Kolonkarzinom: Prävention / Screening

Facts and Fantasy

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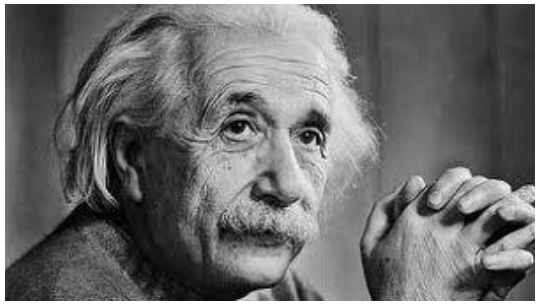
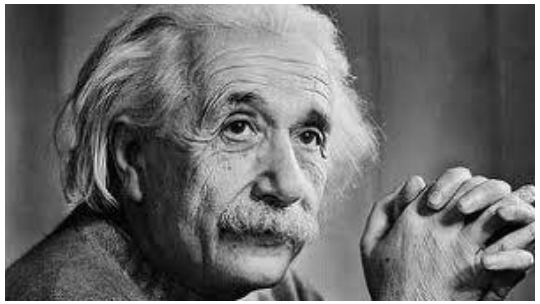


Incidence:	**men**	**6%**
	women	**3.7%**
CRC related mortality:		**39%**

***NICER 2009**

****www.vskr.ch**

1. prevention



- slim

  daily physically active,

  a lot of fruits and vegetables,

  no smoke, no alcohol

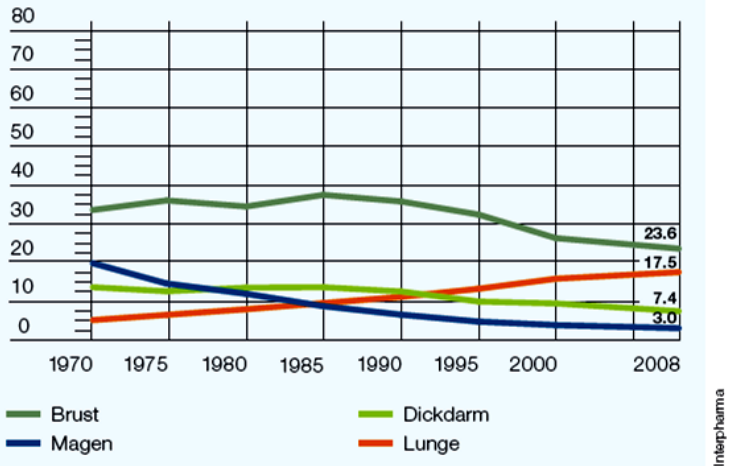
➢ … you have a lower risk to get

a colorectal cancer

- … up to 95% of colorectal cancers are due to eating habits, smoking and environmental factors ….

Krebssterblichkeit bei Frauen (nach Organ)

Pro 100 000 weibliche Einwohner



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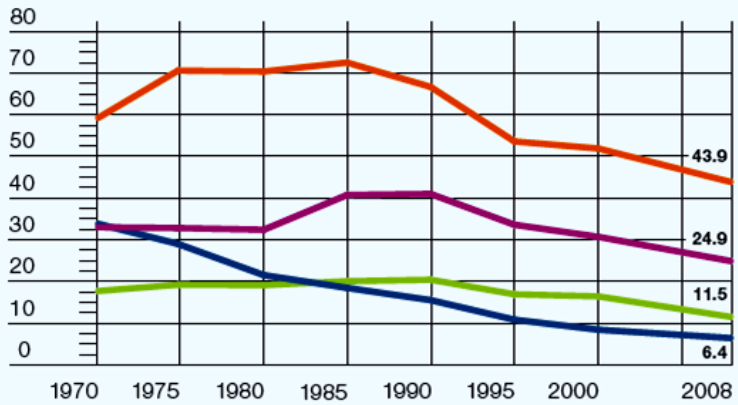
Quelle: Todesursachenstatistik 2008. Bundesamt für Statistik, Neuchâtel.

Krebssterblichkeit bei Männern (nach Organ)

Pro 100 000 männliche Einwohner



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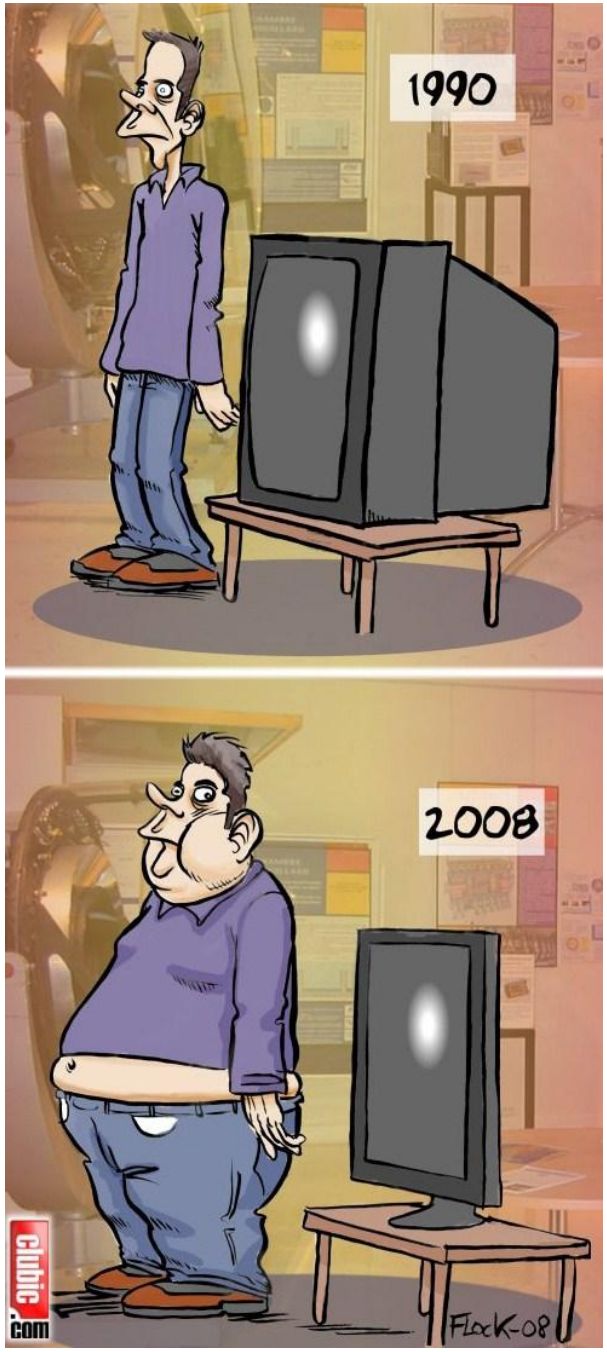
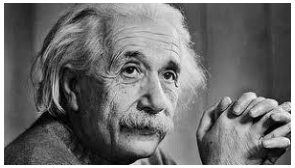
Quelle: Todesursachenstatistik 2008. Bundesamt für Statistik, Neuchâtel.



European Prospective Investigation into Cancer and Nutrition (EPIC)

- 519‘978 persons
- 1‘939‘011 patient years



European Prospective Investigation into Cancer and Nutrition (EPIC)

2003

CRC: RR 0.75 (95%CI 0.59-95)

highest vs lowest quintile 0.58 (0.41-0.85)

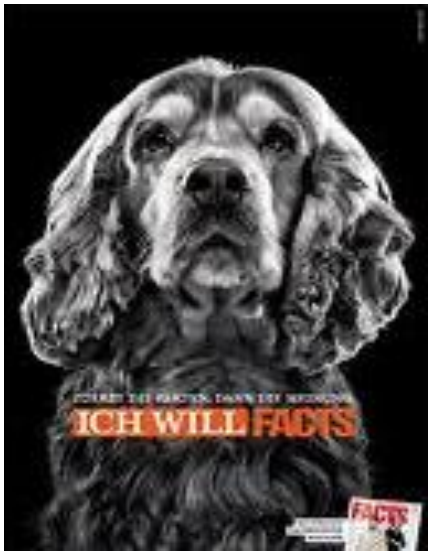
…. an approximate doubling of total fibre intake

from foods could reduce the risk of colorectal cancer by 40%

Bingham SA: Lancet 2003;361:1496

European Prospective Investigation into Cancer and Nutrition (EPIC)

2010



… cancer risk and increased intake of fruits and vegetables

HR 0.97 (95% CI 0.96-0.99)

sign. for women only

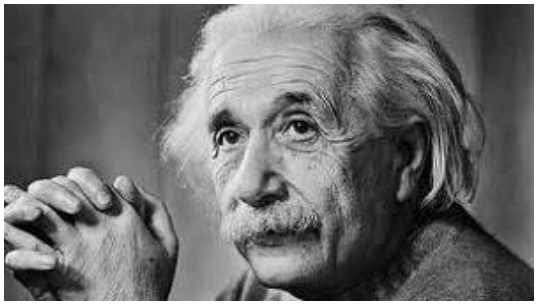
…. not enough data to correlate with different cancers by statistics

Boffetta P: J Natl Cancer Inst 2010;102:529

A prospective Danish cohort study

Kirkegaard H: BMJ 2010; 341:c5504

55‘487 men and women, 9.9 years follow-up

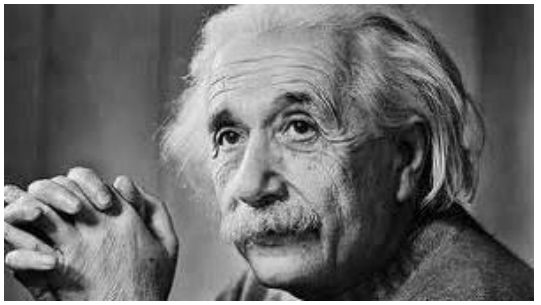


- not smoking
- not much alcohol
- small waist
- daily physical activity
- fruits and vegetables

A prospective Danish cohort study

Kirkegaard H: BMJ 2010; 341:c5504

55‘487 men and women, 9.9 years follow-up



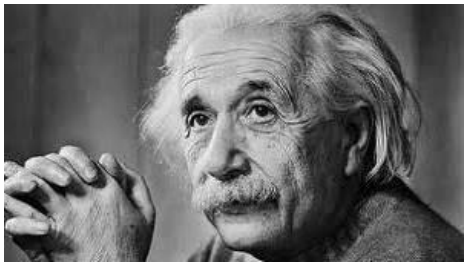
- 23% of the colorectal cancer (95% CI 9-37) would be preventable

  if all five recommendations would have been followed.

