Gastroenterology 2018;155:1383–1391

CLINICAL AT

Effects of Organized Colorectal Cancer Screening on Cancer Incidence and Mortality in a Large Community-Based Population

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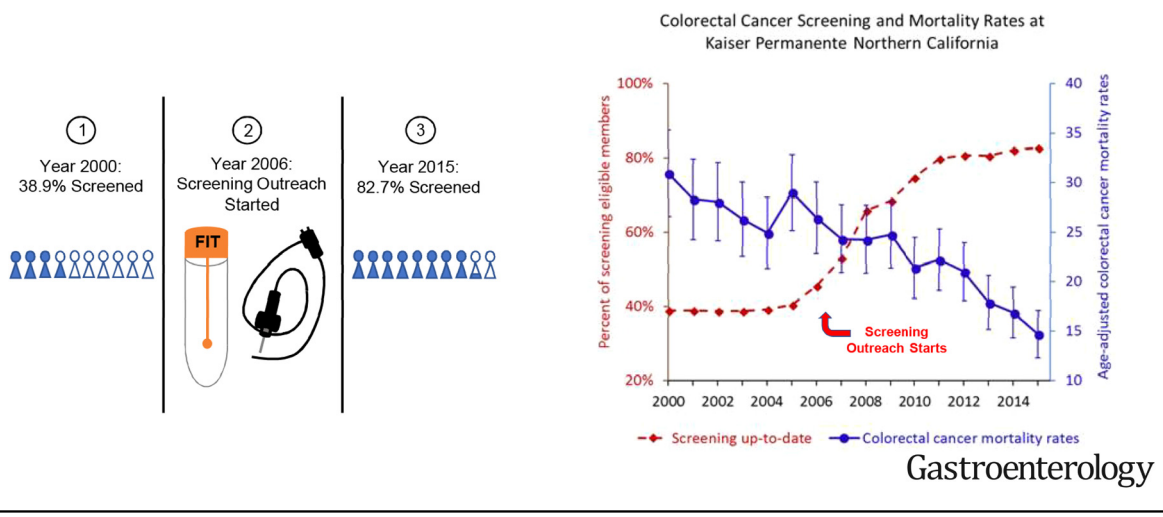
This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e21. Learning Objective: Upon completion of this CME activity, successful learners will be able to identify modalities for colorectal cancer (CRC) screening and evaluate the impact of those screening modalities on health outcomes



See editorial on page 1302.

BACKGROUND & AIMS: Little information is available on the effectiveness of organized colorectal cancer (CRC) screening on screening uptake, incidence, and mortality in community-based populations. **METHODS:** We contrasted screening rates, age-adjusted annual CRC incidence, and incidence-based mortality rates before (baseline year 2000) and after (through 2015) implementation of organized screening outreach, from 2007 through 2008 (primarily annual fecal immunochemical testing and colonoscopy), in a large community-based population. Among screening-eligible individuals 51–75 years old, we calculated annual up-to-date status for cancer screening (by fecal test, sigmoidoscopy, or colonoscopy), CRC incidence, cancer stage distributions, and incidence-based mortality. **RESULTS:** Initiation of organized CRC screening significantly increased the up-to-date status of screening, from 38.9% in 2000 to 82.7% in 2015 ($P < .01$). Higher rates of screening were associated with a 25.5% reduction in annual CRC incidence between 2000 and 2015, from 95.8 to 71.4 cases/100,000 ($P < .01$), and a 52.4% reduction in cancer mortality, from 30.9 to 14.7 deaths/100,000 ($P < .01$). Increased screening was initially associated with increased CRC incidence, due largely to greater detection of early-stage cancers, followed by decreases in cancer incidence. Advanced-stage CRC incidence rates decreased 36.2%, from 45.9 to 29.3 cases/100,000 ($P < .01$), and early-stage CRC incidence rates decreased 14.5%, from 48.2 to 41.2 cases/100,000 ($P < .04$). **CONCLUSIONS:** Implementing an organized CRC screening program in a large community-based population rapidly increased screening participation to the ≥80% target set by national organizations. Screening rates were sustainable and associated with

substantial decreases in CRC incidence and mortality within short time intervals, consistent with early detection and cancer prevention.

Keywords: Colon Cancer; Neoplasm; FIT; Early Detection.

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Colorectal cancer (CRC) is the second leading cause of cancer death in the United States.[1] Screening can prevent CRC through the removal of precancerous adenomatous polyps and reduce deaths through early detection and treatment of cancer.[2,3] The US Preventive Services Task Force recommends several screening tests, including high-sensitivity guaiac-based fecal occult blood testing (gFOBT), fecal immunochemical testing (FIT), multi-targeted stool DNA testing, colonoscopy, computed tomography colonography, and flexible sigmoidoscopy with or without FIT.[4] The National Colorectal Cancer Roundtable set a goal of increasing the screening rate from 58% in 2013 to ≥80% of the eligible US population by 2018, and estimated that achieving this goal would result in 19% fewer CRC deaths.[5,6] However, more recent data indicate only 63% of eligible US residents, and <50% of some race/ethnicity groups, are up to date with screening,[7] leading to concern that rates may be plateauing,[8] and making it unclear whether the 80% target is achievable or sustainable.

Colonoscopy and FIT are commonly used screening tests worldwide, but the population-level impact of screening programs is largely unknown.[5,9] Modeling studies suggest these 2 screening strategies have comparable effectiveness for reducing CRC-associated mortality.[10] However, the strongest evidence to date of screening benefit comes from randomized controlled trials that demonstrated reduced mortality for both gFOBT and sigmoidoscopy,[11] tests that are no longer widely used in the United States.[12] The evidence for colonoscopy's effectiveness comes indirectly from sigmoidoscopy trials[13–19] and observational studies.[2,20–24] The evidence for FIT effectiveness comes indirectly from gFOBT trials,[25–35] given that FIT operates by a similar mechanism and has a higher sensitivity for CRC and advanced adenomas than gFOBT.[36–38] Using multiple screening options may help increase screening uptake,[39,40] but few data exist regarding the influence of population-based organized screening programs on CRC screening rates, incidence, and mortality.

The present study, in a large community-based integrated health care delivery system, evaluated whether an organized CRC screening program could achieve and sustain the ≥80% screening target proposed by national organizations, and whether changes in screening were associated with changes in CRC incidence and mortality.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Little information is available on the effectiveness of organized colorectal cancer (CRC) screening on screening uptake, incidence, and mortality in community-based populations.

NEW FINDINGS

Initiation of organized CRC screening (annual fecal immunochemical testing and colonoscopy) increased the up to date status of screening, from 38.9% in 2000 to 82.7% in 2015, and was associated with a 25.5% reduction in annual CRC incidence and a 52.4% reduction in cancer mortality.

