Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Impact of SARS-CoV-2 Pandemic on Colorectal Cancer Screening Delay: Effect on Stage Shift and Increased Mortality

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BACKGROUND & AIMS: **The SARS-CoV-2 pandemic had a sudden, dramatic impact on healthcare. In Italy, since the beginning of the pandemic, colorectal cancer (CRC) screening programs have been forcefully suspended. We aimed to evaluate whether screening procedure delays can affect the outcomes of CRC screening.**

METHODS: **We built a procedural model considering delays in the time to colonoscopy and estimating the effect on mortality due to up-stage migration of patients. The number of expected CRC cases was computed by using the data of the Italian screened population. Estimates of the effects of delay to colonoscopy on CRC stage, and of stage on mortality were assessed by a meta-analytic approach.**

RESULTS: **With a delay of 0-3 months, 74% of CRC is expected to be stage I-II, while with a delay of 4-6 months there would be a 2%-increase for stage I-II and a concomitant decrease for stage III-IV ($P = .068$). Compared to baseline (0-3 months), moderate (7-12 months) and long (> 12 months) delays would lead to a significant increase in advanced CRC (from 26% to 29% and 33%, respectively; $P = .008$ and $P < .001$, respectively). We estimated a significant increase in the total number of deaths (+12.0%) when moving from a 0-3-months to a >12-month delay ($P = .005$), and a significant change in mortality distribution by stage when comparing the baseline with the >12-months ($P < .001$).**

CONCLUSIONS: **Screening delays beyond 4-6 months would significantly increase advanced CRC cases, and also mortality if lasting beyond 12 months. Our data highlight the need to reorganize efforts against high-impact diseases such as CRC, considering possible future waves of SARS-CoV-2 or other pandemics.**

Keywords: SARS-CoV-2; Colorectal Cancer Screening; Colonoscopy; Colon Cancer; Fecal Immunochemical Test.

The severe acute respiratory syndrome–associated corona virus 2 (SARS-CoV-2) pandemic era affected the healthcare organizations/systems in every country, irrespective of differences in political governance, economic resources, or type of healthcare reimbursement. Mounting pressure for emergency admissions and intensive care support resulted in a surge of access to hospitals, prompting the downscaling of almost all clinical activities to face the unexpected spread of the disease and its life-threatening complications.[1] In Europe, the enormous diversion of medical resources toward SARS-CoV-2–dedicated wards dominated the clinical scenarios,[2] with almost all planned public healthcare activities,

[a]Authors share co-first authorship. [b]Authors share co-senior authorship.

Abbreviations used in this paper: CRC, colorectal cancer; DS, delay stage; FIT, fecal immunochemical test; SARS-CoV-2, severe acute respiratory syndrome–associated coronavirus 2; SM, stage mortality.

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including cancer screening, being suspended. As of now, in Italy it is difficult to discern the excess of deaths registered in the early spring according to their relationship with SARS-CoV-2 or with high-impact illnesses that remained unrecognized and possibly untreated.

Regarding cancer incidence and mortality, colorectal cancer (CRC) represents a major burden worldwide[3] but can be counteracted by screening strategies. Currently in the United States, the implementation of an opportunistic approach by screening colonoscopy has contributed to a gradual reduction of CRC incidence,[4] whereas European countries mostly rely on programmatic screening by biannual fecal immunochemical test (FIT).[5] The adoption of FIT reduces CRC mortality mainly through the detection of early stage tumors, which leads to a down-staging process.[6] To meet their benchmark reduction of CRC burden, FIT-based screening programs rely on a multilayer system involving public health authorities, kit distribution facilities, FIT measuring labs, and ultimately hospitals/centers where FIT+ subjects undergo colonoscopy. Since the beginning of the pandemic, this entire system has been put on hold. On March 8 and 11, 2020, the Italian government issued decrees that greatly reduced gathering and interpersonal contacts, which added to the above-mentioned pressures on the healthcare system, further restraining cancer screening.[7] Heterogeneous decisions involved the management of tests at the first level (by interrupting active calls) as well as at the second level (by placing on hold endoscopic examination for FIT+ subjects), with some coordinating units opting to shut down both levels.

Recent data highlighted the detrimental effects on mortality of delaying diagnosis in symptomatic patients with CRC in the United Kingdom[8] because of SARS-Cov-2 pandemic. However, screening delays might have even more dramatic effects than delayed diagnosis, once the down-staging effect is reversed by the delays. Accordingly, we sought to assess the impact of the pandemic on programmatic CRC screening by building a meta-analytic procedural model that considers time delays in the access to colonoscopy and estimates the effect on mortality because of the consequent up-stage migration of patients over time.

What You Need to Know

Background

Because of the SARS-CoV-2 pandemic, colorectal cancer screening programs have been suspended in many countries.

Findings

Delays beyond 6 months would progressively lead to increased disease mortality rates through the shift to more advanced stages detected at screening. Results were obtained by applying meta-analytic estimates to the Italian population.

Implications for patient care

Our data highlight the need to avoid breaking the workflow of colorectal cancer screening beyond 12 months in the light of possible future waves of SARS-CoV-2 or other pandemics.

Methods

Study Design

We followed a stepwise rationale in building the procedural model, which was based on the following relationships: (1) the stage at the time of diagnosis affects CRC mortality; and (2) the stage at diagnosis largely depends on an early detection of malignant and premalignant lesions, which is strictly related to and improved by timeliness of screening programs. Considering the delay in the screening procedures imposed by SARS-CoV-2 pandemic, we explored the relationships of delay stage (DS) and stage mortality (SM) under the constraints of different delay spans, with the aim of providing an estimate of the effect of pandemic on CRC mortality. The evaluation of the 2 relationships DS and SM was based on literature evidence that was obtained by performing 2 separate meta-analyses.

Eventually the chain effect of the screening delay due to Sars-Cov-2 pandemic was quantified in terms of the number of deaths expected to occur in a general, asymptomatic population that would have otherwise adhered to and undergone programmatic screening (Figure 1).

