Contributions of early detection and cancer prevention to colorectal cancer mortality reduction by screening colonoscopy: a validated modeling study

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Background and Aims: Screening colonoscopy, recommended every 10 years, reduces mortality from colorectal cancer (CRC) by early detection of prevalent but undiagnosed CRC, as well as by removal of precursor lesions. The aim of this study was to assess the relative contribution of both components to total CRC mortality reduction over time.

Methods: Using a validated multistate Markov model, we simulated hypothetical cohorts of 100,000 individuals aged 55 to 64 years with and without screening at baseline. Main outcomes included proportions of prevented CRC deaths arising from (asymptomatic) CRC already present at baseline and from newly developed CRC during 15 years of follow-up, and mortality rate ratios of screened versus nonscreened groups over time.

Results: Early detection of prevalent cases accounted for 52%, 30%, and 18% of deaths prevented by screening colonoscopy within 5, 10, and 15 years, respectively. Relative reduction of mortality was estimated to be much larger for mortality from incident cancers than for mortality from cancers that were already present and detected early at screening endoscopy and for total CRC mortality (ie, 88% versus 67% and 79%, respectively, within 10 years from screening).

Conclusions: Reduction of CRC mortality mainly arises from early detection of prevalent cancers during the early years after screening colonoscopy, but prevention of incident cases accounts for the majority of prevented deaths in the longer run. Prevention of incident cases leads to sustained strong reduction of CRC mortality, possibly warranting an extension of screening intervals. (Gastrointest Endosc 2024;100:710-7.)

Screening by means of colonoscopy can substantially reduce incidence and mortality from colorectal cancer (CRC).[1-4] Two major components may contribute to the reduction of CRC mortality: earlier detection of prevalent (and asymptomatic) but previously undiagnosed CRC, and prevention of CRC by detecting and removing precancerous lesions. Timing of manifestation of the effects of both components may differ, with the former component expected to be more relevant in the earlier years of follow-up, and the latter component expected to increasingly exert its impact on CRC mortality in the longer run.

Data on mortality in the NordICC trial, the only randomized trial reporting on effects of screening colonoscopy, are so far restricted to 10 years of follow-up, during which a nonsignificant decrease in CRC mortality by 10% was observed in intention-to-screen analysis and a significant 50% reduction was observed in adjusted per-protocol analysis.[4] However, it is unclear to what extent these results are driven by earlier detection of prevalent CRC compared with removing precancerous lesions, and how these mortality prevention effects might vary over time. Better understanding of these components might help optimizing screening strategies, for example,

Abbreviations: COSIMO, Colorectal Cancer Multistate Simulation Model; CRC, colorectal cancer; MRR, mortality rate ratio; RCT, randomized controlled trial.

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regarding screening intervals, where previous evidence focused on prevalences and incidence reductions suggests that currently recommended intervals could possibly be extended.[5-7] Disentangling mortality effects could also contribute to improved patient communication regarding the benefits of early detection and removal of precursor lesions.

Unfortunately, in a real-life study (such as NordICC), the proportion of individuals with prevalent CRC at baseline in those not screened is unobservable and cannot be known. Simulation models are a powerful tool to overcome such evidence gaps. In the present modeling study largely based on data from the German national screening colonoscopy registry, we aimed to explore to what extent the prevention of CRC deaths by screening colonoscopy is due to early detection of prevalent cases and to prevention of incident cases by removal of precursor lesions. A particular focus is on the contributions of both components according to time since colonoscopy and potential implications for defining length of screening colonoscopy intervals.

METHODS

Study concept

For this modeling study, we combined data on baseline prevalences of various types of colorectal neoplasms (nonadvanced and advanced adenomas, CRC) of men and women aged 55 to 64 years (the recruitment age range in the NordICC trial[4]) with no previous CRC diagnosis and no previous screening colonoscopy and data on transition rates between the various stages of colorectal carcinogenesis and CRC survival rates according to type of cancer diagnosis.

Baseline prevalences of colorectal neoplasms

Baseline prevalences of various types of colorectal neoplasms in the age range of 55 to 64 years were derived from the German national screening colonoscopy registry, the largest registry of its kind. Details on this registry have been reported elsewhere.[8,9] Briefly, the registry was implemented in October 2002, along with introduction of the offer of screening colonoscopy in Germany. Complete registration of screening colonoscopies is ensured as it is a prerequisite for reimbursement. Along with introduction of screening colonoscopy, major efforts of quality assurance were implemented and only well qualified endoscopists are certified to conduct screening colonoscopies. For our analyses, prevalences of colorectal neoplasms by age (55-59 and 60-64 years) and sex for the calendar years 2006 to 2010 (the recruitment years of the NordICC trial) were derived (Supplementary Table 1, available online at www.giejournal.org) and weighted according to the age and sex distribution of the NordICC study population as reported by Brethauer et al.[4]

Transition rates and modeling

Modeling of expected CRC cases and deaths with and without screening colonoscopy during 15-year follow-up was performed by means of COSIMO (Colorectal Cancer Multistate Simulation Model), a previously developed and validated multistate Markov model based on the natural history of CRC development and outcome.[10] The structure of COSIMO is illustrated in Supplementary Figure 1 (available online at www.giejournal.org). Further details on the conceptual model structure, input parameters and the validation process are provided in Supplementary Appendix 1 (available online at www.giejournal.org).

Sex- and age-specific annual transition rates between states, which were previously derived from data of the German national screening colonoscopy registry (ie, the same source as for the baseline prevalences) and German cancer registries are summarized in Supplementary Table 2 (available online at www.giejournal.org). Briefly, transition rates were derived by several birth cohort analyses (an analysis technique) for a German screen-eligible but previously nonscreened population at average risk for CRC.[11-13] Diagnostic performance measures of screening colonscopy as used in the model are provided in Supplementary Table 3 (available online at www.giejournal.org). Mortality rates from CRC according to mode of detection (screening, other) and year following CRC diagnosis are presented in Supplementary Table 4 (available online at www.giejournal.org). Briefly, mortality rates were derived by combining data on the proportion of screening-detected cases among all CRC cases in Germany with the overall CRC-specific mortality rates by year after diagnosis, and then applying the hazard ratios for patients detected by screening versus symptoms as obtained from the mortality follow-up of a cohort of patients who were recruited in a German population-based case-control study on CRC screening. Details are provided in the literature[14,15] and in Supplementary Appendix 1. Sex- and age-specific general mortality rates, which were derived from life tables provided by the German Federal Statistical Office, are presented in Supplementary Table 5 (available online at www.giejournal.org).[14,16]

Simulations were conducted in hypothetical cohorts of 100,000 individuals (weighted by age and sex) with and without use of a single screening colonoscopy at baseline. Individuals with detection of polyps at screening colonoscopy were assumed to undergo surveillance examinations at recommended intervals[17] (5 and 10 years after detection of advanced and nonadvanced adenomas, respectively), and no further use of endoscopy was assumed throughout follow-up for both groups.

