NordICC at 10 years: Results, Surprises, and Questions for the Investigators

May 5, 2023

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Stanford University School of Medicine

Agenda

- NordICC 10-year results
- The context of the FS RCTs
- Delving into details of the trial
- Questions for the investigators

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Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death

M. Bretthauer, M. Løberg, P. Wieszczy, M. Kalager, L. Emilsson, K. Garborg, M. Rupinski, E. Dekker, M. Spaander, M. Bugajski, Ø. Holme, A.G. Zauber, N.D. Pilonis, A. Mroz, E.J. Kuipers, J. Shi, M.A. Hernán, H.-O. Adami, J. Regula, G. Hoff, and M.F. Kaminski, for the NordICC Study Group*

- Population-based: invitation to colonoscopy vs. usual care
- Participation rate in invitation arm: 42%
- Interim 10-year results (plan 15 years)

Published online October 9, 2022

EDITORIAL

Understanding the Results of a Randomized Trial of Screening Colonoscopy

Jason A. Dominitz, M.D., M.H.S., and Douglas J. Robertson, M.D., M.P.H.

- "…surprising and disappointing"
- Factors: Participation rate, time to realize benefit, quality of colonoscopy, higher-risk screened in Poland

Published online October 9, 2022

Norway

Sweden

Netherlands

Poland

Norway
31% of n

Sweden
4% of n

Netherlands
Excluded
NEJM 22

Poland
64% of n

Norway
31% of n
45% of colo

Sweden
4% of n
4% of colo

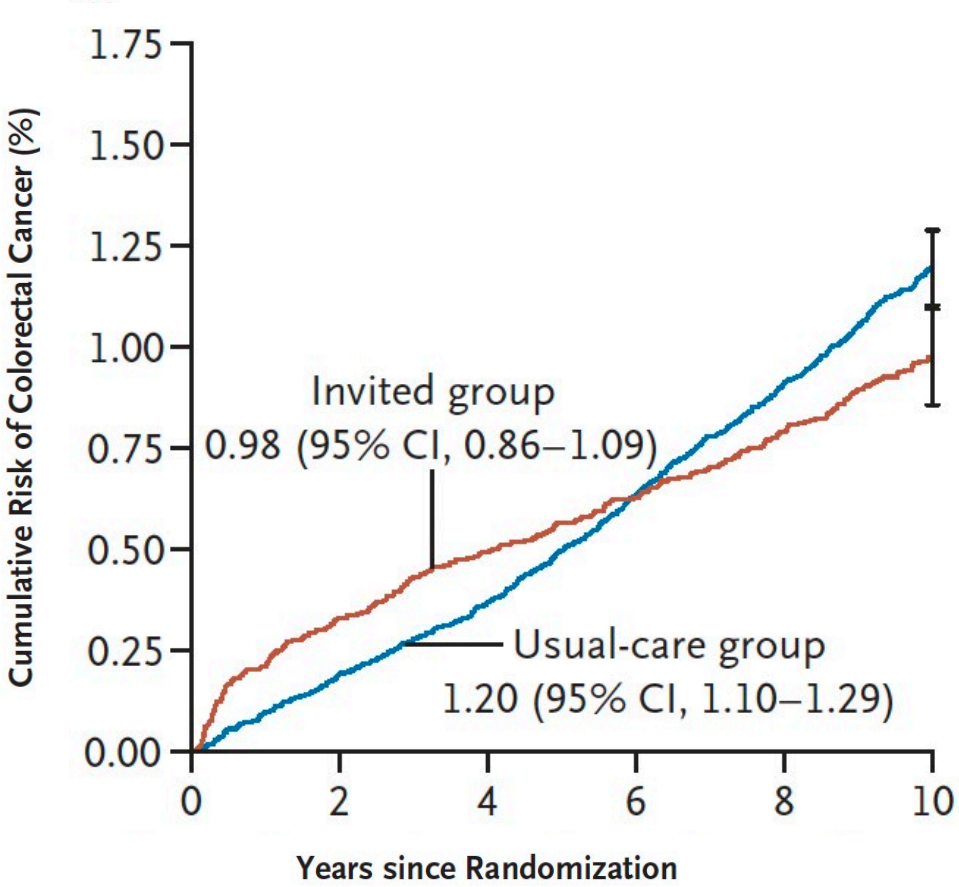
Netherlands
Excluded
NEJM 22

Poland
64% of n
51% of colo

NordICC Trial: 10-year results

CRC Incidence: Intention to Screen

Screening participation 42%

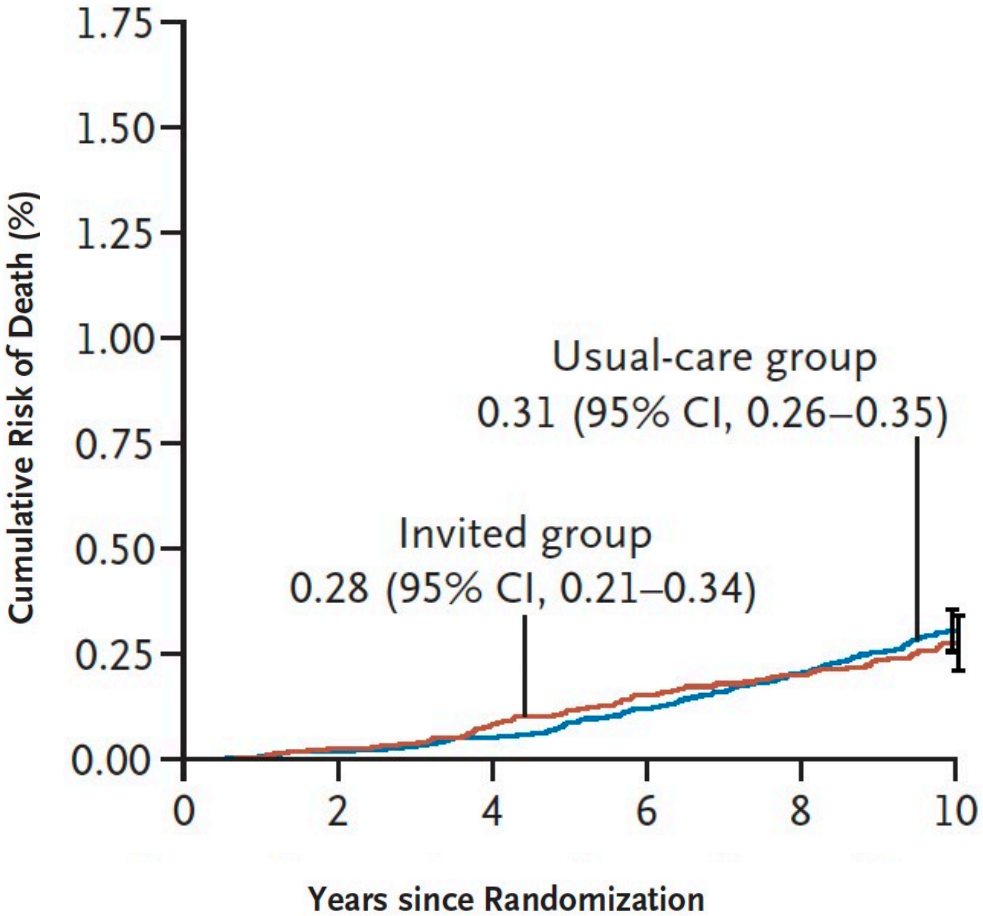


Risk ratio 0.82 (0.70-0.93)

Bretthauer et al, NEJM 2022;387:1547

CRC Mortality: Intention to Screen

Screening participation 42%



Bretthauer et al, NEJM 2022;387:1547

Risk ratio 0.90 (0.64-1.16)

Adjusted per-protocol analyses

Analysis	CRC incidence	CRC mortality
Intention to screen (42% uptake)	0.82 (0.70-0.93)	0.90 (0.64-1.16)
Adjusted per-protocol		

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Adjusted per-protocol	*0.69 (0.55-0.83)*	

Adjusted per-protocol analyses

Analysis	CRC incidence	CRC mortality
Intention to screen (42% uptake)	0.82 (0.70-0.93)	0.90 (0.64-1.16)
Adjusted per-protocol	*0.69 (0.55-0.83)*	*0.50 (0.27-0.77)*

NordICC Trial: 10-year results

- How to reconcile with FS RCTs?