LIMITATIONS

The observational design precludes confirming a direct causal link between the increases in screening and the decreases in colorectal cancer outcomes.

IMPACT

Implementing an organized CRC screening program in a large, community-based population rapidly increased screening participation to the ≥80% target set by national organizations and was associated with substantial decreases in CRC incidence and mortality.

Methods

Study Population and Oversight

The study was performed using a dynamic cohort of Kaiser Permanente Northern California (KPNC) health plan members for the years 2000–2015. KPNC is an integrated health care delivery organization that serves approximately 4.0 million members in urban, suburban, and semi-rural regions throughout California; membership is similar in demographic and socioeconomic characteristics to the region's census demographics.[41]

The study was approved by the KPNC Institutional Review Board, which waived the requirement for individual informed consent. The listed authors had sole responsibility for the study design, data collection, decision to submit the manuscript for publication, and drafting of the manuscript. This study was conducted within the National Cancer Institute–funded Population-based Research Optimizing Screening through Personalized Regimens (PROSPR) Consortium (U54 CA163262), which conducts multisite, coordinated, transdisciplinary research to evaluate and improve cancer-screening processes.

Organized Colorectal Cancer Screening Program

Prior to 2006, CRC screening within the cohort was performed by physician request, predominantly using sigmoidoscopy and gFOBT. FIT was pilot-tested in 2006. Starting in 2007, screening transitioned region-wide to direct-to-patient annual FIT outreach for members 60–69 years of age who were not screening up-to-date by other methods and, in 2008, it was expanded to those 51–75 years of age; colonoscopy was a screening option throughout this period, by request. As

***Authors share co-first authorship.**

Abbreviations used in this paper: **CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical testing; gFOBT, guaiac-based fecal occult blood testing; KPNC, Kaiser Permanente Northern California; SEER, Surveillance Epidemiology and End Results.**

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0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2018.07.017

described previously,[42–44] each year FIT kits are mailed to health plan members without a record of a colonoscopy within 10 years or a sigmoidoscopy within 5 years. The program's goal is, primarily through FIT or colonoscopy, to screen all screening-eligible members by December 31 of each calendar year, starting the year they turn 51 through 75 years of age, in accordance with the Healthcare Effectiveness Data and Information Set measurement approach.[45,46] Screening outreach includes mail, secure e-mail, and telephone reminders as needed. In-reach includes in-person reminders for members attending office or preventive health visits with any health care provider through prompts in the electronic medical record. FIT is analyzed by an automated OC-Sensor Diana (Polymedco Inc, Cortlandt Manor, NY) with a cutoff level of $\geq$20 μg hemoglobin per gram of stool for a positive result. Patients with a positive FIT were contacted by their primary care physician or local gastroenterology department staff to schedule a follow-up colonoscopy through a combination of telephone calls, secure messaging, and mail.

Cohort Eligibility Criteria

The study cohort was comprised of KPNC members 51–75 years of age in 2000–2015, who were continuously enrolled (allowing a coverage gap of $\leq$45 days) in the calendar year before cohort entry to allow time to document screening history, including outside of KPNC, and enrolled in the measurement year (any year in which screening status was ascertained).

Censoring

Cohort members were censored at the first of the following: end of the study interval (December 31, 2015), December 31 in the year in which they reached 75 years of age, or ended continuous health plan membership (defined as any gap of >45 days in a calendar year), or their date of death.

Study Outcomes

We evaluated the influence of organized screening on 3 primary outcomes: screening up-to-date status, CRC incidence, and CRC-specific mortality; and 2 secondary outcomes: FIT/gFOBT positivity and the percentage of fecal test–positive patients who received a follow-up colonoscopy within 6 months of their positive test. An individual was considered up-to-date with screening if they completed fecal testing (FIT or gFOBT) in a given year, or had a sigmoidoscopy (for any indication) within 5 years or colonoscopy (for any indication) within 10 years (including the measurement year). To avoid double counting of screening tests, the first test performed on a patient in a given year was counted as the screening method. For example, if a colonoscopy was performed after a positive FIT, the patient was counted as screened by FIT.

New CRC diagnoses (first primary only) among cohort members were used to generate annual incidence rates and incidence-based mortality rates; the latter was defined as a CRC-related death in any individual aged 51–75 years who had a CRC diagnosis in the prior 10 years. Incidence-based mortality (derived from cancer registry data rather than death certificates) is less subject to bias from migration than non-incidence–based CRC mortality.[47] A 10-year interval between diagnosis and death was selected to allow sufficient time for disease progression to result in death.

Data Sources and Definitions

Data regarding CRC screening, diagnoses and deaths, demographics, and other covariates were obtained from validated electronic laboratory, cancer registry, medical visit, demographic, and membership databases.[48,49] Colonoscopy procedures were identified using Current Procedural Terminology codes (44388–44394, 44397, 44398, 44401–44403, 44405, 45355, 45378–45393), International Classification of Disease procedure codes (45.21–45.23, 45.25, 45.42, 45.43, 98.04, as well as codes 48.24 and 48.36 [rectal biopsy] when there was no corresponding sigmoidoscopy procedure on or near the procedure date), Healthcare Common Procedure Coding System codes (G0105, G0121), and internal codes for tracking colonoscopies performed before joining KPNC (12142332, 204456, 230847, 235525). Sigmoidoscopy procedures were identified using Current Procedural Terminology codes (45300, 45303, 45305, 45307–45309, 45315, 45317, 45320, 45321, 45327, 45330–45335, 45337–45342, 45345), International Classification of Disease procedure codes (45.24, 48.21–48.23), and internal codes for tracking sigmoidoscopies performed before joining (224770, 230854).

CRC was defined as an adenocarcinoma within the colon or rectum using Surveillance Epidemiology and End Results (SEER) cancer site group codes 21040 and 21050, and International Classification of Disease oncology codes C18.0–C18.9, C19.9, and C20.9. The KPNC cancer registry reports to the SEER registry and maintains a >97% population-based completeness standard as verified by random audits by the cancer registry and SEER. Additional retrospective audits and death clearance processes have historically captured approximately 1%–2% additional cases.

Colorectal cancer staging definitions. Advanced-stage cancers were defined as stage III (regional disease with spread to the regional lymph nodes only) or stage IV (distant metastasis) according to the American Joint Committee on Cancer staging system. For members without such staging information, advanced-stage cancers were defined as SEER stage 3 (disease in the regional lymph nodes), 4 (regional disease with direct extension and spread to the regional lymph nodes), or 7 (distant metastasis) according to the SEER Program Coding and Staging Manual 2013.[50]

Colon location definitions. Proximal cancers were those located in the cecum, ascending colon, hepatic flexure, and transverse colon; distal cancers were those in the splenic flexure, descending colon, sigmoid colon, and rectum.

