Efficacia dello screening con sigmoidoscopia per il carcinoma del colon retto: i risultati del Trial SCORe

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Osservatorio Nazionale Screening

Firenze, 16 novembre 2011

METHODS

SCREENING TEST

Flexible sigmoidoscopy :

Scope advanced beyond the sigmoid-descending colon junction (complete test).

Small (< 6 mm) polyps removed using cold-snare technique.

BOWEL PREPARATION:

Single enema (133 ml sodium-phosphate) self-administered 2 hours before the test.

REFERRAL FOR COLONOSCOPY

- 1 distal polyp >= 6 mm

- >=3 adenomas < 6 mm

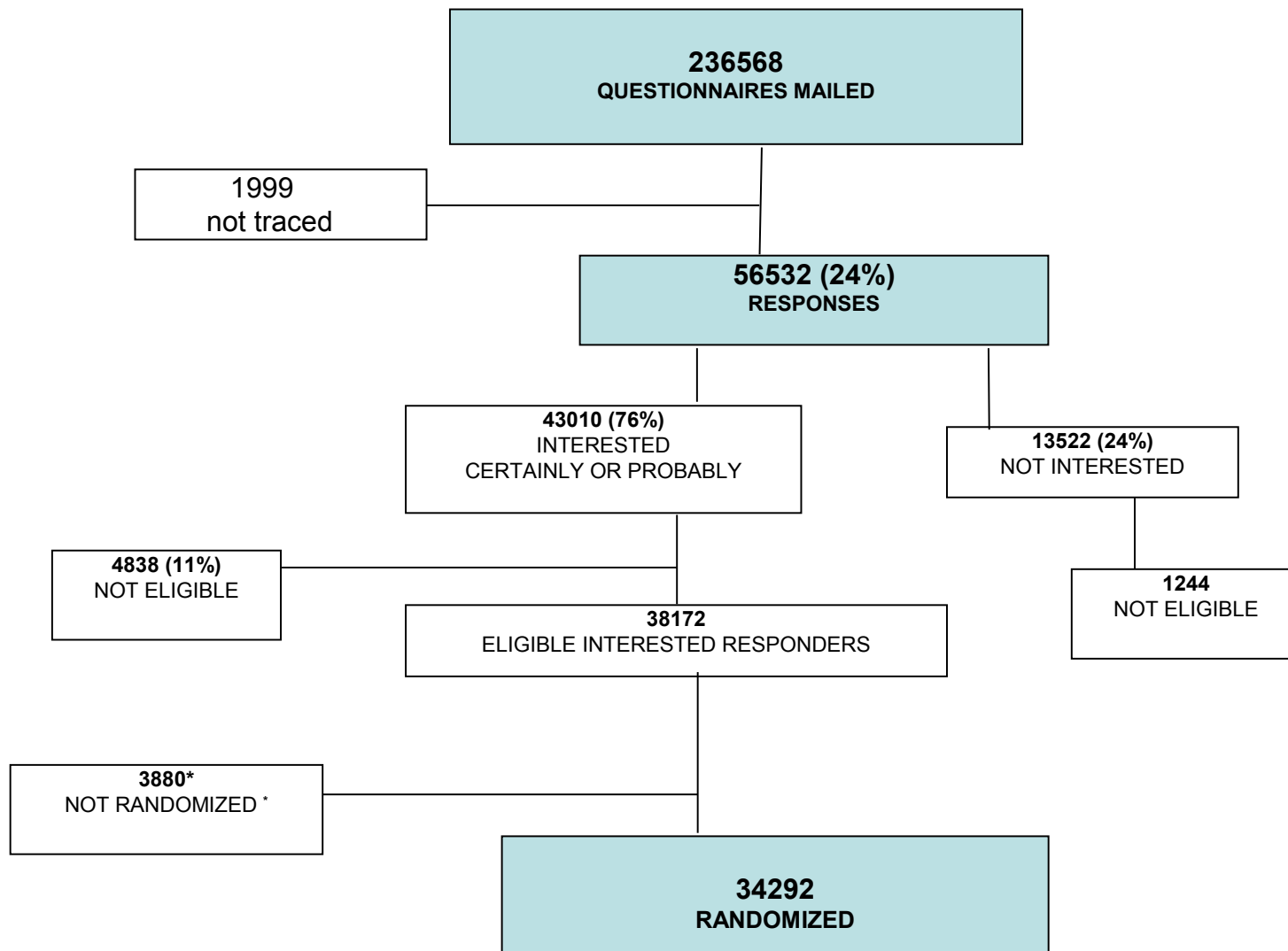- 1 high risk (severe dysplasia or cancer, villous histology) adenoma < 6 mm

ANALYSIS

Primary outcomes: **CRC incidence and mortality**

Intention to treat and per protocol analysis:

- Cumulative incidence & mortality **rates** per 10^5 person-years and **Rate Ratios** (RR) with 95% confidence interval (CI)
- We illustrate time to CRC and to death by estimating the **Nelson Aalen cumulative hazard function**
- We estimate **RR adjusted for non-compliance** in the per protocol analysis, using the method proposed by Cuzick et al.
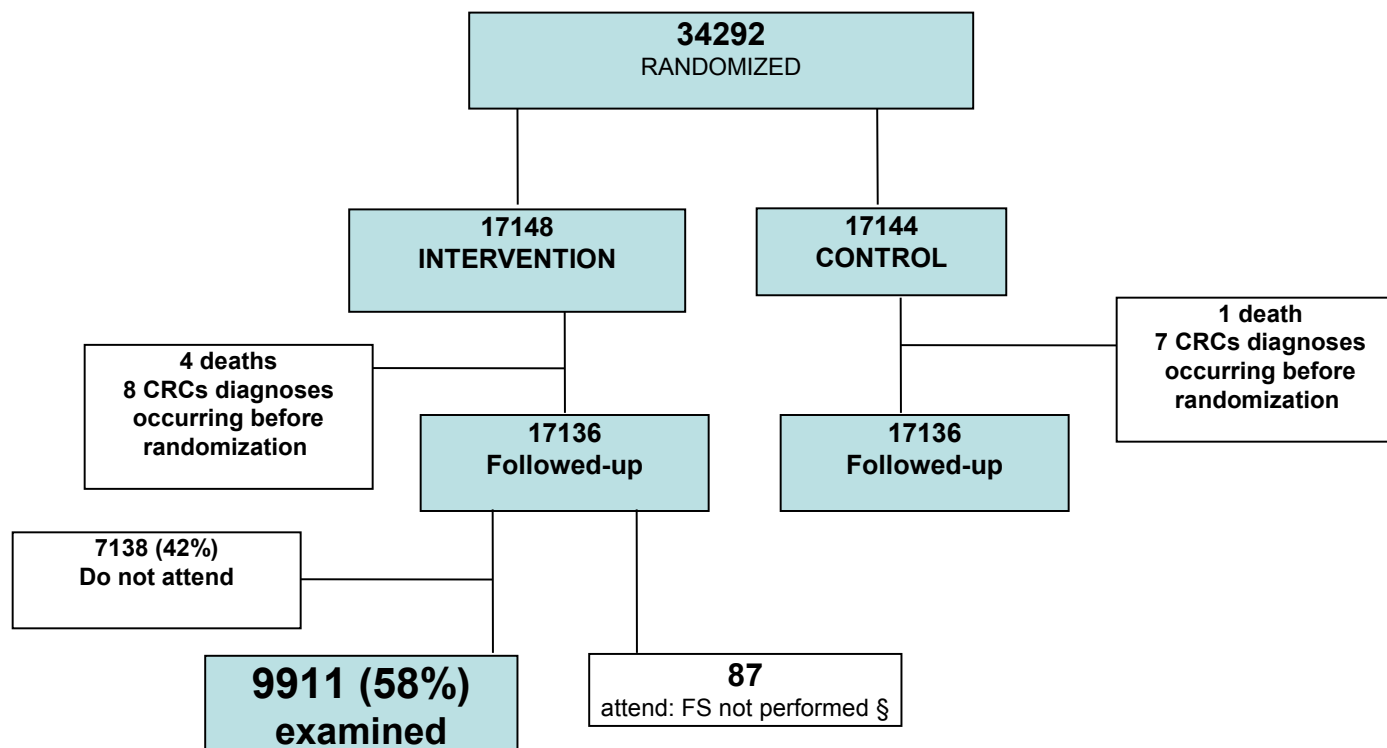
All statistical tests were two-sided and were considered to be statistically significant at $p < .05$

SCORE Trial profile-1

236568
QUESTIONNAIRES MAILED

1999
not traced

56532 (24%)
RESPONSES

43010 (76%)
INTERESTED
CERTAINLY OR PROBABLY

13522 (24%)
NOT INTERESTED

4838 (11%)
NOT ELIGIBLE

38172
ELIGIBLE INTERESTED RESPONDERS

1244
NOT ELIGIBLE

3880*
NOT RANDOMIZED *

34292
RANDOMIZED

* Based on the low response rate observed in Genoa among people responding that they would probably have the test if invited, these subjects where no longer randomized in that centre, starting from December 1996.

SCORE Trial profile-2

34292
RANDOMIZED

17148
INTERVENTION

17144
CONTROL

4 deaths
8 CRCs diagnoses
occurring before
randomization

1 death
7 CRCs diagnoses
occurring before
randomization

17136
Followed-up

17136
Followed-up

7138 (42%)
Do not attend

9911 (58%)
examined

87
attend: FS not performed §

§ 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.