Search Strategy and Study Selection

To pursue the main aim of the study, we conducted a systematic literature search through the PubMed and Scopus databases in a 2-step process. For the first literature review on DS, we built a pipeline of articles providing the distribution of CRC stage by delay strata (outcome of interest: percentage/proportion of CRC by stage and delay), identified by the time for access to colonoscopy after a positive FIT. For the second step concerning SM, the outcome of interest was the 5-year (age-adjusted) survival rates stratified by stage of CRC patients. Specifically, we applied the following search strategies:

(1) for the DS meta-analysis, the search string was "(delay OR time to colonoscopy) AND (fecal immunochemical test OR screening) AND (colon OR colorectal AND cancer) AND (stage OR tnm)";

(2) for the SM meta-analysis, the string was "(colon cancer OR colorectal cancer) AND (stage OR tnm) AND (mortality OR survival)".

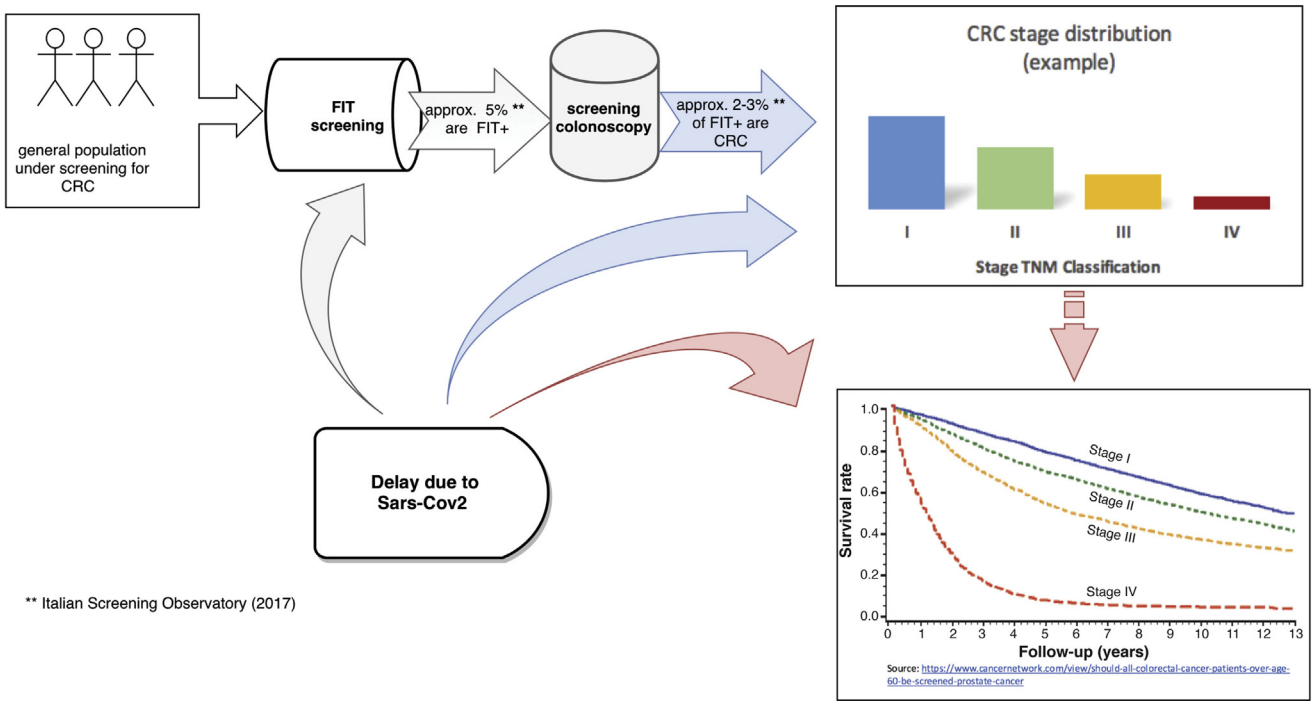

Figure 1. Illustrative description of the rationale: SARS-Cov-2 effects on screening programs and consequently on the CRC stage distribution and survival rates. CRC, colorectal cancer; FIT, fecal immunochemical test; SARS-Cov-2, severe acute respiratory distress syndrome–associated coronavirus 2.

In addition, the following filters were applied for both strings and databases: Journal article; Publication date from January 1, 2010 to May 19, 2020; Humans; English. The "sort by: Best Match Filters" approach was used for all the PubMed queries. Moreover, for the second string, the search was limited to [Title/Abstract] fields in both databases and limited to Subject area "Medicine" and "Multidisciplinarity" in Scopus database. We performed these systematic literature reviews according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines and flow diagrams.[9] Records were first screened by checking titles and abstracts; subsequently, relevant eligible articles were assessed by reading the full texts. For both the DS and SM meta-analyses, 2 of the authors (LR, LL) carried out the search independently. Any disagreements were discussed and resolved with the involvement of a third researcher. All the screened articles and corresponding decisions were recorded in an Excel (Microsoft Corp, Redmond, WA) spreadsheet. The detailed search sequences are shown in Supplementary Figures 1 and 2 (PROSPERO registration number CRD42020186832).

Data Extraction and Assessment of the Quality of the Included Studies

From the DS search we selected 8 articles (Supplementary Figure 1)[10–17] and extracted the following variables (Supplementary Table 1): year of publication, country, delay (in months), stage, number of CRC cases by stage and delay, and total number of CRC cases.

Because delay categories were not homogeneous across the included studies (with some articles using monthly delay intervals and others adopting longer time lags), we adopted 4 categories for delay times (ie, 0–3 months, 4–6 months, 7–12 months, and >12 months) because these intervals covered most waiting times across the selected studies. The studies also differed as to the reported stage categories; some used TNM classification (ie, stage I, II, III, IV), and others reported pooled stages (ie, "advanced" for stages III and IV). To allow comprehensive data capture for the analysis, we adopted the early vs advanced stage classification by aggregating data of stages I and II (early stage) and data of stages III and IV (advanced stage).

For the SM search, 10 articles were selected (Supplementary Figure 2),[18–27] and the following variables were extracted (Supplementary Table 2): year of publication, country, stage, 5-year age-standardized survival rate by stage, and total number of CRC cases. Also, for this analysis we adopted the stage classification of early vs advanced tumors.

