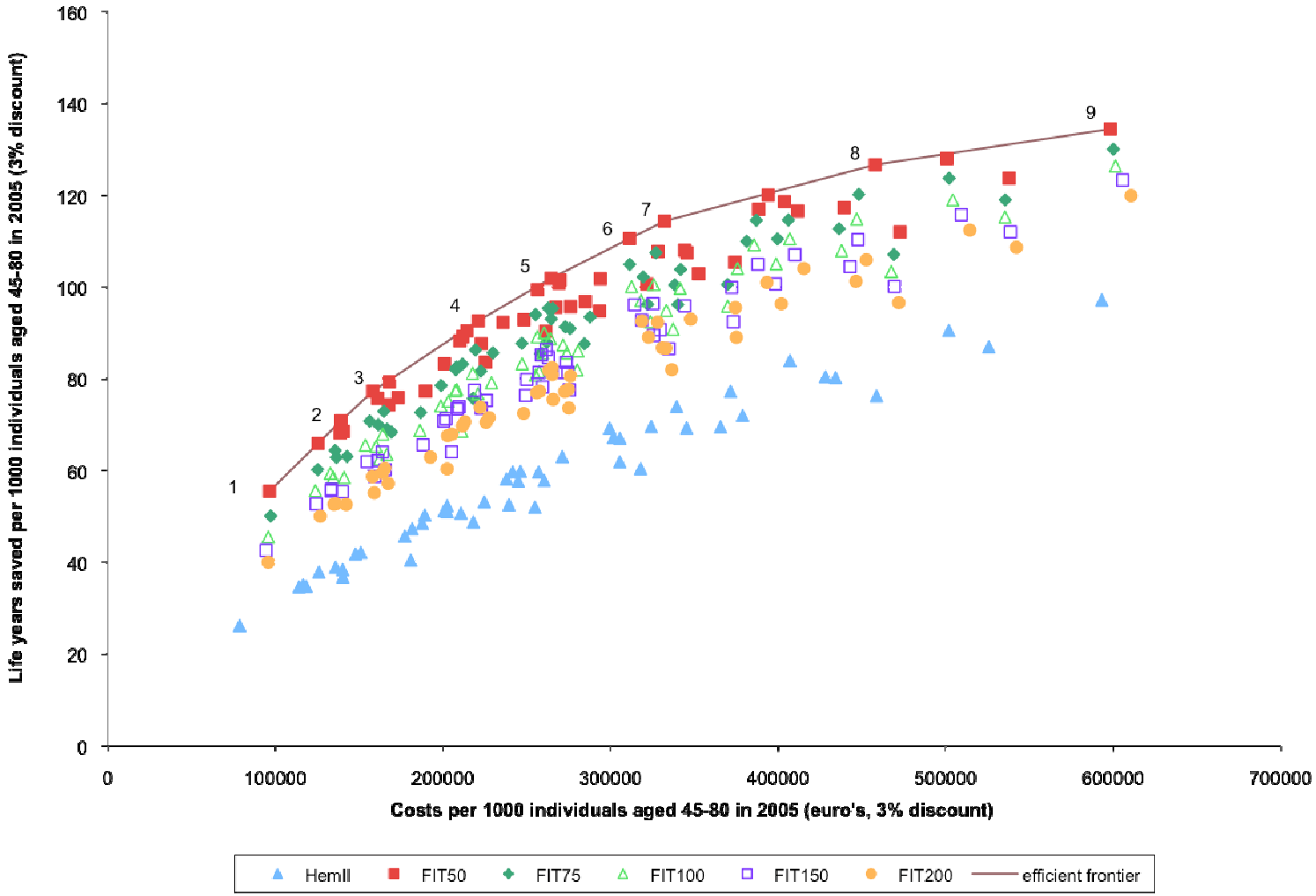
** of those with positive test*

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

CRC prevented cases

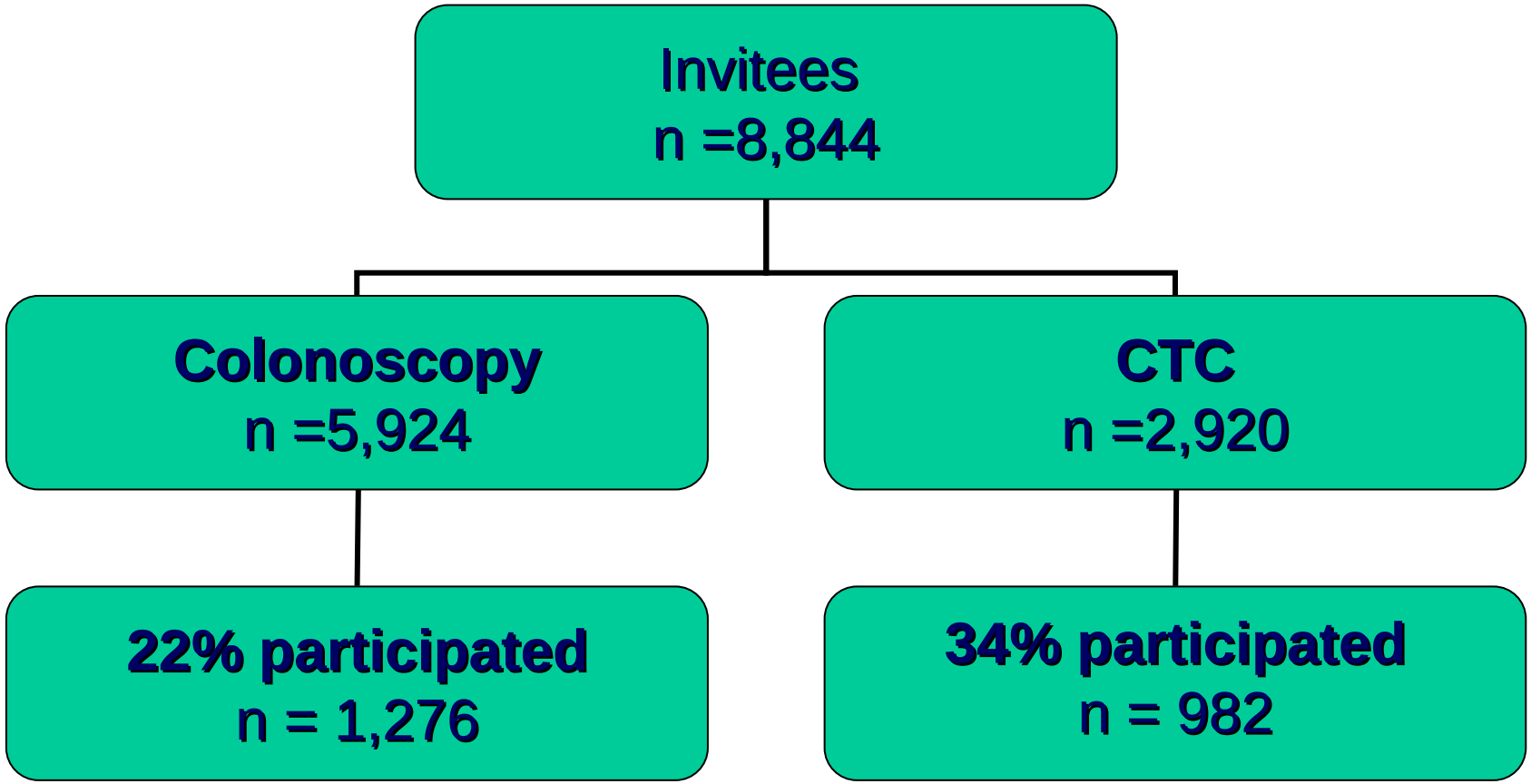
UPTAKE	FS 58 YRS	4 FIT 50-69 YRS	5FIT 50-69 YRS	6 FIT 58-69 YRS
	%	%	%	%
	N	N	N	N
30%	10.3%	8.9%	11.0%	9.2%
	349	480	595	312
40%	13,7%	9.9%	12.1%	12.3%
	466	538	654	417
50%	16,5%	10.9%	13.1%	15.4%
	582	595	713	523
65%	22.3%	12.5%	14.7%	20.0%
	757	680	801	681