FOLLOW-UP

Participants were followed-up until

31/12/2007 for incidence

31/12/2008 for mortality

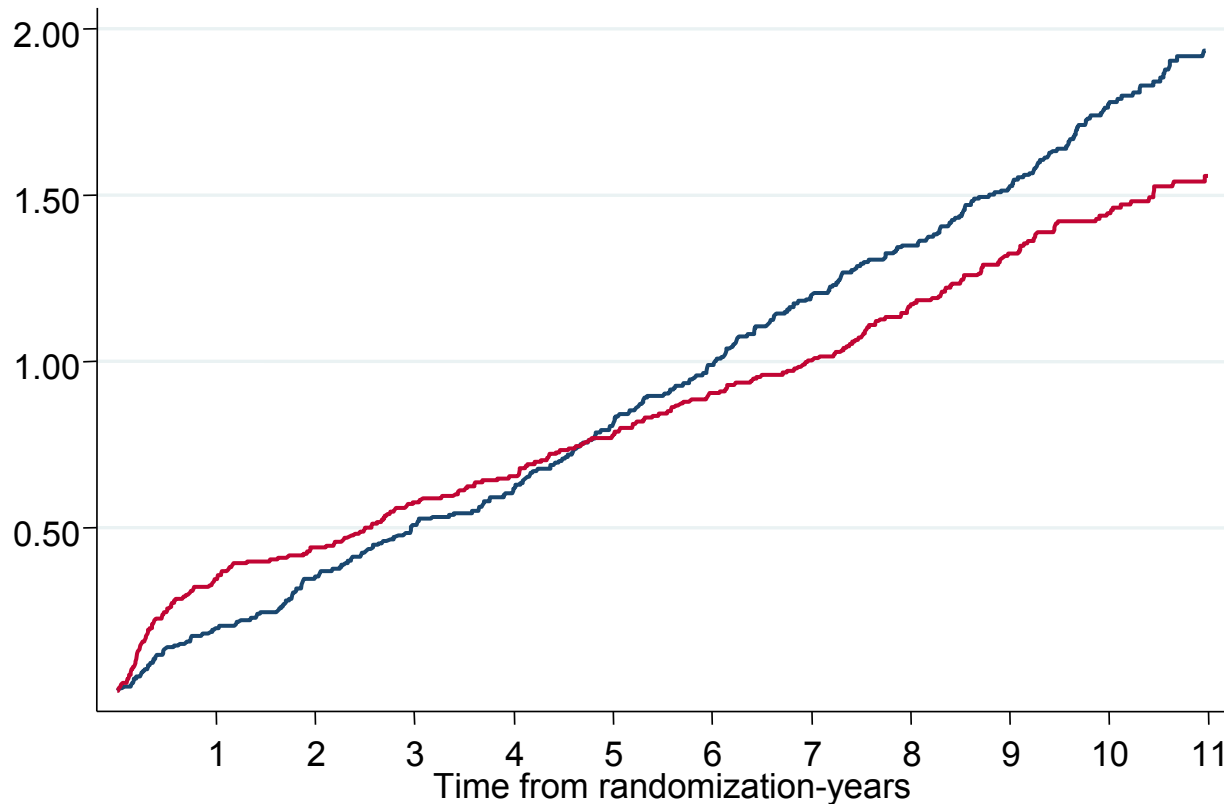Median follow-up time to death, emigration, or end of follow-up:

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, ALL SITES
Nelson Aalen Cumulative Hazard (%) by time from randomization
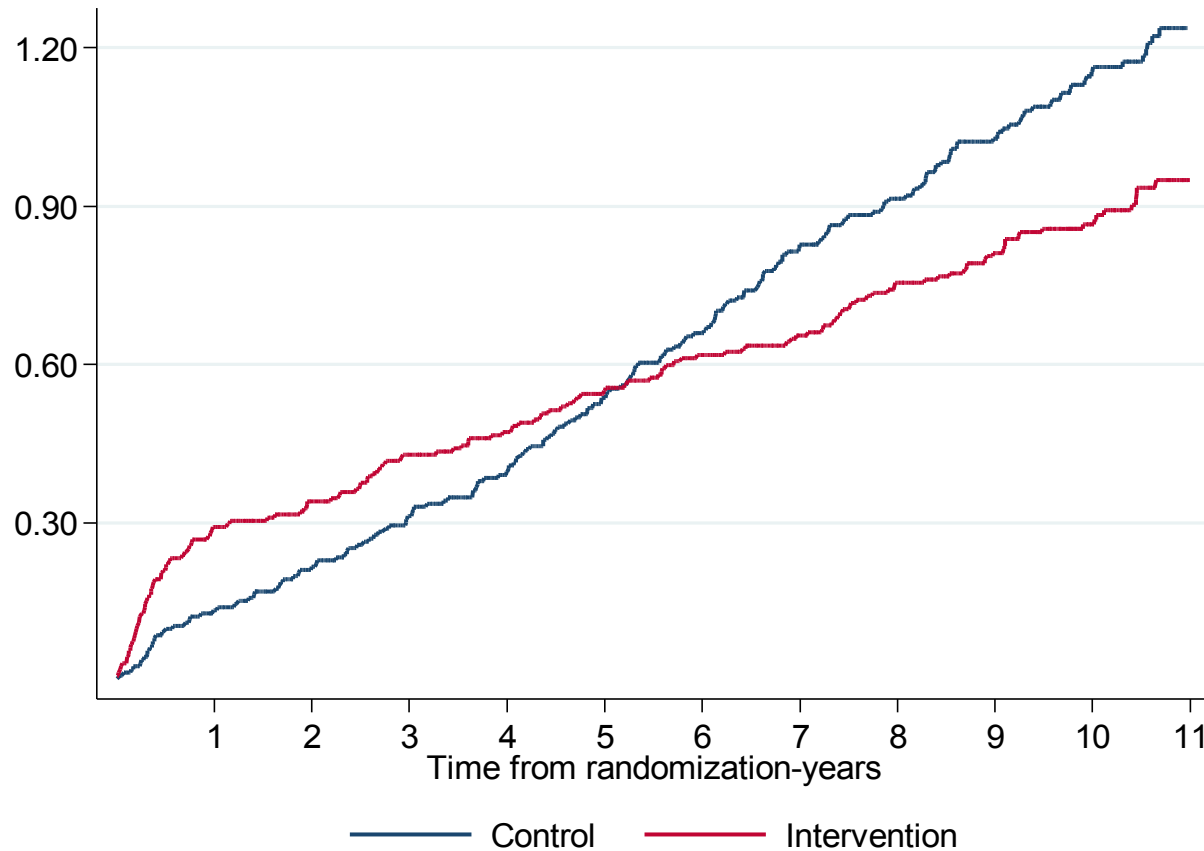

RR (95%CI) = 0.82 (0.69-0.96)

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

Intention to treat analysis-Colorectal cancer
INCIDENCE, Distal&Descendent
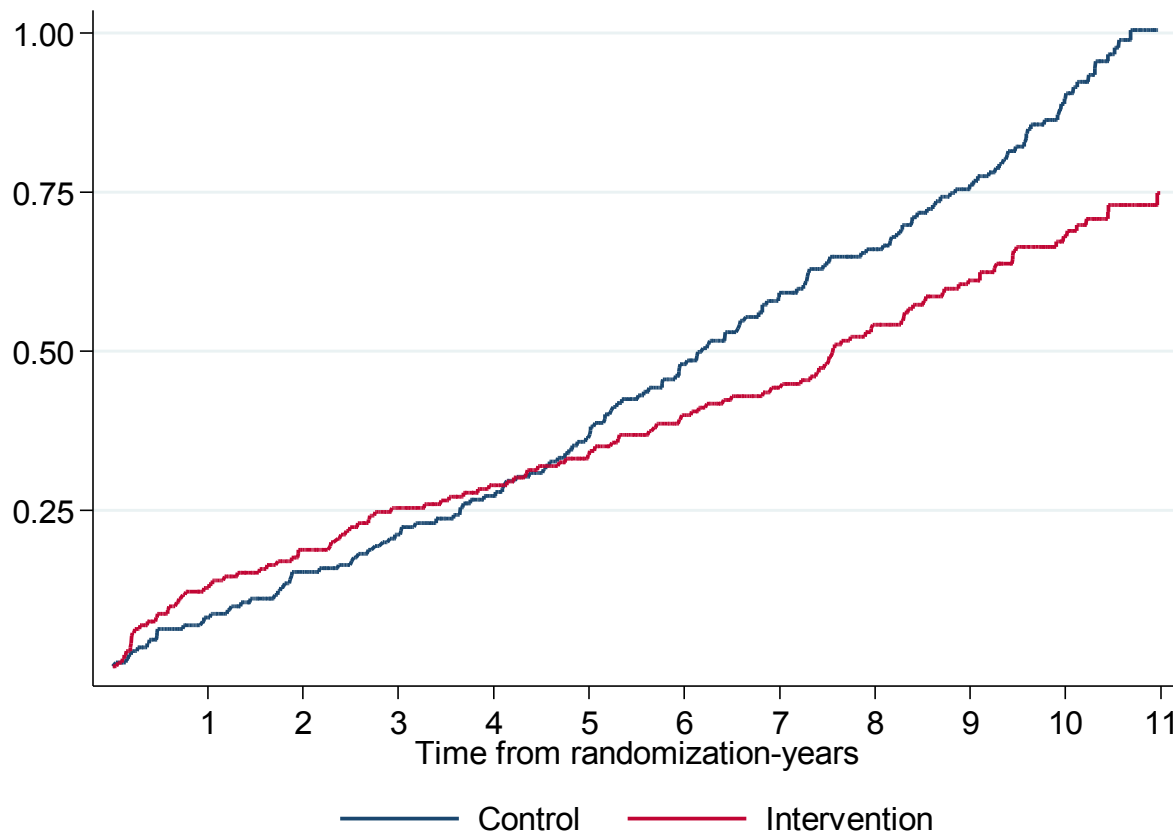### Nelson Aalen Cumulative Hazard (%) by time from randomization

