# Cumulative Risk of Colorectal Cancer and Colorectal Cancer Mortality in Screen-Eligible Older Adults with History of Adequate Screening

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**Abstract**

Cumulative Risk of Colorectal Cancer and Colorectal Cancer Mortality in Older Screen-Eligible Adults with Adequate Screening Histories

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The decision of whether or not to continue colorectal cancer (CRC) screening at older ages is complex. Although most guidelines recommend routine screening of adults older than age 45 years for CRC, there is ambiguity on when to stop screening. The United States Preventive Services Task Force (USPSTF), American Cancer Society, and the Multi-Society Task Force all recommend screening until age 75 years, followed by individualized and shared decision-making for people 76-85 years and cessation after 85 years. However, few empirical data are available to inform older adults' decision-making based on prior screening, particularly among persons with a prior negative test. Using a retrospective cohort of older adults in the Optimizing Colorectal Cancer Screening PREcision and Outcomes in CommunIty-baSEd Populations (PRECISE) cohort, I estimated cumulative risk of CRC incidence and mortality among two groups of screen-eligible older adults. The first had a negative colonoscopy ten years earlier; the second had a negative stool-based test one year earlier. Each group had a low risk of CRC diagnosis and of CRC mortality. Overall, cumulative CRC incidence and mortality among screen-eligible older adults occur in the context of much higher risk of death from other causes, reinforcing guidelines that recommend the benefits of ongoing screening be carefully weighed against the burdens and risks.

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# Introduction: Hypothetical Clinical Vignettes

We begin with three hypothetical case vignettes to illustrate the evidence gap in a clinical setting that motivates this body of work.

Three patients attend an annual wellness exam with their primary care providers. All are older than 75 years, the upper age limit of universally recommended CRC screening, and younger than age 86, when screening cessation is strongly recommended.

Patient 1: the Golfer
Sex: Male
Age: 80 years old
Comorbidities: Osteoarthritis (Charlson Comorbidity Index = 1)
Screening history: Colonoscopy at age 70, negative result (no findings to indicate elevated risk)
Patient notes: Plays 9-holes of golf twice weekly; planning to take an around-the-world cruise for his 85th birthday

> *Scenario*: A man with osteoarthritis attends an annual wellness visit with his primary care provider the day after his 80th birthday. His provider wishes him a happy birthday and asks if he did anything special for such a big birthday. The patient replies he had a big party with his family and remarks it was an improvement over his last big birthday (70th) because he'd been prepping for a colonoscopy on that one ("Can you believe it? I delayed my big birthday dinner just so I could do the colonoscopy?! Good thing I plan to live for a lot more big birthdays."). The patient then asks with a slight grimace, "Given that it's been ten years, shouldn't I be due for another one of those soon? I've got grand plans to cruise around the world on my 85th birthday. What's my risk of getting [colorectal] cancer before that?"

Patient 2: the Gardener
Sex: Female
Age: 81 years old
Comorbidities: None (Charlson Comorbidity Index = 0)
Screening history: Colonoscopy at age 71, negative result (no findings to indicate elevated risk)
Patient notes: Loves to garden; close friend died of CRC one year ago; a gastroenterologist said she should continue screening if she's healthy.

> *Scenario:* An 81-year-old woman with no comorbidities attends an annual wellness visit with her primary care provider. Her primary care provider asks whether she has any topics she'd like to discuss during the visit and the patient answers that she's confused about whether or not she's due for colonoscopy. She watched her friend battle CRC for over two years and eventually die from the disease one year ago. When the Gardener accompanied her friend to appointments with the gastroenterologist, to physician mentioned colonoscopy could be continued until age 85 years. While she wants to avoid the type of death her friend suffered, she's reluctant to go through a colonoscopy ("To say it's highly unpleasant is to put it politely," she says). Her last colonoscopy was ten years ago and resulted negative (no polyps or CRC).

Patient 3: the Baker
Sex: Female
Age: 76 years old
Comorbidities: Peripheral vascular disease, renal disease, uncomplicated diabetes mellitus (Charlson Comorbidity Index = 4)
Screening history: annual FIT (most recent at age 75, test result negative)
Patient notes: Owner of a local bakery and works in the shop 4 days a week; mother died of breast cancer at age 60 years.

> *Scenario*: A 76-year-old woman with peripheral vascular disease, renal disease, and uncomplicated diabetes mellitus attends an annual wellness visit with her primary care provider. Given her family history of breast cancer (mother died of it many years ago), she's highly adherent to and aware of cancer screening recommendations. She notes that she received a mailed FIT kit (part of the screening program offered by her health system that mails annual kits to screen-eligible members ages 50-80 years) and remarks "I thought I was done with these when I turned 75? Do I still have to worry about CRC?"

# Chapter 1: Risk of colorectal cancer and colorectal cancer mortality beginning ten years after a negative colonoscopy, among screen-eligible adults 76-85 years old [Aim 1]

**Abstract**

Few empirical data are available to inform older adults' decisions about whether to screen or continue screening for colorectal cancer (CRC) based on their prior history of screening, particularly among individuals with a prior negative exam. Using a retrospective cohort of older adults receiving healthcare at three Kaiser Permanente integrated healthcare systems in Northern California (KPNC), Southern California (KPSC), and Washington (KPWA), we estimated the cumulative risk of CRC incidence and mortality among older adults who had a negative colonoscopy ten years earlier, accounting for death from other causes. Screen-eligible adults aged 76-85 years who had a negative colonoscopy ten years earlier were found to be at a low risk of CRC diagnosis, with a cumulative incidence of 0.39% (95% CI: 0.31-0.48%) at two years that increased to 1.29% (95% CI: 1.02-1.61%) at eight years. Cumulative mortality from CRC was 0.04% (95% CI: 0.02-0.08%) at two years and 0.46% (95% CI: 0.30-0.70%) at eight years. These low estimates of cumulative CRC incidence and mortality occurred in the context of much higher risk of death from other causes.

**Introduction**

Age is a strong predictor of CRC risk and mortality (1), but other characteristics could bear on the decision of older adults to undergo screening for CRC. Recent recommendations from the United States Preventive Services Task Force (USPSTF), American Cancer Society, and the Multi-Society Task Force advise that, among people ages 76-85 years, the decision of whether or not to screen should be individualized and shared between clinicians and patients (2-5). The guidelines further suggest a consideration of prior screening history and overall health, since the degree to which a person may benefit from screening depends on both their risk of CRC and the life expectancy over which the benefit may accrue (6-9). Understanding for whom CRC screening could be of great or only marginal benefit (because they have a high or low risk of CRC, respectively) may inform patient and provider decision-making and more targeted test offerings to older adults, which are key components of the USPSTF's new draft recommendations for CRC screening in adults 76-85 years old (10).

However, there is great uncertainty about the value of continued screening beyond age 75 (11, 12) and few data are available to inform the decision. Prior studies have shown a low incidence of CRC in the years immediately following a negative colonoscopy or sigmoidoscopy , particularly for persons ages 50-75 years. Existing recommendations for older adults are based primarily on microsimulation models of CRC incidence, colonoscopy harms, and life expectancy (13). This evidence gap leaves age as a default (and sometimes preferred) determinant (14), which ignores tremendous variability in biological age and health status (8, 15) among adults aged 76-85 years and may obscure differences in risk of CRC and CRC-related mortality, especially based on screening history. It is unknown how these differences may translate to differences in the cumulative risk of CRC incidence and mortality.

Using a large multi-healthcare system dataset of patients in Washington and California, we provide absolute estimates of CRC incidence and mortality among people aged 76-85 years with recent screening by colonoscopy (i.e., a negative result ten years ago).

## Methods

### Study Design and Setting

We conducted a retrospective cohort study among older adult members of three Kaiser Permanente integrated healthcare systems: Northern California (KPNC), Southern California (KPSC), and Washington (KPWA). These healthcare systems contribute to the Optimizing Colorectal Cancer Screening PREcision and Outcomes in CommunIty-baSEd Populations (PRECISE) Research Center, part of the National Cancer Institute-funded Population-based Research to Optimize the Screening Process (PROSPR II) consortium (16). Details of these healthcare systems, particularly with respect to the CRC screening process, have been previously published (17). Cumulatively, these populations include more than 1 of every 70 of the total United States population and are generally representative of the census demographics of their regional populations (18-21).

All three integrated healthcare systems include older populations. Compared with the broader United States population aged 65 and older, the study population had similarly high levels of Medicare coverage (~90%) and had greater racial and ethnic diversity (22, 23). Further details about the PRECISE cohort have been published elsewhere (17, 24). The study was approved by Institutional Review Boards at the study sites and the University of Washington.

### Eligibility Criteria

The study population included patients who had previously undergone a colonoscopy (for any indication) and were eligible (based on the criteria below) for CRC screening sometime between ages 76-85 years. The population of interest comprised patients older than 75 years, the upper recommended screening age for universal screening, but younger than age 86 years, when cessation is strongly recommended. Between these age cutoffs, patients are recommended to engage in shared-decision-making with their clinician about whether to continue screening (4). Patients were included in the study population if they had a negative colonoscopy (i.e., no adenoma or cancer detected) between January 1, 2000 and December 31, 2009, when they were 66-75 years old and were alive ten years following that colonoscopy. The time point ten years after colonoscopy was considered as the study's index date (i.e., the time point at which the person might consider screening again). To ensure a screening-eligible population, patients with a history of inflammatory bowel disease (IBD), CRC, or gastrointestinal surgery prior to their index date were excluded. Patients with CRC testing between their negative colonoscopy and index dates (lower endoscopy or any positive fecal test during the ten years prior to their index date or any fecal test during the one year prior to their index date) were also excluded, since these individuals would have been up-to-date or otherwise ineligible for screening at their index date. Patients were considered ineligible for screening if they had a computed tomography (CT) colonography, barium enema, or abdominal CT during the 180 days prior to their index date, because these procedures could be used to detect CRC, and thus anyone with a recent procedure would not be eligible for screening in the near term. Patients were also excluded if they had no recorded encounters (acute inpatient, intuitional stay, or primary care) with the healthcare system during the 365 days prior to the index date, which served as a measure of interaction with a

healthcare provider at which symptoms, if present, would have been reported. This exclusion also improves the likelihood of up-to-date coding of other relevant conditions for analysis (e.g., for calculation of comorbidity index described in the "Measures" section below).

Finally, patients with any symptoms (i.e., abdominal pain, iron deficiency or unspecified anemias, gastrointestinal bleeding or blood in stools, diarrhea, weight loss or underweight, diverticulitis, constipation, abdominal mass, or change in bowel habits) during the 180 days prior to their index date were also excluded because the presence of these signs or symptoms makes patients ineligible for screening, which, by definition, occurs in patients without signs or symptoms of cancer.

**Data Collection**

The PRECISE Research Center collected information on patient demographics and clinical characteristics, CRC screening process data (i.e., risk factors, screening tests, diagnostic evaluations, treatment procedures, and outcomes), CRC screening history prior to cohort entry, CRC diagnoses, and CRC deaths. Data on CRC tests, patient demographics, and comorbidities diagnosed during cohort eligibility were obtained from administrative and clinical databases including electronic health records. Patient data regarding prior testing history and conditions were collected with look-back depending on site constraints: KPWA extended back to 1/1/1993 while KPNC and KPSC looked back to 1/1/2000 for enrollment, visits, and CRC tests, and extended further back (to the full extent of information available in electronic records databases) for CRC diagnoses and gastrointestinal surgeries. CRC diagnoses were obtained from local and central cancer registries: Seattle Puget-Sound Surveillance, Epidemiology and End Results (SEER) registry for KPWA, and the facility-based cancer registries at KPNC and KPSC, which report to the State of California Cancer Registry. Information on patient deaths was sourced from state vital records data, as well as a variety of internal sources (e.g., insurance membership, discharge status on claims, etc.). CRC-related deaths were ascertained using each site's state death records as the primary source for cause of death.

For procedures occurring after the index date, colonoscopy indication was assigned based on manual chart review and natural language processing or using a modified version of a colonoscopy indication algorithm that incorporates administrative and clinical data (25) and considers data elements related to recent procedures, IBD, signs and symptoms, past findings of CRC screening procedures, and personal history of CRC.