Outcome measures

First, for both nonscreened and screened groups, we derived cumulative numbers and proportions of CRC deaths arising from CRC already prevalent at baseline and from newly developed CRC during 15 years of follow-up. Numbers and proportions of prevented CRC deaths by screening can then be derived through the differences in deaths between nonscreened and screened groups. CRC deaths arising from newly developed CRC during follow-up were derived by rerunning the models while omitting all prevalent preclinical

TABLE 1. Cumulative CRC deaths arising from CRC already prevalent at baseline and from newly developed CRC during follow-up in a hypothetical cohort of 100,000 nonscreened and screened participants aged 55-64 years

Follow-up, y	Total CRC deaths, n (col %)	Death from prevalent CRC, n (row %)	Death from incident CRC, n (row %)
Nonscreened			
3	92 (7)	78 (85)	14 (15)
5	213 (16)	144 (68)	69 (32)
8	458 (34)	218 (48)	240 (52)
10	663 (50)	251 (38)	412 (62)
12	904 (68)	272 (30)	632 (70)
15	1330 (100)	289 (22)	1041 (78)
Screened			
3	54 (19)	53 (98)	1 (2)
5	79 (28)	74 (94)	5 (6)
8	111 (40)	89 (80)	22 (20)
10	141 (50)	93 (66)	48 (34)
12	184 (65)	95 (52)	89 (48)
15	281 (100)	95 (34)	186 (66)

Results are presented as n (%).
CRC, Colorectal cancer.

cancers at baseline and then calculating the difference versus the total numbers of CRC deaths in the original model.

Then we calculated mortality rate ratios (MRRs) for total CRC deaths (MRR_{TOT}), CRC deaths arising from prevalent cancers (MRR_{PREV}), and CRC deaths arising from incident cancers (MRR_{INC}) by first deriving the mortality rate as number of cases per number of patient-years for each group, and then calculating the ratio of mortality rates of screened versus nonscreened groups. All analyses were repeated for subgroups by sex and age.

Patient and public involvement

Patients and the public were neither involved in the design and conduct of this study, nor in writing or editing of this report. Research at the German Cancer Research Center is generally informed by a patient advisory committee.

RESULTS

Total cumulative CRC deaths in the simulated nonscreened group increased markedly and steadily over time (Table 1). After 5, 10, and 15 years, 213, 663, and 1330 individuals, respectively, out of simulated 100,000 men and women, were predicted to have died of CRC. Cumulative deaths were strongly dominated by deaths arising from prevalent CRC in the initial years of follow-up. However, their relative contribution diminished over time, as ever larger proportions of deaths were attributable to newly developed CRC with increasing length of follow-up. Proportions of deaths arising from prevalent and incident CRC, respectively, were 68% and 32% after 5 years, 38% and 62% after 10 years, and 22% and 78% after 15 years.

In the screened group, the total number of CRC deaths followed a much less pronounced growth trajectory compared with the nonscreened group, with 79, 141, and 281 CRC deaths after 5, 10, and 15 years, respectively (Table 1). Although deaths arising from incident CRC dominated at the end of the observation period, deaths from prevalent CRC contributed a relatively larger share over most years of follow-up, also in relation to the corresponding numbers for the nonscreened group. After 5, 10, and 15 years, respectively, 94%, 66%, and 34% of all CRC deaths were attributable to prevalent CRC, and 6%, 34% and 66% were attributable to newly developed CRC. Thus, while cumulative numbers for both components were substantially smaller in the screened group versus the nonscreened group, deaths from prevalent CRC accounted for a relatively larger share and deaths from incident CRC accounted for a relatively smaller share over a longer period of follow-up in the screened group (Fig. 1).

Cumulatively prevented CRC deaths followed an analogous pattern of initially higher shares of prevented deaths arising from prevalent CRC which diminished over time to the favor of prevented deaths from incident CRC (Table 2). Early detection of prevalent cases versus prevention of incident cancers was estimated to account for 52% versus 48%, 30% versus 70%, and 18% versus 82% of total deaths prevented by screening colonoscopy within 5, 10, and 15 years, respectively.

Table 3 presents estimates of MRR_{TOT}, MRR_{PREV}, and MRR_{INC} (calculated using the total number of CRC deaths, those arising from prevalent CRC only, and those arising from incident CRC only, respectively) according to year of follow-up, and Figure 2 provides a graphic visualization. All MRRs were lower than 1, starting after 3 years of follow-up (when the first deaths occurred), indicating a strong protective effect of screening. However, MRR_{INC} was consistently lower

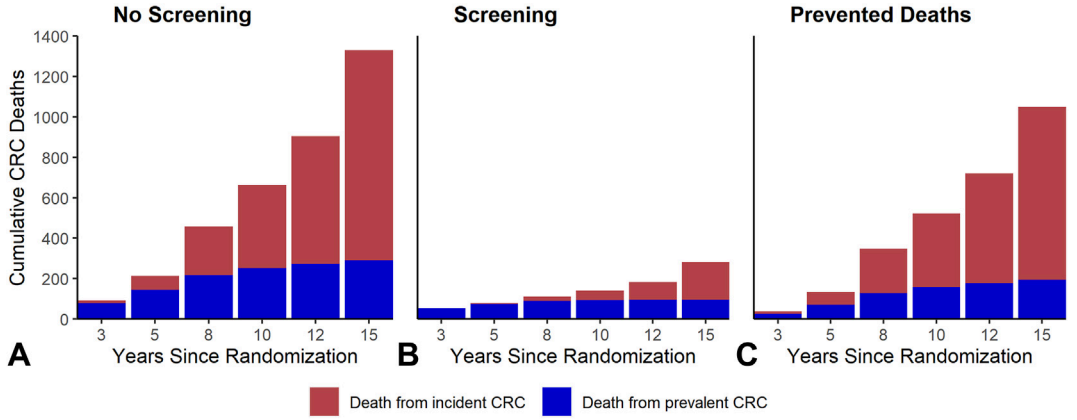

Figure 1. Combined numbers of cumulative colorectal cancer (CRC) deaths from incident and prevalent CRC in nonscreened and screened groups, as well as prevented CRC deaths.