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

Time from randomization-years

—— Control   —— Intervention

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
INCIDENCE, All sites Advanced
Nelson Aalen Cumulative Hazard (%) by time from randomization
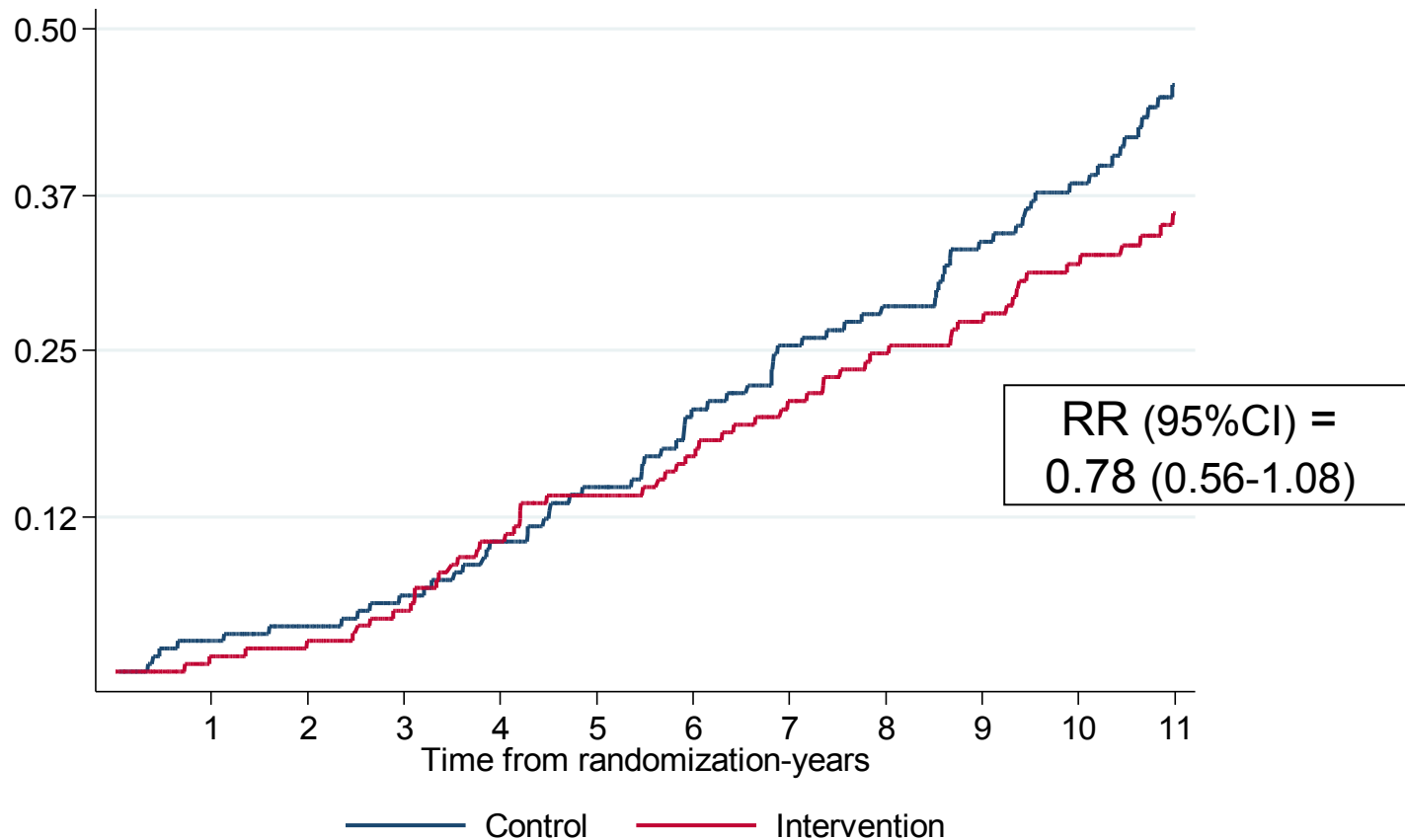

RR (95%CI) = 0.73 (0.57-0.94)

Cumulative Events by years from randomization						
	≤2	≤4	≤6	≤8	≤10	>10
Control	26	44	77	105	140	**152**
Intervention	30	46	63	85	104	**112**

Intention to treat analysis-Colorectal cancer
MORTALITY, ALL SITES

Nelson Aalen Cumulative Hazard (%) by time from randomization

RR (95%CI) =
0.78 (0.56-1.08)

Control   Intervention

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**

Colorectal cancer MORTALITY
by screening arm and colonic site
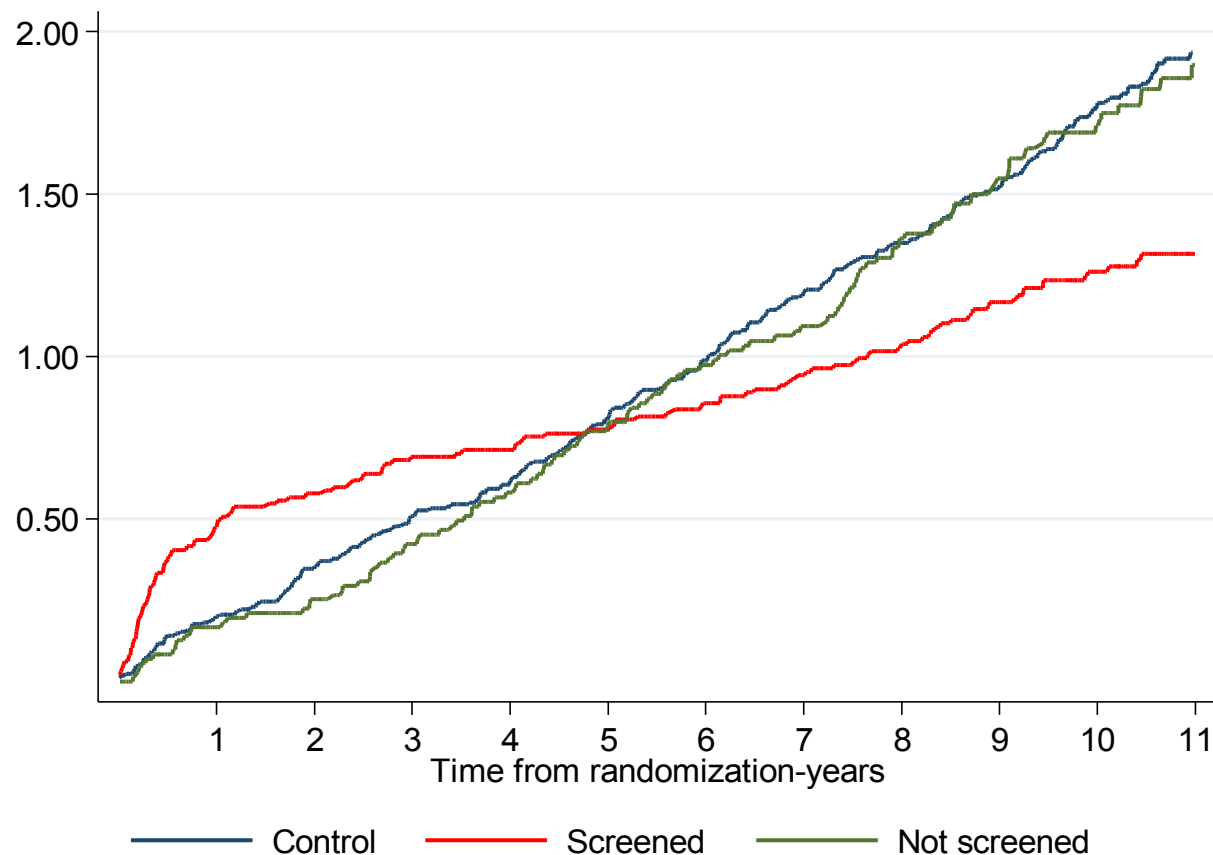## (Number of cases, Persons Years, Rates Ratios and 95% CI)

INTENTION TO TREAT ANALYSIS

	Control	Intervention	Rate ratio (95% CI)
	Cases	Cases	Intervention vs Control group
Mortality among patients diagnosed with CRC (all deaths, related or unrelated to CRC)			
	186 745 PY	187 532 PY	
All sites	94	71	0.75 (0.55-1.02)
Distal & descendent	55	40	0.72 (0.48-1.09)
CRC Mortality	186 745 PY	187 532 PY	
All sites	83	65	0.78 (0.56-1.08)
Distal & descendent	48	35	0.73 (0.47-1.12)
NON CRC MORTALITY	1150	1137	0.98 (0.91-1.07)

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)

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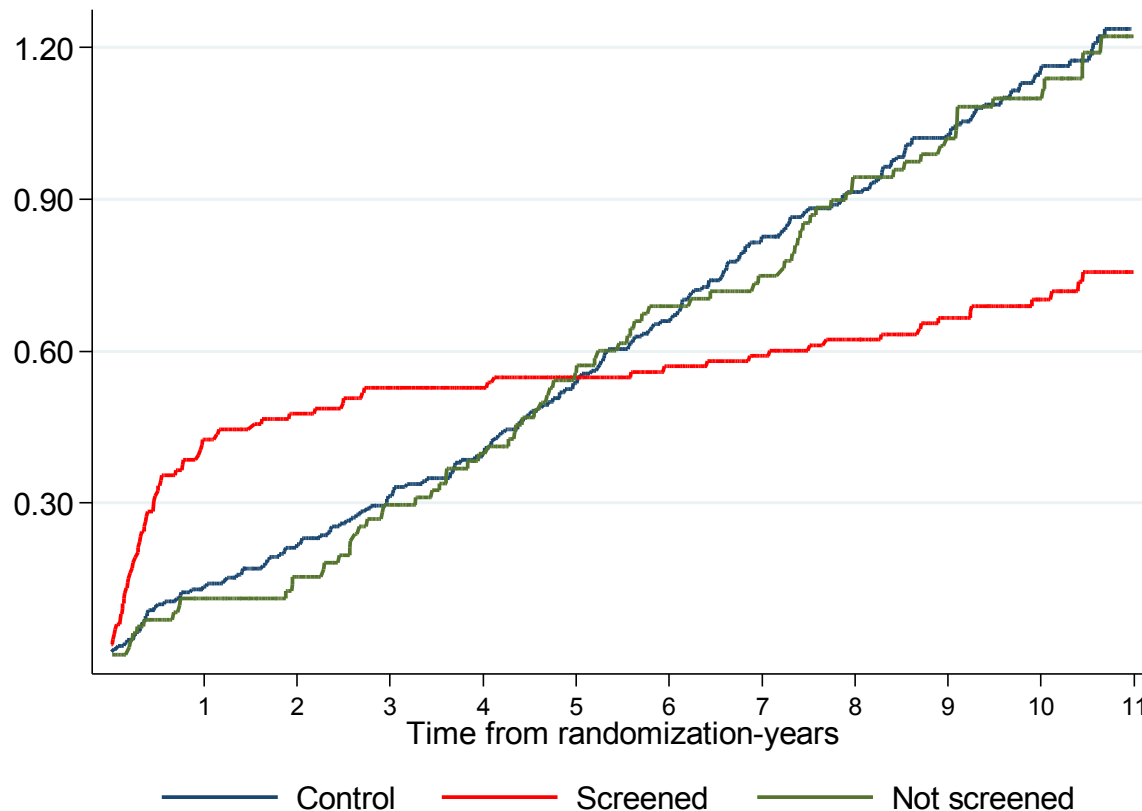
Cumulative Events by years from randomization						
	≤2	≤4	≤6	≤8	≤10	>10
Control	60	104	165	223	286	306
Not Screened	18	41	68	94	116	125
Screened	57	70	84	101	121	126