FIT/gFOBT positivity was defined as the percentage of individuals who completed a FIT or gFOBT in a given year and had a positive result. Colonoscopy follow-up was defined as, among those with a positive FIT or gFOBT in a given year, the percentage that received a follow-up colonoscopy within 6 months after the positive test.

Statistical Analyses

Comparisons of proportions were evaluated using χ^2 tests. Annual CRC incidence rates and incidence-based mortality rates for the years 2000–2015 were adjusted to the 2000 US Census population using single-year age intervals (eg, 51, 52, 53 . . . 74 or 75 years) as provided by SEER.[51] Single-year age-adjusted incidence rates were also stratified by age categories (51–64, 65–75 years), sex, stage (early, advanced), and colon location (proximal, distal). Statistical comparisons of incidence

and mortality rates utilized 95% confidence intervals (CI) for age-adjusted rates and the z test. Hypothesis testing was 2-sided with an α of .05, and analyses used SAS statistical software, version 9.3 (Cary, NC).

Role of the Funding Source

The study was funded by the National Cancer Institute. The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit for publication.

Results

Characteristics of the Screening-Eligible Population

Patient cohort characteristics at 3 points during the study interval (years 2000, 2008, and 2015) are provided in Table 1. At each point, the cohort was predominately 51–64 years of age (68.5%–74.0%), female (52.5%–53.0%), and non-Hispanic white (58.4%–64.4%). The overall size of the screening-eligible cohort increased 49.7% during the study interval, from 651,675 in 2000 to 975,637 in 2015, although membership duration was stable. In 2000, the mean (±SD) length of membership was 11.2 ± 4.6 years and 17% were members for ≤5 years, 18% for 6–10 years, and 64% for ≥11 years. In 2008, the average length of membership was 11.3 ± 4.6 years and 17% were members for ≤5 years, 18% for 6–10 years, and 65% for ≥11 years. In 2015, the average length of membership was 11.4 ± 4.6 years and 17% were members for ≤5 years, 17% for 6-10 years, and 66% for ≥11 years.

During follow-up, 1,768 CRC cases were diagnosed; 141 (1.2%) had unknown stage and 382 (3.2%) had unknown location; these latter cases were not included in analyses stratified by stage or location, respectively.

Screening Participation

Screening participation was stable in years 2000–2005, between 39.7% and 40.5%. Participation began to rise after the initiation of FIT pilot testing in 2006 and organized screening in 2007 and 2008 (Figure 1 and Supplementary Table 1). The percentage of the cohort up-to-date with screening significantly increased from 38.9% in 2000 to 82.7% in 2015 ($P < .01$); the increase was primarily due to increased uptake of FIT and colonoscopy.

Fecal Immunochemical Testing/Guaiac-Based Fecal Occult Blood Testing Positivity and Colonoscopy Follow-Up

FIT/gFOBT positivity across the study interval ranged between 3.1% and 5.3%, and the percentage of individuals with colonoscopy follow-up within 6 months after a positive fecal test increased from 41.1% in 2000 to 83.1% in 2015 (Supplementary Table 1).

Colorectal Cancer Incidence Rates

Age-adjusted CRC incidence rates increased significantly from 95.8 cases/100,000 (95% CI, 88.1–103.4) in 2000 to a peak of 117.8/100,000 (95% CI, 110.4–125.2; $P < .01$) in 2008, which coincided with rapidly rising screening rates after implementation of organized screening (Figure 2 and Supplementary Table 2), before declining to significantly below baseline (year 2000) in years 2012–2015 ($P < .01$ for all years). Overall, age-adjusted cancer incidence rates decreased 25.5% between 2000 and 2015, from 95.8 cases/100,000 to 71.4/100,000 (95% CI, 66.1–76.7; $P < .01$) (Figure 2 and Supplementary Table 2).

The initial increase in CRC incidence associated with the rapid rise in screening rates was largely due to greater

Table 1. Cohort Characteristics in 2000, 2008, and 2015

	2000		2008		2015	
Characteristics	n	%	n	%	n	%
Total cohort members	65,1675	100.0	821,710	100.0	975,637	100.0
Age						
50–64 y	463,325	71.1	608,138	74.0	668,658	68.5
65–75 y	188,350	28.9	213,572	26.0	306,979	31.5
Sex						
Male	309,394	47.5	386,751	47.1	458,263	47.0
Female	342,281	52.5	434,959	52.9	517,374	53.0
Race/ethnicity						
Non-Hispanic white	419,850	64.4	498,576	60.7	569,317	58.4
Black	48,248	7.4	59,820	7.3	70,225	7.2
Asian or Pacific Islander	73,458	11.3	121,092	14.7	163,516	16.8
Hispanic	60,412	9.3	91,723	11.2	124,155	12.7
Other	4755	0.7	6949	0.8	9039	0.9
Unknown	44,952	6.9	43,550	5.3	39,385	4.0
KPNC membership duration						
≤5 y	111,939	17.2	141,794	17.3	162,945	16.7
6–10 y	119,773	18.4	146,977	17.9	169,290	17.4
≥11 y	419,963	64.4	532,939	64.9	643,402	66.0
Mean ± SD, *y*	11.2 ± 4.6	—	11.3 ± 4.6	—	11.4 ± 4.6	—