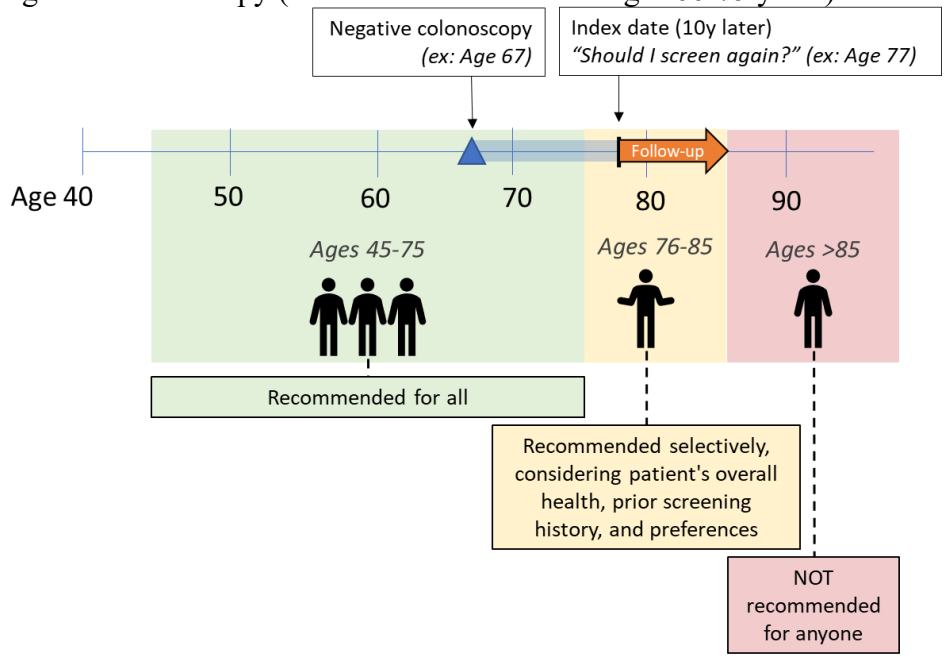
**Study Measures**

The Charlson Comorbidity Index (CCI) was used to measure comorbidity burden and was calculated by applying modified Charlson/Deyo comorbidity algorithm weights (26) to an updated set of diagnosis and procedure codes associated with both inpatient and outpatient visits. CCI was assessed as of the last day of the calendar quarter prior to the index date, using a look-back period of 365 days for relevant codes, and categorized (0, 1, 2, 3, 4, ≥5) for analysis. Sensitivity analyses stratified patients based on the individual comorbid conditions that contributed to the CCI. Other covariates included age at index date, sex, race and ethnicity, and recent encounters with the healthcare system, which were classified as primary care or inpatient stays (both acute and institutional) and used as a supplementary proxy for health status, along with CCI.

**Statistical Analysis**

Descriptive statistics were calculated to characterize the cohort demographics. Cumulative incidence functions (CIFs) (27, 28) were used to estimate cumulative incidence for two outcomes: 1) CRC incidence and 2) CRC mortality in the years following the index date, with estimates at two-, five-, and eight-years post-index date. Follow-up began at the index date (i.e., ten years after a prior negative colonoscopy where no adenoma or CRC was detected; Figure 1) and continued until diagnosis of CRC or death from CRC, aging out of cohort eligibility (>95 years of age), disenrollment from health plan, moving out of SEER coverage area, end of cohort follow-up on December 31, 2019, or 180 days after a subsequent screening colonoscopy (mortality and incidence analyses) or FIT (mortality analysis only). Follow-up was censored if they received a subsequent screening colonoscopy or FIT so the estimates approximate the natural history of CRC beginning ten years after a negative colonoscopy (i.e., in the absence of screening interventions that may have affected the risk of the outcome). The exact date of censoring was delayed 180 days post-colonoscopy to avoid the exclusion of cancers detected at screening colonoscopies. Follow-up was not censored after a colonoscopy with a diagnostic indication since diagnostic colonoscopy is routine clinical care when indicated, rather than a preventative health measure. Follow-up for CRC mortality was additionally censored at 180 days after a fecal test (fecal immunochemical test or fecal occult blood test) because the test reduces risk of CRC mortality (29-31); the 180-day censoring delay avoids excluding CRC deaths.

Figure 1: Diagram of follow-up for study outcomes.
Follow-up began between ages 76-85 years at the index date, defined as ten years after a negative colonoscopy (which occurred between ages 66-75 years).




Deaths from causes other than CRC were counted as competing events (28, 32). This approach ensured that the population estimate generated is a realistic one: only individuals who are alive, and thus have the potential to be diagnosed with CRC, are included in the at-risk population. The

more familiar Kaplan-Meier (KM) method [1-KM estimator] censors follow-up at death from another cause, which means deceased participants are assumed to have the same risk of the outcome (CRC) as the alive individuals remaining in the population. This approach thus misrepresents the incidence of CRC among older adults remaining alive. To demonstrate the effect of this difference in calculation, cumulative mortality and incidence for the total population were also computed using a Kaplan Meier approach as a secondary analysis. CIF incidence and mortality estimates were stratified by patient demographic and health status variables: age at index date (in years); sex (male vs. female); CCI (0, 1, 2, 3, 4, ≥5); number of primary care encounters or inpatient stays (both acute and institutional) during the 180 days prior to index date.

A sensitivity analysis was also used to estimate cumulative CRC incidence and mortality without censoring after screening colonoscopy, since retrospective classification of colonoscopy indication based on electronic data is known to be imperfect and censoring at a screening colonoscopy could lead to an inaccurate estimate of CRC risk if persons who have a screening colonoscopy after age 75 years are not representative of CRC risks and lifespan.

## Results

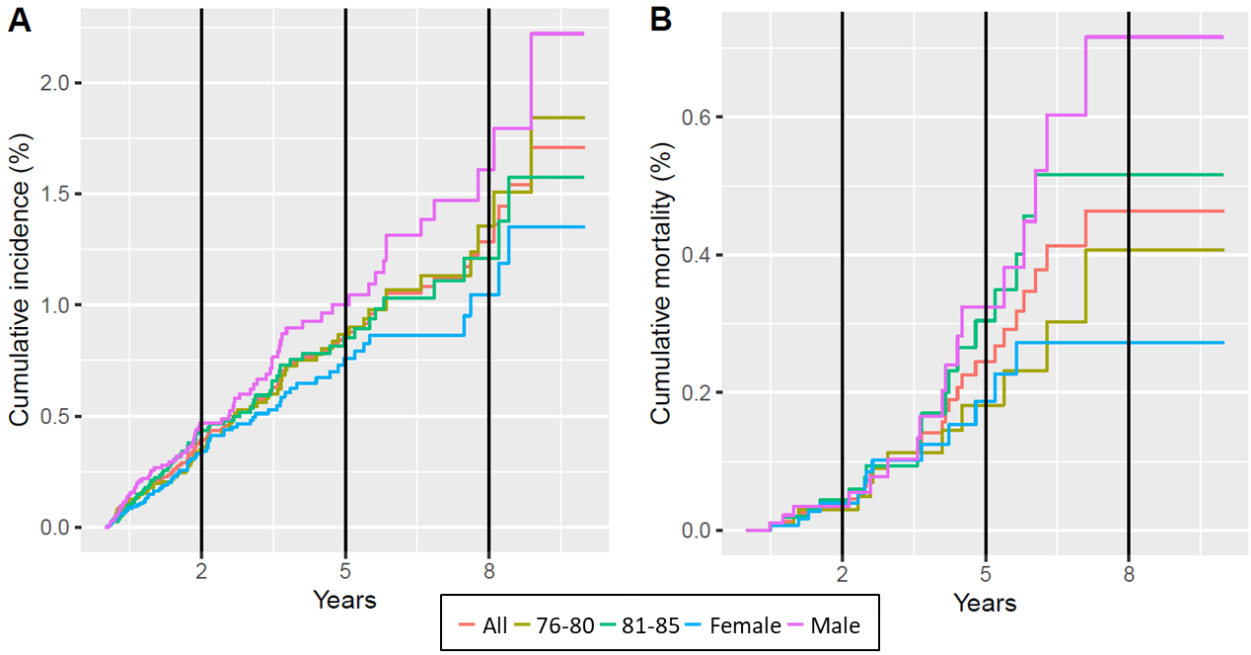
### Study Population

Characteristics of the 25,974 screen-eligible patients aged 76-85 years at their index date (i.e., with a negative colonoscopy ten years prior) are provided in Table 1. The study population skewed slightly towards younger ages in that range (54.7% aged 76-80 years vs. 45.3% aged 81-85 years). Cohort members were primarily White (75.4%), Asian (11.8%), or Black (9.4%). Other racial groups comprised less than 2% of the total population, and 13.4% patients were of Hispanic or Latinx ethnicity. As expected in a cohort of older adults, there was a higher proportion of females (58.0%) than males (42.0%). In general, the cohort was highly heterogenous in terms of comorbidity: nearly one quarter had no major comorbidities (CCI=0) while more than half (54.1%) had a CCI score of two or more. The three most prevalent comorbid conditions at the index date were peripheral vascular disease (37.8%), renal disease (29.3%), and diabetes (24.3%). Characteristics of the study population stratified by healthcare system are shown in Table S-1. We observed slight differences in the distribution of characteristics by healthcare system, with greater racial diversity at KPNC and KPSC and lower comorbidity scores at KPWA (Table S-1).

### Cumulative CRC Incidence and Mortality

Overall, cumulative CRC incidence and mortality were low in this population. Cumulative incidence of CRC was estimated as 0.39% (95% CI: 0.31-0.48%) two years after index date and 1.29% (95% CI: 1.02-1.61%) eight years after index date (Table 2). Cumulative CRC mortality was an order of magnitude lower: 0.04% (95% CI: 0.02-0.08%) two years after index date and 0.46% (95% CI: 0.30-0.70%) eight years after index date (Table 3). Sensitivity analyses found that these estimates were not changed if subsequent screening colonoscopy were not treated as censoring events (Tables S-2 and S-3). Estimates for cumulative CRC incidence and mortality are provided in Tables 2 and 3, respectively; corresponding estimates of cumulative mortality from another cause are provided in Figure S-4. Cumulative incidence curves that generated overall estimates are illustrated in Figure 2, with stratified curves provided in Figure S-2.

Figure 2: Cumulative incidence curves for (A) CRC and (B) CRC mortality, stratified by age and sex, starting ten years after colonoscopy.




Estimates of cumulative risk of death from non-CRC causes were 100-fold higher than their corresponding CRC mortality estimates. Cumulative mortality from non-CRC causes (competing event in the measurement of CRC incidence) was estimated as 7.84% (95% CI: 7.47-8.23%) two years after index date and 39.91% (95% CI: 38.36-41.44%) eight years after index date (Table S-4).

**Stratification by Age and Sex**

Cumulative CRC incidence and mortality were higher among males compared to females and among 81-85-year-olds compared to 76-80-year-olds (Figure 2). Strata defined by both characteristics showed even more variation across time points (Figure S-2A and S-2E). At two years following index date, the highest incidence was observed among males aged 81-85 years and lowest among females aged 76-80 years.

**Stratification by Health Status: Charlson Comorbidity Index and Healthcare Encounters**

CCI scores did not have a clear association with cumulative risk of CRC or CRC mortality (Tables 2 and 3); this heterogeneity may be related to which conditions are included in an individual patient's comorbidity score. Estimates for specific comorbid conditions are shown in Tables S-2 and S-3. Individuals with diabetes appear to have an elevated risk of CRC mortality (0.12% two-year risk; 95% CI: 0.05-0.27%) compared to overall study population risks (0.04% two-year risk).

At eight years following index date, patients with no encounters during 180 days prior to index date had nearly equivalent CRC risk to patients with acute inpatient or institutional stays prior to index date (Table 2). For CRC mortality, patients with no encounters had higher risk at eight years (0.81%; 95% CI: 0.31-1.79%) than patients with any recent encounters (Table 3). Meanwhile, the corresponding risk of death from other causes at the same time point was much

higher for patients with acute inpatient or institutional stays compared to no encounters (62.83% vs. 40.24%) (Table S-4).

