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

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Summary

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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

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

DESIGN

Randomised controlled trial, undertaken in 14 UK centres.

Recruitment between November 1994 and March 1999. Follow-up until December 2008.

170 432 eligible men and women, who had indicated on a previous questionnaire that they would accept an invitation for screening, were randomly allocated to the intervention group (offered flexible sigmoidoscopy screening, n=57237) or the control group (not contacted, n=113195).

AIM

To examine the hypothesis that only one flexible sigmoidoscopy screen undertaken between ages 55 and 64 years is a cost-effective and acceptable method to reduce colorectal cancer incidence and mortality.

This hypothesis is based on observations suggesting that most people who develop a distal colon cancer will have developed an adenoma by 60 years of age, and that removal of adenomas by sigmoidoscopy provides long-term protection against the development of distal colorectal cancer.

OUTCOME

The primary outcomes were the incidence of colorectal cancer, including prevalent cases detected at screening, and mortality from colorectal cancer.

Secondary outcomes were incidence of distal and proximal cancer, all-cause mortality, and mortality due to non-colorectal cancer causes.

Analyses were intention-to-treat and per-protocol (according to screening attendance).

Flexible sigmoidoscopy is a safe and practical test and, when offered only once between ages 55 and 64 years, confers a substantial and longlasting benefit.

Colorectal cancer incidence and mortality in control and intervention group (intention to treat analysis)

	Control group (n=112 939)			Intervention group (n=57 099)			Hazard ratio (95% CI); intervention vs control group	p value
	Cases	Person-years	Rate (per 100 000 person-years; 95% CI)	Cases	Person-years	Rate (per 100 000 person-years; 95% CI)		
Incidence								
All sites	1818*	1218 334	149 (143–156)	706*†	616 981	114 (106–123)	0.77 (0.70–0.84)	<0.0001
Distal: rectum and sigmoid colon	1192‡	1220 175	98 (92–103)	386†‡	618 053	62 (57–69)	0.64 (0.57–0.72)	<0.0001
Proximal	628‡	1222 639	51 (48–56)	311†‡	618 962	50 (45–56)	0.98 (0.85–1.12)	0.75
Mortality								
All-cause	13 768	1224 523	1124 (1106–1143)	6775	620 045	1093 (1067–1119)	0.97 (0.94–1.00)	0.0519
Colorectal cancer§	538	1224 523	44 (40–48)	189	620 045	30 (26–35)	0.69 (0.59–0.82)	<0.0001
Non-colorectal cancer causes§	13 230	1224 523	1080 (1062–1099)	6586	620 045	1062 (1037–1088)	0.98 (0.95–1.01)	0.25
Colorectal cancer (verified¶)	637	1224 523	52 (48–56)	221	620 045	36 (31–41)	0.68 (0.59–0.80)	<0.0001
Non-colorectal cancer causes (verified¶)	13 131	1224 523	1072 (1054–1091)	6554	620 045	1057 (1032–1083)	0.99 (0.96–1.02)	0.33

41 cancers with site not specified were included, 29 in control group and 12 in the intervention group. Only the earliest cancer was counted for patients with more than one cancer. 140 patients had cancers detected at baseline screening (126 distal cancers and 14 proximal cancers).

34 patients had both a distal and a proximal cancer (19 synchronous and 15 metachronous): 31 patients in control group and three in the intervention group.

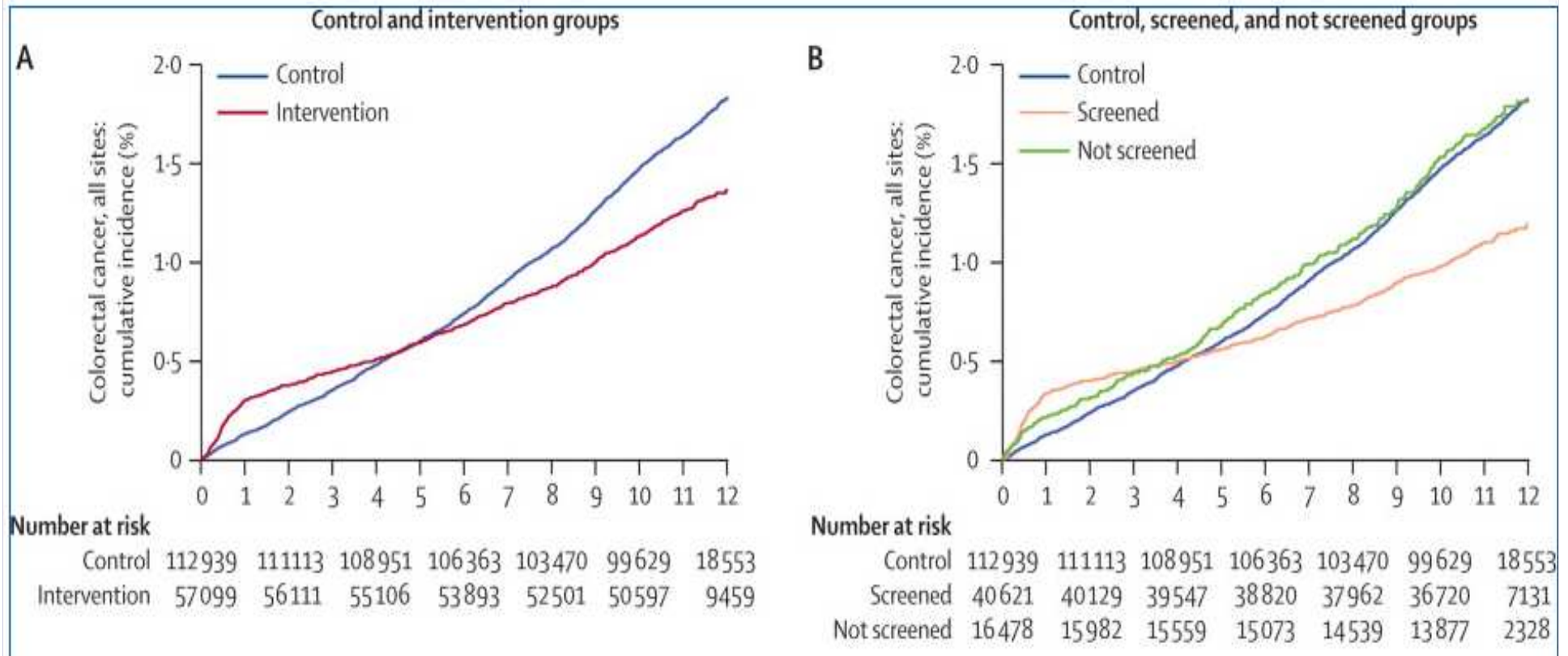
Deaths certified by the Office for National Statistics as colorectal cancer as underlying cause of death by automatic coding.