FS RCTs

Study	Patients (n)	Yrs F/U (median)	Uptake	Incidence reduction	Mortality reduction
UK Flex Sig	170,432	11.2	71%	23%	31%
SCORE (Italy)	34,292	10.5	58%	18%	22% (NS)
PLCO (US)	154,910	11.9	84%	21%	26%
NORCAPP (Norway)	98,792	10.9	63%	20%	27%

Atkin *et al*, Lancet 2010;375:1624, Segnan *et al*, JNCI 2011;103:1310, Schoen *et al*, NEJM 2012;366:2345
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FS RCTs and NordICC at 10 years

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NordICC	**84,585**	**10**	**42%**	**18%**	**10% (NS)**

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"NordICC x1.5"	**84,585**	**10**			

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**assumes no self-selection*

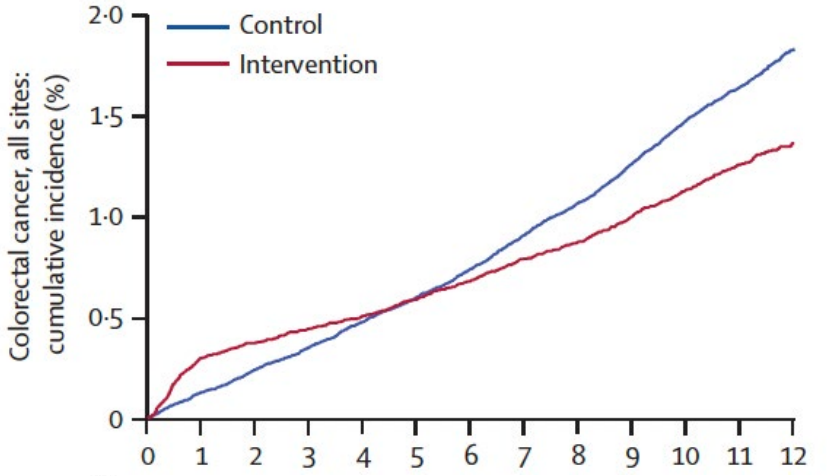
FS RCTs and NordICC at 10 years: Per protocol

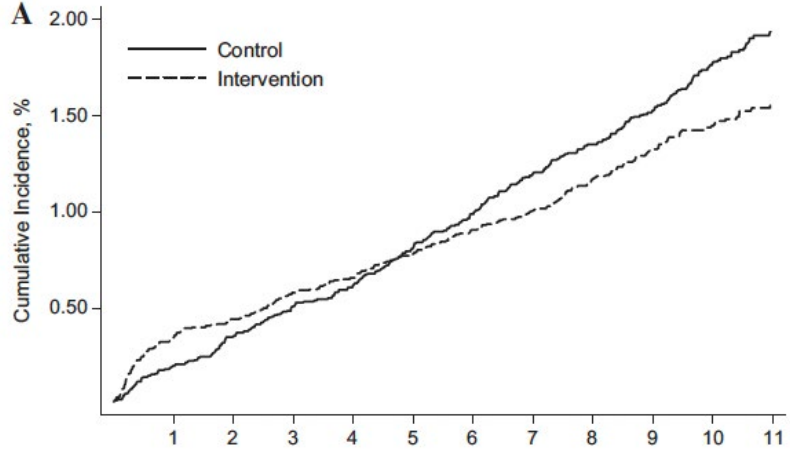
	CRC incidence reduction	CRC mortality reduction
UK Flex Sig Trial (UK)	33%	43%
SCORE Trial (Italy)	31%	38%
NordICC		

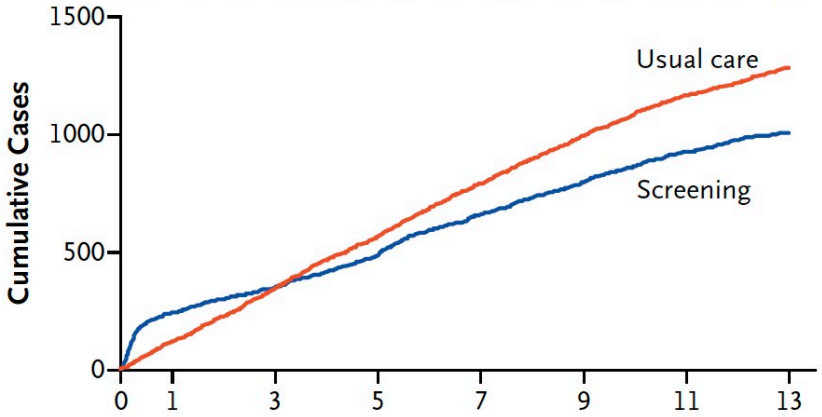
FS RCTs and NordICC at 10 years: Per protocol

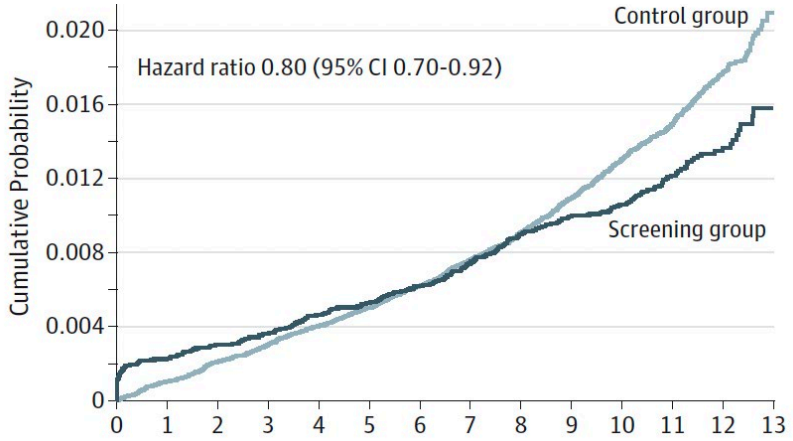
	CRC incidence reduction	CRC mortality reduction
UK Flex Sig Trial (UK)	33%	43%
SCORE Trial (Italy)	31%	38%
NordICC	31% (17-45%)	50% (23-73%)

FS RCTs: CRC incidence curves









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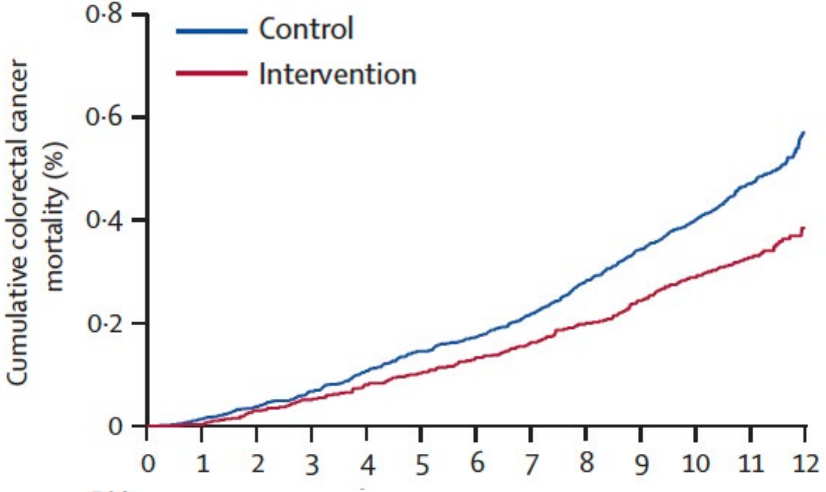