than MRR_{PREV}, most markedly in the initial years of follow-up (risk reduction, absolute difference, and margin >20% units until year 10 of follow-up), with diminishing differences over time (risk reductions for MRR_{PREV} vs MRR_{INC} after 5, 10, and 15 years, 50% vs 93%, 67% vs 88%, and 73% vs 82%, respectively). Results were consistent across sex- and age-specific subgroups (Supplementary Tables 6 and 7; Supplementary Fig. 2; available online at www.giejournal.org).

DISCUSSION

This study explored to what extent reduction of CRC mortality by screening colonoscopy over time is achieved by early detection of prevalent cancer and by prevention of incident cancers. In our simulations, deaths arising from prevalent CRC dominated cumulative deaths in the initial years of follow-up, but their relative contribution decreased over time. By comparing screened versus nonscreened groups, we found that the majority of prevented deaths due to CRC are prevented through early detection of prevalent cases in the initial 5 years after colonoscopy and through prevention of incident cancers in the longer run. Separating mortality effects revealed that relative mortality reduction was for many years much larger for mortality from incident cancers (which were prevented by screening) than for mortality from cancers that were already present at baseline (which were detected early by screening). These findings underscore that the preventive potential of early removal of CRC precursor lesions is significantly larger than early detection of already prevalent cases and that the former ensures sustained strong long-term reduction of CRC mortality.

Findings in context

Compelling evidence demonstrated the strong potential of endoscopic screening to prevent deaths from CRC. For screening sigmoidoscopy, long-term follow-up analyses of large, randomized trials (ie, the Norwegian NORCCAP,[18] the American PLCO,[19] the British UKFSS,[20] and the Italian SCORE[21] trials) consistently found a significant and sustained effect on CRC mortality.[3] Across these trials, CRC mortality was reduced by approximately 20% in intention-to-screen analysis and by approximately 40% in per-protocol analysis. The benefit is limited to the distal colon, and the benefits are possibly greater in men and in older people.[22] Meta-analyses of observational studies suggest similarly strong or even stronger risk reductions than seen in the randomized trials.[1]

For screening colonoscopy, the initial results of the NordICC trial (conducted in Poland, Norway, and Sweden), published in late 2022, constitute the only randomized trial evidence so far (other studies are ongoing[23-25]). The authors reported a nonsignificant decrease in CRC mortality by 10% in intention-to-screen and a significant 50% reduction in per-protocol analysis within 10 years of follow-up.[4] These effects have been perceived as smaller than expected, because a comprehensive body of observational studies points to much stronger mortality reductions compared with screening sigmoidoscopy.[1,7,26-28] However, several factors may help to explain the smaller than expected effect in NordICC, including the preliminary nature of results (final analysis is planned after 15 years of follow-up),[15,29,30] low screening uptake (only 42% of those invited used screening colonoscopy), performance bias (based on large variation across participating countries),[4,31] and dilution (to an unknown extent) of effects by common use of diagnostic colonoscopies during the follow-up period.[32,33]

Previous evidence exists on improved prognosis of patients with screening-detected compared with symptom-detected CRC.[34-36] However, to our knowledge, no previous study has explored to what extent the prevention of CRC deaths in randomized screening endoscopy studies is driven by early detection of prevalent cases and prevention of incident cases, the research question addressed in our study.

TABLE 2. Cumulative prevented deaths arising from CRC already prevalent at baseline and from newly developed CRC during follow-up in a hypothetical cohort of 100,000 screened participants aged 55-64 years

Follow-up, y	Total prevented CRC deaths, n (col %)	Prevented deaths from prevalent CRC, n (row %)	Prevented deaths from incident CRC, n (row %)
3	38 (4)	25 (66)	13 (34)
5	134 (13)	70 (52)	64 (48)
8	347 (33)	129 (37)	218 (63)
10	522 (50)	158 (30)	364 (70)
12	720 (69)	177 (25)	543 (75)
15	1049 (100)	194 (18)	855 (82)

Results are presented as n (%).
CRC, Colorectal cancer.

TABLE 3. CRC mortality rate ratios and risk reductions of screened versus nonscreened groups over time, overall and according to prevalent and incident CRC

	Mortality rate ratio			Risk reduction, %		
Follow-up, y	All CRC deaths	Deaths from prevalent CRC	Deaths from incident CRC	All CRC deaths	Deaths from prevalent CRC	Deaths from incident CRC
3	0.59	0.68	0.07	41	32	93
5	0.37	0.50	0.07	63	50	93
8	0.24	0.38	0.09	76	62	91
10	0.21	0.33	0.12	79	67	88
12	0.20	0.30	0.14	80	70	86
15	0.21	0.27	0.18	79	73	82

CRC, Colorectal cancer.