Cost – performance modelling of gFOBT and FIT



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

Primary screening with colonoscopy vs CT colonograpy; a randomized trial



RR 1.56
(1.46-1.68; p<0.001)

Erasmus MC
Universitair Medisch Centrum Rotterdam

Stoop E et al. Lancet Oncol 2011

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)

Erasmus MC
Universitair Medisch Centrum Rotterdam

Stoop E et al. Lancet Oncol 2011

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[1], MD; L. Correale[2], PhD; C. Senore[3], MD; D. Campanella[1], MD; G. Galatola[1], MD; C. Laudi[1], MD; P. Falco[2], PhD; N. Segnan[3], MD; D. Regge[1], MD

[1]Institute for Cancer Research and Treatment (IRCC), Candiolo, Italy
[2]im3D S.P.A - Medical Imaging Lab, Torino, Italy
[3]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

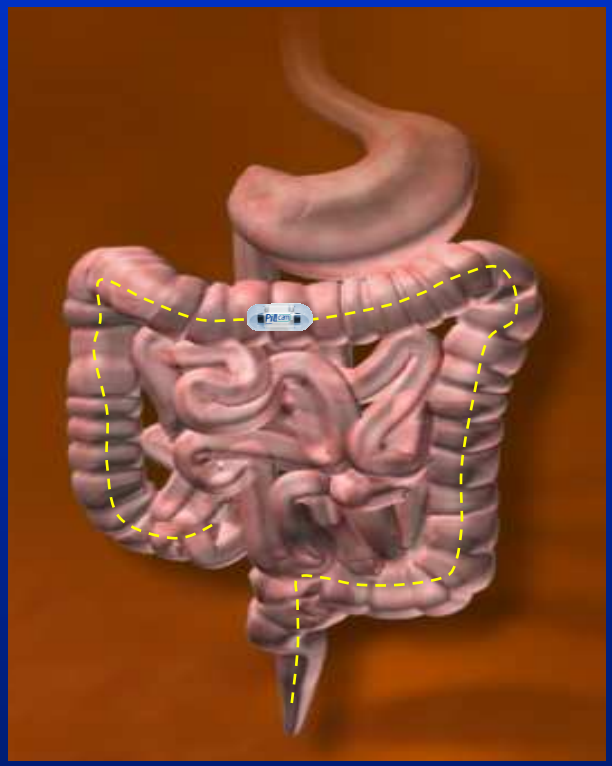
The difference in sensitivity between SR and DR with FR CAD was not statistically significant (P=0.5)
Compared to the Unassisted reading, CAD increased sensitivity for both reading paradigm (P=0.03)
For both CAD reading modes, the AUcs increased with CAD (P=0.02)

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

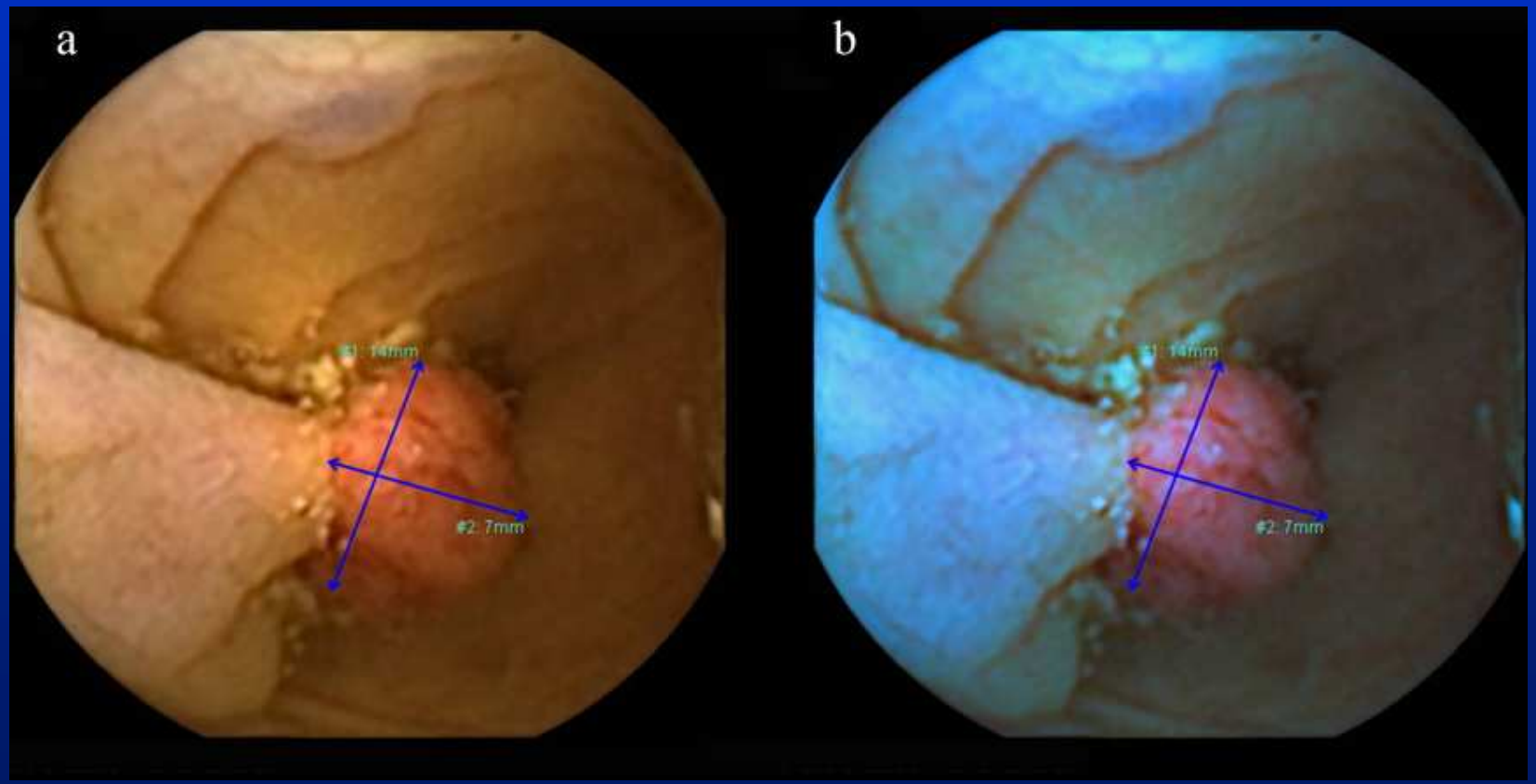
PillCam® COLON Capsule: the optimistic view

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

N. Segnan CPO - 2009

PillCam® COLON Capsule: the pessimistic view

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


a
#1: 14mm
#2: 7mm
b
#1: 14mm
#2: 7mm

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, Andrè Van Gossum, MD, PhD, Carolien A. Wientjes, MD, Sylvie Sacher-Huvelin, MD, Michel Delvaux, MD, PhD, Artur Nemeth, MD, Lucio Petruzziello, 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