CRC risk was not appreciably different across racial/ethnic groups. Eight-year cumulative risk estimates for CRC incidence were 0.91% (95% CI: 0.55-1.43%) for Hispanic or Latinx patients; 1.29% (0.99-1.66%) for White patients; 1.64% (0.66-3.45%) for Black patients; and 1.08% (0.56-1.91%) for Asian patients (Table 2). Eight-year cumulative risk estimates for CRC mortality were 0.33% (95% CI: 0.10-0.89) for Hispanic or Latinx patients; 0.41% (0.24-0.67%) for White patients; 0.75% (0.21-2.09%) for Black patients; and 0.59% (0.13-1.89%) for Asian patients (Table 3). Descriptive estimates are not robust for patients who identified as Native American/Alaska Native and Native Hawaiian/Other Pacific Islander, due to small numbers ($\leq$0.5% study population).

## Discussion

In this study, across three integrated healthcare systems in the western United States, adults aged 76-85 years who had a negative colonoscopy ten years earlier and were eligible for screening were at low risk of being diagnosed with CRC and of dying from this disease. These very low CRC incidence and mortality risk estimates occurred in the context of much higher cumulative risks of death from other causes.

These data substantially extend existing information on CRC incidence and mortality by incorporating screening history into estimates, as well as stratifying by health status. SEER estimates for nearly the same age group (75-84 years) are higher: [cumulative incidence of CRC] 0.58% (two-year) and 2.28% (eight-year); [cumulative mortality from CRC] 0.20% (two-year) and 0.78% (eight-year) (1). However, SEER estimates reflect the risks of a population that is heterogeneous and, on average, higher risk than this study population, because SEER includes individuals who may have less-than-adequate screening histories (e.g., none, or longer than ten years ago) and/or prior positive findings on a CRC test that would put an individual at higher risk of developing CRC.

Importantly, these current estimates account for a critical selection factor that affects most disease risk estimates in older adults: death from other causes. The current analysis acknowledges that death from causes other than CRC are a significant consideration for the assessment of disease risk among older adults. Without accounting for risk of death from another cause (e.g., by using a Kaplan-Meier estimator for cumulative incidence (1-KM) and censoring patients at time of death), risk estimates of CRC incidence and mortality are higher: 1.58% vs. 1.29% and 0.60% vs. 0.46%, respectively, eight years after index date. Accounting for deaths from other causes in the generation of cumulative risk estimates thus implicitly acknowledges that lower life expectancy ultimately affects cumulative risk of CRC. Since discussions of individual life expectancy are difficult during shared decision-making conversations between older adults and their care providers (33), these cumulative risk figures may be a useful population-level alternative.

Although the risk of death from other causes increased dramatically for individuals with a recent inpatient stay, outcome measures (CRC incidence and mortality) were similar across encounter

strata, which suggests a competing risks approach was sufficient to account for differences in life expectancy that might have otherwise affected incidence estimates.

Estimates of cumulative incidence and mortality differed little when stratified by a limited set of ethnicity and race identities due to wide confidence intervals, and caution in their interpretation is warranted. While some participants reported belonging to more than one race category, the choices offered are limited and may not capture the full diversity of the population. Furthermore, although this study cohort of 76–85-year-olds has a higher representation of Black (9.5% vs. 8.8%) and Asian (11.8% vs. 4.0%%) patients than the general United States population (23), representation was still insufficient to provide stratified estimates for other listed race categories. We also caution that stratifying a disease-specific risk estimate by race may exacerbate inequality if a group with higher cumulative risk of other causes of death appears to have a lower risk of CRC and thus is denied otherwise appropriate screening opportunities.

There are several strengths and limitations of the current study. Strengths include the high-quality long-term data (including prior testing history) and use of a large and diverse screen-eligible cohort. However, the estimates presented in this analysis are not individual-level risk prediction (as the ability to gauge person-level life expectancy was quite limited) but rather provide empirical evidence of population-level CRC risk among previously tested older adults. These estimates are stratified by univariate characteristics, one or two at a time; individuals are, of course, much more complex. Furthermore, the estimates are specific to a population of individuals with negative colonoscopy ten years ago and do not include patients undergoing surveillance for a polyp or other findings of concern. The risks estimated in this study should be considered in the context of the described population, and any application to a new population setting should evaluate both differences in background rates of CRC as well as population characteristics. Another limitation is that despite efforts made to include a diverse cohort, absolute number of events in ethnicity and race strata were insufficient to produce robust estimates stratified by race and ethnicity.

In summary, this study documents that adults aged 76-85 years who had a negative colonoscopy ten years earlier were at low risk for CRC and CRC-related mortality during the ensuing eight years. Knowledge of these results could well have a bearing on older adults' decision to undergo or not undergo further CRC screening, including choice of modality, should they decide to continue screening.

Tables

Table 1: Characteristics at index date of screen-eligible patients aged 76-85 years.

| | All Ages | Age 76-80 Years | Age 81-85 Years |
|---|---|---|---|
| | (N=25974) | (N=14220) | (N=11754) |
| Characteristic | n (%) | n (%) | n (%) |
| **Age (years)** | | | |
| 76 | 3059 (11.8) | 3059 (21.5) | 0 (0.0) |
| 77 | 2981 (11.5) | 2981 (21.0) | 0 (0.0) |
| 78 | 2827 (10.9) | 2827 (19.9) | 0 (0.0) |
| 79 | 2644 (10.2) | 2644 (18.6) | 0 (0.0) |
| 80 | 2709 (10.4) | 2709 (19.1) | 0 (0.0) |
| 81 | 2647 (10.2) | 0 (0.0) | 2647 (22.5) |
| 82 | 2472 (9.5) | 0 (0.0) | 2472 (21.0) |
| 83 | 2369 (9.1) | 0 (0.0) | 2369 (20.2) |
| 84 | 2231 (8.6) | 0 (0.0) | 2231 (19.0) |
| 85 | 2035 (7.8) | 0 (0.0) | 2035 (17.3) |
| **Age group (years)** | | | |
| 76-80 | 14220 (54.7) | 14220 (100.0) | 0 (0.0) |
| 81-85 | 11754 (45.3) | 0 (0.0) | 11754 (100.0) |
| **Sex** | | | |
| Male | 10914 (42.0) | 5965 (41.9) | 4949 (42.1) |
| Female | 15060 (58.0) | 8255 (58.1) | 6805 (58.1) |
| **Ethnicity**[+] | | | |
| Hispanic or Latinx | 3489 (13.4) | 1900 (13.4) | 1589 (13.5) |
| Not Hispanic or Latinx | 12891 (49.6) | 7015 (49.3) | 5876 (50.0) |
| Missing[++] | 9594 (36.9) | 5305 (37.3) | 4289 (36.5) |
| **Race**[i] | | | |
| White | 19593 (75.4) | 10570 (74.3) | 9023 (76.8) |
| Black | 2433 (9.4) | 1345 (9.5) | 1088 (9.3) |
| Asian | 3074 (11.8) | 1773 (12.5) | 1301 (11.1) |
| Native American/Alaska Native | 127 (0.5) | 77 (0.5) | 50 (0.4) |
| Native Hawaiian/Other Pacific Islander | 116 (0.4) | 70 (0.5) | 46 (0.4) |
| Multiple or not otherwise specified | 142 (0.5) | 72 (0.5) | 70 (0.6) |
| No race information | 1019 (3.9) | 614 (4.3) | 405 (3.4) |
| **Charlson Comorbidity Index score** [ii] | | | |
| 0 | 6193 (23.8) | 3724 (26.2) | 2469 (21.0) |
| 1 | 5164 (19.9) | 2961 (20.8) | 2203 (18.7) |
| 2 | 4834 (18.6) | 2598 (18.3) | 2236 (19.0) |
| 3 | 3001 (11.6) | 1544 (10.9) | 1457 (12.4) |
| 4 | 2423 (9.3) | 1213 (8.5) | 1210 (10.3) |
| ≥5 | 3785 (14.6) | 1885 (13.3) | 1900 (16.2) |
| Missing | 574 (2.2) | 295 (2.1) | 279 (2.4) |
| **Individual comorbid conditions** | | | |
| Myocardial infarction | 1947 (7.5) | 995 (7.0) | 952 (8.1) |
| Congestive heart disease | 2015 (7.8) | 958 (6.7) | 1057 (9.0) |
| Peripheral vascular disorder | 9815 (37.8) | 4948 (34.8) | 4867 (41.5) |
| Cerebrovascular disease | 2215 (8.5) | 1061 (7.5) | 1154 (9.8) |
| Dementia | 1317 (5.1) | 499 (3.5) | 818 (7.0) |

| | | | |
|---|---|---|---|
| Chronic pulmonary disease | 5358 (20.6) | 2898 (20.4) | 2460 (21.0) |
| Rheumatic disease | 831 (3.2) | 428 (3.0) | 403 (3.4) |
| Peptic ulcer | 148 (0.6) | 59 (0.4) | 89 (0.8) |
| Mild liver disease | 144 (0.6) | 79 (0.6) | 65 (0.6) |
| Diabetes | 6309 (24.3) | 3504 (24.7) | 2805 (23.9) |
| Diabetes with chronic complications | 4699 (18.1) | 2531 (17.8) | 2168 (18.5) |
| Hemiplegia or paraplegia | 174 (0.7) | 93 (0.7) | 81 (0.7) |
| Renal disease | 7613 (29.3) | 3771 (26.5) | 3842 (32.7) |
| Malignancy (incl. leukemia and lymphoma) | 1928 (7.4) | 1024 (7.2) | 904 (7.7) |
| Moderate or severe liver disease | 44 (0.2) | 21 (0.1) | 23 (0.2) |
| Metastatic solid tumor | 429 (1.7) | 238 (1.7) | 191 (1.6) |
| HIV/AIDS | 14 (0.1) | 14 (0.1) | 0 (0.0) |
| **Encounters (≤180 days prior to index date)[iii]** | | | |
| 0 encounters | 5073 (19.5) | 2915 (20.5) | 2158 (18.4) |
| 1 primary care only | 8557 (32.9) | 4828 (34.0) | 3729 (31.7) |
| 2 primary care only | 5000 (19.3) | 2803 (19.7) | 2197 (18.7) |
| ≥3 primary care only | 5929 (22.8) | 2982 (21.0) | 2947 (25.1) |
| Institutional/acute inpatient stay | 1415 (5.4) | 692 (4.9) | 723 (6.2) |

Index date was defined as ten years after a negative colonoscopy that occurred between ages 66-75 (i.e., index occurs between ages 76-85 years).

+ Hispanic or Latinx ethnicity was considered distinct from race categories (and was selected in conjunction with race categories by some participants).

++KPNC recorded Hispanic or Latinx ethnicity as either present or missing. Not Hispanic or Latinx was not offered as an option.

i. Will not sum to 100% since some patients were identified with >1 race and/or ethnic group.

ii. Charlson Comorbidity Index score was calculated using patient-level administrative codes from 365 days preceding the start of the calendar quarter in which the index date occurred. For example, an index date of 2/15/10 would use a Charlson score calculated based on data collected between 1/1/09-12/31/09. Calendar quarters began January 1, April 1, July 1, and Oct 1 annually.

iii. Includes acute inpatient, institutional, and primary care encounters; does not include specialty or telemedicine encounters.

