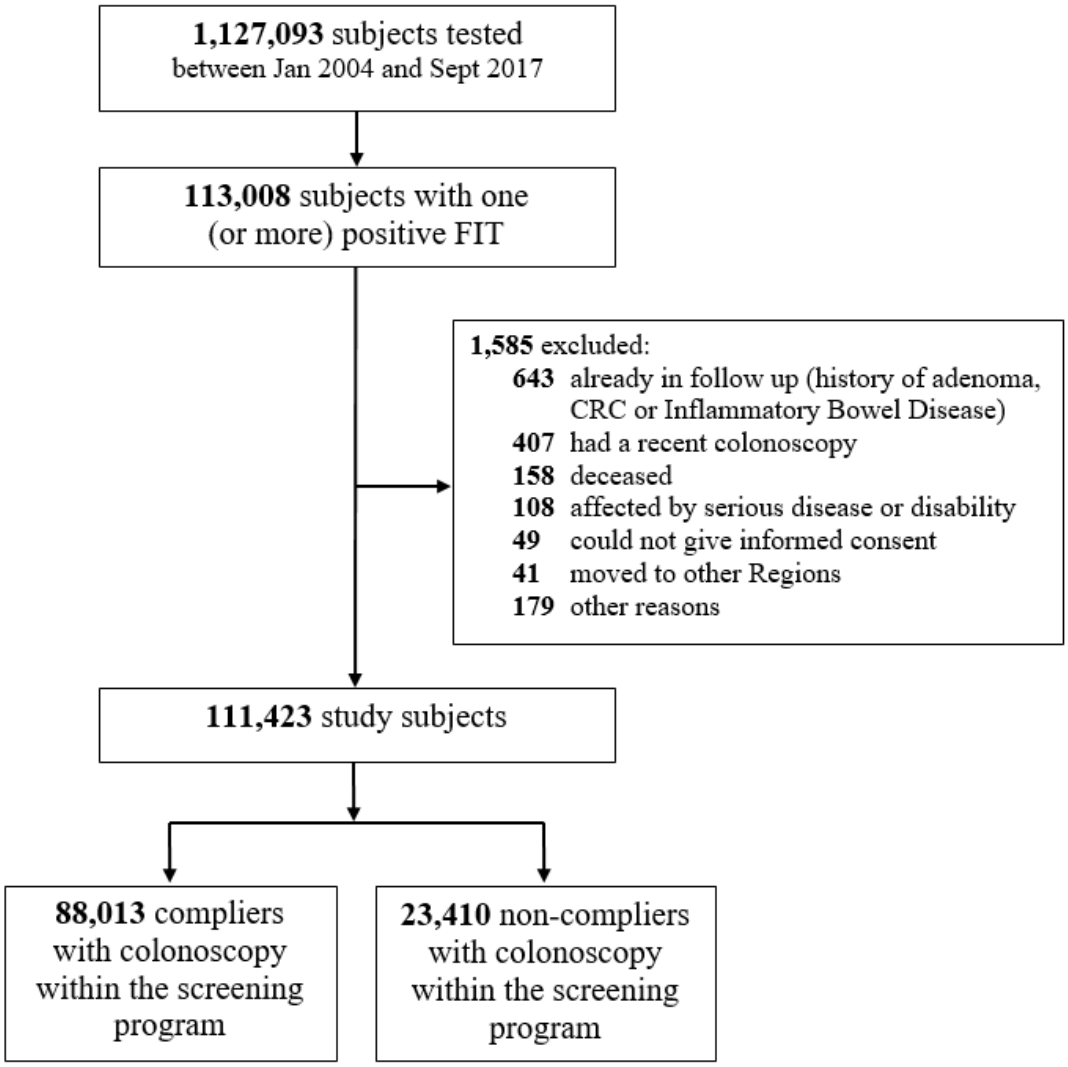
Supplementary Appendix 1

Figure S1. Flowchart of the study

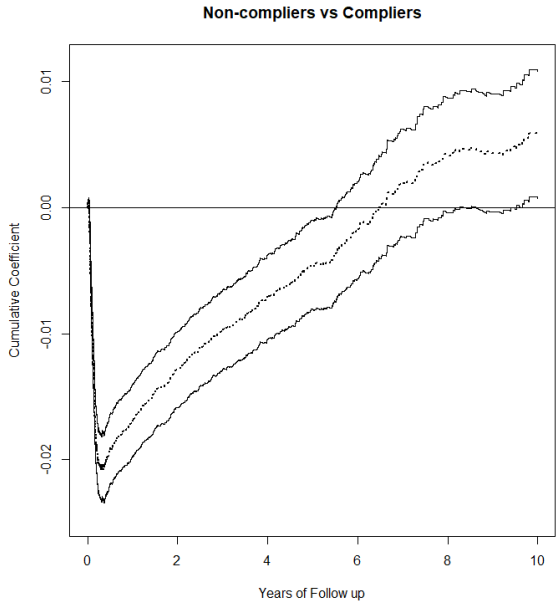


Supplementary Appendix 2

Statistical analysis to handle for non-proportionality of hazards at Cox analysis

The Cox model [1] was not applicable to the analysis of CRC incidence because the hypothesis of proportionality of the effect was not met for the covariate "colonoscopy compliance". We then applied the Cox-Aalen model [2], where an additive component allows for covariates with time-varying effects. The Cox-Aalen model estimates the hazard ratios for the variables with time-constant effect, while plotting the cumulative regression function for time-varying variables.
Figure S2 shows that the effect in term of hazard (the slope of the curve) for colonoscopy compliance is negative in the first six months after the FIT (i.e., the hazard is higher for colonoscopy compliers), then it starts growing until the end of the follow up, crossing the horizontal zero line at six year. Such two-phase pattern confirms the time-varying effect of colonoscopy compliance on the risk of CRC incidence.
To estimate the hazard ratio separately for the first six months and the remaining follow up period, we finally used an extended Cox model [3] with a piecewise function for the effect of compliance with colonoscopy.

Figure S2. Cumulative regression functions estimated for the additive part of Cox-Aalen model, with 95% pointwise confidence intervals



References

1. Cox DR. Regression models and life tables, Journal of the Royal Statistics Society. 1972;34:187-220.
2. Scheike TH, Zhang MJ. An additive-multiplicative Cox-Aalen model. Scand J Statist. 2002;28:75-88.
3. Therneau T, Grambsch P. Modeling survival data: extending the Cox model. Springer, 2000.

