ORIGINAL ARTICLE

Colorectal cancer prevention by a CLEAR principles–based colonoscopy protocol: an observational study

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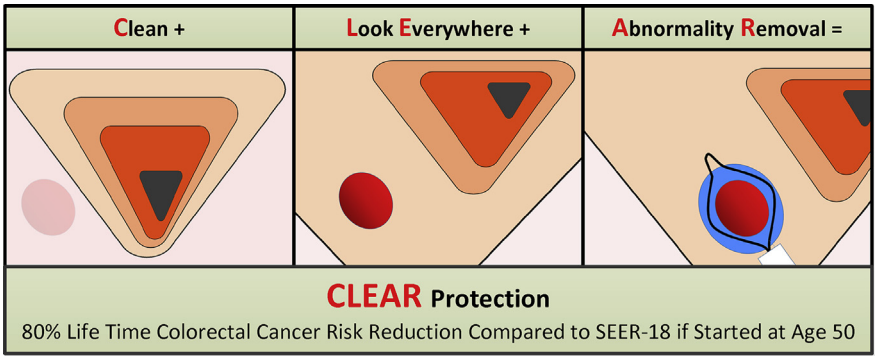
GRAPHICAL ABSTRACT



Background and Aims: Colorectal cancer (CRC) prevention by colonoscopy has been lower than expected. We studied CRC prevention outcomes of a colonoscopy protocol based on Clean the colon, Look Everywhere, and complete Abnormality Removal (CLEAR) principles.

Methods: This observational follow-up study studied patients provided screening colonoscopy at a free-standing private ambulatory surgery center in South Carolina by 80 endoscopists from October 2001 to December 2014, followed through December 2015. The colonoscopy protocol, optimized for polyp clearance, featured in-person bowel preparation instructions reinforced by phone, polyp search and removal throughout insertion and gradual withdrawal with circumferential tip movements, and a team approach using all personnel present to maximize polyp detection, patient safety, and clear-margin polypectomy including requesting repeat inspection or additional tissue removal. Outcome measures were postscreening lifetime CRC risk relative to Surveillance Epidemiology and End Results (SEER)-18 and interval cancer rate (postcolonoscopy CRCs among cancer-free patients at screening).

Results: Of 25,862 patients (mean age, 58.1 years; 52% black; 205,522 person-years of observation), 159 had CRC at screening and 67 patients developed interval CRC. The interval CRC rate was 3.34 per 10,000 person-years of observation, 5.79 and 2.24 among patients with and without adenomas, respectively. The rate was similar among older patients (mean age 68.5 years at screening) and with prolonged follow-up. Postscreening lifetime CRC risk was 1.6% (bootstrap 95% confidence interval, 1.3%-1.8%) versus 4.7% in SEER-18, 67% lower. Subgroups with mean screening ages of 50 and 68.5 years showed risk reductions of 80% and 72%, respectively. The adverse event rate was less than usually reported rates: perforation 2.6 per 10,000, bleeding with hospitalization 2.4 per 10,000, and no deaths.

Conclusions: A colonoscopy protocol optimized for polyp clearance prevented 67% of CRC compared with a SEER-18 population given ongoing population screening. (Gastrointest Endosc 2019;■:1-12.)

(footnotes appear on last page of article)

Colorectal cancer (CRC) affects about 4% to 6% of the Western population.[1,2] In theory, most CRCs can be prevented by screening with colonoscopy to remove precancerous polyps. Experts agree that colonoscopy is the most-accurate screening method to prevent CRC. However, community-based clinical trials have reported modest CRC reductions compared with a 76% prevention rate documented in the National Polyp Study.[3-6] In 2013, 58% of age-eligible Americans had completed colonoscopy screening, yet CRC deaths (~51,000) and lifetime CRC risk (~4.3%) remain almost similar to 1997 rates.[1,7] Simulation modeling studies project optimistic population-wide reductions in the future based, however, on certain assumptions that are contradicted by empirical studies of community-based, usual-practice colonoscopy.[2,8-10]

Clinical trials have relied on usual-practice colonoscopy provided by community-based physicians without specifying a colonoscopy protocol and reported outcomes similar to population screening programs, at 26% to 43% prevention.[11,12] A key weakness of most trials is viewing colonoscopy as a commodity, a binary treatment, either "done" or "not done" within the trial protocol timeline. The "treatment" (colonoscopy procedure) is not protocolized to ensure the goal of colonoscopy, complete polyp clearance, which requires compliance with the CLEAR criteria: (1) Clean the colon (adequate bowel preparation), (2) Look Everywhere (maximum adenoma detection), and (3) Abnormality Removal (complete polypectomy of all detected polyps).[13] Thus, usual-practice "colonoscopy done" does not translate to complete polyp clearance, the true test of "done." The current quality indicators of withdrawal time and adenoma detection rate (ADR) are imperfect measures of colonoscopy quality and do not reflect completeness of polyp clearance.

The most challenging and weakest links for achieving polyp clearance are endoscopist-dependent variations in the ADR and completeness of polypectomy.[14-19] ADR is adversely affected by time-constrained colonoscopy.[20] Tandem colonoscopies show that 22% to 27% of polyps are missed.[14,15] Further, to prevent CRC, all abnormal tissue must be completely removed (akin to R0 tumor resection). Incomplete polypectomy (R1 resection) leaves behind residual neoplastic tissue that may evolve into interval cancer. Polyp clearance requires time and optimum technique, described in the United Kingdom's Joint Advisory Group (JAG) criteria applied during direct observation of procedure skills (DOPS) and direct observation of polypectomy skills (DOPyS) for credentialing National Health Service physicians for colonoscopy.[16,21-24]

We present here a colonoscopy protocol and the long-term outcomes of an endoscopy group who—preceding publication of CLEAR principles and the JAG guidelines—created and consistently implemented across 80 endoscopists a standardized colonoscopy protocol optimized to overcome all weak links in the CLEAR chain of events. Similar to the JAG, the study center credentialed all endoscopists based on direct observation of procedure and polypectomy skills as well as ADR.[16,21,22] We present their screening cohort's interval CRC rates and cumulative lifetime CRC risk over the remaining life expectancy compared with the prevailing risk of the Surveillance, Epidemiology, and End Results (SEER) program population given ongoing population screening activities.

METHODS

Study design and data sources

An independent observational study was conducted to assess CRC incidence prevention after screening colonoscopies performed by 80 endoscopists at a licensed ambulatory surgery center for endoscopy in South Carolina from October 2001 to December 2014. Patient data were linked to the South Carolina Central Cancer Registry's (SCCCR) incidence and mortality databases from January 1, 1996 to December 31, 2015 using patient identifying variables (Appendix 1, Note 1, available online at www.giejournal.org).[25] The study was approved by the University of South Carolina Institutional Review Board and the South Carolina Department of Health and Environmental Control Data Oversight Committee.

The SCCCR, a state population-based registry, was gold certified by the North American Association of Central Cancer Registries in most study years (criteria: >95% cancer data complete within 2 years, ~100% error-free data, <3% of cancers based on death certificates) and silver rated in 4 years (>90% data completeness).[26] The Registry's final data completeness was >96.5% (99.7% in 2012), achieved by continued addition of new data indefinitely, based on cancer care/cancer death abstracts on South Carolina residents received from 43 states under reciprocal data exchange agreements.

