

Effectiveness of flexible sigmoidoscopy screening

Wendy Atkin

Professor in Gastrointestinal Epidemiology, Department of Surgery and Cancer

Evidence for efficacy of FS

Case-control and cohort studies

- 40-50% reduction in overall colorectal cancer incidence
- 60-80% reduction in distal cancer incidence

Long duration of protection against distal cancer

- Selby et al., NEJM 1992; 326:653-7

At least 10 years

- Newcombe et al., JNCI 2003; 95:623

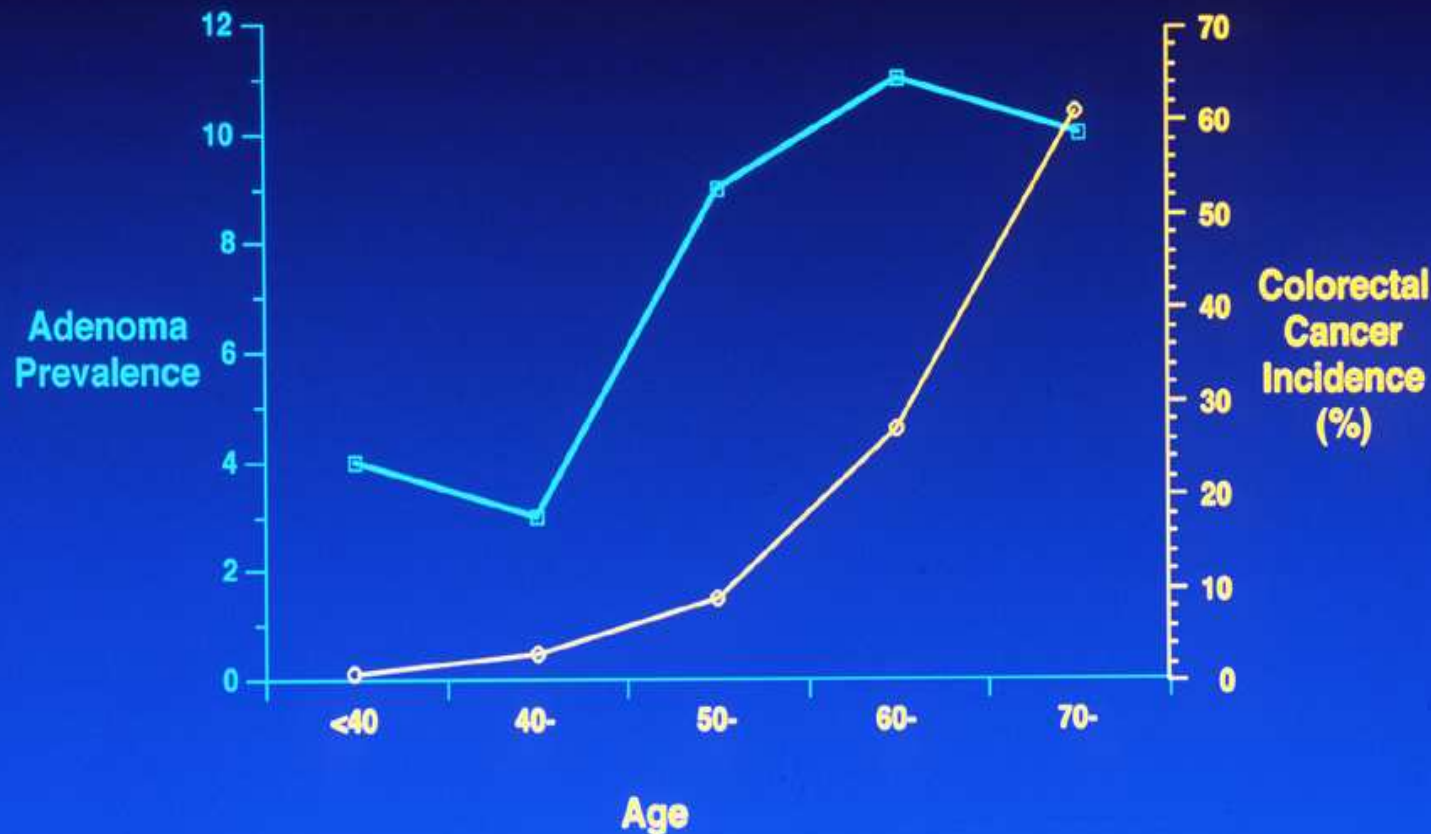
At least 15 years

- Atkin et al., NEJM 1992; 326:658-62

Risk of rectal cancer reduced for remainder of life

Rationale for once-only flexisig at around age 60

Distal adenomas detected at screening by sigmoidoscopy vs. colorectal cancer incidence



UK Flexible Sigmoidoscopy Screening Trial

Examine efficacy and duration of effect of:

- a once-only flexible sigmoidoscopy screen between ages 55 and 64 years
- removal of small polyps (< 10 mm) during screening
- colonoscopy only for high-risk adenomas:
≥3, ≥ 10 mm, ≥ 25% villous, high grade dysplasia



Randomised clinical trials on flexible sigmoidoscopy

USA	PLCO	154 000	3-5 yrly
UK	 Flexi-SCOPE trial	170 000	Once-only
Italy	SCORE	35 000	Once-only
Norway	NORCAPP	56 000	Once-only