The Newcastle-Ottawa Scale for cohort studies (score range 0–9) was used to assess the quality of the included studies.[28] Studies with score greater than 5 were considered of high quality (Supplementary Table 3).

Statistical Analysis

We used the data gathered from the DS literature search to calculate the meta-analytic pooled estimate of the proportion of CRC cases by stage that are detected

at programmatic screening. Considering the SM relationship, the same approach was adopted to obtain a pooled estimate of the 5-year survival/mortality rate, stratified by stage. For all the estimates, 95% confidence intervals were computed. Because of the heterogeneity in patient populations and methods of measurement of stage and survival among selected articles, we applied a random-effects meta-analysis. To evaluate homogeneity of findings among studies, the I^2 index (defined as the percentage of total variability due to the heterogeneity across studies) was computed. Proportions/percentages were compared through test for binomial proportions.

To assess the burden on mortality caused by delayed screening procedures because of the SARS-CoV-2 pandemic, we applied the pooled estimates obtained from the DS-SM meta-analyses to the annual expected number of CRC cases in Italy. To obtain the latter, we first computed the screening program target population (ie, the population invited to undergo FIT) by using the Italian population data (ISTAT; data available on http://demo.istat.it/pop2019/index.html; last available data referring to January 1, 2019) stratified by age classes (50–69 years). Finally, using the data from the National Screening Observatory (https://www.osservatorionazionalescreening.it/content/lo-screening-colorettale; Report 2018, containing data referring to 2017, was the most updated information at the time of this writing) regarding the percentage of invited persons who performed the test, the percentage of positive screening tests, and the CRC detection rate, we estimated the annual numbers of participants, of positive screening tests, and of incident CRC cases.

Statistical analyses were performed by using R: a Language and Environment for Statistical Computing, version 3.6.3 (R Core Team, 2019; R Foundation for Statistical Computing) and its metafor package.[29] The level of statistical significance was set at $P < .05$.

Results

Pooled Estimates From the Delay Stage and Stage Mortality Meta-analyses

The pooled estimates of stage distribution of screen-detected CRC according to pre–SARS-CoV-2 era data are reported in Supplementary Figure 3. With a brief, already present delay of 0–3 months, 74% of the CRC is expected to be stage I–II, and a delay of 4–6 months will lead to a nonsignificant increase in stage I–II prevalence (from 74% to 76%) and to a concomitant decrease of stage III–IV (from 26% to 24%) prevalence ($P = .068$) (Table 1). Conversely, compared with the reference 0–3 months, our analysis estimated a significant increase in advanced cancers detected at screening for a moderate 7- to 12-month delay (from 26% to 29%; $P = .008$), which progressively worsened after a 12-month delay (up to 33%; $P < .001$). These results indicate a shift in the distribution of screen-detected CRC by stage at diagnosis, marked by a significant rise in the proportion of advanced cases with a delay beyond 6 months.

Next, we evaluated the survival of subjects supposed to undergo programmatic screening according to pooled survival rates (at 5 years) estimated by SM meta-analysis (Supplementary Figure 4, Table 2). This analysis revealed a survival rate of 0.85 (95% confidence interval, 0.81–0.88) for stage I–II diagnoses and 0.39 (95% confidence interval, 0.33–0.44) for stage III–IV.

Table 1. Prevalence (and Corresponding Expected Number of CRCs) of Early and Advanced Stages for CRCs Detected at Delayed Screening, According to Increasing Time Delays to Access to Colonoscopy (Estimates by DS Meta-analysis)

Diagnostic delay (*mo*)	Stage at diagnosis	Stage prevalence	95% Confidence interval[a]	Expected CRCs[b]	*P* value[c]
0–3	I–II	0.74	(0.69–0.80)	2356	Reference
	III–IV	0.26	(0.20–0.31)	828	
4–6	I–II	0.76	(0.71–0.81)	2420	.068
	III–IV	0.24	(0.19–0.29)	764	
7–12	I–II	0.71	(0.66–0.77)	2261	.008
	III–IV	0.29	(0.23–0.34)	923	
>12	I–II	0.67	(0.57–0.77)	2133	<.001
	III–IV	0.33	(0.23–0.43)	1051	

CRC, colorectal cancer; DS, delayed stage.
[a]Lower and upper limit of 95% confidence interval.
[b]Total number of cases is always equal to 3184 for each delay scenario.
[c]*P* values refer to comparison of binomial proportions by stage of expected number of CRCs at 0–3 months vs higher delays on total number of CRC cases (3184), eg, .068 is the *P* value of the hypothesis test for comparing 2420/3184 vs 2356/3184.

Table 2. Five-Year Survival Rates of Patients With Colorectal Cancer Detected at Screening by the Stage at Diagnosis

Stage at diagnosis	Survival rate at 5 y	95% Confidence interval[a]
I–II	0.85	(0.81–0.88)
III–IV	0.39	(0.33–0.44)

NOTE. Pooled estimates by stage mortality meta-analysis.
[a]Lower and upper limits of the 95% confidence interval.

Estimate of Screening Participants and Number of Colorectal Cancers in Italy: An Illustrative Example of the Delay Effect on Stage and Mortality

To quantify the expected number of deaths resulting from the funnel effect on the otherwise ongoing screening, we focused on the Italian population and determined the number of individuals targeted by the screening program (in the 50- to 69-year old group equaling 834,4721 individuals). We estimated a total of 6,439,047 invitations for screening according to Vicentini et al.[30] Furthermore, on the basis of 2017 data from the most recent National Screening Observatory report, we estimated 3184 CRC cases for the whole year, corresponding to 2.28% subjects with a positive FIT (Supplementary Table 4). The number of CRC cases was used to quantify the expected number of deaths.

By applying the proportions of the estimates in the pre–SARS-CoV-2 era (Table 1) to 3184 incident CRC cases, we derived the expected number of cases, stratified by stage occurring in the scenario overrun by delays. These estimates, combined with the mortality rates (derived from Table 2), allowed calculating the expected number of deaths at 5 years for each delay-stage scenario, which are reported in Table 3. A significant increase in the total number of deaths (+12%) was estimated when moving from a 0- to 3-month (reference delay) to a >12-month delay ($P = .005$). We did not detect significant changes in the number of deaths with respect to baseline for delays <12 months.