  13% risk reduction, if one additional factor would have been followed.**

***to start at which age? … for how long… = ?*

Aspirin daily….



Effect of daily aspirin on long-term risk of death due to cancer:

analysis of individual patient data from 8 randomized trials

Rothwell PM: Lancet 2011;377:31

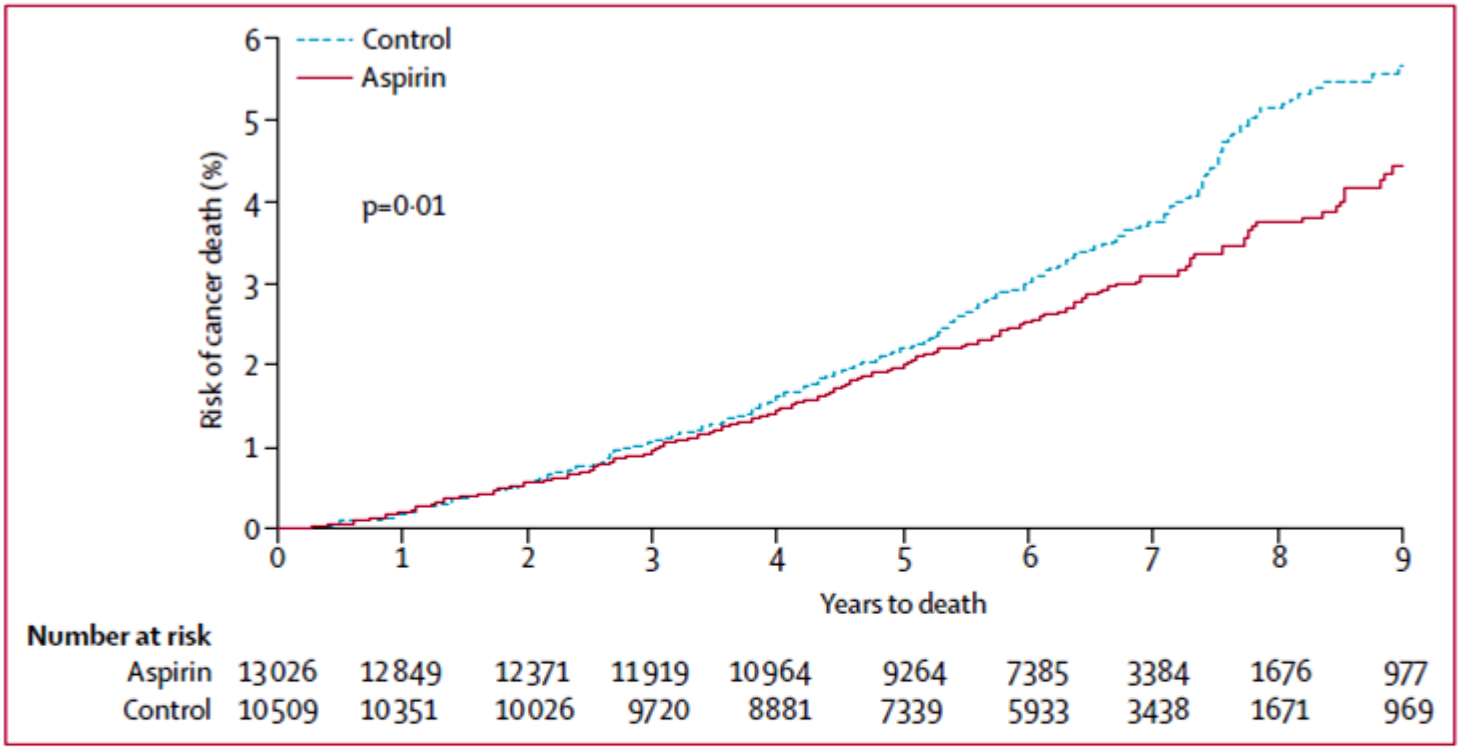


Figure 2: **Effect of allocation to aspirin versus control on risk of death due to cancer during the trial treatment periods in a pooled analysis of the 23 535 patients in seven trials[17–21,23,24]**

	n	0–5 years' follow-up		≥5 years' follow-up	
		HR (95% CI)	p value	HR (95% CI)	p value
Site of primary cancer*					
Gastrointestinal					
Colorectal	54	0·78 (0·39–1·56)	0·48	0·41 (0·17–1·00)	0·05

All cause mortality reduction – 10%

Rothwell PM: Lancet 2011;377:31

Ruder EH: Am J Gastroenterol 2011; 106:1340

NIH: 334‘908 - 10 years follow-up: incidence of colorectal cancer…

- Daily use of aspirin:
  - in the distal colon HR=0.84, 95% CI: 0.71 - 0.99
  - In the rectum HR=0.76, 95% CI: 0.64 - 0.90

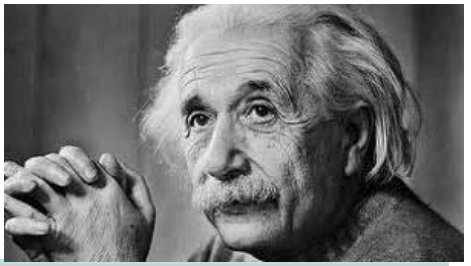
- The effect was more pronounced in persons with 1° relatives with CRC
  - aspirin: HR= 0.38, 95% CI: 0.19 - 0.78

Aspirin, NSAID

- US Preventive Services Task Force:
  - harms outweighed the benefit in low risk persons……
  - ➢ might be beneficial in a high risk population!

Chan AT: Gastroenterology 2010;138:2029

Aspirin in a high risk population:



- 1‘279 patients with established colorectal cancer median follow-up 11 years

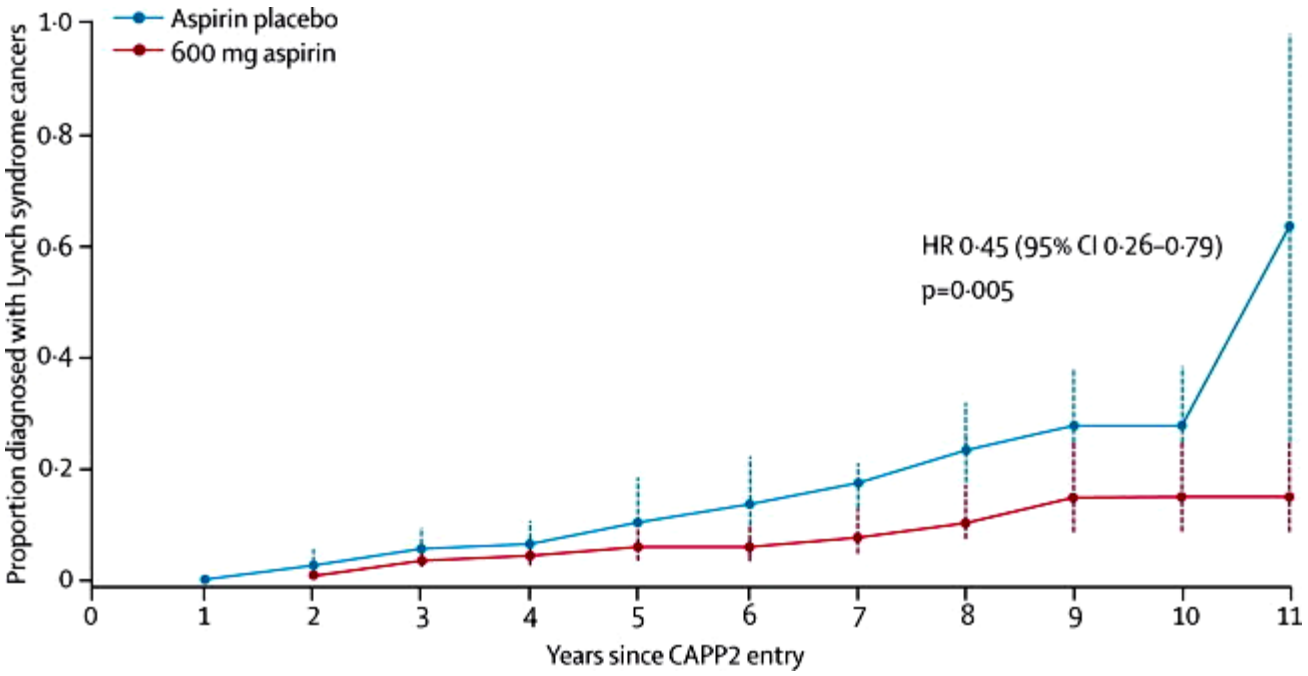
  – with regular intake of aspirin

    - 29% reduction of CRC specific mortality
    - 21% reduction of overall mortality

