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ORIGINAL ARTICLE

Screening colonoscopy similarly prevented distal and proximal colorectal cancer: a prospective study among 55−69-year-olds

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Abstract

Objectives: We aimed to evaluate the effectiveness of screening colonoscopy in reducing incidence of distal vs. proximal colorectal cancer (CRC) in persons aged 55−69 years.

Study Design and Setting: Using observational data from a German claims database (German Pharmacoepidemiological Research Database), we emulated a target trial with two arms: Colonoscopy screening vs. no-screening at baseline. Adjusted cumulative incidence of total, distal, and proximal CRC over 11 years of follow-up was estimated in 55−69-year-olds at an average CRC risk and without colonoscopy, polypectomy, or fecal occult blood test before baseline.

Results: Overall, 307,158 persons were included (screening arm: 198,389 and control arm: 117,399). The adjusted 11-year risk of any CRC was 1.62% in the screening group and 2.38% in the no-screening group resulting in a relative risk of 0.68 (95% CI: 0.63−0.73). The relative risk was 0.67 for distal CRC (95% CI: 0.62−0.73) and 0.70 (95% CI: 0.63−0.79) for proximal CRC. The cumulative incidence curves of the groups crossed after 6.7 (distal CRC) and 5.0 years (proximal CRC).

Conclusion: Our results suggest that colonoscopy is effective in preventing distal and proximal CRC. Unlike previous studies not using a target trial approach, we found no relevant difference in the effectiveness by location.

Keywords: Screening colonoscopy; Colorectal neoplasms; Observational study; Effectiveness; Target trial emulation; Proximal

1. Introduction

Colorectal cancer (CRC) is among the most common cancers and leading causes of cancer death worldwide [1]. An intention-to-screen meta-analysis of randomized controlled trials (RCTs) on screening with flexible sigmoidoscopy showed a reduction of CRC incidence by 18% and of CRC mortality by 28% [2]. The ongoing Nordic-

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Ethics approval: In Germany, the utilization of data from health insurances for scientific research is regulated by the Code of Social Law. All involved health insurance providers and the responsible authorities approved the use of the health claims data for this study. The Ethics Committee of the University of Bremen determined that studies based on claims data are exempt from an institutional review board review.

Data transparency statement: In Germany, use of personal data is protected by the Federal Data Protection Act and particularly the use of claims data for research is regulated by the Code of Social Law. Researchers must apply for a project-specific permit from the statutory health insurance providers which then need an approval from their governing authorities. The use of the data on which this publication is based was only allowed for BIPS employees within the framework of the specified project and limited to a predefined time span. Researchers who want to access the data on which this publication is based need to ask for a new approval by the statutory health insurance providers DAK-Gesundheit (service@dak.de), die Techniker (service@tk.de), hkk Krankenkasse (info@hkk.de), and AOK Bremen/Bremerhaven (info@hb.aok.de) which upon granting approval will ask their respective authorities for approval. Please contact gepard@leibniz-bips.de for help with this process.

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What is new?

Key findings

- Using a target trial approach that avoids self-inflicted biases, we found no notable difference in effectiveness between distal and proximal colon among persons aged 55−69 years at baseline.

What this adds to what is known?

- Previous observational studies suggested a lower effectiveness of screening colonoscopy to prevent colorectal cancer in the proximal than distal colon, but these studies might be compromised by self-inflicted selection bias.

What is the implication, what should change now?

- Our findings support the use of colonoscopy for screening purposes in persons aged 55−69 years to prevent both distal and proximal colorectal cancer.

European Initiative on Colorectal Cancer study, the only RCT assessing the effectiveness of screening colonoscopy compared to no screening, will provide key insights into the overall effect of colonoscopy on CRC incidence and mortality [3]. Nonetheless, despite its large sample size, it is not powered to investigate differences in the effect as per tumor location.