Assignment of colorectal cancer as underlying cause of death by independent expert coder.

Colorectal cancer incidence and mortality by randomisation and compliance with screening (pre-protocol analysis)

	Control group (n=112 939)			Intervention group (n=57 099)						Hazard ratio (95% CI); screened vs control group*
				Not screened (n=16 478)			Screened (n=40 621)			
	Cases	Person- years	Rate (per 100 000 person-years; 95% CI)	Cases	Person- years	Rate (per 100 000 person-years; 95% CI)	Cases	Person- years	Rate (per 100 000 person-years; 95% CI)	
Incidence										
All sites	1818†	1 218 334	149 (143–156)	261†	1 722 260	152 (134–171)	445†‡	4 447 21	100 (91–110)	0.67 (0.60–0.76)
Distal: rectum and sigmoid colon	1192§	1 220 175	98 (92–103)	171§	1 725 65	99 (85–115)	215‡§	4 454 88	48 (42–55)	0.50 (0.42–0.59)
Proximal	628§	1 222 639	51 (48–56)	87§	1 728 79	50 (41–62)	224‡§	4 460 84	50 (44–57)	0.97 (0.80–1.17)
Mortality										
All-cause	13 768	1 224 523	1124 (1106–1143)	2713	1 731 191	1566 (1509–1627)	4062	4 468 54	909 (881–937)	0.95 (0.91–1.00)
Colorectal cancer¶	538	1 224 523	44 (40–48)	78	1 731 191	45 (36–56)	111	4 468 54	25 (21–30)	0.57 (0.45–0.72)
Non-colorectal cancer causes¶	13 230	1 224 523	1080 (1062–1099)	2635	1 731 191	1521 (1461–1581)	3951	4 468 54	884 (857–912)	0.97 (0.93–1.02)
Colorectal cancer (verified)	637	1 224 523	52 (48–56)	94	1 731 191	54 (44–66)	127	4 468 54	28 (24–34)	0.56 (0.45–0.69)
Non-colorectal cancer causes (verified)	13 131	1 224 523	1072 (1054–1091)	2619	1 731 191	1512 (1455–1571)	3935	4 468 54	881 (854–909)	0.98 (0.93–1.03)

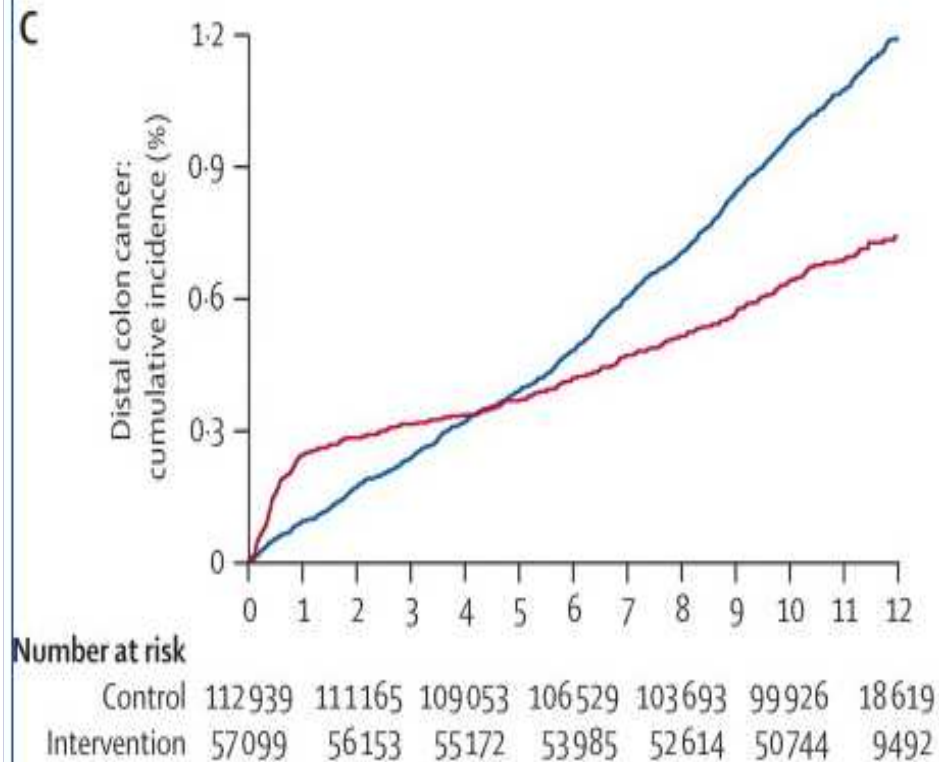
Colorectal cancer incidence (Kaplan-Meier estimates)