…. in tumours with Cox 2 overexpression

Chan AT: JAMA 2009;302:649

861 patients with Lynch syndrome – 48 patients with 53 CRC



HR 0.45 (95% CI 0.26-0.79) p=0.005

Burn J: Lancet 2012; 378: 2081

2. SCREENING FOR COLORECTAL CANCER

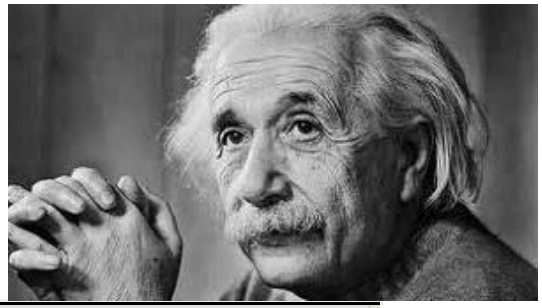


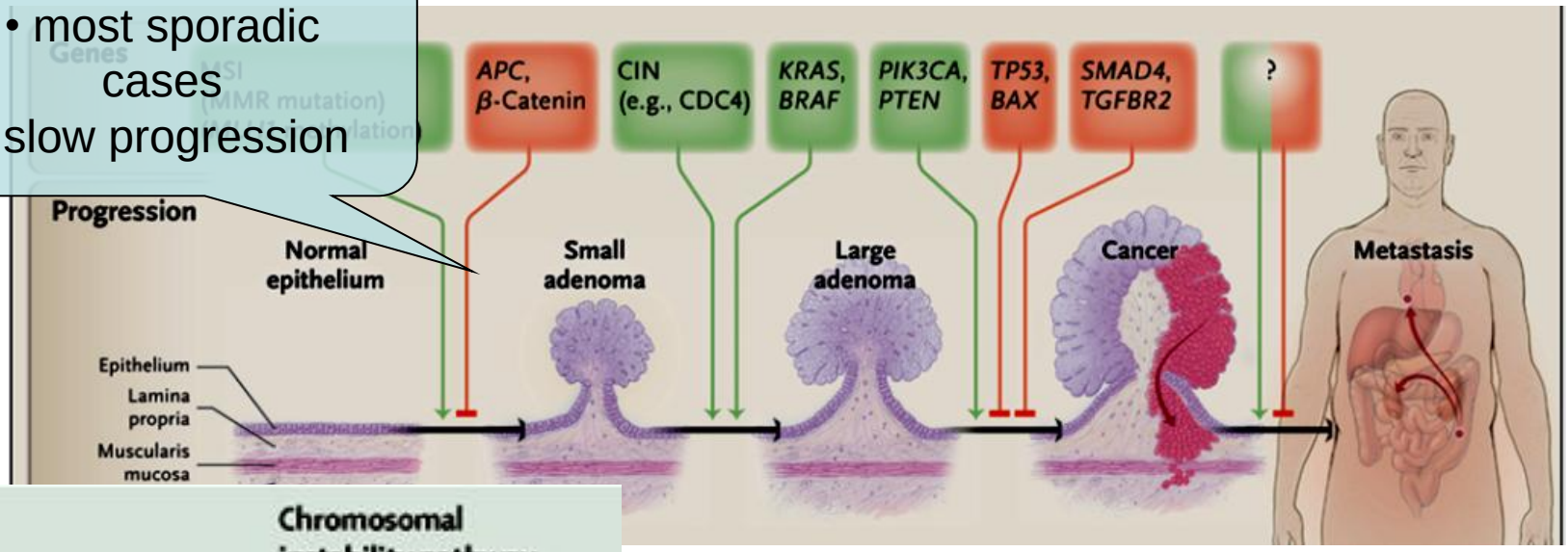
Table 2. TNM Staging System for Colorectal Cancer. *

Stage	TNM Classification	Five-Year Survival
		%
I	T1–2, N0, M0	>90
IIA	T3, N0, M0	60–85
IIB	T4, N0, M0	
IIIA	T1–2, N1, M0	
IIIB		
IIIC		
IV		

Imperiale TF: New Engl J Med. 2000; 343: 169
Lieberman DA: New Engl J Med. 2000; 343: 162
Schoenfeld P: New Engl J Med. 2005; 352: 2061
Regula J: New Engl J Med. 2006; 355: 1863
Marbet UA: Endoscopy 2008; 40: 650

Meyerhardt, J. A. et al. N Engl J Med 2005;352:476

• most sporadic cases
• slow progression

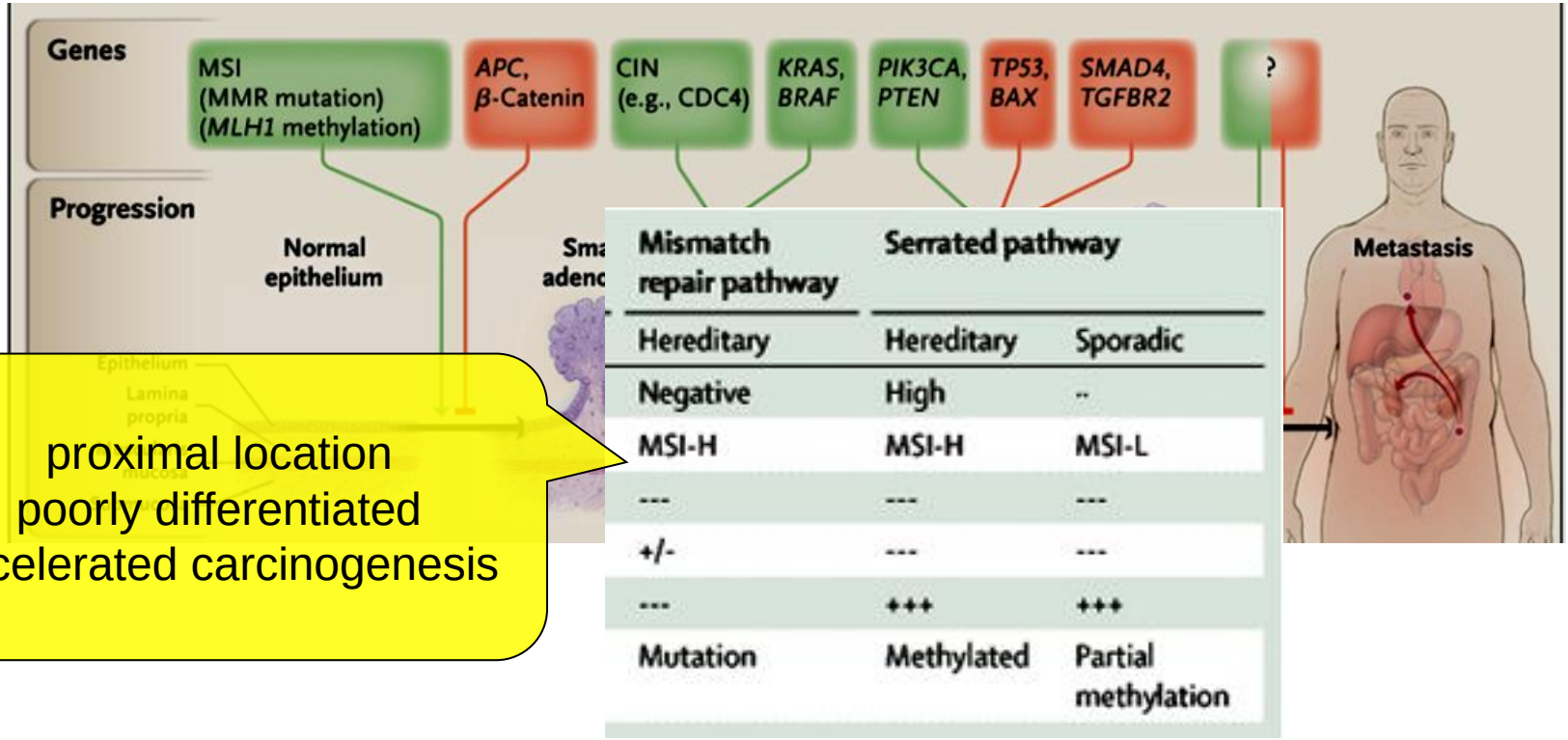


	Chromosomal instability pathway
	Hereditary and sporadic
CIMP status	Negative
MSI status	MSS
Chromosomal instability	+++
KRAS mutation	+++
BRAF mutation	---
MLH1 status	Normal