Observational studies suggested a markedly lower effectiveness of screening colonoscopy in reducing CRC incidence in the proximal vs. distal part of the colorectum [4−6]. For example, a recent cohort study by Guo et al. suggested an incidence reduction of 64% for distal and 31% for proximal CRC. However, validity of existing observational studies on this topic is questionable due to possibly self-inflicted biases introduced by the analytical approach. García-Albéniz et al. demonstrated how effects of screening colonoscopy on CRC incidence are overestimated when treatment/exposure assignment is done before baseline, whereas eligibility is assessed at baseline [7]. This overestimate may differentially affect CRCs in the distal vs. proximal colon. An accurate assessment of the difference of colonoscopy in reducing incidence in the distal vs. proximal colon is important, particularly for estimating the risk-benefit ratio of screening colonoscopy compared to the less invasive screening sigmoidoscopy.

As it seems unlikely that any RCT will be powered to clarify this question, observational studies on screening colonoscopy remain important to complement existing evidence. These studies should exploit large databases with sufficiently long follow-up. Furthermore, the observational data must be analyzed in a way that facilitates causal conclusions and avoids self-inflicted biases. The emulation of target trials is well recognized in this regard and was successfully applied by García-Albéniz et al. to estimate the effectiveness of screening colonoscopy in Medicare beneficiaries aged 70 years or older [8].

Extending this approach, we aimed at evaluating the effectiveness of screening colonoscopy in reducing incidence of distal vs. proximal CRC in persons aged 55−69 years using a large German claims database.

2. Methods

We emulated target trials comparing the strategies "screening colonoscopy at baseline" vs. "no screening at baseline", both with access to further screening and diagnostic colonoscopies during follow-up. Supplement Table S1 contains a summary of our target trial protocol and its emulation.

2.1. Data source and study population

We used the German Pharmacoepidemiological Research Database (GePaRD) which comprises claims data from four statutory health insurance providers in Germany and covers about 20% of the German population [9]. We used data from 2004 to 2017. Information on utilization of screening colonoscopy, offered in Germany to persons aged 55 years or older since 2002, is distinguishable from diagnostic colonoscopy. Supplement 4 provides details on GePaRD and the identification and classification of CRCs in GePaRD.

To be eligible, persons had to be aged 55−69 years at baseline, that is, at the start of the respective trial and had to be continuously insured for at least 3 years before baseline. As detailed in Figure 2 and Supplement 1, further inclusion and exclusion criteria were applied to focus on an average-risk population, corresponding to ongoing colonoscopy trials and prior target trials on colonoscopy [2,3,8].

2.2. Treatment arms and follow-up

The first quarter of 2007 was the baseline quarter of the first trial. In this quarter, we assessed eligibility criteria for all persons. The persons meeting the eligibility criteria were assigned to the screening arm if they underwent colonoscopy screening in the baseline quarter or to the no-screening arm otherwise. As previously described [8], this procedure was repeated for all quarters from 2007 to 2011, yielding 20 successive trials. Persons could be enrolled in more than one trial (Fig. 1). In particular, our sample consisted of n_{unique} persons, some of which were included in more than one emulated trial, so that the final sample size (including nonunique persons) was $n \geq n_{unique}$. To reduce computational time, we used a 5% random sample of those in the no-screening arm (drawn at person level), which still yielded a high number of persons in this arm.