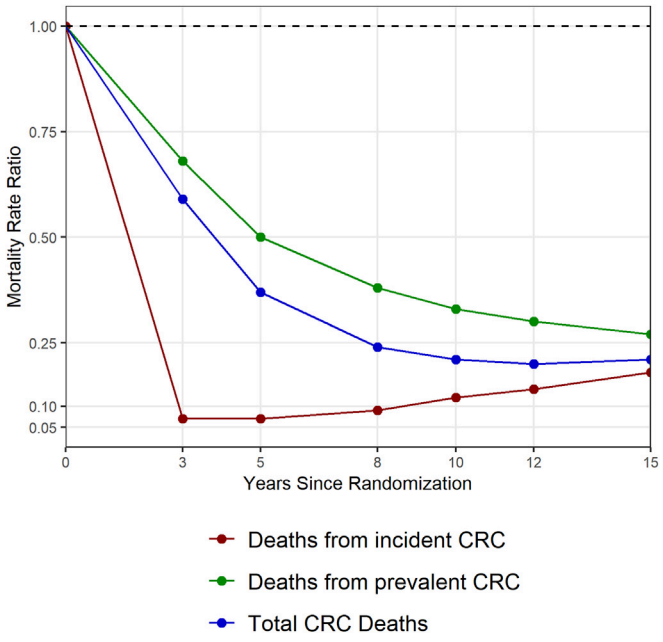

Figure 2. Mortality rate ratios of total colorectal cancer (CRC) deaths, deaths arising from prevalent CRC, and deaths arising from incident CRC over time.

Implications for CRC screening

Our findings have several implications for the interpretation of randomized screening endoscopy studies. First, mortality effects for early cancer detection and actual cancer prevention need to be distinctly differentiated. Although most screening-detected cases are amendable to treatment with curative intent, patients with screen-detected CRC still differ prognostically from those without any malignant finding. Approximately 30% of early-stage cancers recur within a few years,[37] and 20% to 30% of screening-detected cancers have already spread to adjacent lymph nodes or other parts of the body, detrimentally affecting prognosis.[38-40] In contrast, in surveillance-compliant patients with polyps (but no cancer) at screening, the overall long-term CRC risk after polypectomy is similar to that of patients without polyps.[17,41,42] Thus, a differentiated view on individual mortality effects is warranted. In the example of the NordICC study, cancer was detected in 0.5% of subjects at baseline screening, which accounted for 24% and 61% of all detected cancers in intention-to-screen and per-protocol analyses, respectively. The impact of such prevalent cases should be carefully discussed when interpreting, reporting, and communicating results.

Second, from a methodologic point of view, in a randomized screening study, the presence of CRC at baseline mod-

ifies the effect of screening: In simple terms, both groups (ie, those with and without cancer) are expected to benefit in terms of mortality reduction, but at varying magnitudes. Exploratory investigation of the individual effects in separate strata, as suggested by established randomized controlled trial (RCT) methodology for such situations,[43,44] is not straightforward, because the proportion of prevalent cancers in the control group (where no screening intervention took place) can only be estimated. However, extensive sensitivity analysis including modeling approaches is a well established option for large-scale RCTs, and the far-reaching, possibly practice-changing, implications of such studies make closer examination worthwhile. Future research should investigate how best to address the methodologic difficulties in such analysis.

Third, better understanding of these individual components of mortality reduction, that is, early cancer detection versus cancer prevention, might help inform screening strategies in terms of intervals or starting ages. Screening colonoscopy is currently recommended at 10-year intervals by major American and international guidelines.[45,46] However, an increasing body of evidence suggests that these could be extended in those with negative baseline examination, especially for female and younger patients without GI symptoms.[5-7] The present study illustrates that prevention of incident cases leads to sustained strong reduction of CRC mortality in the longer run (with consistently very low MRRs of <0.2 for deaths from incident CRC after 10, 12, and 15 years), which possibly also warrants an extension of screening colonoscopy intervals. Further studies will be needed to strengthen the evidence base and to derive specific recommendable interval lengths.

Finally, this study could also contribute to improved patient communication on the benefits of early detection and removal of precursor lesions. In 2021, the U.S. Preventive Service Task Force updated their recommendations to move eligibility for CRC screening of the general public from age 50 years to 45 years.[45] Earlier start of screening likely implies a shift toward the cancer prevention effect, because few prevalent CRCs would be expected in younger age groups, particularly those aged less than 50 years. Our findings suggest that the mortality risk reductions by screening endoscopy in younger patients might possibly be larger than the estimates from published RCTs, because the proportion of CRC deaths resulting from incident cancers would be expected to be larger in younger age groups. The impact of such age-related shift on mortality effects deserves further examination.

Limitations

Specific limitations of COSIMO have been described previously.[10,47] Briefly, major limitations concern simplifying model assumptions and uncertainties related to input parameters. For example, because the true adenoma miss rate at colonoscopy in Germany is unknown, we used representative estimates derived from a comprehensive systematic review and meta-analysis that used data not limited by geographic region.[48] Furthermore, the German national screening colonoscopy registry, our key data source for deriving transition rates between stages, did not include sufficiently detailed data to calculate specific transition rates for proximal and distal neoplasms. Therefore, no subsite-specific analysis can be conducted using the model. Furthermore, the model is limited in that the biological origin of polyps is not accounted for, because averaged incidence and transition rates reflecting the natural history of CRC on a population-level are used. Consequently, no impact of specific classes of lesions (eg, serrated polyps) could be estimated. On similar as well as on methodologic grounds, no surveillance intervals differentiated by lesion at index screening could be implemented in the model, and 5-year surveillance intervals, instead of 3-year intervals as recommended by some guidelines,[17] were used as a proxy for all surveillance colonoscopies to avoid potential over-screening. However, given the relatively short follow-up duration, the impact of more differentiated surveillance intervals would likely be limited.

Furthermore, mortality analysis of participants registered in the German national screening colonoscopy registry (which was a key data source for the development of COSIMO) to supplement the research in this study was not possible, because confidentiality rules prohibited record linkage between the colonoscopy registry and population registries and cancer registries.

Of note, CRC detected at baseline screening will also significantly affect estimates on incidence reduction. In all screening endoscopy RCTs, reported incidence shows an initial apparent increase in the screened group, which is attributed to the detection of prevalent, preclinical cancers. Assessing the impact of those cancers on incidence reduction estimates was beyond the scope of the present study and, although it is already commented on in the literature,[49] should be further elaborated upon in future research.

CONCLUSION

Reduction of CRC mortality mainly arises from early detection of prevalent cancers during the early years after screening colonoscopy whereas strong sustained prevention of incident cases accounts for the majority of prevented deaths in the longer run. Relative reduction of mortality is much stronger for mortality from incident cancers than for mortality from prevalent cancers. Prevention of incident cancers leads to sustained strong reduction of CRC mortality, possibly warranting an extension of screening colonoscopy intervals.