Per protocol analysis-Colorectal cancer
INCIDENCE, Distal&Descendent
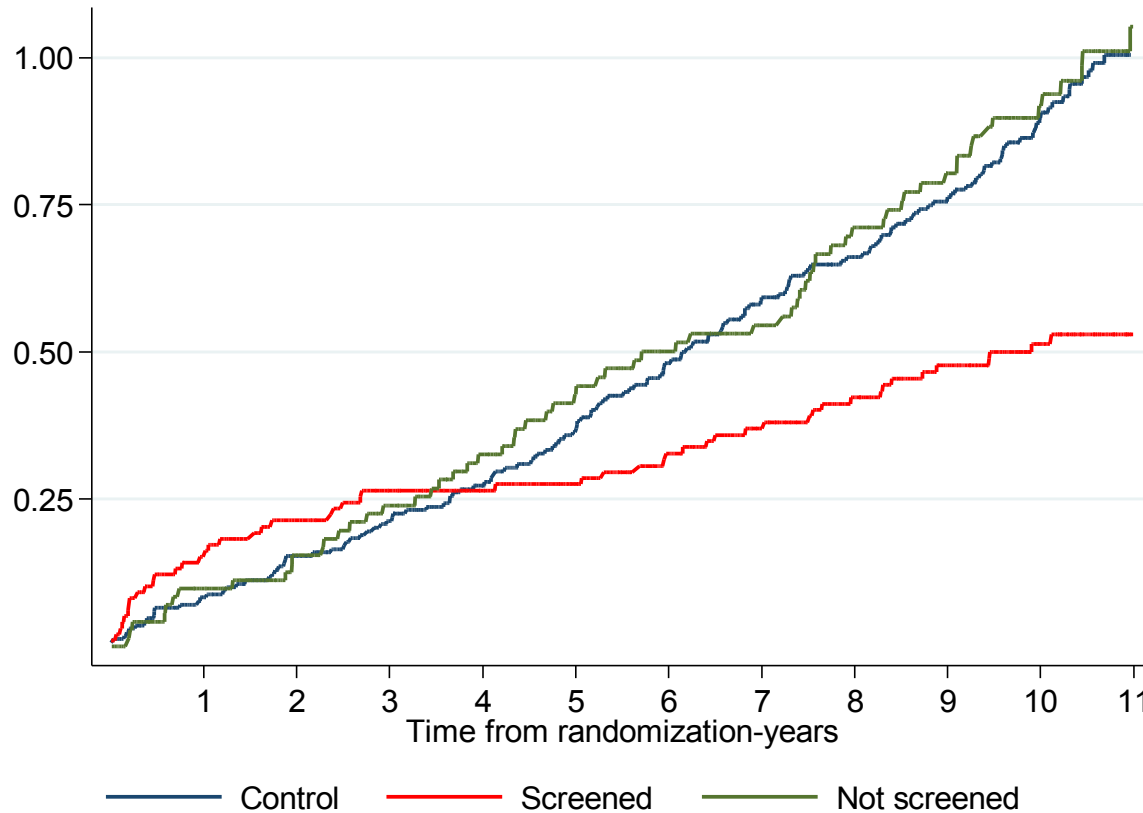Nelson Aalen Cumulative Hazard (%) by time from randomization

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

— Control — Screened — Not screened

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
INCIDENCE, All sites Advanced
Nelson Aalen Cumulative Hazard (%) by time from randomization
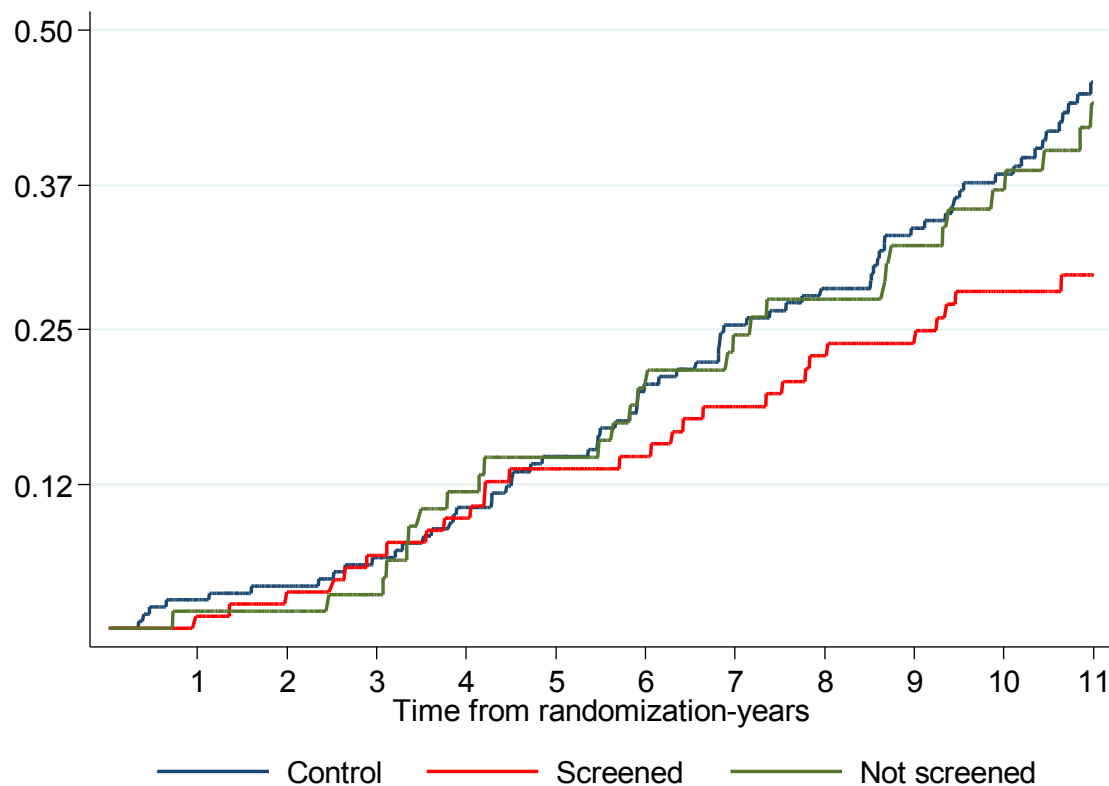

RR (95%CI) = 0.54 (0.39-0.76)

Cumulative Events by years from randomization						
	≤2	≤4	≤6	≤8	≤10	>10
Control	26	44	77	105	140	**152**
Not Screened	9	20	31	45	57	**64**
Screened	21	26	32	40	47	**48**

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**

Colorectal cancer MORTALITY
by screening arm and colonic site
(Number of cases, Persons Years, Rates Ratios and 95% CI)

PER PROTOCOL ANALYSIS

	Control	Not screened	Screened	Screened vs Control group
	Cases	Cases	Cases	Rate ratio (95% CI) adjusted*
Mortality among patients diagnosed with CRC (all deaths, related or unrelated to CRC)				
	186 745 PY	78 586 PY	108 946 PY	
All sites	94	38	33	**0.58 (0.38-0.87)**
Distal & descendent	55	26	14	**0.50 (0.26-0.94)**
CRC Mortality	186 745 PY	78 586 PY	108 946 PY	
All sites	83	35	30	**0.62 (0.40-0.96)**
Distal & descendent	48	23	12	**0.48 (0.24-0.94)**
NON CRC Mortality	1150	603	534	0.97 (0.85-1.09)

*Cuzick et al method (1997)

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

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)

N. Segnan – CPO 2010

Distal cancer incidence (Kaplan-Meier estimates)

C

Distal colon cancer: cumulative incidence (%)

HR=0.64

Number at risk

Control	112939	111165	109053	106529	103693	99926	18619
Intervention	57099	56153	55172	53985	52614	50744	9492

D

Distal colon cancer: cumulative incidence (%)

HR=0.50

Number at risk

Control	112939	111165	109053	106529	103693	99926	18619
Screened	40621	40156	39595	38885	38043	36827	7157
Not screened	16478	15997	15577	15100	14571	13917	2335
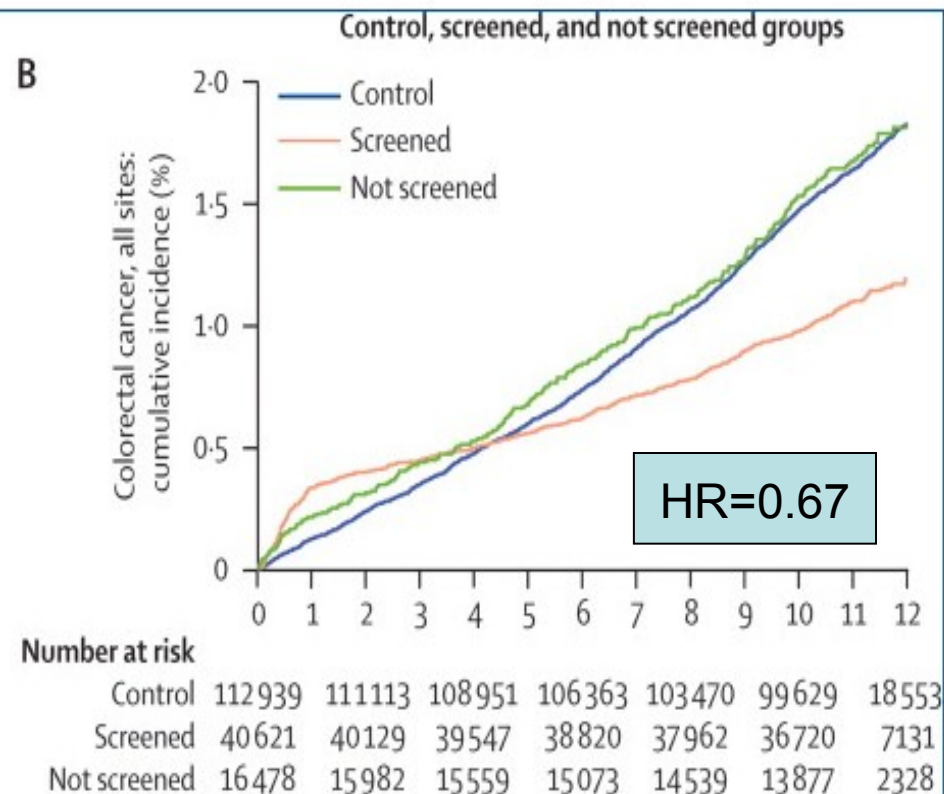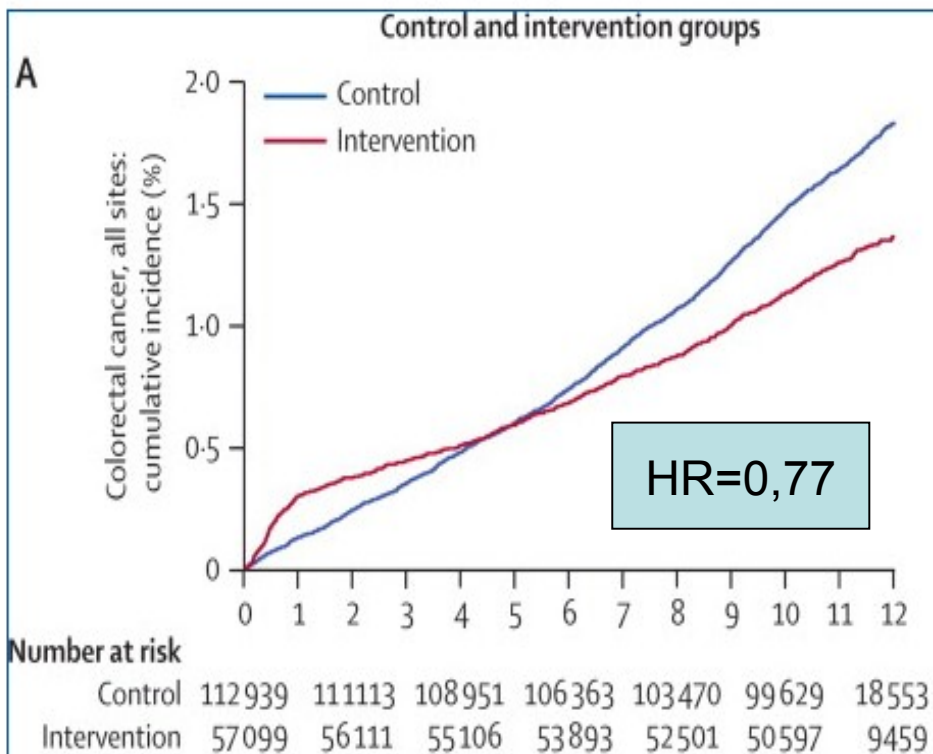
Colorectal cancer mortality (Kaplan-Meier estimates)