Furthermore, we computed the relative percentage changes in expected deaths by stage (Table 3). At 4–6 months, we observed 2.8% increase in mortality for stage I–II cancers and 7.7% decrease for stage III–IV. These changes correspond to 2% shift in the early vs advanced stage distribution reported in Table 1. However, mortality by stage at 4–6 months as well as at 7–12 months was not significantly different from the baseline scenario ($P = .294$ and $P = .139$, respectively). Conversely, we observed a significant change by comparing the baseline with the >12-month mortality distribution by stage ($P < .001$).

Discussion

We estimated the effects of the lockdown because of the SARS-CoV-2 pandemic on programmatic CRC screening and their impact on disease burden by a rigorous, meta-analytical model. Our analysis indicates that delays up to 4–6 months do not significantly reduce the performance of screening, whereas a lockdown sustained for longer time frames would negatively affect mortality rates. This should be ascribed to the progressive shift of screen-detected cancers toward advanced stages, a change becoming significant in the 7- to 12-

Table 3. Expected Number of Deaths at 5 Years for Colorectal Cancer Detected at Delayed Screening According to Diagnostic Delays and Stage at Diagnosis

Diagnostic delay (*mo*)	Stage at diagnosis	Expected deaths[a]	Relative change (%)	*P* value[b]	All stages		
					Expected deaths[a]	Relative change (%)	*P* value[b]
0–3	I–II	353	Reference	—	858	Reference	
	III–IV	505					
4–6	I–II	363	2.8	.294	829	–3.4	.427
	III–IV	466	–7.7				
7–12	I–II	339	–4.0	.139	902	5.1	.228
	III–IV	563	11.5				
>12	I–II	320	–9.3	<.001	961	12.0	.005
	III–IV	641	26.9				

[a]For example, 353 is given by 2356 (Table 1) multiplied by mortality rate (1–0.85) derived from Table 2. Sum of 353 and 505 (equal to 858) represents the expected total number of deaths at 0–3 months in the target population of 3184 colorectal cancer cases.
[b]*P* values refer to comparison of proportions by stage of expected number of deaths at 0–3 months vs higher delays on total number of deaths, eg, 0.294 is the *P* value of the hypothesis test for comparing 363/829 vs 353/858. Test for binomial proportions is also used for comparing the proportion of deaths with respect to total number of colorectal cancer cases (3184), eg, 0.427 is the *P* value of the comparison of 829/3184 vs 858/3184.

month delay interval. In usual circumstances, only a minor fraction of FIT-positive subjects would receive a delayed colonoscopy (ranging from 0.8% to 6.2% after 6 months).[11,17] The effects of the pandemic may modify previously reassuring estimates in a time-dependent way, because a fraction of neoplastic lesions detected by FIT may progress from months 6 to 12,[17] increasing overall CRC deaths by more than one tenth, including an excess of 1 out of 4 advanced cases.

At 6 months, the model envisioned a nonsignificant, transitory additional 2% diagnostic rate of stage I–II tumors, coupled with 2% reduction in stage III–IV tumors, in keeping with data used in the DS meta-analysis,[11,17] in which some studies reported reduced risks of detecting advanced stages. We do not have a direct explanation for these changes, which might be interpreted as "waiting time paradox" at the first delay interval. Of interest, diagnostic delays up to 6 months have been associated with earlier stages across symptomatic patients, in keeping with a similar paradox[31,32] that needs to be investigated in further research. Our analysis indicates that the backlog sustained beyond 6 months would unequivocally ensue in a significant excess of advanced stages detected through screening and thus in up-staging rather than down-staging. Although such an increase of advanced stages in the 7- to 12-month interval of delay will not affect the mortality rate at 5 years, it will nevertheless increase disease burden and human and economic costs.

The results presented in this study were obtained by applying the meta-analytic estimates to the Italian screened population. However, the figures obtained from the DS-MS meta-analyses could be easily applied to other CRC target screening populations. Moreover, the proposed procedural model could be recommended also for other cancers amenable to screening programs.

The main limitation of our study, which is based on meta-analytic results rather than on direct data, is the small number of primary studies included in the 2 meta-analyses. Although this could affect the robustness of the findings, the adopted random-effect meta-analysis models mitigate this drawback. Importantly, our meta-analytic approach represents a strength, because it generated a prompt quantification of the results of the delay on the outcome of CRC screening that may help planning timely public health decisions.

In addition, it is worth noting that our quantification on the Italian screening population should be considered as an illustrative example of the consequence of the screening delay on CRC stage shift and mortality. Once the observed data on CRC stage and mortality are gathered after the pandemic, it will be very informative to make a comparison with our results.

Finally, from the studies included in our meta-analysis, we could not unequivocally extrapolate the reasons explaining the delays in colonoscopy after a positive FIT test. Only Flugelman et al[12] reviewing the data from the 304 patients (17% of the cohort) who deferred follow-up beyond 1 year found that the main reason (in 90% of them) was the lack of adherence to positive fecal test follow-up guidelines.

The appearance of an urgent, unexpected, and unmet medical need is bringing collateral, unestimated impact on fields subject to constant improvement in the last decades. Steering resources to counteract the SARS-CoV-2 pandemic creates a bottleneck in other medical areas, queuing scheduled procedures and second level exams. In Italy, programmatic screenings have been suspended since mid-March according to government transitory regulation plan. Concerns raised by institutional players did not result in an objective evaluation of the situation ahead.

In the United States, the Centers for Medicare and Medicaid Services issued guidance that colonoscopies for CRC screening had to be delayed from mid-March, raising the concern that delay of CRC screening for 23 million U.S. adults would lead to a delayed diagnosis and increased mortality.[33] The need to resume key healthcare activities, including oncologic screening programs, is not counterbalanced by strategic plans considering the backlog. Indeed, in Italy, these stops will break a chain of about 6,000,000 yearly invitations for FIT, so that just a 2-month delay accounts for the lack of approximately 1,000,000 notices, with a parallel decrease in the 50% rate of pick-up, and a consequent loss of the estimated 5% positive tests among responders. Unfortunately, because of the highly unlikely scenario of full resumption of screening activities in the short-term, we could envision that such backlog would lead to a long-lasting carryover with significant negative consequences on the epidemiology of the disease.