Supplementary Appendix 3

Sensitivity analysis including only the study subjects with a potential follow-up time of 5 years or more

CRC were diagnosed earlier in compliers (90% within one year) than in non-compliers (62%). Therefore, the follow up of non-compliers with a recent positive FIT could be insufficient for cancers to surface. We therefore performed a sensitivity analysis including only the subjects with a potential follow-up time of 5 years or more.

Methods

We selected the subjects with a positive FIT prior to 31st December 2013.

The cumulative incidence and mortality at 10 years of follow up were computed using the Kaplan-Meyer estimator.

A Cox model and an Extended-Cox model [1] with piecewise-constant time-varying coefficients were used to estimate the hazard ratio of CRC incidence and mortality for compliers vs. non-compliers, adjusting for gender, age and screening round (first, subsequent).

Results

The sensitivity analysis involved 44,975 compliers and 10,475 non-compliers. During the study period, 2,413 CRC were diagnosed in the cohort of compliers (5.4%)) and 607 in the cohort of non-compliers (5.8%). The cumulative incidence at 10 years was 55.8 per 1,000 (95% CI, 53.6 to 58.0) for compliers and 66.5 per 1,000 (95% CI, 61.0 to 72.0) for non-compliers (Figure S3.1).

The cumulative CRC-specific mortality at 10 years of follow up was 7.5 per 1,000 (95% CI, 6.6 to 8.4) for compliers and 17.5 per 1,000 (95% CI, 14.3 to 20.6) for non-compliers (Figure S3.2).

The hazard of being diagnosed with a CRC beyond the sixth month of the FIT among non-compliers was 3.86 (95% CI, 3.31 to 4.49) (Table S3.1). The risk of death from CRC was 2.1 higher among non-compliers (HR 2.09; 95% CI, 1.70 to 2.57).

