Supplementary Appendix

Content

1. Assumption of distribution of adenomas in FOBT trial

1.1 Screening group

1.1.1. First round

In the FOBT trial report (6) the adenomas removed in patients were reported in the following groups: at first round of screening; at subsequent screening; in individuals who were randomized to screening but did not participate (non-participants); adenomas detected in the interval between two screening rounds either within 2 years or after 2 years; adenomas detected during follow-up; in the control group. To take account of length of follow-up time in our analyses, we assumed that all adenomas detected in the first screening round were followed for 19 years.

1.1.2. Subsequent screening rounds

Since biennial screening by FOBT was offered, we assumed that maximum follow-up time for subsequent screening is 17 years (first 2 years we assigned as first round) and subsequent screening took 8 years (total enrollment period was 10 years). We also assumed that constant number of adenomas was removed each year. Thus that out of adenomas removed at subsequent screening, 1/8 of adenomas had 17 years of follow-up, 1/8 of adenomas had 16 years of follow-up, ect. Detailed assumptions on the follow-up time for the rest of the sub-groups are described below.

1.1.3. Non-participants

We assumed that more adenomas occurred later in the follow-up, as the risk of adenomas increases with age. We used exponential distribution with λ=0.12 to calculate probability (p) of detecting the adenoma $p_t = \lambda \exp(-\lambda \cdot (19 - t))$, where t is time t=1,2,…,19. The parameter

λ was chosen, so that approximately 33% of adenomas were detected during the first 11 years of follow-up and 66% of adenomas were detected in the last 8 years of follow-up.

1.2 Control group

We assumed that the detection rate of adenomas in the control group was higher in the late period of follow-up, i.e. that 33% of adenomas were detected during first 11 years of follow-up and 66% of adenomas were detected during last 8 years of follow-up. Exponential distribution with λ=0.12 was used.

2. Population

Our analyses were based on a gender distribution of 60% males and 40% females (13). We based our models on the UK population from 1981 to 2009. All models were adjusted for mortality rates based on life tables (available at www.ons.gov.uk/peoplepopulationand community/birthsdeathsandmarriages/lifeexpectancies/bulletins/pastandprojecteddatafromthe periodandcohortlifetables/2012baseduk19812062, access on Mar 5, 2018). On average, individuals with adenomas were 60 years old at the beginning of the study period and 78 years old at the end of follow-up. Since the individuals were recruited between 1981 and 1991, we calculated an average mortality in those years for the 1st year or follow-up, an average for years 1982 to 1992 for the 2nd year of follow- up, etc.

Supplementary Table 1. Annual transition rates from adenoma to colorectal cancer (sensitivity analysis).

Name of the model	MISCAN	MISCAN	CRC-SPIN
Model description	Exponential distribution of dwell time with mean of 140**	Exponential distribution of dwell time with mean of 140***	Using estimates from (16)
Annual transition from adenoma to cancer (%)*	0.69 (0.26)	0.71	0.07

This table is a continuation of Table 2 in the main paper. The rates presented here comes from the data provided by the models' authors after contacting them. *Number of cancers that would be predicted to develop from 100 patients with at least one adenoma followed for 10 years. **We drawn 100 samples (corresponds to 100 patients) from exponential distribution with mean of 140 (time from adenoma to cancer) and count how many of them had a value ≤10 (corresponds to the 10 years of follow-up). Such experiment was repeated 1,000 times and mean (standard deviation) was calculated over the observations. ***We drawn a sample of 100,000 from exponential distribution with mean of 140 years and calculated a median over the observations. Annual transition rate was calculated using discrete time Markov model with one year interval.

Supplementary Table 2. Number of observed and prevented cancers (sensitivity analysis).