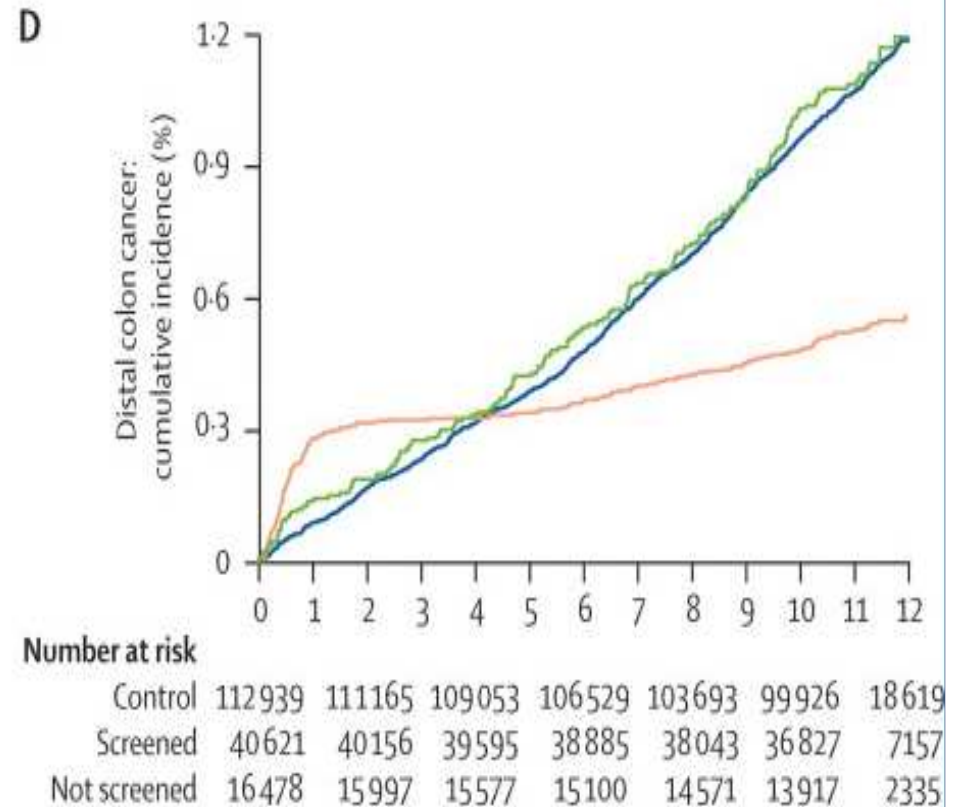
intention-to-treat analysis

per-protocol analysis

Distal cancer incidence (Kaplan-Meier estimates)