Colonoscopy protocol

All endoscopists complied with the colonoscopy protocol featuring (1) bowel preparation with phospho-soda until 2009 and magnesium citrate-bisacodyl since 2007, both split doses, and, importantly, bowel preparation instructions explained in person and reinforced by a phone call when preparation was due to begin; (2) midazolam-meperidine or propofol sedation; (3) a team approach using all personnel present to achieve efficient cecal intubation with minimal endoscope shaft insertion, optimum patient/endoscope/snare positioning, maximal polyp detection and R0 resection with clear margins, and minimal adverse events including bleeding and perforation; (4) maximizing mucosal exposure by gradual shaft withdrawal while cleaning the mucosa and use of circumferential tip movements; (5) polyp search and polypectomy during both insertion and withdrawal except for flat polyps larger than 20 mm (removed only during withdrawal); (6) all team members observing the monitor and requesting repeat inspection or additional tissue removal as needed

(the Jidoka principle); (7) hot snare/hot biopsy forceps, as appropriate for polyp size, used for all adenomatous-appearing polyps, all right-sided colon polyps, and hyperplastic-appearing left-sided colon polyps ≥5 mm (cold snare for anticoagulated patients and diminutive hyperplastic-appearing polyps in the rectum); (8) submucosal lift used for flat/depressed polyps and tattooing polyps >20 mm, unsure of complete removal or appearance suggesting high-grade dysplasia; (9) retroflexion in the rectum during insertion; (10) real-time documentation of procedure and polyp details by note-taker assistant and photo-documentation of cecal landmarks, polyps, polypectomy sites, and rectal retroflexion field; (11) an expert in difficult polyp removal available onsite if needed; and (12) quarterly in-house quality reviews and identification-protected display of providers' cumulative ADRs and procedure time averages on a bulletin board in the physicians' breakroom to encourage self-driven benchmarking.[16,27-34]

All polyps were removed except ≤2-mm hyperplastic polyps in the rectum (identified by narrow-band imaging) and invasive, large, or vascular polyps (referred for removal at a hospital). All polyps were sent for histopathology examination, except clusters of similar polyps <2 mm or a carpet-like patch (sample collected and the remaining destroyed). Nonvillous-appearing polyps from a colonic segment were placed in a single container.[25] Surveillance colonoscopy schedules complied with prevailing professional consensus/U.S. Multi-Society Task Force guidelines.[28] Patient compliance was not systematically monitored; however, the initial letter conveying the histopathology results mentioned the due date of next colonoscopy. When surveillance became due (tracked by an informal chart marking system), a letter was sent. No additional follow-up was done to pursue compliance.

Patients and data

The study population consisted of average-risk patients from primary care practices provided screening colonoscopy from October 2001 to December 2014. By policy the center does not accept patients with known bowel pathology or CRC-predisposing genetic syndromes. Accuracy of procedure and polyp data was verified by a 2% sample chart review (error rate, .6%). Missing/discrepant data were extracted from patient records.[28] Study exclusion criteria were age below 40 or over 89 years, other bowel pathology, and prior colon resection or CRC diagnosis.[35-37] Patients with CRC at screening (SCCCR diagnosis date within 6 months of colonoscopy) were included in the lifetime risk analyses. Interval CRC was SCCCR-documented incident CRC or CRC death more than 6 months after colonoscopy. CRC family history, smoking, and lifestyle data were not available.

Measures of CRC prevention

Two measures of CRC prevention were used: (1) interval CRC rate per 10,000 person-years of observation (PYO) compared with the National Polyp Study and community-based colonoscopy studies using χ^2 tests and (2) postscreening lifetime CRC risk ratio relative to the SEER-18 population. Patient PYO were calculated from the colonoscopy date up to death, CRC diagnosis, or end of study period (December 31, 2015), whichever occurred first. Postscreening lifetime CRC risk ratio relative to the SEER-18 population (usual care, comparison group) was calculated using published age-conditional SEER-18 lifetime risk, the cumulative probability of incident CRC after a given age over the remaining life expectancy estimated from historic incidence and mortality data.[38] For the main analysis, we estimated the SEER lifetime risk at age 58 (cohort mean age at screening) by prorating SEER lifetime risks at age 50 and 60 in 2007-2009 (cohort accrual mid-point, 2008).[3,38,39] This was the cohort's expected CRC risk. SEER-18 comparison was deemed appropriate because the South Carolina CRC incidence has closely tracked SEER-18 rates (122.8/100,000 population aged over 50 in 2009-2013 vs 119.3/100,000 in SEER-18 in 2016, the difference consistent with the annual rate of CRC decline).[1]

Postscreening lifetime CRC risk

The cohort's postscreening lifetime CRC risk was calculated based on follow-up CRCs, the sum of all CRCs found at screening, and interval CRCs. This assumes that CRCs detected at screening are equivalent to clinically silent, undiagnosed CRCs in the SEER "CRC-free" population (dwell-time CRC).[37] Postscreening lifetime CRC risk was the sum of the follow-up CRC rate and projected CRC risk during post–follow-up life expectancy. Postscreening life expectancy was life expectancy at the cohort mean age at screening, sourced from U.S. life tables.[40] Follow-up CRC rate was follow-up CRCs converted into a per-person, per-year rate multiplied by mean years of follow-up per patient. Projected CRC risk during post–follow-up life expectancy was the observed annual interval cancer rate during follow-up multiplied by years of post–follow-up life expectancy. The lifetime risk ratio was the calculated cohort lifetime risk divided by the SEER lifetime risk at the corresponding age. Its complement is the cohort's risk reduction relative to SEER-18. Detailed calculations are shown in Appendix 1, Exhibit 1. To assess accuracy of the lifetime CRC risk and interval cancer rate estimates, we used bootstrapping (1000 random samples with replacement) to estimate 95% confidence intervals (CIs).

Sensitivity analyses were done as follows: (1) lifetime CRC prevention estimated after adjustment for racial composition of the cohort (the expected SEER-18 lifetime risk of the cohort weighted to reflect cohort racial composition) and (2) calculating the cohort lifetime risk after prorating the cohort baseline CRC rate to SEER using the SEER annual incidence rate (instead of including all CRCs found at screening). The resulting annual rate of follow-up CRC was applied to all life expectancy years at age 58.

Subgroup analyses were conducted to assess the risk reduction among patients screened around the U.S.

Preventive Services Taskforce–recommended age (up to 55 years, mean 50 years) and compare it with the full cohort using the χ^2 test and to detect potential attrition of prevention at advanced age or over prolonged follow-up. Nationally, CRC incidence among the 65+ age group is 3 times the rate of the 50- to 65-year age group.[41]

To test attrition of CRC prevention with time since screening and at advanced ages, we compared the full cohort interval CRC rate and lifetime risk ratio with patients screened between 2001 and 2008 who had longer follow-up using χ^2 tests, plotted the 2 groups trends of calendar year-wise interval CRC rates, and plotted the trends among patients aged 70 to 90 years at the end of follow-up. These analyses also verify the validity of assuming stable interval CRC rates over subjects' remaining life expectancy.

Control cancer

A control cancer, primary brain cancer, was used to verify the completeness of follow-up CRC data. Brain cancer incidence and mortality has been stable for decades, is unrelated to lifestyle or CRC risk, and is unlikely to be misclassified in death certificates. Expected brain cancer deaths were estimated using South Carolina mortality rates within age–sex–race strata during 2001 to 2015 (Appendix 1, Note 2). The standardized mortality ratio was observed divided by expected deaths. Statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA), except for bootstrapping performed in R (R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org).

RESULTS

Study population

Figure 1 presents the exclusion criteria and patients studied in the main and subgroup analyses. Of 25,862 study-eligible patients, 159 had CRC at screening, a rate of 611 per 100,000, 5 times the South Carolina incidence (122.8/100,000 population aged over 50 years).[1] Table 1 presents the characteristics of 25,008 CRC-free patients at screening: 54% women, 52% black, mean age 58.1 years (standard deviation, 9.2), cecum intubation rate 97.6%, median total procedure time 22 minutes (interquartile range, 25th and 75th percentiles, 16-30), and median withdrawal time 10 minutes (interquartile range, 25th and 75th percentiles, 7-14). Polypectomy occurred when a polyp was found, including during insertion, except for flat polyps larger than 20 mm. Mean ADR was 30.1%. ADR range for endoscopists with at least 200 procedures was 14.1% to 42.3%; the range was 24.2% to 42.3% after excluding 2 outliers who declined to follow protocol and left the practice. Advanced adenomas or ≥3 nonadvanced adenomas were present in 8.3%, and 67 patients developed interval cancer.