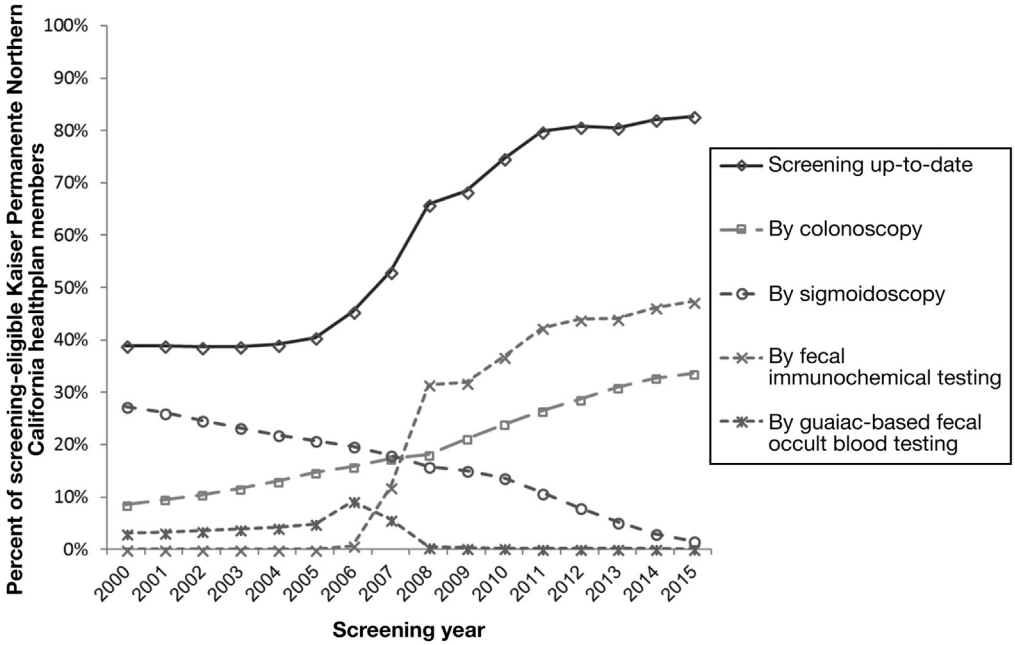

Figure 1. Percentage of eligible cohort members screening up-to-date: overall and by modality.

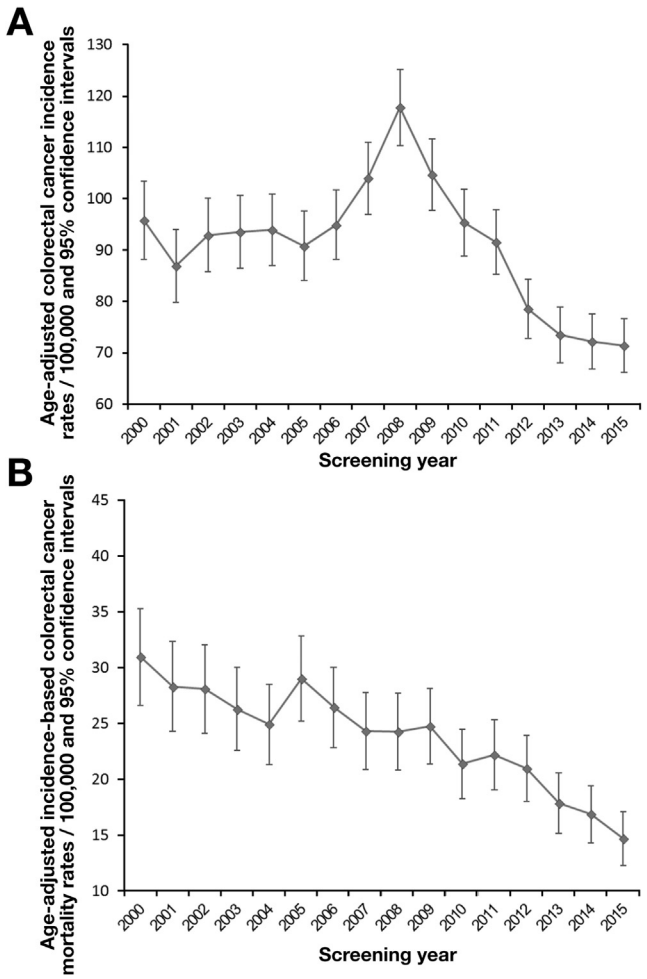

Figure 2. Cohort age-adjusted CRC incidence rates and incidence-based mortality rates: age-adjusted to the US 2000 Census population.

detection of early-stage cancers, which peaked in 2008 (Figure 3 and Supplementary Table 3). Age-adjusted early-stage cancer incidence rates subsequently decreased, despite enhanced early detection; across the full study period rates declined 14.5%, from 48.2 cases/100,000 (95% CI, 42.8–53.6) in 2000, to 41.2/100,000 (95% CI, 37.2–45.2) in 2015 ($P < .04$). Age-adjusted advanced-stage incidence rates decreased 36.2%, from 45.9 cases/100,000 (95% CI, 40.6–51.1) to 29.3/100,000 (95% CI, 25.9–32.6; $P < .01$).

Age-adjusted CRC incidence rates were consistently higher for distal compared to proximal cancers (Supplementary Figure 1), men compared to women (Supplementary Figure 2), and older vs younger cohort members (Supplementary Figure 3), and in all groups rates peaked in 2008, following implementation of organized screening. Incidence rates decreased significantly among patients 65–75 years of age (from 148.5 cases/100,000 in 2000 to 90.1/100,000 in 2015; $P < .01$), but not among patients 50–64 years of age (from 68.0 cases/100,000 in 2000 to 61.5/100,000 in 2015; $P = .19$).

Incidence-Based Colorectal Cancer Mortality Rates

Age-adjusted incidence-based mortality rates decreased by 52.4%, from 30.9 deaths/100,000 (95% CI, 26.6–35.3) in 2000, to 14.7/100,000 (95% CI, 12.3–17.1) in 2015 ($P < .01$) (Figure 2 and Supplementary Table 2).

Discussion

The replacement of an opportunistic CRC screening program based primarily on sigmoidoscopy and gFOBT, with an organized screening program of annual FIT combined with opportunistic colonoscopy doubled the percentage of patients screening up-to-date, from almost 40%

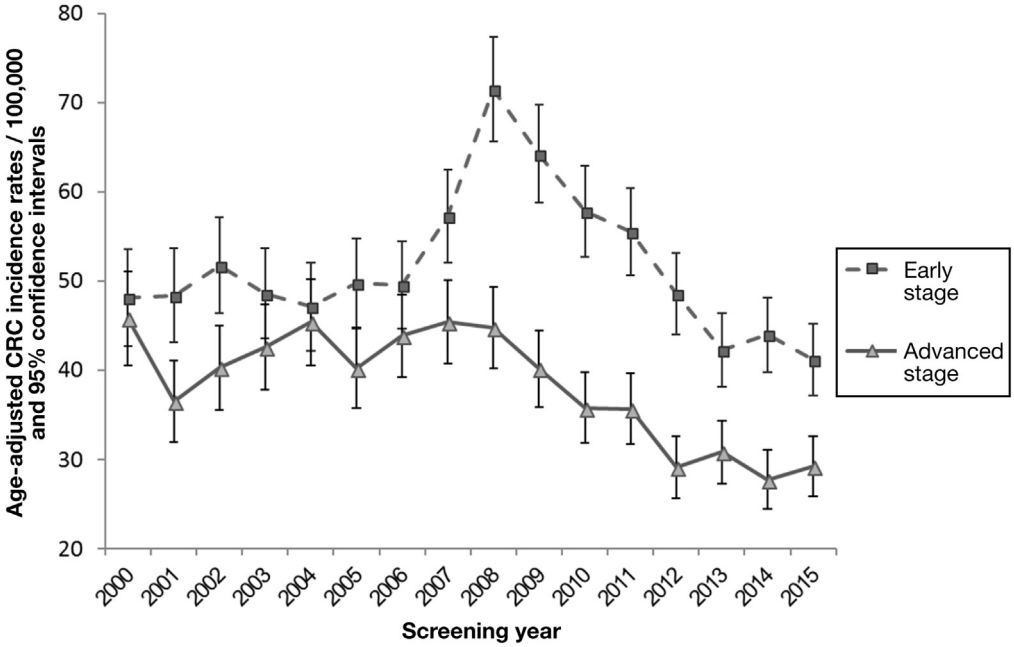

Figure 3. Cohort CRC incidence rates by stage: age-adjusted to the US 2000 Census Population.