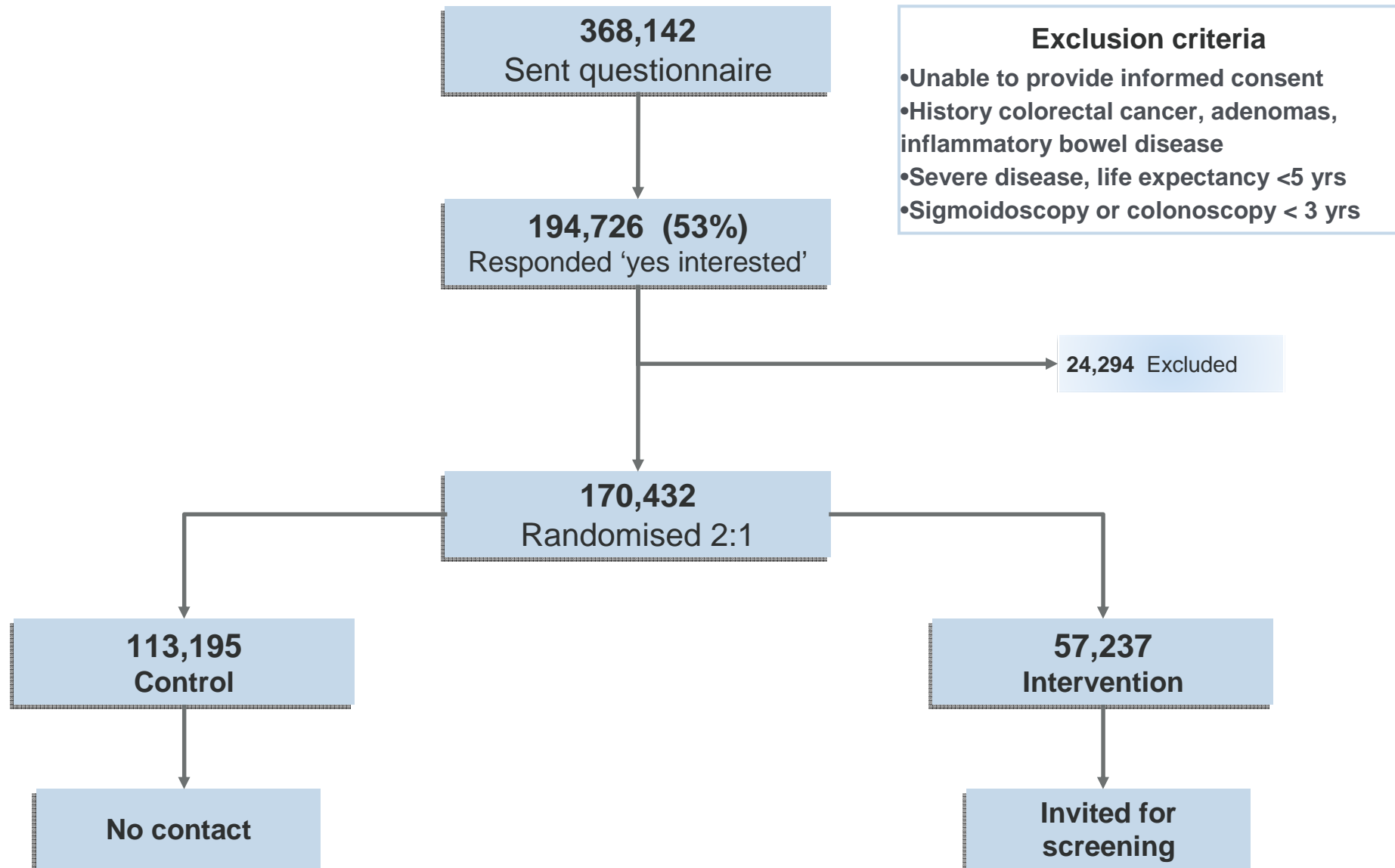
Weissfeld et al., JNCI 2005;97:989-92

Segnan et al., JNCI 2002;94:1763-72.

Hoff et al., BMJ 2009;338:1846

Atkin et al., Lancet 2010, 375:1624-33

UK Trial recruitment



Follow-up

Median follow-up time

- 11.2 years
- 1.8 million person-years

Sources of data for whole UK

- NHS Central Register

Cancer registrations, dates of death, emigrations, name changes

- Office for National Statistics

Causes of death, underlying cause of death

- UK cancer registries, Hospital Episodes Statistics (HES)

Reduce time to ascertainment of cancer registrations

Follow-up censored

- Emigration, death or 31st December 2008

UK Flexible Sigmoidoscopy Screening Trial

Primary

- Incidence colorectal cancer, all sites
- Mortality due to colorectal cancer

Sample size: 170,000

- 90% power
- 20% reduction in CRC incidence at 10 years, mortality at 15 years
- 2:1 ratio of controls to intervention (screening) groups
- 55% attendance for screening

Secondary

- Incidence distal cancer (rectum and sigmoid colon)
- Incidence proximal cancer (proximal to the sigmoid colon)
- All-cause mortality

Intent-to-treat analysis

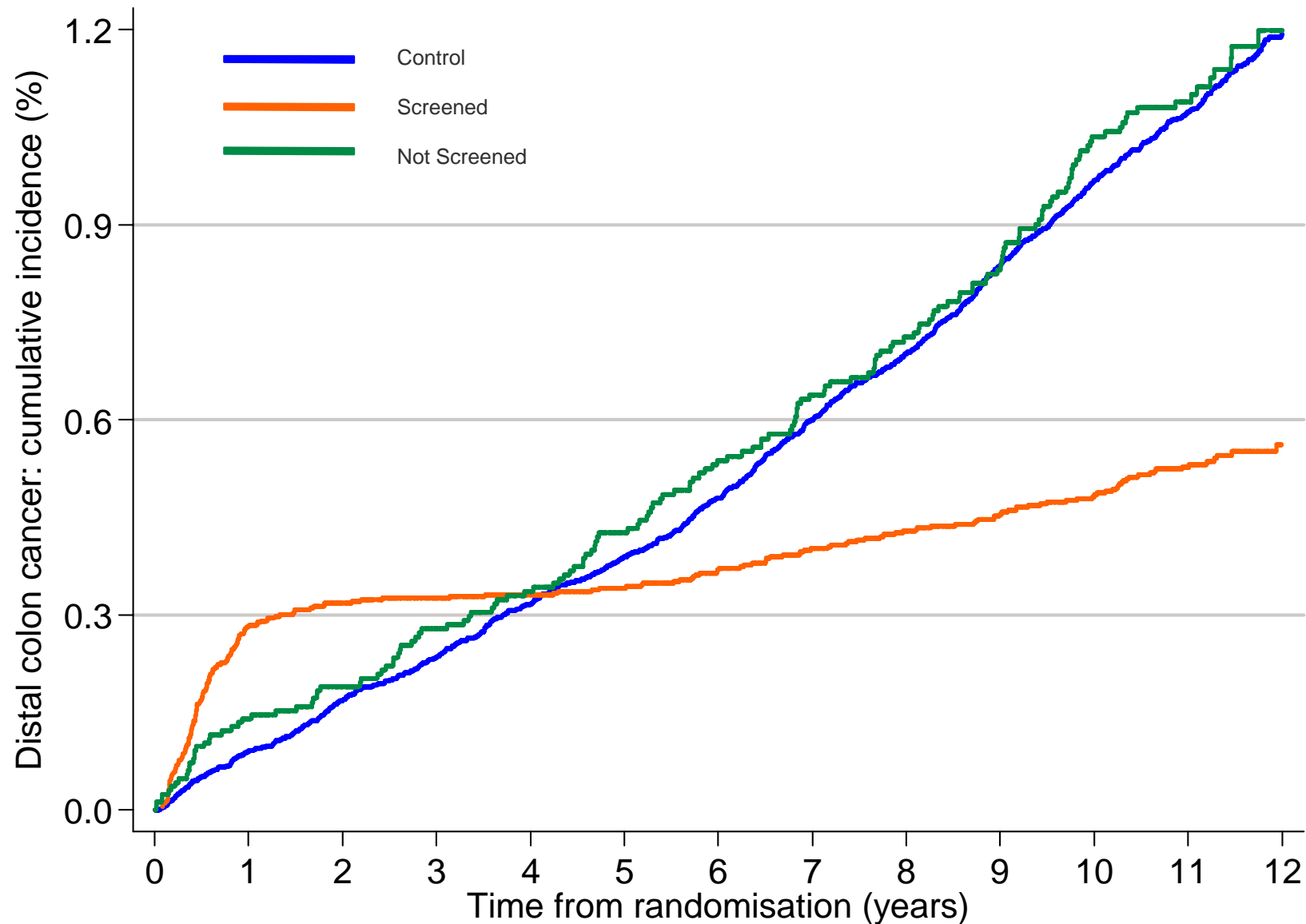
	Control group 112,939		Intervention group 57,099		<u>Intervention</u> vs. Control	
	Cases N	Rate /100,000 py	Cases N	Rate /100,000 py	Hazard ratio (95% CI)	p-value
Incidence						
	Distal	1,192 98	386 62		0.64 (0.57 - 0.72)	<0.01
	Proximal	628 51	311 50		0.98 (0.85 - 1.12)	ns
Colorectal cancer all sites		1,818 149	706 114		0.77 (0.70 - 0.84)	<0.01
Mortality						
Colorectal cancer		538 44	189 30		0.69 (0.59 - 0.82)	<0.01

Screened vs control groups (adjusted*)