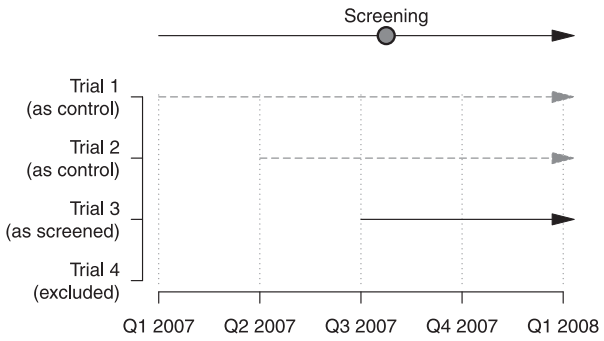

Fig. 1. Illustration of emulation of a series of target trials. The figure displays a hypothetical person who met all eligibility criteria at the start of 2007. This person was included in the emulated trial starting on January 1, 2007. One-quarter later, the same person was still eligible and was included in the emulated trial starting on April 1, 2007. The person was assigned to the control arm in both these trials, as no screening colonoscopy was observed during the respective baseline quarters. The person was still eligible for the emulated trial starting on July 1, 2007. However, the person was allocated to the screening arm as a screening colonoscopy was observed in the quarter following July 1, 2007. The person was not eligible for the trial starting on October 1, 2007 because a screening colonoscopy before this trial's baseline was observed. Data from all these trials were pooled and time since baseline (of the respective trial) was used in all time-to-event analyses.

Persons were followed up until the end of study period (end of 2017), end of continuous insurance coverage, death, or CRC diagnosis, whichever occurred first. The arms were defined as screening vs. no-screening in the respective baseline quarter regardless of screening behavior during the remaining follow-up. Persons were not censored from earlier trials once they changed strategy in subsequent trials. We chose this approach over imposing full adherence during follow-up by analysis because it avoids strong assumptions on time-varying confounding (details in Supplement 3).

2.3. Outcome and confounding variables

The outcome was the time until first diagnosis of CRC during follow-up. This was analyzed for any type of CRC and further analyzed separately for CRCs proximal and distal to the splenic flexure (no separate analysis for the category "both/unknown location" due to small numbers) (Supplement 4).

We adjusted for confounding baseline covariates using direct (e.g., age, gender, menopausal hormone therapy) or proxy information (e.g., use of preventive services) on relevant factors (Supplement 4).

2.4. Statistical analysis

We pooled persons across all emulated trials. The effect of interest was measured as contrast between cumulative incidence functions (CIF). We used pooled logistic regression to estimate a parametric version of the Aalen–Johansen estimator (details in Supplement 3). Adjustment for baseline confounding was achieved by inverse probability of treatment (i.e., propensity score) weighting. Covariate balance after weighting was examined using absolute standardized differences. Overlap of the propensity score distributions was assessed using histograms. Point wise, percentile-based 95% confidence intervals were obtained using a robust, person-level bootstrap with 250 iterations.

The above contrast of adjusted CIFs is known as total effect where death is not eliminated as competing event; in a sensitivity analysis, we also estimated the direct effect (i.e., censoring and thus hypothetically eliminating death), expecting no relevant difference between the two approaches in the age group of our study (details in Supplement 3).

Confounding variables were mostly operationalized as binary variables. Missing values for educational attainment were included as a distinct category. A negative control analysis with pancreatic cancer as outcome variable was conducted to assess residual confounding.

Supplement 3 contains a detailed description of the statistical methods. Data management and statistical analyses were done in SAS software version 9.4 (SAS Institute, North Carolina).

3. Results

Overall, 2,378,416 persons fulfilled all eligibility criteria. Of these, 198,389 persons were assigned to the screening colonoscopy arm. The random sample of controls assigned to the no-screening arm included 117,399 persons (1,247,913 nonunique persons, Fig. 2). Results reported below refer to nonunique persons and outcome events, that is, *n* always includes nonunique persons. Median follow-up was 8.3 years (interquartile range: 3.0).

About half of the study population was female with median age 60–62 years in both arms (Table 1). The proportion of persons with higher education was 20% in the screening and 15% in the control arm. The group differences in the prevalence of the further confounders were $\leq$3 percentage points, except for menopausal hormone therapy (23% among screened vs. 14% among controls) and uptake of at least one preventive service before baseline (85% among screened vs. 66% among controls). Covariate balance checks and propensity score overlap were satisfactory (Supplement Figures S4–S5).