to >80%. The increase in screening was associated with an immediate increase in CRC incidence, particularly early-stage disease, followed by a substantial 25.5% decline in cancer incidence and a remarkable 52.4% decrease in cancer mortality during a relatively short 12- to 16-year period. FIT positivity fluctuated between 3.1% and 5.3% across the study interval and colonoscopy follow-up within 6 months after a positive test increased from 41.1% in 2000 to 83.1% in 2015.

Our findings indicate that, even in very large community-based settings, the 80% screening target set by the National Colorectal Cancer Roundtable is both feasible and sustainable using organized screening programs.[5] These findings underscore the potential for organized screening programs to achieve national target screening rates.

The temporal changes in CRC outcomes after the implementation of organized screening are consistent with shorter duration community-based CRC mortality studies that have evaluated programmatic FIT, as well as modeling studies of the ≥80% screening target. An Italian study with staggered initiation of biennial FIT reported that the region starting FIT in 2002–2004 had a 22% greater reduction in subsequent CRC mortality than the region starting FIT in 2008–2009.[52] A Taiwanese study of FIT demonstrated lower CRC mortality rates among a cohort exposed to 1–3 rounds of biennial FIT compared to an unscreened cohort (adjusted relative risk, 0.90; 95% CI, 0.84–0.95).[53] A modeling study estimated that increasing US screening rates from 58% in 2013 to the 80% target by 2018 would reduce CRC incidence and mortality rates by 17% and 19% in the short-term, and 22% and 33% in the long-term, respectively, and avert approximately 280,000 new cancer cases and 200,000 cancer deaths within <20 years.[6] In the current study, between 2000 and 2015, the increase in screening coincided with decreases in CRC incidence and mortality within the cohort of 25.5% and 52.4%, respectively.

Although the observational design precludes confirming a direct causal link between the increases in screening and the decreases in CRC outcomes, temporal changes in cancer risk factors or treatment are unlikely sole alternative explanations for several reasons. First, CRC incidence is stable or increasing in many comparable developed countries without substantial screening programs, including Finland, Norway, France, and Australia. Substantial declines are reported almost exclusively in countries with at least moderate use of cancer screening tests.[54] Second, a sophisticated modeling study suggested that changes in risk factors and treatment have relatively small influences on population-level CRC mortality statistics.[55] For example, between 1975 and 2000, when there was an overall 26% absolute decrease in CRC mortality in the United States, 53% of this reduction was attributed to screening and only 12% to improved treatment.[55] Third, CRC incidence rates in the study cohort were stable in the baseline pre-intervention period, an interval with stable screening rates within the cohort; cancer incidence changes abruptly coincided with increased screening. Fourth, the observed incidence changes, with lower cancer mortality among all age groups, but lower cancer incidence mainly among older patients, are concordant with biological knowledge regarding progression of polyps to cancer, and known effects of screening tests on early cancer detection.[56,57] Changes from modified risk factors, for example, would be expected to influence both cancer incidence and mortality among all age groups, whereas reduced incidence from CRC screening, such as through polyp removal in the younger age group, would largely be anticipated, as seen in the current data, with cancer incidence until several years later, among older patients.[56]

Also, concordant with randomized trials and observational studies, increased screening in the study cohort coincided with an immediate increase in early-stage cancer

diagnoses.[13,20,58] In addition, as would be expected for FIT and colonoscopy, which evaluate the entire colon, we observed reductions in both right- and left-sided cancer. This is in contrast to sigmoidoscopy, which has been demonstrated to mainly decrease the risk of left-sided CRC.[13,14,21] CRC screening rates nationally in the United States increased among those 50 years and older during the study period, from about 38% in 2000 to 62% in 2015,[59,60] while CRC incidence and mortality nationally decreased during this period,[1,59] largely likely related to increased use of screening.[55] The reported results suggest that an organized screening program can achieve higher rates of screening and greater incidence and mortality reductions; the CRC mortality rate in the study cohort for 2014 (10.2/100,000) (the most recent year with comparable date), for example, was 28% lower than the rate reported nationally (14.1/100,000).[59]

The study design has several strengths, including a large, diverse, and stable community-based population and 16 years of data covering the periods before and after implementation of organized screening. There was systematic and comprehensive capture of screening tests using validated methods[48] and of CRC outcomes through a SEER-affiliated cancer registry. The study directly ascertained individual-level screening completion; this differs from US population screening estimates, which largely utilized indirect measures, such as surveys, which overestimate screening prevalence.[61] The pre-existing opportunistic screening program provided the study population with stable pre-outreach screening and incidence rates from 2000–2005. This permitted evaluation of background temporal CRC trends; the stable CRC incidence during this period provides reassurance that the subsequent changes seen were not solely from background risk factors or cancer treatment. The large cohort size allowed evaluation of important strata by age, sex, and cancer location. The study design also eliminated the healthy volunteer bias associated with screening trials,[62] because all health plan members, screened and unscreened, were followed for clinical outcomes. A potential question is whether similar rates can be reached outside of an integrated health care system. However, comparable screening rates have been achieved in challenging populations using organized screening,[63–65] although the sustainability of the described interventions, in these populations, has not been well evaluated.

In conclusion, these findings suggest that implementing organized CRC screening, using annual FIT and colonoscopy, can rapidly increase screening participation. They also suggest that the screening target of $\geq$80%, set by the National Colorectal Cancer Roundtable,[5] is achievable, sustainable in a large population, and associated with substantial decreases in CRC incidence and mortality within short time intervals.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.07.017.

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Received April 19, 2018. Accepted July 16, 2018.