		Screening group			Control group		Primary analysis	Secondary analysis
		Prevented CRC among attenders	Prevented CRC among non-attenders and by interval adenomas	Observed CRC	Prevented CRC	Observed CRC	Overdiagnosed cancers*	Overdiagnosed cancers**
FOBT	MISCAN [a]	71 (8)	83 (9)	2,279	60 (7)	2,354	-4	19
	MISCAN [b]	70	83	2,279	61	2,354	-5	17
	CRC-SPIN[c]	92	73	2,279	50	2,354	17	40
Sigmoidoscopy [$]	MISCAN [a]	214 (14)		393		452	155	
	MISCAN [b]	212		393		452	153	
	CRC-SPIN[c]	135		393		452	76	

*Primary analysis (overdiagnosis include only adenomas in the screening arm). **Secondary analysis (overdiagnosis include all adenomas in the screening and control arms; only FOBT). [$]Number of observed CRC in control group was recalculated to adjust for unbalanced sample size of screening and control group. [a]Exponential distribution of dwell time with mean of 140 (mean and standard deviation over 1,000 replications). [b]Exponential distribution of dwell time with mean of 140 (using median time from adenoma to cancer). [c]Using estimates from (16).

Supplementary Table 3. Number of overdiagnosed cancers and the amount of overdiagnosis (in percent) in the different models (sensitivity analysis).

		Primary analysis				Secondary analysis				
		Number of overdiagnosed cancers	Rate of overdiagnosis			Number of overdiagnosed cancers	Overdiagnosis			
			% of CRC observed in the control group	% of CRC observed in the screening group	% of CRC expected in the screening group		% of CRC observed in the control group	% of CRC expected in the control group	% of CRC observed in the screening group	% of CRC expected in the screening group
FOBT	MISCAN [a]	-4	-0.2	-0.2	-0.2	19	0.8	0.8	0.8	0.8
	MISCAN [b]	-5	-0.2	-0.2	-0.2	17	0.7	0.7	0.7	0.7
	CRC-SPIN[c]	17	0.7	0.7	0.7	40	1.7	1.7	1.8	1.7
Sigmoidoscopy [$]	MISCAN [a]	155	34.3	39.4	25.5					
	MISCAN [b]	153	33.8	38.9	25.3					
	CRC-SPIN[c]	76	16.8	19.3	14.4					

*Primary analysis (overdiagnosis include only adenomas in the screening arm). **Secondary analysis (overdiagnosis include all adenomas in the screening and control arms; only FOBT). [$]Number of observed CRC in control group was recalculated to adjust for unbalanced sample size of screening and control group. [a]Exponential distribution of dwell time with mean of 140 (mean over 1,000 replications). [b]Exponential distribution of dwell time with mean of 140 (using median time from adenoma to cancer). [c]Using estimates from (16).

Supplementary Table 4. Number of overdiagnosed cancers and the amount of overdiagnosis (in percent) in the different models

		Primary analysis				Secondary analysis						
		Number of overdiagnosed cancers	Overdiagnosis			Prevented CRC among non-attenders and by interval adenomas	Prevented CRC in control group	Number of overdiagnosed cancers	Overdiagnosis			
			% of CRC observed in the control group	% of CRC observed in the screening group	% of CRC expected in the screening group				% of CRC observed in the control group	% of CRC expected in the control group	% of CRC observed in the screening group	% of CRC expected in the screening group
FOBT	MISCAN	-3	-0.1	-0.1	-0.1	113	90	20	0.8	0.8	0.9	0.9
	CRC-SPIN	125	5.3	5.5	5.0	215	138	202	8.6	8.1	8.9	8.1
	SimCRC	133	5.6	5.8	5.3	217	138	212	9.0	8.5	9.3	8.5
	German, low	46	2	2	1.9	86	58	74	3.1	3.1	3.2	3.1
	German, high	179	7.6	7.9	7.1	198	137	240	10.2	9.6	10.5	9.5

Sigmoidoscopy [$]	MISCAN	148	32.7	37.7	24.7	
	CRC-SPIN	551	121.9	140.2	54.9	
	SimCRC	579	128.1	147.3	56.2	
	German, low	114	25.2	29	20.1	
	German, high	334	73.9	85	42.5	

*Primary analysis (overdiagnosis include only adenomas in the screening arm). **Secondary analysis (overdiagnosis include all adenomas in the screening and control arms; only FOBT). [$]Number of observed CRC in control group was recalculated to adjust for unbalanced sample size of screening and control group.

Abbreviations: CRC: colorectal cancer