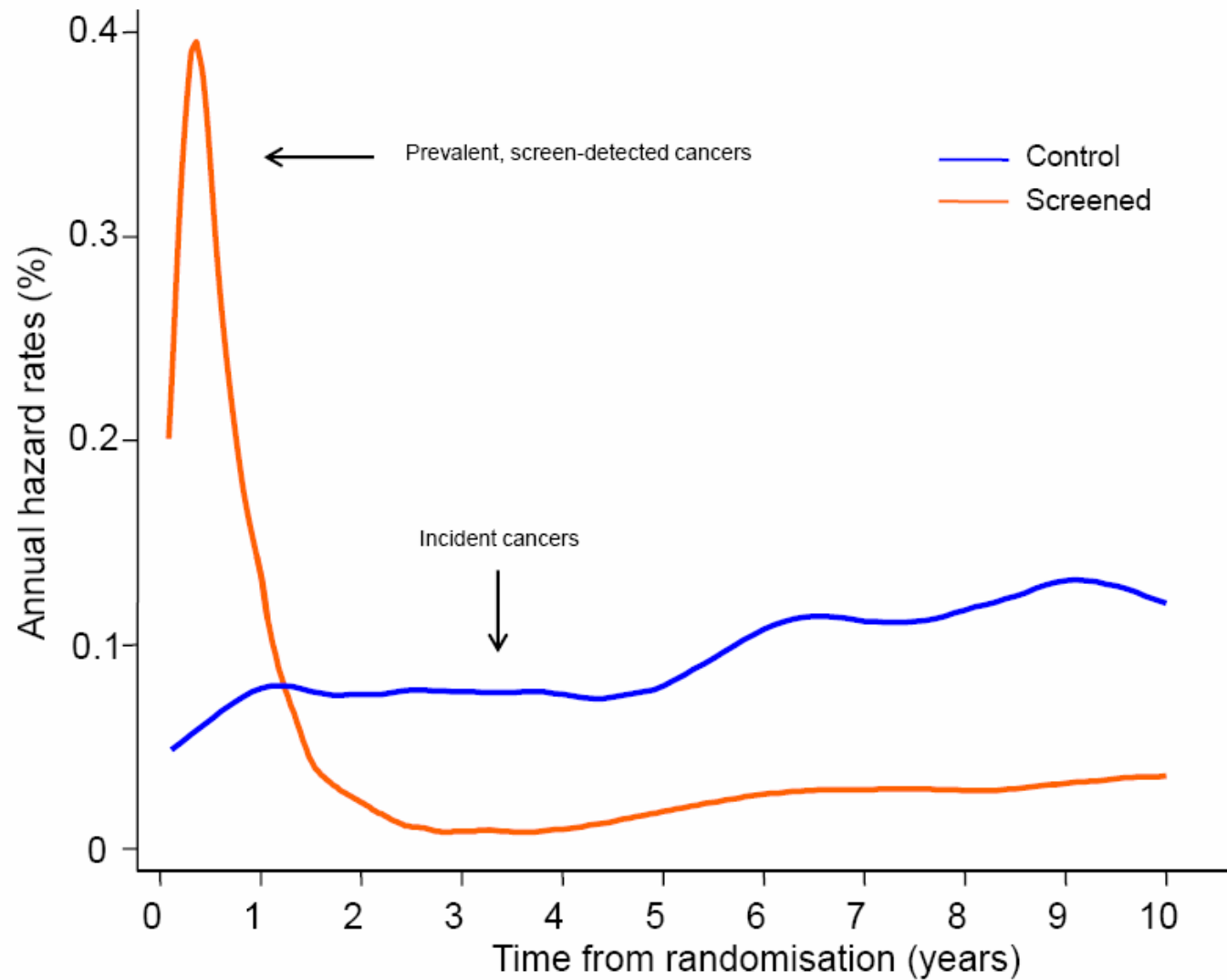
	Control group (n=112,939)		Screened (n=40,621)		Screened vs. Control
	Cases N	Rate /100,000 py	Cases N	Rate /100,000 py	Hazard ratio adjusted* (95% CI)
Incidence					
Distal	1,192	98	215	48	0.50 (0.42 - 0.59)
Proximal	628	51	224	50	0.97 (0.80 - 1.17)
Colorectal cancer all sites	1,818	149	445	100	0.67 (0.60 - 0.76)
Mortality					
Colorectal cancer	538	44	111	25	0.57 (0.45 - 0.72)

Cuzick et al. Stat Med. 1997; 16:1017-1029.

Cumulative incidence distal cancer (%)



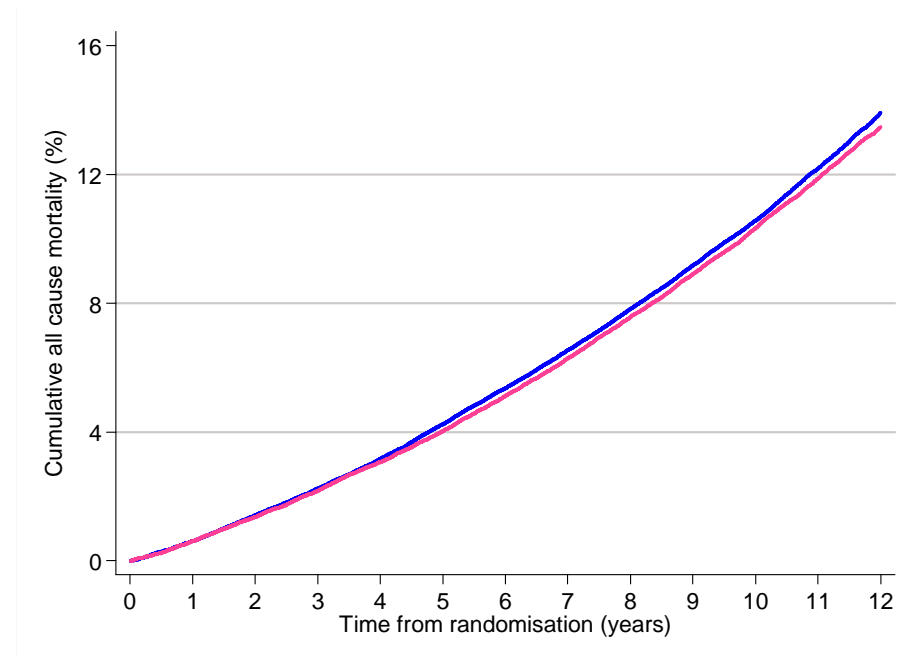
Annual incidence rates for distal cancer (%)



Curves are truncated at 10 years of follow-up because of incomplete ascertainment of cancers in the final calendar year of the study.

All-cause mortality

	Control group (n=112,939)		Screened (n=40,621)		Screened vs. Control
	Cases N	Rate /100,000 py	Cases N	Rate /100,000 py	Hazard ratio adjusted (95% CI)
Mortality					
All-cause	13,768	1,124	4,062	909	0.95 (0.91 - 1.00)