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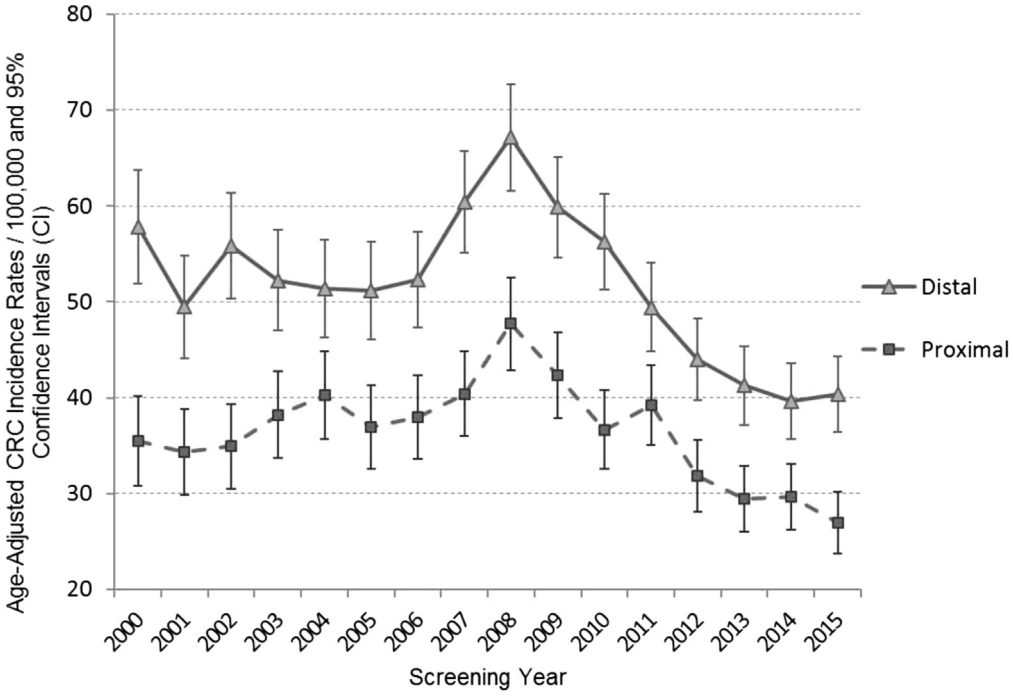
Acknowledgment
Chyke A. Doubeni is a member of the US Preventive Services Task Force (USPSTF). This article does not necessarily represent the views and policies of the USPSTF. Author contributions: TRL, DAC, CDJ, JES, VPQ, AGZ, JKL, NRG, ATL, CPQ, BHF, and CAD were involved with the study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; and study supervision. WKZ and NU were involved with acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and statistical analysis.

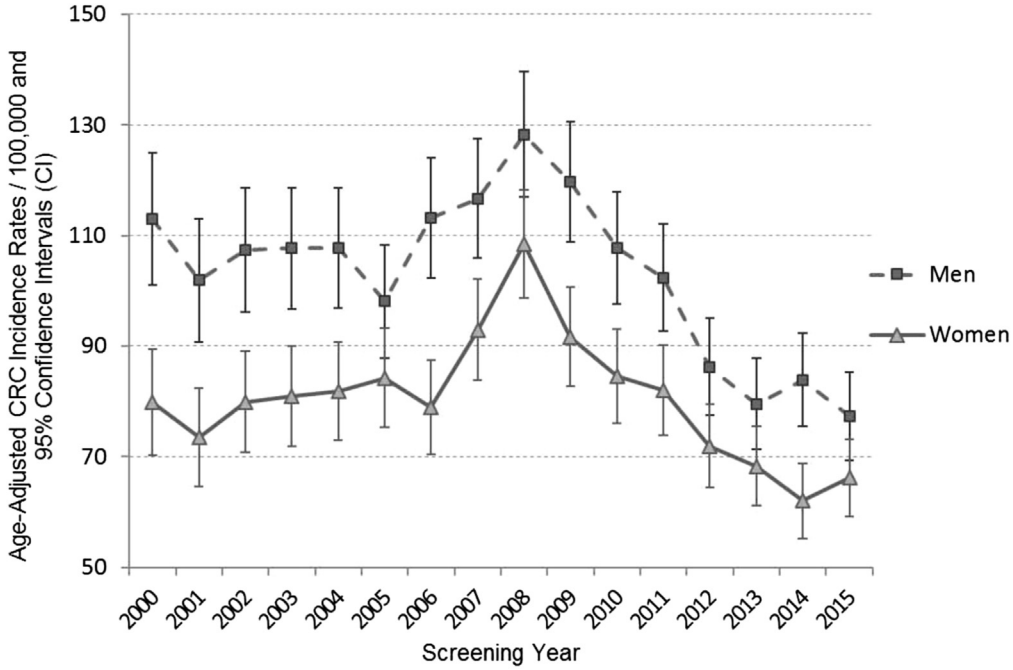
Conflicts of interest
The authors disclose no conflicts.

Funding
The study was funded by the National Cancer Institute. The study sponsor had no role in the study design or in the collection, analysis, and interpretation of data.