AVAILABILITY OF DATA, CODE, AND MATERIAL

All analyses relevant to the study are included in the article or uploaded as supplementary information. The

model source code is available from https://www.dkfz.de/en/klinepi/download/index.html. Further information is available from the corresponding author on request.

DISCLOSURE

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SUPPLEMENTARY APPENDIX 1. COSIMO DOCUMENTATION

Conceptual model structure

The Markov-based Colorectal Cancer Multistate Simulation Model (COSIMO) simulates the natural history of colorectal cancer (CRC) based on the process of precursor lesions (nonadvanced and advanced adenomas) developing into preclinical (asymptomatic) and then clinical (symptomatic) cancer. The simulation is performed on a hypothetical previously nonscreened German population, with the number of simulated subjects and their corresponding baseline age (minimum 50 years) being variables to be chosen before model start. COSIMO can principally be used for simulating any population with updated or appropriately adjusted input parameters.

At start of the simulation, certain proportions of no neoplasm, nonadvanced adenoma, advanced adenoma, and preclinical CRC are assigned to the hypothetical population. The simulation runs up to a predefined number of cycles of each 1 year. Each year, people at each state have a certain probability (transition rate) to progress to the next state. Subjects with CRC may die from the disease, and at each state people may experience non-CRC death, reflecting the general background mortality from other causes.

Screening can alter the progression between states. People with adenoma will be moved backward to the state of no neoplasm, assuming removal of their adenoma at colonoscopy (for screening or diagnostic workup, eg, after a positive fecal test). Subjects will then continue to have the same probabilities to progress to the next states as those without findings at screening. We assume that, although these people are under a higher risk of developing adenomas or cancers than the general population,[1] the excess risk will be effectively compensated through the protection provided by surveillance colonoscopies.[2,3] Preclinical CRC detected at screening will be moved forward to the state of diagnosed cancer.

After each cycle where a screening test was applied, the model differentiates the simulated population into "screening negative" and "screening positive" groups, which allows for modeling different trajectories depending on the screening outcome. In such scenarios, subjects receive the next screening round only if they had a negative test result in the respective previous round. In the base case model, subjects with false-positive test results (eg, a diagnostic colonoscopy without finding after a positive fecal immunochemical test) return to the screening population after a latency period of 10 years. Subjects with detected nonadvanced adenomas are assumed to undergo surveillance colonoscopies at intervals of 10 years up to a predefined end age of 75 years. In case an advanced adenoma was detected, either at the primary screening test or at a surveillance colonoscopy, subjects are assumed to undergo periodic surveillance colonoscopies at 5-year intervals up a predefined end age of 85 years.

The model source code, developed in the R statistical software (version 4.1.2), is available for download from our website.[4]

Model parameters

Starting prevalences and transition rates. An overview of key model parameters is presented in Supplementary Tables 1-3.

Data source. The data basis of our analyses on model starting prevalences and transition rates was the nationwide screening colonoscopy registry run by the Central Research Institute of Ambulatory Health Care in Germany. The registry, which was built up along with the introduction of the screening colonoscopy offer in the year 2002, is a repository of all screening colonoscopies conducted in Germany. Reporting is virtually complete because it is a prerequisite for physicians' reimbursement by the health insurance funds. The registry includes only primary screening examinations (ie, colonoscopies conducted for surveillance, work-up of symptoms, and other screening tests are not included). Items reported include, besides basic sociodemographic variables, findings at colonoscopy including number, size, and histologic characteristics of polyps. In case of multiple neoplasms, only the most advanced one (nonadvanced adenoma, advanced adenoma, or cancer) is recorded. Advanced adenomas are defined as at least 1 adenoma $\geq$1 cm or at least 1 adenoma with villous components or high-grade dysplasia.

The reporting for the screening colonoscopy registry does not differentiate by the class of lesion. Therefore, the term "adenoma" used here refers to conventional and serrated adenomas (polyps) alike. Although we preferred to refer to our model as being based on the adenoma-carcinoma pathway in previous publications[5-9] for the sake of simplicity and comprehensibility (because the great majority of CRCs develop through this well established pathway of cancer development[10,11]), in fact COSIMO's defining parameters were derived using polyp/adenoma prevalences as detected and reported at screening colonoscopy, regardless of their underlying mechanism or pathway of development. Therefore, it is more precise to refer to the model as being based on the "natural history of CRC," without restrictions on underlying CRC development pathways.

Starting prevalence. For this study, the proportions of no neoplasm, nonadvanced adenoma, advanced adenoma, and preclinical CRC at the beginning of simulation were calculated based on the data from 1,222,439 participants of the German screening colonoscopy program who had their first screening colonoscopy during 2006 to 2010 at the age of 55 to 64 years, weighted by the sex and age distribution as reported in the NordICC study.[12] To take into account that a certain proportion of neo-

plasms needs to be assumed to have been missed at colonoscopy screening, particularly for serrated or flat polyps,[13,14] we assumed representative miss rates of 25% for nonadvanced adenomas and 5% for advanced neoplasms (advanced adenomas and preclinical cancers).

Transition rates. Transition rates between states were estimated based on data from the nationwide screening colonoscopy registry by several separate birth cohort and mean sojourn time analysis. Details on the principles of these methods have been described previously.[15-17] Briefly, sex- and age-specific annual incidence and transition rates were estimated from sex- and age-specific prevalences of adenomas among 3.6 to 4.3 million screening participants from the same birth cohorts in 2003 to 2011 (2003-2009) and 2004 to 2012 (2004-2010). The analysis on mean sojourn time of preclinical cancers additionally incorporated registry-reported CRC incidence and participation rates in screening colonoscopy from 2003 to 2006.

Similarly as for the starting prevalences, because colonoscopy was shown to be less effective in detecting serrated lesions (and because the true proportions of missed conventional adenomas and serrated lesions in the registry-reported prevalences is unknown), we recalculated previously reported transition rates[15-17] to adjust for representative colonoscopy miss rates.[13,14] This adjustment resulted in slightly higher overall prevalences of adenomas and, therefore (compared with previously reported rates), slightly higher transition rates of incidence adenomas as well as slightly lower transition rates from nonadvanced to advanced adenomas and from adenomas to cancer. Furthermore, to adjust for uncertainties resulting from the cycle length of 1 year used in COSIMO, we updated the model to allow for a small proportion of subjects with very rapidly progressing lesions with limited potential for early detection and associated worse prognosis. Age- and sex-specific annual transition rates between the states were estimated for age groups from 55 to 79 years in steps of 5 years. Estimates for ages 50 to 54 and ≥80 (or ≥85) were assumed to be the same as those for ages 55 to 59 and 75 to 79 (or 80-84), respectively.

