Supplementary Figure 1. Colorectal cancer incidence, colonoscopy use, and colorectal cancer stage at diagnosis in patients age 18-49 years, stratified by age, 1998-2018

(A) Trends in age-standardized (2000 United States census population) colorectal cancer incidence per 100,000 person-years. *(B)* Trends in colonoscopy use per 1,000 person-years. *(C)* Trends in age-standardized (2000 United States census population) early- and advanced-stage colorectal cancer incidence per 100,000 person-years. *(D)* Trends in diagnostic and screening colonoscopy use per 1,000 person-years.

SUPPLEMENTARY METHODS

Kaiser Permanente Northern California (KPNC) is a large integrated health system that provides comprehensive inpatient and outpatient services to over 4.3 million members in suburban, urban, and semi-rural regions throughout Northern California. All KPNC members are insured with complete access to primary and specialty care. All patient encounters, medical diagnoses and procedures, laboratory results and vital statistics, as well as information on demographics, membership, and social behaviors are recorded in electronic databases. In 2006-2008, KPNC implemented an organized colorectal cancer (CRC) screening program based on annual mailed fecal immunochemical test (FIT) outreach and opportunistic colonoscopy for members age 50-75 years; during the study period, no organized CRC screening program existed for patients <50 years.[1] Membership within KPNC is similar in demographic and socioeconomic characteristics to the Northern California region.[2]

Study participants were KPNC members 18-49 and 50-54 years of age, respectively, in 1998-2018, with no prior diagnosis of CRC. Gaps in membership of ≤90 days were permitted, and members could re-enter the cohort following periods of membership termination. Age, membership, and death data were extracted from the KPNC Virtual Data Warehouse demographics and enrollment databases, the KPNC Cancer Registry and the KPNC Mortality file, respectively.

CRC diagnoses, defined as an adenocarcinoma of the colon or rectum, were extracted from the KPNC Cancer Registry using International Classification of Disease oncology codes (C18.0, C18.2-C18.9, C19.9, C20.9) and morphology codes (8000, 8010, 8020-8021, 8140-8141, 8143-8144, 8147, 8200, 8210-8211, 8215, 8220-8221, 8230, 8255, 8260-8263, 8323, 8410, 8430, 8440, 8470, 8480-8481, 8490, 8510, 8560, 8570-8574, 8576). A single SEER summary stage variable encompassing all diagnosis years was used to determine cancer stage at diagnosis (early stage: localized disease and regional disease with direct extension only; advanced stage: disease in regional lymph nodes, regional disease with direct extension and spread to regional lymph nodes and distant metastasis).

Colonoscopies were extracted from the KPNC Virtual Data Warehouse procedure database using Current Procedure Terminology codes (44388-44394, 44397, 44401-44402, 44404-44408, 45355, 45378-45393, 45398), International Classification of Disease procedure codes (45.23, 98.04, V76.51, 0DBB8ZX, 0DBB8ZZ, 0DBC8ZX, 0DBC8ZZ, 0DBF8ZX, 0DBF8ZZ, 0DBH8ZX, 0DBH8ZZ, 0DBK8ZX, 0DBK8ZZ, 0DBL8ZX, 0DBL8ZZ, 0DBM8ZX, 0DBM8ZZ), Healthcare Common Procedure Coding System codes (G0105, G0121, G6019-G6020, G9252-G9253, G9659-G9661, G9935-G9937) and local KPNC-specific codes (106504, 129133, 204456, 204716, 207490-207493, 208340, 214417, 219377, 226145, 226395, 230847, 231512, 233387-233390, 235525, 242883, 244893, 244895, 246300-246301, 250625, 253994, 279802, 299458-299461, 566735, 643763-643764, 696739). An indication algorithm was applied to each colonoscopy to determine whether it was performed for diagnostic (e.g., history of partial colectomy or inflammatory bowel disease, abdominal symptoms or CRC diagnosis in the past 6 months, follow-up to a positive sigmoidoscopy), surveillance (e.g., history of CRC, adenoma, hereditary CRC syndromes), FIT-positive follow-up (positive FIT result in past year), or screening purposes.[3]