Satisfactory bowel preparation was achieved for 93.7% of procedures; among patients with unsatisfactory preparation, 90.7% complete colonoscopy was achieved by lavage, and the remaining were subjected to make-up colonoscopy (data not shown). ADR among patients with satisfactory bowel preparation was 31.4% versus 27.9% in procedures completed despite unsatisfactory preparation. Adverse event rates were perforation, 2.6 per 10,000, bleeding, 2.4 per 10,000, aspiration, 1.2 per 10,000, and no deaths.

Among total patients, 11,188 patients (43.3%) were aged ≤55 years at screening (mean age, 50.0 years) and 8253 patients (33%) aged 70 to 90 years at the end of follow-up (mean screening age, 68.5 years), who contributed 88,793 and 77,404 PYO, respectively (Supplementary Table 1, available online at www.giejournal.org). Additional colonoscopies (surveillance or rescreening) during the study period were completed by 31.3% of patients, amounting to an average of 1 colonoscopy per patient every 5.6 years including the screening procedure (1 every 6.6 years for 2001-2008 screened patients).

Interval CRC rate

The interval cancer rate was 3.34 per 10,000 PYO (bootstrap 95% CI, 2.54-4.13), being 5.79 and 2.24 among the adenoma and no-adenoma groups, respectively (Table 2). Similar interval cancer rates were observed among the subgroup aged 70 to 90 at the end of follow-up (3.10/1000 PYO, $P = .76$) and the 2001 to 2008 screened subgroup (3.46/10,000 PYO, $P = .87$). Patients aged ≤55 years at screening (mean age, 50.0 years) had a significantly lower rate (1.81/10,000 PYO, $P = .03$). Rates were similar for right-sided versus left-sided colon cancers ($P = .35$).

Control cancer standardized mortality ratio

The standardized mortality ratio for brain cancer was 1.0 (19 deaths observed vs 19.0 expected, $P = .42$).

Postscreening lifetime CRC risk relative to SEER-18

Table 3 shows that the study cohort had a postscreening lifetime CRC risk of 1.57% (bootstrap 95% CI, 1.3%-1.8%) after counting all 159 CRCs at screening as follow-up CRCs. SEER-18 lifetime risk at age 58 was 4.71%, cohort CRC risk ratio .33, and CRC reduction 66.7% (95% CI, 61.8%-71.9%). The subgroup aged ≤55 years at screening showed substantially greater risk reduction than the full cohort: 79.5% less CRC than the corresponding SEER-18 population. Patients aged 70 to 90 years at the end of follow-up (mean age at screening, 68.5 years) experienced CRC reduction similar to the full cohort, 71.7% (risk calculations and P values shown in Appendix 1, Exhibit 1). Sensitivity analyses showed a race-adjusted lifetime CRC reduction of 67.2%. The rate was 69.2% when the cohort baseline CRCs were standardized to the SEER incidence rate.

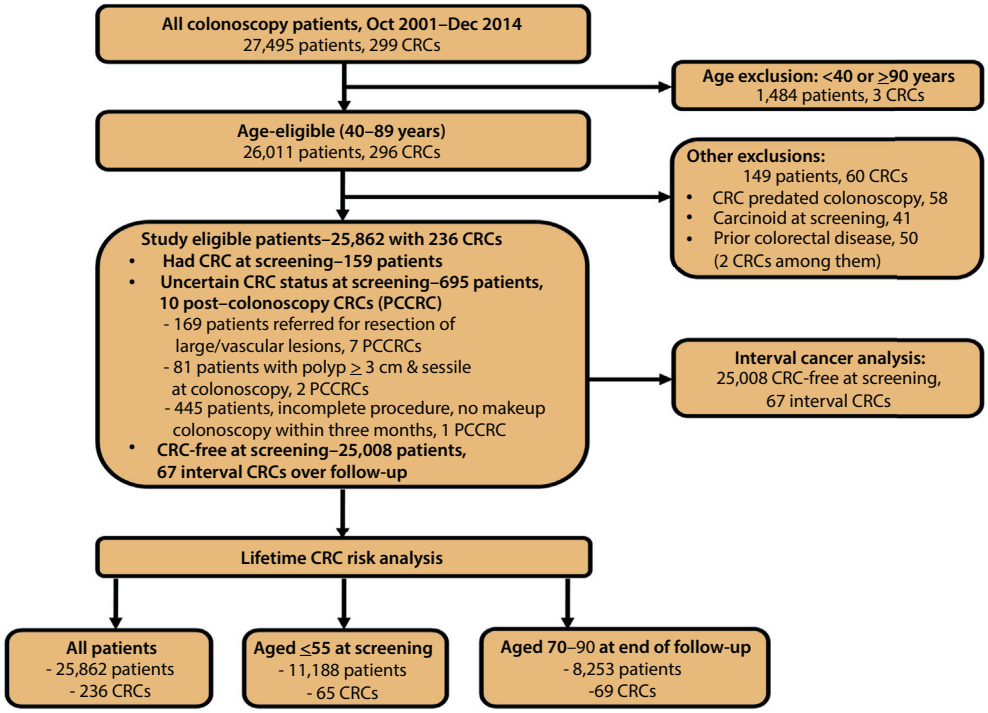


Figure 1. Study inclusion criteria and patient selection for each analysis. *CRC*, Colorectal cancer.

Figure 2 presents calendar year-wise interval CRC rate per 100 person-years and the CRC rate at screening per 100 screened subjects. Figure 2A (full cohort) and 2B (2001-2008 screened cohort) show stable interval CRC rates over follow-up (and, by implication, stable CRC prevention effect). Figure 2C and D presents patients aged ≤55 years at screening and 70 to 90 years at the end of follow-up, respectively, and illustrates stable CRC prevention effects over prolonged follow-up regardless of age. The data also show homogeneity of subjects' baseline CRC rates over the long study period.

Interval cancer rate compared with documented studies

Table 4 shows that the cohort's interval CRC rate among the adenoma subgroup was similar to the National Polyp Study rate of 5.9 per 10,000, a study that used protocolized colonoscopy personally performed by the study investigators ($P = .95$).[3,36] All other documented studies of community-based, usual-practice colonoscopy services showed much higher interval CRC rates than the study cohort (all $P < .001$). The Polyp Prevention Trial and Kaiser Permanente 2014 studies (cohort age comparable with the study cohort) showed 3 times and 2 times the study cohort rate, respectively. The Prostate Lung Colorectal and Ovarian Cancer study cohort, 10 years older, had 3 times the study cohort rate.[4-6,11,35] The Kaiser Permanente 2019 study of adenoma-free patients at screening showed twice the study cohort rate ($P < .001$) with half the follow-up duration of the study cohort.[42] Supplementary Table 2 (available online at www.giejournal.org) presents the exclusion criteria applied by each study.