The incoming challenge is to look forward to the demand for medical activities in the post–SARS-CoV-2 era, not only with respect to acute disorders but also for chronic and multifactorial diseases such as cancer, for which preventive attitudes and screening programs play a major role in reducing disease burden and mortality. In this perspective, designing new, proactive plans requires the proper evaluation of the scenarios ahead to counteract stops and delays imposed by the SARS-Cov-2 pandemic. This is of outmost importance in the view of possible future waves of SARS-CoV-2 infections.[34]

In conclusion, our study shows that CRC screening delays beyond 6 months would result in a significantly higher number of more advanced CRC cases; correspondingly, delays beyond 12 months would increase disease mortality. Thus, we believe that alternative strategies should envision future lockdowns and social distancing, rethinking the paths of distribution and analysis of the tests, and the possibility of managing screening-only, SARS-CoV-2–free, dedicated facilities.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical*

Gastroenterology and Hepatology at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.09.008.

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Reprint requests
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The authors disclose no conflicts.

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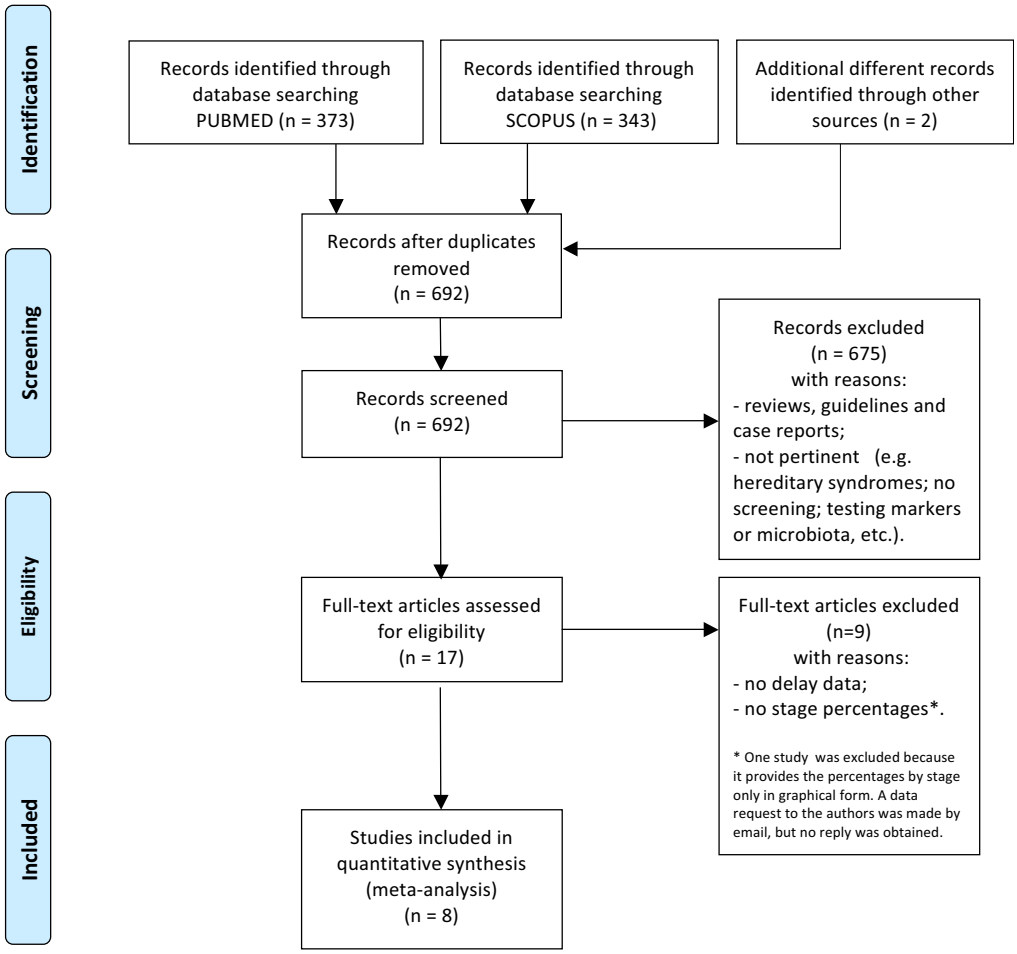
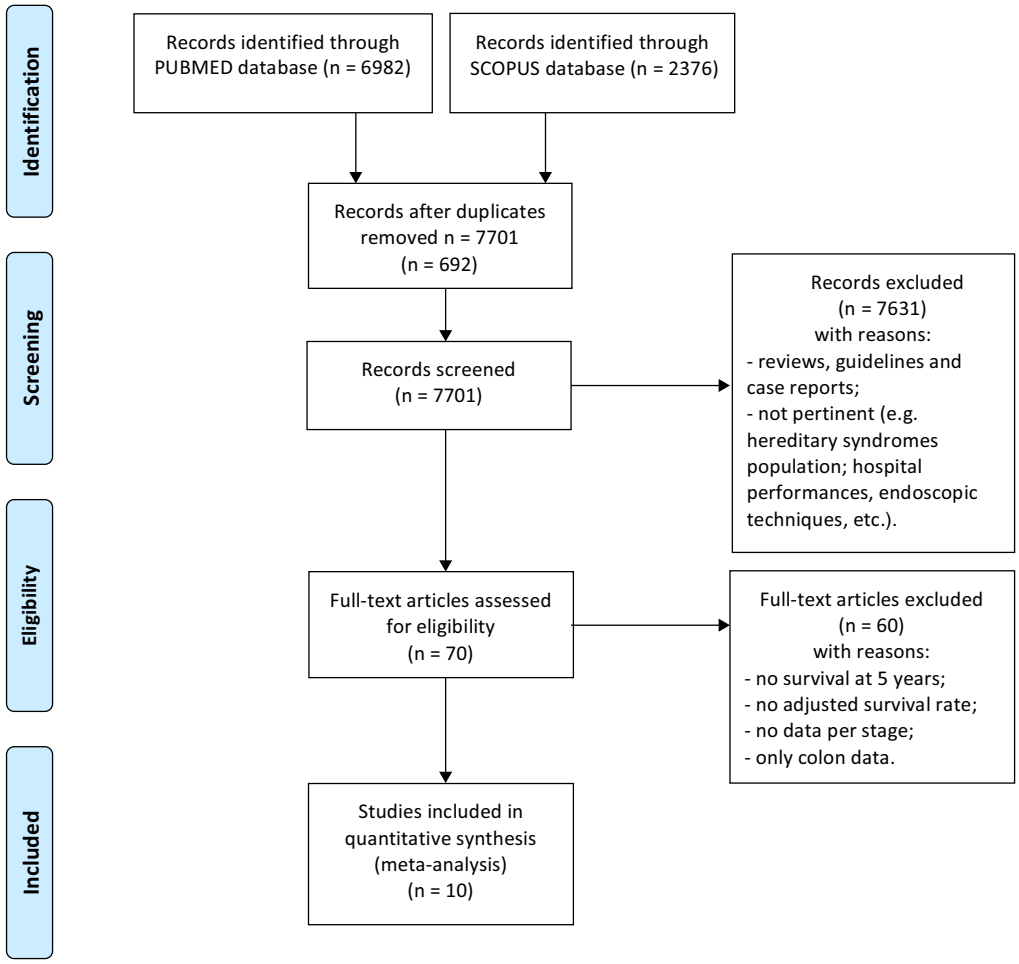
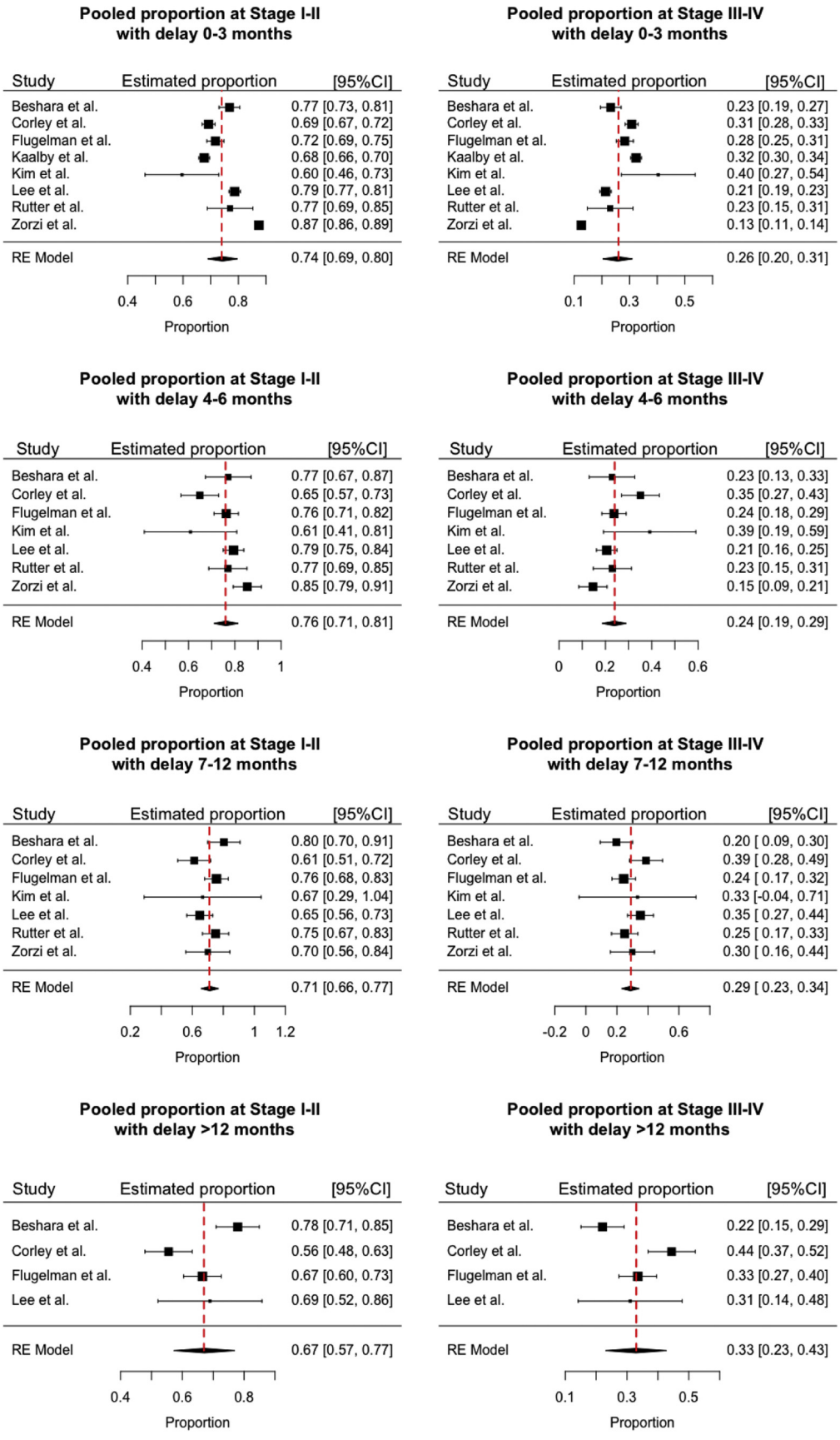


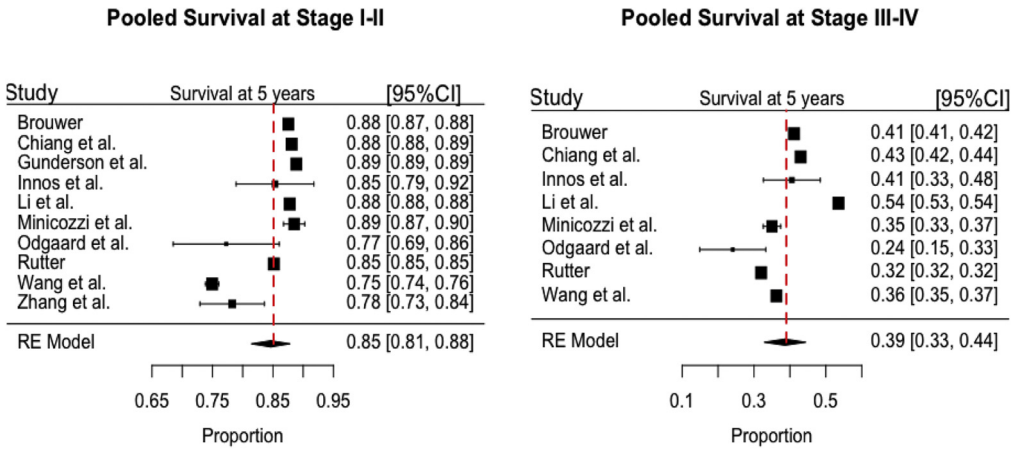
Supplementary Figure 1. Flowchart for the delay stage meta-analysis.