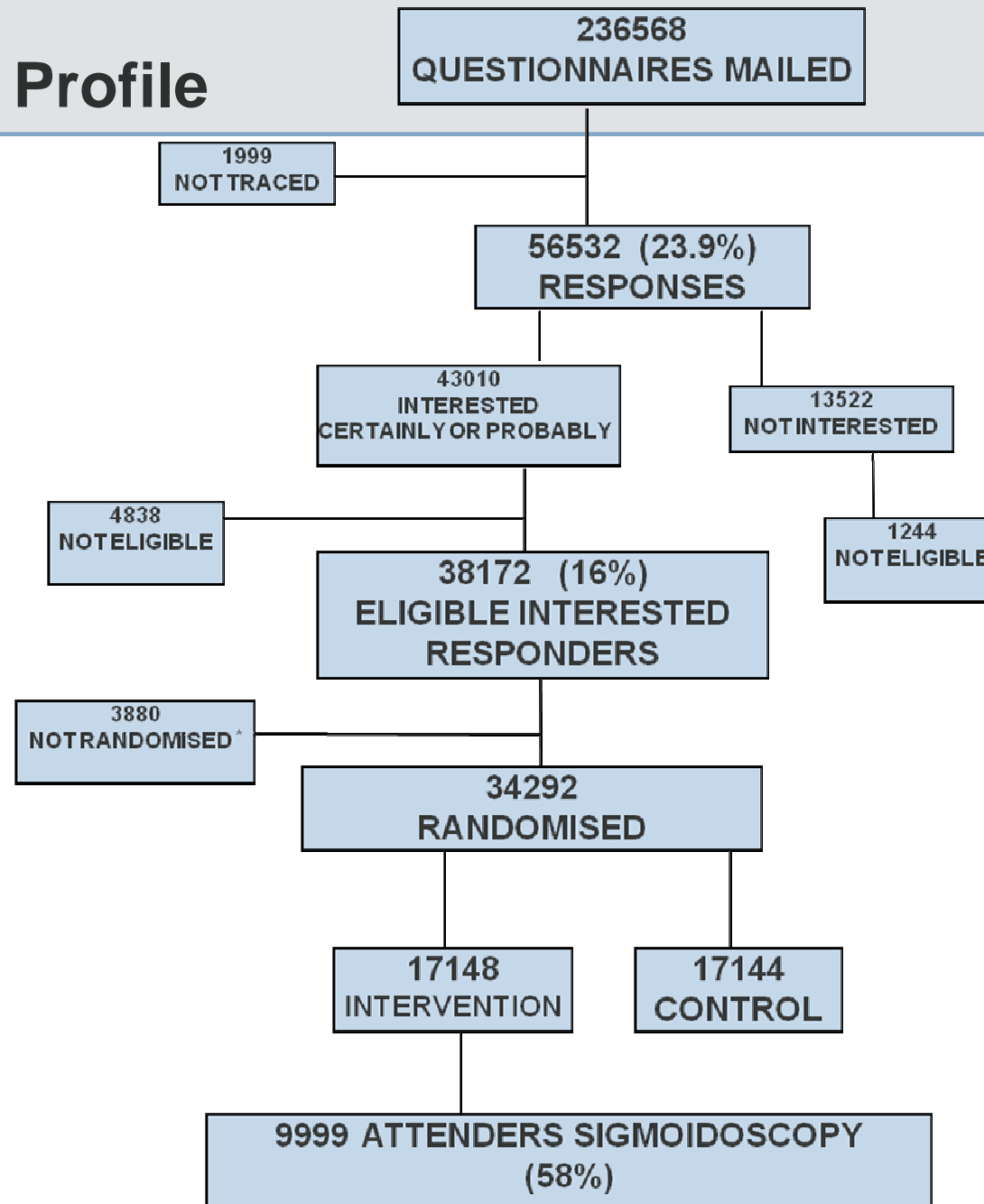
Efficacy of a once-only flexible sigmoidoscopy

Atkin et al. Lancet. 2010;375: 1624-33

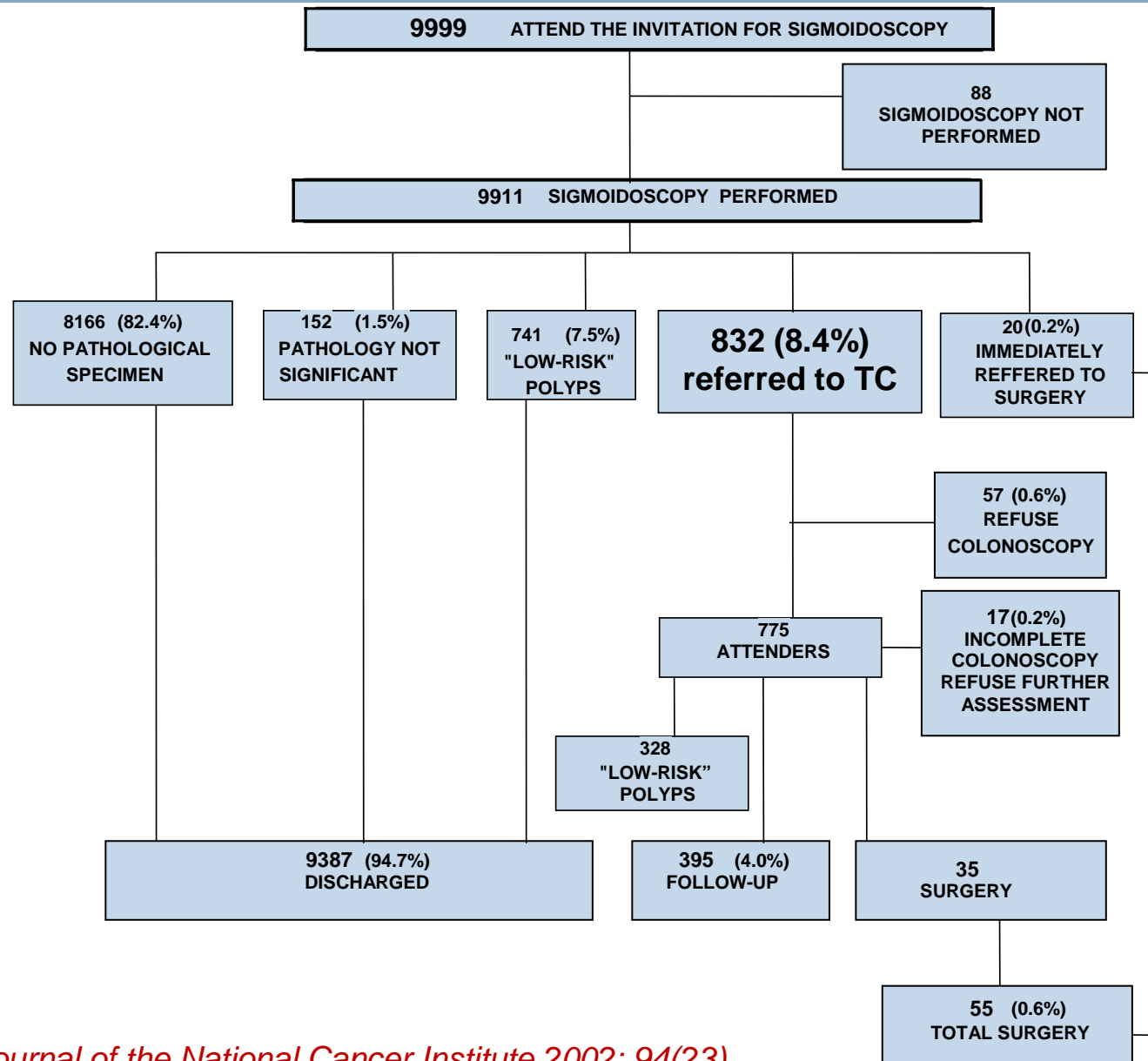
After 11 years of follow-up, in people who had the screening:

- Cumulative incidence, including prevalent cancers detected at screening, reduced by
 - 50% for distal cancers (rectum and sigmoid colon)
 - 33% for colorectal cancer overall
- Colorectal cancer mortality was reduced by 43%
- No sign of a waning of effect at longer follow-up times