HR=0.69

HR=0.57

G

Cumulative colorectal cancer mortality (%)

Time from randomisation (years)

Number at risk

Control	112939	111321	109319	106907	104196	100597	18748
Intervention	57099	56300	55325	54164	52809	50972	9539

H

Cumulative colorectal cancer mortality (%)

Time from randomisation (years)

Number at risk

Control	112939	111321	109319	106907	104196	100597	18748
Screened	40621	40279	39705	39004	38169	36959	7187
Not screened	16478	16021	15620	15160	14640	14013	2352

Conclusions

- The findings of this trial confirm that a single sigmoidoscopy screening between age 55 and 64 can confer a substantial and long-lasting protective effect.

- Overall, CRC incidence was reduced by 31% among those who underwent screening and by 40%% when considering the distal colon only(rectum, sigmoid and descending colon).

- The observed reduction of CRC mortality among screened subjects was just slightly lower in the SCORE than in the UK Flexible Sigmoidoscopy screening trial (38% versus 43%).

- A statistically significant reduction in CRC mortality cannot be observed yet in the intention to treat analysis in the Italian trial.

Conclusions

- The selection process associated with the two-stage recruitment procedure was not as important with respect to CRC risk. The cumulative CRC incidence in the control group was about the same (306 cases observed) as it could be expected (316 cases), based on age, gender and calendar period specific incidence rates. This would suggest that the observed effect of screening on CRC incidence might be generalizable to the source population.

European guidelines for quality assurance in colorectal cancer screening and diagnosis

First Edition

Editors
N. Segnan
J. Patnick
L. von Karsa

Level of evidence

FOBT	**I**
Sigmoidoscopy	**II**
Colonoscopy	**III**

Estendere la sigmoidoscopia come test di screening per il CCR?

- Costi: circa 4 episodi di FIT per una FS?
- Detection Rate (cumulativa): 4 episodi di FIT ogni FS per adenomi avanzati e cancro?
- Detection di stadi avanzati: FIT > FS?
- Partecipazione cumulativa: a 4 FIT in 6 anni <=> che in 6 anni a 1 FS?
- Preferenze individuali?
- Proporzione di colonscopie: FIT(4 episodi) 20% vs <10% per FS?
- Riduzione incidenza e mortalità (50-80 aa) FS (once only) > che FIT 50-69 aa?

Workshop sullo screening con FS

Torino, Marzo 2012

COLORECTAL CANCER PREVENTION
BY ONCE-ONLY SIGMOIDOSCOPY SCREENING:
FOLLOW UP FINDINGS
OF THE ITALIAN TRIAL– SCORE

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

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Rimini: G. Fabbretti (Pathology Unit, Infermi Hospital, AUSL Rimini), S. Gasperoni (Gastroenterology Unit, S Maria delle Croci Hospital, Ravenna);

Turin: A. Bertone, M. Pennazio, M. Spandre (Gastroenterology Unit, San Giovanni AS Hospital, AOU S Giovanni Battista), M.Fracchia (Gastroenterology Unit ,Mauriziano Umberto I Hospital), S. Patriarca, and S. Rosso (Piedmont Cancer Registry and CPO Piemonte), D. Brunetti (CPO Piemonte), M. Demaria (ARPA Piemonte)

SCORE TRIAL
per protocol analysis

Table 2. CRC incidence and mortality among the SCORE trial subjects by per-protocol analysis*

Incidence	Control† 173 437 person-years§ No. of subjects with CRC	Control† Rates per 100 000 person-years (95% CI)	Intervention‡ Not screened 72 832 person-years§ No. of subjects with CRC	Intervention‡ Not screened Rates per 100 000 person-years (95% CI)	Intervention‡ Screened 101 345 person-years§) No. of subjects with CRC	Intervention‡ Screened Rates per 100 000 person-years (95% CI)	Rate ratio (95% CI) adjusted‖ Screened vs control group
All sites	306	176.43 (157.73 to 197.35)	125	171.63 (144.03 to 204.51)	126	124.33 (104.41 to 148.05)	0.69 (0.56 to 0.86)
Distal¶	198	114.16 (99.32 to 131.22)	81	111.21 (89.45 to 138.27)	71	70.06 (55.52 to 88.40)	0.60 (0.46 to 0.80)
Proximal#	108	62.27 (51.57 to 75.19)	44	60.41 (44.96 to 81.18)	55	54.27 (41.67 to 70.69)	0.85 (0.61 to 1.19)
Advanced CRC**							
All sites	152	87.64 (74.76 to 102.74)	64	87.87 (68.78 to 112.27)	48	47.36 (35.69 to 62.85)	0.54 (0.39 to 0.76)
Distal¶	90	51.89 (42.21 to 63.80)	46	63.16 (47.31 to 84.32)	23	22.70 (15.08 to 34.15)	0.52 (0.31 to 0.86)
Proximal#	62	35.75 (27.87 to 45.85)	18	24.71 (15.57 to 39.23)	25	24.67 (16.67 to 36.51)	0.56 (0.36 to 0.87)

Mortality	Control† 186 745 person-years†† No. of deaths	Control† Rates per 100 000 person-years (95% CI)	Intervention‡ Not screened (78 586 person-years††) No. of deaths	Intervention‡ Not screened Rates per 100 000 person-years (95% CI)	Intervention‡ Screened (108 946 person-years††) No. of deaths	Intervention‡ Screened Rates per 100 000 person-years (95% CI)	Rate ratio (95% CI) adjusted‖ Screened vs control group
All deaths among subjects diagnosed with CRC‡‡							
All sites	94	50.34 (41.12 to 61.61)	38	48.35 (35.18 to 66.44)	33	30.29 (21.53 to 42.61)	0.58 (0.38 to 0.87)
Distal¶	55	29.45 (22.61 to 38.36)	26	33.08 (22.52 to 48.58)	14	12.85 (7.61 to 21.70)	0.50 (0.26 to 0.94)
Proximal#	39	20.88 (15.26 to 28.58)	12	15.27 (8.67 to 26.88)	19	17.44 (11.12 to 27.34)	0.66 (0.39 to 1.12)
CRC deaths							
All sites	83	44.45 (35.84 to 55.11)	35	44.54 (31.97 to 62.02)	30	27.54 (19.25 to 39.38)	0.62 (0.40 to 0.96)
Distal¶	48	25.70 (19.37 to 34.11)	23	29.27 (19.45 to 44.03)	12	11.01 (6.25 to 19.39)	0.48 (0.24 to 0.94)
Proximal#	35	18.74 (13.45 to 26.10)	12	15.27 (8.67 to 26.89)	18	16.52 (10.41 to 26.22)	0.78 (0.45 to 1.35)
Non-CRC deaths§§							
	1150	615.81 (581.23 to 652.45)	603	767.31 (708.32 to 830.91)	534	490.15 (450.29 to 533.54)	0.97 (0.85 to 1.09)

* CRC incidence and mortality were analyzed by all sites, distal, and proximal cancers. CI = confidence interval; CRC = colorectal cancer; RR = rate ratio; SCORE = Screening for Colon Rectum

Colorectal cancer MORTALITY
by screening arm and colonic site
(Number of cases, Persons Years, Rates Ratios and 95% CI)

PER PROTOCOL ANALYSIS

	Control	Not screened	Screened	Screened vs Control group
	Cases	Cases	Cases	Rate ratio (95% CI) adjusted*
Mortality among patients diagnosed with CRC (all deaths, related or unrelated to CRC)				
	186 745 PY	78 586 PY	108 946 PY	
All sites	94	38	33	**0.58 (0.38-0.87)**
Distal & descendent	55	26	14	**0.50 (0.26-0.94)**
CRC Mortality	186 745 PY	78 586 PY	108 946 PY	
All sites	83	35	30	**0.62 (0.40-0.96)**
Distal & descendent	48	23	12	**0.48 (0.24-0.94)**
NON CRC Mortality	1150	603	534	0.97 (0.85-1.09)

*Cuzick et al method (1997)

	Control[†]		Intervention[‡]				Rate ratio (95% CI) adjusted[‖]
	173437 person-years[§]		Not screened		Screened		
			72832 person-years[§]		101345 person-years[§])		
Incidence	No. of subjects with CRC	Rates per 100000 person-years (95% CI)	No. of subjects with CRC	Rates per 100000 person-years (95% CI)	No. of subjects with CRC	Rates per 100000 person-years (95% CI)	Screened vs control group
All sites	306	176.43 (157.73 to 197.35)	125	171.63 (144.03 to 204.51)	126	124.33 (104.41 to 148.05)	0.69 (0.56 to 0.86)
Distal¶	198	114.16 (99.32 to 131.22)	81	111.21 (89.45 to 138.27)	71	70.06 (55.52 to 88.40)	0.60 (0.46 to 0.80)
Proximal#	108	62.27 (51.57 to 75.19)	44	60.41 (44.96 to 81.18)	55	54.27 (41.67 to 70.69)	0.85 (0.61 to 1.19)
Advanced CRC**							
All sites	152	87.64 (74.76 to 102.74)	64	87.87 (68.78 to 112.27)	48	47.36 (35.69 to 62.85)	0.54 (0.39 to 0.76)
Distal¶	90	51.89 (42.21 to 63.80)	46	63.16 (47.31 to 84.32)	23	22.70 (15.08 to 34.15)	0.52 (0.31 to 0.86)
Proximal#	62	35.75 (27.87 to 45.85)	18	24.71 (15.57 to 39.23)	25	24.67 (16.67 to 36.51)	0.56 (0.36 to 0.87)