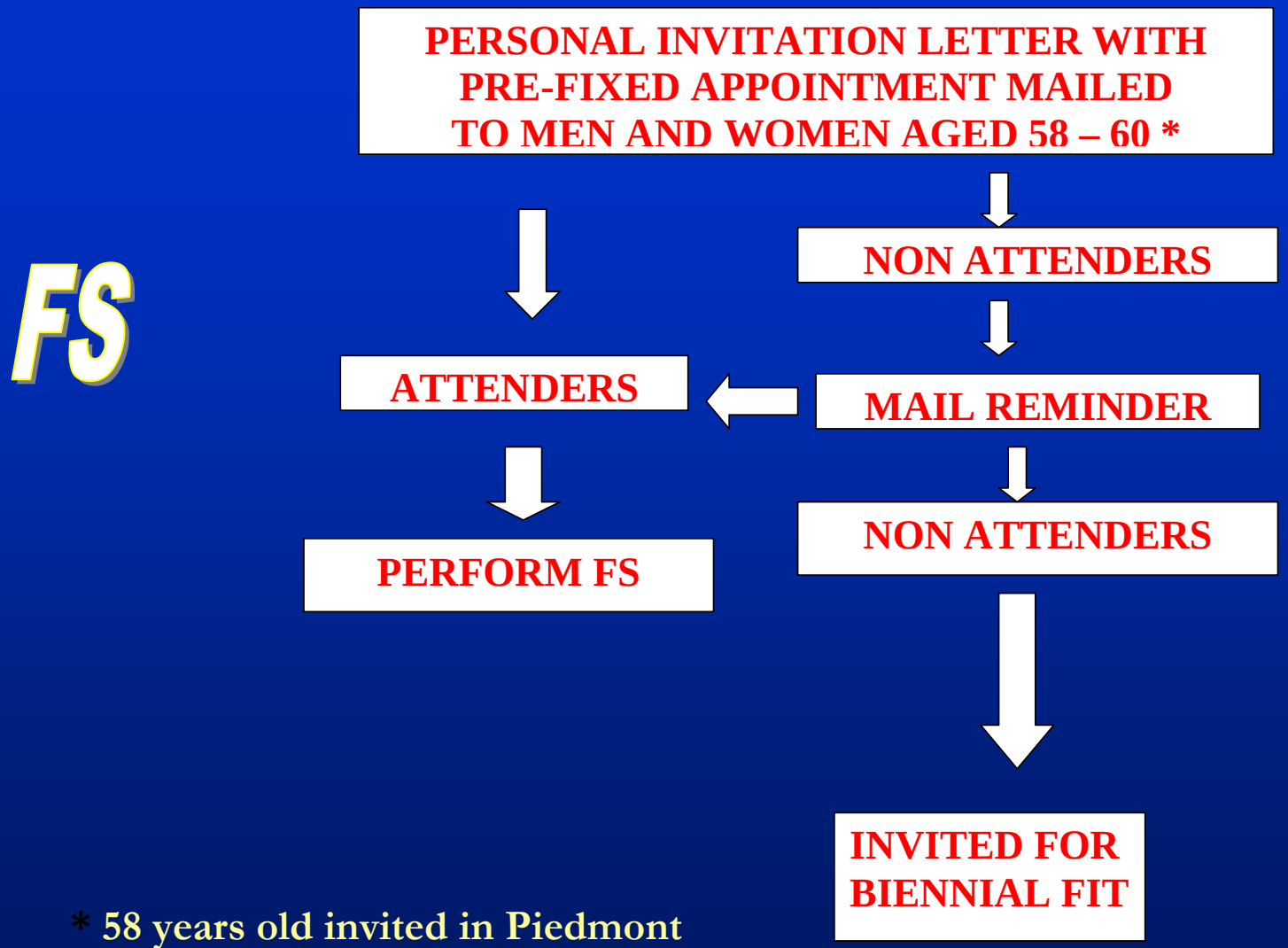
Rome, Italy; Pamplona, Spain; Düsseldorf, Germany; Brussels, Belgium; Amsterdam, The Netherlands; Nancy, France; Malmö, Sweden

TABLE 2. Accuracy characteristics for detection of patients with at least one lesion ≥ 6 mm or ≥10 mm

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

CI, Confidence interval.