We observed 2,540 incident CRCs in the screening and 21,973 in the control arm (Table 2). In men, the ratio of the number of distal to proximal CRCs was 2.7 in the screening (women: 1.5) and 2.5 in the control arm (women: 1.6). Figure 3 shows the adjusted CIF curves for any distal and proximal CRC. After the initial spike in cumulative CRC incidence in the screening arm (0.79%), the slope of the CIF curve remained lower than in the no-screening arm throughout follow-up. The CIF curves for any CRC of both arms crossed after 6 years. After 11 years, the adjusted risk

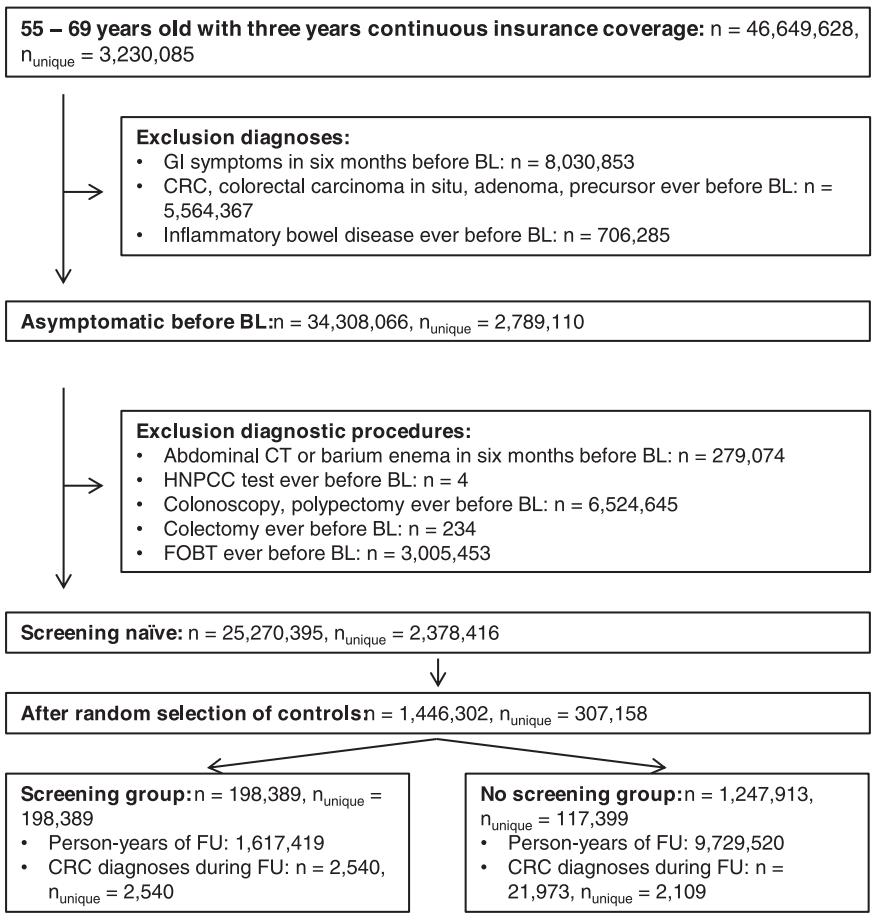

Fig. 2. Flow into study cohort of persons aged 55 to 69 years with at least 3 years continuous health insurance coverage prior to baseline (allowing for 15-day gaps in insurance coverage). GePaRD data from 2004 to 2017 were used, with emulated target trials in every calendar quarter from 2007 to 2011.

was 1.62% (1.54−1.68%) in the screening arm compared to 2.38% (2.26−2.51%) in the control arm (adjusted absolute risk difference: 0.77%, adjusted relative risk [aRR]: 0.68, Table 2). The overall pattern of the CIF curves for distal and proximal CRC was similar to any CRC. For proximal CRC, the curves crossed earlier (after 5.0 years) compared to distal CRC (after 6.7 years). After 11 years, the adjusted absolute risk difference for distal CRC was 0.47% and the aRR was 0.67. For proximal CRC, the adjusted absolute risk difference was 0.22% and the aRR was 0.70 (Table 2). Supplement 9 provides a comparison of adjusted and unadjusted CIF curves.