The natural history of polyps and even advanced lesions is fairly unknown

D Cunningham, W Atkin et al: Lancet 2010; 375: 1030 - 47

SD Markowitz, MM Bertagnolli: New Engl J Med 2009; 361: 2449

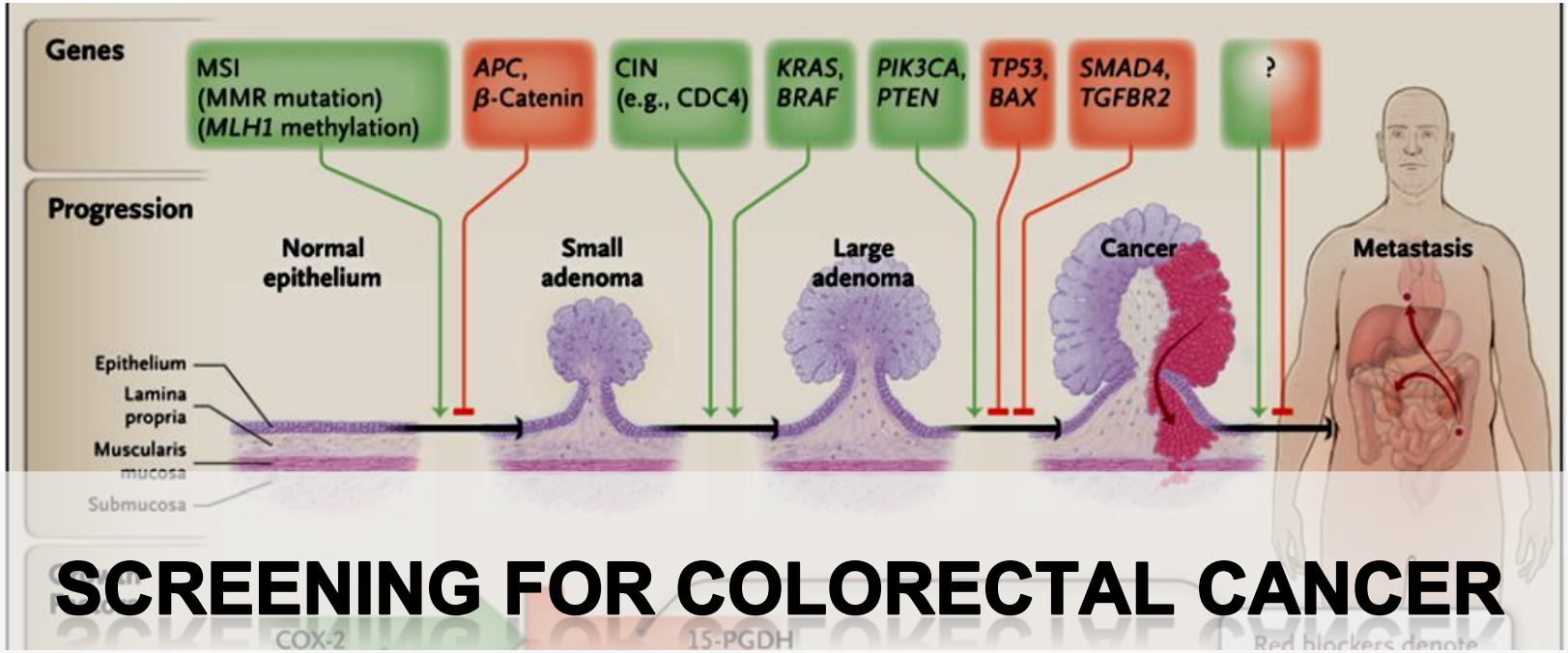


Mismatch repair pathway	Serrated pathway	
Hereditary	Hereditary	Sporadic
Negative	High	--
MSI-H	MSI-H	MSI-L
---	---	---
+/-	---	---
---	+++	+++
Mutation	Methylated	Partial methylation

proximal location
poorly differentiated
accelerated carcinogenesis

D Cunningham, W Atkin et al: Lancet 2010; 375: 1030 - 47

SD Markowitz, MM Bertagnolli: New Engl J Med 2009; 361: 2449

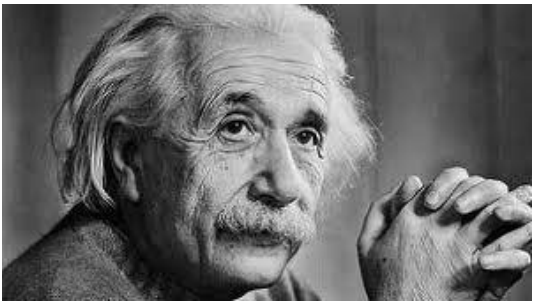


SCREENING FOR COLORECTAL CANCER

Prevention

Early recognition

- Faecal tests
- blood tests
- CT colonoscopy



FOBT reduces CRC related mortality!! .

not all cause mortality

	No. of CRC deaths		Incidence Ratio		
RCTs	*Screen*	*Control*	*Screen*	*Control*	*Mort.Red.*
Nottingham	593/76466	684/76384	0.70/1000py	0.81/1000py	13%
Funen	362/30967	431/30966	0.84/1000py	1.00/1000py	16%
Goteborg	252/34144	300/34164	0.53/1000py	0.64/1000py	16%
Minnesota-A	121/15570	177/15384	0.67/1000	1.00/1000	33%
Minnesota-B	148/15587	-	0.79/1000	-	21%

Cochrane library 2011 (Hewitson P)

FOBT is the method of choice for population screening for colorectal cancer

LONG TIME ADHERENCE IS LOW .....

Gellad ZF: Am J Gastroenterol 2011;106:1125

- 384‘525 men: 42.1% 1 test, 26.0% 2, 14.1% $\geq$ 4 in five years
- 10‘469 females: 42.9% 1 test, 26.1% 2, 13.7% $\geq$ 4 in five years

S Hundt. Annals Intern Med 2009; 150: 162

Prospective study in 1319 persons with screening colocoscopy

Table 2. **Positivity Rates, Sensitivities, and Specificities of FOBTs**

Performance Characteristic	Immunochemical FOBT*						HemOccult Gualac-Based FOBT)*
	Bionexia FOBplus	Bionexia Hb/Hp Complex	PreventID CC	ImmoCARE-C	FOB advanced	QuickVue IFOB	
Overall positivity rates							
Patients, *n/n*†	310/1319	612/1319	286/1319	76/1319	138/1319	455/1319	57/1275
Percentage (95% CI)	23.5 (21.2–25.9)	46.4 (43.7–49.1)	21.7 (19.5–24.0)	5.8 (4.6–7.2)	10.5 (8.9–12.2)	34.5 (31.9–37.1)	4.5 (3.4–5.8)
Sensitivity							
Any adenoma							
Patients, *n/n*‡	145/405	235/405	120/405	46/405	73/405	183/405	21/388
Percentage (95% CI)	35.8 (31.1–40.7)	58.0 (53.1–62.9)	29.6 (25.2–34.3)	11.4 (8.4–14.9)	18.0 (14.4–22.1)	45.2 (40.3–50.2)	5.4 (3.4–8.2)
Advanced adenoma							
Patients, *n/n*‡	68/130	93/130	64/130	33/130	35/130	73/130	12/128
Percentage (95% CI)	52.3 (43.4–61.1)	71.5 (63.0–79.1)	49.2 (40.4–58.1)	25.4 (18.2–33.8)	26.9 (19.5–35.4)	56.2 (47.2–64.8)	9.4 (4.9–15.8)
Other adenoma							
Patients, *n/n*‡	77/275	142/275	56/275	13/275	38/275	110/275	9/260
Percentage (95% CI)	28.0 (22.8–33.7)	51.6 (45.6–57.7)	20.4 (15.8–25.6)	4.7 (2.5–8.0)	13.8 (10.0–18.5)	40.0 (34.2–46.1)	3.5 (1.6–6.5)
Specificity							
None or hyperplastic polyp							
Patients, *n/n*§	749/914	537/914	748/914	884/914	849/914	642/914	851/887
Percentage (95% CI)	81.9 (79.3–84.4)	58.8 (55.5–62.0)	81.8 (79.2–84.3)	96.7 (95.4–97.8)	92.9 (91.0–94.5)	70.2 (67.2–73.2)	95.9 (94.4–97.1)

S Hundt. Annals Intern Med 2009; 150: 162

Prospective study in 1319 persons with screening colocoscopy

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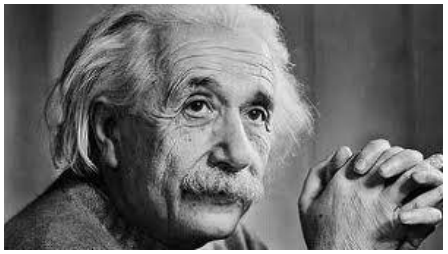
Overall positivity rate %							
	23.5	46.4	21.7	5.8	10.5	34.5	4.5
Percentage (95% CI)	52.3 (43.4–61.1)	71.5 (63.0–79.1)	49.2 (40.4–58.1)	25.4 (18.2–33.8)	26.9 (19.5–35.4)	56.2 (47.2–64.8)	9.4 (4.9–15.8)
Lower detection limit:							
	40	25	10	50	40	50	
Percentage (95% CI)	81.9 (79.3–84.4)	58.8 (55.5–62.0)	81.8 (79.2–84.3)	96.7 (95.4–97.8)	92.9 (91.0–94.5)	70.2 (67.2–73.2)	95.9 (94.4–97.1)
Specifity %							
	81.9	58.8	81.8	96.7	92.9	70.2	95.9

No data: FIT every year, every second year, every fifth year....

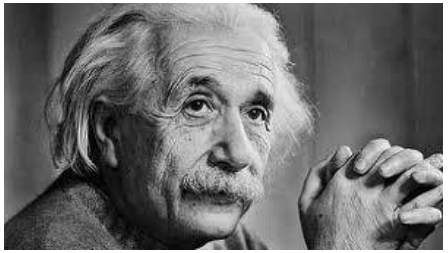


Biomarkers to detect colorectal cancer by examination of the blood, stool, urine…

Circulating methylated SEPT9 DNA in plasma

…… is associated with apoptosis ….. and colorectal cancer

» 8 pg tumor DNS / ml = 3 genome copies



Septin 9 test at screening conditions

- Sensitivity for cancer stage I-III: 50% (28-72)
- Sensitivity for adenomas: 14% (3– 35)

Ahlquist DA Clin Gastroenterol Hepatol : Epub ahead of print

Septin 9 test

- Prospective Multicenter Study USA / D
  - Controlled by colonoscopy
  - 7940 persons - - - 6‘890 included ….