SCREENING FLOW

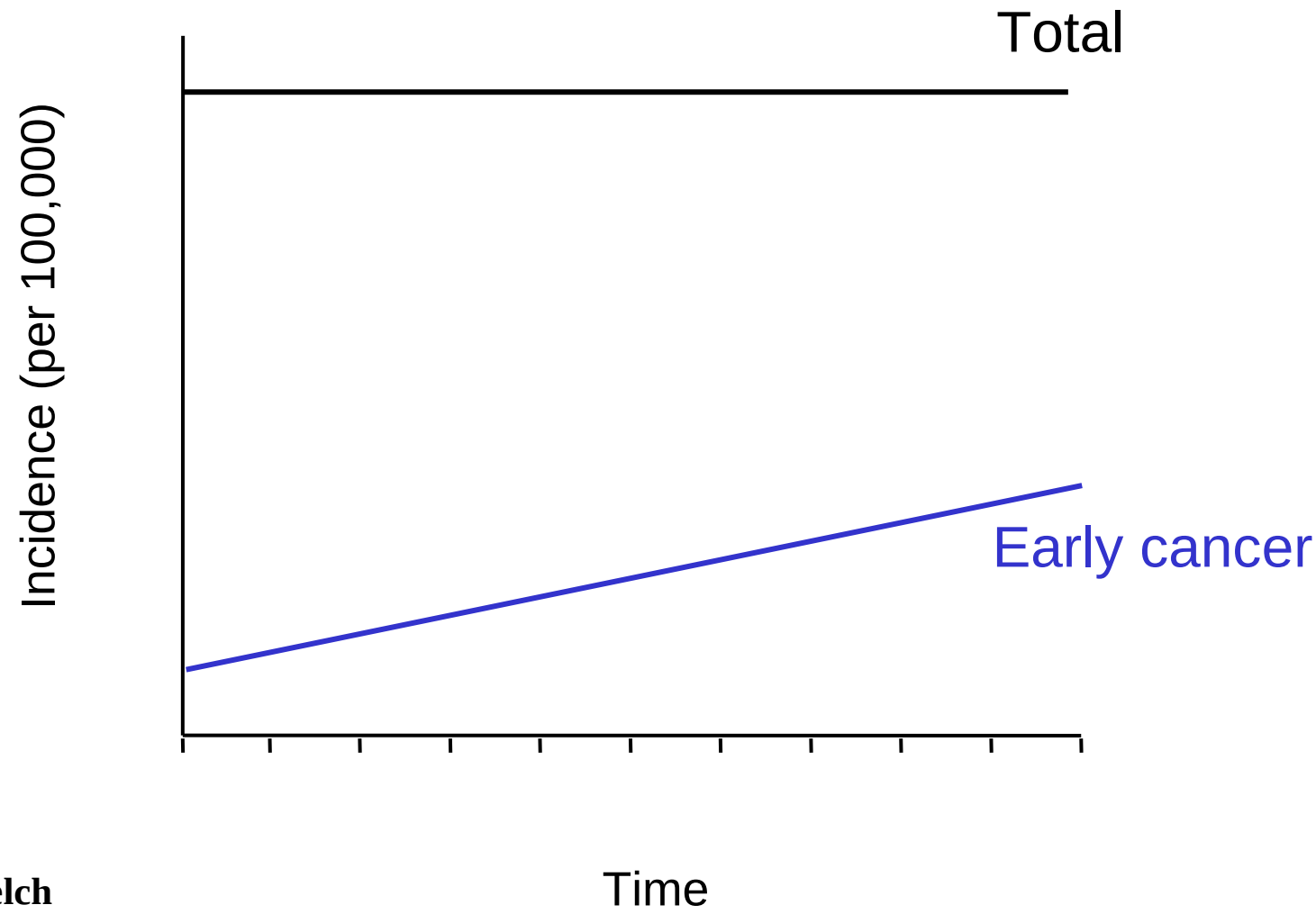


* 58 years old invited in Piedmont

ATTENDANCE RATE

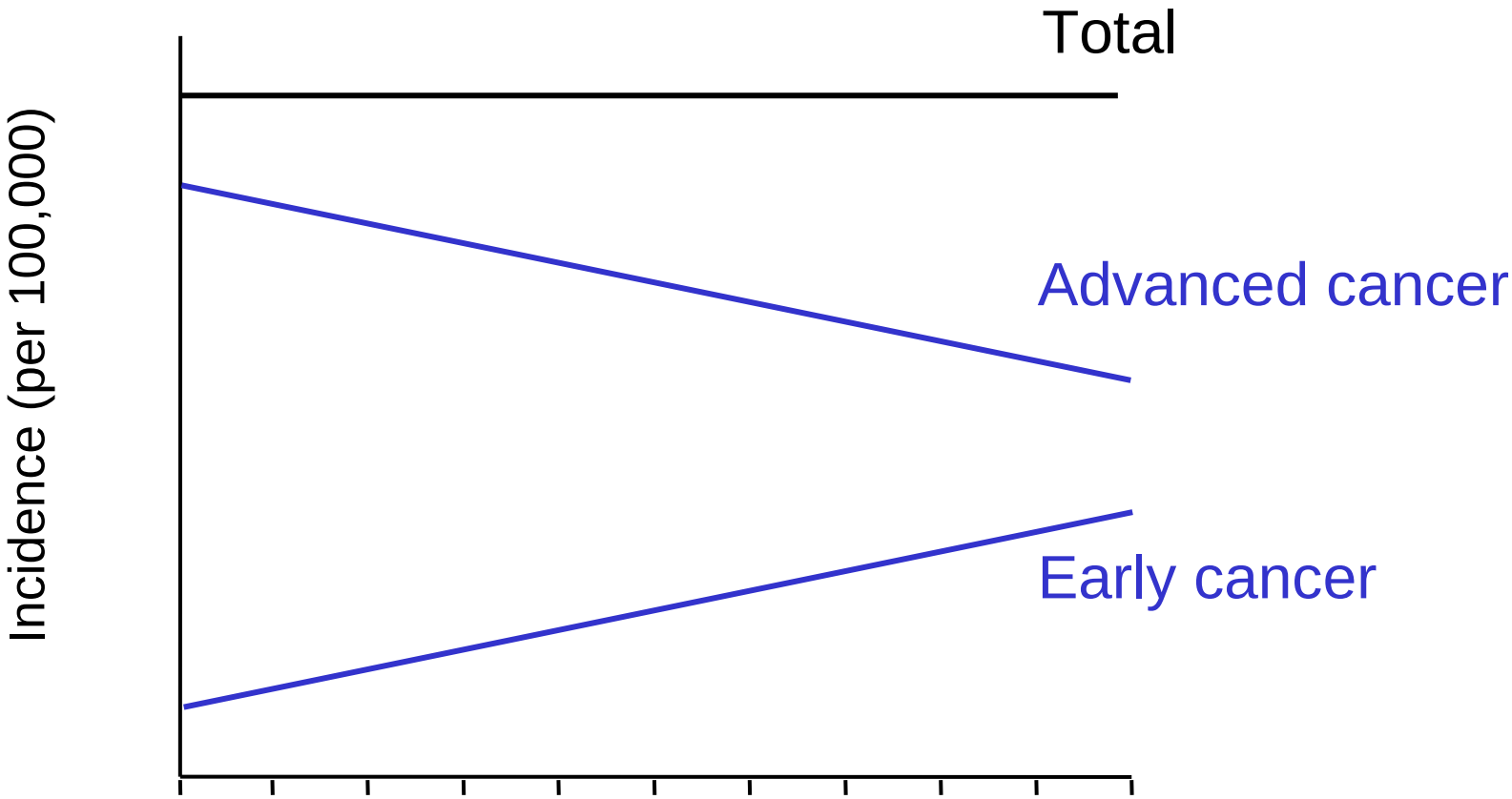
		Invited	FS performed	Attendance rate	Invited to FIT	FIT performed	Attendance rate	Overall coverage
Verona	**MEN**	9662	4152	**43.0%**	5040	1201	**23.8%**	**55,4%**
	WOMEN	10308	3705	**35.9%**	6139	1974	**32.2%**	**55,1%**
Torino	**MEN**	20947	7019	**33.5%**	12183	1518	**12.5%**	**40.8%**
	WOMEN	22801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

Classic model of early detection



Da G. Welch

Classic Model: early detection reduces the number of advanced cases



Da G. Welch

Does overdiagnosis really happen?