Colonoscopy use and CRC incidence were calculated as the number of events (i.e., individuals receiving a colonoscopy or new CRC diagnosis) per 1,000 and 100,000 person-years (PY) of enrollment, respectively; PY was defined as the cumulative years of enrollment per membership year, minus any gaps >90 days. CRC incidence rates were age-adjusted to the 2000 United
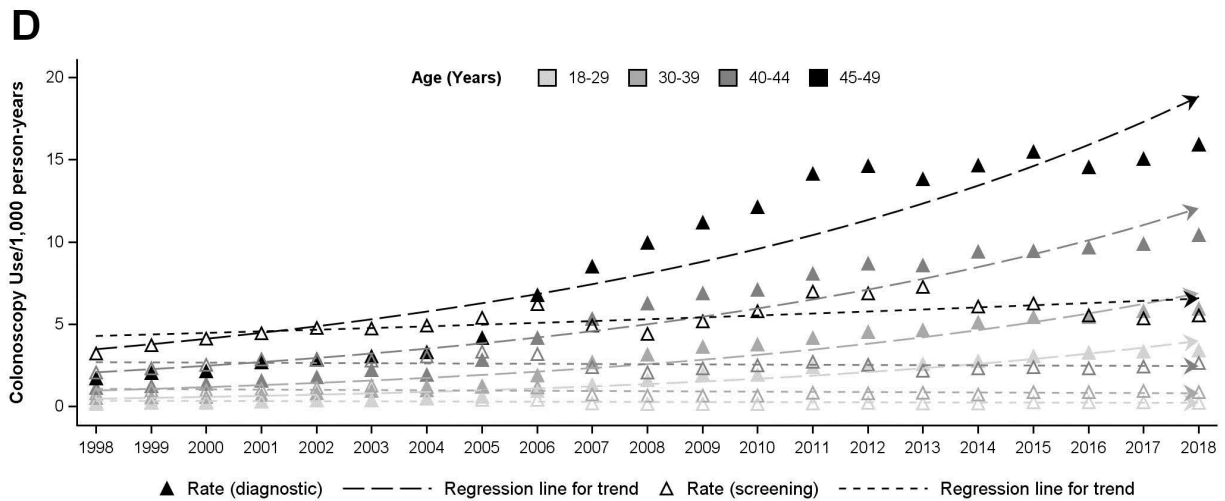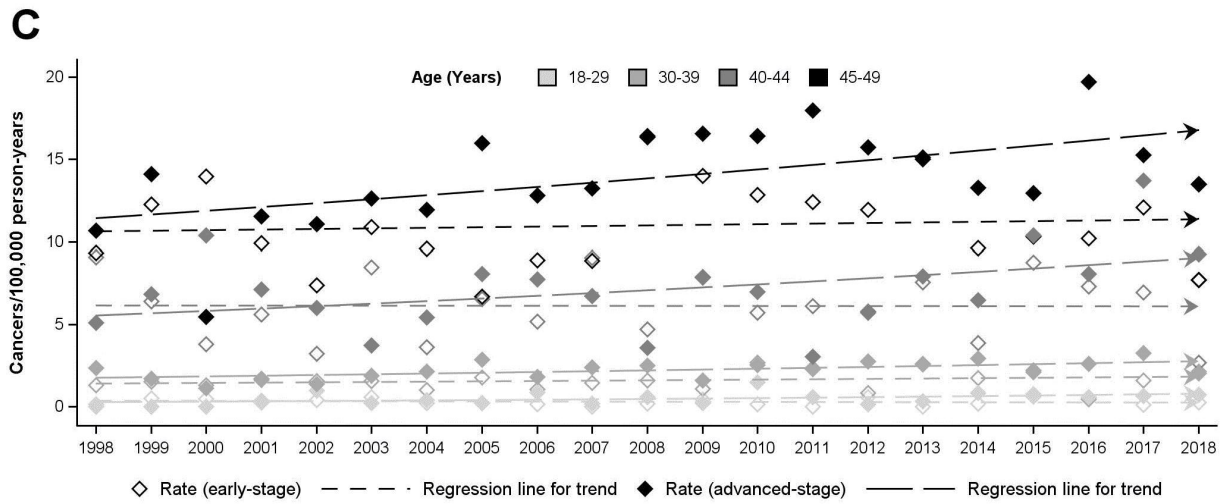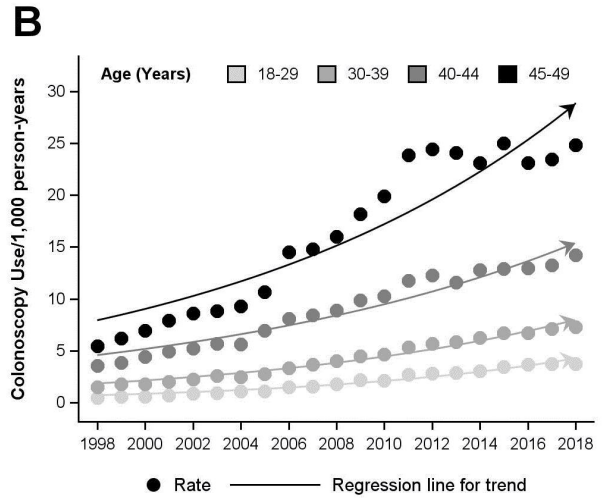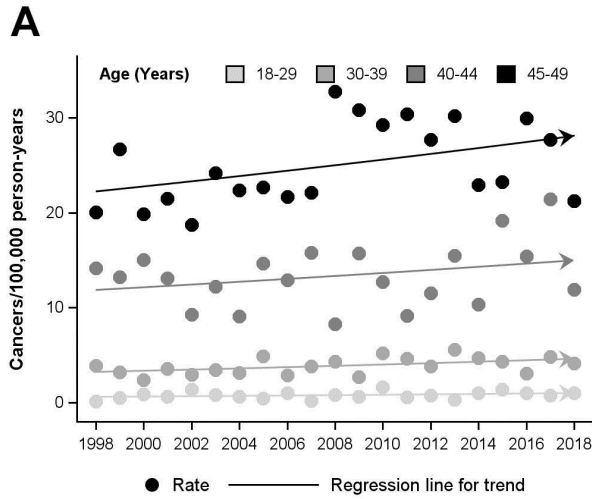
States standard population using single-year age intervals provided by SEER.[4] Overall CRC incidence rates were also adjusted for colonoscopy use (using the 1998 rate as the baseline) to factor in the potential for greater colonoscopy use to increase the opportunity for CRC diagnoses. In addition, temporal trends were assessed based on the absolute change over the study period in predicted rates per 100,000 PY and average percent change (APC) in annual incidence using Poisson regression. All analyses were performed using SAS 9.4.

