Supplement 1

1. Baseline characteristics of study participants of the Norwegian Colorectal Cancer Prevention Trial. *

	No(%)			
	Group			
	Control (n=78 220)		Screening (n=20 572)	
Age, mean (SD), y*	56.1	(3.8)	56.9	(3.8)
Sex				
Men	38922	(49.8)	10269	(49.9)
Women	39298	(50.2)	10303	(20.1)
Age group, y				
50-54	37131	(47.5)	6920	(33.6)
55-64	41089	(52.5)	13652	(66.4)
Area of residence				
Telemark County	15176	(19.4)	10314	(50.1)
City of Oslo	63044	(80.6)	10258	(49.9)

*Data retrieved from Table 1, Holme et al. (2014). There was no data available regarding personal or family history for any of the individuals selected for the trial.

2. Comparison of incidence rate in NORCCAP trial control group and in intervention group: adherers and non-adherers.

	No. Individuals*	**CRC incidence***	**Incidence rate**	**Baseline incidence**
Control group	78220	1086	0.0139	1
Non-Adherers	7617	111	0.0146	1.05
Adherers	12955	142	0.0110	0.971**

*Data retrieved from Table 4, Holme et al. (2014)

**Computation of incidence rate for adherers:

incidence ratio non adherers relative to control group =

(111/7617)/(1086/78220)=1.050

incidence ratio adherers relative to control group = $(1-1.05*(1-0.63^{\#}))/0.63^{\#}$

#adherence in intervention group'

3. Observed adherence rates in the NORCCAP trial compared to simulated adherence rates in MISCAN-Colon

Characteristic	**NORCCAP trial**	**MISCAN-Colon**
Adherence flexible sigmoidoscopy	63.0%*	63.0%
Adherence FOBT in adherers to flexible sigmoidoscopy (involving only one intervention arm) **	86.7%**	86.7%
Adherence diagnostic colonoscopy	95.6%*	95.6%
Adherence surveillance colonoscopy	*unknown*	80%
Reach sigmoid sigmoidoscopy	97% ***	97%
Reach coecum colonoscopy	89%***	89%

Abbreviation: FOBT, fecal occult blood test.

*Data retrieved from Gondal et al. (2003)

** FOBT was performed in adherers to flexible sigmoidoscopy, before flexible sigmoidoscopy was performed

***Provided by research leader G. Hoff

4. Screening test characteristics used in MISCAN-Colon to simulate the NORCCAP trial

Test characteristic	Sigmoidoscopy	Colonoscopy	FOBT
Sensitivity small adenomas (<5 mm)	75%	75%	0%
Sensitivity medium adenomas (6-9 mm)	85%	85%	7.6%
Sensitivity large adenomas (>10 mm)	95%	95%	17.6%
Sensitivity CRC long before clinical detection*	95%	95%	35.2%
Sensitivity CRC short before clinical detection*	95%	95%	71.6%
Specificity	97.6%	100 %	96.3%

Abbreviation: CRC, colorectal cancer.
*Sensitivity of FOBT is higher in the stage in which the cancer would have been diagnosed in the absence of screening than in earlier stages.(2)
FOBT: fecal occult blood test.

5. Observed positivity rate* and positive predictive values** of screening tests of the NORCCAP trial compared to those simulated in MISCAN-Colon

	FOBT		Sigmoidoscopy	
	NORCCAP trial	**MISCAN-Colon**	**NORCCAP trial**	**MISCAN-Colon**
Positivity rate	5.6%	5.5%	18.8%	16.5%
PPV	44.1%	45.3%	96.0%	94.7%
PPV adenomas	17.8%	18.7%	69.7%	70.6%
PPV Advanced adenomas	22.0%	22.3%	24.8%	22.8%
PPV cancer	4.3%	4.3%	1.6%	1.4%

Abbreviations: FOBT, fecal occult blood test; PPV, positive predictive value

*positivity rate: the number of individuals with a positive FOBT or flexible sigmoidoscopy (either false or true positive) divided by the total number of individuals adhering to FOBT or flexible sigmoidoscopy.

** positive predictive value: the number of individuals with adenomas, advanced adenomas or CRC detected at follow-up colonoscopy divided by the number of individuals adhering to follow-up colonoscopy after a positive FOBT or sigmoidoscopy.

6. Mathematical formulations of the study outcomes

Primary outcome targets	Formula	Confidence Interval	Comments
Incidence and mortality rates	$$incidence\ (or\ mortality)\ rate = \frac{d_{(i)}}{n_{(i)}}$$ $n_{(i)}$= number of person years until year i $d_{(i)}$ = number of events until year i	We computed corresponding 95% Confidence Intervals assuming a Poisson distribution as follows: Lower bound: $$L = \frac{\chi^2_{2d_{(i)},0.025}}{2n_{(i)}}$$ Upper bound: $$U = \frac{\chi^2_{2(d_{(i)}+1),0.975}}{2n_{(i)}}$$	For the NORCCAP Trial Results these were directly computed from the results published in Holme et al. 2014 (as authors did not report 95% confidence intervals for incidence and mortality rates)
Hazard ratio	In the NORCCAP trial, authors computed age-adjusted Hazard ratios (HRs) using a Cox models including age as covariate in the models. In our analysis, using Cox model was not a feasible way. Thus, we adjusted the model to simulate age-specific population with and without screening and we computed, therefore, "*age-adjusted*" rate ratios as: $$\frac{incidence\ (or\ mortality)\ rate\ intervention\ group}{incidence\ (or\ mortality)\ rate\ control\ group}$$ Assuming that these measures were for definition age-adjusted, we assumed those consistent estimations of trial's HR. Furthermore, we assumed those measures as an accurate estimation of relative risk $$Rate\ Ratios\ \approx HR\ \approx RR$$	Confidence intervals for HRs were computed in Holme et al. (2014) using Cox models.	For the NORCCAP trial results these were directly obtained from the results as published in Holme et al. (2014)
Secondary outcome targets			
Cumulative probability	$$Cumulative\ probability = 1 - \hat{S}(t) = 1 - \prod_{t_{(i)} \le t} \frac{n_{(i-)} - d_{(i)}}{n_{(i-)}}$$ With $\hat{S}(t) = 1\ for\ t < t_{(i)}$ t = time in years $n_{(i-)}$= number of person years in year i $d_{(i)}$ = number of events in year i	95% Confidence Interval may be computed as follow: Lower bound: $$L = 1 - (\hat{S}(t) + 1.96\sqrt{\hat{V}\{\hat{S}(t)\}})$$ Upper bound: $$U = 1 - (\hat{S}(t) - 1.96\sqrt{\hat{V}\{\hat{S}(t)\}})$$ With variance V computed using Greenwood's formula:	For the NORCCAP Trial Results and the MISCAN-Colon predictions the same formula was used. Required inputs from the NORCCAP trial were provided by the trial leaders.