References

1. Therneau T, Grambsch P. Modeling survival data: extending the Cox model. Springer, 2000.

Table S3.1. Adjusted Hazard Ratio with 95% confidence intervals of colorectal cancer incidence and of death caused by colorectal cancer in subjects with a positive fecal immunochemical test, by gender, age and compliance with colonoscopy

	Adjusted[1] Hazard Ratio	**95% confidence intervals**
Colorectal cancer incidence		
Gender		
Male	1.00	–
Female	0.83	0.77 – 0.89
Age at time of FIT (years)		
50-59	1.00	–
60-69	1.51	1.41 – 1.63
Screening round		
First	1.00	–
Subsequent	0.58	0.54 – 0.62
Compliance with colonoscopy		
Yes	1.00	–
No - up to 6 months	0.57	0.51 – 0.65
No - beyond 6 months	3.86	3.31 – 4.49
Colorectal cancer mortality		
Gender		
Male	1.00	–
Female	0.63	0.51– 0.77
Age at time of FIT (years)		
50-59	1.00	–
60-69	1.73	1.41– 2.12
Screening round		
First	1.00	–
Subsequent	0.50	0.40-0.61
Compliance with colonoscopy		
Yes	1.00	–
No	2.09	1.70 – 2.57

[1] adjusted by all the variables reported in the table

Figure S3.1 Cumulative incidence of CRC (per 1,000) in subjects with a positive fecal immunochemical test, according to compliance with colonoscopy. Subjects with a potential follow-up time of 5 years or more

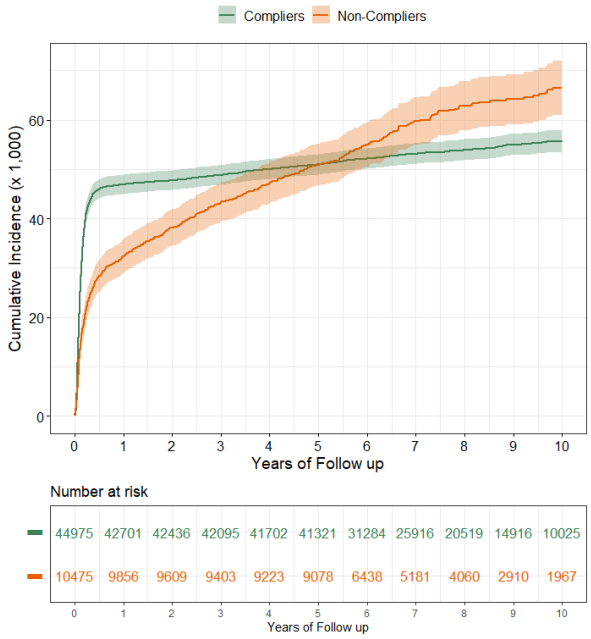
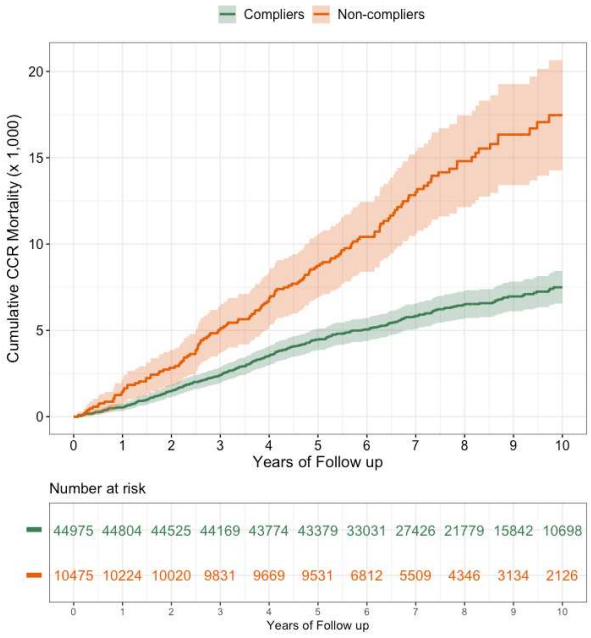


Figure S3.2 Cumulative CRC-specific mortality (per 1,000) in subjects with a positive fecal immunochemical test, according to compliance with colonoscopy. Subjects with a potential follow-up time of 5 years or more



Supplementary Appendix 4

Sensitivity analysis to account for immortal time bias in the cohort of compliers

By definition, compliers could not be diagnosed with CRC before the date of colonoscopy. This might introduce immortal time bias in the results of the study [1]. We therefore performed a sensitivity analysis replacing in the cohort of compliers the date of the FIT with the date of colonoscopy.

Methods

The date of the FIT was used to start follow up for non-compliers, while the date of colonoscopy was used for compliers.

The cumulative incidence and mortality at 10 years of follow up were computed using the Kaplan-Meyer estimator.

A Cox model and an Extended-Cox model [2] with piecewise-constant time-varying coefficients were used to estimate the hazard ratio of CRC incidence and mortality for compliers vs. non-compliers, adjusting for gender, age and screening round (first, subsequent).