SCORe TRIAL
Age and Gender results

Table 3. CRC incidence by sex and age at randomization by intention-to-treat and per-protocol analysis*

Intention-to-treat analysis

	Control group†			Intervention group‡			Intervention vs control group
	No. of subjects with CRC	Person-years§	Rate per 100 000 person-years (95% CI)	No. of subjects with CRC	Person-years§	Rate per 100 000 person-years (95% CI)	RR (95% CI)
Sex							
Women	118	86734	136.05 (113.36 to 162.95)	87	88 288	98.54 (79.87 to 121.58)	0.72 (0.55 to 0.96)
Men	188	86703	216.83 (187.95 to 250.15)	164	85 889	190.94 (163.85 to 222.52)	0.88 (0.71 to 1.09)
Age, y‖							
55–59	157	98773	158.95 (135.93 to 185.86)	131	97 980	133.70 (112.66 to 158.67)	0.84 (0.67 to 1.06)
>60	149	74664	199.56 (169.96 to 234.32)	120	76 197	157.49 (131.69 to 188.34)	0.79 (0.62 to 1.00)

Per-protocol analysis

	Control group†			Intervention group‡						Screened vs control group
				Not screened			Screened			
	No. of subjects with CRC	Person-years§	Rate per 100 000 person-years (95% CI)	No. of subjects with CRC	Person-years§	Rate per 100 000 person-years (95% CI)	No. of subjects with CRC	Person-years§	Rate per 100 000 person-years (95% CI)	Adjusted RR (95% CI)¶
Sex										
Women	118	86734	136.05 (113.36 to 162.95)	47	40335	116.52 (87.55 to 155.09)	40	47953	83.42 (61.19 to 113.72)	0.55 (0.39 to 0.77)
Men	188	86703	216.83 (187.95 to 250.15)	78	32497	240.02 (192.25 to 299.66)	86	53392	161.07 (130.39 to 198.98)	0.79 (0.60 to 1.06)
Age, y‖										
55–59	157	98773	158.95 (135.93 to 185.86)	65	39762	163.47 (128.19 to 208.46)	66	58218	113.37 (89.06 to 144.30)	0.73 (0.54 to 0.99)
>60	149	74664	199.56 (169.96 to 234.32)	60	33071	181.43 (140.87 to 233.67)	60	43126	139.13 (108.02 to 179.18)	0.65 (0.48 to 0.89)

Colorectal cancer INCIDENCE
by screening arm and colonic site
(Number of cases, Persons Years, Rates Ratios and 95% CI)

INTENTION TO TREAT ANALYSIS

	Control	Intervention	Rate ratio (95% CI)
	Cases	Cases	Intervention vs Control group
Incidence	173 437 PY	174 177 PY	
All sites	306	251	**0.82 (0.69-0.96)**
Distal & descendent	198	152	**0.76 (0.62-0.94)**
Advanced	173 437 PY	174 177 PY	
All sites	152	112	**0.73 (0.57-0.94)**
Distal & descendent	90	69	0.76 (0.56-1.04)

Subjects by characteristics of screen-detected lesions in the distal and proximal colon by gender

	Total N (%)	Men N (%)	Women N (%)
No polyp	8169 (82.4)	4112 (78.0)	4057 (87.4)
Non- neoplastic polyp	1338 (13.5)	872 (16.5)	466 (10.0)
High risk adenoma	350 (3.5)	245 (4.6)	105 (2.3)
Cancer	54 (0.5)	40 (0.8)	14 (0.3)
Total screened	9911	5269	4642

Modified from Segnan et al. Journal of the National Cancer Institute 2002; 94(23)

Colorectal cancer INCIDENCE
by screening arm and colonic site
(Number of cases, Persons Years, Rates Ratios and 95% CI)

PER PROTOCOL ANALYSIS   *Cuzick et al method (1997)

	Control	Not screened	Screened	Screened vs Control group
	Cases	Cases	Cases	Rate ratio (95% CI) adjusted*
Incidence	173 437 PY	72 832 PY	101 345 PY	
All sites	306	125	126	**0.69 (0.56-0.86)**
Distal & descendent	198	81	71	**0.60 (0.46-0.80)**
Advanced	173 437 PY	72 832 PY	101 345 PY	
All sites	152	64	48	**0.54 (0.39-0.76)**
Distal & descendent	90	46	23	**0.52 (0.31-0.86)**

POPULATION

- **Males and females aged 55 to 64 years** recruited between October 1995 and April 1999 in 6 Italian towns

EXCLUSION CRITERIA

✓ **Previous CRC, polyps, IBD**

✓ **Endoscopy within previous 2 years**

✓ **2 first degree relatives with CRC**

✓ **Severe disease**

✓ **Severe psychiatric symptoms**

Persons at risk at the beginning of the period by years from randomization

Intention to treat analysis							Per protocol analysis						
Years from randomization	≤2	≤4	≤6	≤8	≤10	>10	Years from randomization	≤2	≤4	≤6	≤8	≤10	>10
INCIDENCE													
Persons at risk at the beginning of the period by years from randomization													
Control	17136	16833	16540	16220	15914	11795	Control	17136	16833	16540	16220	15914	11795
Intervention	17136	16836	16582	16273	15984	12048	Not screened	7225	7066	6924	6762	6134	5098
							Screened	9911	9772	9659	9512	9373	6950
MORTALITY													
Persons at risk at the beginning of the period by years from randomization													
Control	17136	16884	16623	16363	16081	14557	Control	17136	16884	16623	16363	16081	14557
Intervention	17136	16906	16671	16410	16133	14710	Not screened	7225	7082	6955	6823	6686	6277
							Screened	9911	9825	9717	9587	9448	8434

Number (%) of people with polyps or cancer detected in the PROXIMAL COLON by gender - SCORE Trial

	TOTAL N (%)	Men N (%)	Women N (%)
Underwent colonoscopy	747	509	238
Any polyp	174 (23.3)	129 (25.3)	45 (18.9)
Adenomas	116 (15.5)	86 (16.9)	30 (12.6)
≥ 3 adenomas	21 (2.8)	14 (2.8)	7 (2.9)
Tubulo-villous / villous histology severe dysplasia	27 (3.6)	24 (4.7)	3 (1.3)
Cancers	7 (0.9)	6 (1.2)	1 (0.4)
Advanced pathology	35 (4.7)	29 (5.7)	6 (2.5)

Segnan et al. Journal of the National Cancer Institute 2002; 94(23)

Colorectal cancer INCIDENCE
by screening arm and colonic site
(Number of cases, Persons Years, Rates Ratios and 95% CI)

INTENTION TO TREAT ANALYSIS

	Control	Intervention	Rate ratio (95% CI)
	Cases	Cases	Intervention vs control group
Incidence	173 437 PY	174 177 PY	
Proximal	108	99	0.91 (0.69-1.20)
Advanced	173 437 PY	174 177 PY	
Proximal	62	43	0.69 (0.47-1.02)

Colorectal cancer MORMALITY
by screening arm and colonic site
(Number of cases, Persons Years, Rates Ratios and 95% CI)

INTENTION TO TREAT ANALYSIS

	Control	Intervention	Rate ratio (95% CI)
	Cases	Cases	Intervention vs control group
Mortality among patients diagnosed with CRC (all deaths, related or unrelated to CRC)			
	186 745 PY	187 532 PY	
Proximal	39	31	0.79 (0.49-1.27)
CRC Mortality	186 745 PY	187 532 PY	
Proximal	35	30	0.85 (0.52-1.39)

Colorectal cancer INCIDENCE
by screening arm and colonic site
(Number of cases, Persons Years, Rates Ratios and 95% CI)

PER PROTOCOL ANALYSIS

	Control	Not screened	Screened	Screened vs Control group
	Cases	Cases	Cases	Rate ratio (95% CI) adjusted
Incidence	173 437 PY	72 832 PY	101 345 PY	
Proximal	108	44	55	0.85 (0.61-1.19)
Advanced	173 437 PY	72 832 PY	101 345 PY	
Proximal	62	18	25	0.56 (0.36-0.87)

Colorectal cancer MORTALITY
by screening arm and colonic site
## (Number of cases, Persons Years, Rates Ratios and 95% CI)

PER PROTOCOL ANALYSIS

	Control	Not screened	Screened	Screened vs Control group
	Cases	Cases	Cases	Rate ratio (95% CI) adjusted
Mortality among patients diagnosed with CRC (all deaths, related or unrelated to CRC)				
	186 745 PY	78 586 PY	108 946 PY	
Proximal	39	12	19	0.66 (0.39-1.12)
CRC Mortality	186 745 PY	78 586 PY	108 946 PY	
Proximal	35	12	18	0.78 (0.45-1.35)