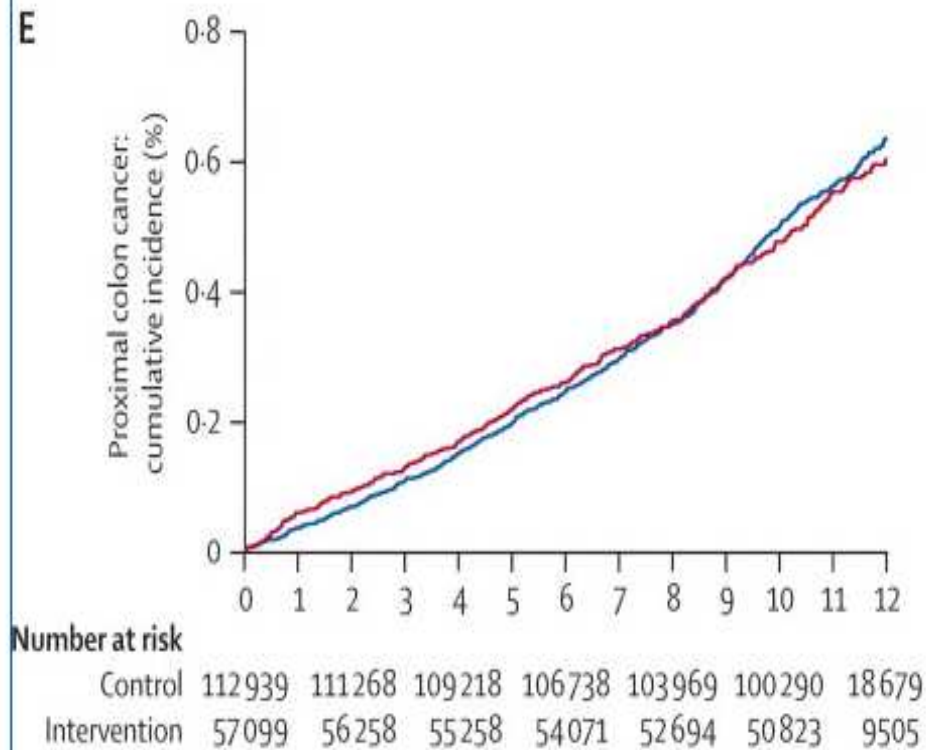


intention-to-treat analysis

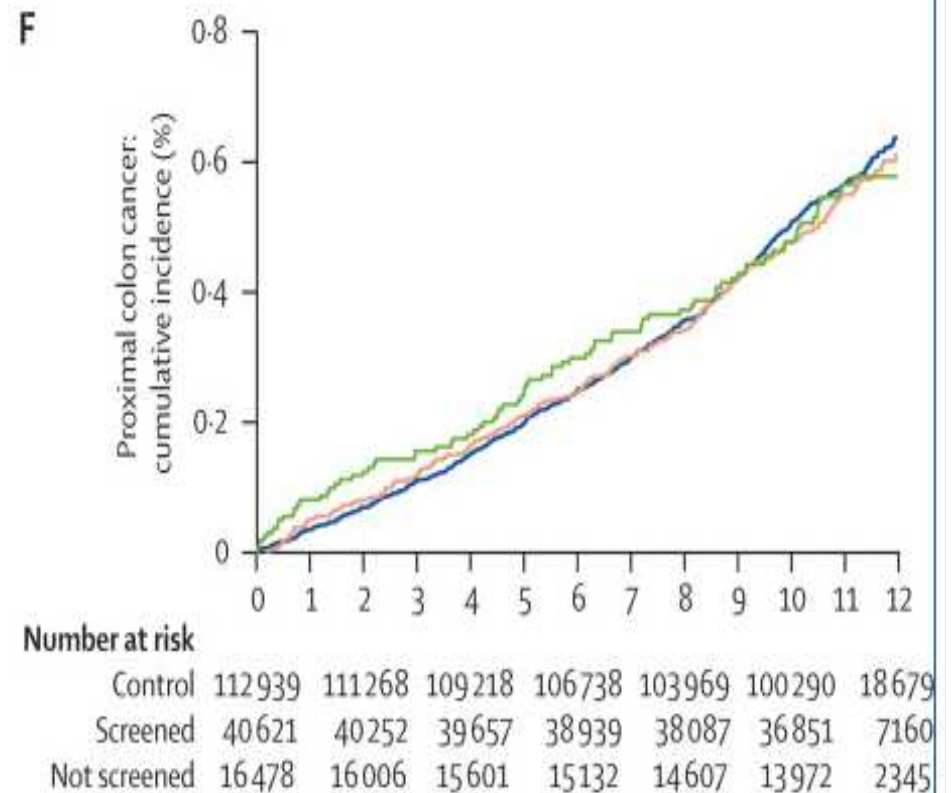


per-protocol analysis

Proximal cancer incidence (Kaplan-Meier estimates)