Supplement Table S2 provides characteristics of incident CRCs, by screening arm and site of CRC. It also shows that 4.2% of distal CRCs and 4.8% of proximal CRCs in the screening arm were included in at least one earlier emulated trial in the control group. Overall, 16.9% of controls were included in the screening arm of a later trial. Supplement 8 presents the results of additional analyses restricting to persons aged 55−64 years. Sensitivity analyses treating death as a censoring event, that is, estimating the direct instead of the total effect did not deviate substantially from the main results (Supplement 10). Supplement 6 displays the results of a negative control analysis using pancreatic cancer incidence as an outcome.

4. Discussion

This study including more than 300,000 persons aged 55−69 years is—to our knowledge—the largest observational study on the effectiveness of colonoscopy in preventing distal vs. proximal CRC. Unlike previous observational studies, our study did not show any substantial difference in effectiveness between proximal and distal CRC. The 11-year risk of CRC in the colonoscopy vs. control arm was reduced by 33% (confidence interval [CI]: 27−38%) for distal and by 30% (CI: 21−37%) for proximal CRC. The cumulative incidence curves of the screening and control arm crossed after 6.7 years follow-up for distal CRC and after 5.0 years for proximal CRC.

This is the first observational study on the effectiveness of screening colonoscopy in reducing distal vs. proximal CRC incidence using a target-trial emulation. The advantage of

Table 1. Baseline characteristics stratified by gender and treatment arm (screening colonoscopy arm vs. control arm). All numbers refer to nonunique persons

	Male				Female				Total			
	Screening (*N* = 99,101)		No screening (*N* = 583,861)		Screening (*N* = 99,288)		No screening (*N* = 664,052)		Screening (*N* = 198,389)		No screening (*N* = 1,247,913)	
Characteristic	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Age												
Median (Q1–Q3)	61	57–65	61	58–66	60	57–65	62	58–66	61	57–65	62	58–66
Mean (SD)	61.3	4.50	61.6	4.47	60.9	4.55	61.9	4.51	61.1	4.53	61.8	4.49
Education												
No degree/unknown	51,793	52.3	343,765	58.9	66,309	66.8	495,934	74.7	118,102	59.5	839,699	67.3
Basic or secondary degree	19,876	20.1	117,450	20.1	20,391	20.5	109,463	16.5	40,267	20.3	226,913	18.2
Higher education	27,432	27.7	122,646	21.0	12,588	12.7	58,655	8.8	40,020	20.2	181,301	14.5
Region												
East Germany	21,926	22.1	114,590	19.6	22,423	22.6	131,645	19.8	44,349	22.2	246,235	19.7
West Germany	77.175	77.9	469,271	80.4	76,865	77.4	532,407	80.2	154,040	77.6	1,001,678	80.3
Codes indicating obesity[a]	12,178	12.3	71,137	12.2	13,649	13.7	94,443	14.2	25,827	13.0	165,580	13.3
Diabetes type 2	14,762	14.9	98,120	16.8	8,689	8.8	75,849	11.4	23,451	11.8	173,969	13.9
Codes indicating a family history of CRC[a]	91	0.1	145	<0.05	409	0.4	851	0.1	500	0.3	996	0.1
Menopausal hormone therapy	N.A.		N.A.		22,759	22.9	95,439	14.4	N.A.		N.A.	
Use of acetylsalicylic acid	4,743	4.8	31,008	5.3	1,527	1.5	13,164	2.0	6,270	3.2	44,172	3.5
Codes for alcohol abuse[a]	2,911	2.9	27,212	4.7	1,485	1.5	14,477	2.2	4,396	2.2	41,689	3.3
Codes for heavy smoking[a]	5,487	5.5	42,871	7.3	4,742	4.8	35,438	5.3	10,229	5.2	78,309	6.3
Use of other preventive services during 3 years before baseline[b]												
None	23,109	23.3	258,419	44.3	5,888	5.9	162,228	24.4	28,997	14.6	420,647	33.7
One or more	75,992	76.7	325,442	55.7	93,400	94.1	501,824	75.6	169,392	85.4	827,266	66.3

Q1–Q3, interquartile range; SD, standard deviation.