Table 2: Cumulative CRC incidence, stratified by patient characteristics at index date

| | **Cumulative incidence of CRC, percent (95% CI)** | | |
|---|---|---|---|
| | **2-year** | **5-year** | **8-year** |
| All patients | 0.39 (0.31,0.48) | 0.86 (0.71,1.04) | 1.29 (1.02,1.61) |
| via Kaplan-Meier approach[#] | 0.40 (0.31,0.49) | 0.96 (0.77,1.15) | 1.58 (1.16,2.00) |
| **Sex and age (years)** | | | |
| 76-80 | 0.35 (0.25,0.48) | 0.87 (0.66,1.12) | 1.36 (0.97,1.86) |
| 81-85 | 0.44 (0.32,0.59) | 0.85 (0.64,1.12) | 1.21 (0.87,1.64) |
| Female | 0.33 (0.24,0.45) | 0.76 (0.57,0.99) | 1.05 (0.74,1.44) |
| Male | 0.47 (0.34,0.64) | 1.00 (0.76,1.3) | 1.61 (1.16,2.18) |
| Female, age 76-80 | 0.28 (0.17,0.43) | 0.73 (0.49,1.05) | 0.98 (0.59,1.55) |
| Female, age 81-85 | 0.40 (0.25,0.60) | 0.79 (0.53,1.15) | 1.11 (0.69,1.71) |
| Male, age 76-80 | 0.45 (0.29,0.69) | 1.06 (0.72,1.51) | 1.86 (1.17,2.82) |
| Male, age 81-85 | 0.49 (0.30,0.75) | 0.93 (0.62,1.36) | 1.34 (0.84,2.04) |
| **Charlson Comorbidity Index (CCI)** | | | |
| 0 | 0.40 (0.26,0.61) | 0.95 (0.66,1.34) | 1.53 (1.05,2.16) |
| 1 | 0.35 (0.20,0.59) | 0.61 (0.36,0.97) | 0.99 (0.41,2.09) |
| 2 | 0.38 (0.22,0.64) | 0.74 (0.44,1.18) | 1.51 (0.75,2.76) |
| 3 | 0.34 (0.15,0.69) | 0.69 (0.35,1.25) | 0.69 (0.35,1.25) |
| 4 | 0.67 (0.37,1.12) | 1.15 (0.68,1.83) | 1.62 (0.92,2.67) |
| ≥5 | 0.33 (0.17,0.60) | 1.18 (0.71,1.85) | 1.18 (0.71,1.85) |
| **Encounters (≤180 days prior to index date)[i]** | | | |
| 0 encounters | 0.44 (0.27,0.70) | 0.81 (0.50,1.26) | 1.50 (0.90,2.37) |
| 1 primary care only | 0.42 (0.29,0.60) | 1.14 (0.83,1.53) | 1.40 (0.94,2.02) |
| 2 primary care only | 0.39 (0.23,0.64) | 0.74 (0.46,1.14) | 0.96 (0.58,1.51) |
| ≥3 primary care only | 0.25 (0.14,0.44) | 0.55 (0.34,0.85) | 1.15 (0.61,2.02) |
| Institutional/acute inpatient stay | 0.55 (0.23,1.17) | 1.13 (0.57, 2.07) | 1.47 (0.71, 2.73) |
| **Ethnicity and race** | | | |
| Hispanic or Latinx | 0.54 (0.32,0.88) | 0.91 (0.55,1.43) | 0.91 (0.55,1.43) |
| White | 0.39 (0.30,0.50) | 0.84 (0.67,1.04) | 1.29 (0.99,1.66) |
| Black | 0.45 (0.21,0.88) | 0.81 (0.43,1.40) | 1.64 (0.66,3.45) |
| Asian | 0.32 (0.15,0.62) | 1.08 (0.56,1.91) | 1.08 (0.56,1.91) |
| Native American/Alaska Native | 0.88 (0.08,4.37) | 0.88 (0.08,4.37) | 0.88 (0.08,4.37) |
| Native Hawaiian/Other Pacific Islander | * | 5.56 (0.96,16.58) | 5.56 (0.96,16.58) |

[#]Kaplan-Meier approach (1-Kaplan-Meier estimator) provides an estimate of cumulative incidence that censors at death from another cause (competing event).

* No incident outcomes in this group.

Table 3: Cumulative CRC mortality, stratified by patient characteristics at index date

| | Cumulative mortality from CRC, percent (95% CI) | | |
|---|---|---|---|
| | **2-year** | **5-year** | **8-year** |
| All patients | 0.04 (0.02,0.08) | 0.25 (0.15,0.38) | 0.46 (0.30,0.70) |
| via Kaplan-Meier approach[#] | 0.04 (0.01,0.07) | 0.29 (0.16,0.42) | 0.60 (0.32,0.88) |
| **Sex and age (years)** | | | |
| 76-80 | 0.03 (0.01,0.09) | 0.18 (0.09,0.36) | 0.41 (0.19,0.80) |
| 81-85 | 0.04 (0.02,0.11) | 0.30 (0.17,0.52) | 0.52 (0.30,0.85) |
| Female | 0.04 (0.01,0.10) | 0.19 (0.09,0.35) | 0.27 (0.14,0.49) |
| Male | 0.04 (0.01,0.10) | 0.32 (0.17,0.58) | 0.72 (0.39,1.22) |
| Female, age 76-80 | 0.03 (0.01,0.12) | 0.10 (0.03,0.26) | 0.10 (0.03,0.26) |
| Female, age 81-85 | 0.04 (0.01,0.15) | 0.27 (0.11,0.57) | 0.44 (0.20,0.86) |
| Male, age 76-80 | 0.03 (0,0.15) | 0.30 (0.11,0.70) | 0.81 (0.33,1.71) |
| Male, age 81-85 | 0.05 (0.01,0.17) | 0.35 (0.15,0.74) | 0.63 (0.28,1.27) |
| **Charlson Comorbidity Index (CCI)** | | | |
| 0 | * | 0.28 (0.12,0.61) | 0.68 (0.33,1.27) |
| 1 | 0.03 (0,0.18) | 0.16 (0.04,0.47) | 0.16 (0.04,0.47) |
| 2 | 0.06 (0.01,0.20) | 0.18 (0.06,0.47) | 0.18 (0.06,0.47) |
| 3 | 0.05 (0.01,0.28) | 0.24 (0.04,0.98) | 0.24 (0.04,0.98) |
| 4 | * | 0.17 (0.02,0.91) | 0.68 (0.19,1.91) |
| ≥5 | 0.08 (0.02,0.29) | 0.46 (0.17,1.05) | 0.46 (0.17,1.05) |
| **Encounters (≤180 days prior to index date)** | | | |
| 0 encounters | 0.03 (0,0.19) | 0.25 (0.08,0.67) | 0.81 (0.31,1.79) |
| 1 primary care only | 0.06 (0.02,0.15) | 0.34 (0.16,0.65) | 0.41 (0.20,0.77) |
| 2 primary care only | 0.03 (0,0.15) | 0.21 (0.07,0.56) | 0.38 (0.12,0.99) |
| ≥3 primary care only | 0.03 (0,0.15) | 0.17 (0.06,0.44) | 0.27 (0.09,0.68) |
| Institutional/inpatient stay | * | 0.14 (0.01,0.77) | 0.55 (0.09,2.07) |
| **Ethnicity and race** | | | |
| Hispanic or Latinx | 0.08 (0.02,0.29) | 0.33 (0.10,0.89) | 0.33 (0.10,0.89) |
| White | 0.04 (0.02,0.09) | 0.24 (0.14,0.38) | 0.41 (0.24,0.67) |
| Black | * | 0.19 (0.02,1.00) | 0.75 (0.21,2.09) |
| Asian | 0.05 (0.01,0.29) | 0.25 (0.04,1.01) | 0.59 (0.13,1.89) |
| Native American/Alaska Native | * | * | * |
| Native Hawaiian/Other Pacific Islander | * | 4.07 (0.27,17.72) | 4.07 (0.27,17.72) |

[#]Kaplan-Meier approach (1-Kaplan-Meier estimator) provides an estimate of cumulative incidence that censors at death from another cause (competing event).

* No incident outcomes in this group.

Supplementary Materials

Table S-1: Characteristics at index date of screen-eligible patients aged 76-85 years, stratified by healthcare system.

| Variable | KPWA (N=1064) | KPNC (N=10168) | KPSC (N=14742) |
|---|---|---|---|
| Characteristic | n (%) | n (%) | n (%) |
| **Age (years)** | | | |
| 76 | 122 (11.5) | 1241 (12.2) | 1696 (11.5) |
| 77 | 128 (12.0) | 1161 (11.4) | 1692 (11.5) |
| 78 | 107 (10.1) | 1123 (11.0) | 1597 (10.8) |
| 79 | 121 (11.4) | 1016 (10.0) | 1507 (10.2) |
| 80 | 105 (9.9) | 1046 (10.3) | 1558 (10.6) |
| 81 | 105 (9.9) | 1007 (9.9) | 1535 (10.4) |
| 82 | 76 (7.1) | 974 (9.6) | 1422 (9.6) |
| 83 | 111 (10.4) | 941 (9.3) | 1317 (8.9) |
| 84 | 99 (9.3) | 845 (8.3) | 1287 (8.7) |
| 85 | 90 (8.5) | 814 (8.0) | 1131 (7.7) |
| **Age group (years)** | | | |
| 76-80 | 583 (54.8) | 5587 (54.9) | 8050 (54.6) |
| 81-85 | 481 (45.2) | 4581 (45.1) | 6692 (45.4) |
| **Sex** | | | |
| Male | 425 (39.9) | 4139 (40.7) | 6350 (43.1) |
| Female | 639 (60.1) | 6029 (59.3) | 8392 (56.9) |
| **Ethnicity**[+] | | | |
| Hispanic or Latinx | 24 (2.3) | 938 (9.2) | 2527 (17.1) |
| Not Hispanic or Latinx | 787 (74.0) | 0 | 12104 (82.1) |
| Missing | 253 (23.8) | 9230[++] (100) | 111 (0.8) |
| **Race**[i] | | | |
| White | 910 (85.5) | 7985 (78.5) | 10698 (72.6) |
| Black | 31 (2.9) | 534 (5.3) | 1868 (12.7) |
| Asian | 90 (8.5) | 1261 (12.4) | 1723 (11.7) |
| Native American/Alaska Native | 9 (0.8) | 43 (0.4) | 75 (0.5) |
| Native Hawaiian/Other Pacific Islander | 2 (0.2) | 33 (0.3) | 81 (0.5) |
| Other | 16 (1.5) | 0 (0.0) | 126 (0.9) |
| No race information | 33 (3.1) | 343 (3.4) | 643 (4.4) |
| **Charlson Comorbidity Index score**[ii] | | | |
| 0 | 425 (39.9) | 2542 (25.0) | 3226 (21.9) |
| 1 | 201 (18.9) | 2154 (21.2) | 2809 (19.1) |
| 2 | 182 (27.2) | 1824 (17.9) | 2828 (19.2) |
| 3 | 88 (8.3) | 1161 (11.4) | 1752 (11.9) |
| 4 | 77 (7.3) | 908 (8.9) | 1438 (9.8) |
| ≥5 | 85 (8.0) | 1512 (14.9) | 2188 (14.8) |
| Missing | 6 (0.6) | 67 (0.7) | 501 (3.4) |
| **Individual comorbid conditions** | | | |
| Myocardial infarction | 101 (9.5) | 741 (7.3) | 1105 (7.5) |
| Congestive heart disease | 71 (6.7) | 875 (8.6) | 1069 (7.3) |
| Peripheral vascular disorder | 89 (8.4) | 4057 (40.0) | 5669 (38.5) |
| Cerebrovascular disease | 72 (6.8) | 927 (9.1) | 1216 (8.3) |
| Dementia | 43 (4.0) | 492 (4.8) | 782 (5.3) |
| Chronic pulmonary disease | 181 (17.0) | 2422 (23.9) | 2755 (18.7) |
| Rheumatic disease | 32 (3.0) | 362 (3.6) | 437 (3.0) |
| Peptic ulcer | 4 (0.4) | 57 (0.6) | 87 (0.6) |

| | | | |
|---|---|---|---|
| Mild liver disease | 5 (0.5) | 52 (0.5) | 87 (0.6) |
| Diabetes | 182 (17.1) | 2204 (21.7) | 3923 (26.6) |
| Diabetes with chronic complications | 133 (12.5) | 1677 (16.5) | 2889 (19.6) |
| Hemiplegia or paraplegia | 8 (0.8) | 79 (0.8) | 87 (0.6) |
| Renal disease | 235 (22.1) | 2879 (28.4) | 4499 (30.5) |
| Malignancy (incl. leukemia and lymphoma) | 84 (7.9) | 697 (6.9) | 1147 (7.8) |
| Moderate or severe liver disease | 3 (0.3) | 19 (0.2) | 22 (0.1) |
| Metastatic solid tumor | 16 (1.5) | 172 (1.7) | 241 (1.6) |
| HIV/AIDS | 0 (0.0) | 4 (0.0) | 10 (0.1) |
| **Encounters (≤180 days prior to index date)[iii]** | | | |
| 0 encounters | 236 (22.2) | 2236 (22.0) | 2601 (17.6) |
| 1 primary care only | 350 (32.9) | 3538 (34.8) | 4669 (31.7) |
| 2 primary care only | 221 (20.8) | 1847 (18.2) | 2932 (19.9) |
| ≥ 3 primary care only | 196 (18.4) | 1936 (19.0) | 3797 (25.8) |
| Institutional/acute inpatient stay | 61 (5.7) | 611 (6.0) | 743 (5.0) |

+ Hispanic or Latinx ethnicity was considered distinct from race categories (and was selected in conjunction with race categories by some participants).