<table>
<tr>
<td></td>
<td></td>
<td>$\hat{V}\{\hat{S}(t)\} = \hat{S}(t)^2 \sum_{t_{(i)} \le t} \frac{d_{(i)}}{n_{(i-)}(n_{(i-)} - d_{(i)})}$</td>
<td></td>
</tr>
<tr>
<td>Yearly risk ratio</td>
<td>$\widehat{RR}_i = \frac{a_i/(a_i + b_i)}{c_i/(c_i + d_i)}$

a_i = number of persons with events in year i in intervention group
b_i = number of persons without events in year i in intervention group
c_i = number of persons with events in year i in control group
d_i = number of persons without events in year i in control group</td>
<td>95% Confidence Interval are computed as follows:

Lower bound:
$l = e^{\ln \widehat{RR}_i - 1.96\widehat{SD}[\ln \widehat{RR}_i]}$
Upper bound:
$U = e^{\ln \widehat{RR}_i + 1.96\widehat{SD}[\ln \widehat{RR}_i]}$
Where:
$\widehat{SD}[\ln \widehat{RR}_i] = \sqrt{\frac{b_i/a_i}{a_i + b_i} + \frac{d_i/c_i}{c_i + d_i}}$</td>
<td>For the NORCCAP Trial Results and the MISCAN-Colon predictions the same formula was used. Required inputs from the NORCCAP trial were provided by the trial leaders.</td>
</tr>
<tr>
<td>Colonoscopy attendance

Screen-detected adenomas and cancers

Stage distribution</td>
<td>These values were computed as proportions. Thus, ratio between events e and population under study n, as follows:

$proportion = \hat{p} = \frac{e}{n}$

In the following table we reported the values used in computing each fraction:

<table>
<tr><th>Proportion</th><th>e</th><th>n</th></tr>
<tr><td>Colonoscopy attendance</td><td>Individuals that performed colonoscopy</td><td>Invited individuals</td></tr>
<tr><td>Screen-detected adenomas/cancer</td><td>Screen-detected adenomas (cancers)</td><td>Invited individuals</td></tr>
<tr><td>Localized cancer</td><td>Localized cancer diagnosed</td><td>All cancer diagnosed</td></tr>
<tr><td>Advanced cancer</td><td>Advanced cancer diagnosed</td><td>All cancer diagnosed</td></tr>
</table>
</td>
<td>95% Confidence Interval are computed as follows:

Lower bound:
$L = \hat{p} - 1.96\widehat{SD}$
Upper bound:
$U = \hat{p} + 1.96\widehat{SD}$
Where:
$\widehat{SD} = \sqrt{\frac{\hat{p}(1-\hat{p})}{n}}$

These proportions and corresponding 95% confidence intervals were reported in relation to n. Thus, $\hat{p}$, L , and U were multiplied for n (total individuals invited or total number of cancer diagnosed in NORCAAP trial) before reporting those values in study's tables.

In addition, we compared localized (advanced) cancer proportions using Pearson χ^2test (Rothman KJ, Greenland S. Modern Epidemiology (2nd edition). Philadelphia: Lippincott-Raven 1998).</td>
<td>For the NORCCAP Trial Results these were directly obtained from the values as published in Holme et al. (2014). Confidence intervals were computed using the formulas reported in this table.</td>
</tr>
</table>

1. Human Mortality Database [Internet]. Accessed 01-10-2018. Available from: http://www.mortality.org/.
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Supplement 2: Model appendix – MISCAN-Colon

General Model Structure

MISCAN-Colon is a stochastic microsimulation model for colorectal cancer (CRC) programmed in Delphi (Borland Software Corporation, Scotts Valley, California, United States). It can be used to explain and predict trends in CRC incidence and mortality and to quantify the effects and costs of primary prevention of CRC, screening for CRC, and surveillance after polypectomy.

The term 'microsimulation' implies that individuals are moved through the model one at a time, rather than as proportions of a cohort. This allows future state transitions to depend on past transitions, giving the model a 'memory'. Furthermore, unlike most traditional Markov models, MISCAN-Colon does not use yearly transition probabilities; instead it generates durations in states, thereby increasing model flexibility and computational performance. The term 'stochastic' implies that the model simulates sequences of events by drawing from distributions of probabilities/ durations, rather than using fixed values. Hence, the results of the model are subject to random variation.

MISCAN-Colon consists of 3 modules: a demography module, natural history module, and screening module.

The Demography Module

Using birth- and life-tables representative for the population under consideration, MISCAN-Colon draws a date of birth and a date of non-CRC death for each individual simulated. In MISCAN-Colon the maximum age an individual can achieve is exactly 100 years.

The Natural History Module

Transitions

As each simulated person ages, one or more adenomas may develop (Model Appendix Figure 1). These adenomas can be either progressive or non-progressive. Both progressive and non-progressive adenomas can grow in size from small (≤5mm), to medium (6-9mm), to large (≥10mm); however, only progressive adenomas can develop into preclinical cancer. A preclinical cancer may progress through stages I to IV; however, during each stage CRC may be diagnosed because of symptoms. After clinical

diagnosis, the survival depends on the stage of the cancer. For individuals with synchronous CRCs at time of diagnosis, the survival of the most advanced cancer is used. The date of death for individuals with CRC is set to the earliest simulated death (either due to CRC or due to another cause (see: 'The demography module')).