Septin 9 test:
a prospective multicenter study for CRC screening

Range of sensitivity (2 or 3 probes)

- KRK I° 36% - 43%
  KRK III° 79% - 82%

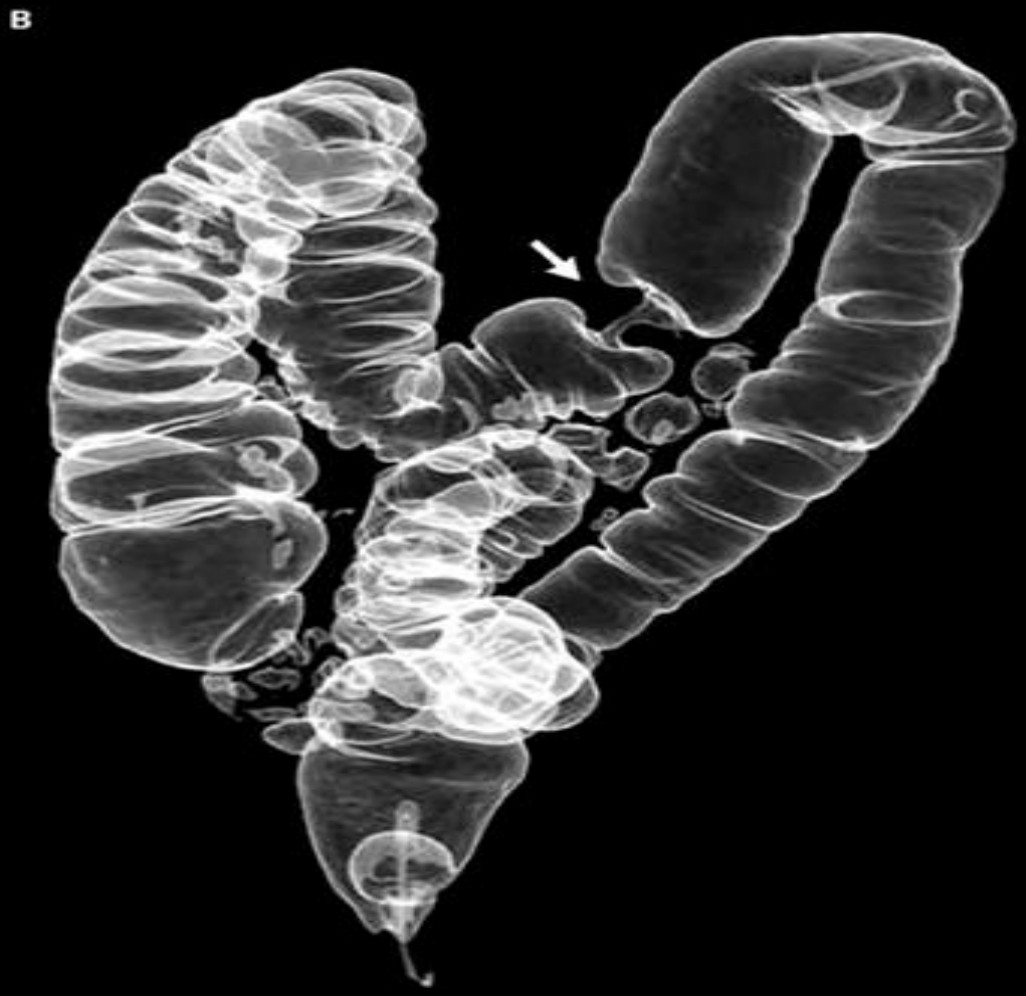
- Specifity 91% - 88%

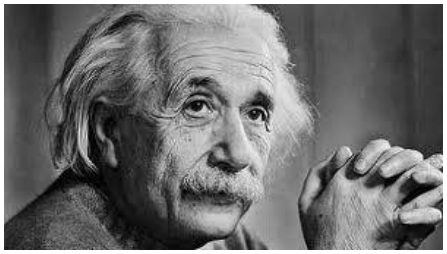
abstract, not published yet

Septin 9: a good test for CRC screening

- ✓ Advantage of a blood test
- Insufficient published data
- All the problems of FIT
- Problem of false positive tumour markers….

Colonoscopy by computer tomography (virtuel colonoscopy)





good to **detect** CRC earlier….

	PJ Pickhardt NEJM 2003,349, 2191	
	1310 lesions	
	virtuel colonoscopy	**optical colonoscopy**
Sensitivity for polyps >10mm	94% 82.8-98.7	86% 74.8-95.3

good to **prevent** CRC ….???

	virtuel colonoscopy	**optical colonoscopy**
Sensitivity for polyps >10mm	94% 82.8-98.7	86% 74.8-95.3

missed flat lesions

- 25.9% of of precancerous lesions are non polypoid neoplasia

MA Bianco: Endoscopy 2010; 42: 279

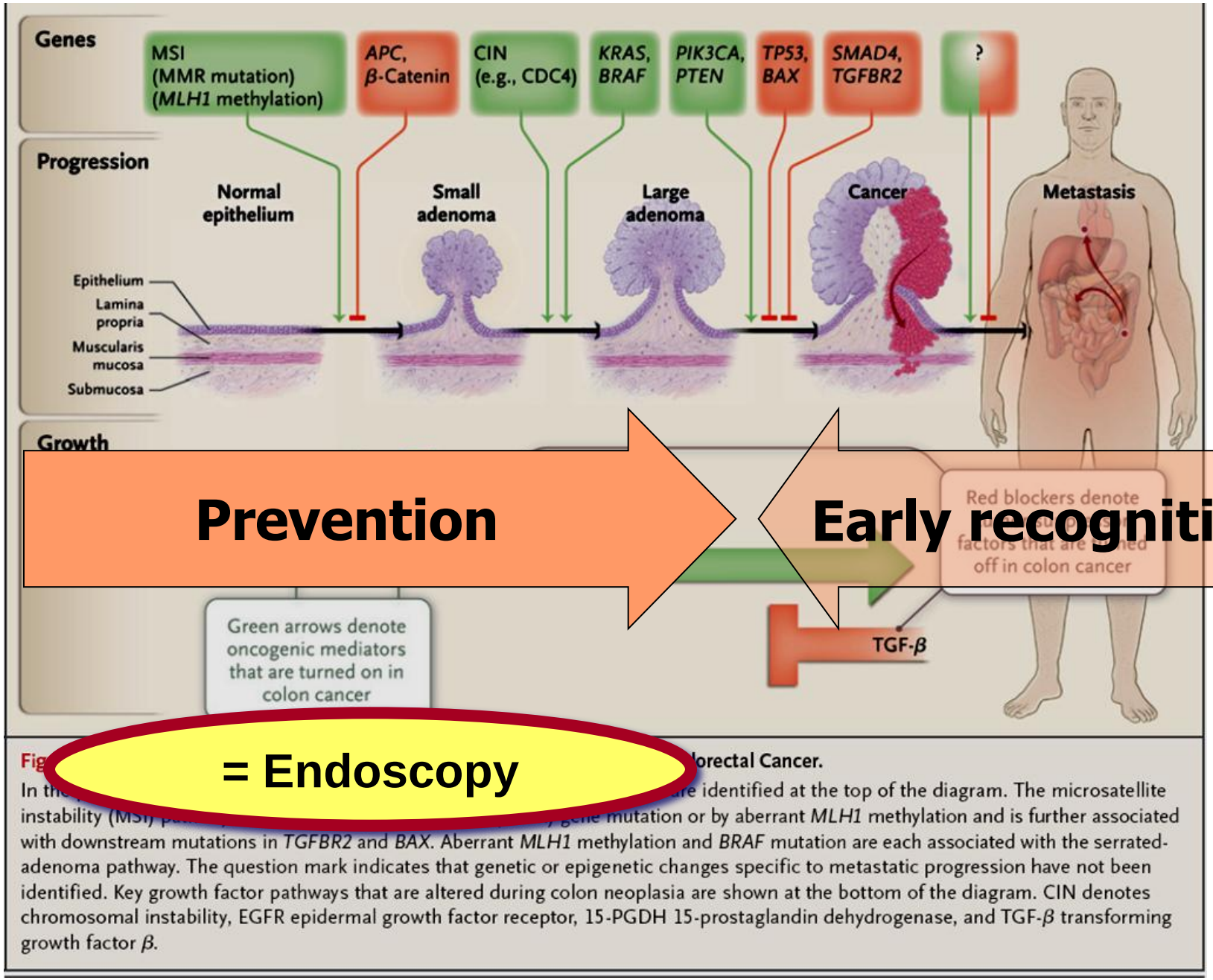


Fig **orectal Cancer.**

In th identified at the top of the diagram. The microsatellite instability (MSI) p mutation or by aberrant *MLH1* methylation and is further associated with downstream mutations in *TGFBR2* and *BAX*. Aberrant *MLH1* methylation and *BRAF* mutation are each associated with the serrated-adenoma pathway. The question mark indicates that genetic or epigenetic changes specific to metastatic progression have not been identified. Key growth factor pathways that are altered during colon neoplasia are shown at the bottom of the diagram. CIN denotes chromosomal instability, EGFR epidermal growth factor receptor, 15-PGDH 15-prostaglandin dehydrogenase, and TGF-β transforming growth factor β.

SD Markowitz, MM Bertagnolli: New Engl J Med 2009; 361: 2449

Flexible sigmoidoscopy to prevent colorectal cancer
a randomized controlled trial

W Atkin: Lancet 2002; 359: 1291

W Atkin: Lancet 2010;375:1624

preparation with Fletcher‘s phosphate enema

113 195 control group

57 237 intervention group

40 674 (71%) underwent flexible sigmoidoscopy

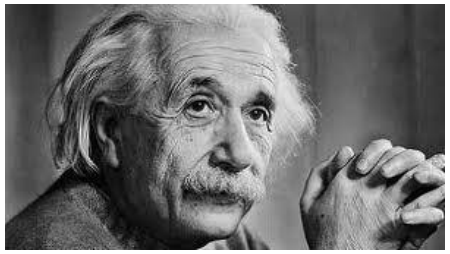
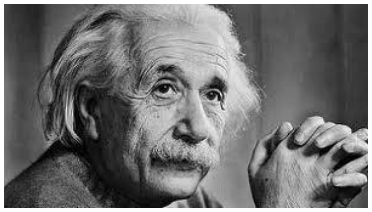


Table 1
Colorectal cancer incidence and mo

	Hazard ratio (95% CI); intervention vs control group	p value
Incidence		
All sites	0·77 (0·70–0·84)	<0·0001
Distal: rectum and sigmoid colon	0·64 (0·57–0·72)	<0·0001
Proximal	0·98 (0·85–1·12)	0·75
Mortality		
All-cause	0·97 (0·94–1·00)	0·0519
Colorectal cancer§	0·69 (0·59–0·82)	<0·0001
Non-colorectal cancer causes§	0·98 (0·95–1·01)	0·25
Colorectal cancer (verified¶)	0·68 (0·59–0·80)	<0·0001
Non-colorectal cancer causes (verified¶)	0·99 (0·96–1·02)	0·33

Intention to treat analysis:

- CRC Incidence reduction by 23% (HR 0.77 (0.70-0.84))
- CRC related mortality reduction by 31% (HR 0.69 (0.59-0.82))



Hoff G: Risk of colorectal cancer seven years after flexible sigmoidoscopy screening.