++KPNC recorded Hispanic or Latinx ethnicity as either present or missing. Not Hispanic or Latinx was not offered as an option.

i. Will not sum to 100% since some patients were identified with >1 race and/or ethnic group.

ii. Charlson Comorbidity Index score was calculated using patient-level administrative codes from 365 days preceding the start of the calendar quarter in which the index date occurred. For example, an index date of 2/15/10 would use a Charlson score calculated based on data collected between 1/1/09-12/31/09. Calendar quarters began January 1, April 1, July 1, and Oct 1 annually.

iii. Includes acute inpatient, institutional, and primary care encounters; does not include specialty or telemedicine encounters.

Table S-2: Cumulative CRC incidence, additional covariate strata (sensitivity analysis; CCI by age group; comorbid conditions)

| | Percent (95% CI) | | |
|---|---|---|---|
| | **2-year** | **5-year** | **8-year** |
| Sensitivity analysis (no censoring at subsequent screening colonoscopy) | 0.38 (0.31,0.48) | 0.84 (0.69,1.01) | 1.25 (0.99,1.56) |
| **CCI by age group (years)**[i] | | | |
| CCI=0, Age 76-80 | 0.30 (0.15,0.55) | 0.94 (0.56,1.49) | 1.37 (0.81,2.18) |
| CCI=1, Age 76-80 | 0.35 (0.16,0.70) | 0.41 (0.20,0.80) | 1.09 (0.26,3.22) |
| CCI=2, Age 76-80 | 0.28 (0.12,0.60) | 0.69 (0.34,1.29) | 1.62 (0.58,3.68) |
| CCI=0, Age 81-85 | 0.43 (0.26,0.68) | 1.14 (0.75,1.66) | 1.38 (0.90,2.03) |
| CCI=1, Age 81-85 | 0.56 (0.31,0.95) | 0.99 (0.58,1.59) | 1.71 (0.99,2.78) |
| CCI=2, Age 81-85 | 0.35 (0.15,0.74) | 0.85 (0.41,1.57) | 0.85 (0.41,1.57) |
| CCI≥3, Age 81-85 | 0.50 (0.24,0.96) | 0.80 (0.37,1.54) | 1.38 (0.49,3.17) |
| **Comorbid condition** | | | |
| Congestive heart disease | 0.24 (0.08,0.61) | 0.53 (0.23,1.09) | 0.53 (0.23,1.09) |
| Dementia | 0.13 (0.01,0.69) | 0.68 (0.10,2.73) | 0.68 (0.10,2.73) |
| Diabetes | 0.43 (0.28,0.64) | 0.94 (0.64,1.34) | 1.34 (0.76,2.21) |
| Diabetes & chronic complications | 0.51 (0.31,0.79) | 1.06 (0.70,1.56) | 1.32 (0.85,1.98) |
| Hemiplegia or paraplegia | * | * | * |
| HIV/AIDS flag | * | * | * |
| Moderate or severe liver disease | * | * | * |
| Mild liver disease | * | * | * |
| Malignancy (incl. leukemia, lymphoma) | 0.34 (0.14,0.72) | 1.01 (0.49,1.88) | 1.38 (0.63,2.67) |
| Myocardial infarction | 0.38 (0.16,0.80) | 0.79 (0.40,1.44) | 0.79 (0.40,1.44) |
| Peptic ulcer disease | 0.96 (0.08,4.76) | 0.96 (0.08,4.76) | 0.96 (0.08,4.76) |
| Chronic pulmonary disease | 0.45 (0.28,0.70) | 0.97 (0.65,1.41) | 1.25 (0.71,2.06) |
| Rheumatological disease | 0.44 (0.12,1.23) | 1.56 (0.72,3.00) | 1.56 (0.72,3.00) |
| Metastatic solid tumor | * | * | * |
| Cerebrovascular disease | 0.31 (0.12,0.71) | 1.05 (0.56,1.83) | 1.68 (0.68,3.52) |
| Peripheral vascular disorder | 0.45 (0.31,0.64) | 1.10 (0.74,1.6) | 1.10 (0.74,1.60) |
| Renal disease | 0.35 (0.23,0.54) | 0.93 (0.66,1.3) | 1.29 (0.82,1.96) |

* No incident outcomes in this group.

i. Charlson Comorbidity Index score was calculated using patient-level administrative codes from 365 days preceding the start of the calendar quarter in which the index date occurred. For example, an index date of 2/15/10 would use a Charlson score calculated based on data collected between 1/1/09-12/31/09. Calendar quarters began January 1, April 1, July 1, and Oct 1 annually.

Table S-3: Cumulative CRC mortality, additional covariate strata (sensitivity analysis; CCI by age group; comorbid conditions).

| | Percent (95% CI) | | |
|---|---|---|---|
| | **2-year** | **5-year** | **8-year** |
| Sensitivity analysis (no censoring at subsequent screening colonoscopy) | 0.04 (0.02,0.08) | 0.24 (0.15,0.37) | 0.45 (0.29,0.68) |
| **CCI by age group (years)**[i] | | | |
| CCI=0, Age 76-80 | * | 0.18 (0.04,0.66) | 0.42 (0.10,1.28) |
| CCI=1, Age 76-80 | * | 0.10 (0.01,0.53) | 0.01 (0.01,0.53) |
| CCI=2, Age 76-80 | 0.06 (0.01,0.34) | 0.06 (0.01,0.34) | 0.06 (0.01,0.34) |
| CCI≥3, Age 76-80 | 0.06 (0.01,0.20) | 0.29 (0.10,0.70) | 0.71 (0.25,1.69) |
| CCI=0, Age 81-85 | * | 0.38 (0.13,0.96) | 0.94 (0.40,1.93) |
| CCI=1, Age 81-85 | 0.06 (0.01,0.36) | 0.22 (0.04,0.83) | 0.22 (0.04,0.83) |
| CCI=2, Age 81-85 | 0.06 (0.01,0.31) | 0.28 (0.07,0.83) | 0.28 (0.07,0.83) |
| CCI≥3, Age 81-85 | 0.06 (0.01,0.20) | 0.29 (0.10,0.71) | 0.42 (0.15,0.97) |
| **Comorbid condition** | | | |
| Congestive heart disease | * | 0.11 (0.01,0.62) | 0.11 (0.01,0.62) |
| Dementia | 0.13 (0.01,0.69) | 0.68 (0.10,2.73) | 0.68 (0.10,2.73) |
| Diabetes | 0.12 (0.05,0.27) | 0.42 (0.20,0.80) | 0.65 (0.32,1.20) |
| Diabetes & chronic complications | 0.12 (0.04,0.31) | 0.52 (0.24,1.01) | 0.80 (0.39,1.51) |
| Hemiplegia or paraplegia | * | * | * |
| HIV/AIDS flag | * | * | * |
| Moderate or severe liver disease | * | * | * |
| Mild liver disease | * | * | * |
| Malignancy (incl. leukemia, lymphoma) | * | * | * |
| Myocardial infarction | 0.06 (0.01,0.31) | 0.45 (0.14,1.17) | 0.45 (0.14,1.17) |
| Peptic ulcer disease | * | * | * |
| Chronic pulmonary disease | 0.03 (0,0.18) | 0.15 (0.04,0.47) | 0.15 (0.04,0.47) |
| Rheumatological disease | * | 0.26 (0.03,1.36) | 0.26 (0.03,1.36) |
| Metastatic solid tumor | * | * | * |
| Cerebrovascular disease | * | 0.10 (0.01,0.54) | 0.10 (0.01,0.54) |
| Peripheral vascular disorder | 0.07 (0.02,0.17) | 0.43 (0.12,1.26) | 0.43 (0.12,1.26) |
| Renal disease | 0.04 (0.01,0.13) | 0.29 (0.13,0.58) | 0.45 (0.22,0.86) |

* No incident outcomes in this group.

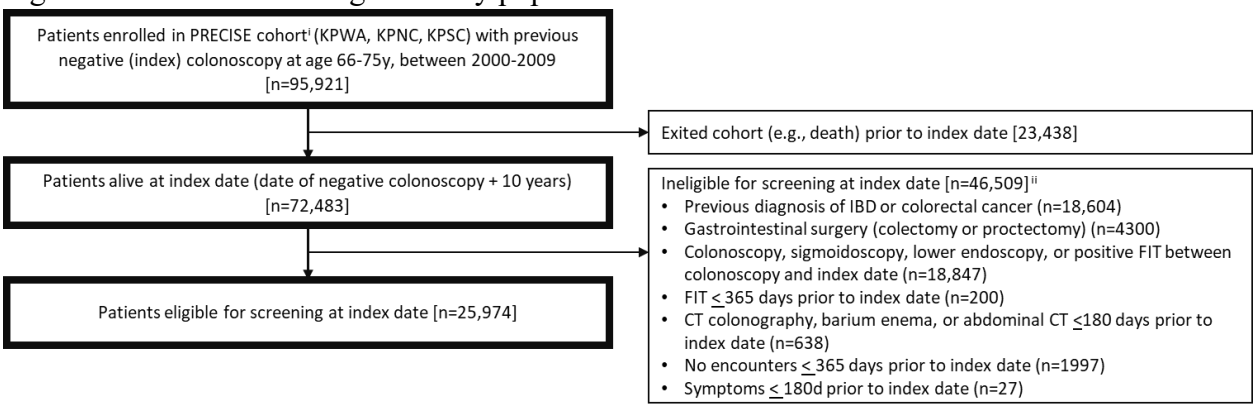
i. Charlson Comorbidity Index score was calculated using patient-level administrative codes from 365 days preceding the start of the calendar quarter in which the index date occurred. For example, an index date of 2/15/10 would use a Charlson score calculated based on data collected between 1/1/09-12/31/09. Calendar quarters began January 1, April 1, July 1, and Oct 1 annually.