Transition Probabilities and Durations in States

An individual's risk of developing adenomas depends on the individual's age and a personal risk index. As a result of the latter most individuals develop no adenomas, whilst some develop many. We assumed that the distribution of adenomas over the colon and rectum equals the distribution of cancers in Norway during the NORCCAP trial, before the introduction of screening (between 1999 and 2011). Data was provided by the Norwegian Cancer Registry. The age-specific onset of adenomas and the dispersion of the personal risk index were calibrated to data on the prevalence and multiplicity distribution of adenomas as observed in autopsy studies (Model Appendix Figure 2).(2-11) The age-specific probability of adenoma-progressivity and the age- and localization-specific transition probabilities between preclinical cancer stages and between preclinical and clinical cancer stages were simultaneously calibrated to data on the age-, stage-, and localization-specific incidence of CRC in Norway during the NORCCAP trial, before the introduction of screening (between 1999 and 2011) (Model Appendix Figure 3). Data was provided by the Norwegian Cancer Registry.

The average durations between the preclinical cancer stages were calibrated to the rates of screen-detected and interval cancers observed in randomized controlled trials evaluating screening using guaiac fecal occult blood tests.(12-14) This exercise has been described extensively in a publication by Lansdorp-Vogelaar and colleagues.(15) The average duration from the emergence of an adenoma (state 2) until progression into preclinical cancer (state 7) (i.e. the adenoma dwell-time) was calibrated to the rates of interval cancers (including surveillance detected cancers) observed in a randomized controlled trial evaluating once-only sigmoidoscopy screening (Model Appendix Figure 4). (16) We assumed an equal overall dwell-time for adenomas developing into CRC from a medium size (30% of all CRCs) and from a large size (70% of all CRCs). All durations in the adenoma and preclinical cancer phase were drawn from exponential distributions. Durations within the adenoma phase and within the preclinical

cancer phase were assumed to be perfectly correlated (i.e. if a small adenoma grows into a medium-sized adenoma rapidly, it will also grow into a large adenoma or develop into CRC rapidly); however, durations in the adenoma phase were assumed to be uncorrelated with durations in the preclinical cancer phase (i.e. a rapidly growing adenoma does not necessarily develop into a rapidly progressing cancer). The proportion of medium sized, non-progressive adenomas growing large and the average duration in duration in the medium size, non-progressive adenoma state (state 5) were calibrated to size-specific adenoma detection rates observed in a Dutch randomized controlled trial on colonoscopy screening (73% small adenomas, 15% medium sized adenomas, 12% large adenomas).(17)

The Screening Module

Screening will alter some of the simulated life histories: Some cancers will be prevented by the detection and removal of adenomas; other cancers will be detected in an earlier stage with a more favorable survival. As the stage-specific survival of screen-detected CRC as observed in randomized controlled trials on guaiac fecal occult blood testing was substantially more favorable than that of clinically detected CRC, even after correcting for lead-time bias, we assigned those screen-detected cancers that would have been clinically detected in the same stage the survival corresponding to a one stage less progressive cancer. Hence, a cancer screen-detected in stage II, that would also have been clinically diagnosed in stage II, is assigned the survival of a clinically diagnosed stage I cancer. The only exceptions were screen-detected stage IV cancers. These cancers were always assigned the survival of a clinically diagnosed stage IV cancer.

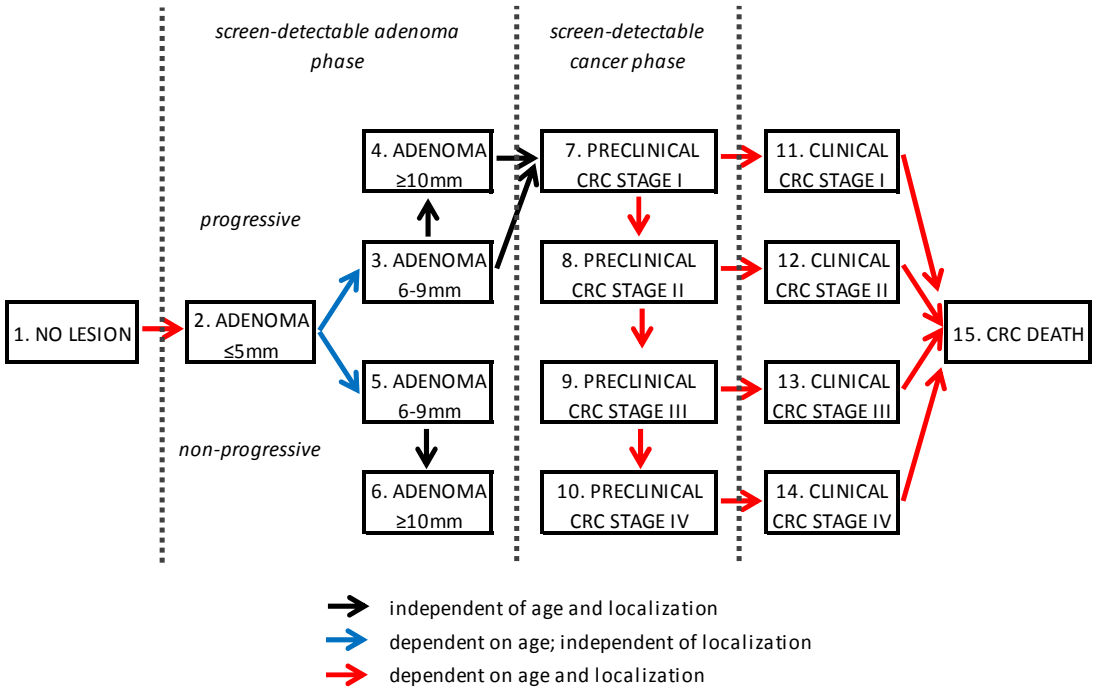
Besides modeling positive health effects of screening, we also model colonoscopy-related complications and over-diagnosis and over-treatment of CRC (i.e. the detection and treatment of cancers that would not have been diagnosed without screening).