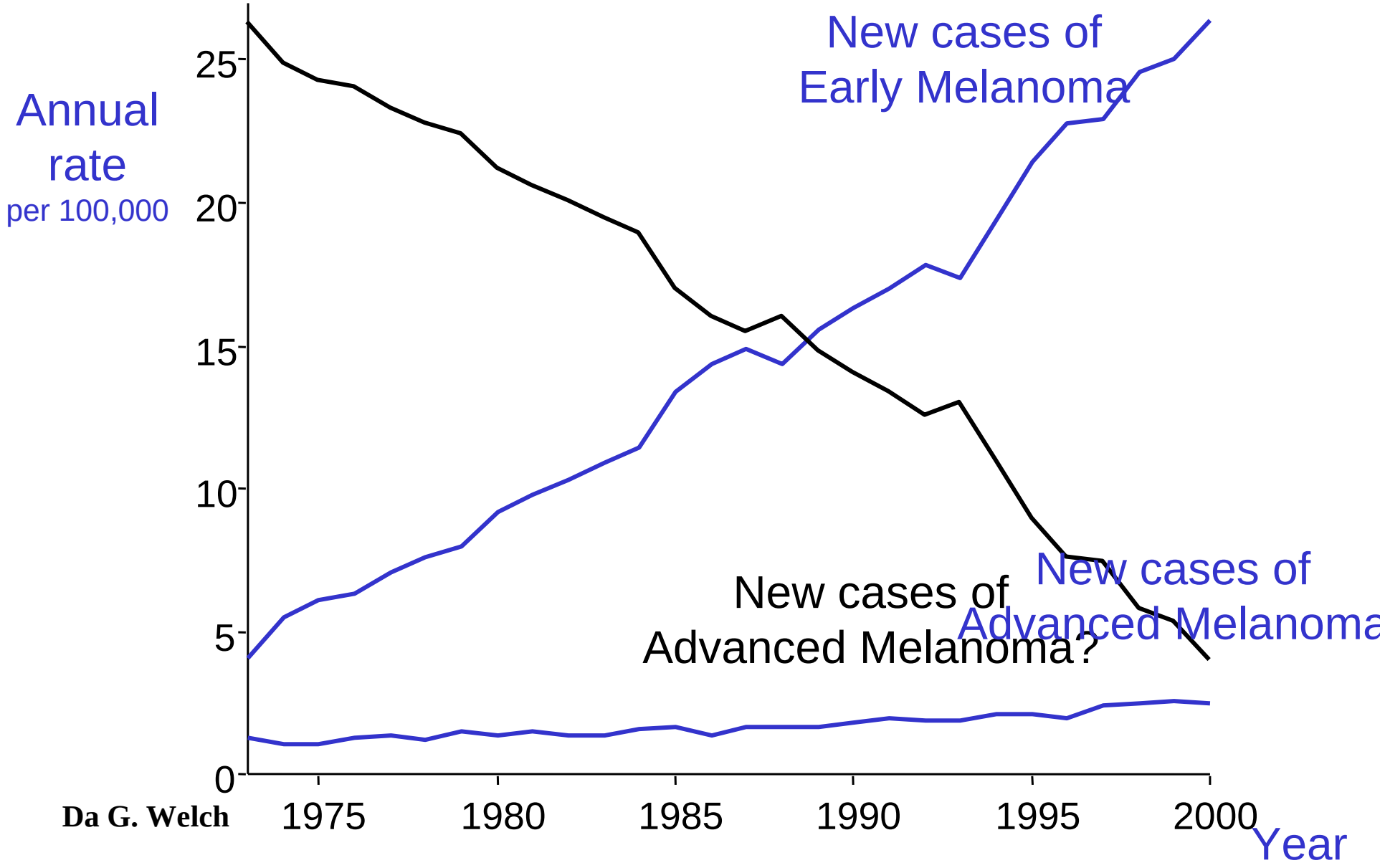
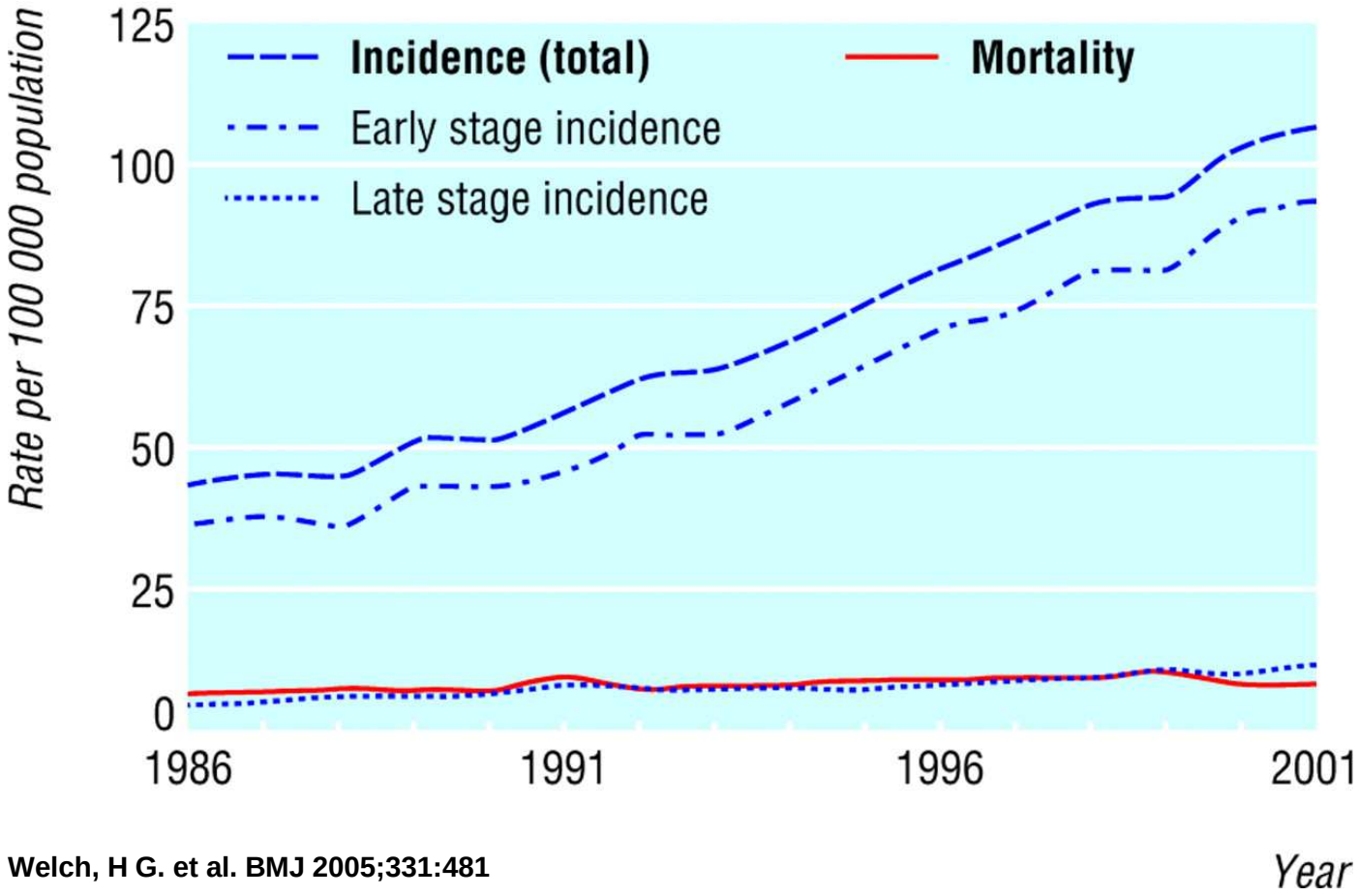


Fig 1 Incidence of melanoma and mortality in population aged 65 and older residing in one of nine US areas participating in Surveillance Epidemiology and End Results programme, 1986-2001. Early stage refers to in situ and local disease; late stage refers to regional and distant disease