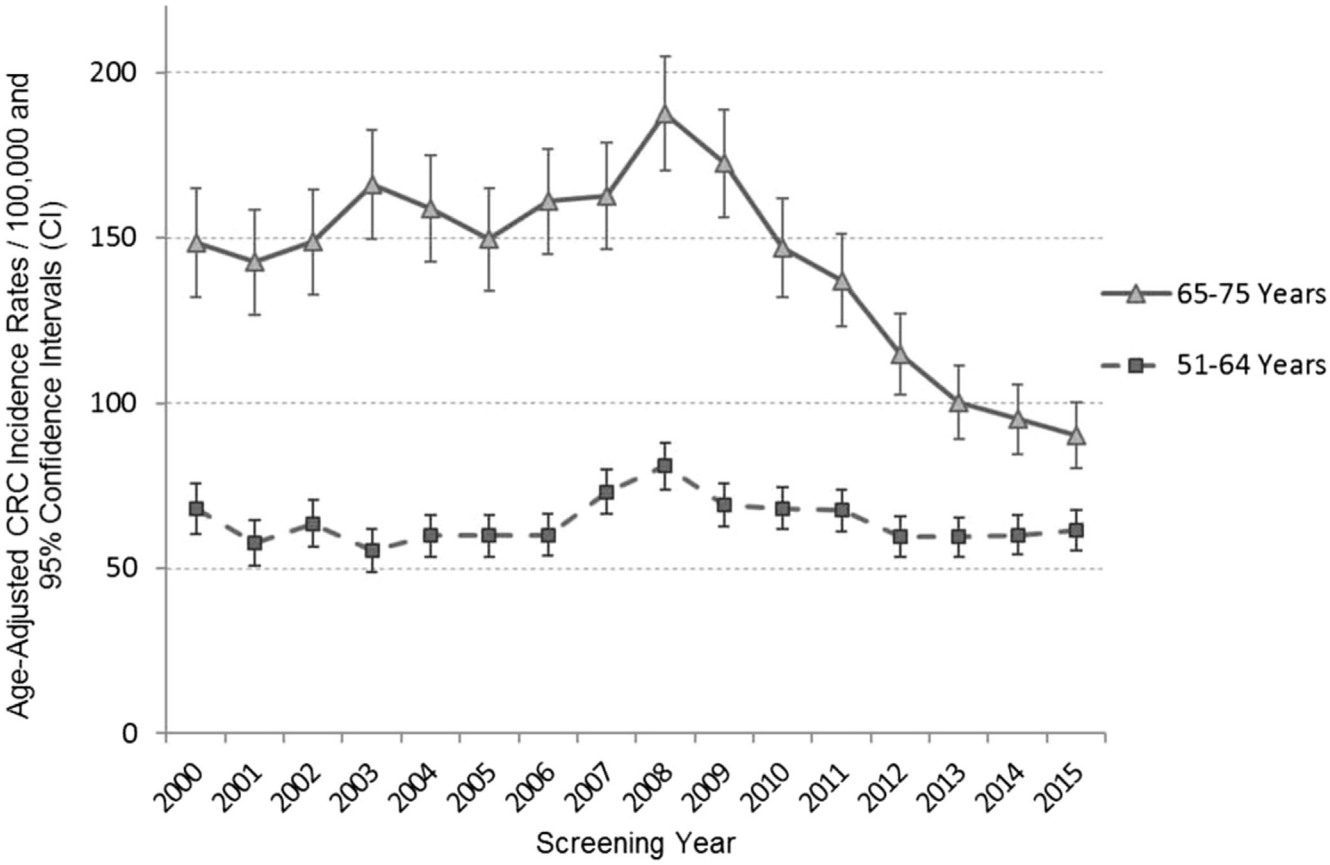
Year	Proximal Cases/100,000 (95% CI)	Distal Cases/100,000 (95% CI)
2000	35.5 (30.8, 40.2)	57.9 (51.9, 63.8)
2001	34.3 (29.9, 38.8)	49.5 (44.2, 54.8)
2002	34.9 (30.5, 39.4)	55.9 (50.3, 61.4)
2003	38.2 (33.7, 42.7)	52.2 (47.0, 57.5)
2004	40.3 (35.7, 44.8)	51.4 (46.3, 56.5)
2005	36.9 (32.6, 41.3)	51.2 (46.1, 56.3)
2006	38.0 (33.6, 42.4)	52.4 (47.3, 57.4)
2007	40.4 (36.0, 44.8)	60.4 (55.1, 65.8)
2008	47.7 (42.9, 52.5)	67.1 (61.6, 72.7)
2009	42.3 (37.8, 46.8)	59.9 (54.6, 65.1)
2010	36.7 (32.6, 40.8)	56.2 (51.2, 61.2)
2011	39.2 (35.1, 43.4)	49.5 (44.9, 54.1)
2012	31.9 (28.1, 35.6)	44.0 (39.7, 48.3)
2013	29.4 (26.0, 32.9)	41.3 (37.2, 45.3)
2014	29.7 (26.2, 33.1)	39.6 (35.7, 43.6)
2015	26.9 (23.7, 30.2)	40.3 (36.4, 44.3)

Supplementary Figure 1. Cohort CRC incidence rates by colon location: age-adjusted to the US 2000 Census population.



Year	Men CRC Incidence Rates Cases/100,000 (95% CI)	Women CRC Incidence Rates Cases/100,000 (95% CI)
2000	113.0 (101.1, 125.0)	79.8 (70.2, 89.4)
2001	101.9 (90.8, 113.0)	73.5 (64.5, 82.4)
2002	107.5 (96.2, 118.7)	79.9 (70.8, 89.1)
2003	107.7 (96.7, 118.7)	81.0 (72.0, 90.0)
2004	107.8 (96.9, 118.7)	81.9 (73.0, 90.8)
2005	98.1 (87.8, 108.4)	84.2 (75.3, 93.2)
2006	113.3 (102.4, 124.2)	78.9 (70.4, 87.4)
2007	116.7 (105.9, 127.5)	92.9 (83.8, 102.1)
2008	128.3 (116.9, 139.6)	108.5 (98.7, 118.2)
2009	119.7 (108.8, 130.6)	91.7 (82.7, 100.6)
2010	107.8 (97.6, 118.0)	84.6 (76.1, 93.0)
2011	102.4 (92.7, 112.1)	82.0 (73.8, 90.2)
2012	86.3 (77.4, 95.1)	71.9 (64.4, 79.4)
2013	79.5 (71.2, 87.8)	68.3 (61.1, 75.5)
2014	83.8 (75.4, 92.3)	62.0 (55.2, 68.8)
2015	77.3 (69.3, 85.3)	66.2 (59.2, 73.2)

Supplementary Figure 2. Cohort CRC incidence rates by sex: age-adjusted to the US 2000 Census population.



Year	51-64 Years CRC Incidence Rates Cases/100,000 (95% CI)	65-75 Years CRC Incidence Rates Cases/100,000 (95% CI)
2000	68.0 (60.3, 75.7)	148.5 (131.9, 165.0)
2001	57.6 (50.7, 64.4)	142.6 (126.8, 158.4)
2002	63.5 (56.5, 70.6)	148.8 (132.8, 164.7)
2003	55.3 (48.9, 61.7)	166.1 (149.6, 182.6)
2004	59.8 (53.3, 66.3)	158.7 (142.7, 174.8)
2005	59.9 (53.4, 66.3)	149.5 (134.0, 165.1)
2006	60.1 (53.9, 66.4)	161.0 (145.0, 176.9)
2007	73.1 (66.3, 79.9)	162.6 (146.6, 178.6)
2008	81.0 (73.9, 88.1)	187.6 (170.5, 204.7)
2009	69.0 (62.5, 75.5)	172.5 (156.2, 188.7)
2010	68.2 (61.8, 74.5)	146.9 (132.1, 161.7)
2011	67.5 (61.2, 73.9)	137.2 (123.4, 151.0)
2012	59.6 (53.6, 65.6)	114.6 (102.4, 126.9)
2013	59.4 (53.5, 65.4)	100.3 (89.2, 111.3)
2014	60.1 (54.1, 66.1)	95.1 (84.6, 105.6)
2015	61.5 (55.4, 67.6)	90.1 (80.2, 100.1)

Supplementary Figure 3. Cohort CRC incidence rates by age group: age-adjusted to US 2000 Census population.