Word Count: 672 / 1,000

REFERENCES

1. Levin TR, Corley DA, Jensen CD, et al. Effects of Organized Colorectal Cancer Screening on Cancer Incidence and Mortality in a Large Community-Based Population. *Gastroenterology*. 2018;155:1383-1391 e5.
2. S Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. *Am J Public Health*. 1992;82:703–710.
3. Lee JK, Jensen CD, Lee A, Doubeni CA, Zauber AG, Levin TR, Zhao WK, Corley DA. Development and validation of an algorithm for classifying colonoscopy indication. Gastrointest Endosc. 2015 Mar;81(3):575-582.
4. National Institutes of Health, National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Standard populations–single ages.

A Cancers/100,000 person-years

Age (Years): □ 18-29 □ 30-39 ▨ 40-44 ■ 45-49

● Rate   — Regression line for trend

B Colonoscopy Use/1,000 person-years

Age (Years): □ 18-29 □ 30-39 ▨ 40-44 ■ 45-49

● Rate   — Regression line for trend

C Cancers/100,000 person-years

Age (Years): □ 18-29 □ 30-39 ▨ 40-44 ■ 45-49

◇ Rate (early-stage)   — · — Regression line for trend   ◆ Rate (advanced-stage)   —— Regression line for trend

D Colonoscopy Use/1,000 person-years

Age (Years): □ 18-29 □ 30-39 ▨ 40-44 ■ 45-49

▲ Rate (diagnostic)   — · — Regression line for trend   △ Rate (screening)   - - - - Regression line for trend

Supplemental Table 1. Baseline Characteristics and Outcomes Among Patients Age 18-49 and 50-54 years, 1998-2018

	Age 18-49 years			Age 50-54 years		
	Total	**Colonoscopy Received**	**Cancer Diagnosed**	**Total**	**Colonoscopy Received**	**Cancer Diagnosed**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Total Patients	5,982,616	151,363	2,280	1,625,690	181,322	2,259
Age*						
18-29 years	3,219,551 (53.8)	19,105 (12.6)	89 (3.9)	-	-	-
30-39 years	2,779,017 (46.5)	37,748 (24.9)	377 (16.5)	-	-	-
40-44 years	1,798,254 (30.1)	42,436 (28.0)	623 (27.3)	-	-	-
45-49 years	1,738,253 (29.1)	79,714 (52.7)	1,191 (52.2)	-	-	-
Sex						
Female	2,940,737 (49.2)	85,228 (56.3)	1,114 (48.9)	832,958 (51.2)	94,898 (52.3)	1,004 (44.4)
Male	3,041,879 (50.8)	66,135 (43.7)	1,166 (51.1)	792,732 (48.8)	86,424 (47.7)	1,255 (55.6)
Race/Ethnicity						
Asian/Pacific Islander	909,346 (15.2)	25,448 (16.8)	467 (20.5)	262,990 (16.2)	32,389 (17.9)	417 (18.5)
Hispanic	1,019,709 (17.0)	29,205 (19.3)	409 (17.9)	239,773 (14.7)	27,615 (15.2)	335 (14.8)
Non-Hispanic Black	367,331 (6.1)	11,566 (7.6)	217 (9.5)	120,200 (7.4)	14,205 (7.8)	228 (10.1)
Non-Hispanic White	2,041,120 (34.1)	78,763 (52.1)	1,164 (51.1)	814,348 (50.1)	101,176 (55.8)	1,259 (55.7)
Other	1,645,110 (27.5)	6,381 (4.2)	23 (1.0)	188,379 (11.6)	5,937 (3.3)	20 (0.9)
Colonoscopy Indication*						
Diagnostic	-	98,917 (65.4)	-	-	72,329 (39.9)	-
Screening	-	44,593 (29.5)	-	-	64,972 (35.8)	-
FIT-positive Follow-up	-	3,121 (2.1)	-	-	32,299 (17.8)	-
Surveillance	-	5,265 (3.5)	-	-	10,425 (5.7)	-
Unknown	-	7,255 (4.8)	-	-	8,213 (4.5)	-
Stage at Diagnosis						
Early	-	-	982 (43.1)	-	-	1,313 (58.1)
Advanced	-	-	1,278 (56.1)	-	-	928 (41.1)
Unknown	-	-	20 (0.8)	-	-	18 (0.8)

*Patients can occupy more than one age group and receive more than one colonoscopy with different indications during the study period and therefore percentage totals for "Age" and "Colonoscopy Indication" exceed 100.