DISCUSSION

We report here that a group of endoscopists complying with a rigorous colonoscopy protocol reduced the post-screening lifetime CRC risk by 67% compared with the SEER-18 population given its prevailing screening activity with usual-practice colonoscopy. This is the estimated prevention after counting all CRCs detected at screening as follow-up CRCs. To clarify in simple terms, cohort patients provided screening colonoscopy have one-third the lifetime risk of getting CRC compared with the SEER-18 population, which already had a colonoscopy screening rate of 48% in 2008, the SEER reference year (Table 3).[43] Accuracy of the lifetime CRC risk estimates is supported by narrow 95% bootstrap CIs. Bootstrapping generates the sampling distribution of lifetime risk estimates for the bootstrapped random samples, and the 95% CI shows the range within which the true lifetime risk lies. The narrow CIs, both for lifetime risk and interval cancer rate, validate accuracy of the calculated rates. The cohort's low interval cancer rate is validated by comparisons with published cohorts of usual-practice colonoscopy, which

TABLE 1. Demographic characteristics of CRC-free patients at screening by adenoma status

Characteristics	CRC-free patients at screening	Patients without adenoma	Patients with adenoma
No. of CRC-free patients at screening†	25,008	17,478 (69.9)	7530 (30.1)
Age*			
40-49 years	3794 (15.2)	2930 (77.2)	864 (22.8)
50–59 years	11,805 (47.2)	8599 (72.8)	3206 (27.2)
60–69 years	6449 (25.8)	4196 (65.1)	2253 (34.9)
70–89 years	2960 (11.8)	1753 (59.2)	1207 (40.8)
Mean (standard deviation)	58.1 (9.2)	57.3 (9.0)	59.9 (9.4)
Sex*			
Male	11,422 (45.7)	7402 (64.8)	4020 (35.2)
Female	13,482 (53.9)	9988 (74.1)	3494 (25.9)
Missing	104 (.4)	88 (84.6)	16 (15.4)
Race*			
White	10,937 (43.7)	7325 (67.0)	3612 (33.0)
Black	12,961 (51.9)	9343 (72.1)	3618 (27.9)
Other	984 (3.9)	708 (72.0)	276 (28.0)
Missing	126 (.5)	102 (81.0)	24 (19.0)
Had adenoma*			
ADR	7530 (30.1)	—	7530
Had advanced adenoma*	1436 (5.7)	—	1436
≥3 nonadvanced adenomas*	639 (2.6)	—	639
Cecum intubation rate, %	97.6	97.6	97.5
Procedures			
First screening only	17,189 (68.7)	13,363 (77.7)	3826 (22.3)
+1 additional procedure	5352 (21.4)	3209 (60.0)	2143 (40.0)
+2 or more procedures	2,467 (9.9)	906 (36.7)	1561 (63.3)
Median total procedure time,† min (25th, 75th percentile)	22.0 (16, 30)	18.0 (14, 25)	24.0 (18, 32)
Median withdrawal time,† min (25th, 75th percentile)	10.0 (7, 14)	8.0 (6, 10)	11.0 (8, 16)
Interval CRCs	67	31 (46.3)	36 (53.7)
2001-2014 screened cohort, PYO	200,834	138,608	62,226
Mean years of follow-up (median)	8.1 (8.5)	7.9 (8.5)	8.3 (8.5)
2001-2008 cohort‡			
Patients	15,808	10,746 (68.0)	5062 (32.0)
PYO	164,804	113,035	51,769
Mean years of follow-up (median)	10.5 (10.5)	10.5 (10.5)	10.3 (10.5)

Values are n (%) unless otherwise defined. Advanced adenoma is defined as adenoma with villous/tubulovillous features, size ≥1 cm, or high-grade dysplasia. Follow-up duration is from screening date to the first of 3 events: diagnosed with CRC, died from any cause, or end of follow-up period (December 31, 2015). Student *t* test was used for continuous variables, χ^2 test for count variables.
CRC, Colorectal cancer; *PYO*, person-years of observation; *ADR*, adenoma detection rate.

*Includes 55 persons with missing polyp histopathology reports.
†$P < .001$.
‡In a previous study the 2001-2008 screened cohort followed through 2009 was documented using the standardized incidence ratio method.[25] The current study uses this cohort followed through 2015 to compare the lifetime risk ratio with that of the full cohort to evaluate persistence of CRC risk reduction with cohort aging and time since first screening.

show multifold higher rates than those of the cohort, with all differences statistically significant. Finally, the magnitude of CRC risk reduction is supported by the colonoscopy procedure quality indicators shown in Table 1. Our estimated lifetime risk reduction assumes and requires continuing compliance with surveillance and receipt of CLEAR colonoscopy over patients' remaining life expectancy. Notably, the total colonoscopy burden was only 1 procedure per patient every 6.6 years including screening and surveillance procedures.

TABLE 2. Interval CRC rate among CRC-free patients

	No. of patients	PYO	Interval CRCs	Interval CRCs/10,000 PYO	*P* value*
Full cohort					—
All patients, all ages	25,008	200,834	67	3.34	
Adenoma at screening	7530	62,226	36	5.79	
No adenoma	17,478	138,608	31	2.24	
Age ≤55 y at screening	11,139	88,404	16	1.81	.03
Age 70-90 y at end of follow-up	8253	77,404	24	3.10	.76
Anatomic location†					.35
Right-sided colon	25,008	200,834	31	1.54	
Left-sided colon	25,008	200,834	24	1.2	
Subgroup					
Screened 2001-2008	15,808	165,984	57	3.46	.87

Expected distribution of right- and left-sided colon cancers out of 67 is 28 and 34, respectively (per 42% and 51% of CRCs among Surveillance Epidemiology and End Results-18 incidence cases).[45] Observed right-sided colon CRCs vs expected are similar, 31 vs 28 ($P = .70$); left-sided colon CRCs are also similar, 24 vs 34 ($P = .19$).
CRC, Colorectal cancer; *PYO*, person-years of observation.
**P* value compared with the full cohort all ages, except anatomic location where *P* is for difference between right- and left-sided CRC.
†Left-sided colon CRC excludes 4 appendix cancers (considered as other location in current literature).[45] For 7 CRCs laterality data were missing. *P* value shown is upon comparing right- vs left-sided interval CRCs.

TABLE 3. Postscreening lifetime CRC risk reduction relative to SEER-18 population*

	Full cohort (screened 2001-2014)	Screened 2001-2008
All ages		
Patients	25,862	16,306
Person-years of observation	205,522	168,643
Mean age at screening, y	58.1	58.6
Mean age at end of follow-up, y	66.1	69.1
Follow-up CRCs (interval CRCs + CRCs at screening)	236	176
Life expectancy at mean screening age, y	27.4	27.4
Postscreening lifetime CRC risk (%)†	1.57	1.77
Expected SEER-18 lifetime CRC risk at 58 years, %	4.71	4.71
Lifetime CRC risk ratio relative to SEER‡	.333	.376
Lifetime CRC risk reduction, %	66.7	62.4
Subgroup aged ≤55 at screening		
Patients	11,188	6731
Mean age at screening, y	50.0	50.0
Lifetime CRC risk reduction relative to SEER at age 50, %	79.5‡	80.7‡
Subgroup aged ≥70 years at end of follow-up		
Patients	8253	6669
Mean age at screening, y	68.5	67.8
Lifetime CRC risk reduction relative to SEER at age 68, %	71.7	75.1

CRC risk reductions of all subgroups other than those noted are statistically similar to that of the full cohort-all ages (p>.05).
SEER, Surveillance Epidemiology and End Results; *CRC*, colorectal cancer.
*See Appendix 1, Exhibit 1 for detailed calculations and sources of reference population (SEER-18) data.
†Estimated risk ÷ expected risk per SEER-18.
‡Statistically significant difference relative to the full cohort-all ages, all $P < .05$.