SCORE Trial Profile



Management of the SCORE trial participants



Distribution of Follow-up

Duration - Months

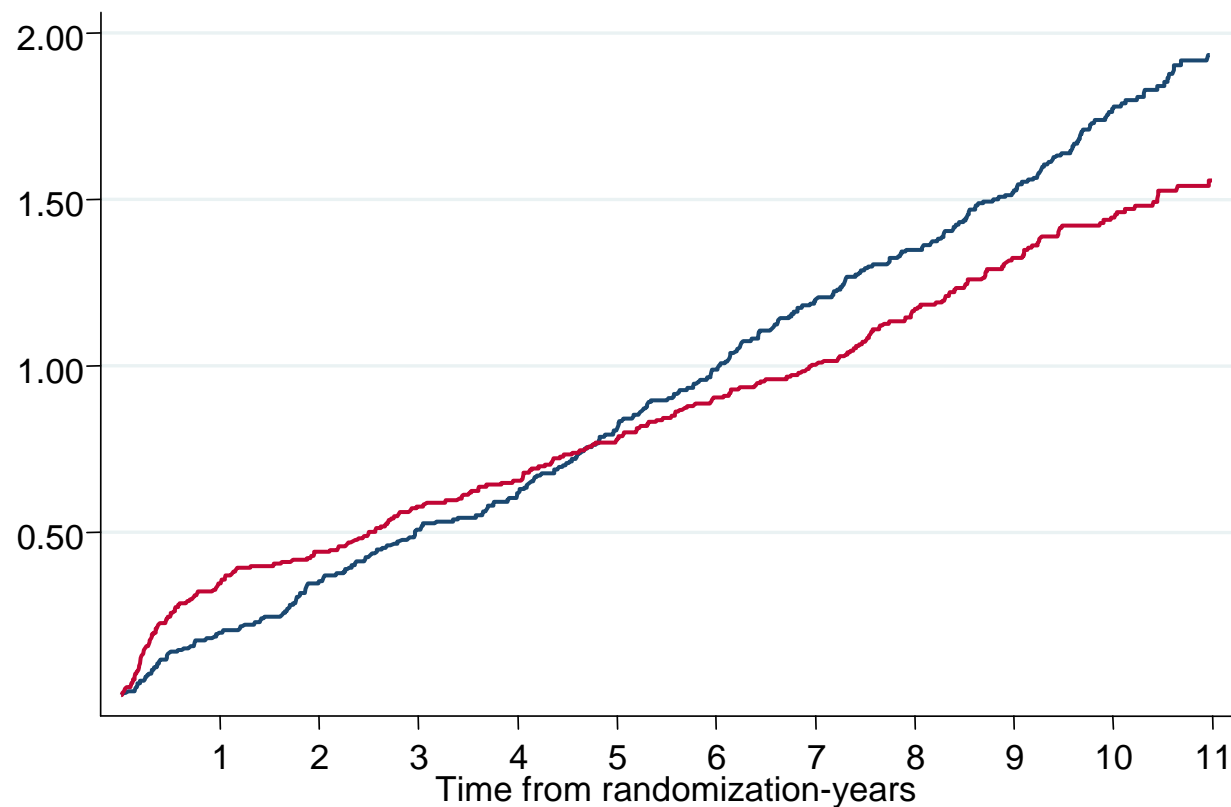
	MEDIAN	10° PERCENTILE	90° PERCENTILE	MEAN
intervention (N=17148)	127	114	140	124.5
Control (N=17144)	127	114	140	124.3

SCORE Trial Intention to treat analysis - Colorectal cancer

INCIDENCE, ALL SITES

Nelson Aalen Cumulative Hazard (%) by time from randomization

Segnan N et al. JNCI 2011



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

— Control — Intervention

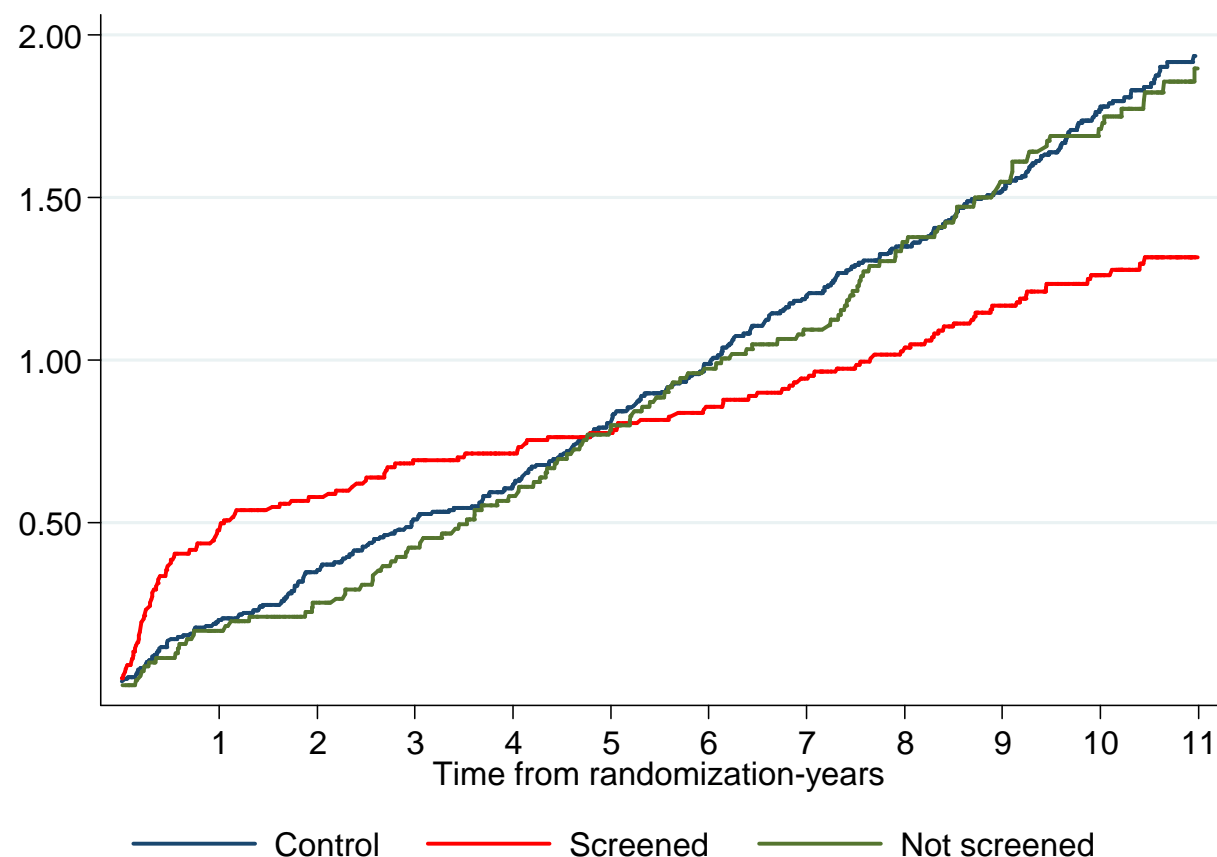
Cumulative Events by years from randomization						
	≤2	≤4	≤6	≤8	≤10	>10
Control	60	104	165	223	286	306
Intervention	75	111	152	195	237	251

SCORE trial: Per protocol analysis - Colorectal cancer

INCIDENCE, ALL SITES

Segnan N et al. JNCI 2011

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

The PLCO Cancer Screening Trial



Robert E. Schoen, MD, MPH
Professor of Medicine & Epidemiology
University of Pittsburgh, Pittsburgh, PA