Integrating Modules

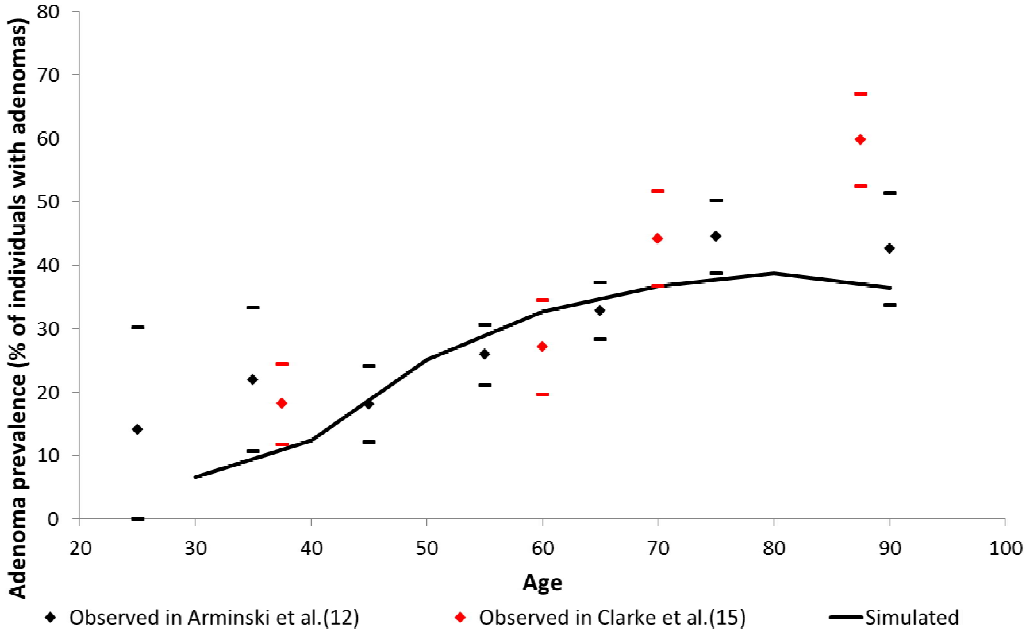
The demography module generates a date of birth and a date of non-CRC death for each individual simulated, creating a life-history without adenomas or CRC. In Patient A in Model Appendix Figure 5, the natural history module generates an adenoma. This adenoma progresses into preclinical

cancer, which is diagnosed because of symptoms in stage II and results in CRC death before non-CRC death would have occurred. In the screening module a screening examination is simulated, indicated by the blue arrow. During this examination the adenoma is detected, and as a result both CRC and CRC death are prevented. Hence, in Patient A, screening prolongs life by the amount indicated by the green arrow. Patient B also develops an adenoma, and although this adenoma does progress into preclinical cancer, Patient B would never have been diagnosed with CRC in a scenario without screening (see *life history 2*). However, during the screening examination simulated in the screening module, again indicated by the blue arrow, CRC is screen-detected in stage I. Hence, in this patient screening results in over-diagnosis of CRC: It detects a cancer that would never have been diagnosed in a scenario without screening. Hence, screening does not prolong life, but it does result in additional LYs with CRC care (over-treatment) as indicated by the red arrow.

Model Appendix Figure 1. **An Overview of the Natural History Module of MISCAN-Colon.**



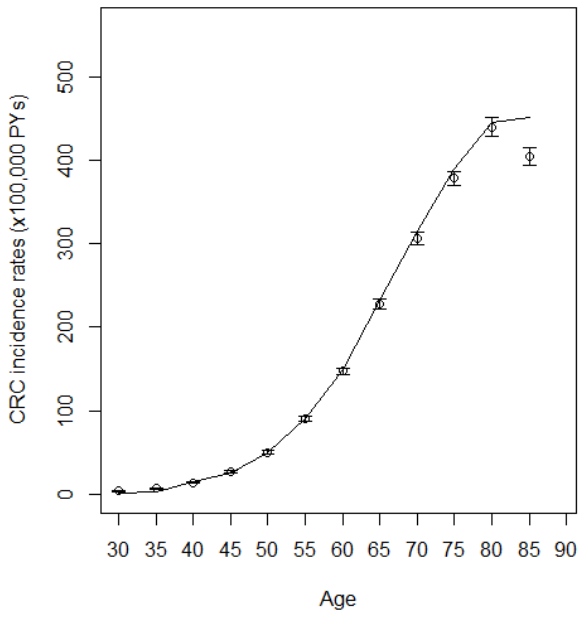
Model Appendix Figure 2. **Adenoma Prevalence Simulated by MISCAN-Colon Versus Observed in Selected Autopsy Studies and corrected for country specific differences in CRC incidence (% of individuals with adenomas).***



*Observed results are only shown for the two largest studies on which the model has been calibrated.

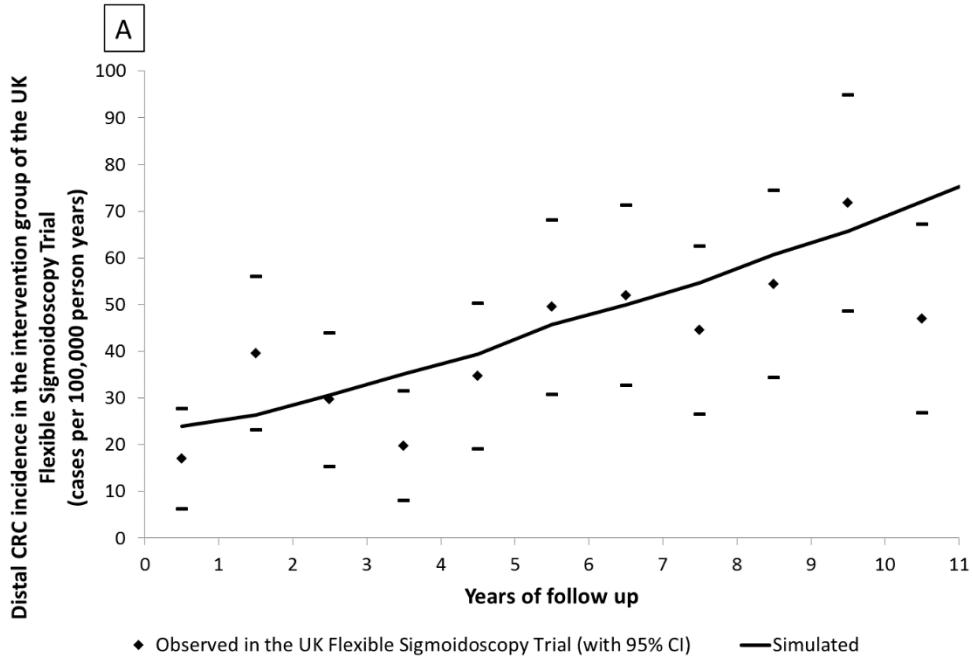
MISCAN-Colon has additionally been calibrated to 8 other autopsy studies.