Confidence intervals for both starting prevalences and transition rates were derived by bootstrap analysis with resampling within sex- and age-specific subgroups. Ninety-five percent confidence intervals were determined as the 2.5th and 97.5th percentiles of transition rate estimates obtained in 1000 runs.

Mortality rates

Mortality rates for patients whose cancer was detected by screening or by symptoms were estimated in previous analyses.[8,9] We combined data on the proportion of screening-detected cases among all CRC cases in Germany during 2003 to 2012 in people aged 55 to 79 years[5,18] and the overall CRC-specific mortality rates by year after diagnosis in Germany in 2011 to 2012.[18] We then used hazard ratios for patients detected by screening versus symptoms as obtained from a German population-based case-control study on CRC screening with long-term mortality follow-up of CRC patients[8,19] to estimate CRC-specific mortality rates by mode of detection (Supplementary Table 4). Sex- and age-specific general mortality rates and average life expectancy of the population were extracted from German population life tables for 2010 to 2012 (Supplementary Table 5).[20]

Model validation

COSIMO has been validated for the German screening-eligible population. Details on the model validation process can be found in the literature.[21] Briefly, we pursued a 3-fold approach using the best available evidence from epidemiologic data sources in Germany. We compared model-derived cumulative incidence and prevalences of colorectal neoplasms with (1) results from KolosSal, a study in German screening colonoscopy participants, (2) registry-based estimates of CRC incidence in Germany, and (3) outcome patterns of randomized sigmoidoscopy screening studies. This approach enabled us to scrutinize the model's natural history component (parts 1 and 2) as well as the modeled effect of screening colonoscopy (parts 2 and 3) at the same time.

We found that (1) more than 90% of observed prevalences in the KolosSal study were within the 95% confidence intervals of the model-predicted neoplasm prevalences, (2) the 15-year cumulative CRC incidences estimated by simulations for the German population deviated by 0.0% to 0.2% units in men and by 0.0% to 0.3% units in women compared with corresponding registry-derived estimates, and (3) the time course of cumulative CRC incidence and mortality in the modeled intervention and control groups closely resembles the time course reported from sigmoidoscopy screening trials. Overall, COSIMO adequately predicted colorectal neoplasm prevalences and incidences in a German population for up to 25 years, with estimated patterns of the effect of screening colonoscopy resembling those seen in registry data and real-world studies.

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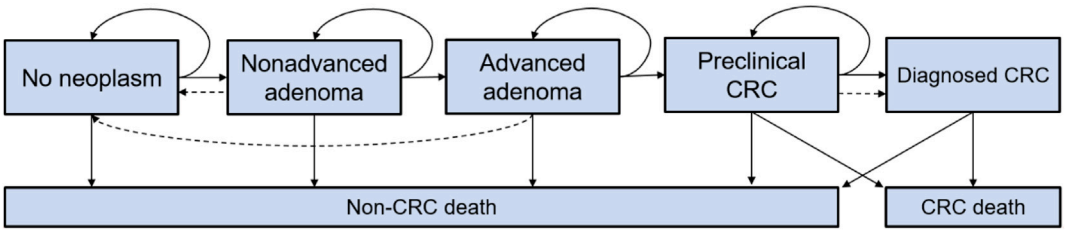
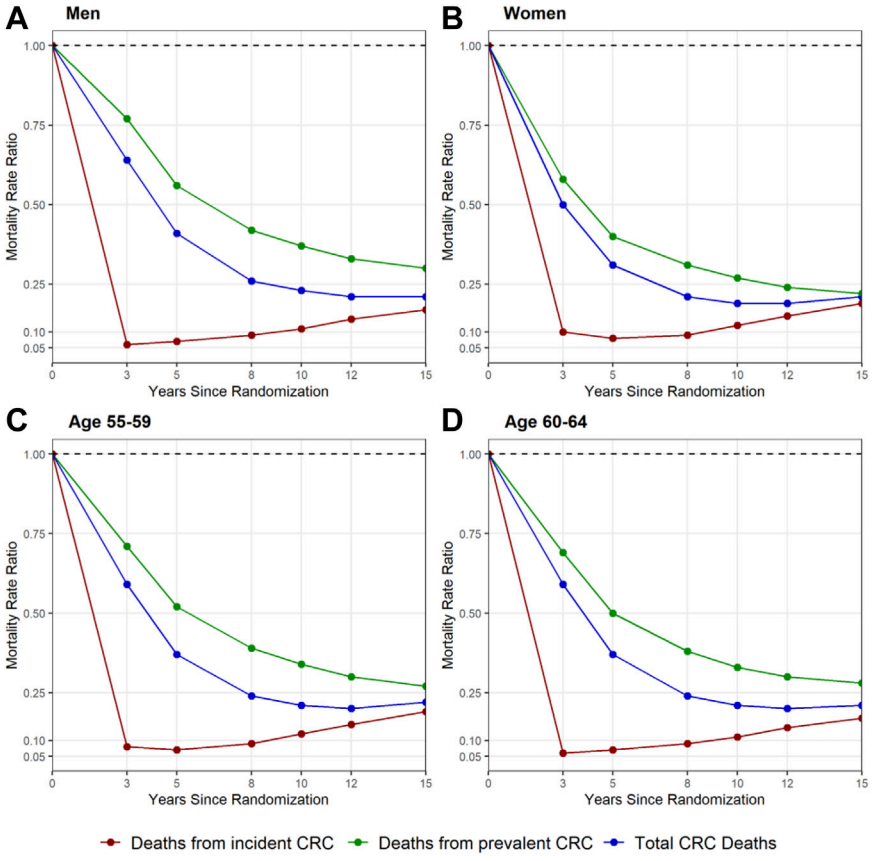


Supplementary Figure 1. Schematic illustration of the Colorectal Cancer Multistate Simulation Model (COSIMO). *Solid arrows* represent the progression of colorectal cancer (CRC) through the adenoma-carcinoma sequence in the absence of screening; *dashed arrows* show the movement between states because of the detection and removal of adenomas and the detection of asymptomatic CRC at screening.