A recent study showed declining CRC prevention in adenoma-free subjects' later years of follow-up, with zero prevention after 12 years.[42,44] The interval CRC rate was 6.29 per 10,000 PYO in patients' first year of follow-up, increasing to 22.48 per 10,000 PYO after the 12th year.[42] In our study, the rate among adenoma-free patients was 2.24 per 10,000 PYO with no change over time or with advanced age. The

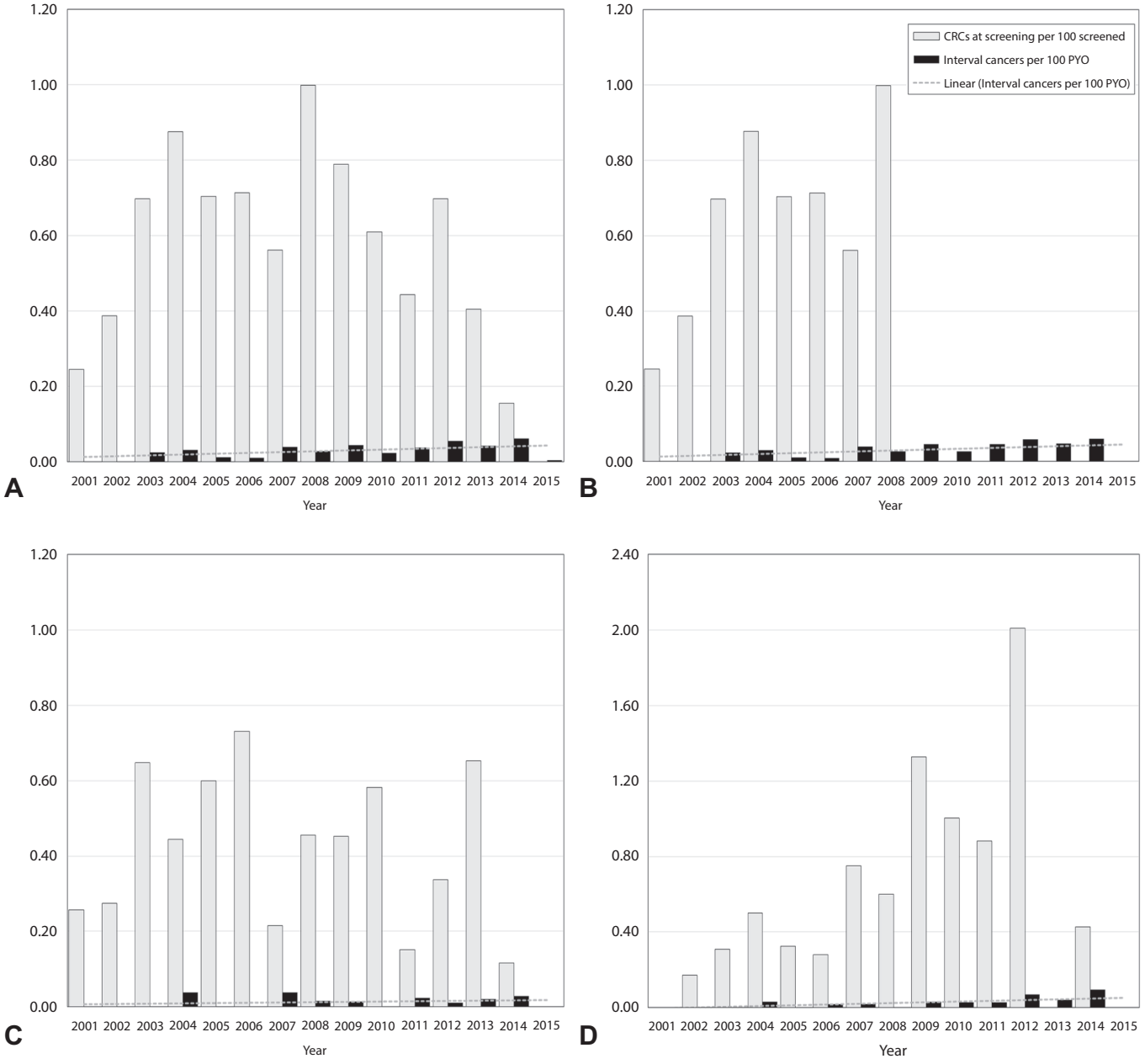


Figure 2. Colorectal cancer (CRC) detected at screening per 100 persons and interval CRCs per 100 person-years of observation (PYO) over follow-up, 2001 to 2015. **A,** Cohort screened 2001 to 2014 (mean age at screening, 58.1 years; mean age at end of follow-up, 66.1 years). **B,** Cohort screened 2001 to 2008 (mean age at screening, 58.6 years; mean age at end of follow-up, 69.1 years). **C,** Cohort screened at or below 55 years (mean age, 50.01 years; mean age at end of follow-up, 58.01 years). **D,** Cohort aged 70 to 90 years at end of follow-up (mean age at screening, 68.5 years). In A, interval CRC rate of .06/100 PYO in 2014 is random; in 2015 it was .0, 2-year average, .03/10,000 PYO. A similar pattern is seen in D.

consistent multifold higher rates of interval cancer in every other study that used usual-practice colonoscopy implies that the standardized CLEAR protocol implemented by the study endoscopists merits consideration for widespread use. Incomplete polypectomy affects up to 36% of polyps (50% if polyps are >5 mm) under direct observation by peers.[16] Missed adenoma rates are 22% to 26% despite endoscopists participating in tandem colonoscopy by a peer.[15,20] Both rates under usual-practice conditions are likely higher. A simulation study of lifetime CRC risk reduction under Germany's colonoscopy screening program projected very high prevention rates after 15 and 25 years, assuming near-100% adenoma detection, all complete polypectomies, and unvarying CRC risk regardless of adenoma status, assumptions that are

TABLE 4. Interval CRC rate among CRC-free study patients at screening compared with published studies

	Current study	National Polyp Study[3,36]	Polyp Prevention Trial[4,5,11]	Prostate Lung Colorectal and Ovarian Cancer study[6]	Kaiser Permanente 2014[35]	Kaiser Permanente 2019[42]
Procedure used	CLEAR colonoscopy	All performed by study investigators	Usual-care, community-based colonoscopy			
Total patients (age [y])	26,011 (>40)	9112 (NA)	37,175 (>35)	15,395 (50-75)	273,742 (≥50)	99,166 (50-75)
Indication	Screening	Diagnostic	Screen/ diagnostic	Diagnostic	57% diagnostic	Screening
Exclusions,* n (%)	1003 (3.9)	7694 (84.4)	35,096 (94.4)	NA	49,900 (18.2)	—
CRC-free patients (adenoma status at screening)	25,008 (7530 adenoma, 17,478 no-adenoma)	1418 (adenoma patients)	2079 (adenoma patients)	15,935 (7950 adenoma, 7985 no-adenoma)	223,842 (all patients)	99,166 (no-adenoma)
Mean age at colonoscopy, y (± standard deviation)	58.1 (±9.2)	61 (±10)	61.0 (±0.3)	64 (median)	64 (median)	55.6
Interval CRCs	67	5	14	196	712	184
Person-years of observation (mean follow-up years)	200,834 (8.0)	8401 (5.9)	7620 (4.0)	189,891 (11.9)	927,523 (4.1)	417,987
Interval CRC/10,000 person-years of observation						
All patients	3.34	—	—	10.32	7.68	—
Adenoma patients	5.79	5.9	18.3	13.07	NA	—
No adenoma	2.24	—	—	NA	NA	4.4
P value, current vs comparison study	—	.95	<.0001	<.0001	<.0001	.0004
Interval CRC rate ratio	1.0	1.0	3.2	3.1	2.3	2.0

CRC, Colorectal cancer; *NA*, not available.
*See Supplementary Table 2 for the exclusion criteria applied in each study.

contradicted by empirical studies of usual-practice colonoscopy.[2,3,15,16,44]

Previous observational studies without internal comparison groups excluded CRCs detected at screening to calculate standardized incidence ratios relative to the general population, potentially overestimating the prevention rate.[3,11,25] When this method was used, our earlier study with a 4.8-year follow-up reported 83% CRC prevention.[25] In the current study, we included all CRCs detected at screening as follow-up CRCs, attributing the excess CRCs to dwell time CRC. Dwell time is the lag between preclinical CRC and clinical diagnosis, estimated at 4.5 to 5.8 years.[37] Including all CRCs at screening in estimating the postscreening lifetime risk strongly ensures that our cohort baseline CRC status is not biased toward showing greater-than-actual CRC prevention (overestimation bias). The number of CRCs detected at screening testifies to near-100% detection of all cancers, including small lesions, by the CLEAR protocol.

However, racial composition did impact our CRC rate at screening, showing that 52% of blacks had a 46% higher rate than white and other races (SEER-18 has an 11% black population). To assess the impact of cohort racial composition on the estimated lifetime CRC prevention, a sensitivity analysis was done by adjusting the analysis for race, which showed that the prevention outcome (67.2% CRC risk reduction, Appendix 1, Exhibit 1) is robust to race-associated CRC risk (66.3% without race adjustment). This is because CLEAR colonoscopy confers high postscreening CRC prevention (ie, a low interval cancer rate) over the remaining lifetime regardless of race.