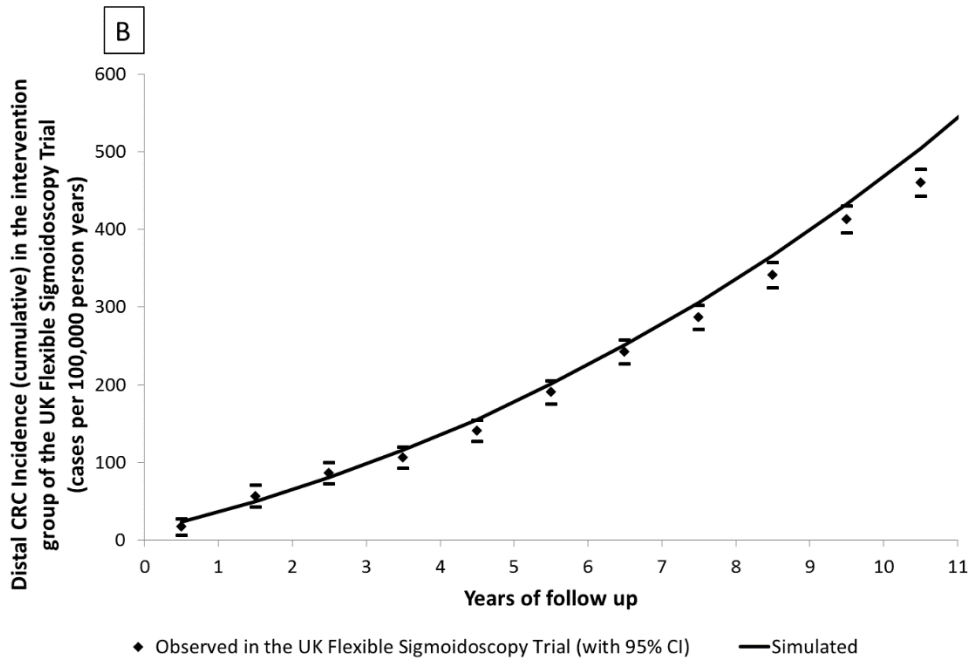
Model Appendix Figure 3. **Norwegian CRC Incidence Observed during the NORCCAP trial period Versus Simulated by MISCAN-Colon; cases per 100,000 person years)**



Solid line: simulated; error bars and point estimates: observed in Norway 1999-2011 (with 95% CI)

Model Appendix Figure 4. **Distal CRC Incidence Observed in the Intervention Group of the UK Flexible Sigmoidoscopy Trial Versus Simulated by MISCAN-Colon (per year of follow-up (A), cumulative (B); cases per 100,000 person years).**





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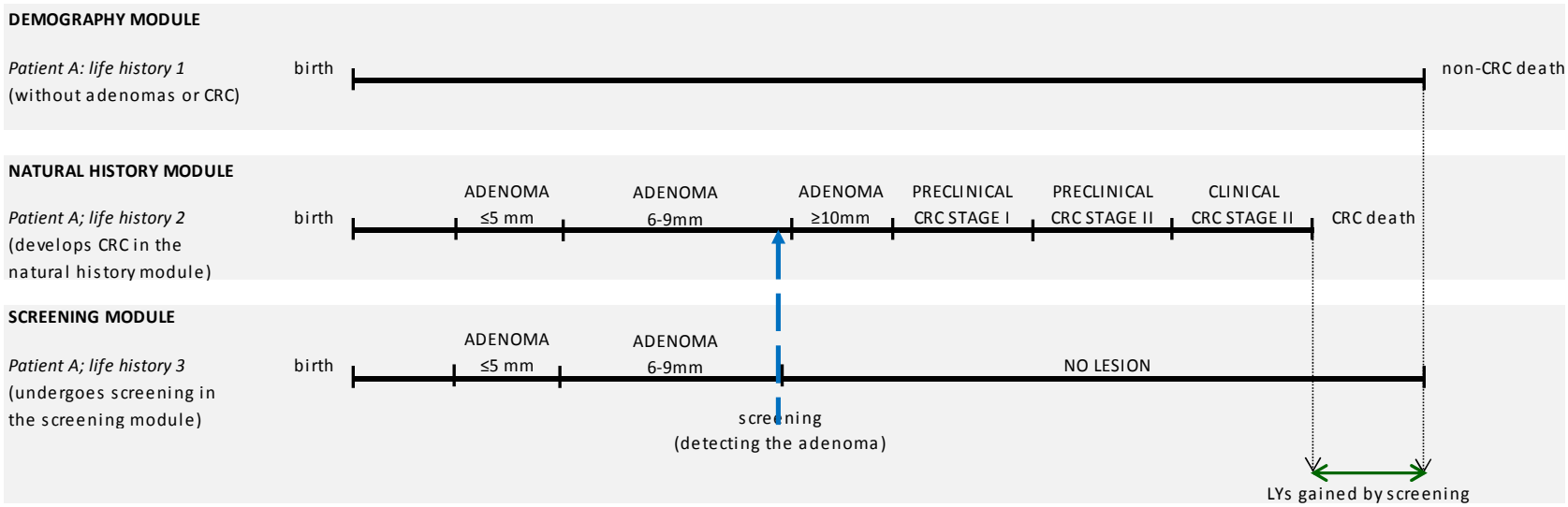
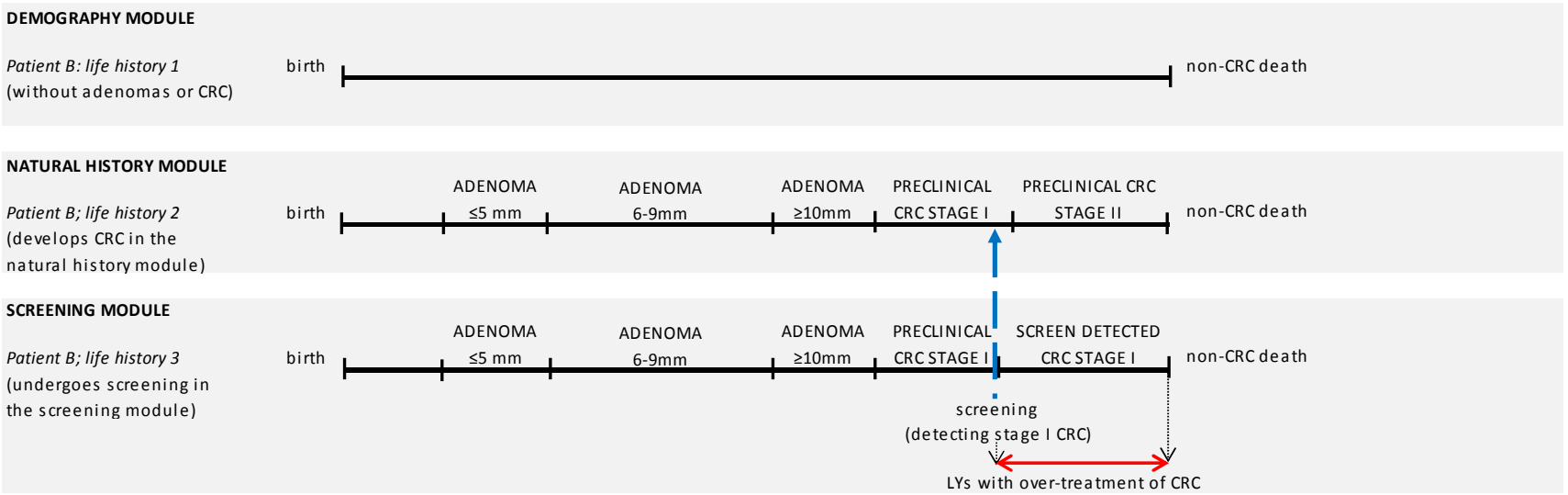
Model Appendix Figure 5. **Integrating Modules: Two example Patients.**