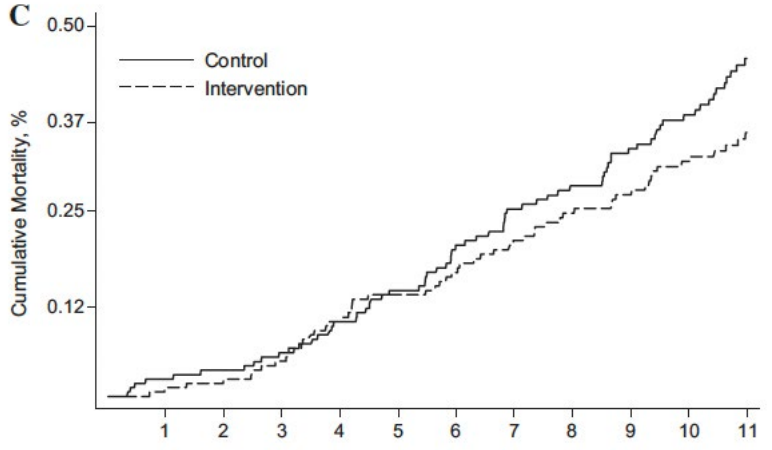

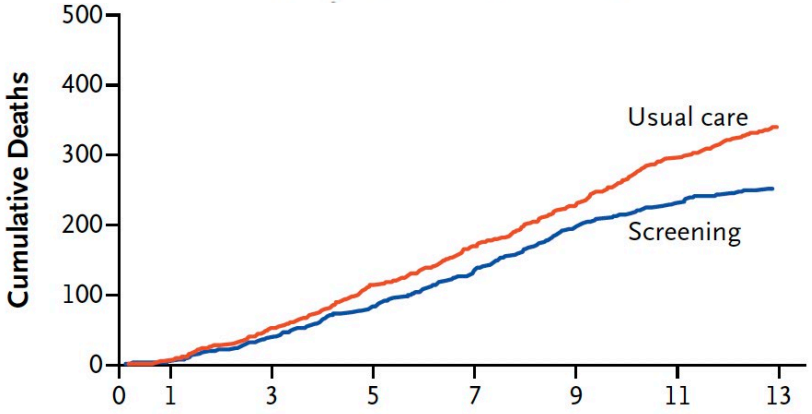

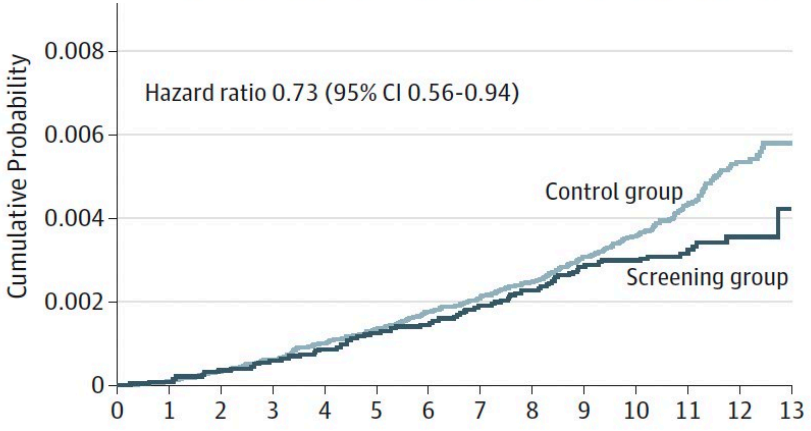

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"Textbook" Graphs for Flex Sig

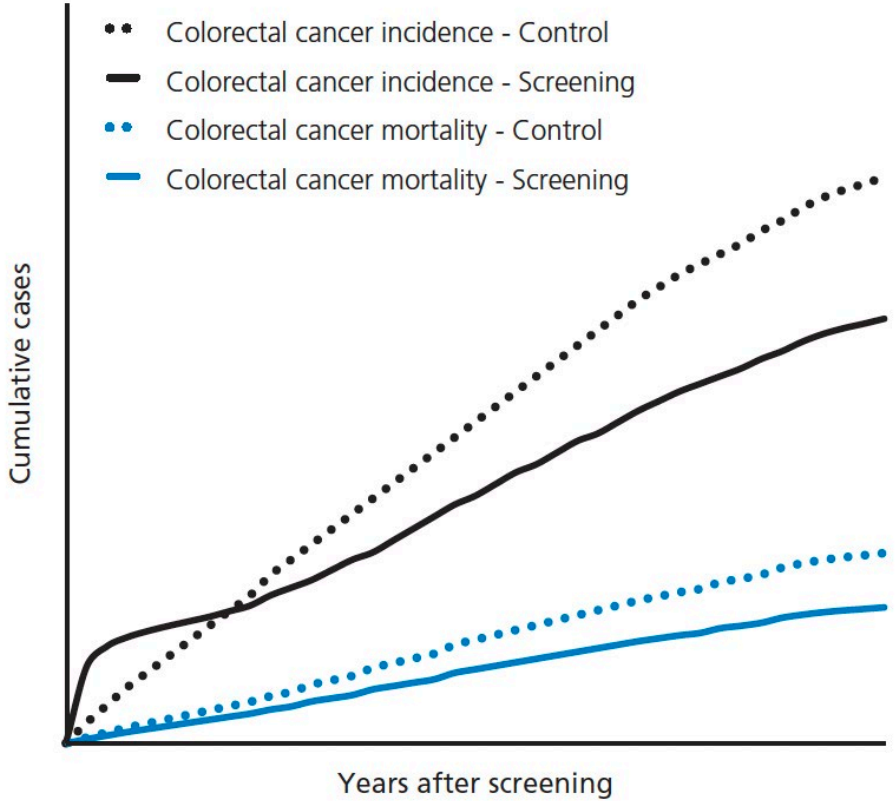
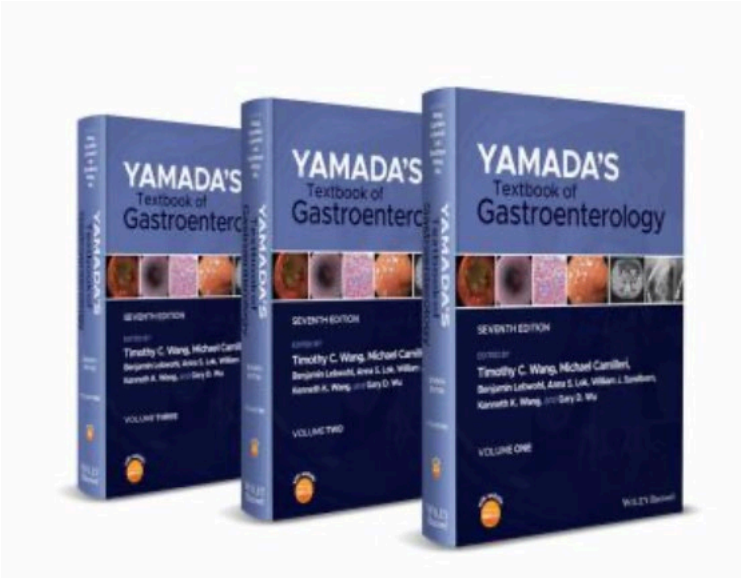


Figure 72.2 Idealized representation of the impact of screening flexible sigmoidoscopy on colorectal cancer incidence and mortality. Curves with these shapes were observed in all five randomized controlled trials of screening flexible sigmoidoscopy versus no screening or usual care [29–

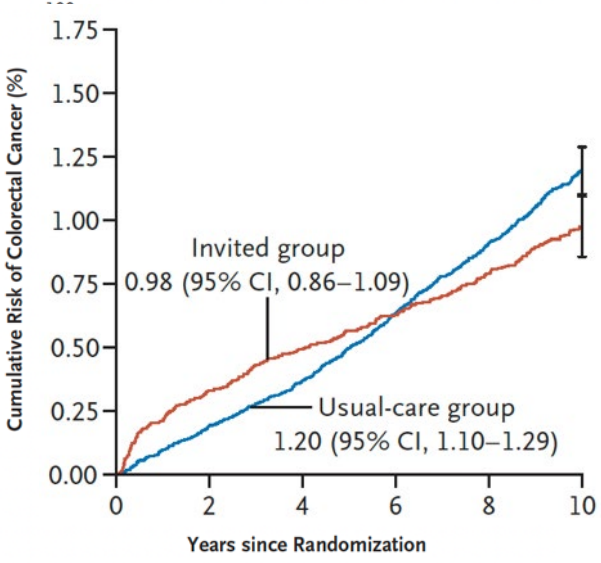


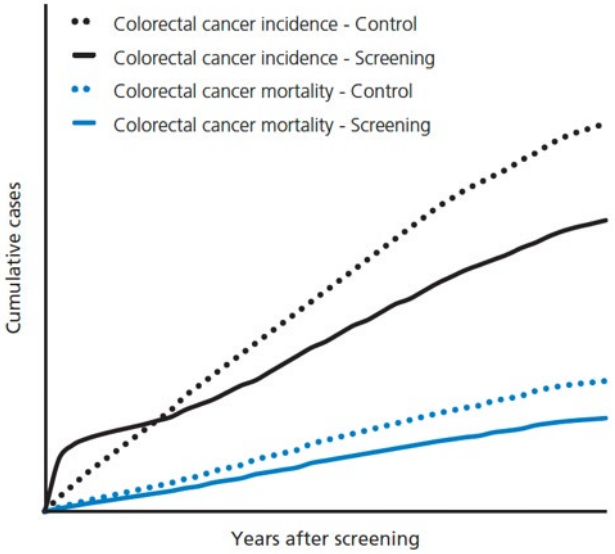
Ladabaum U, Colorectal cancer screening, Yamada's Textbook of Gastroenterology, 7th Ed, 2022