Supplementary Figure 2. Mortality rate ratios of total colorectal cancer (CRC) deaths, deaths arising from prevalent CRC, and deaths arising from incident CRC over time—subgroup analyses by sex and age.

SUPPLEMENTARY TABLE 1. Sex- and age-specific prevalence of various types of neoplasms among first-time participants of screening colonoscopy, Germany, 2006-2010

			Most advanced finding at screening colonoscopy		
Sex	**Age, y**	**n**	**Nonadvanced adenoma**	**Advanced adenoma***	**CRC**
Men	55-59	321,432	23.5 (23.4-23.7)	7.1 (7-7.2)	0.6 (0.6-0.7)
	60-64	224,817	26.6 (26.4-26.8)	9.2 (9.1-9.3)	1.1 (1.1-1.2)
Women	55-59	422,519	14.4 (14.3-14.5)	3.8 (3.7-3.9)	0.3 (0.3-0.4)
	60-64	253,671	17.2 (17.1-17.4)	5.1 (5-5.2)	0.6 (0.6-0.6)

Results are presented as % (95% confidence interval).
CRC, Colorectal cancer.
*Defined as adenomas with at least 1 of the following features: ≥1 cm in size, tubulovillous or villous components, high-grade dysplasia.

SUPPLEMENTARY TABLE 2. Sex- and age-specific annual transition rates between states*

Sex	Age, y	Annual transition rates				
		No neoplasm to nonadvanced adenoma	Nonadvanced adenoma to advanced adenoma	Advanced adenoma to preclinical CRC	Preclinical CRC to clinical CRC	Preclinical CRC to CRC death
Men	50-54	3.1 (2.9-3.4)	3.3 (2.8-3.9)	2.6 (2.2-3.1)	15.5 (14.9-16.6)	1.5 (1.4-1.6)
	55-59	3.1 (2.9-3.4)	3.3 (2.8-3.9)	2.6 (2.2-3.1)	15.5 (14.9-16.6)	1.5 (1.4-1.6)
	60-64	3.1 (2.8-3.4)	3.2 (2.6-3.7)	3.1 (2.6-3.4)	16.4 (15.7-17.4)	1.6 (1.6-1.7)
	65-69	3.2 (2.9-3.4)	3.2 (2.6-3.7)	3.8 (3.4-4.3)	18.2 (17.4-19.1)	1.8 (1.7-1.9)
	70-74	2.9 (2.6-3.3)	3.3 (2.6-4.0)	5.1 (4.5-5.8)	17.6 (16.8-18.5)	1.7 (1.7-1.8)
	75-79	2.3 (1.8-2.9)	3.0 (1.9-4.2)	5.2 (4.2-6.2)	17.3 (16.3-18.3)	1.7 (1.6-1.8)
	≥80	2.3 (1.8-2.9)	3.0 (1.9-4.2)	5.2 (4.2-6.2)	15.7 (14.5-17.1)	1.6 (1.4-1.7)
Women	50-54	1.8 (1.7-2.0)	3.2 (2.6-3.8)	2.5 (2.0-2.9)	18.2 (16.8-19.7)	1.9 (1.8-2.1)
	55-59	1.8 (1.7-2.0)	3.2 (2.6-3.8)	2.5 (2.0-2.9)	18.2 (16.8-19.7)	1.9 (1.8-2.1)
	60-64	2.0 (1.8-2.2)	2.9 (2.2-3.4)	2.7 (2.2-3.2)	19.1 (17.8-20.3)	2.0 (1.9-2.1)
	65-69	2.1 (1.9-2.3)	2.9 (2.3-3.5)	3.8 (3.3-4.3)	18.7 (17.7-19.7)	2.0 (1.9-2.1)
	70-74	2.0 (1.7-2.2)	3.8 (3.0-4.6)	5.0 (4.2-5.7)	17.8 (16.8-18.9)	1.9 (1.8-2.0)
	75-79	1.6 (1.1-2.0)	3.0 (1.7-4.4)	5.6 (4.4-6.8)	16.5 (15.5-17.7)	1.7 (1.6-1.9)
	≥80	1.6 (1.1-2.0)	3.0 (1.7-4.4)	5.6 (4.4-6.8)	14.9 (13.9-16.1)	1.6 (1.4-1.7)

Results are presented as % (95% confidence interval).
CRC, Colorectal cancer.
*Estimates extracted and recalculated from supplementary references 15-17.

SUPPLEMENTARY TABLE 3. Diagnostic performance parameters

Test	Parameter	Performance			
		No neoplasm	Nonadvanced adenoma	Advanced adenoma	Preclinical CRC
Colonoscopy*	Sensitivity	–	75.0	95.0	95.0
	Specificity	100	–	–	–

Results are presented as %.
CRC, Colorectal cancer.
*Estimates based on supplementary references 13 and 14.

SUPPLEMENTARY TABLE 4. Annual CRC-specific mortality rates of CRC patients by mode of cancer detection*

	Annual CRC-specific mortality rate			
	Screening colonoscopy–detected cases		Symptom-detected cases	
Year after diagnosis	Men	Women	Men	Women
1	4.6	3.7	19.7	20.6
2	2.2	1.9	9.3	10.7
3	2.1	1.3	8.8	7.4
4	1.5	0.9	6.3	4.8
5	1.2	0.6	5.0	3.3
6	0.8	0.3	3.5	1.7
7	0.4	0.3	1.8	1.8
8	0.4	0.3	1.9	1.8
9	0.4	0.0	1.9	0.0
10	0.0	0.0	0.0	0.0

Results are presented as %.
CRC, Colorectal cancer.
*Estimates extracted from supplementary references 8 and 9.