PATIENT A: BENEFITTING FROM SCREENING



PATIENT B: OVER-DIAGNOSING CRC



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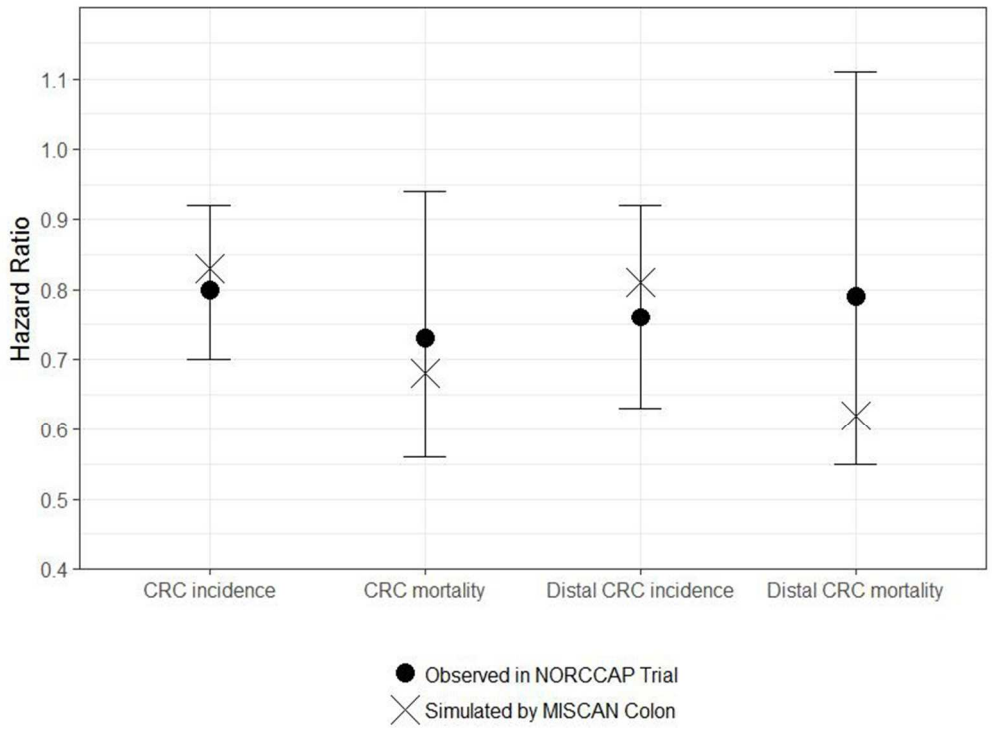
Supplement 3 - Figures

In this supplement the external validation results without corrections based on CRC incidence in the control group and in the non adherers are shown.

Figure captions and subscripts

1. Hazard ratios: 10- to 12-year follow-up intervention effects of NORCCAP trial including 95% confidence intervals for these effects and MISCAN-Colon predictions of these effects.
   Abbreviations: CRC, colorectal cancer; NORCCAP, Norwegian Colorectal Cancer Prevention Trial; MISCAN, Microsimulation Screening Analysis.
2. Cumulative probability of overall CRC incidence, overall CRC mortality, distal CRC incidence and distal CRC mortality: 10- to 12-year follow-up intervention effects of NORCCAP trial including 95% confidence intervals for these effects and MISCAN-Colon predictions of these effects. This figure is a replication of Figure 2 as published in Holme et al. (2014).
   Abbreviations: CRC, colorectal cancer; NORCCAP, Norwegian Colorectal Cancer Prevention; MISCAN, Microsimulation Screening Analysis.
3. Yearly risk ratios for colorectal cancer incidence and mortality in screening group relative to the control group: 10- to 12-year follow-up intervention effects of NORCCAP trial including 95% confidence intervals for these effects and MISCAN-Colon predictions of these effects. This figure is a replication of Figure 3 as published in Holme et al. (2014)
   Abbreviations: CRC, colorectal cancer; NORCCAP, Norwegian Colorectal Cancer Prevention Trial; MISCAN, Microsimulation Screening Analysis.
4. Yearly risk ratios for overall and distal colorectal cancer incidence in screening adherers relative to control group: 10- to 12-year follow-up intervention effects of NORCCAP trial including 95% confidence intervals for these effects and MISCAN-Colon predictions of these effects. This figure is a replication of Figure 4 as published in Holme et al. (2014)
   Abbreviations: CRC, colorectal cancer; NORCCAP, Norwegian Colorectal Cancer Prevention Trial; MISCAN, Microsimulation Screening Analysis.