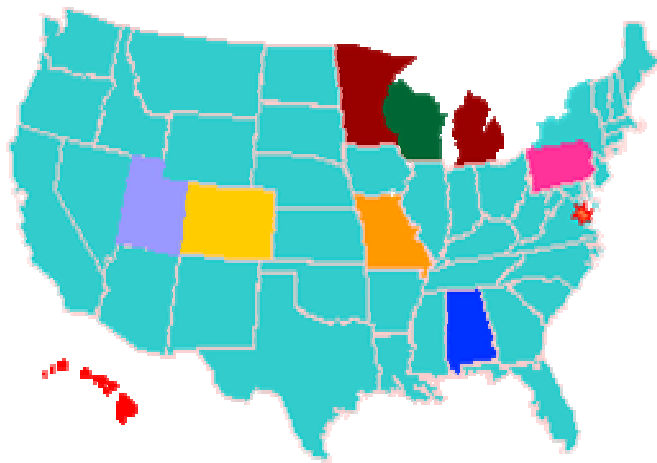
Aim of the Colorectal Portion of the PLCO Trial

To determine in screened subjects ages 55 -74 whether flexible sigmoidoscopy can reduce **colorectal cancer mortality**



The PLCO Trial

- Multicenter (10) randomized trial
- Intervention vs. Usual Care



- N = 154,906 Enrolled
- $\approx 77,000$ in each arm
- 50:50 by Gender
- 13 Year follow up from end of screen, 23 yrs overall

PLCO Protocol

- 60 cm FSG: NP's and physicians
- FSG at enrollment and 3 yrs later
- Mid 90's: Timing for repeat FSG changed from 3 to 5 years
- Bx's not part of protocol: subjects referred to primary physicians for decisions re: diagnostic follow up

Sample Size Calculations

- Prostate cancer was impetus for trial and was primary focus for sample size calculations
- One sided hypothesis testing approach: determining whether screening reduces mortality
- Endpoint Total CRC mortality: no separation of proximal vs. distal disease

Power by % Reduction in Mortality

Colorectal	Mortality Reduction		
	.15	.20	.25
All	.89	.99	.999
Male	.72	.92	.99
Female	.56	.79	.93

NORCAPP TRIAL Flowchart

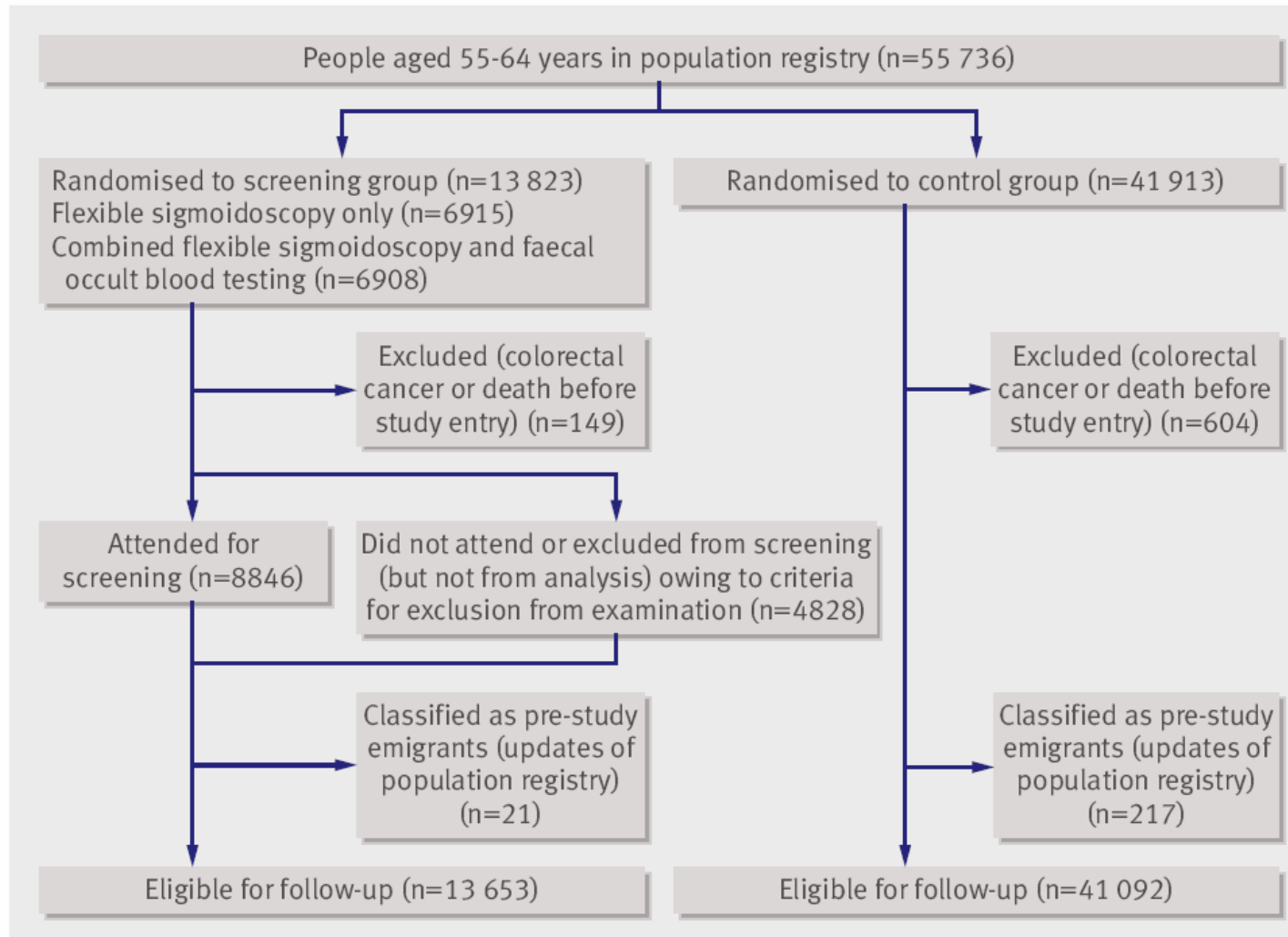


Fig 1 | Flow chart for Norwegian Colorectal Cancer Prevention trial 1 cohort screened January 1999 to December 2001

Table

Accumulated cases (accumulated No/1000 people) of colorectal cancer in subsets of screening group and control group after six to eight years' follow-up

	Screening group (n=13 653)					Control group (n=41 092)
	Attended (n=8846)			*Did not attend (n=4807)	Total	
	Screen detected	Post-screen detected	Subtotal attending			
Localised colorectal cancer	20	6	26	7	33 (2.4)	62 (1.5)
Advanced colorectal cancer	11 (1.2)	29 (3.3)	40 (4.5)	38 (7.9)	78 (5.7)	262 (6.4)
Stage unspecified	2	3	5	7	12 (0.9)	38 (0.9)
Total	33	38	71 (8.0)	52 (10.8)	123 (9.0)	362 (8.8)

*Includes 459 people excluded from examination (but not from analysis) according to exclusion criteria.