Supplementary Figure 2. Flowchart for the stage mortality meta-analysis.



Supplementary Figure 3. Proportion of colorectal cancer by stage (I–II and III–IV) at different delays (0–3 months, 4–6 months, 7–12 months, >12 months). Pooled estimates by delay stage meta-analysis. I^2 index: 97% (0–3 months), 72.4% (4–6 months), 48.2% (7–12 months), 82.6% (>12 months). CI, confidence interval.



Supplementary Figure 4. Survival rates at 5 years by stage (I–II and III–IV). Pooled estimates by stage mortality meta-analysis. I^2 index: 99% (stage I–II), 99% (stage III–IV). CI, confidence interval.

Supplementary Table 1. Articles Included in the Delay-Stage Meta-analysis

Article	Year	Country	Age (*y*)	Delay (*mo*)	Stage	n CRC	n total CRC
Beshara et al	2019	Israel	50–74	0–3	1–2	377	753
Beshara et al	2019	Israel	50–74	0–3	3-	114	
Beshara et al	2019	Israel	50–74	4–6	1–2	54	
Beshara et al	2019	Israel	50–74	4–6	3–4	16	
Beshara et al	2019	Israel	50–74	7–12	1–2	45	
Beshara et al	2019	Israel	50–74	7–12	3–4	11	
Beshara et al	2019	Israel	50–74	>12	1–2	106	
Beshara et al	2019	Israel	50–74	>12	3–4	30	
Corley et al	2017	USA	50–70	0–3	1–2	1017	1834
Corley et al	2017	USA	50–70	0–3	3–4	452	
Corley et al	2017	USA	50–70	4–6	1–2	85	
Corley et al	2017	USA	50–70	4–6	3–4	46	
Corley et al	2017	USA	50–70	7–12	1–2	50	
Corley et al	2017	USA	50–70	7–12	3–4	31	
Corley et al	2017	USA	50–70	>12	1–2	81	
Corley et al	2017	USA	50–70	>12	3–4	72	
Flugelman et al	2019	Israel	50+	0–3	1–2	583	1419
Flugelman et al	2019	Israel	50+	0–3	3–4	230	
Flugelman et al	2019	Israel	50+	4–6	1–2	193	
Flugelman et al	2019	Israel	50+	4–6	3–4	60	
Flugelman et al	2019	Israel	50+	7–12	1–2	93	
Flugelman et al	2019	Israel	50+	7–12	3–4	30	
Flugelman et al	2019	Israel	50+	>12	1–2	153	
Flugelman et al	2019	Israel	50+	>12	3–4	77	
Kaalby et al	2019	Denmark	50+	0–3	1–2	1498	3639
Kaalby et al	2019	Denmark	50+	0–3	3–4	716	
Kaalby et al	2019	Denmark	50+	NA	1–2	1099	
Kaalby et al	2019	Denmark	50+	NA	3–4	326	
Kim et al	2019	Korea	50+	0–3	1–2	31	81
Kim et al	2019	Korea	50+	0–3	3–4	21	
Kim et al	2019	Korea	50+	4–6	1–2	14	
Kim et al	2019	Korea	50+	4–6	3–4	9	
Kim et al	2019	Korea	50+	7–12	1–2	4	
Kim et al	2019	Korea	50+	7–12	3–4	2	
Lee et al	2019	Taiwan	50–69	0–3	1–2	1202	2003
Lee et al	2019	Taiwan	50–69	0–3	3–4	326	
Lee et al	2019	Taiwan	50–69	4–6	1–2	255	
Lee et al	2019	Taiwan	50–69	4–6	3–4	66	
Lee et al	2019	Taiwan	50–69	7–12	1–2	81	
Lee et al	2019	Taiwan	50–69	7–12	3–4	44	

Supplementary Table 1. Continued

Article	Year	Country	Age (*y*)	Delay (*mo*)	Stage	n CRC	n total CRC
Lee et al	2019	Taiwan	50–69	>12	1–2	20	
Lee et al	2019	Taiwan	50–69	>12	3–4	9	
Rutter et al[a]	2018	USA	50–75	0–3	1–2	77	300
Rutter et al[a]	2018	USA	50–75	0–3	3–4	23	
Rutter et al[a]	2018	USA	50–75	4–6	1–2	77	
Rutter et al[a]	2018	USA	50–75	4–6	3–4	23	
Rutter et al[a]	2018	USA	50–75	7–12	1–2	75	
Rutter et al[a]	2018	USA	50–75	7–12	3–4	25	
Zorzi et al	2020	Italy	50–69	0–3	1–2	2457	2981
Zorzi et al	2020	Italy	50–69	0–3	3–4	354	
Zorzi et al	2020	Italy	50–69	4–6	1–2	111	
Zorzi et al	2020	Italy	50–69	4–6	3–4	19	
Zorzi et al	2020	Italy	50–69	7–12	1–2	28	
Zorzi et al	2020	Italy	50–69	7–12	3–4	12	

NOTE. n CRC represents the number of CRC cases for each delay and stage; n total CRC is the total number of CRC cases.
[a]Data from the MIcrosimulation SCcreening ANalysis-ColoRectal Cancer (MISCAN-colon) microsimulation model were used.