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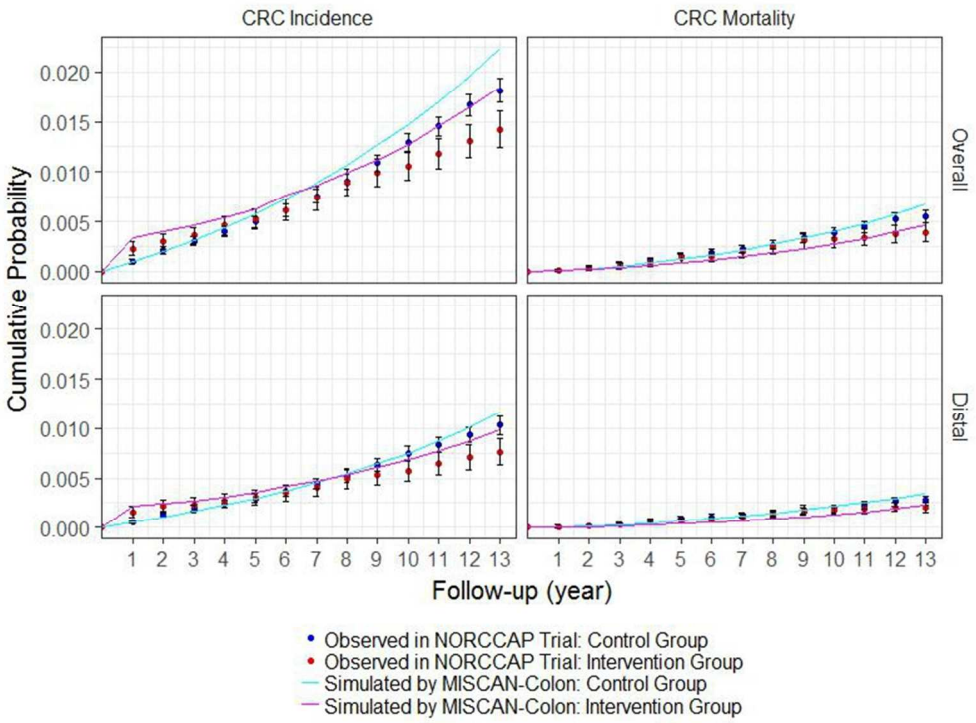

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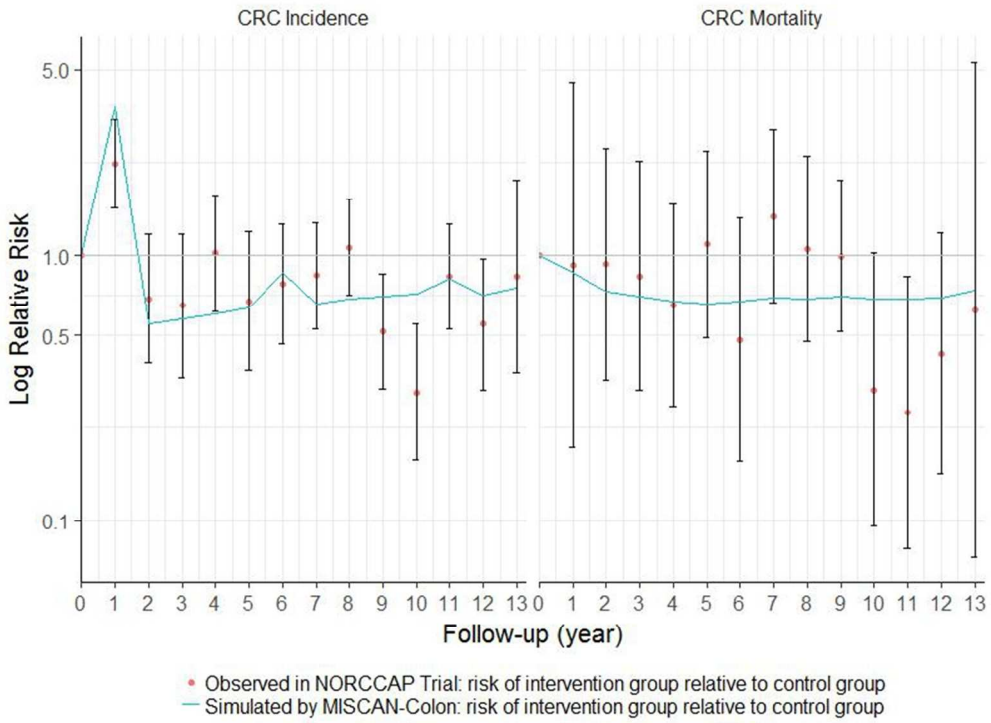