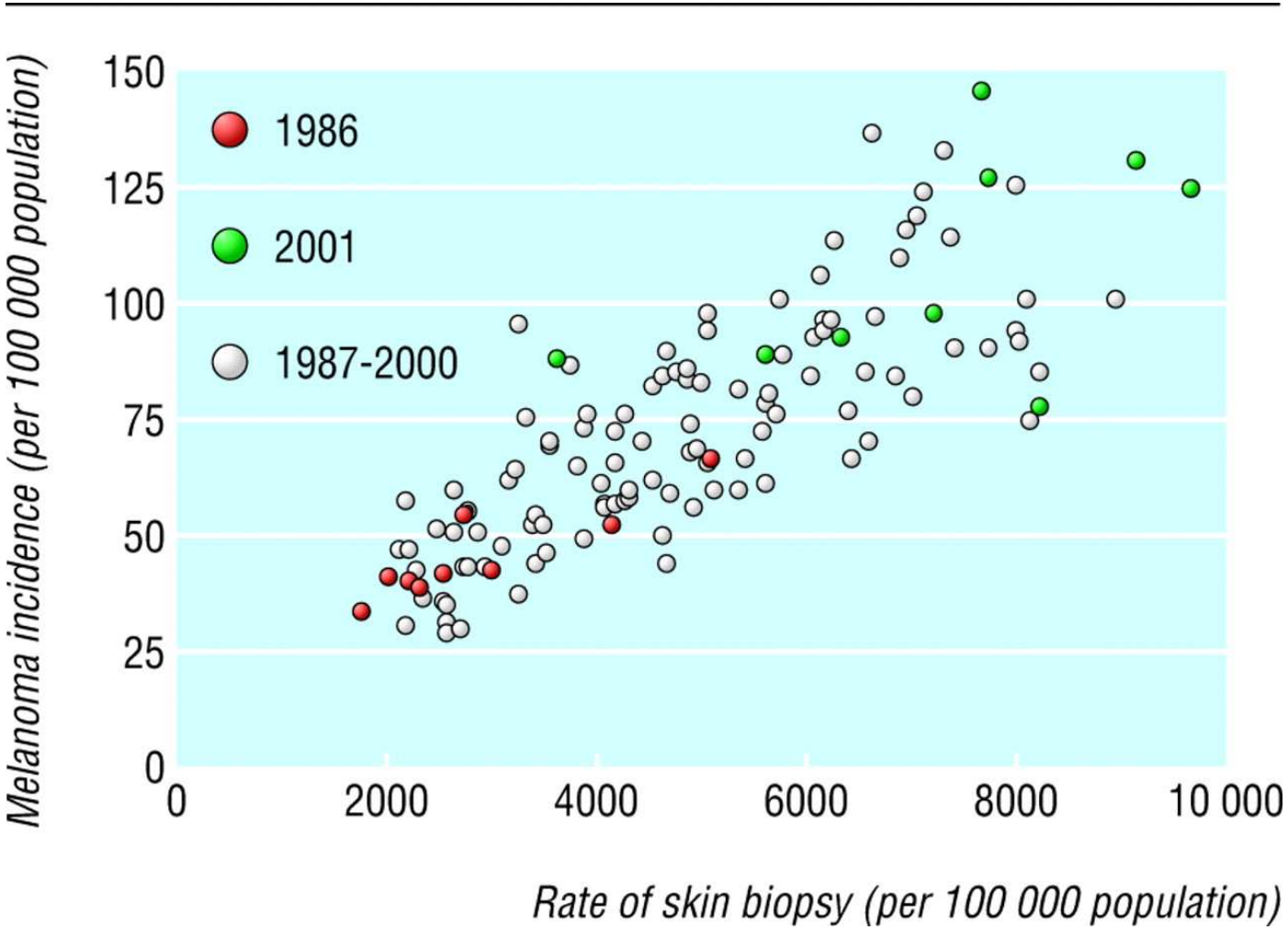


Welch, H G. et al. BMJ 2005;331:481

N. Segnan – CPO 2005

bmj.com

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

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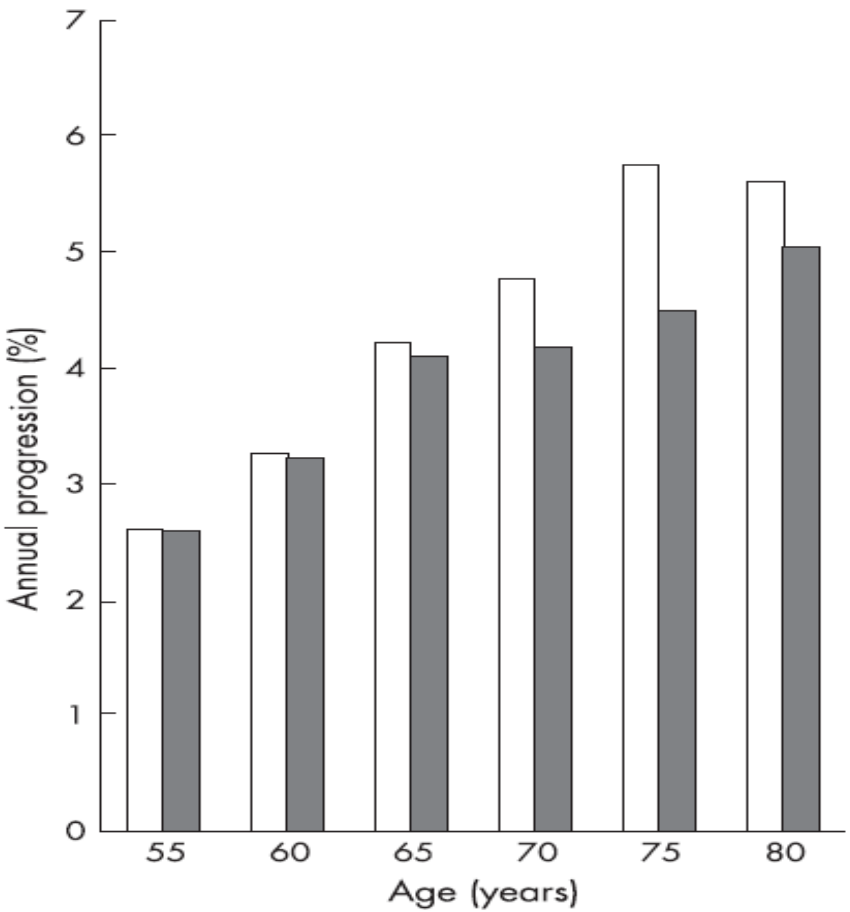
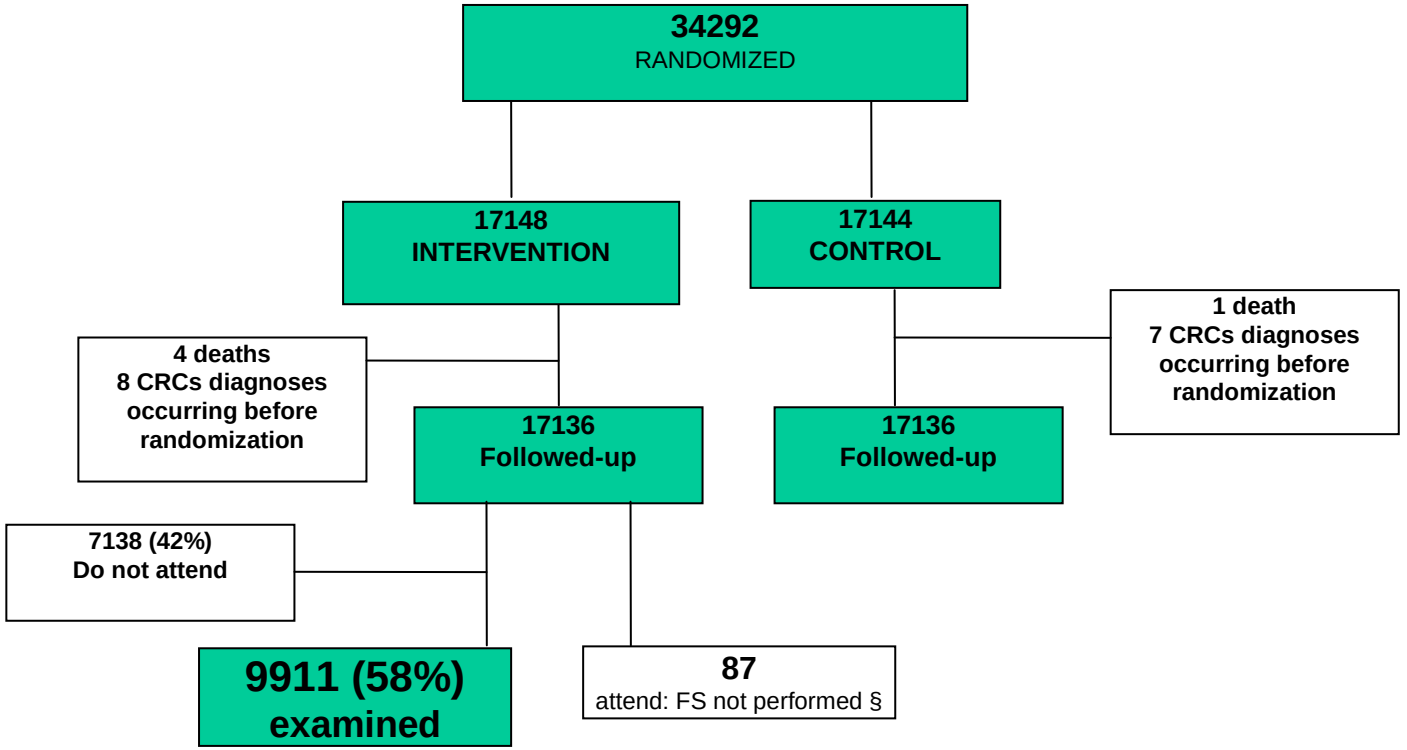
Projected annual progression of advanced adenomas