Supplementary Table 2. Articles Included in the Stage-Mortality Meta-analysis

Article	Year	Country	Age (*y*)	Stage	n SURV	n CRC
Brouwer et al	2018	Netherlands	0+	1–2	28,714	32,802
Brouwer et al	2018	Netherlands	0+	3–4	13,426	32,633
Chiang et al	2016	Taiwan	15+	1–2	13,465	15,286
Chiang et al	2016	Taiwan	15+	3–4	8001	18,613
Gunderson et al	2010	USA	0+	1–2	64,258	72,307
Gunderson et al	2010	USA	0+	3–4	NA	NA
Innos et al	2018	Estonia	15+	1–2	99	116
Innos et al	2018	Estonia	15+	3–4	60	148
Li et al	2018	China	0+	1–2	117,167	133,483
Li et al	2018	China	0+	3–4	55,199	103,135
Minicozzi et al	2013	Italy	15+	1–2	1124	1270
Minicozzi et al	2013	Italy	15+	3–4	520	1485
Odgaard et al	2018	Greenland	28–92	1–2	68	88
Odgaard et al	2018	Greenland	28–92	3–4	20	83
Rutter et al	2013	USA	20+	1–2	103,971	122,114
Rutter et al	2013	USA	20+	3–4	35,752	111,764
Wang et al	2019	USA	3–129	1–2	4418	5895
Wang et al	2019	USA	3–129	3–4	2492	6875
Zhang et al	2014	China	30–93	1–2	180	230
Zhang et al	2014	China	30–93	3–4	NA	NA

NOTE. n SURV and n CRC represent the number of people who survived and of colorectal cancer cases for each stage, respectively.

Supplementary Table 3. Quality Index for the Studies Included in the DS and SM Meta-analysis Computed by using the Newcastle-Ottawa Scale

	Newcastle-Ottawa scale domains			
	Selection	Comparability	Outcome	Total
DS meta-analysis				
Beshara et al				
Items	1B, 2C, 3A, 4A	1AB	1B, 2A, 3A	
Point	3	2	3	8
Corley et al				
Items	1B, 2C, 3A, 4A	1AB	1B, 2A, 3A	
Point	3	2	3	8
Flugelman et al				
Items	1B, 2C, 3A, 4A	1AB	1B, 2A, 3A	
Point	3	2	3	8
Kaalby et al				
Items	1A, 2C, 3A, 4A	1AB	1B, 2B, 3A	
Point	3	2	2	7
Kim et al				
Items	1B, 2C, 3A, 4A	1AB	1B, 2A, 3A	
Point	2	2	3	7
Lee et al				
Items	1B, 2C, 3A, 4A	1AB	1B, 2A, 3A	
Point	3	2	3	8
Rutter et al				
Items	1C, 2C, 3A, 4A		1B, 2A, 3A	
Point	2	0	3	5
Zorzi et al				
Items	1B, 2C, 3A, 4A	1AB	1B, 2A, 3A	
Point	3	2	3	8
SM meta-analysis				
Brouwer et al				
Items	1B, 2C, 3A, 4A	1AB	1B, 2A, 3A	
Point	3	2	3	8
Chiang et al				
Items	1B, 2A, 3A, 4A	1AB	1B, 2A, 3A	
Point	4	2	3	9
Gunderson et al				
Items	1C, 2C, 3A, 4A	1A	1B,2A,3C	
Point	2	1	2	5
Innos et al				
Items	1C, 2C, 3A, 4A	1A	1B, 2A, 3A	
Point	2	1	3	6
Li et al				
Items	1A, 2A, 3A, 4A	1AB	1B, 2A, 3A	
Point	4	2	3	9
Minicozzi et al				
Items	1B, 2C, 3A, 4A	1A	1B, 2A, 3A	
Point	3	1	3	7
Odgaard et al				
Items	1A, 2C, 3A, 4A	1A	1B, 2A, 3A	
Point	3	1	3	7
Rutter et al				
Items	1A, 2C, 3A, 4A	1AB	1B, 2A, 3A	
Point	3	2	3	8
Wang et al				
Items	1A, 2A, 3A, 4A	1AB	1B, 2A, 3A	
Point	4	2	3	9
Zhang et al				
Items	1B, 2C, 3A, 4A	1AB	1B, 2A, 3A	
Point	3	2	3	8

NOTE. Scale range is 0–9.
DS, delay stage; SM, stage mortality.

Supplementary Table 4. Details Regarding Computation of the Screening Target Population and Expected Number of CRC Cases in Italy

Italy macro-region	50- to 69-year-old Italian total population	Target population	N invitations	N participants	N FIT+	CRC
North	7,727,209	3,863,605	3,670,424	1,908,621	89,705	1909
Center	3,342,758	1,671,379	1,504,241	526,484	27,904	790
South-Islands	5,619,474	2,809,737	1,264,382	303,452	21,849	486
Total	16,689,441	8,344,721	6,439,047	2,738,557	139,457	3184

NOTE. The Italian population data stratified by age are retrieved from the Italian National Statistics Institute (ISTAT) website (http://demo.istat.it/pop2019/index.html; last available data referring to January 1, 2019). In particular, we consider 3 macro-regions (North, Center, and South-Islands) and the 50 to 69 age class that is the target population of the screening program. Considering that the screening program is biennial, we compute the screening target population by halving the 50 to 69 age total population. As reported in Vicentini et al,[30] there are differences in the Italian macro-regions in covering the target population (ie, sending invitations for screening), with 95% coverage in the North, 90% in the Center, and 45% in the South-Islands. Because of these percentages, we estimate a total of 6,439,047 sent invitations. The last report of the National Screening Observatory (https://www.osservatorionazionalescreening.it/content/lo-screening-colorettale; last available data referring to year 2017) provides information about the percentage of invited population that performed the FIT test (52% in the North, 35% in the Center, and 24% in the South-Islands) and the percentage of positive tests (4.7% in the North, 5.3% in the Center, and 7.2% in the South-Islands). We thus obtain a total of 2,738,557 participants and 139,457 positive tests. Moreover, because of a CRC detection rate (provided by the National Screening Observatory) equal to 1% (North), 1.5% (Center), and 1.6% (South-Islands), we estimate to have 3184 CRC cases in the whole year, corresponding to 2.28% of the estimated number of FIT+.

CRC, colorectal cancer; FIT, fecal immunochemical test.