Table S-4: Cumulative mortality from non-CRC causes (competing events), corresponding to incidence and mortality estimates.

| | **Cumulative mortality from non-CRC causes (Competing risk for CRC incidence, Table 2), percent (95% CI)** | | | **Cumulative mortality from non-CRC causes** (Competing risk for CRC mortality, Table 3), percent (95% CI)** | | |
|---|---|---|---|---|---|---|
| | **2-year** | **5-year** | **8-year** | **2-year** | **5-year** | **8-year** |
| All incidence | 7.84 (7.47,8.23) | 21.96 (21.18,22.76) | 39.91 (38.36,41.44) | 8.24 (7.83,8.66) | 23.34 (22.46,24.23) | 41.45 (39.74,43.16) |
| **Sex and age (years)** | | | | | | |
| 76-80 | 6.07 (5.62,6.54) | 16.93 (15.97,17.91) | 31.25 (29.30,33.21) | 6.55 (6.03,7.09) | 18.30 (17.16,19.47) | 32.73 (30.50,34.98) |
| 81-85 | 9.95 (9.34,10.59) | 27.78 (26.52,29.05) | 49.43 (47.07,51.74) | 9.99 (9.37,10.63) | 28.11 (26.79,29.43) | 49.67 (47.13,52.16) |
| Female | 6.74 (6.28,7.21) | 19.14 (18.16,20.14) | 35.76 (33.78,37.74) | 7.13 (6.63,7.65) | 20.55 (19.45,21.68) | 37.59 (35.38,39.80) |
| Male | 9.38 (8.76,10.03) | 25.91 (24.63,27.21) | 45.57 (43.13,47.98) | 9.79 (9.11,10.49) | 27.21 (25.79,28.66) | 46.68 (43.98,49.33) |
| Female, age 76-80 | 4.90 (4.38,5.46) | 14.13 (12.98,15.34) | 28.08 (25.50,30.70) | 5.35 (4.74,6.01) | 15.40 (14.02,16.84) | 29.58 (26.65,32.57) |
| Female, age 81-85 | 8.94 (8.18,9.75) | 24.98 (23.38,26.60) | 44.38 (41.40,47.31) | 8.96 (8.18,9.77) | 25.49 (23.81,27.21) | 45.19 (41.95,48.37) |
| Male, age 76-80 | 7.72 (6.95,8.54) | 20.89 (19.28,22.54) | 35.66 (32.73,38.61) | 8.23 (7.34,9.19) | 22.41 (20.50,24.37) | 37.10 (33.69,40.52) |
| Male, age 81-85 | 11.34 (10.35,12.38) | 31.62 (29.62,33.63) | 56.09 (52.32,59.68) | 11.42 (10.41,12.47) | 31.66 (29.59,33.75) | 55.61 (51.57,59.46) |
| **Charlson Comorbidity Index (CCI)** | | | | | | |
| 0 | 3.13 (2.67,3.65) | 11.86 (10.73,13.04) | 26.00 (23.41,28.66) | 3.39 (2.87,3.97) | 12.78 (11.50,14.12) | 27.71 (24.77,30.72) |
| 1 | 4.45 (3.82,5.15) | 16.41 (14.70,18.19) | 33.88 (30.24,37.55) | 4.58 (3.89,5.34) | 17.60 (15.68,19.61) | 34.55 (30.66,38.46) |
| 2 | 5.92 (5.16,6.74) | 18.63 (16.90,20.43) | 37.35 (33.48,41.21) | 6.43 (5.59,7.36) | 20.43 (18.45,22.48) | 39.57 (35.26,43.85) |
| 3 | 8.62 (7.46,9.88) | 26.45 (23.60,29.38) | 49.71 (43.53,55.58) | 9.02 (7.77,10.39) | 27.90 (24.78,31.10) | 51.25 (44.48,57.60) |
| 4 | 10.42 (9.05,11.89) | 30.10 (27.17,33.08) | 49.27 (43.92,54.40) | 10.93 (9.45,12.53) | 31.75 (28.47,35.06) | 52.25 (46.05,58.08) |
| >=5 | 19.38 (17.90,20.91) | 46.16 (43.24,49.03) | 67.95 (62.77,72.56) | 19.87 (18.29,21.50) | 47.00 (43.79,50.15) | 67.66 (61.96,72.69) |
| **Encounters (<=180 days prior to index date)** | | | | | | |
| 0 encounters | 6.95 (6.17,7.80) | 20.49 (18.74,22.30) | 38.08 (34.68,41.47) | 7.37 (6.51,8.29) | 21.61 (19.65,23.63) | 40.24 (36.42,44.02) |
| 1 primary care only | 6.43 (5.84,7.06) | 18.31 (17.02,19.64) | 34.13 (31.47,36.80) | 6.83 (6.18,7.52) | 19.47 (18.03,20.95) | 35.29 (32.36,38.23) |
| 2 primary care only | 6.21 (5.45,7.03) | 20.26 (18.49,22.10) | 40.31 (36.34,44.24) | 6.56 (5.73,7.45) | 21.67 (19.66,23.75) | 40.97 (36.56,45.33) |
| ≥ 3 primary care only | 7.97 (7.20,8.79) | 23.62 (21.99,25.30) | 43.12 (39.97,46.23) | 8.25 (7.42,9.13) | 25.03 (23.18,26.91) | 45.32 (41.77,48.80) |
| Institutional/inpatient stay | 24.05 (21.60,26.57) | 45.05 (41.32,48.69) | 61.39 (55.89,66.39) | 24.73 (22.16,27.39) | 47.53 (43.45,51.49) | 62.83 (56.80,68.25) |
| **Ethnicity and race** | | | | | | |
| Hispanic or Latinx | 8.13 (7.10,9.24) | 21.76 (19.59,24.02) | 37.23 (33.03,41.43) | 8.63 (7.50,9.85) | 23.08 (20.64,25.61) | 38.23 (33.56,42.87) |
| White | 8.30 (7.86,8.75) | 22.95 (22.05,23.86) | 41.28 (39.53,43.02) | 8.69 (8.22,9.18) | 24.25 (23.25,25.27) | 42.61 (40.66,44.54) |
| Black | 8.29 (7.08,9.63) | 22.47 (19.81,25.23) | 43.10 (37.65,48.41) | 8.97 (7.61,10.47) | 24.90 (21.81,28.10) | 46.26 (40.17,52.13) |
| Asian | 4.82 (3.97,5.79) | 16.23 (14.05,18.55) | 28.95 (24.61,33.41) | 5.05 (4.12,6.12) | 17.46 (15.00,20.07) | 30.77 (26.05,35.59) |
| Native American/Alaska Native | 5.54 (2.02,11.73) | 17.89 (9.00,29.25) | 35.30 (19.39,51.63) | 5.09 (1.58,11.76) | 12.33 (4.94,23.30) | 32.16 (15.31,50.37) |
| Native Hawaiian/Other Pacific Islander | 9.42 (4.32,16.94) | 34.48 (17.69,51.96) | 34.48 (17.69,51.96) | 10.48 (4.72,18.87) | 37.51 (19.51,55.52) | 37.51 (19.51,55.52) |

**Small differences in the estimates of cumulative mortality from other causes of death (competing risks) corresponding to the two CRC outcomes are due to differences in censoring criteria between the outcomes. Specifically, the occurrence of a fecal-based test during follow-up was treated as a censoring event for the mortality outcome analysis but not in the incidence analysis (362 participants who were counted as having had a competing event (death from another cause) in the incidence analysis were instead censored prior to that time point in the mortality analysis due to the occurrence of a fecal test). A sensitivity analysis where fecal test was omitted as a censoring event made the incidence of competing events for CRC mortality nearly identical to the incidence of competing events for CRC incidence. However, the estimates for the outcome of interest (mortality) were unaffected and were equal to the primary analysis estimates. Additionally, follow-up time is inherently longer for a mortality outcome compared to an incidence one, meaning there was the opportunity for some individuals diagnosed with CRC to die of another cause (competing risk) before the outcome of interest (CRC death). Eleven patients were diagnosed with CRC during follow-up (the outcome of interest in the incidence analysis) but died from another cause (competing event in the mortality outcome).

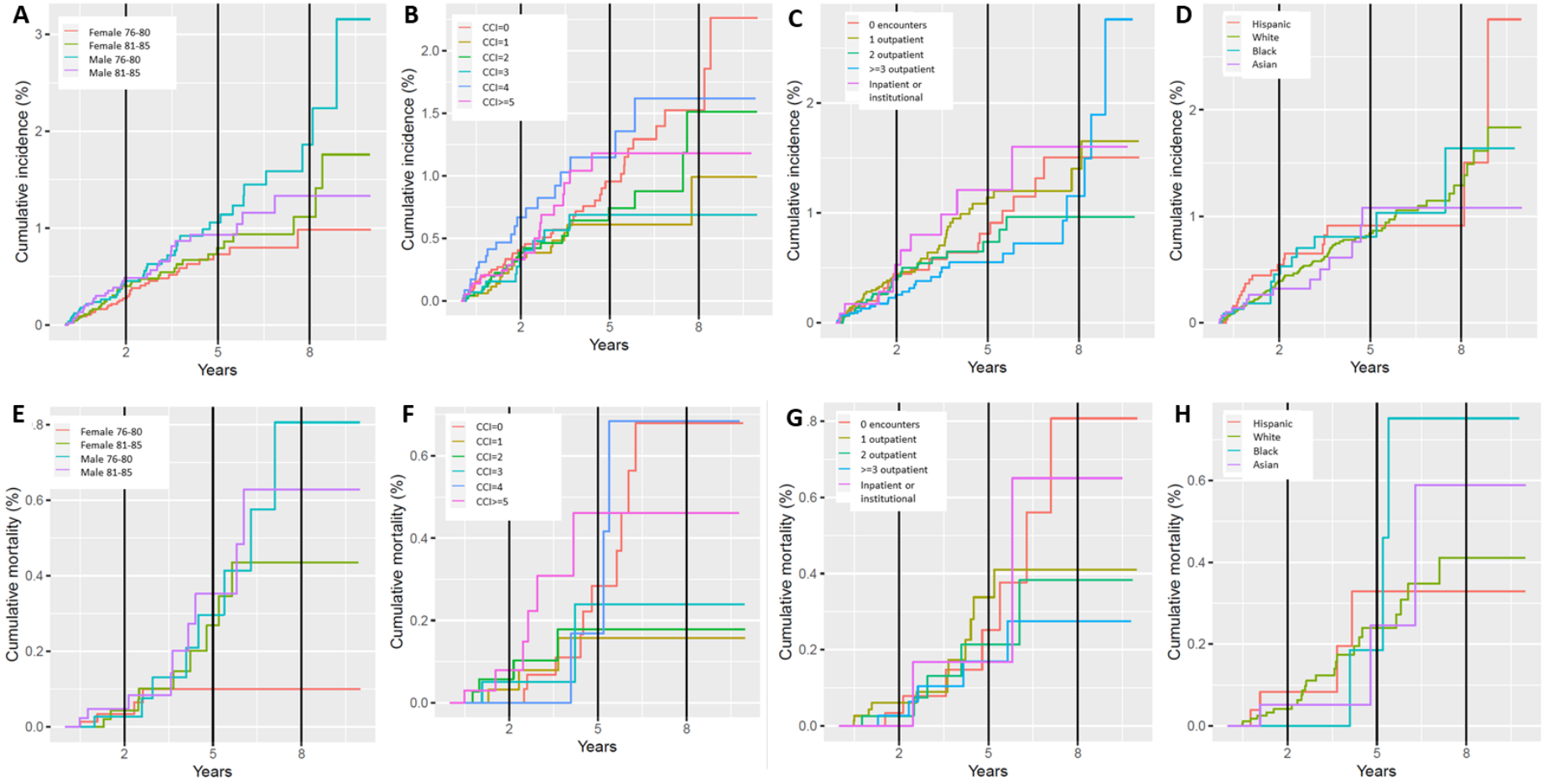
Figure S-1: Selection of eligible study population from PRECISE cohort




i. PRECISE cohort eligibility requirements: living at least one day between 1/1/2010-12/30/20, aged 40-95 years, and enrolled in KPNC, KPSC, or KPWA health plan. KPWA patients were also required to have selected or be assigned/attributed to a KPWA primary care provider (to ensure more complete data availability), reside in the Seattle-Puget Sound SEER Registry catchment area (to ensure capture of CRC occurrence), not be insured via Medicaid, and not be on any study exclusion lists.

ii. Exclusions were counted incrementally, in the order presented.

Figure S-2: Stratified cumulative incidence curves for CRC and CRC mortality. A-D show cumulative CRC incidence; E-H show cumulative CRC mortality. A and E stratify by age and sex combinations (female 76-80, female 81-85, male 76-80, male 81-85); B and F stratify by Charlson Comorbidity Index (1, 2, 3, 4, ≥5); C and G stratify by recent encounters in the 180 days prior to index date (0 encounters, primary care only (1, 2, or ≥3), and ≥1 inpatient); D and H stratify by racial and ethnic categories with >5% representation in study population members (Hispanic or Latinx, White, Black, and Asian).