[a] Only coded if there is a reimbursement of treatment or services due to these conditions, not coded for all persons with the respective condition.

[b] Used as a proxy variable for preventive behavior.

this approach lies in avoiding time-related and other biases that can be introduced by a poor study design, also called self-inflicted biases because they are avoidable [10]. Previous observational studies addressing this research question may have suffered from such biases. For example, a study by Guo et al. suggesting a 64% risk reduction for distal CRC but only a 31% risk reduction for proximal CRC inquired at baseline about past colonoscopies and—based on this information—assigned persons as exposed or unexposed to colonoscopy. Persons reporting at baseline CRC in the past were excluded [6]. Given that colonoscopy is typically used for CRC diagnosis, this exclusion criterion mainly affects the colonoscopy group, leading to an imbalance regarding prevalent CRCs yet undetected at baseline (i.e., less in the colonoscopy group). As a result, the cumulative CRC incidence in the colonoscopy group during follow-up is artificially lowered, leading to an overestimate of the preventive effect of colonoscopy as described by Garcia–Albeniz et al [7]. As the vast majority of CRCs diagnosed at an age when persons are typically included into screening studies are in the distal colon [11], whereas proximal CRC is more common at an older age, it seems plausible that the overestimation mainly concerned the preventive effect for distal rather than proximal CRC. Accordingly, also the difference in the effectiveness of colonoscopy by location was overestimated. It seems likely that the differential age distribution of distal and proximal CRC also introduced considerable bias in case-control studies and other types of cohort studies suggesting a substantially higher effectiveness of colonoscopy in the incidence or mortality of distal vs. proximal CRC [4,5,12].

In the interpretation of prior studies suggesting a substantially lower effectiveness of colonoscopy for proximal vs. distal CRC, a higher miss rate of colonoscopy or special biological properties of precursor lesions in the proximal colon were assumed to explain the findings. Particularly, sessile serrated lesions play a major role in this reasoning as they primarily occur in the proximal colon. They act as precursors to CRC developing via the serrated pathway characterized by the CpG methylator phenotype and microsatellite instability and are assumed to account for 25% of sporadic CRCs [13]. Some studies reported that the

Table 2. Number of incident CRC and adjusted effect estimates at 11 years of follow-up, stratified by site

Site	Gender	# Nonunique cases		NNS	11-year absolute risk difference		11-year relative risk	
		Screening (N = 198,389)	No screening (N = 1,247,913)		%	[95% CI[a]]		[95% CI[a]]
Distal	Male	1,046	8,211					
	Female	521	5,004					
	Total	1,567	13,215	213	0.47	[0.35; 0.57]	0.67	[0.62; 0.73]
Proximal	Male	385	3,244					
	Female	350	3,215					
	Total	735	6,459	463	0.22	[0.14; 0.29]	0.70	[0.63; 0.79]
Both distal and proximal or unknown site	Male	133	1,153					
	Female	105	1,146					
	Total	238	2,299					
Total	Male	1,564	12,608					
	Female	976	9,365					
	Total	2,540	21,973	131	0.77	[0.62; 0.91]	0.68	[0.63; 0.73]

Abbreviation: NNS, number needed to screen, calculated as the inverse of the absolute risk reduction.

No effect estimates are given for both distal and proximal or unknown site and for gender-specific incidence, as there were too few cases for reliable estimation.

[a] Person-level percentile bootstrap confidence intervals based on 250 bootstrap samples.

detection rate for sessile serrated lesions varied between endoscopists and correlated with their adenoma detection rate [14,15]. In the real-world setting, variation in the detection of sessile serrated lesions might thus be relevant. Our findings, however, do not suggest a strong impact of this variability regarding potential differences in the effectiveness of colonoscopy by site as proposed previously. Colonoscopies in our study were performed in 2007 or later, that is, at a time of heightened attention toward the quality of colonoscopy but we think it is unlikely that this explains the large discrepancy with the results of prior studies on site-specific effectiveness of colonoscopy.