Intention to treat analysis - Colorectal cancer
INCIDENCE, PROXIMAL
Nelson Aalen Cumulative Hazard (%) by time from randomization
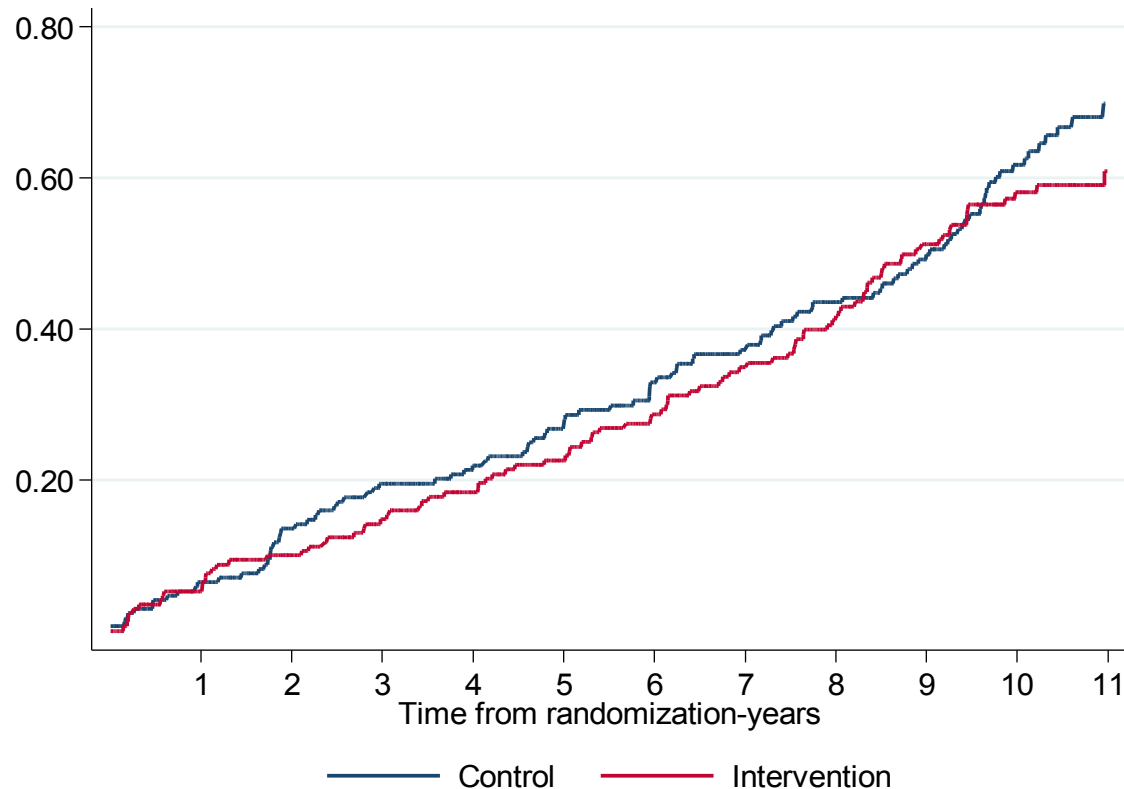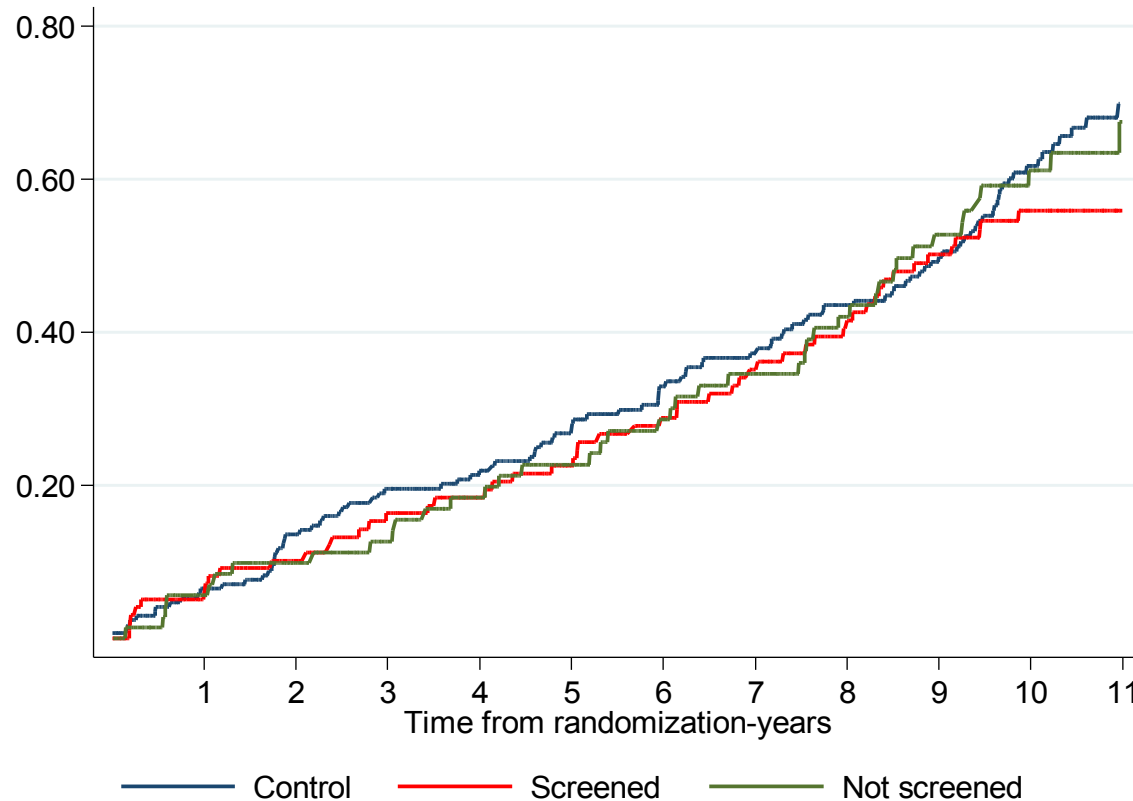

RR (95%CI) = 0.91 (0.69-1.20)

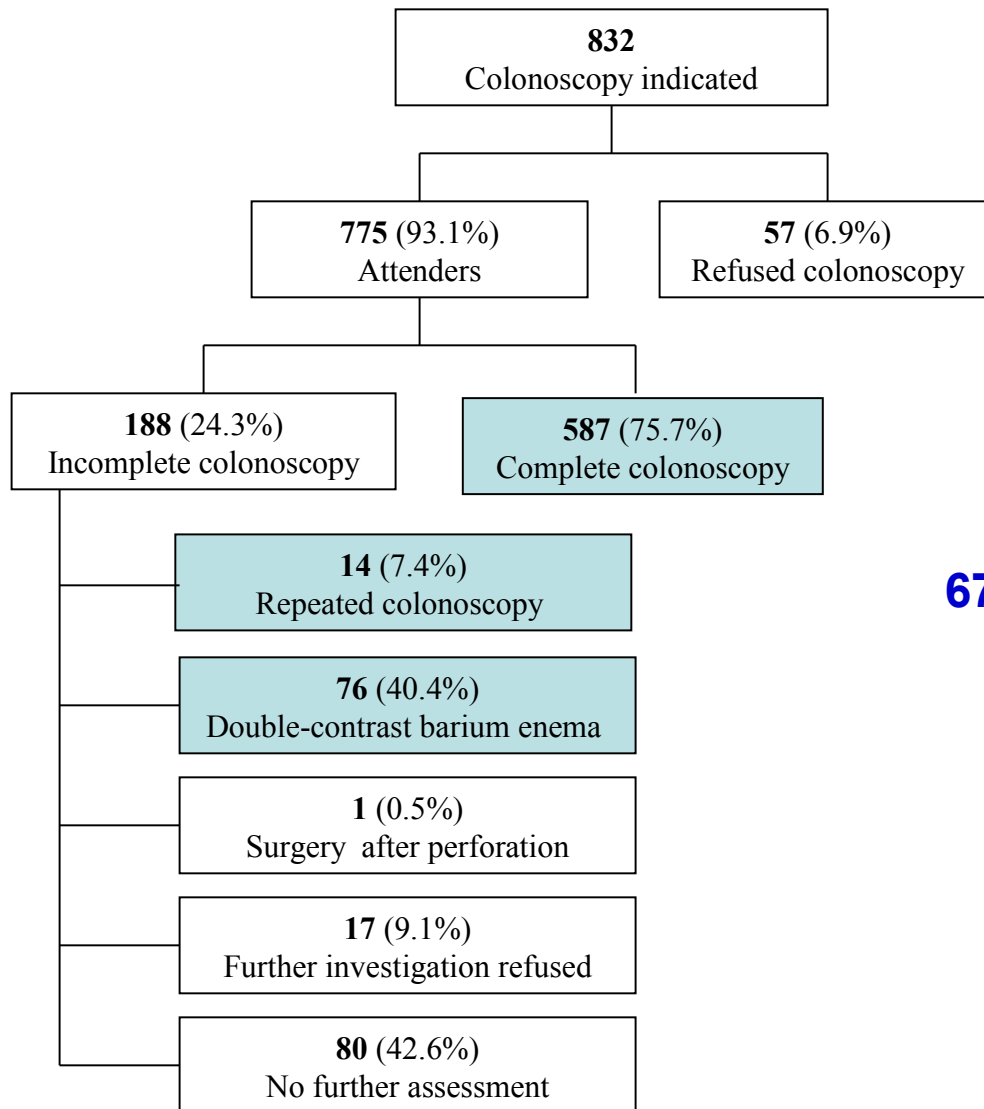| Cumulative Events by years from randomization						
	≤2	≤4	≤6	≤8	≤10	>10
Control	23	37	55	72	99	**108**
Intervention	17	31	48	69	94	**99**

Per protocol analysis - Colorectal cancer
INCIDENCE, PROXIMAL
Nelson Aalen Cumulative Hazard (%) by time from randomization

RR (95%CI) =
0.85 (0.61-1.19)

Control — Screened — Not screened

Cumulative Events by years from randomization						
	≤2	≤4	≤6	≤8	≤10	>10
Control	23	37	55	72	99	108
Not Screened	11	28	48	65	75	81
Screened	47	52	56	61	68	71

Trial Profile showing indication to colonoscopy after screening sigmoidoscopy, and management of subjects who received colonoscopy

832
Colonoscopy indicated

775 (93.1%)
Attenders

57 (6.9%)
Refused colonoscopy

188 (24.3%)
Incomplete colonoscopy

587 (75.7%)
Complete colonoscopy

14 (7.4%)
Repeated colonoscopy

76 (40.4%)
Double-contrast barium enema

1 (0.5%)
Surgery after perforation

17 (9.1%)
Further investigation refused

80 (42.6%)
No further assessment

677 complete bowel examinations

Completion rate: 87%

Segnan et al. Journal of the National Cancer Institute 2002; 94(23)

Characteristics of screen-detected lesions in the **DISTAL COLON** by gender

	Total N (%)	Men N (%)	Women N (%)
No polyp	8169 (82.4)	4112 (78.0)	4057 (87.4)
Non- neoplastic polyp	515 (5.2)	358 (6.8)	157 (3.4)
High risk adenoma	341 (3.44)	239 (4.54)	102 (2.20)
Cancer	47 (0.5)	34 (0.6)	13 (0.3)
Total screened	9911	5269	4642

Segnan et al. Journal of the National Cancer Institute 2002; 94(23)

Intention to treat analysis - Colorectal cancer
INCIDENCE, ALL SITES
Nelson Aalen Cumulative Hazard (%) by time from randomization