NORCAPP Norwegian trial of once only FS screening

Cumulative Hazard

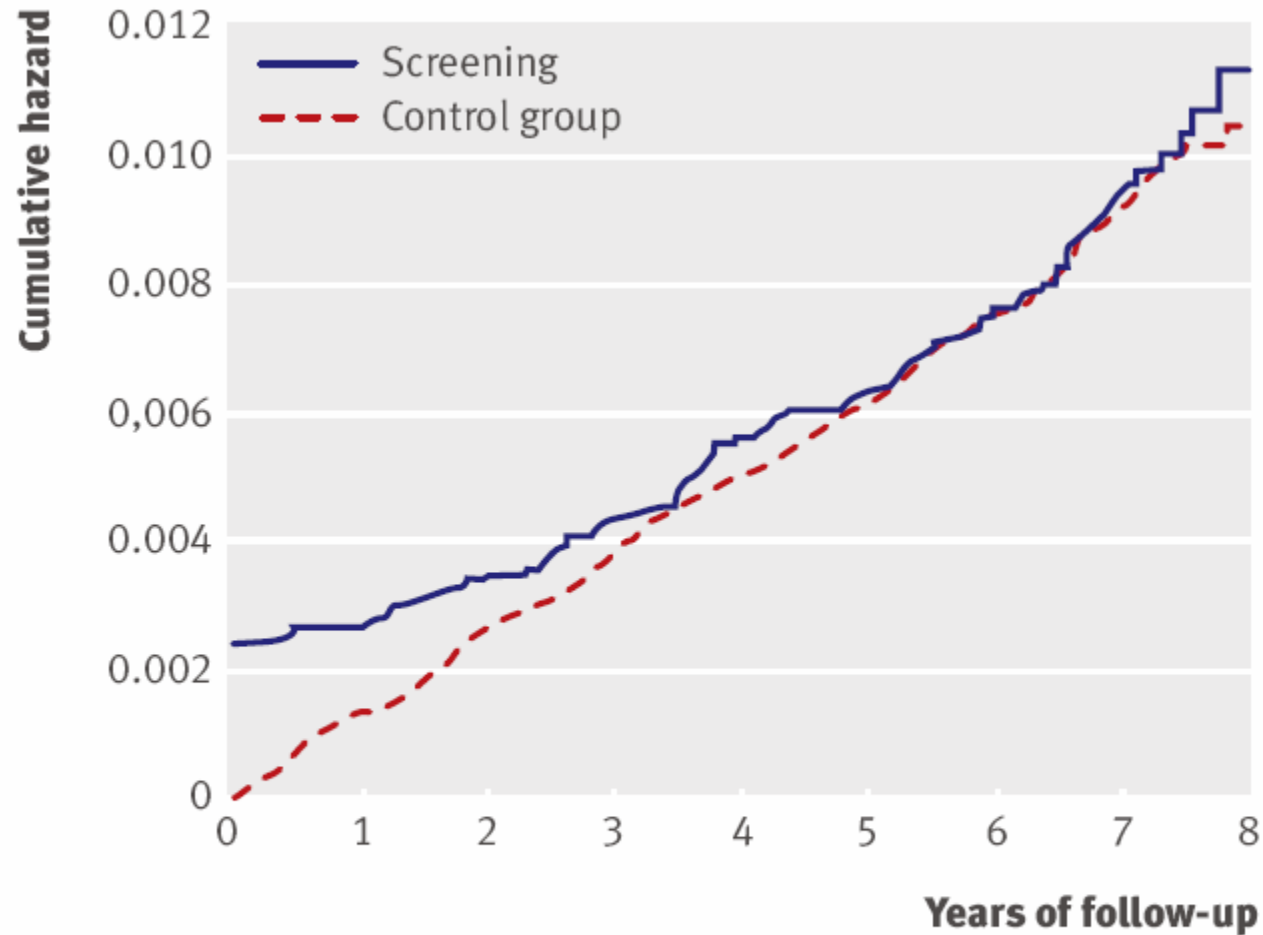
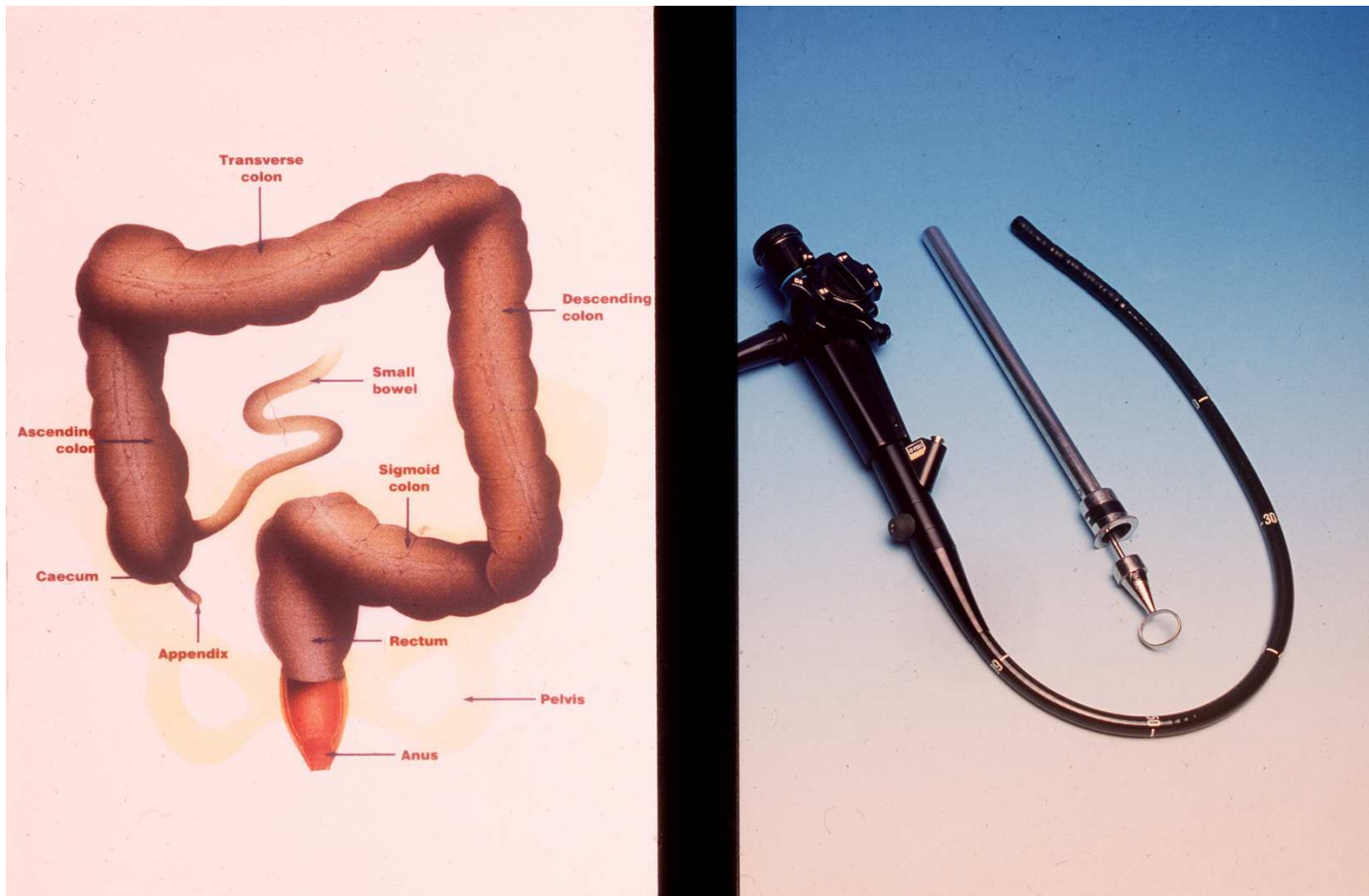
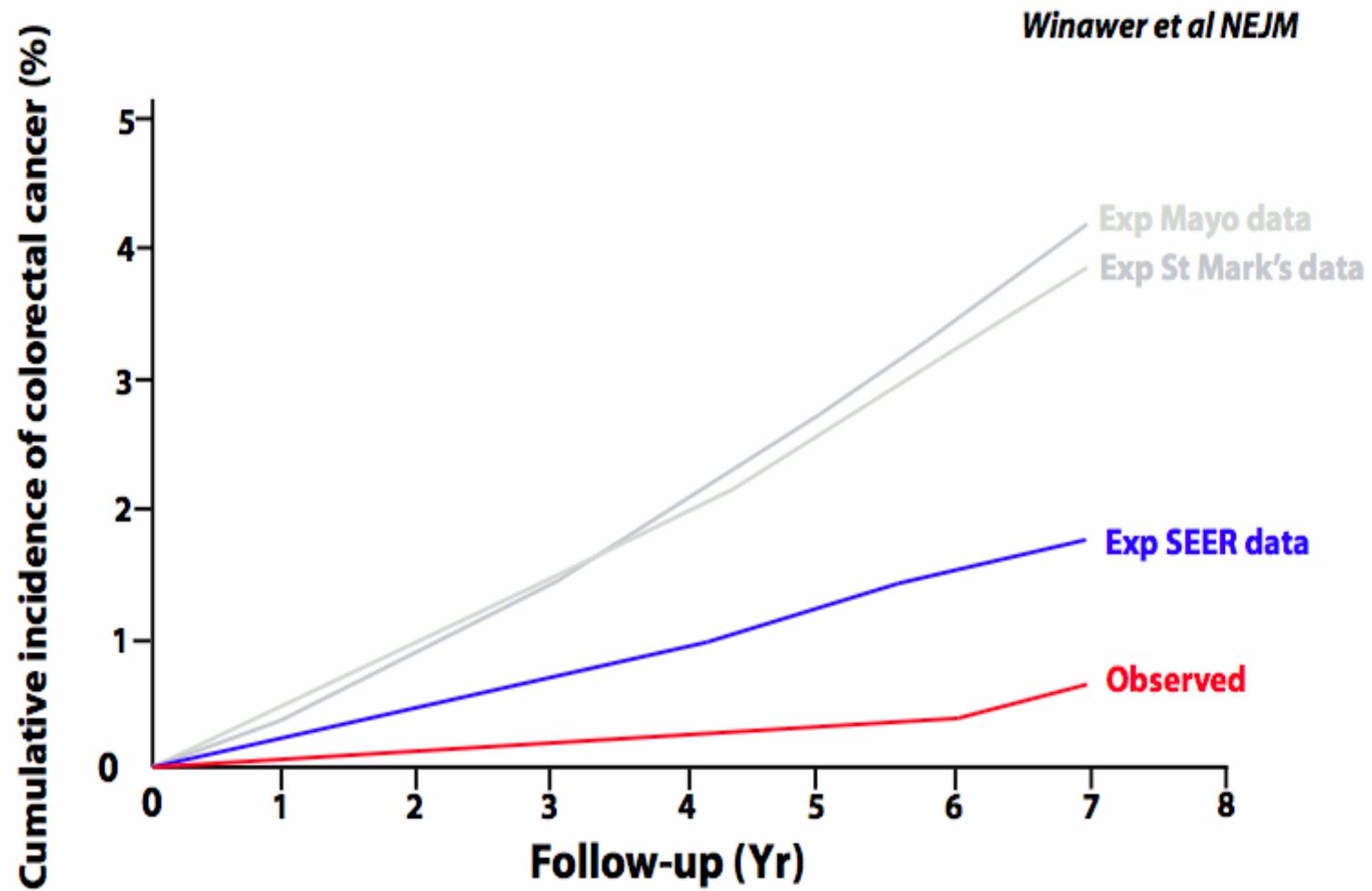