# Chapter 2: Risk of colorectal cancer and colorectal cancer mortality beginning one year after a negative fecal occult blood test, among screen-eligible adults aged 76-85 years [Aim 2]

**Abstract**

Empirical data to inform older adults' decisions about whether to screen or continue screening for colorectal cancer (CRC) are sparse, in particular for individuals with a prior negative exam. Using a retrospective cohort of older adults receiving healthcare at three Kaiser Permanente integrated healthcare systems in Northern California (KPNC), Southern California (KPSC), Washington (KPWA), and Parkland Health and Hospital System (PHHS) in Dallas, Texas, we estimated the cumulative risk of CRC incidence and mortality among older adults who had a negative stool-based screening test one year earlier, accounting for death from other causes. Cumulative incidence of CRC was 0.19% (95% CI: 0.17-0.22%) two years after index date and 1.17% (95% CI: 1.09-1.27%) eight years after index date (Table 2). Cumulative CRC mortality was 0.02% (95% CI: 0.01-0.03%) two years after index date and 0.28% (95% CI: 0.23-0.34%) eight years after index date (Table 3). Estimates of cumulative CRC incidence and mortality in this population are low and occur in the presence of a much higher risk of death from other causes.

**Introduction**

Several screening modalities are effective in reducing the incidence of and mortality from CRC (34). However, among older adults, the high rate of death from other causes limits the number of additional years of life that such screening can yield and the risks of screening increase with age (35). As a result, though rates of CRC among 80-84-year-olds are almost ten times the rates among 50-54-year-olds (1), many guidelines recommend cessation of routine screening at age 75 years (2-5, 36). The United States Preventive Services Task Force (USPSTF) notes an uncertainty in the benefit from screening for patients aged 76-85, instead advising that the decision to screen for CRC in these older adults "be an individual one, taking into account the patient's overall health and prior screening history (2)." However, there are few empirical data to inform this individual decision process (37).

Especially for older adults at higher risk for complications from more invasive tests like colonoscopy (38, 39), stool-based testing is an attractive screening option (40): there are no bowel preparation requirements, a minimal risk of adverse events (41), no office visit is required, and the cost is low. In part due to the COVID-19 pandemic and curtailing of nonemergency procedures to conserve resources and reduce infection risk, use of these low-burden stool-based tests has grown rapidly in recent years (42).

Appropriate CRC screening of older adults requires communicating the balance between long-term benefits and short-term risks so as to enable informed decision-making (12). The benefit of CRC screening is determined by a person's life expectancy combined with risk of morbidity and mortality from CRC. Studies demonstrating benefit of screening by various testing modalities, including randomized trials of repeat guaiac fecal occult blood testing (gFOBT) (43-46), commonly exclude or have limited representation of adults older than 75 years (37). While some studies suggest individuals with repeat negative fecal immunochemical tests (FIT) subsequently

have a relatively low risk of advanced CRC (47, 48), cumulative risk estimates of CRC incidence and mortality, among older adults with previous screening by stool-based tests, are sparse.

This study provides estimates of cumulative CRC incidence and mortality among older adults (ages 76-85 years) following a negative stool-based screening test one year ago, with the goal of facilitating individualized decision-making about desirability of continuing stool-based screening.

## Methods

### Study Design and Settings

We conducted a retrospective cohort study of members of three Kaiser Permanente integrated healthcare systems in Northern California (KPNC), Southern California (KPSC), and Washington (KPWA), as well as patients receiving primary care in the Parkland Health and Hospital System (PHHS) in Texas. PHHS is an integrated health system and one of the largest public hospital systems in the United States, serving as the primary provider of healthcare for under- and un-insured residents of Dallas County. These healthcare systems each contribute to the Optimizing Colorectal Cancer Screening PREcision and Outcomes in CommunIty-baSEd Populations (PRECISE) Research Center, part of the National Cancer Institute-funded Population-based Research to Optimize the Screening Process (PROSPR II) consortium (16). Descriptions of the CRC screening processes and other details of these healthcare systems have been previously published (24). All four integrated healthcare systems include older populations that have high levels of Medicare coverage (~90%), similar to the United States population as a whole (22, 23). Importantly, PHHS prioritizes utilization of mailed FIT kits (using a "FIT-first" approach) compared to other modalities of screening. KPSC prioritizes colonoscopy (vs. FIT) but continues its mailed FIT kit program through age 79 years (vs. other sites that cease automatic mailings at age 75 years). Further details about the PRECISE cohort have been published elsewhere (17). The study was approved by Institutional Review Boards at the study sites and the University of Washington.

### Eligibility Criteria

Patients between ages 76-85 years with a negative stool-based test result one year earlier and otherwise eligible for CRC screening (see full details below) were included in this study. This age group ranges beyond 75 years (the upper age recommended for universal screening) but younger than age 86 years (when cessation is strongly recommended) and thus focuses on a population for which USPSTF recommendations note uncertainty in the benefits of screening and defer instead to shared decision-making between patients and clinicians (4). The index date for initiation of follow-up was defined as 365 days after a negative FIT or gFOBT result (i.e., the time at which the person might consider screening again). In the PRECISE cohort overall, 1.6% of fecal-based tests were gFOBT and 98.4% were FIT. In the present analysis, all fecal-based tests were grouped together and are referred to collectively as FITs. To ensure a screening-eligible population, patients with history of inflammatory bowel disease (IBD), CRC, or gastrointestinal surgery prior to index date were excluded. Patients with recent CRC testing using other modalities were also excluded (e.g., sigmoidoscopy, other lower endoscopy, or any positive stool-based test in the five years preceding index date; any stool-based test occurring between 1-364 days prior to index date; colonoscopy in the ten years preceding index date) since these individuals would have been ineligible for screening at the time of index date due to being up-to-date or in need of a diagnostic colonoscopy (for a positive fecal-based test). Patients were also

considered ineligible for screening if they had a computed tomography (CT) colonography, barium enema, or abdominal CT during the180 days prior to index date, because evidence of CRC detected by these imaging procedures would make a participant ineligible for screening at index date. Patients with any known history of polyps detected at an earlier colonoscopy, sigmoidoscopy, or lower endoscopy were excluded from the screen-eligible population. Patients with any signs or symptoms associated with CRC (abdominal pain, iron deficiency or unspecified anemias, gastrointestinal bleeding or blood in stools, diarrhea, weight loss or underweight, diverticulitis, constipation, abdominal mass, or change in bowel habits) reported in the 180 days prior to index date were also excluded: the presence of these signs or symptoms makes patients ineligible for screening which, by definition, occurs in patients without signs or symptoms of cancer.

**Observations Per Patient: Limited to One**

Although some patients may have had repeated negative FIT results and thus multiple index dates at which they would be eligible for screening and inclusion in this study, successive older index ages were not included in the analysis. Inclusion would have led to a dataset of non-independent observations because tests performed on the same individual at different ages would have had a clustered data structure. Methods for clustered data in survival analysis are underdeveloped, especially for analyses accounting for competing risks. One approach we considered was to include repeat observations for individuals so long as the ages at index date were distinct (e.g., only one observation per year of age). The goal of including such observations was to have a pragmatic population: one where older adults with a negative FIT are likely highly screening adherent and thus have had additional screening at earlier ages (i.e., repeat observations in the cohort period). However, upon exploration of the data, repeat testing occurred less frequently than expected (yielding a relatively small number of additional useful observations for analysis and a small impact on statistical precision). It also added analytical complexity in that there are few methods for survival analysis of clustered data and the best option was to stratify all estimates by year of age so that each age had only one observation per patient. This degree of stratification dramatically affected group sizes for estimates, especially at ages older than 80 years. Use of the earliest observation in the age range of interest allowed for the combination of age groups to achieve larger sample sizes and estimates with greater statistical precision. It also means that the results should be taken with the understanding that interpretation is limited to individuals without subsequent screening that would impact the outcome.

**Data Collection**

Data on patient demographics, clinical characteristics, CRC screening procedures (i.e., risk factors, screening tests, diagnostic evaluations, treatment, and outcomes), CRC diagnoses, and deaths were obtained from administrative and clinical databases including electronic health records by PRECISE Research Center sites. Patient data on prior testing history and conditions were collected with look-back period varying by site: KPWA extended back to 1/1/1993; PHHS look-back for CRC diagnoses extended to 1/1/1995 and non-CRC variables to 1/1/2006; KPNC and KPSC looked back to 1/1/2000 for enrollment, visits, and CRC tests, and extended further back (to the full extent of information available in electronic records databases) for CRC diagnoses and gastrointestinal surgeries. CRC diagnoses were obtained from local and central cancer registries: Seattle Puget-Sound Surveillance, Epidemiology and End Results (SEER)

registry for KPWA, Texas Cancer and Parkland Health & Hospital System registries for PHHS, and facility-based cancer registries at KPNC and KPSC, which report to the State of California Cancer Registry. Information on patient deaths was sourced from state vital records data, as well as a variety of internal sources (e.g., insurance membership, discharge status on claims, etc.). CRC-related deaths were ascertained using each site's corresponding state death records as the primary source for cause of death. PHHS derived death data from the EHR and Texas Cancer Registry data, which means deaths occurring outside Dallas County, at a non-PHHS facility, or not reported by payers or family members to PHHS may not be documented (i.e., under-ascertainment of deaths).

Indication for colonoscopies performed after index date was assigned based on manual chart review and natural language processing or a modified version of a colonoscopy indication algorithm that incorporated administrative and clinical data (25), as well as data elements related to recent procedures, IBD diagnosis, signs and symptoms, past results of CRC screening tests, and personal history of CRC.

**Study Measures**

To measure comorbidity burden for each patient in the cohort, the Charlson Comorbidity Index (CCI) was calculated by applying modified Charlson/Deyo comorbidity algorithm weights (26) to an updated set of diagnosis and procedure codes associated with both inpatient and outpatient visits. CCI was assessed as of the last day of the calendar quarter prior to index date, computed based on relevant codes from the 365 days prior, and categorized (0, 1, 2, 3, 4, $\geq$5) for analysis. Other covariates for descriptive strata include year of age at index date, sex, number of inpatient or institutional encounters less than 180 days prior to index date, and number of negative FITs in the five years preceding index date (1 or >=2), where one is the recent negative FIT that occurred exactly one year prior to index date.

**Statistical Analysis**

Descriptive statistics were calculated to characterize the cohort demographics. Cumulative incidence functions (CIFs) were used to estimate cumulative incidence for two outcomes: 1) CRC incidence and 2) CRC mortality in the years following index date, with estimates at two-, five-, and eight-years post-index date. Follow-up began at index date (i.e., one year after a negative FIT result) and continued until diagnosis of CRC or death from CRC, exit from cohort (i.e., due to end of cohort period on December 31, 2019, aging out of cohort eligibility (>95 years age), disenrollment from health plan, or moving out of health plan or cancer registry coverage area). Follow-up was also censored at 180 days after a screening colonoscopy, with the 180 days included as a buffer to avoid the exclusion of cancers detected at screening colonoscopies. Follow-up for CRC mortality was additionally censored at 180 days after a FIT because the test modality lowers a person's risk of CRC mortality (29-31),[1] again using a 180-

[1] Subsequent stool-based testing was not treated as a censoring event for estimates of incidence because FIT/gFOBT has minimal to no effect on incidence (Kronborg et al., 1996 and Faivre et al., 2004) and thus uncensored follow-up is warranted for an estimate of natural course of disease. This is consistent with the analytical approach I used in Aim 1 and estimates cumulative risk in the absence of subsequent screening that would impact the outcome. If I were to censor at FIT, I would be estimating risk in the absence of any further screening (regardless of impact). However, I think the distinction is mostly theoretical.
[*continued in footer of next page*]

day buffer to account for potential misuse of FIT as a diagnostic rather than screening test[2]. Deaths from causes other than CRC were analyzed as competing events, which ensured that the population estimate considers only individuals who are alive (and thus have the potential to be diagnosed with CRC) to be at risk from CRC. CIF incidence and mortality estimates were further computed in subgroups stratified by patient characteristics: year of age at index date, sex, race and ethnicity, CCI, recent healthcare encounters, and number of recent FIT.

The impact of treating death from another cause as a censoring event (rather than a competing event) was shown by estimating cumulative incidence using the Kaplan-Meier (KM) method [1-KM estimator], which censors follow-up at a death from any cause and assumes deceased participants have the same outcome risk as individuals alive and remaining in the population. This approach overestimates the incidence of CRC among older adults remaining alive in the cohort population.