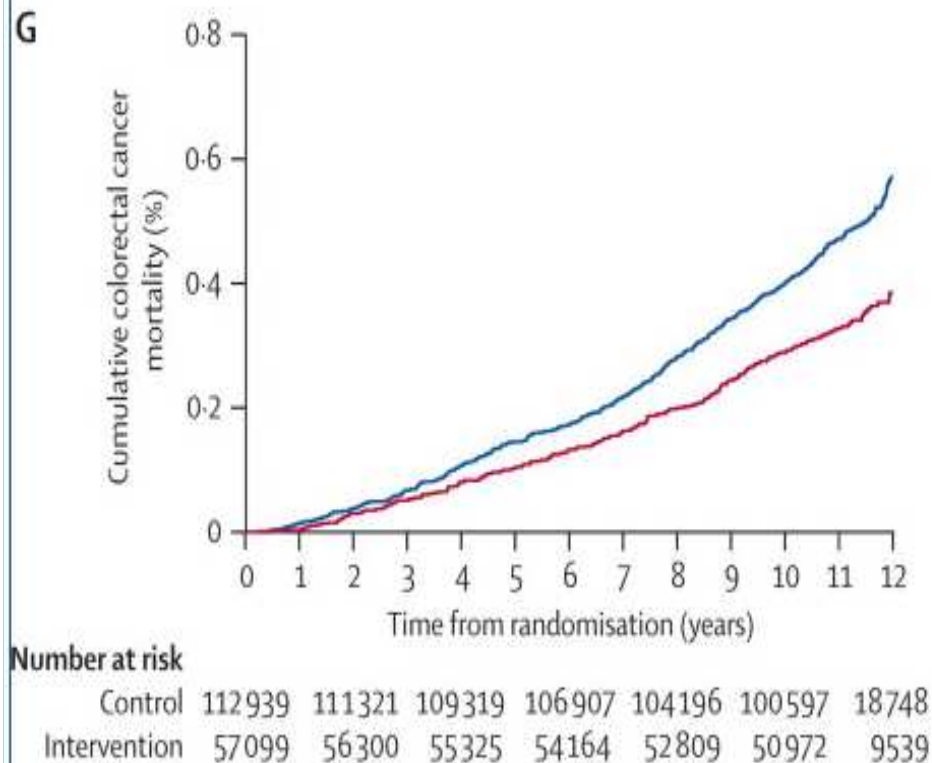


intention-to-treat analysis

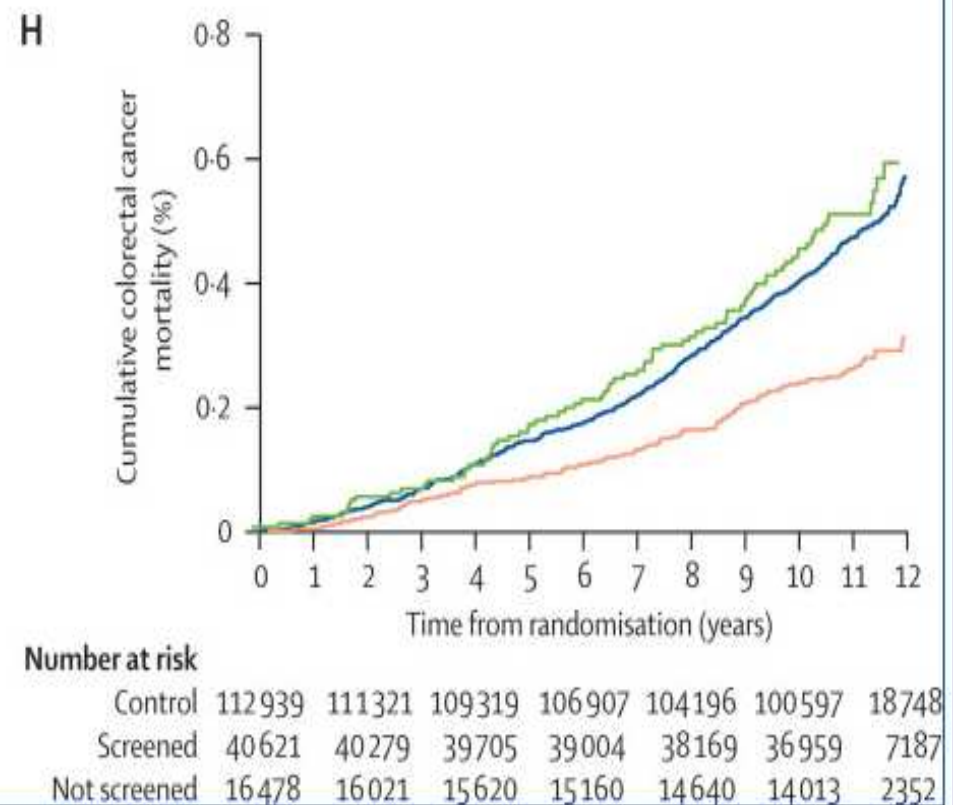


per-protocol analysis

Colorectal cancer mortality (Kaplan-Meier estimates)



intention-to-treat analysis



per-protocol analysis

Cumulative incidence of and mortality from colorectal cancer, and the number needed to screen to prevent one event in the present follow-up period

	Control group (n=112 939)		Intervention group				Number of events expected in intervention group	Number of events prevented in intervention group	Number needed to screen to prevent one event (95% CI)
			Total (n=57 099)		Screened (n=40 621)				
	n	Rate (per 1000; 95% CI)	n	Rate (per 1000; 95% CI)	n	Rate (per 1000; 95% CI)			
Colorectal cancer diagnosis	1818	16.1 (15.4–16.9)	706	12.4 (11.5–13.3)	445	11.0 (10.0–12.0)	919	213	191 (145–277)
Colorectal cancer death*	538	4.8 (4.4–5.2)	189	3.3 (2.9–3.8)	111	2.7 (2.3–3.3)	272	83	489 (343–852)
Colorectal cancer death (verified†)	637	5.6 (5.2–6.1)	221	3.9 (3.4–4.4)	127	3.1 (2.6–3.7)	322	101	402 (291–647)

* Deaths certified by the Office for National Statistics as colorectal cancer as underlying cause of death by automatic coding.

† Assignment of colorectal cancer as underlying cause of death by independent expert coder.

	SCORE (Italy)	FST (United Kingdom)
Study population	Intervention: N=17148 Control: N=17144	Intervention: N=57237 Control: N=113195
Cases	ICDO code: 153-154 codes of surgical or diagnostic, medical procedures possibly related to CRC	ICD code: C18-C20

Baseline Findings of the Italian Multicenter Randomized Controlled Trial of “Once-Only Sigmoidoscopy”—SCORE

Nereo Segnan, Carlo Senore, Bruno Andreoni, Hugo Aste, Luigina Bonelli, Cristiano Crosta, Roberto Ferraris, Stefano Gasperoni, Angelo Penna, Mauro Risio, Francesco Paolo Rossini, Stefania Sciallero, Marco Zappa, Wendy S. Atkin