BMJ 2009;338:b1846

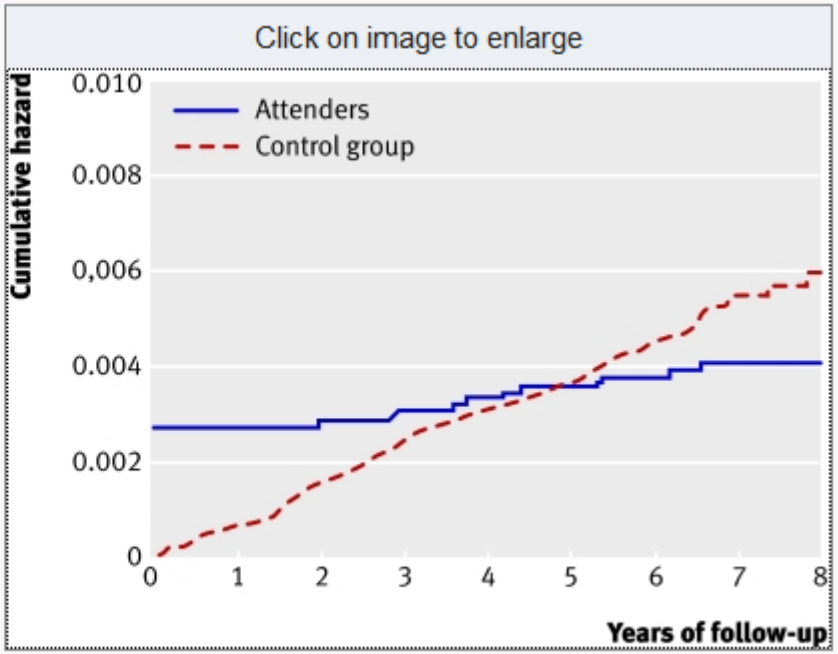
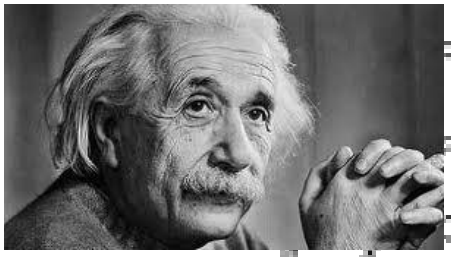
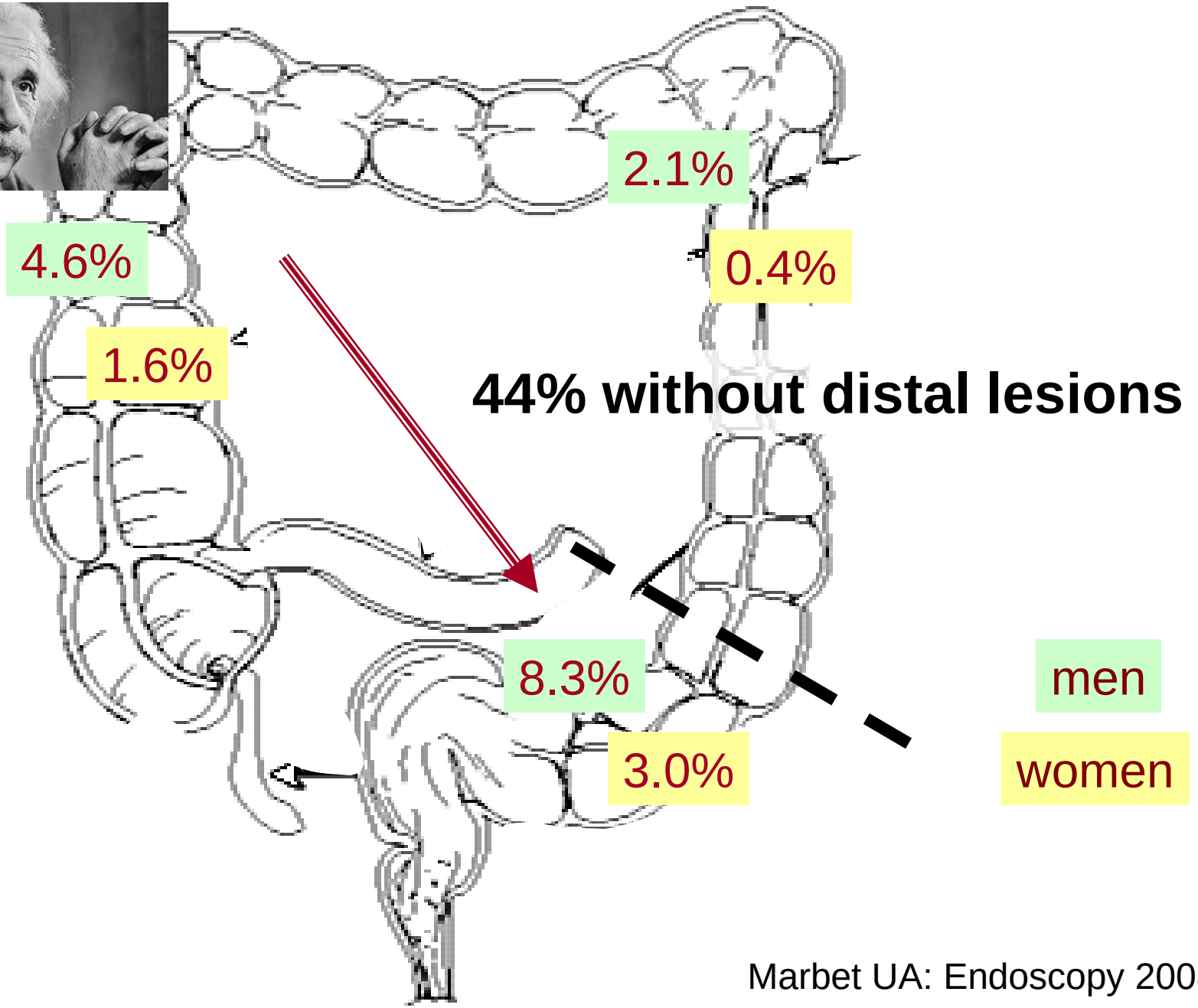


Fig 3 Cumulative hazard for rectosigmoidal cancer among attenders compared with control group

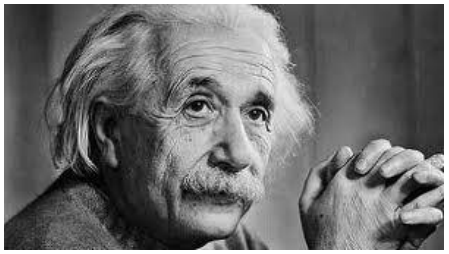
Reduction of CRC mortality 0.41 (0.28-82)

Intention to treat analysis: 0.73 (0.47-1.13)