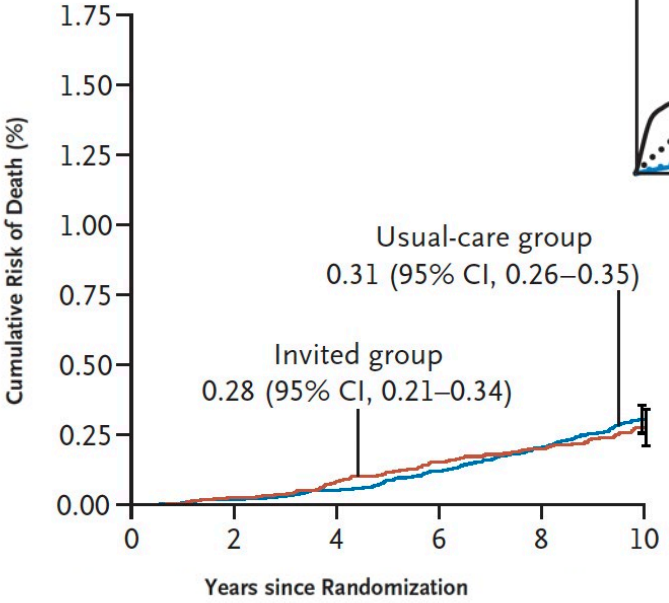
NordICC Trial: 10-year results

Some “head-scratchers”

How to reconcile NordICC vs. FS “textbook graphs”?







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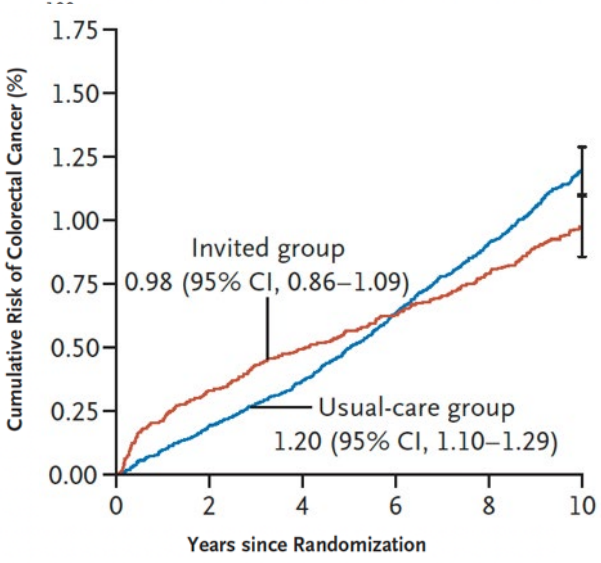

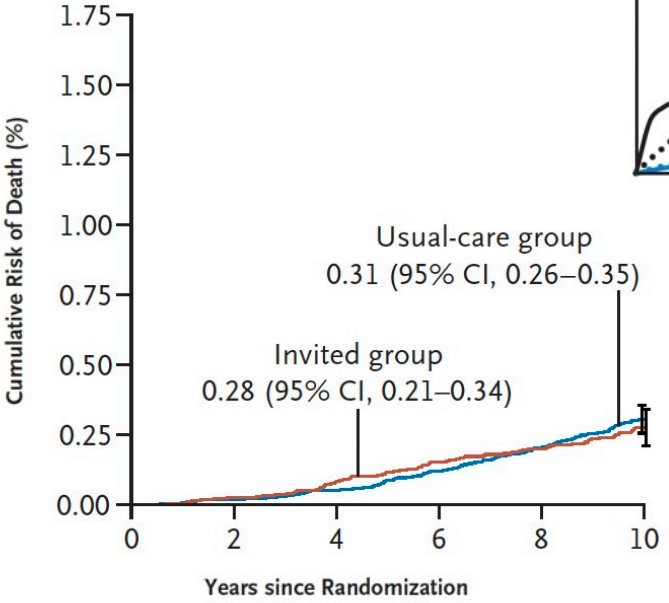

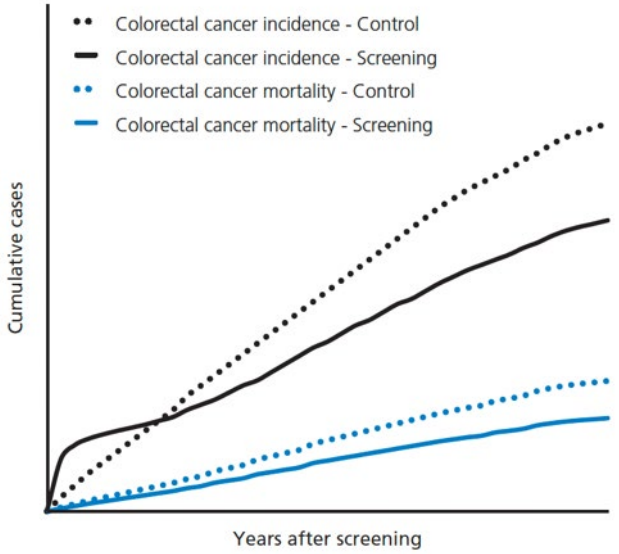

Q1a: Mortality curve?

Stage distribution: Why no notable shift?

Stage	Intervention 259 CRCs / 28,220	Control 622 CRCs / 56,365
A	39 (15%)	78 (13%)
B	69 (27%)	169 (27%)
C	66 (25%)	174 (28%)
D	47 (18%)	107 (17%)
Unknown	38 (15%)	94 (15%)

Bretthauer et al, NEJM 2022;387:1547 Appendix

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Q1b:
Why no
stage shift?

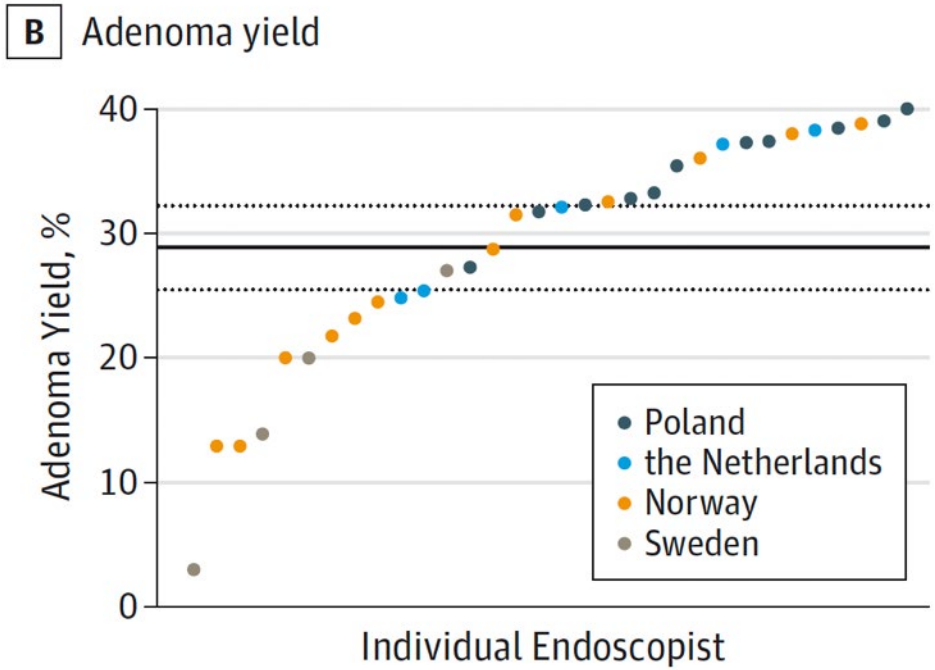
Bretthauer et al, NEJM 2022;387:1547 Appendix