And the SCORE Working Group - Italy

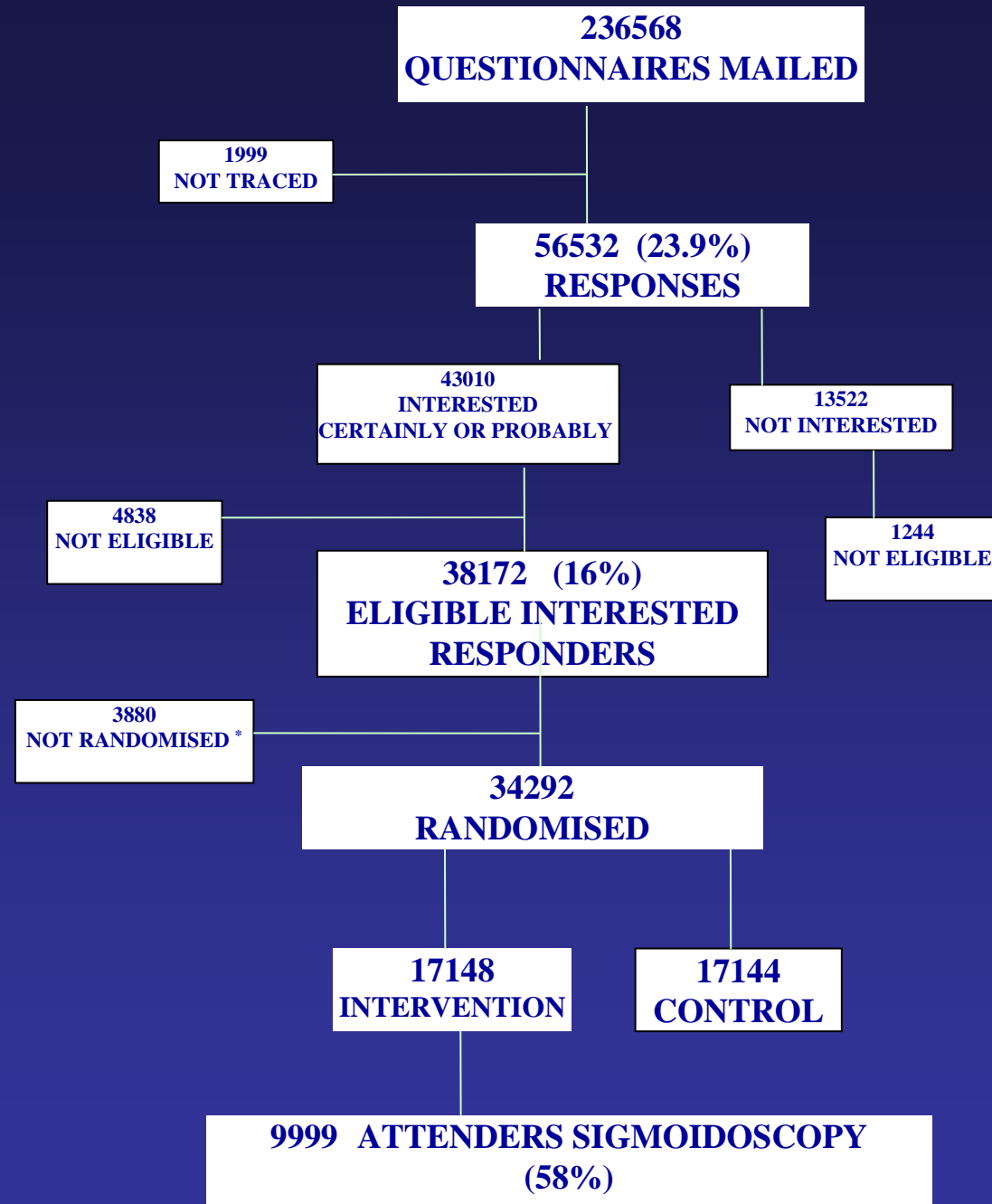
Background: A single sigmoidoscopy examination at around age 60 years has been proposed as a cost-effective strategy to prevent colorectal cancer. A multicenter randomized controlled trial, the SCORE trial, is in progress in Italy to estimate the impact of this strategy on colorectal cancer incidence and mortality and the duration of the protective effect. We present the baseline screening outcomes. **Methods:** A questionnaire was mailed to a random sample of 236 568 people aged 55–64 years to assess their eligibility for and

colorectal cancer incidence. [J Natl Cancer Inst 2002;94:1763–72]

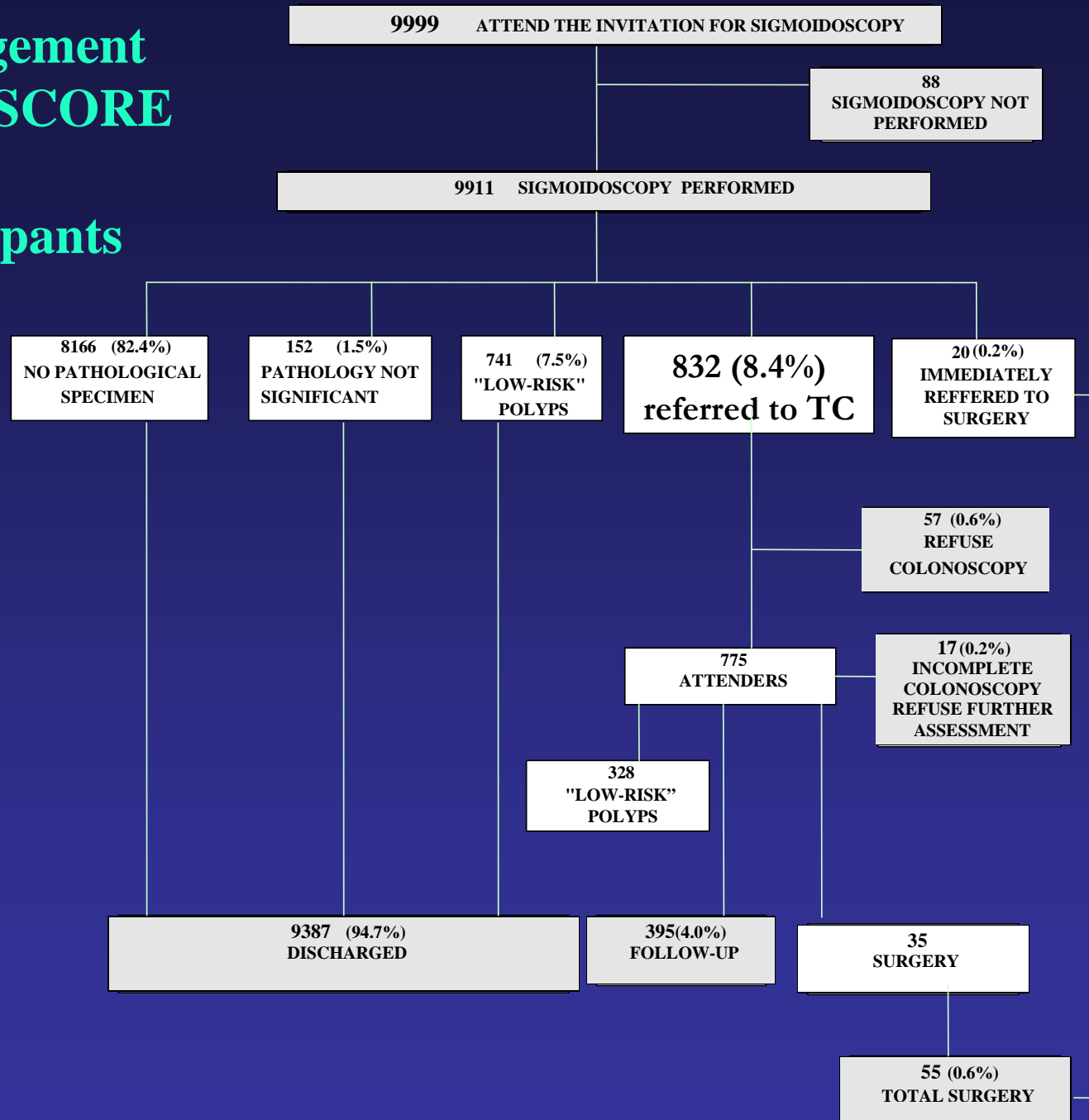
Colorectal cancer is the second leading cause of cancer death in Europe (1). In Italy, mortality rates from the disease have remained fairly constant over the past decade, with approximately 17 000 deaths per year (2). Based on projections from past trends, about 40 000 new cases were expected in 2000 in Italy (3). Several observational and intervention studies have shown consistent and marked reductions in both colorectal can-