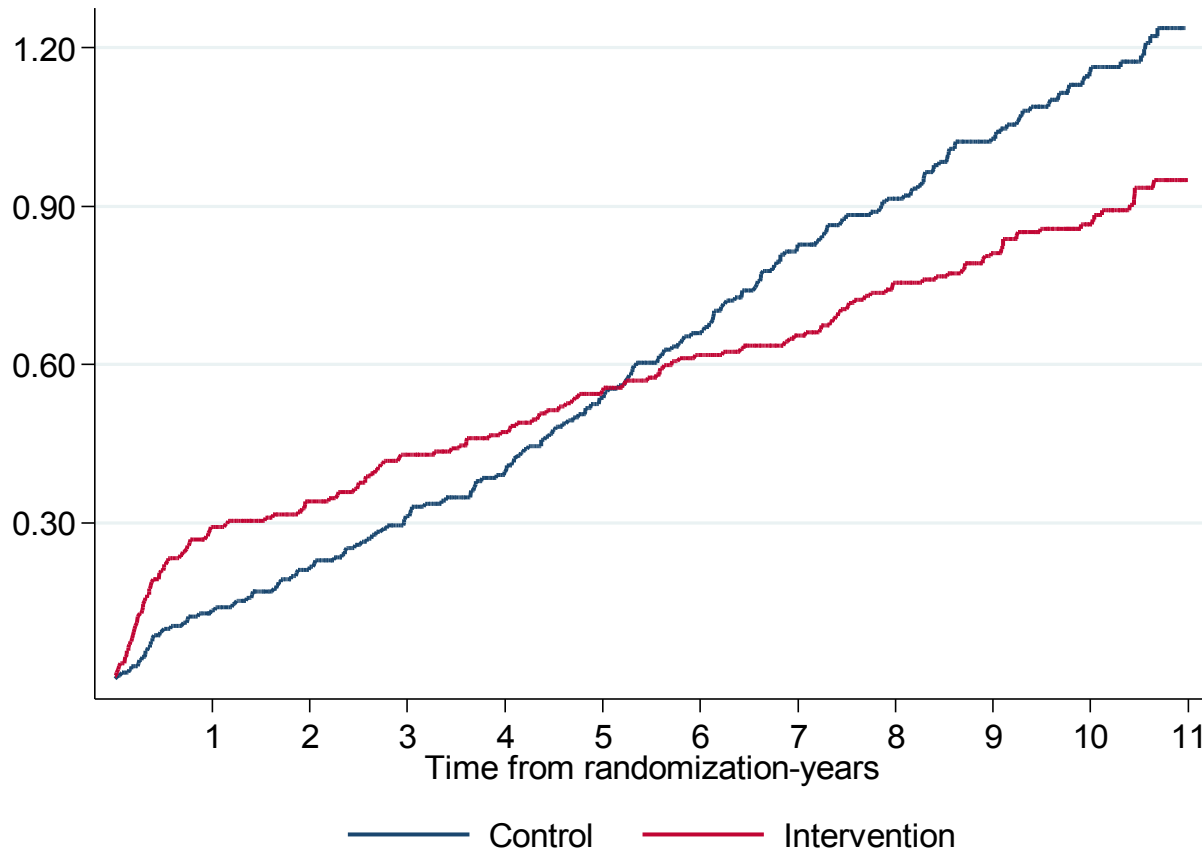

RR (95%CI) = 0.82 (0.69-0.96)

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**

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)

Control — Intervention

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**

Colorectal cancer MORTALITY
by screening arm and colonic site
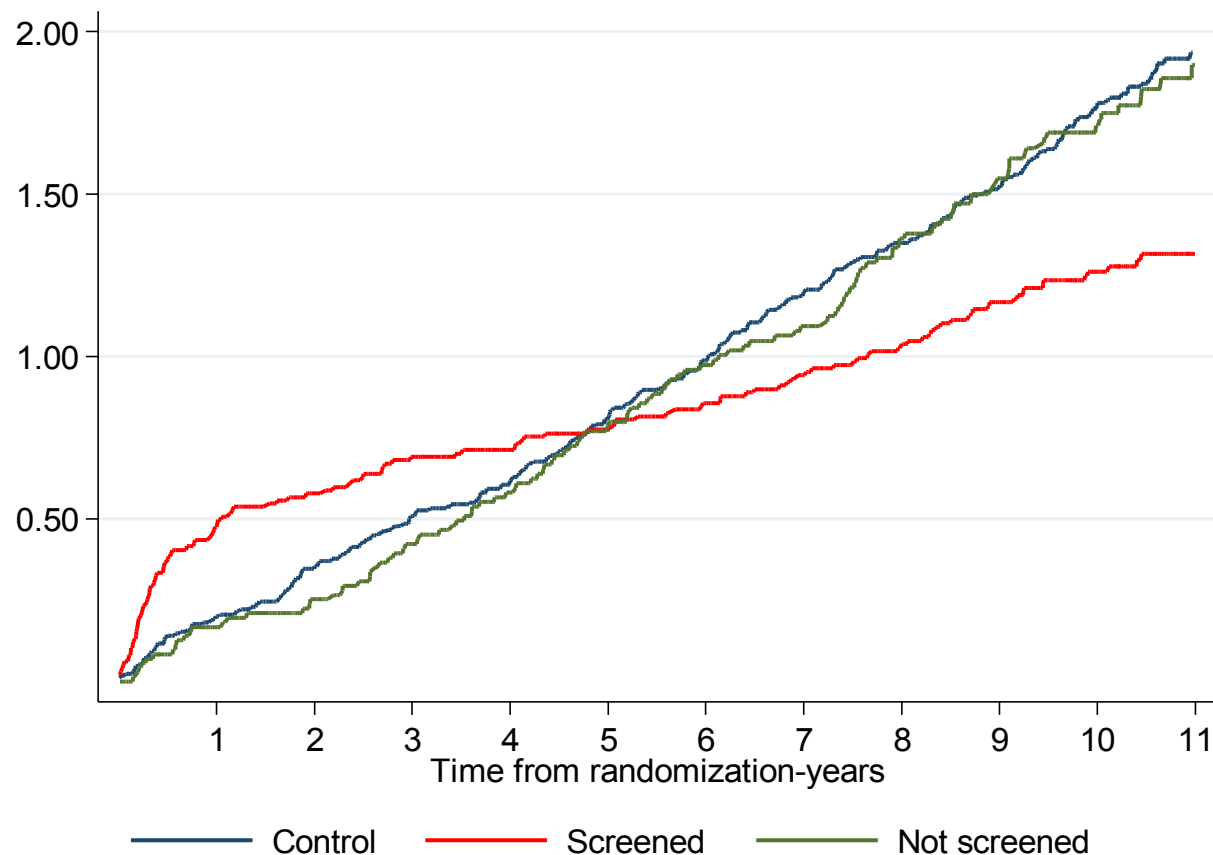### (Number of cases, Persons Years, Rates Ratios and 95% CI)

INTENTION TO TREAT ANALYSIS

	Control	Intervention	Rate ratio (95% CI)
	Cases	Cases	Intervention vs Control group
Mortality among patients diagnosed with CRC (all deaths, related or unrelated to CRC)			
	186 745 PY	187 532 PY	
All sites	94	71	0.75 (0.55-1.02)
Distal & descendent	55	40	0.72 (0.48-1.09)
CRC Mortality	186 745 PY	187 532 PY	
All sites	83	65	0.78 (0.56-1.08)
Distal & descendent	48	35	0.73 (0.47-1.12)
NON CRC MORTALITY	1150	1137	0.98 (0.91-1.07)

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)

Control   Screened   Not screened

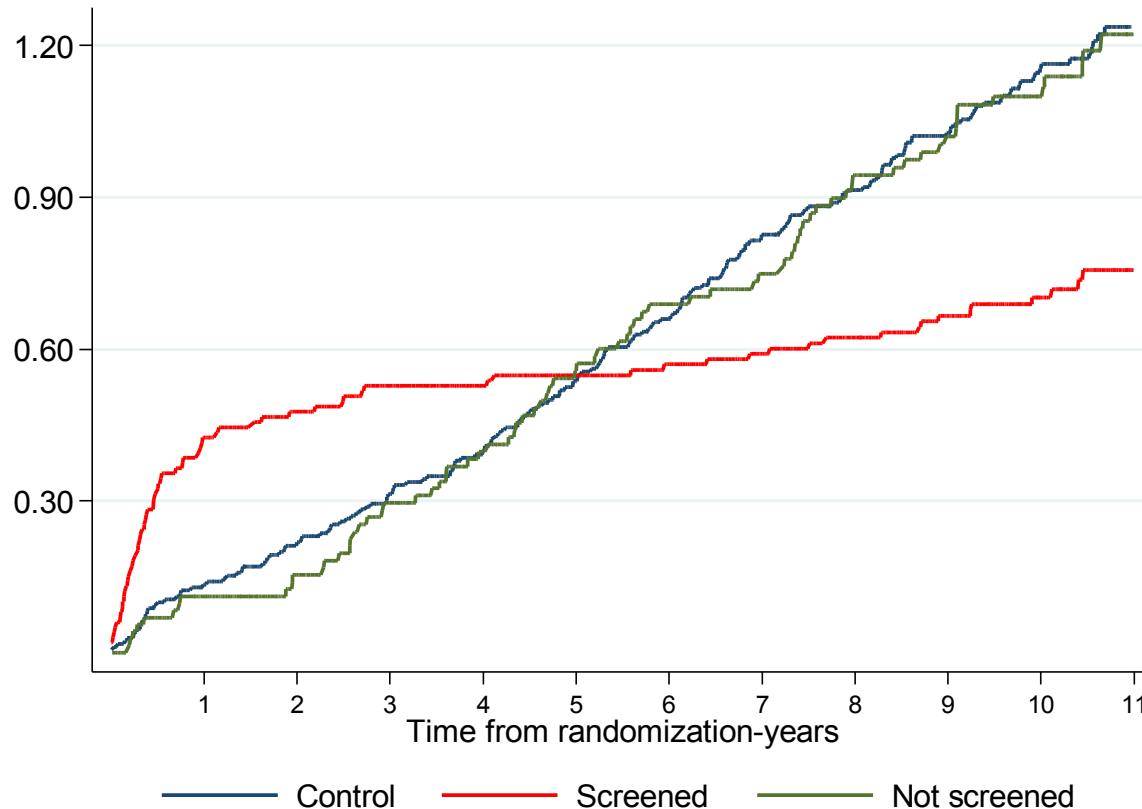| Cumulative Events by years from randomization						
	≤2	≤4	≤6	≤8	≤10	>10
Control	60	104	165	223	286	**306**
Not Screened	18	41	68	94	116	**125**
Screened	57	70	84	101	121	**126**

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)

Control — Screened — Not screened

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**

European guidelines for quality assurance in colorectal cancer screening and diagnosis

First Edition

European Commission