Our study may underestimate the full preventive effect of CLEAR colonoscopy on 2 counts. We compare our cohort with SEER-18, which already reflects CRC reductions achieved by the prevailing usual-practice colonoscopy screenings (48% nationally in 2008 per National Health Interview Survey data and 57.8% in South Carolina per 2008 Behavioral Risk Factor Surveillance System data analysis).[43] Second, colonoscopy-seeking populations may contain a greater-than-average proportion of higher-risk individuals (eg, CRC family history).

Our calculated CRC risk reduction should be robust to potential estimation errors because of certain approximations used: using the midpoint of cohort accrual as the SEER reference year,[3] prorating the available age-conditional risks at 50 and 60 years to estimate SEER risk at age 58 (the cohort mean age at screening), and applying life expectancy at the cohort's mean screening age to the

full cohort. The observed stable interval cancer rates throughout follow-up and among advanced age groups mitigate this concern.

Single-center study remains a limitation; however, it may be mitigated by the number of participating endoscopists. Another study limitation is the use of SEER-18 as the comparison population (instead of the South Carolina population, for which lifetime risk estimates were not available). This issue is mitigated by the similarity of South Carolina and SEER incidence rates and the sensitivity analysis that adjusted for cohort racial composition. Another potential limitation is the absence of data on CRC family history, lifestyle factors, and bowel symptoms. Despite potential inclusion of such higher-risk patients in the cohort, the observed prevention rate testifies to the strengths of the CLEAR colonoscopy protocol.

Why are these results exceptional? First, the group complied with a rigorous colonoscopy protocol that addressed all weak links in the CLEAR chain of events for 13 years. Colon preparation is personally instructed by phone at the right time, when the patient starts colon cleansing.[34] Significant expertise and shaft manipulation skill/effort/mucosal inspection are contributed by team members, facilitating the endoscopist's focus on key instrument manipulations for error-free and safe performance in every case. During insertion the cecum is reached with a minimum shaft length inserted without looping and straightening the entire colon into the shape of a "?," allowing precise tip control during withdrawal. All people present observe the endoscopy monitor for abnormalities. Studies show increasing polyp detection with more observers.[32] During withdrawal, mucosal inspection with circumferential tip movements maximizes lesion detection hidden within folds and flexures. Polypectomy also is a team effort. Team members contribute to patient/shaft/snare repositioning as needed and support safe application of hot snare/forceps for most polyps, ensuring destruction of all abnormal tissue. When difficulties arise, an expert in difficult polypectomies (performing his or her own cases) is available onsite to advise or assist. Any team member can request repeat inspection, resection, or an alternative technique to achieve clear-margin resection (the Jidoka principle).[33] Procedure time points, landmarks, polyps, and resection details are documented concurrently by a note-taker assistant, sparing endoscopist distraction (to mentally note these details) and enabling appropriate surveillance scheduling and periodic quality review.

Second, the group has proactively used published studies to set its own quality targets ahead of the gastroenterology societies' quality guidelines. Individual endoscopist ADRs are tracked and ADR maintenance in the group's ADR range is required to retain endoscopy privileges. Self-driven benchmarking, encouraged by displaying privacy-protected individual ADRs, may also contribute to generally high ADRs. Third, the team approach reinforces mutual accountability for patient outcomes and ensures diligent compliance with protocol in every procedure. Fourth, adequate procedure time slots—45 minutes per procedure for endoscopists—are set to maximize procedure quality and patient outcome; patients are allocated to procedure rooms for 30 minutes, giving endoscopists 15 minutes for administrative tasks and patient interaction.

Are these results replicable in the general population? Potential healthy subject bias is mitigated by the high rate of CRC at screening (consistent with the cohort racial composition and CRC dwell time), ADR (30.1%), and similar lung cancer incidence as the South Carolina general population computed over 4.8 years of follow-up documented earlier.[25] Completeness of follow-up cancer data is robustly validated by the control cancer, identical observed versus expected primary brain cancer deaths. Data completeness is also validated by South Carolina's North American Association of Central Cancer Registries–certified cancer registry data completeness of 97% to 100%, achieved by active data collection from diagnostic and treatment facilities within the state and supplemented by new cases identified from out-of-state cancer care abstracts on South Carolina residents received continually from 43 states under data exchange agreements. A potential challenge to replicate the prevention rate in the general population is the study center's policy of accepting primarily average-risk patients. High-risk patients contribute 5% to 10% of CRCs (genetic syndromes and prior bowel pathology). However, high-risk patients develop CRC at an early age. The cohort mean age was 58 years, and the comparison benchmark, SEER lifetime risk at 58 years, excludes younger-onset CRC. Therefore, the estimated CRC prevention ratio should be robust to this concern. Finally, the feasibility and financial sustainability of this protocol is self-evident, being sustained over 17 years to date at a free-standing private endoscopy center under prevailing reimbursement rates.

In conclusion, this study demonstrates that a strict colonoscopy protocol produced CRC prevention comparable with the National Polyp Study and multifold higher prevention than published studies of usual-practice colonoscopy cohorts. With an average of just 1 colonoscopy per patient every 6.6 years, a low interval cancer rate was maintained throughout follow-up and at advanced ages. Despite being a single-arm, unblinded observational study, 4 study characteristics are critical to evaluate the strength of evidence contributed by this study. First, there was consistent, uniform delivery of a protocolized intervention, CLEAR principles–based colonoscopy, that was verifiable by documented procedure details and photo images for every patient (in these respects similar to clinical trials of

experimental interventions). Second, completeness of follow-up CRC data was verified by an independent control cancer. Third, postscreening lifetime CRC risk incorporated interval cancers and CRCs at screening, and both were used to study prevention outcomes. Fourth, multifold lower interval cancer rates than other published studies were found. The observed 80% CRC reduction after screening colonoscopy by age 55 makes a compelling case for pursuing rapid CRC reductions to 30,000 new cases and 10,000 deaths annually (currently 150,000 and 50,000, respectively) by delivering on average 1 CLEAR colonoscopy per person every 6.6 years.

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Abbreviations: ADR, adenoma detection rate; CI, confidence interval; CLEAR, Clean the colon, Look Everywhere, complete Abnormality Removal; CRC, colorectal cancer; PYO, person-years of observation; SCCCR, South Carolina Central Cancer Registry; SEER, Surveillance Epidemiology and End Results.

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APPENDIX 1

Exhibit 1: Postscreening lifetime colorectal cancer (CRC) risk analyses to estimate % CRC reduction achieved by "Clean the colon, Look Everywhere, and complete Abnormality Removal (CLEAR) colonoscopy relative to Surveillance Epidemiology and End Results (SEER)-18 population"[3,36,38]

Data used for estimations

1. Midpoint of current study cohort accrual[3] = 2008 (reference year for SEER-18 lifetime CRC risk).
2. Applicable age conditional lifetime CRC risk in 2007-2009[36,37]:

At age 50 years (given alive and no CRC diagnosis at 50 years) = 4.97 (all races, both sexes)
At age 60 years = 4.64

3. Study cohort mean age at screening = 58.1 years.
4. Reference population and year: We estimate the expected SEER-18 cumulative lifetime CRC risk at age 58 years by prorating the risk change between 50 and 60 years (.33%) to annual change (.033 per year of age) multiplied by 8 years, .033 × 8 = .264%. Lifetime risk is .264% less at 58 years than at 50 years.[37]
5. Expected lifetime risk of CRC-free individuals at age 58 in the absence of study intervention = 4.71% (if cohort members had similar screening experience as the SEER-18 population). (Interpretation: In 2007-2009 Americans without a CRC diagnosis aged 58 years had a 4.71% risk of being ever diagnosed with CRC in their remaining lifetime. This is the expected risk of study subjects in the absence of intervention, CLEAR colonoscopies.)
6. Although the mostly average-risk screening study cohort does not contain known high-risk subgroups of the population that contributes up to 10% of all CRCs, it is not necessary to adjust the expected lifetime CRC risk of the cohort (4.71%) because most high-risk CRCs likely occur before 58 years of age.
7. Published life expectancy for the 55- to 60-year age group (midpoint 58 years, also the cohort mean age) = 27.4 years (applied to the study cohort).[39]