Results

The cumulative incidence at 10 years was 44.2 per 1,000 (95% CI, 42.6 to 45.8) for compliers and 54.3 per 1,000 (95% CI, 49.9 to 58.7) for non-compliers (Figure S4.1).

The cumulative CRC-specific mortality at 10 years of follow up was 6.8 per 1,000 (95% CI, 5.9 to 7.6) for compliers and 16.0 per 1,000 (95% CI, 13.1 to 18.9) for non-compliers (Figure S4.2).

The hazard of being diagnosed with a CRC beyond the sixth month of the FIT among non-compliers was 4.17 (95% CI, 3.62 to 4.81) (Table S4.1). The risk of death from CRC was 2.0 higher among non-compliers (HR 2.03; 95% CI, 1.69 to 2.45).

Discussion

Non-programmatic colonoscopies performed by non-compliers could determine an immortal time bias in favour of the cohort of non-compliers. Data about such colonoscopies are not available. However, since no significant difference emerged between the results of the baseline analysis and this sensitivity analysis (which addressed the time-to-colonoscopy of the whole cohort of compliers), the expected effect of the bias in favour of non-compliers is negligible (regarding only a limited proportion of non-compliers who underwent non-programmatic colonoscopy).

References

1. Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol 2008;167(4):492-9.
2. Therneau T, Grambsch P. Modeling survival data: extending the Cox model. Springer, 2000.

Table S4.1. Adjusted Hazard Ratio of colorectal cancer incidence and of colorectal cancer mortality in subjects with a positive fecal immunochemical test, with 95% confidence intervals. Follow up starts from the date of the FIT for non-compliers and from the date of colonoscopy for compliers.

	Adjusted[1] Hazard Ratio	**95% confidence intervals**
Colorectal cancer incidence		
Gender		
Male	1.00	–
Female	0.85	0.80 – 0.90
Age at time of FIT (years)		
50-59	1.00	–
60-69	1.70	1.60 – 1.81
Screening round		
First	1.00	–
Subsequent	0.50	0.47 – 0.53
Compliance with colonoscopy		
Yes	1.00	-
No - up to 6 months	0.55	0.50 – 0.61
No - beyond 6 months	4.17	3.62 – 4.81
Colorectal cancer mortality		
Gender		
Male	1.00	–
Female	0.68	0.56 – 0.82
Age at time of FIT (years)		
50-59	1.00	–
60-69	1.91	1.58 – 2.30
Screening round		
First	1.00	–
Subsequent	0.46	0.38 – 0.55
Compliance with colonoscopy		
Yes	1.00	–
No	2.03	1.69 – 2.45

[1] adjusted by all the variables reported in the table

Figure S4.1 Cumulative incidence of CRC (per 1,000) in subjects with a positive fecal immunochemical test, according to compliance with colonoscopy. Follow up starts from the date of the FIT for non-compliers and from the date of colonoscopy for compliers.

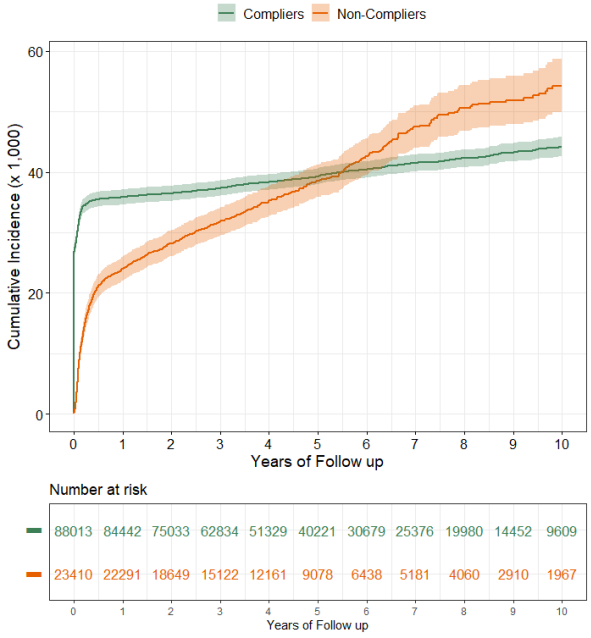


Figure S4.2 Cumulative CRC-specific mortality (per 1,000) in subjects with a positive fecal immunochemical test, according to compliance with colonoscopy. Follow up starts from the date of the FIT for non-compliers and from the date of colonoscopy for compliers.