Journal of the National Cancer Institute 2002; 94(23)

SCORE Trial Profile



Management of the SCORE trial participants



RANDOMISED TRIAL OF ONCE-ONLY FLEXIBLE SIGMOIDOSCOPY SCREENING IN ITALY - SCORE

- **9,999 (58%)** attenders
- 9911 examined
- Polyps : **17%**
- Adenomas : **11%**
- Advanced adenomas : **3.5%**
- Cancer : **0.5%**

Number of patients with colorectal cancer according to method of treatment, Dukes' stage and TNM* status - SCORE Trial

Treatment	Total		T status			N status				M status	
	n	%	T1	T2	T3	N0	N1	N2	Nx	M0/Mx	M1
Endoscopic excision	11	(20.4)	11						11	11	
Local excision	1	(1.9)	1						1	1	
Open abdominal surgery											
Dukes' A	17	(31.5)	13	4		13			4‡	17	
Dukes' B	9	(16.7)			9	9				9	
Dukes' C	14	(25.9)	1		13		10	2	2§	14	
Dukes' D	2	(3.7)			2			2			2
Total n	54	(100)	26	4	24	22	10	4	18	52	2

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

METHODS

ALL SUBJECTS ENROLED IN THE TRIAL

FOLLOWED-UP UNTIL

CRC diagnosis

Death

Emigration

31/12/2007

METHODS