Supplementary Table 1. Percentage of Eligible Cohort Members Screening Up-to-Date: Overall and by Modality

Screening status	2000	2001	2002	2003	2004	2005	2006	2007
Screening eligible, n	651,675	675,152	700,196	732,431	754,247	771,407	791,189	807,447
Screening up-to-date, n (%)	253,790 (38.9)	262,919 (38.9)	270,857 (38.7)	284,024 (38.8)	295,147 (39.1)	312,028 (40.5)	359,336 (45.4)	428,355 (53.1)
By colonoscopy, n (%)	55,544 (8.5)	64,322 (9.5)	72,951 (10.4)	85,115 (11.6)	98,214 (13.0)	113,356 (14.7)	125,081 (15.8)	139,895 (17.3)
By sigmoidoscopy, n (%)	177,863 (27.3)	176,630 (26.2)	172,783 (24.7)	170,708 (23.3)	165,046 (21.9)	160,792 (20.8)	155,918 (19.7)	145,856 (18.1)
By FIT, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5523 (0.7)	96,385 (11.9)
By gFOBT, n (%)	20,383 (3.1)	21,967 (3.3)	25,123 (3.6)	28,201 (3.9)	31,887 (4.2)	37,880 (4.9)	72,814 (9.2)	46,219 (5.7)
FIT/gFOBT positivity, %	4.8	4.3	4.1	3.9	4.2	3.6	3.1	4.2
Colonoscopy follow-up,[a] %	41.1	40.3	40.8	40.7	41.5	48.8	58.0	64.4
Unscreened, n (%)	397,885 (61.1)	412,233 (61.1)	429,339 (61.3)	448,407 (61.2)	459,100 (60.9)	459,379 (59.6)	431,853 (54.6)	379,092 (47.0)
Screening status	2008	2009	2010	2011	2012	2013	2014	2015
Screening eligible, n	821,710	834,678	846,940	865,599	893,158	920,462	938,758	975,637
Screening up-to-date, n (%)	541,714 (65.9)	571,108 (68.4)	632,244 (74.7)	691,001 (79.8)	721,053 (80.7)	741,587 (80.6)	770,382 (82.1)	806,806 (82.7)
By colonoscopy, n (%)	148,980 (18.1)	176,572 (21.2)	202,518 (23.9)	229,103 (26.5)	255,982 (28.7)	285,160 (31.0)	307,540 (32.8)	327,733 (33.6)
By sigmoidoscopy	130,128 (15.8)	126,078 (15.1)	115,837 (13.7)	93,897 (10.9)	71,120 (8.0)	48,854 (5.3)	28,262 (3.0)	15,754 (1.6)
By FIT	258,660 (31.5)	265,901 (31.9)	311,966 (36.8)	366,354 (42.3)	392,550 (44.0)	406,192 (44.1)	433,295 (46.2)	462,153 (47.4)
By gFOBT	3946 (0.5)	2557 (0.3)	1923 (0.2)	1647 (0.2)	1401 (0.2)	1381 (0.2)	1285 (0.1)	1166 (0.1)
FIT/gFOBT positivity, %	5.3	4.6	4.4	4.4	4.1	4.0	3.6	3.6
Colonoscopy follow-up,[a] %	72.2	77.2	78.8	79.8	84.1	83.6	84.1	83.1
Unscreened, n (%)	279,996 (34.1)	263,570 (31.6)	214,696 (25.4)	174,598 (20.2)	172,105 (19.3)	178,875 (19.4)	168,376 (17.9)	168,831 (17.3)

[a]Colonoscopy follow-up within 6 mo after a positive FIT or gFOBT.

Supplementary Table 2. Cohort Age-Adjusted Colorectal Cancer Incidence Rates and Incidence-Based Mortality Rates: Age-Adjusted to the US 2000 Census Population

Year	CRC incidence rates cases/100,000 (95% CI)	CRC mortality rates cases/100,000 (95% CI)
2000	95.8 (88.1–103.4)	30.9 (26.6–35.3)
2001	86.9 (79.8–94.0)	28.3 (24.3–32.4)
2002	92.9 (85.8–100.1)	28.1 (24.1–32.0)
2003	93.6 (86.5–100.6)	26.3 (22.6–30.0)
2004	93.9 (87.0–100.9)	24.9 (21.3–28.5)
2005	90.8 (84.0–97.6)	29.0 (25.2–32.8)
2006	94.9 (88.1–101.7)	26.4 (22.8–30.0)
2007	104.0 (97.0–111.0)	24.3 (20.9–27.8)
2008	117.8 (110.4–125.2)	24.3 (20.8–27.7)
2009	104.7 (97.7–111.7)	24.7 (21.3–28.1)
2010	95.4 (88.8–101.9)	21.4 (18.3–24.5)
2011	91.6 (85.3–97.9)	22.2 (19.1–25.3)
2012	78.6 (72.8–84.3)	21.0 (18.0–24.0)
2013	73.5 (68.1–79.0)	17.9 (15.2–20.6)
2014	72.2 (66.8–77.5)	16.9 (14.3–19.4)
2015	71.4 (66.1–76.7)	14.7 (12.3–17.1)

Supplementary Table 3. Cohort Colorectal Cancer Incidence Rates by Stage: Age-Adjusted to the US 2000 Census Population

Year	Early-stage cases/100,000 (95% CI)	Advanced-stage cases/100,000 (95% CI)
2000	48.2 (42.8–53.6)	45.9 (40.6–51.1)
2001	48.4 (43.1–53.7)	36.5 (32.0–41.1)
2002	51.8 (46.4–57.1)	40.3 (35.6–45.0)
2003	48.6 (43.5–53.7)	42.6 (37.9–47.4)
2004	47.1 (42.2–52.1)	45.4 (40.6–50.2)
2005	49.7 (44.7–54.8)	40.3 (35.8–44.7)
2006	49.6 (44.6–54.5)	43.9 (39.2–48.5)
2007	57.3 (52.0–62.5)	45.4 (40.8–50.1)
2008	71.5 (65.6–77.3)	44.8 (40.3–49.3)
2009	64.3 (58.8–69.7)	40.2 (35.9–44.5)
2010	57.8 (52.7–62.9)	35.8 (31.8–39.8)
2011	55.5 (50.6–60.4)	35.7 (31.8–39.6)
2012	48.6 (44.1–53.2)	29.2 (25.7–32.7)
2013	42.3 (38.1–46.4)	30.9 (27.3–34.4)
2014	44.0 (39.8–48.2)	27.8 (24.5–31.1)
2015	41.2 (37.2–45.2)	29.3 (25.9–32.6)