Sessile serrated lesions have also been associated with a higher risk of metachronous neoplasia compared to conventional adenomas [16–18]. Whether this could lead to lower effectiveness of colonoscopy in the proximal colon also depends on adherence to surveillance colonoscopy. We previously showed that among persons with prior snare polypectomy in Germany about 60% underwent at least one repeat colonoscopy within 5 years and about 80% within 10 years

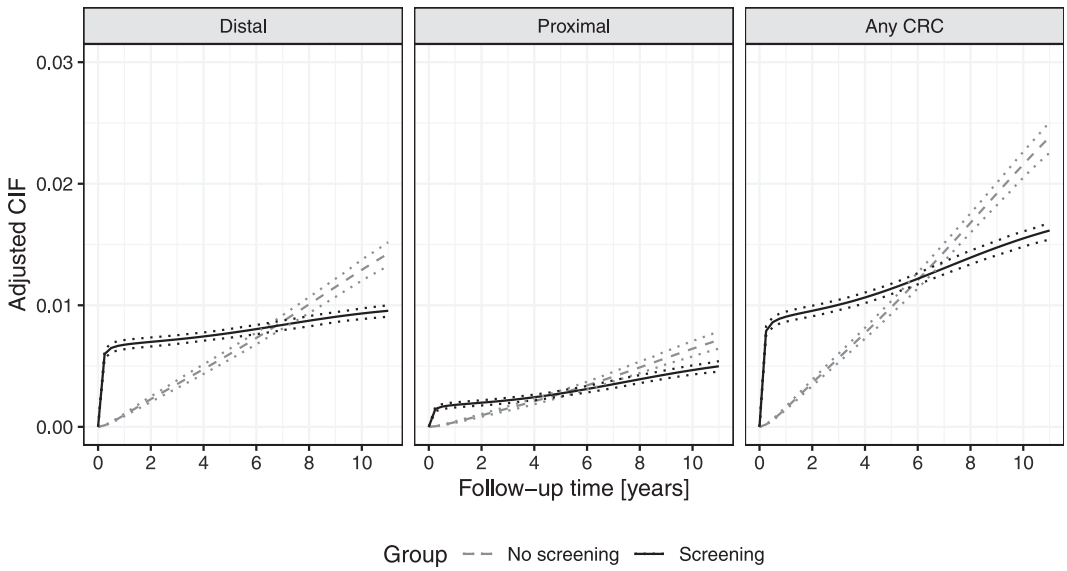

Fig. 3. Adjusted cumulative incidence functions showing 11 years of follow-up. Analyses were done by site of incident CRC. No separate analyses were done for incident CRCs of unknown location and simultaneous distal and proximal incident CRCs because too few events were observed.

[19]. The effectiveness of screening colonoscopy estimated in our study includes the potential effect attributable to these surveillance colonoscopies. Effectiveness might have been higher in case of perfect adherence to surveillance or lower in case of a poorer uptake.

In our study, the curves for proximal CRC crossed about 2 years earlier than for distal CRC. This may suggest that the time between transition from precancerous lesions or preclinical CRC to clinical CRC is, on average, shorter for proximal than for distal CRC. In view of the distinct molecular features of distal and proximal CRC [20], differences in the natural history by location seem plausible and could further be elucidated by the promising field of molecular pathological epidemiology [21]. Although direct evidence on adenoma dwell and sojourn time is hardly obtainable, analyses showing poorer survival for proximal than for distal CRC [22] and case reports on fast-growing sessile serrated lesions indirectly support a high progressive potential of neoplasia in the proximal colon [23,24]. Of note, our findings refer to persons aged 55−69 years at screening colonoscopy. Caution is needed when extrapolating the results to older ages, also because the natural history likely differs by age and the importance of the competing event death increases with age.