SUPPLEMENTARY TABLE 5. Sex- and age-specific general mortality rates

Age, y	General mortality rates from age to age + 1*	
	Men	Women
50	0.4	0.2
51	0.4	0.2
52	0.5	0.3
53	0.6	0.3
54	0.6	0.3
55	0.7	0.4
56	0.7	0.4
57	0.8	0.4
58	0.9	0.4
59	1.0	0.5
60	1.0	0.5
61	1.1	0.6
62	1.2	0.6
63	1.3	0.7
64	1.4	0.7
65	1.5	0.8
66	1.7	0.9
67	1.8	0.9
68	1.9	1.0
69	2.1	1.1
70	2.2	1.2
71	2.4	1.3
72	2.7	1.4
73	3.0	1.6
74	3.3	1.8
75	3.7	2.1
76	4.1	2.4
77	4.6	2.7
78	5.2	3.1
79	5.8	3.6
80	6.5	4.1
81	7.2	4.7
82	8.0	5.4
83	8.9	6.2
84	9.9	7.1
85	11.1	8.2
86	12.3	9.3
87	13.7	10.7
88	15.3	12.1
89	16.9	13.7
90	18.7	15.4
91	20.7	17.2

SUPPLEMENTARY TABLE 5. Continued

Age, y	General mortality rates from age to age + 1*	
	Men	Women
92	22.7	19.1
93	24.8	21.1
94	27.0	23.2
95	29.1	25.3
96	31.2	27.4
97	33.2	29.6
98	35.1	31.7
99	37.2	34.0
100	39.2	36.2

Results are presented as %.

*Estimates were extracted from German population life tables for 2010 to 2012.[20]

SUPPLEMENTARY TABLE 6. Cumulative CRC deaths arising from CRC already prevalent at baseline and from newly developed CRC during follow-up in a hypothetical cohort of 100,000 nonscreened and screened participants aged 55-64 years—subgroup analysis by sex

Follow-up, y	Total CRC deaths, n (col %)	Death from prevalent CRC, n (row %)	Death from incident CRC, n (row %)
Men			
Nonscreened			
3	56 (7)	47 (84)	9 (16)
5	132 (16)	89 (67)	43 (33)
8	289 (35)	138 (48)	151 (52)
10	420 (50)	161 (38)	259 (62)
12	572 (69)	175 (31)	397 (69)
15	834 (100)	187 (22)	647 (78)
Screened			
3	36 (20)	36 (100)	0 (0)
5	54 (31)	51 (94)	3 (6)
8	75 (42)	61 (81)	14 (19)
10	95 (54)	66 (69)	29 (31)
12	121 (68)	66 (55)	55 (45)
15	177 (100)	66 (37)	111 (63)
Prevented			
3	20 (3)	11 (55)	9 (45)
5	78 (12)	38 (49)	40 (51)
8	214 (33)	77 (36)	137 (64)
10	325 (49)	95 (29)	230 (71)
12	451 (69)	109 (24)	342 (76)
15	657 (100)	121 (18)	536 (82)
Women			
Nonscreened			
3	36 (7)	31 (86)	5 (14)
5	81 (16)	55 (68)	26 (32)
8	169 (34)	80 (47)	89 (53)
10	243 (49)	90 (37)	153 (63)
12	332 (67)	97 (29)	235 (71)
15	496 (100)	102 (21)	394 (79)
Screened			
3	18 (17)	18 (100)	0 (0)
5	25 (24)	23 (92)	2 (8)
8	35 (34)	27 (77)	8 (23)
10	46 (44)	28 (61)	18 (39)
12	63 (61)	28 (44)	35 (56)
15	104 (100)	28 (27)	76 (73)
Prevented			
3	18 (5)	13 (72)	5 (28)
5	56 (14)	32 (57)	24 (43)
8	134 (34)	53 (40)	81 (60)
10	197 (50)	62 (31)	135 (69)
12	269 (69)	69 (26)	200 (74)
15	392 (100)	74 (19)	318 (81)

Results are presented as n (%).
CRC, Colorectal cancer.

SUPPLEMENTARY TABLE 7. Cumulative CRC deaths arising from CRC already prevalent at baseline and from newly developed CRC during follow-up in a hypothetical cohort of 100,000 nonscreened and screened participants aged 55-64 years—subgroup analysis by age

Follow-up, y	Total CRC deaths, n (col %)	Death from prevalent CRC, n (row %)	Death from incident CRC, n (row %)
Age 55-59 y			
Nonscreened			
3	34 (6)	28 (82)	6 (18)
5	81 (15)	53 (65)	28 (35)
8	178 (32)	81 (46)	97 (54)
10	263 (47)	94 (36)	169 (64)
12	366 (66)	103 (28)	263 (72)
15	554 (100)	111 (20)	443 (80)
Screened			
3	20 (17)	20 (100)	0 (0)
5	30 (25)	28 (93)	2 (7)
8	43 (36)	34 (79)	9 (21)
10	56 (47)	36 (64)	20 (36)
12	75 (62)	36 (48)	39 (52)
15	120 (100)	36 (30)	84 (70)
Prevented			
3	14 (3)	8 (57)	6 (43)
5	51 (12)	25 (49)	26 (51)
8	135 (31)	47 (35)	88 (65)
10	207 (48)	58 (28)	149 (72)
12	291 (67)	67 (23)	224 (77)
15	434 (100)	75 (17)	359 (83)
Age 60-64 y			
Nonscreened			
3	58 (7)	49 (84)	9 (16)
5	132 (17)	90 (68)	42 (32)
8	279 (36)	136 (49)	143 (51)
10	400 (51)	157 (39)	243 (61)
12	538 (69)	169 (31)	369 (69)
15	777 (100)	179 (23)	598 (77)
Screened			
3	34 (21)	34 (100)	0 (0)
5	49 (30)	46 (94)	3 (6)
8	68 (42)	55 (81)	13 (19)
10	85 (52)	58 (68)	27 (32)
12	109 (67)	59 (54)	50 (46)
15	162 (100)	60 (37)	102 (63)
Prevented			
3	24 (4)	15 (62)	9 (38)
5	83 (13)	44 (53)	39 (47)
8	211 (34)	81 (38)	130 (62)
10	315 (51)	99 (31)	216 (69)
12	429 (70)	110 (26)	319 (74)
15	615 (100)	119 (19)	496 (81)

Results are presented as n (%).
CRC, Colorectal cancer.