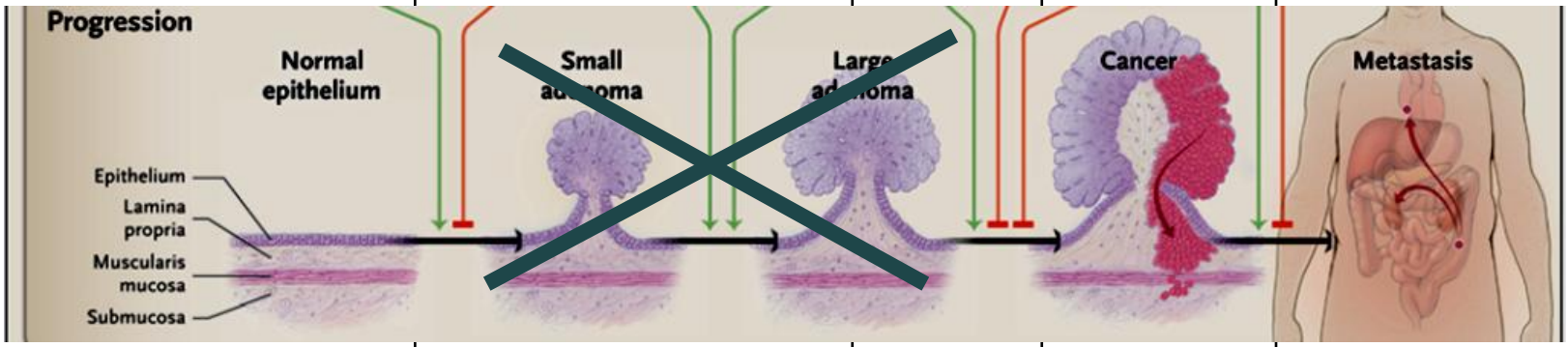




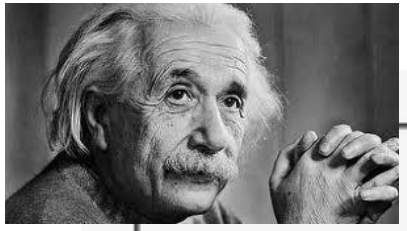
Marbet UA: Endoscopy 2008



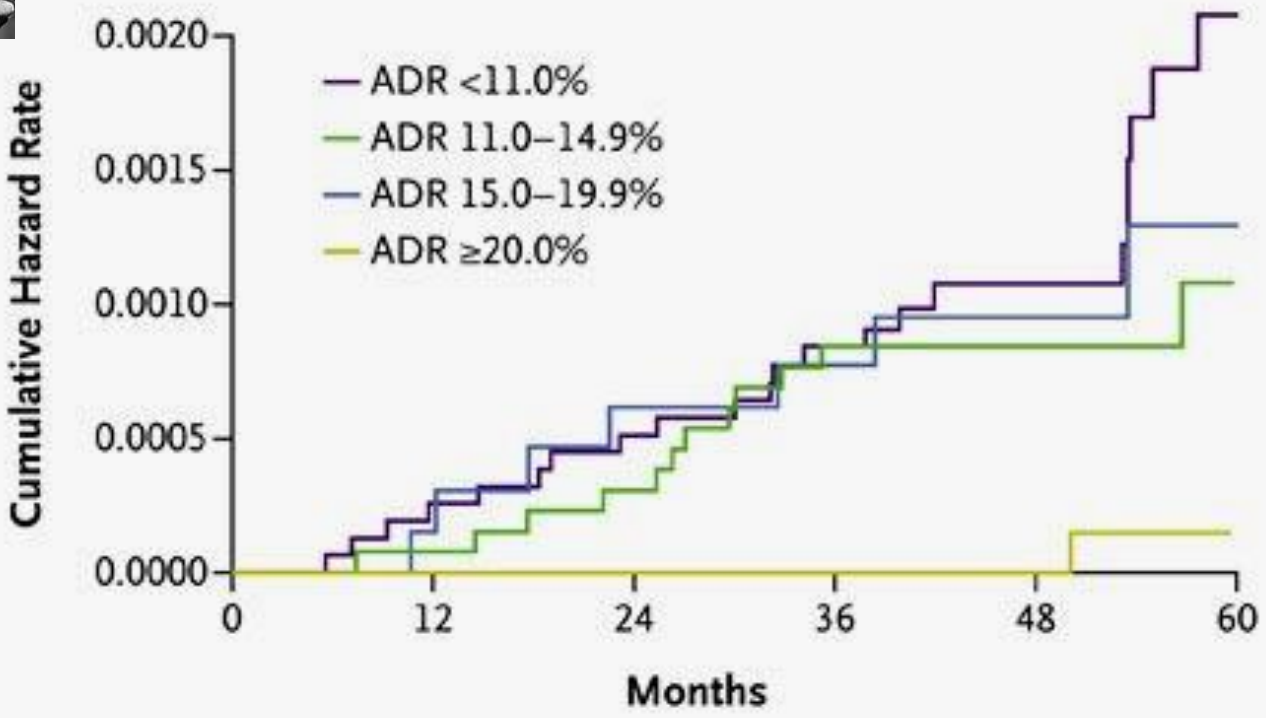
	People with screening n = 1912	People without screening n = 20,774
Number of carcinomas	11	213
UICC Stage I	8 (72%)	42 (19.7%)



Have we proven that the removal of right-sided lesions brings benefit?



Adenoma Detection Rate (ADR)

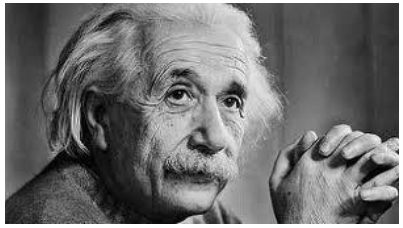


No. at Risk						
ADR <11.0%	15					
ADR 11.0–14.9%	13,281	13,223	13,182	13,120	7571	4003
ADR 15.0–19.9%	6,607	6,582	6,562	6,539	4022	2529
ADR ≥20.0%	9,255	9,235	9,202	9,166	7155	5548

Quality of colonoscopy is crucial.....

Kaminski M et al. N Engl J Med 2010;362:1795-1803

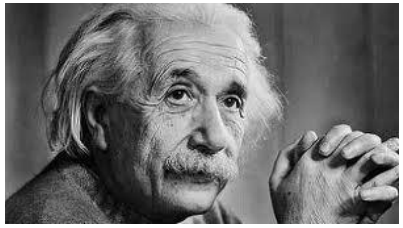
MF Kaminski: New Engl J Med 2010, 362: 1795



Brenner H: protection from colorectal cancer after colonoscopy
a population based case control study
Annals Int Med 2011; 154: 122

Incidence of colorectal cancer

and colonoscopy during last ten years



Brenner H: protection from colorectal cancer after colonoscopy a population based case control study

Annals Int Med 2011; 154: 122

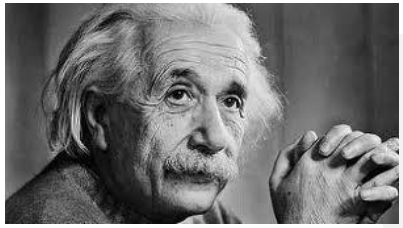
Table 2. **Association of Previous Colonoscopy With Risk for CRC**

Group	Total Participants, *n*	Colonoscopy 1–10 y Before, *n* (%)	Odds Ratio (95% CI)*	
			Adjusted for Age and Sex	Adjusted for Multiple Covariates†
Control participants	1932	793 (41.1)	–	–
Case patients				
Overall	1688	230 (13.6)	0.23 (0.19–0.27)	0.23 (0.19–0.27)
By cancer location				
Cecum	181	41 (22.7)	0.42 (0.30–0.61)	0.42 (0.28–0.61)
Ascending colon	213	59 (27.7)	0.54 (0.40–0.74)	0.58 (0.42–0.80)
Hepatic flexure	81	16 (19.8)	0.34 (0.20–0.60)	0.31 (0.16–0.59)
Transverse colon	72	13 (18.1)	0.32 (0.17–0.59)	0.34 (0.18–0.65)
Right colon combined	537	125 (23.3)	0.43 (0.35–0.54)	0.44 (0.35–0.55)
Splenic flexure	43	8 (18.6)	0.33 (0.15–0.72)	0.33 (0.15–0.73)
Descending colon	71	16 (22.5)	0.42 (0.24–0.73)	0.44 (0.25–0.79)
Sigmoid colon	374	35 (9.4)	0.15 (0.10–0.21)	0.14 (0.10–0.20)
Rectum	585	45 (7.7)	0.12 (0.09–0.17)	0.13 (0.09–0.18)
Left colon and rectum combined	1060	101 (9.5)	0.15 (0.12–0.19)	0.16 (0.12–0.20)
By cancer stage‡				
I	408	68 (16.7)	0.29 (0.22–0.38)	0.27 (0.20–0.36)
II	521	67 (12.9)	0.21 (0.16–0.28)	0.23 (0.17–0.30)
III	522	71 (13.6)	0.23 (0.18–0.30)	0.22 (0.17–0.29)
IV	233	23 (9.9)	0.16 (0.10–0.24)	0.17 (0.11–0.27)
By mode of detection				
Screening	382	67 (17.5)	0.31 (0.23–0.41)	0.28 (0.21–0.37)
Other§	1305	163 (12.5)	0.21 (0.17–0.25)	0.21 (0.18–0.26)

CRC = colorectal cancer.

* Odds ratio for CRC or CRC subgroup, comparing persons who had had colonoscopy 1 to 10 y before with persons who had not had previous colonoscopy.

† Adjusted for age and sex in addition to education level, participation in general health screening examination, family history of CRC, smoking status, body mass index, ever



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Splenic flexure				
Descending colon				
Sigmoid colon				
Rectum				
Left colon and rectum com				
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I				
II				
III				
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Brenner H: protection from right- and left sided colorectal neoplasia after colonoscopy: population based study