NordICC Trial: 10-year results

- Colonoscopy quality? (ADR, sedation)

NordICC: Colonoscopy quality? → ADR

- **ADR <25% in 28.6% of reported endoscopists***



*32 endoscopists with 30+ exams (**960+ ?** / 12,574)*

Bretthauer et al, JAMA Int Med 2016;176:894

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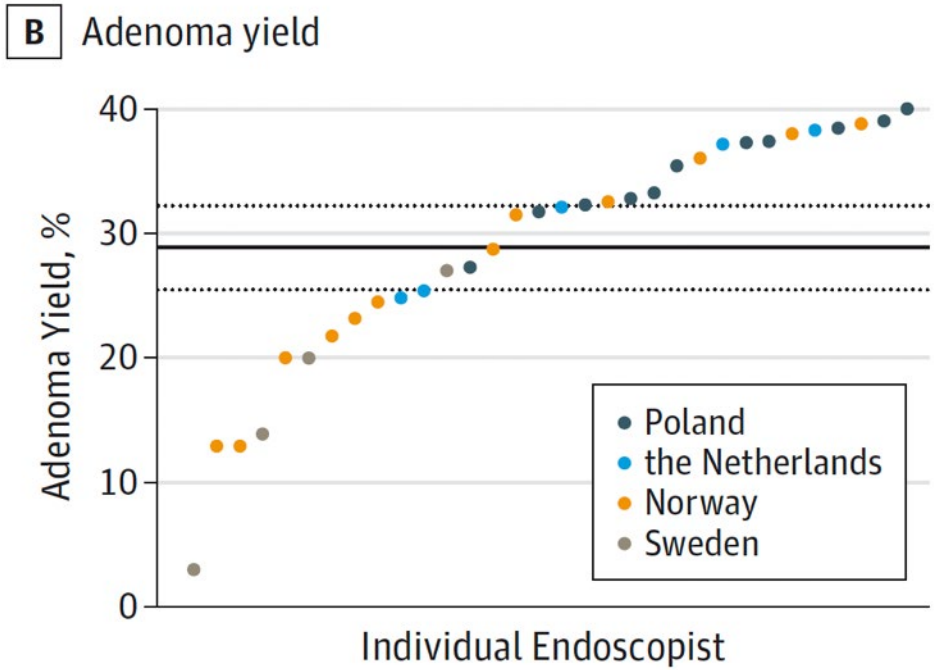


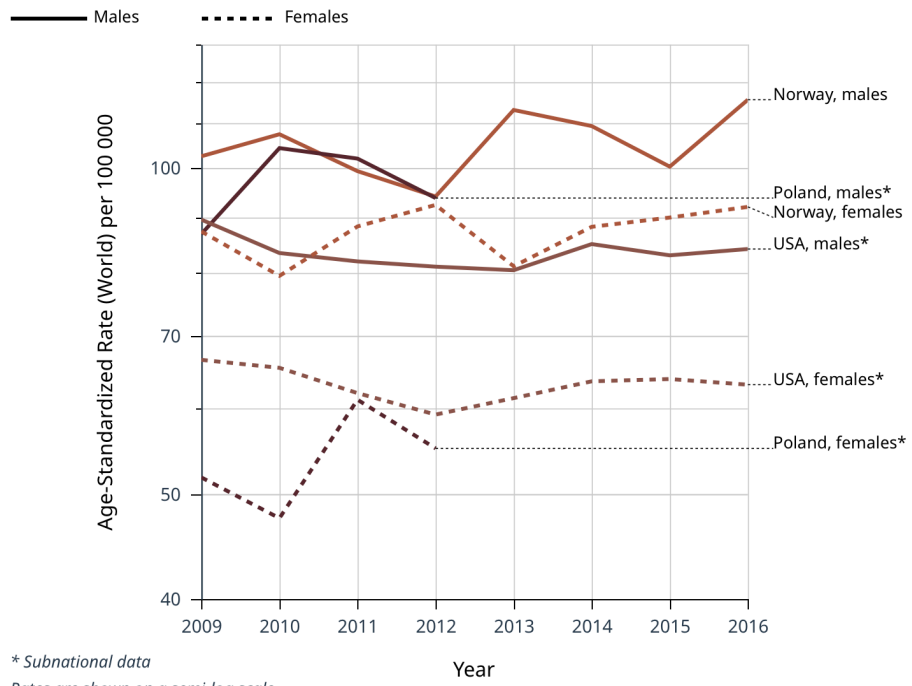
Q2a: Colo quality in the rest?

*32 endoscopists with 30+ exams (**960+ ?** / 12,574)*

Bretthauer et al, JAMA Int Med 2016;176:894

NordICC: Expected ADR? → National CRC Incidence

Age-standardized rate (World) per 100 000, incidence, males and females, age [50-64]
Colorectum
Norway - Poland - USA**



* Subnational data
Rates are shown on a semi-log scale
Lines are smoothed by the LOESS regression algorithm (bandwidth: 0.25)

International Agency for Research on Cancer
World Health Organization

NO
PL
NO
U
S
PL

Norway males

Poland males

Norway females

USA males

USA females

Poland females

* *Inspired by* Dominitz and Robertson, Reply to NEJM letters, Jan 2023

NordICC: Expected ADR? → National CRC Mortality

Age-standardized rate (World) per 100 000, mortality, males and females, age [50-64]
Colorectum
Norway - Poland - USA

Rates are shown on a semi-log scale
Lines are smoothed by the LOESS regression algorithm (bandwidth: 0.25)

International Agency for Research on Cancer
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PLUS PLUS PLUS

Poland males

USA males

Norway males

Poland females

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Expect ADR 55-64 yo in Norway, Poland ≥ USA?

NO PL SE U S

	NordICC	Norway	Poland	Sweden	USA
Years	*2009-2014*				*2010-2020*
% of n					
% of screen					
Adenoma					
Advanced Neoplasia					

Bretthauer et al, JAMA Int Med 2016;176:894
Bretthauer et al, NEJM 2022;387:1547

Liang et al, Gastroenterology 2022;163:742

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	NordICC	Norway	Poland	Sweden	USA
Years		*2009-2014*			*2010-2020*
% of n		*31%*	*64%*	*4%*	
% of screen		*45%*	*51%*	*4%*	
Adenoma					
Advanced Neoplasia					

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Adenoma					37.0%
Advanced Neoplasia					

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Advanced Neoplasia					

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Advanced Neoplasia	10.4%				6.8%

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Advanced Neoplasia	10.4%				6.8%

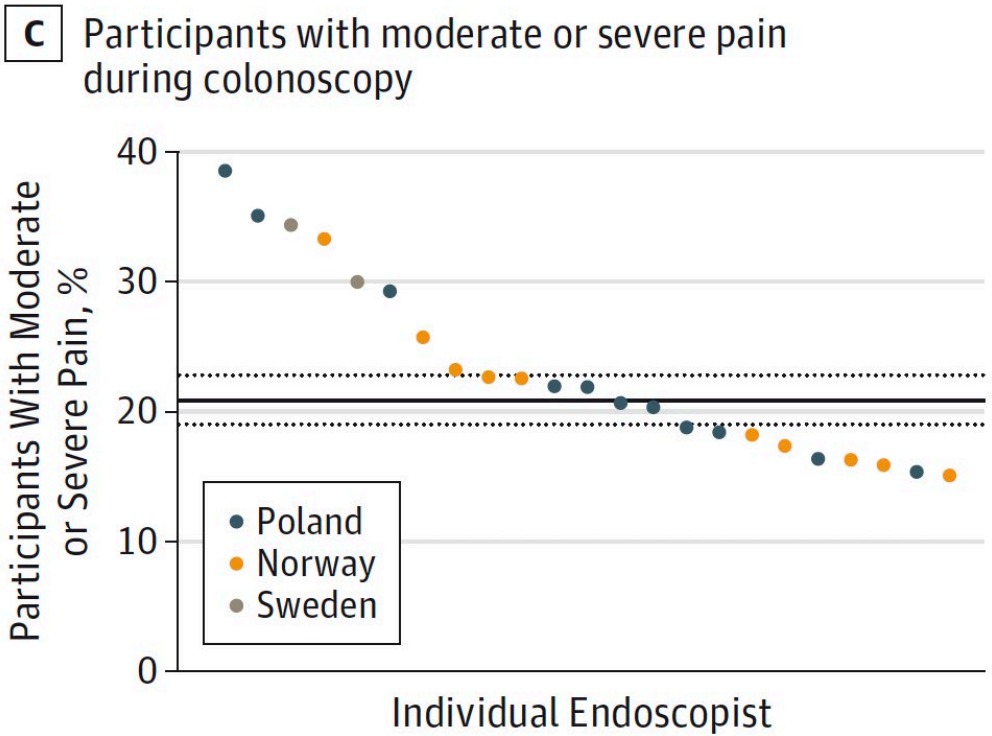
Q2b: Should ADR have been higher?