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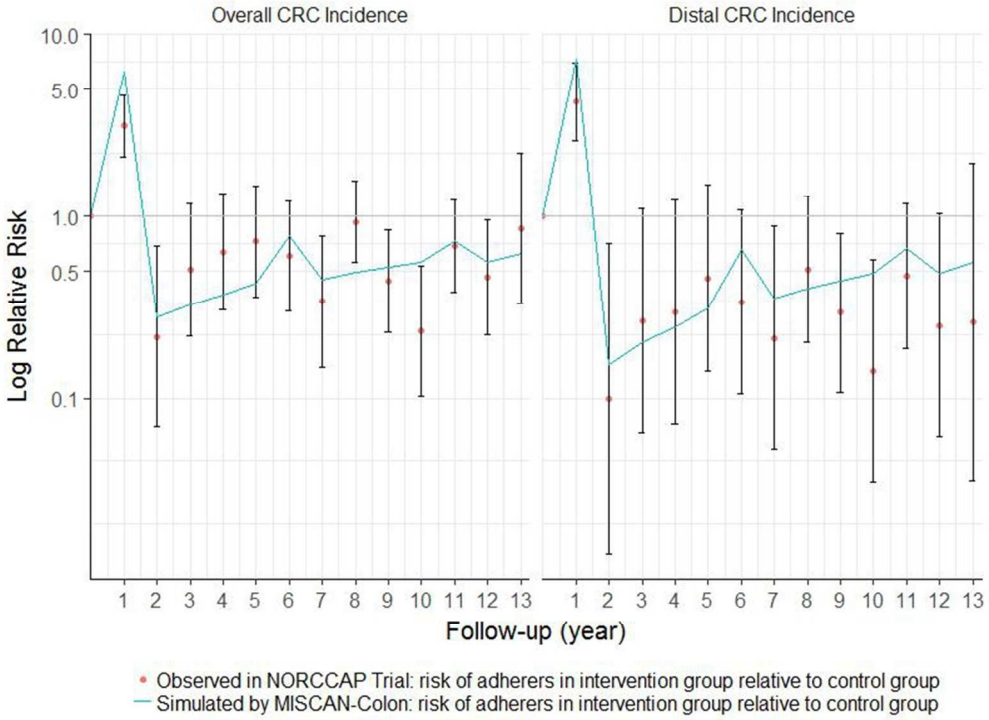

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Supplement 3 - Tables

In this supplement the validation results without corrections based on CRC incidence in the control group and in the non-adherers are shown.

1. Hazard ratios: 10-12 years follow-up interventions effects of the NORCCAP trial including 95% confidence intervals for these effects and MISCAN- Colon predictions of these effects.

A. CRC overall

Outcome	Source	HR	Per 100,000 person years	
			Control	Screened
CRC mortality	NORCCAP trial	0.73 (0.56, 0.94)	43.1 (38.7, 48.1)	31.4 (24.8, 39.7)
	MISCAN Colon	0.68	45.5	30.8
CRC incidence	NORCCAP trial	0.80 (0.70, 0.92)	141 (132.8, 149.7)	112.6 (99.3, 127.7)
	MISCAN Colon	0.83	159.9	133.3

B. CRC distal

Outcome	Source	HR	Per 100,000 person years	
			Control	Screened
Distal CRC mortality	NORCCAP trial	0.79 (0.55, 1.11)	21.8 (18.7, 25.4)	17.2 (12.6,23.5)
	MISCAN-Colon	0.62	24.2	15.0
Distal CRC incidence	NORCCAP-trial	0.76 (0.63, 0.92)	80.1 (74, 86.7)	60.9 (51.4, 72.2)
	MISCAN-Colon	0.82	88.3	71.1

Abbreviations: CRC, colorectal cancer; NORCCAP, Norwegian Colorectal Cancer Prevention Trial; MISCAN, MIcrosimulation SCreening Analysis; HR, hazard ratio

2. Outcomes at screening: NORCCAP trial results and MISCAN Colon predictions of these results. Numbers of individuals are reported with 95% confidence intervals for NORCCAP trial results.

Outcome	Source	Number	95% interval
Diagnostic colonoscopies	NORCCAP trial	2524	(2432, 2616)
	MISCAN-Colon	2732	
CRC detected at screening	NORCCAP trial	41	(28, 54)
	MISCAN-Colon	59	
Adenomas detected at colonoscopy			
Total	NORCCAP trial	2210	(2123, 2297)
	MISCAN-Colon	2432	
Advanced adenomas	NORCCAP trial	582	(535, 629)
	MISCAN-Colon	595	
Non-advanced adenomas	NORCCAP trial	1628	(1552, 1704)
	MISCAN-Colon	1838	

Abbreviations: CRC, colorectal cancer; NORCCAP, Norwegian Colorectal Cancer Prevention Trial; MISCAN, MIcroSimulation Analysis; HR, hazard ratio

3. Stage distribution of diagnosed colorectal cancers during the 10-12 year follow-up of the NORCCAP trial compared to MISCAN Colon predictions

	NORCCAP trial*		**MISCAN Colon**		
Control Group	No.	(%)	No.	(%)	P value
Localized CRC	470	(45.5%)	538	(47.3%)	
Advanced CRC	562	(54.5%)	571	(52.7%)	0.45
Intervention group					
Localized CRC	117	(49.4%)	173	(52.6%)	
Advanced CRC	120	(50.6%)	154	(47.4%)	0.50

Abbreviations: CRC, colorectal cancer; NORCCAP, Norwegian Colorectal Cancer Prevention Trial; MISCAN, Microsimulation Screening Analysis

*Unclassified cancers in the control group (N=16) and in the intervention group (N=4) were excluded from this table

4. Hazard ratios: MISCAN Colon predictions for future follow up results NORCCAP trial.

Follow up years*	End of data retrieval **	Overall CRC mortality			Overall CRC incidence			Distal CRC mortality			Distal CRC incidence		
		HR	Control group	Screen group	HR	Control group	Screen group	HR	Control group	Screen group	HR	Control group	Screen group
10-12	2011	0.68	45.5	30.8	0.83	160	133	0.62	24.2	15.0	0.81	88.3	71.1
11-13	2012	0.68	48.5	33.0	0.82	166	137	0.63	25.8	16.1	0.80	91.8	73.0
12-14	2013	0.69	51.4	35.4	0.82	173	142	0.63	27.4	17.3	0.79	95.4	75.3
13-15	2014	0.69	54.5	37.7	0.82	179	148	0.64	29.0	18.5	0.79	99.0	78.3
14-16	2015	0.70	57.5	40.2	0.83	186	153	0.65	30.6	19.8	0.79	102.5	81.3
15-17	2016	0.71	60.4	42.7	0.83	192	159	0.66	32.2	21.1	0.79	106.1	84.1
16-18	2017	0.71	63.6	45.2	0.82	198	163	0.66	33.9	22.4	0.79	109.6	86.6

Abbreviations: CRC, colorectal cancer; NORCCAP, Norwegian Colorectal Cancer Prevention; MISCAN, Microsimulation Screening Analysis; HR, hazard ratio

Numbers under control group and screen group presented per 100 000 person years.

*The screening intervention was performed in 1999, 2000 and 2001. Since the closure date for data retrieval is the same for all participants, the number of follow-up years differs among the participants.

**Last day of the year