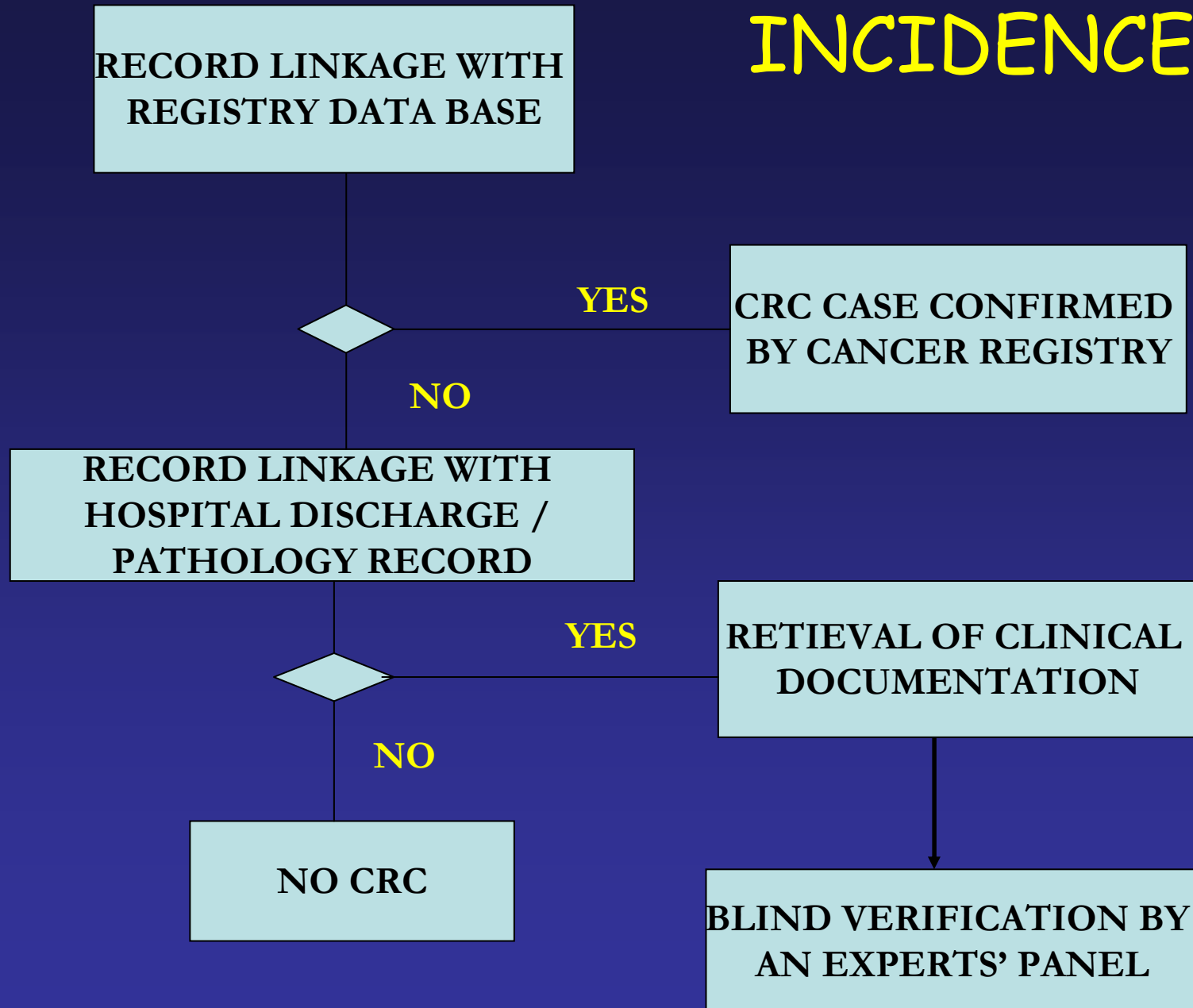
RECORD-LINKAGE WITH

POPULATION CANCER REGISTRIES	(INCIDENCE)
POPULATION REGISTRIES	(MORTALITY)
HOSPITAL DISCHARGE RECORDS	(INCIDENCE)
PATHOLOGY DEPARTMENTS ARCHIVES	(INCIDENCE)

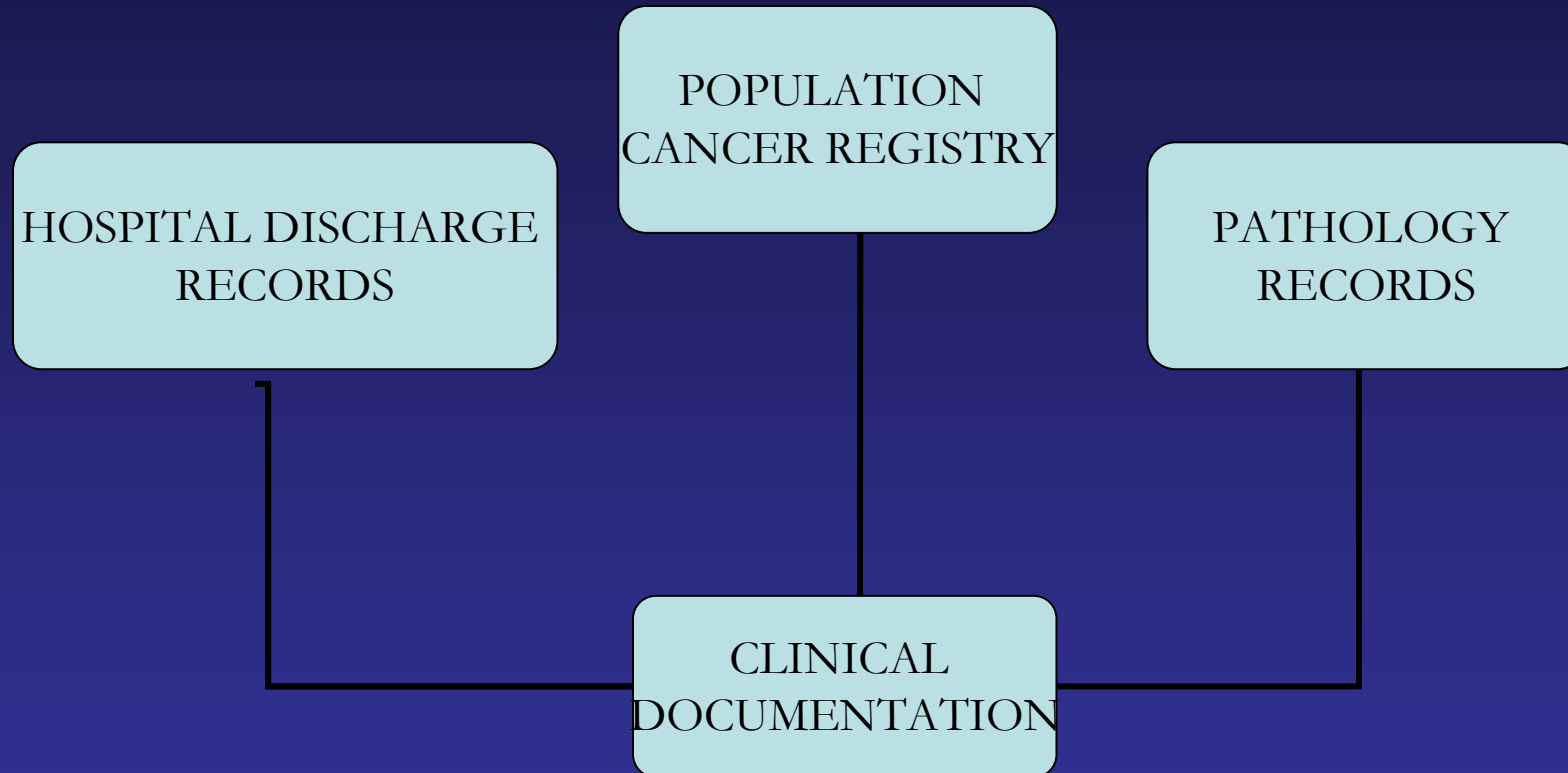
LINKAGE BASED ON TWO INDEPENDENT IDENTIFIERS

SOCIAL SECURITY NUMBER
FAMILY NAME, NAME, BIRTH DATE

INCIDENCE



INCIDENCE



INCIDENCE

Histological review of

all IS and T1 CRCs

**cases of carcinoma where the
histology report was incomplete /
inaccurate**

**by a referent pathologist, masked to the trial
allocation**

MORTALITY

**Independent verification of
all deaths attributed to CRC
a 10% sample of all other death
certificates
to verify assignment of underlying cause of
death**

STUDY SIZE

Given the observed attendance and the DR at screening, the study size allows to detect as statistically significant a 18% incidence reduction in the screening arm at 10 years follow-up

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