When comparing our results for distal CRC to RCT findings on screening with flexible sigmoidoscopy [2,25], one should note that no exact agreement was expected for several reasons. First, most RCTs included persons aged 55−64 years at baseline [2,26], whereas we included persons aged 55−69 years. Second, the intention-to-screen effect reported in these trials depends on adherence at baseline (varying 60−80%) and is thus not directly comparable to the effect estimate in our study where all persons in the screening arm underwent colonoscopy at baseline. Also, the per-protocol effects reported by RCTs are not directly comparable to our results, because in our study, persons in the control arm were not censored if they underwent screening colonoscopy later. This contamination equally affected distal and proximal CRC, so there was no differential effect (Supplement Table S2). As our research question focused on the difference in the effectiveness by location, we favored this approach over censoring nonscreened persons who were screened during follow-up, as it avoided further assumptions and we preferred the more conservative method. Had our aim been to assess the overall efficacy of screening colonoscopy, corresponding to the per-protocol effect of an RCT, this would have been inadequate, so we would have chosen another approach. Third, the effect of screening also depends on adherence to recommended surveillance intervals, which may be lower in a real-world setting compared to trials. In Germany, at least 40% of persons with polypectomy have been estimated to not adhere to recommended surveillance intervals [19]. Furthermore, the effect of screening depends on the background prevalence of diagnostic colonoscopy. In Germany, the 10-year prevalence of diagnostic colonoscopy among persons aged 55−69 years was about 22−26% in 2017 [27], that is, a relevant proportion of persons in the control arm may have had a diagnostic colonoscopy during follow-up. This concerns the control group in general, so it is not expected to bias the comparison of site-specific effectiveness of screening colonoscopy. Also, fecal occult blood testing may have occurred in the control arm during follow-up. However, it is not expected that the recommended fecal occult blood test during the study period—the guaiac test—had a relevant impact on CRC incidence, since RCT evidence on this test mainly showed an effect on CRC mortality rather than on incidence [28].

In the interpretation of our results, some limitations must be considered. First, although we used as much information as possible to control for confounding, claims data are suboptimal in this regard, especially with respect to lifestyle factors. As proxy information we mainly used conditions like obesity or diabetes and the use of other preventive services. However, as discussed by Garcia−Albéniz et al. [8] it is unlikely that residual confounding plays a major role here as adjustment for potential confounders had little impact on previous observational studies [29,30]. Furthermore, CRC incidence in the control group and in noncompliers was similar in RCTs [25,26,31]. There was also no indication of any noteworthy residual confounding in a negative control analysis (Supplement 6). Second, there are specific codes for screening colonoscopy in our database and we additionally used several exclusion criteria to focus on an asymptomatic average-risk population, that is, the target population of screening. Nonetheless, it is possible that symptoms were not coded in the database. We assume this did not play a major role in our study as the CRC detection rate observed in the screening arm at baseline is plausible and comparable to that reported in screening trials (0.6% in an analysis restricted to 55−64-year-olds compared to 0.5% in the Nordic-European Initiative on Colorectal Cancer trial including 55−64-year-olds).

In conclusion, the results of our observational study using an emulated target-trial approach suggest that colonoscopy is effective in preventing distal and proximal CRC. Unlike in previous studies not using a target-trial approach, there was no relevant difference in the effectiveness by location. The distinct temporal patterns of the cumulative incidence curves support hypotheses regarding differences in the natural history of distal vs. proximal CRC.

Author contributions

M.B.: Conceptualization, data curation, formal analysis, investigation, methodology, software, visualization, writing−original draft, and writing−review and editing; S.S.: Conceptualization, investigation, and writing−review and editing; B.K.: Conceptualization, investigation, and writing−review and editing; C.S.: Investigation and writing−review and editing; V.D.: Conceptualization,

investigation, methodology, supervision, and writing−review and editing; U.H.: Conceptualization, funding acquisition, investigation, methodology, project administration, resources, supervision, writing−original draft, and writing−review and editing.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2022.05.024.

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