Bretthauer et al, JAMA Int Med 2016;176:894
Bretthauer et al, NEJM 2022;387:1547

Liang et al, Gastroenterology 2022;163:742

NordICC: Colonoscopy quality affected by patient pain?

- Sedation given: 22.7% (11% Norway, 23% Poland)



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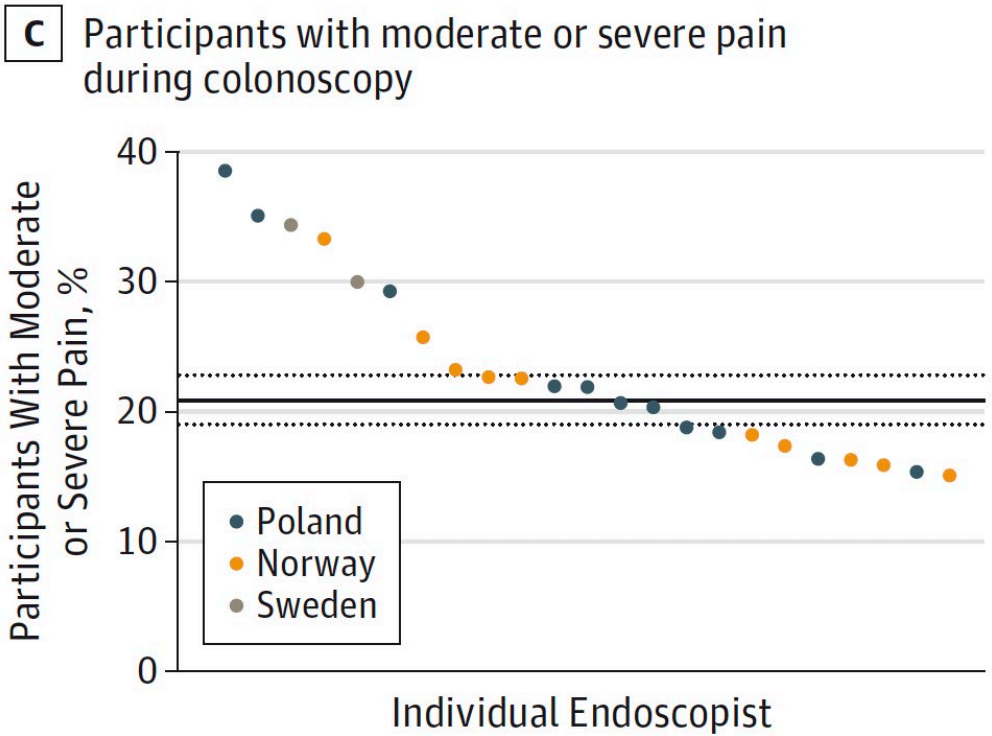


Q2c: Sedation rate impact on ADR?

Bretthauer et al, JAMA Int Med 2016;176:894

NordICC Trial: 10-year results

- Who took up screening?
- Colonoscopy rate in usual care controls?