H. Brenner *et al.* Gut 2007

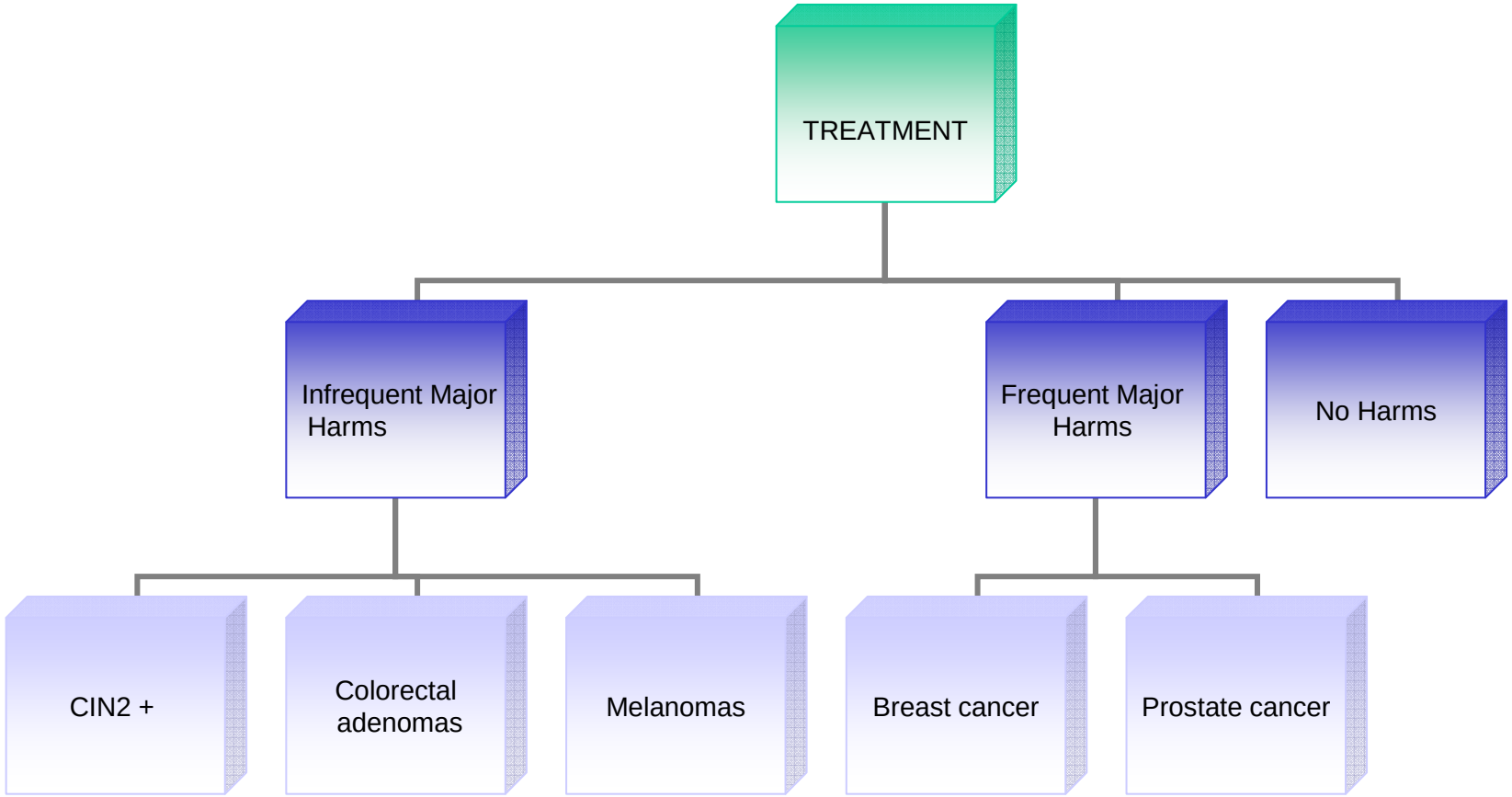
- Advanced andenoma:
  - •size: >10mm
  - •morphology: tubulovillous or villous
  - •pathology: high grade dysplasia
- Women: left, white columns
- Men: right, grey columns

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:

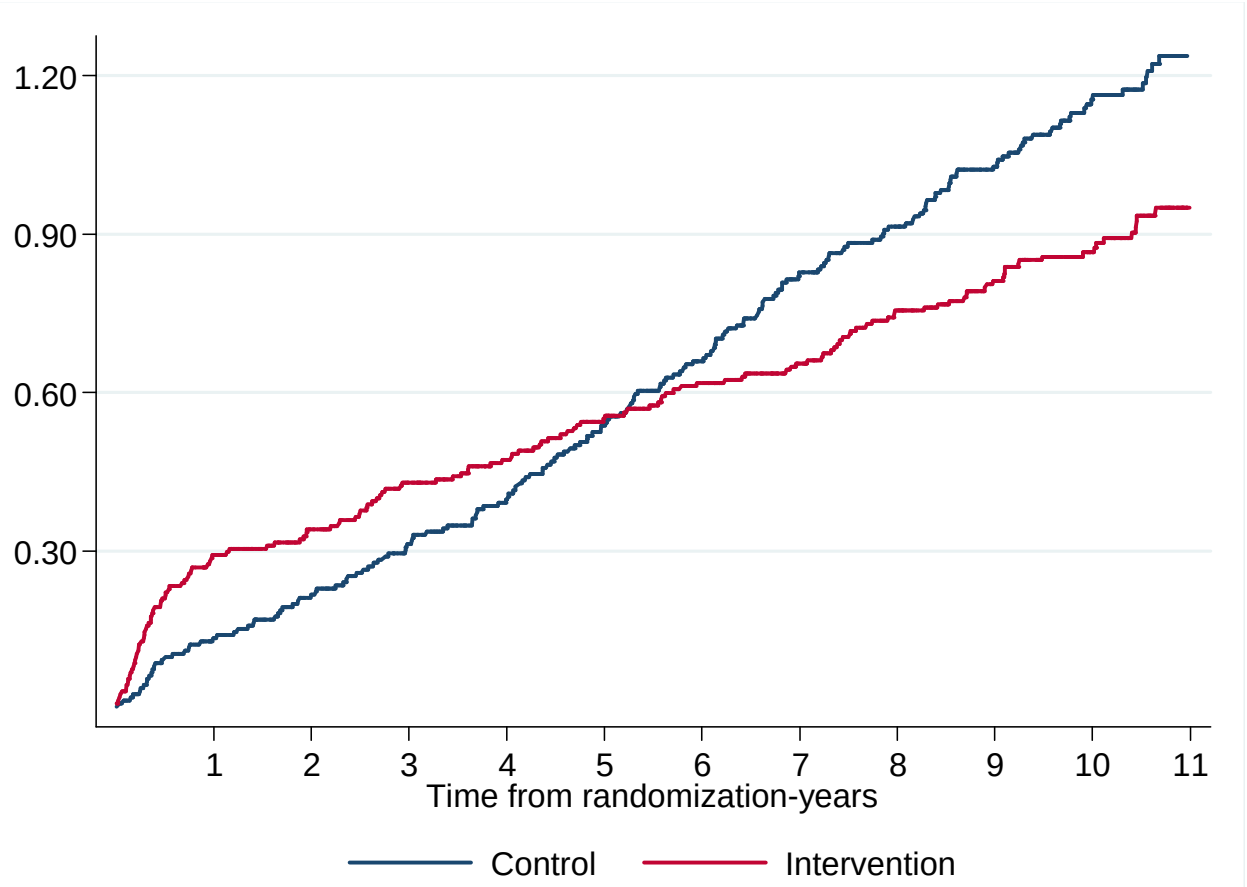
10.5 years (IQR=9.9-11.3) for incidence

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



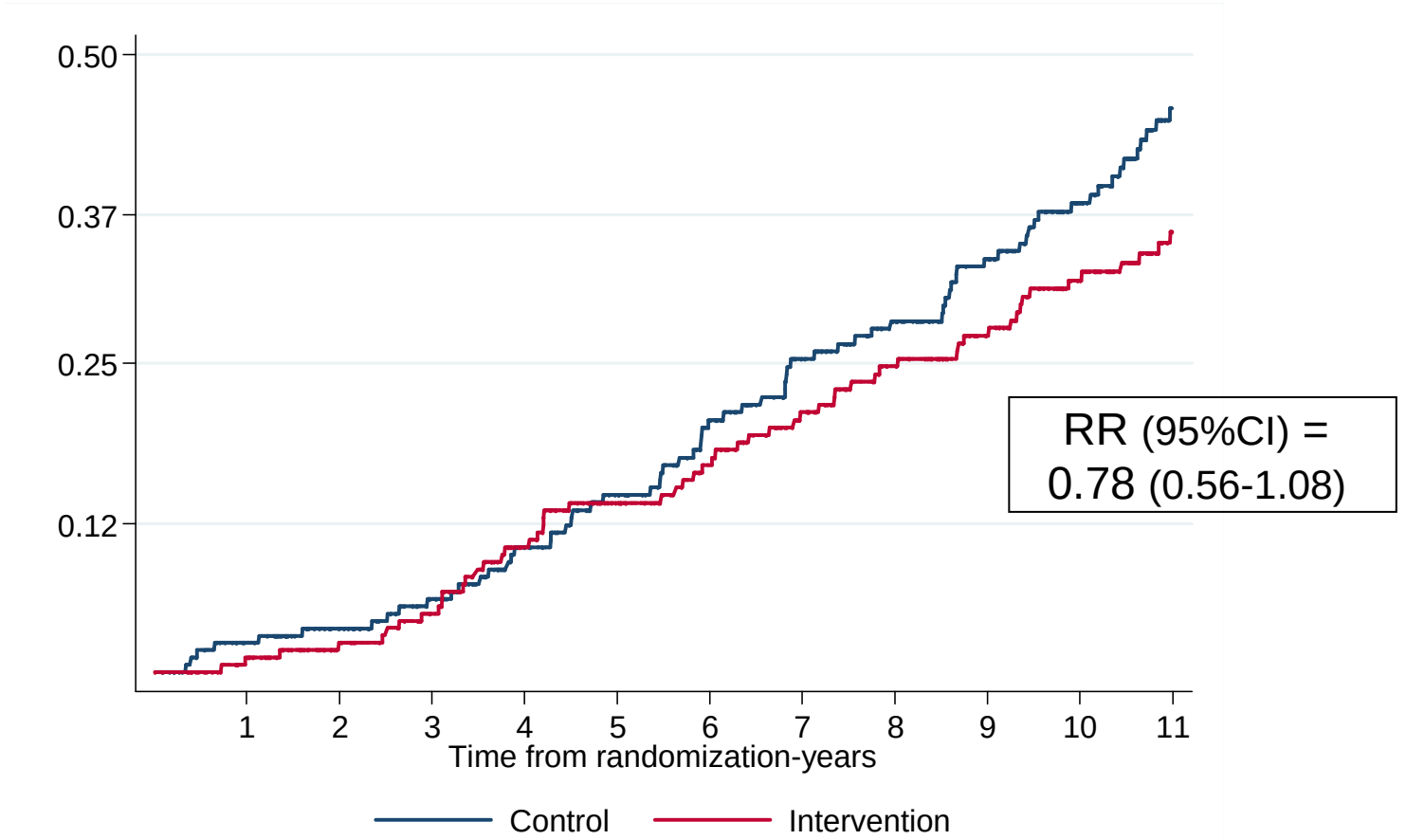
RR (95%CI) = 0.76 (0.62-0.94)

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**

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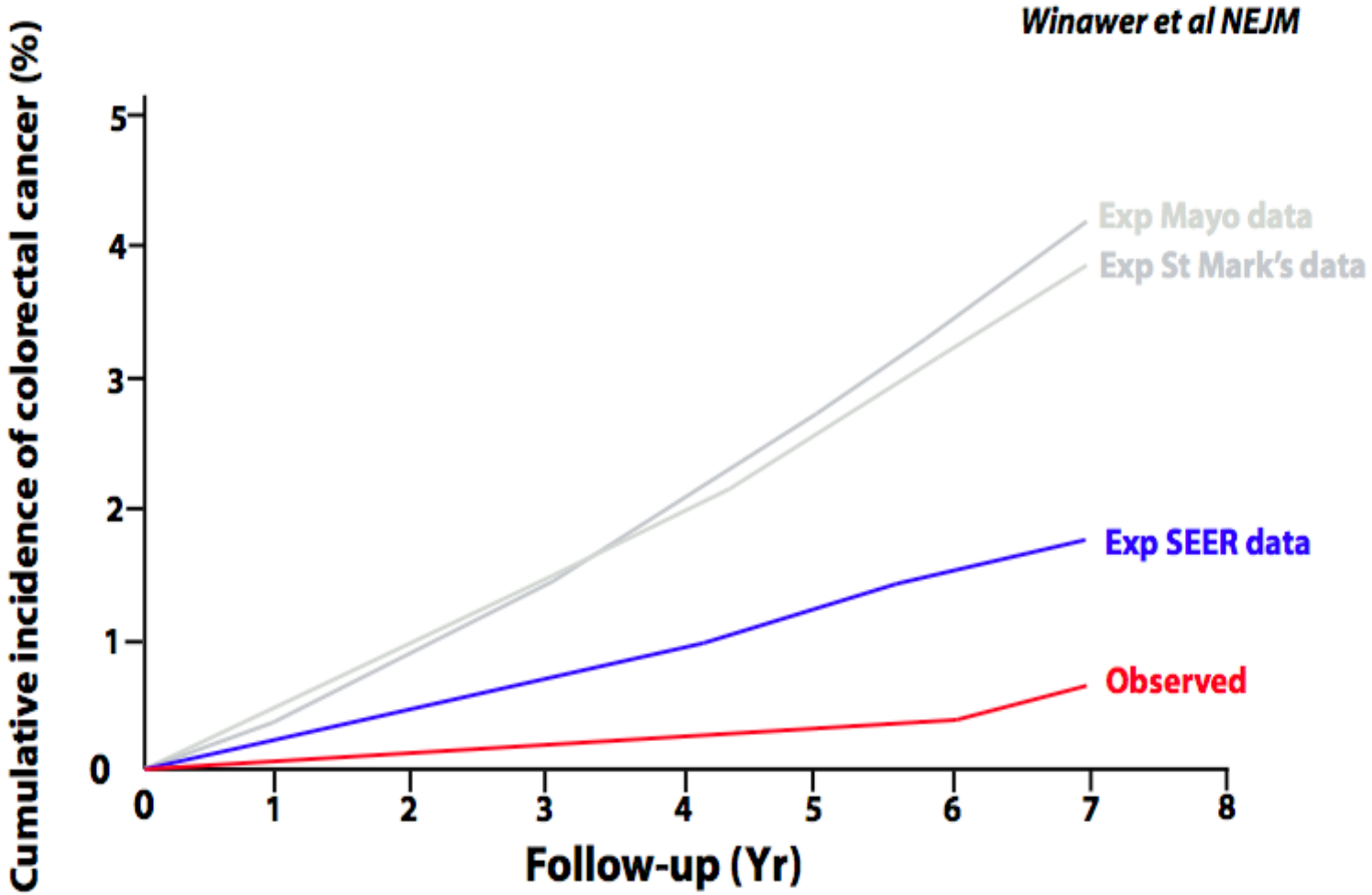
National Polyp Study



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