Percent CRC reduction relative to SEER-18 using lifetime risk analysis, including all CRCs found at screening in the analysis (full cohort, 25,862 patients)

Postscreening lifetime risk was calculated by adding all CRCs found at screening colonoscopy to interval CRCs and counting them as "follow-up CRCs" during the follow-up period. This approach assumes that all cohort CRCs found at screening represent the true prevalence of CRC in the population, which includes clinically diagnosed CRCs (represented in the incidence rate number) and dwell time or preclinical CRCs. CRCs found at screening amount to 5 times the population incidence rate (cohort rate of 611/100,000 vs South Carolina incidence of 122·8/100,000 population aged over 50 years). The documented CRC dwell time from preclinical CRC to clinically diagnosed CRC is 4.5 to 5.8 years. The observed 5-fold CRC incidence in the cohort is consistent with the CRC dwell time.[35] All CRCs found at screening are counted toward "follow-up" CRCs to calculate the postcolonoscopy CRC risk during observed follow-up. For the lifetime after observed follow-up, we multiply the observed interval cancer rate during follow-up by the remaining life expectancy. This is supported by the unchanging CRC incidence with time since colonoscopy and with advancing age shown in Figure 2, which supports the assumption of constant interval CRC rate over all years of post–follow-up life expectancy.

1. Analysis-eligible cohort = 25,862 patients including patients with CRC found at screening (25,008 CRC-free at screening + 159 patients with CRC at screening + 695 unclear CRC status at screening; see Figure 1)
2. Person-years of observation (PYO) = 205,522 after censoring at CRC diagnosis, death, or end of follow-up
3. Follow-up CRCs = 236 (159 at screening + 10 among unclear baseline status + 67 interval CRCs)
4. CRC risk per person per year = 236/ 205,522 = .001148
5. Cohort CRC risk over 8.0 years of observed follow-up = .001148 × 8.0 = .00918
6. CRC risk over unobserved 19.4 years of life expectancy = interval CRC risk per person per year × 19.4 = (67/200,834) × 19.4 = .00647
7. Total lifetime CRC risk = .0092 + .0065 = .0157, or 1.57% lifetime risk
8. Expected CRC risk per SEER-18 = 4.71%
9. Lifetime CRC risk ratio for the cohort = 1.57/4.71 = .333
10. CRC reduction relative to SEER-18 = 66.7%

Subgroup analysis: age ≤55 years at screening (mean, 50.01 years): estimated CRC reduction after including all CRCs found at screening in the analysis

1. Analysis-eligible cohort = 11,188 patients including patients with CRC found at screening

(11,139 CRC-free at screening + 49 patients with CRC at screening)

2. PYO = 88,793
3. Life expectancy at age 50 years (mean age at screening) = 31.7 years[39]
4. CRCs = 65 (49 at screening + 16 interval CRCs)
5. CRC risk per person per year = 65/88,793 = .000732
6. Cohort CRC risk over 8.0 years of observed follow-up = .000732 × 8.0 = .00586
7. CRC risk over unobserved life expectancy = interval CRC risk per person per year × 23.7 = (16/88,793) × 23.7 = .00427
8. Total lifetime CRC risk of cohort = .0059 + .0043 = .0102, or 1.02% (using approach 2 above)
9. Expected CRC risk at age 50 years in SEER-18 population = 4.97%
10. Lifetime CRC risk ratio for the cohort = 1.02/4.97 = .205
11. CRC reduction rate = 79.5% relative to SEER-18 (greater than the reduction in the full cohort, P = .0012)

(*continued on the next page*)

Continued

Subgroup analysis: mean age of 68.5 years at screening (aged 70-90 at end of follow-up): estimated CRC reduction after including all CRCs found at screening in the analysis:

1. Analysis-eligible cohort = 8253 patients including all patients with CRC found at screening (7972 CRC-free at screening + 39 patients with CRC at screening + 242 unclear CRC status at screening)
2. PYO = 77,404
3. Life expectancy at age 68 years (mean age at screening) = 19.4 years[39]
4. CRCs = 69 (39 at screening + 6 among unclear status at screening + 24 interval CRCs)
5. CRC risk per person per year = 69/ 77,404 = .00089
6. Cohort CRC risk over 9.38 years of observed follow-up = .00089 × 9.38 = .0084
7. CRC risk over unobserved 10.02 years of life expectancy = interval CRC risk per person per year × 10.02 = (24/75,394) × 10.02 = .00319
8. Total lifetime CRC risk = .0084 + .00319 = .01159, or 1.159% lifetime risk
9. Expected CRC risk at age 68 years in SEER-18 population = 4.10%
10. Lifetime CRC risk ratio for the cohort = 1.159/4.10 = .2827
11. CRC reduction rate = 71.73% relative to SEER-18 (similar to CRC reduction in the full cohort, P = .06)

Conclusion

CLEAR colonoscopy screening at a mean age of 58 years with subsequent surveillance colonoscopy produced an estimated 67% lifetime CRC incidence reduction relative to SEER-18 with its ongoing population screening activity.

Colonoscopy screening performed at a mean age of 50 years with subsequent surveillance colonoscopy produced lifetime CRC incidence reduction of 79.5% and among patients aged 68.5 years at screening, 71.7% reduction (both estimated after including all CRCs at screening among follow-up CRCs).

Sensitivity analyses

A. Race-adjusted CRC incidence reduction (SEER-18 lifetime risk weighted to mimic cohort race composition): n = full cohort of 25,862 patients including patients with CRC at screening

Notes: According to SEER-18 published rates, other races are close to white lifetime risk. White lifetime risk is lower than black lifetime risk. Because of a low number of patients of other races, they are combined with whites.

- White and other CRC lifetime risk at age 50 years = 4.89 (2007-2009)

At age 60 years = 4.58

White and other mean age = 58.9 years, ~59 years

- Expected SEER-18 cumulative lifetime CRC risk at age 59 years = 4.61 (white and other race)
- Black race: CRC lifetime risk at age 50 years = 5.23 (2007-2009)

At age 60 years = 4.86

Black mean age = 57.5 ~58 years

- Expected SEER-18 cumulative lifetime CRC risk at age 58 years = 4.93 (black)
- Proportion of white/other and black in cohort = 48% and 52% (for race-weighted expected lifetime risk of cohort)
- Race adjusted lifetime CRC risk of cohort = (.48 × 4.61) + (.52 × 4.93) = 2.213 + 2.564 = 4.78
- Total lifetime CRC risk = 1.57% (calculated earlier)

(Published life expectancy (LE) at age 58 race-wise is not available. Because of nearly equal blacks and white/other race in the cohort, the higher LE of white/other at 55 and 60 years of age is expected to make up for lower LE of blacks, resulting in overall cohort LE being unaffected by the slight variation in LE among the races. Hence, lifetime CRC risk calculation remains unchanged.)

- Race-adjusted cohort lifetime CRC risk ratio relative to SEER-18 = 1.57/4.78 = .328
- Race-adjusted CRC risk reduction relative to SEER-18 = 67.2%

B. Percent of CRC incidence reduction estimated by standardizing cohort baseline risk to SEER-18 based on annual CRC incidence

The principle in this approach was to "equalize" the follow-up CRC experience of the study cohort with that of SEER-18 "CRC-free" population, except for the intervention effect. Because our patients are all from South Carolina, we used the South Carolina CRC incidence rate of 122.8/100,000 in the population aged over 50 years to prorate CRCs found at screening and added these CRCs to interval CRCs to standardize the CRC risk of the 2 groups.[1] (SEER-18 incidence is similar to South Carolina incidence.) The analytic sample for this analysis consisted of CRC-free patients at colonoscopy, patients with uncertain CRC status at screening, and patients with CRC detected at screening prorated to the population incidence rate (Fig. 1).[3] The annual CRC rate based on total "follow-up" CRCs was used to calculate their post-colonoscopy lifetime CRC risk per Figure 1.