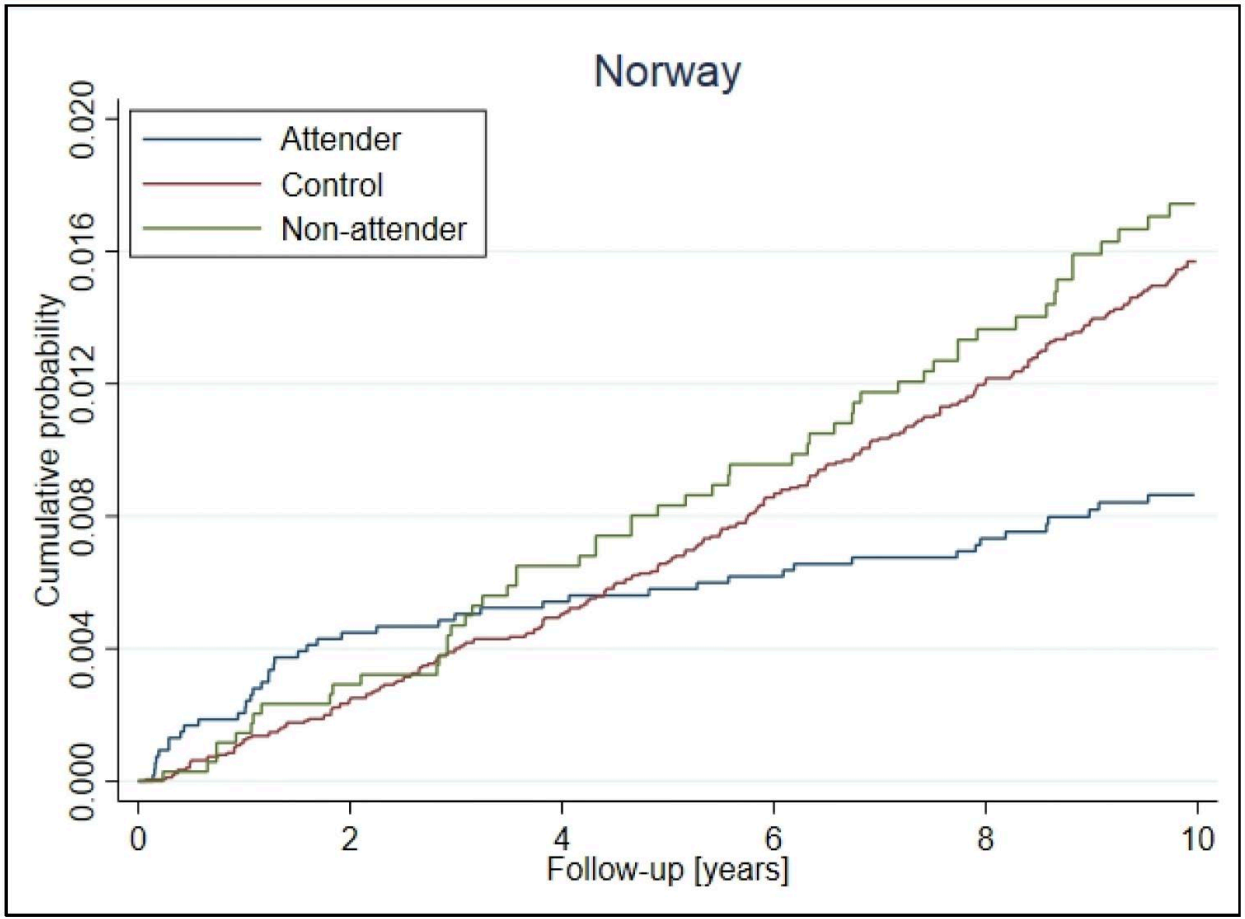
CRC Incidence: Norway

Screening participation 61%

ADR 27%

31% of n

Bretthauer et al, NEJM 2022;387:1547



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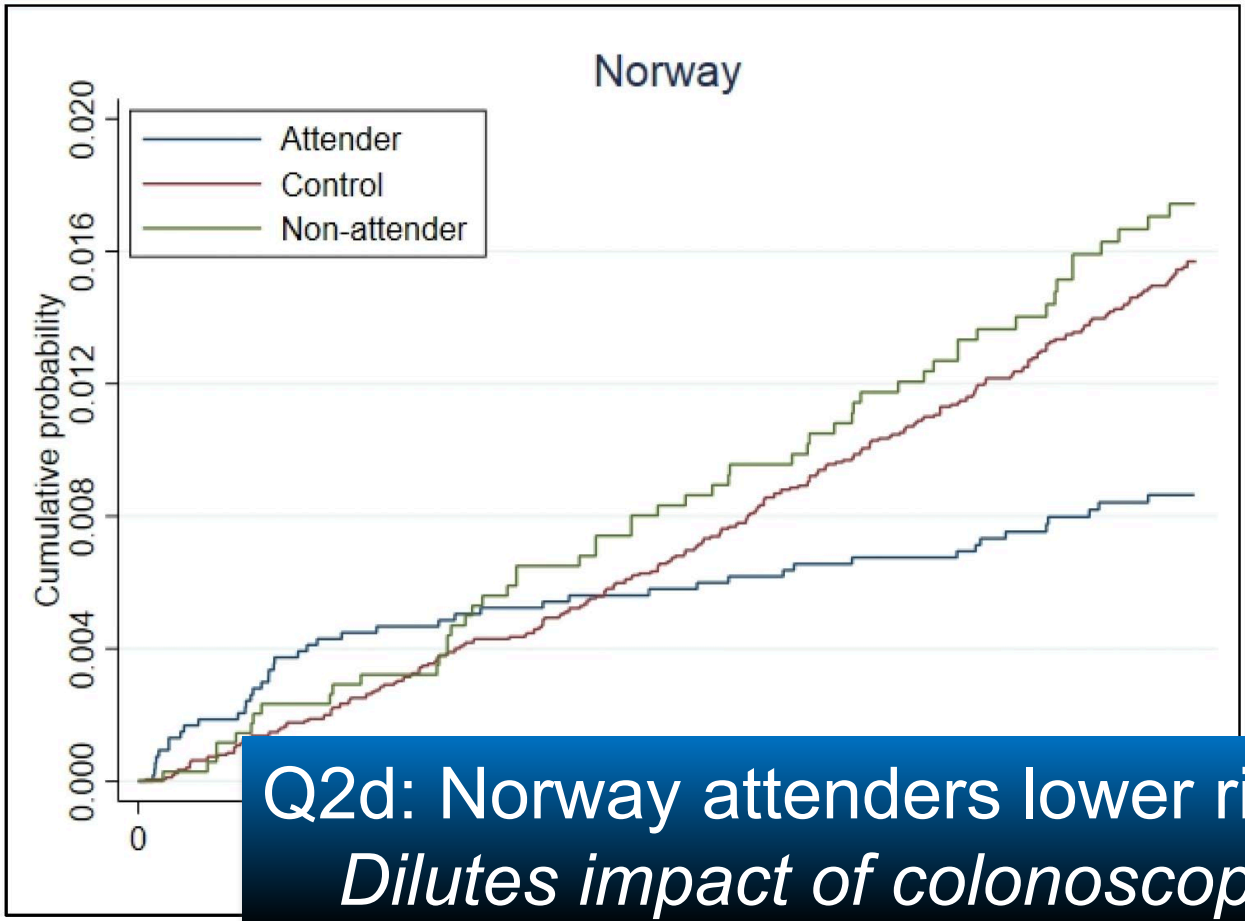
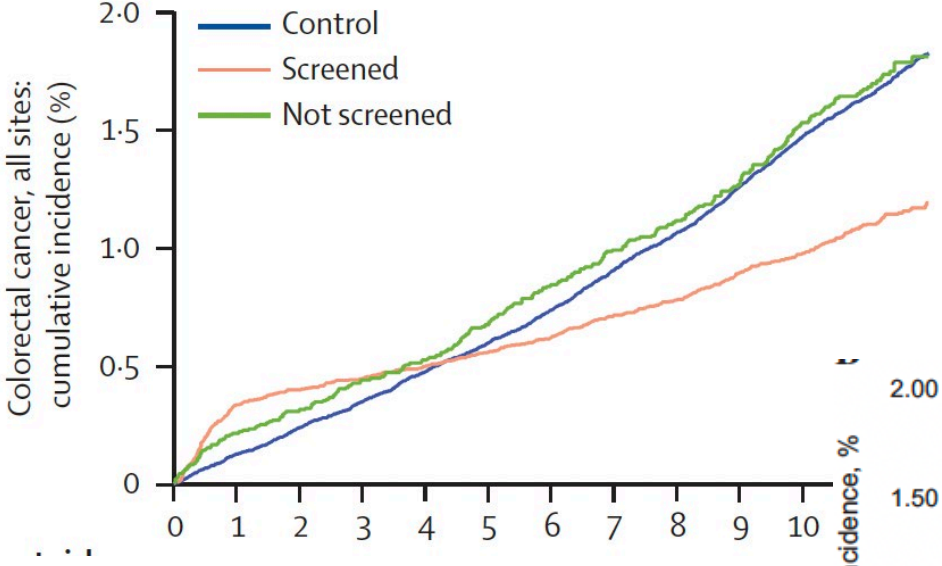
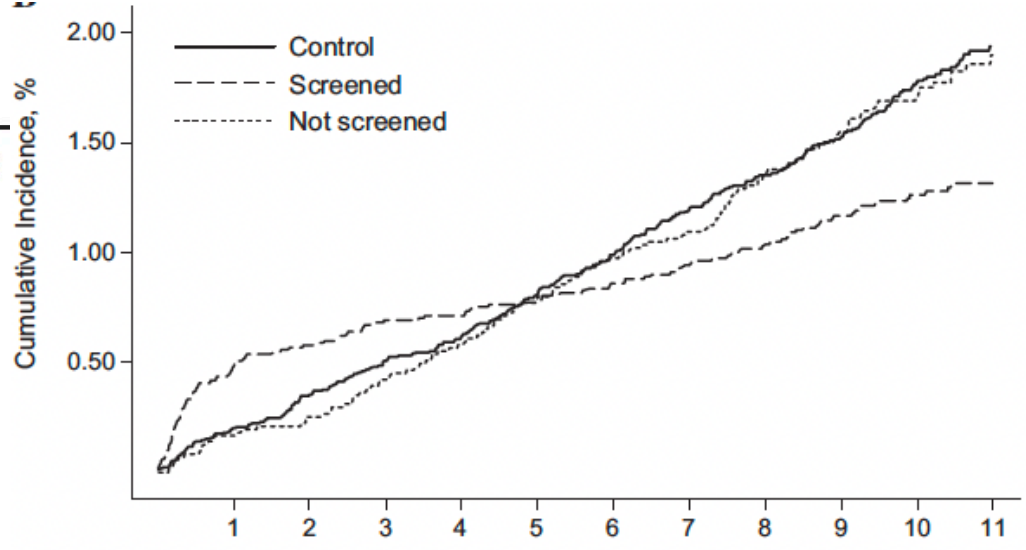


Q2d: Norway attenders lower risk?