Fig 2 | Cumulative hazard for colorectal cancer in screening and control groups

Endoscopic Screening



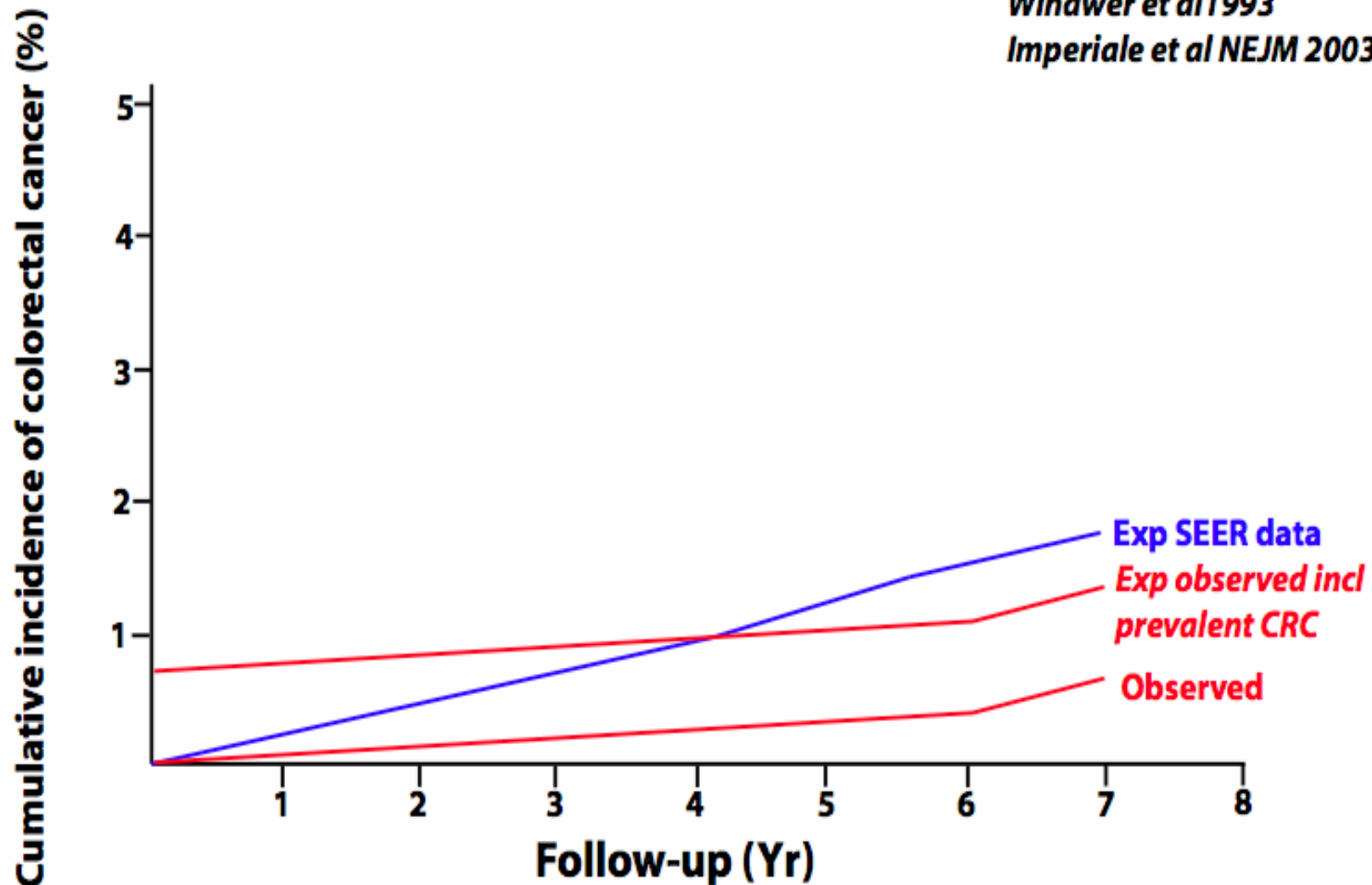
National Polyp Study



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.