Calculations

Step 1: Standardize study cohort CRC risk profile at baseline to SEER-18 CRC-free population, establish analytic sample and follow-up CRCs. To standardize the CRC risk profile of the study cohort at start of follow-up to the comparison population, we attributed follow-up CRCs in the cohort as the sum of the following: (1) interval CRCs during follow-up among those who were CRC-free at screening, (2) CRCs diagnosed among patients who had uncertain CRC status at screening and did not comply with referral instructions (see Fig. 1), and (3) CRCs found at screening in the cohort prorated to the population incidence rate (122/100,000 population aged over 50 years).

The denominator patients for the above CRCs are added to generate the SEER-comparable "CRC-free cohort." Analysis-eligible cohort = 25,735 patients (25,008 CRC-free at screening + 695 patients of uncertain CRC status at screening, + 32 patients with CRC at screening (after prorating 159 CRCs to the general population incidence rate). Follow-up CRCs consisted of 67 interval cancers among the CRC-free + 10 CRCs among uncertain status patients + 32 prorated CRCs = 109. The PYO of 25,735 patients = 205,776.

Step 2: Estimate the incidence-standardized lifetime CRC risk ratio for the cohort and percentage of CRC prevention

1. Expected lifetime CRC risk at 58 years of age per SEER 18 = 4.71%

Continued

2. Baseline risk-standardized follow-up CRC rate of the study cohort over observed follow-up = (109/205,776) = .000529 per PYO, or .0529% (annual risk per person per year)
3. CRC rate applied to calculate cohort's estimated lifetime CRC risk: annual risk multiplied by life expectancy at cohort mean age) = .0529 × 27.4 = 1.45%
4. Study subjects exchanged the SEER population's lifetime risk of 4.71% for 1.45% by getting CLEAR colonoscopy screening.
5. Ratio of observed lifetime CRC risk to expected lifetime risk = 1.45/4.71 = .308 (standardized lifetime risk ratio for study subjects).
6. Reduction in lifetime CRC risk achieved = (4.71-1.45) = 3.26
7. CRC prevention rate = 3.26/4.71 = 69.2% prevention achieved by CLEAR colonoscopy screening relative to SEER-18 given ongoing US population-wide screening activities in 2007-2009.

Note 1: data linkage procedures to identify colorectal and brain cancer cases/deaths in the South Carolina Central Cancer Registry databases

Incident CRC cases in the cohort were identified by linking the study cohort data with the South Carolina Central Cancer Registry cancer data for 1996 to 2015 (to ensure exclusion of those with a predating CRC diagnosis). We used LinkPlus, a probabilistic record linkage program developed by the Centers for Diseases Control and Prevention to support data extraction from the National Program of Cancer Registries.[23]

Cases were matched on first and last name, social security number, and date of birth as blocking variables and race and sex as matching variables. LinkPlus uses the Soundex phonetic coding of last and first names to generate a comprehensive list of perfect, approximate, partial, and remotely plausible matches. It uses a weighted algorithm (accommodating typographic errors and transposition of digits in social security number and date of birth and matching patients on race and sex) and calculates a probabilistic record linkage score: the higher the score, the better the match. LinkPlus recommends a cutoff score of 7.0 to 10.0, suggesting manual review of cases above the cutoff score to finalize cancer matches.[23] For this study, however, we used a much more conservative cutoff score of 1.0, resulting in manual review of a large number of pairs with remote plausibility of being true matches. The score range for the study patients was .2 to 48 (48 being the perfect match). All pairs with scores of 30 to 48 were reviewed to confirm they were indeed true matches. Pairs with linkage scores between 1 and 29.9 were subjected to in-depth manual review by the study principle investigator and a research associate. The goal was to ensure capture of potential cancer cases despite typographic errors or differences in name or address (eg, on marriage). To determine match status, we used additional variables: middle name, sex, race, address, and zip code. Manual review yielded no additional CRC match. The same process was used for deaths and primary brain cancer.

Note 2: PYO calculation for brain cancer standardized mortality ratio estimation[33]

PYO were calculated using brain cancer death as the primary censoring event, secondary censoring events being death from other cause and end of study period. Each patient's PYO was aggregated into age–sex–race strata and the corresponding brain cancer mortality rates applied to calculate total expected brain cancer deaths in the cohort. PYO were prorated to appropriate age strata when cusp birthdays occurred (eg, 60th birthday).

SUPPLEMENTARY TABLE 1. Distribution of study patients by age at the end of follow-up and person-years of observation contributed

Patient age at the end of follow-up (y)	No. of patients	Mean age at end of follow-up (y)	Person-years of follow-up contributed
40-44	130 (.5)	43.8	282.7 (.1)
45-49	648 (2.5)	48.0	2621.5 (1.3)
50-54	2489 (9.7)	53.0	12,404.3 (6.0)
55-59	4331 (16.8)	57.7	28,020.5 (13.6)
60-64	5101 (19.8)	62.5	42,397.2 (20.6)
65-69	4840 (18.8)	67.4	42,392.3 (20.6)
70-74	3344 (13.0)	72.4	29,450.8 (14.3)
75-79	2257 (8.8)	77.3	21,438.4 (10.4)
80+	2652 (10.3)	85.1	26,514.6 (12.9)
Total	25,792*	66.1	205,522.3

Values in parentheses are percents.
*Total patients are 70 less than the total cohort; they had colorectal cancer at screening, with date of cancer diagnosis in the cancer registry matching the colonoscopy date, censored at colonoscopy date because of the cancer diagnosis.

SUPPLEMENTARY TABLE 2. Exclusions applied by the current study and comparison studies of interval cancer

	Current study	Polyp Prevention Trial[4,5,10]	National Polyp Study[3,34]	Prostate Lung Colorectal and Ovarian Cancer study[6]	Kaiser Permanente 2014[16]	Kaiser Permanente 2019[41]
Total first colonoscopy patients	26,011	37,175	9112	15,395	273,742	Complex sample with mixed screening methods
Exclusion criteria	Prior CRC diagnosis (58) CRC at screening (159) Prior bowel pathology or resection (50) Carcinoid (41) Incomplete colonoscopy, no make-up (445) Large/vascular polyp referred for resection (250)	Prior CRC diagnosis (2544) CRC at screening (1029) Prior bowel pathology (2085) Incomplete colonoscopy (2160) Large polyps referred/incomplete removal (3718) Other reasons (161)	CRC at screening (549) Prior bowel pathology (111) Incomplete colonoscopy (208) Large polyp referred (35) Other reasons (38)	No exclusions	CRC at screening (8018)	Previous FIT/FOBT (184,327) Patients with family history of CRC Other exclusions as listed under current study
Other study-specific exclusions	NA	Subject readiness (23,399)	No polyps (4763) Other (1244)	Subject readiness	41,882	
Total all exclusions, n (%)	1003 (3.9)	35,096 (94.4)	7694 (84.4)	NA	49,900 (18.2)	520,499
CRC-free at screening	25,008 (7530 with adenoma, 17,478 no-adenoma)	2079 (all adenoma patients)	1418 (all adenoma patients)	15,935 (7950 with adenoma, 7985 no-adenoma)	223,842 (adenoma-wise NA)	99,166 no-adenoma patients

This table is a supplement to Table 4.
CRC, Colorectal cancer; *FIT/ FOBT*, fecal immunochemical test/fecal occult blood test; *NA*, not available.
*For comparisons, all patients or adenoma patients of the study cohort were compared based on the comparison study patient type.