Dilutes impact of colonoscopy

FS RCTs: non-attenders vs. controls





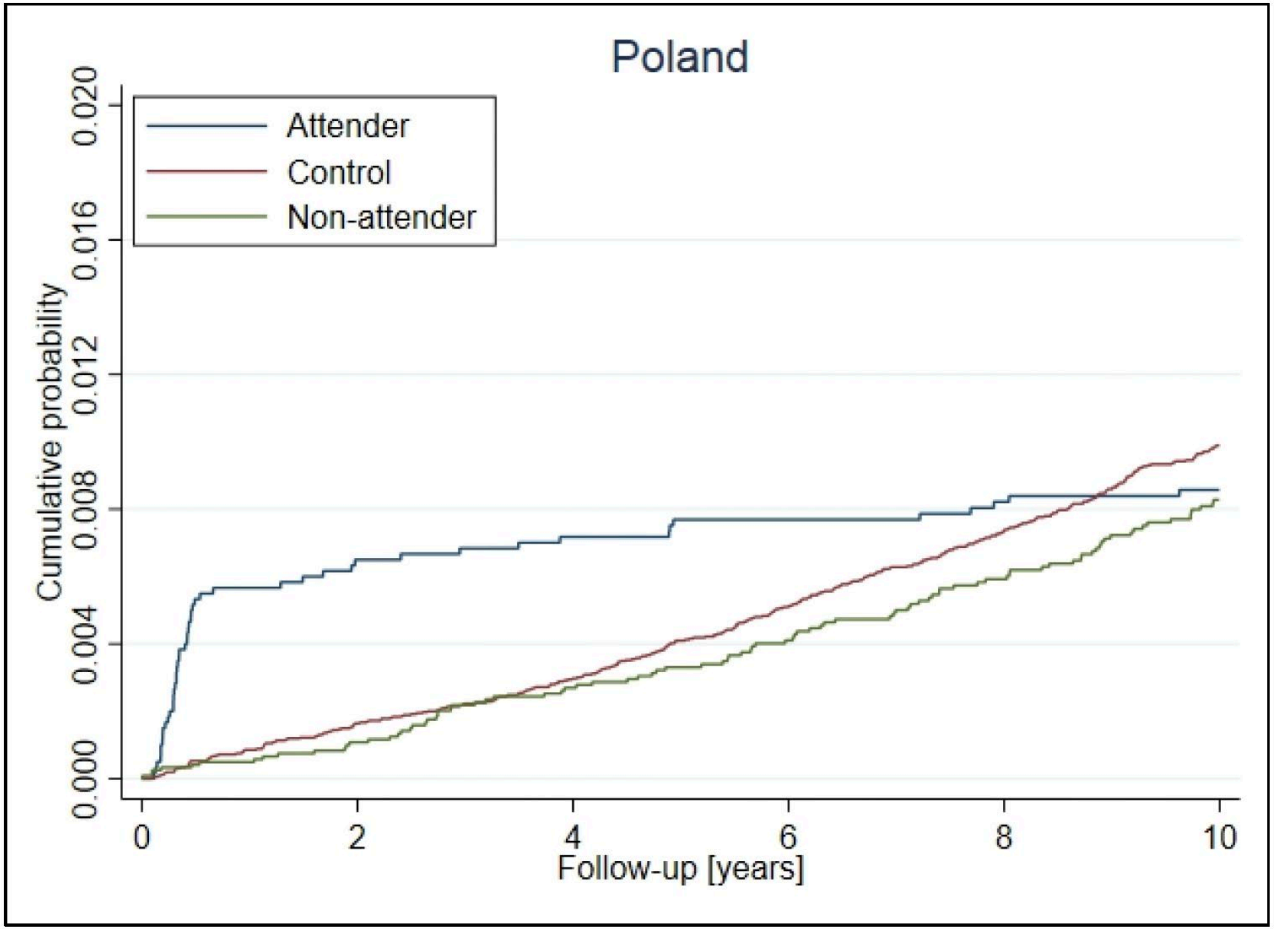
Atkin 2010;375:1624; Segnan 2011;103:1310

CRC Incidence: Poland

Screening participation 33%

ADR 35%

64% of n



Bretthauer et al, NEJM 2022;387:1547

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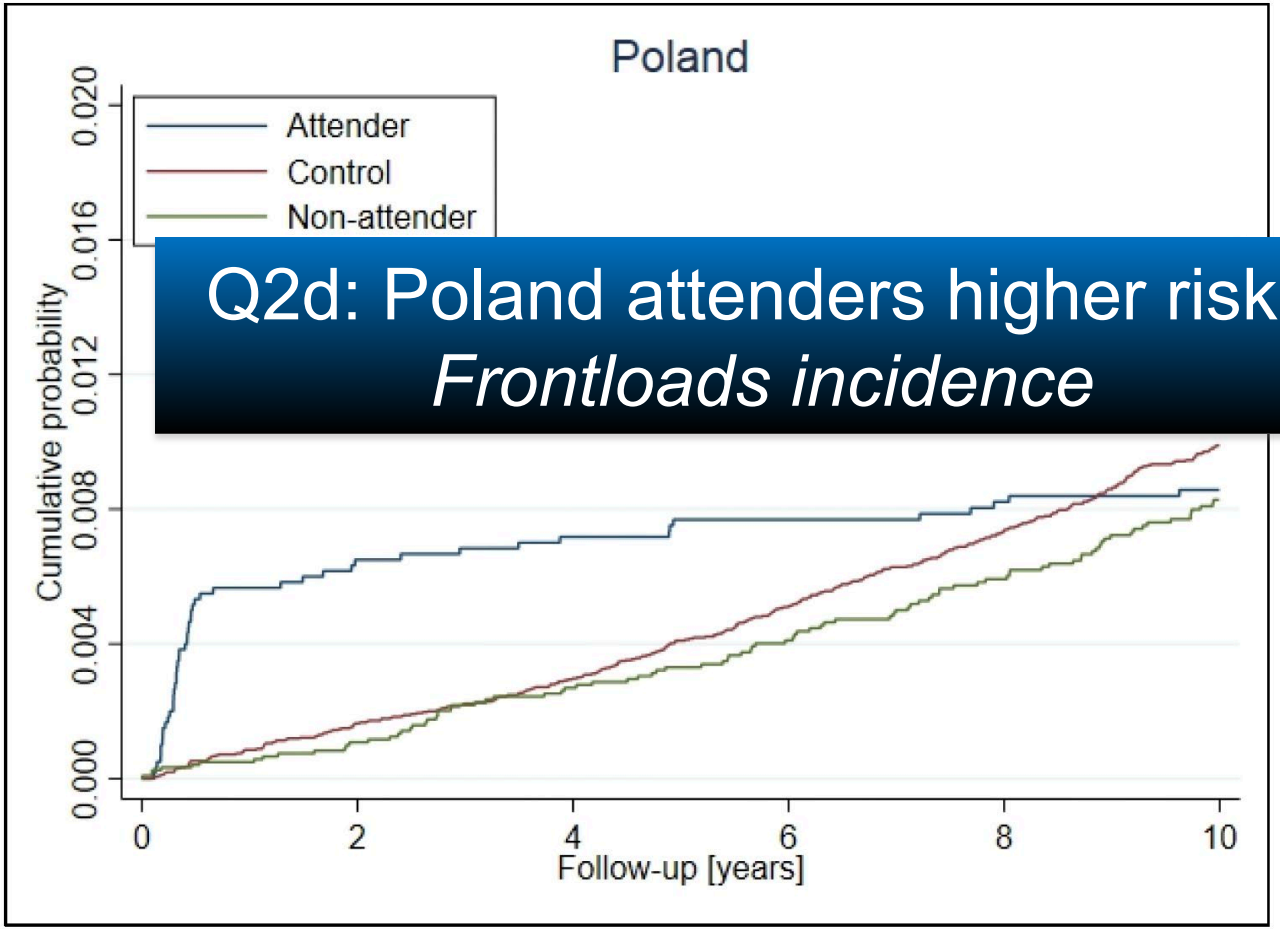

Q2d: Poland attenders higher risk?
Frontloads incidence

Question 1: Mortality curve?

- Why does **mortality curve** differ from FS RCTs?
- Why no stage shift? Success of Rx by stage?
- Confidence in ascertainment of cause of death (i.e. CRC mortality)? And also CRC incidence?
  - Was it more likely to "miss CRC death" and/or "miss CRC Dx" in the usual care arm?
  - (e.g. death with abdominal pain, bleeding, wasting; or deep venous thrombosis and pulmonary embolus; etc.?)

Question 2: Factors affecting incidence?

- Did colonoscopy quality (e.g. “low” ADR?) affect the **CRC incidence** reduction?
  - Should ADR have been higher (e.g. ≥ USA)?
  - Impact of sedation?
- Self-selection into screening?
  - Worried-well in Norway? → dilutes colonoscopy impact
  - Symptomatic* or high-risk** in Poland? → frontloads incidence (improves longer-term prevention)

** NOT SCREENING (presumably balanced across arms, but different colonoscopy rates?)*

*** How would they know?*

Question 3: Colonoscopy rates?

- Could screening colonoscopy uptake rate be higher in the future?
  - Different invitation protocol?
  - Annual invitation?
- Did colonoscopy use in usual care dilute results? *
  - What are ***actual rates and indications*** in the usual care arm?

* *"…Norway …Poland …did not observe more diagnostic colonoscopies in the control group than in the intervention group"* – Authors reply, NEJM letters, Jan 2023

Agenda

- NordICC 10-year results
- The context of the FS RCTs
- Delving into details of the trial
- Questions for the investigators

And now…

And now… M and M

And now… M and M

Michael Bretthauer (Norway)

Michal Kaminski (Poland)