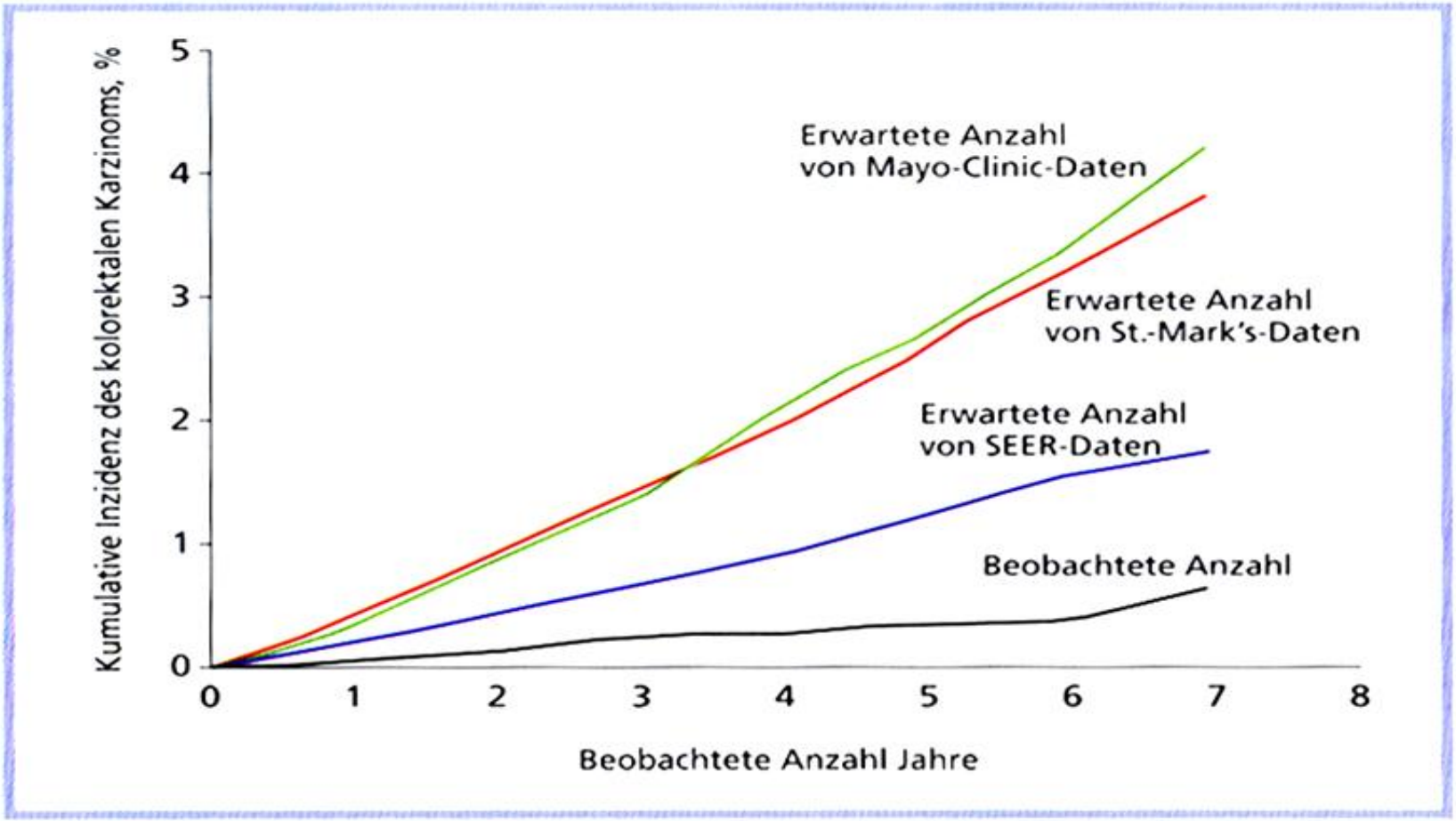
J Natl Cancer Inst 2010; 102: 89

total colon: RR 0.52 (0.37-0.73)

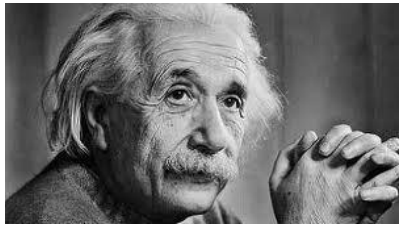
proximal colon: RR 1.05 (0.63-1.76)

left colon and rectum: RR 0.33 (0.21-0.53)

US National Polyp Study



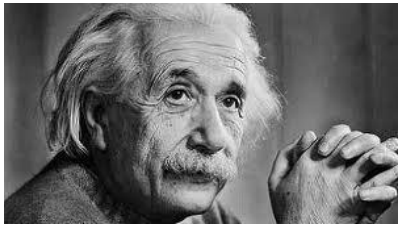
Winawer SJ: N Engl J Med 1993; 329: 1977



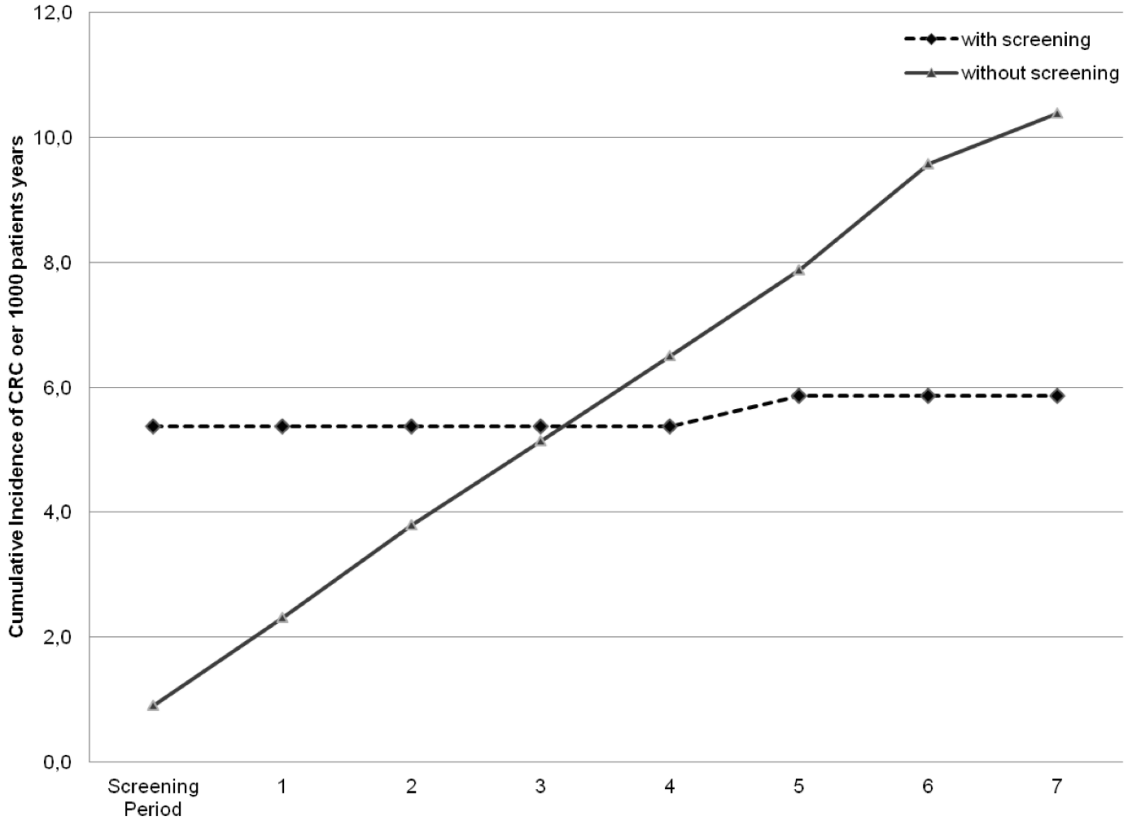
Colonoscopy Screening .....

a prospective Closed Cohort Study

Christine N. Manser[1,5], Lucas M. Bachmann[2], Jakob Brunner[3], Fritz Hunold[4], Peter Bauerfeind[1], Urs A. Marbet*[5]

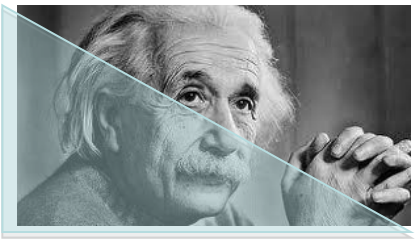


Cumulative incidence of CRC per 1000 patient years during screening period and 7-year follow up



Manser Ch, ... Marbet UA: submitted for publication

Risk stratification



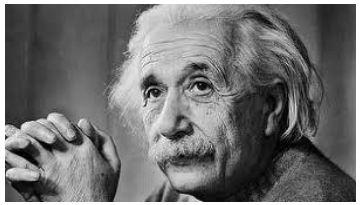
Which is the best screening in which setting?

	colonoscopy	CT / virtual colonoscopy	sigmoido-scopy	FOBT / FIT
scientific data	+++	++	++++	FOBT +++++ FIT ++
efficacy	++++ if high quality	? +++ ?	+++	+ FIT > gFOBT adherence
complications	+	(+)* but Xray...	((+))*	-* false negatives
Efficacy and CRC location is crucial especially if the risk is high				
unplaisent	++	+(+)	(+)	-
absenteism	± .. day	± 1 day	hours	-

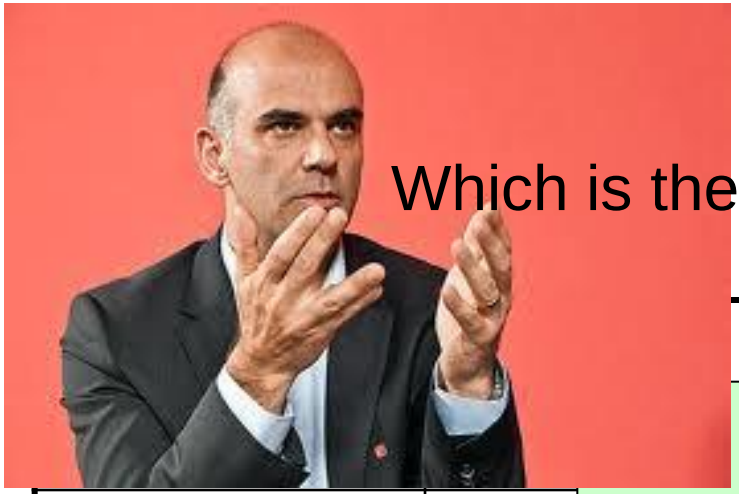
*in case of positive results colonoscopy is necessary

Complications of colonoscopy: Perforation

ESGE: Quality in screening colonoscopy, 4. version, 2011



- Prospective study of colonoscopy practice in UK n = 9‘223
  Bowler CJ: Gut;53:277
  Perforation rate 1 : 923 diagnostic colonoscopies
  1 : 460 therapeutic colonoscopies
  including 6 death within 30 days
- The Norwegian colorectal cancer prevention study: n = 2‘524
  Gondal G: Scand J Gastroenterol 2003;38:635
  Perforation rate **1:336 therapeutic colonoscopies**
- US Medicaire n = 39‘286
  Gatto NM: J Natl Cancer Inst 2003;95:230
  Perforation rate 1 : 510 colonoscopies
- CH Screening study n = 2‘044
  Marbet UA: Endoscopy 2008;40:650
  Perforation rate 1 : 2044 colonoscopies
  0 : 1‘479 diagnostic colonoscopies **1 : 565 therapeutic colonoscopies**
  (with 1279 polypectomies)



Which is the best method for **population screening**?

		CT / virtual	sigmoido-	FOBT / FIT
efficacy	+ if high			+ FIT > gFOBT adherence?
complications				-* false negatives
unplaisent				-
	±			

Harms of healthy people

Compliance

Adherence

Feasibility

Cost

Allocation of Ressources