Sensitivity analyses were performed to estimate cumulative CRC incidence and mortality without censoring after screening colonoscopy, since retrospective classification of colonoscopy indication based on electronic data is known to be imperfect (25). Censoring at a screening colonoscopy could lead to bias if individuals who have a screening colonoscopy after age 75 years are not representative of CRC risks and lifespan. A second sensitivity analysis was applied

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One reason to censor would be to avoid counting CRC diagnoses that may never have been detected if not for the FIT exam. However, in my analysis, I am delaying censoring after screening colonoscopy by 180 days after the test result because censoring immediately at date of a procedure with the potential to detect cancer would prevent the procedure from detecting outcomes. If I were to censor immediately, incident cancer cases would be identified only from diagnostic colonoscopies (or not at all).

Use of this delayed censoring is necessary but means the actual numerical difference between censoring and not censoring at FIT (because I would add a similar 180-day delay) would be very minimal.

In an exploratory analysis this was confirmed: cumulative incidence estimates calculated after censoring at subsequent FIT were nearly equivalent to no censoring:

| | 2-yr | 5-yr | 8-yr |
|---|---|---|---|
| Censor at next FIT | 0.21% (0.18% - 0.24%) | 0.68% (0.62% - 0.70%) | 1.23% (1.12% - 1.34%) |
| No censor at next FIT | 0.19% (0.17%-0.22%) | 0.65% (0.59%-0.70%) | 1.17% (1.09%-1.27%) |

Evidence supporting marginal effect of FIT/gFOBT on incidence:
FIT/gFOBT has no measurable effect on incidence (or slight effect not observable in my analysis timeline: <8 years). FIT has low sensitivity for precursors adenomas (Kronborg, et. al. 1996). Faivre, et. al. (2004) found incidence of stage 4 CRC lower in screening group than control group, but the proportion of stage I CRC was higher in screening than control groups. Mandel, et. al. (1996) found evidence of that FOBT reduces incidence, but not until 13 years of follow-up (12% lower in screening vs. control groups, but p-value not significant). Mandel, et al. (2000) found significant reduction in incidence, but not until 18 years later (cumulative incidence ratio 0.8 for annual screening and 0.83 for biennial-screening. FIT has a clear effect on mortality [RCTs of gFOBT: Mandel, et. al. (1993, 1996); Faivre, et. al. (1996); Kronborg, et. al. (1996)], which is why I censored at subsequent FIT for the cumulative mortality.

[2] Older adults with suspected CRC or worsening health status with nonspecific abdominal symptoms might be offered a FIT instead of colonoscopy by a provider seeking to avoid the appropriate, more invasive diagnostic test (i.e., colonoscopy). These individuals are likely at higher risk of a CRC diagnosis or death (from CRC or another cause) that might be missed if individuals were censored right at the date of FIT result. A delay of 180 days before censoring ensures these instances are not systematically excluded due to censoring.

to the mortality estimation and did not censor if a FIT occurred following index date. While FIT is not intended to be a diagnostic test, we suspect it may be misused in this way, especially among older adults, in an attempt to avoid colonoscopy procedures if possible (11, 49, 50). Thus, censoring at such a test may underestimate the true cumulative CRC mortality. A sensitivity analysis (#3) was conducted to estimate cumulative incidence stratified by recent prior FIT, excluding patients who had less than 5 years of information on FIT results prior to index date. This occurred in a subset of observations where only the most recent FIT prior to PRECISE cohort entry was documented.

## Results

### Study Population

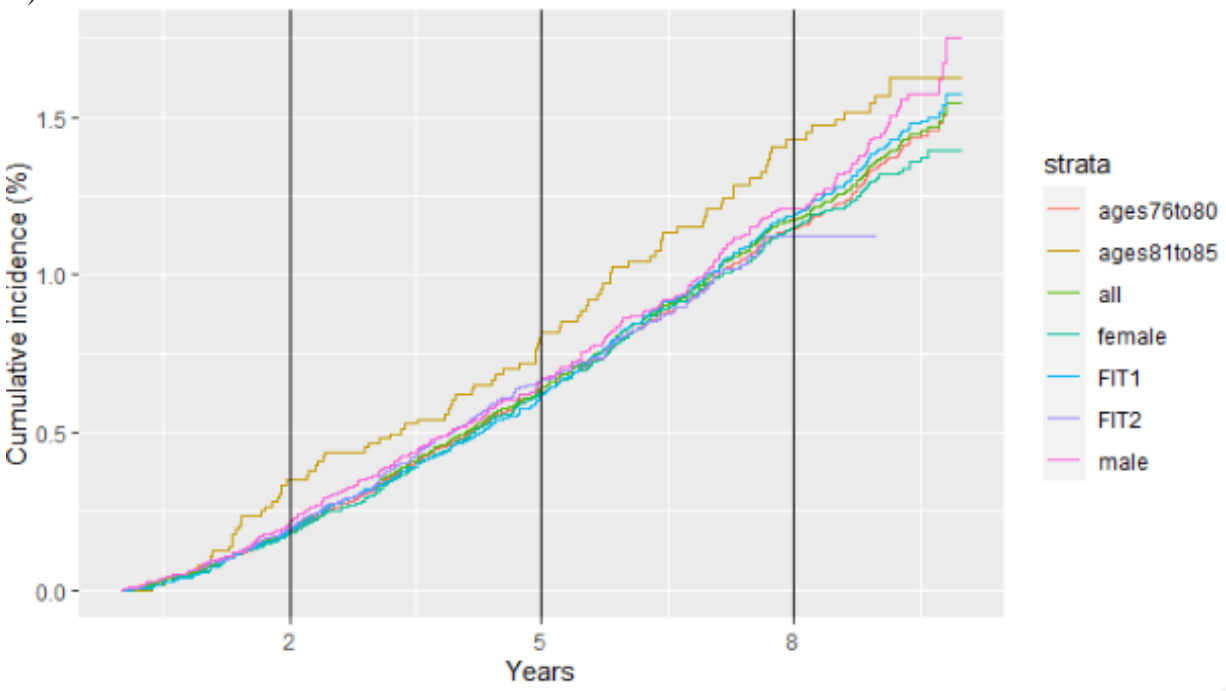
Characteristics of the 114,739 screen-eligible patients aged 76-85 years at study index date (i.e., with a negative FIT one year ago) are provided in Table 1. More than half the study population was 76 years old (meaning their prior negative FIT occurred at age 75 years) and ages 76-80 years old comprised 93.4% of the total study population. More than half of people were female (57.0%). The most frequent racial identities reported were White (71.2%), Asian (13.2%), and Black (7.8%); 16.7% patients identified as being of Hispanic or Latinx ethnicity. Other racial groups comprised less than 2% of the total population. In general, the cohort was highly heterogenous in terms of comorbidity: nearly 40% had no major comorbidities (CCI=0) while more than half (53.3%) had a CCI score of two or more. The three most prevalent comorbid conditions at index date were diabetes (19.9%), renal disease (18.4%), and peripheral vascular disease (16.8%). Just 3.3% had been hospitalized (inpatient or institutional stay) in the 6 months prior to index date. Most of the population (60.5%) had experienced two or more negative FIT tests in the five years preceding the index date. Characteristics of the study population stratified by healthcare system are shown in Table S-1.

### Cumulative CRC Incidence and Mortality

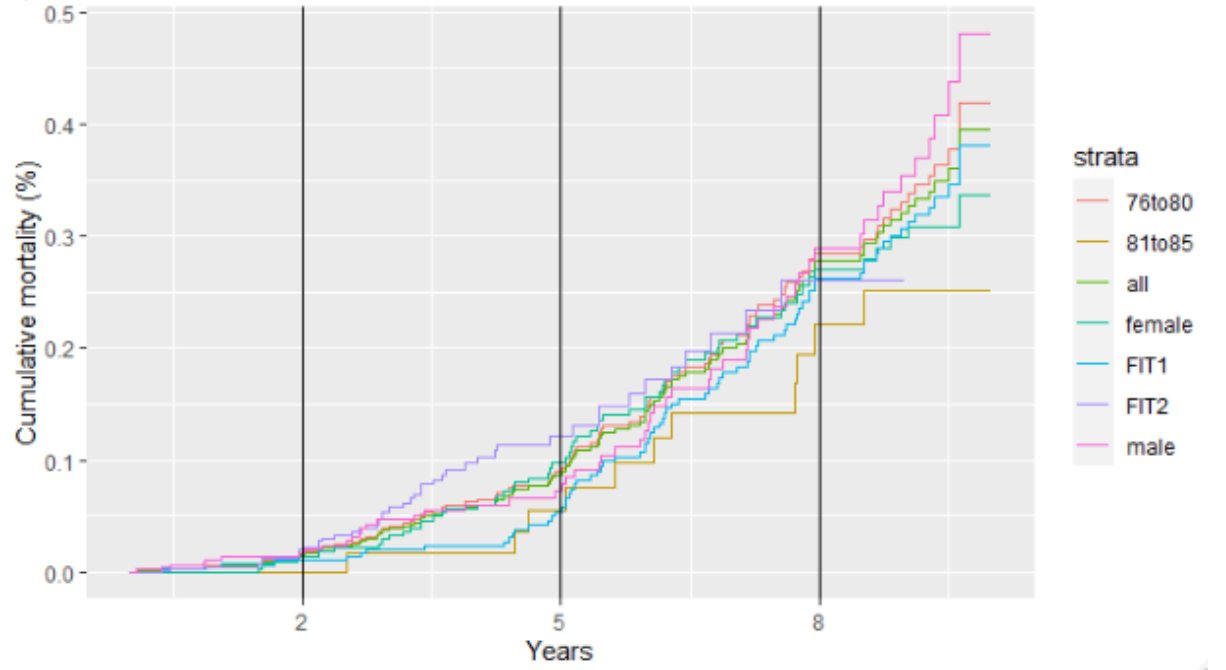
Cumulative incidence of CRC was 0.19% (95% CI: 0.17-0.22%) two years after index date and 1.17% (95% CI: 1.09-1.27%) eight years after index date (Table 2). Cumulative CRC mortality was an order of magnitude lower: 0.02% (95% CI: 0.01-0.03%) two years after index date and 0.28% (95% CI: 0.23-0.34%) eight years after index date (Table 3). Omission of screening colonoscopy during follow-up as a censoring event (sensitivity analysis 1) did not change cumulative risk estimates, though not censoring at subsequent FIT exams (sensitivity analysis 2) led to slightly lower cumulative mortality risk in the short term (0.01% (95% CI: 0.01-0.02%) at two years. Cumulative CRC incidence and mortality estimates are shown in Tables 2 and 3, respectively; corresponding estimates of cumulative mortality from other causes of death for each analysis are provided in Supplementary Tables S-2 and S-3. Cumulative incidence curves that generated estimates for both the primary and sensitivity analysis estimates are presented in Figure 1. Estimates of cumulative CRC incidence and mortality were generally low across covariate strata, with slight variation noted based on age, race, and number of recent FITs.

Figure 1: Cumulative incidence curves for (A) CRC incidence and (B) CRC mortality, stratified by age, sex, and number of recent FITs.

A)




B)



**Stratification by Demographic Characteristics: Age, Sex, Race, and Ethnicity**
Cumulative CRC incidence and mortality were marginally higher among males than females and somewhat higher in persons ages 76-80 years compared to those 81-85 years; however, these differences were within the limits of chance given no true difference. White patients had the highest cumulative risk of CRC while Asian patients had the lowest. The differences were greatest at eight-years post index date when risk for White patients was 1.26% (95% CI: 1.16-1.37%) and 0.93% (95% CI: 0.72-1.18%) for Asian patients (Table 2). These findings were evident in eight-year cumulative mortality estimates as well, though with overlapping confidence intervals: 0.30% (0.24-0.38%) for White patients and 0.24% (0.12-0.46%) for Asian patients (Table 3). Descriptive estimates were statistically imprecise for persons identifying as Native American/Alaska Native and Native Hawaiian/Other Pacific Islander.

**Stratification by Health History: CCI, Recent Healthcare Encounters, Recent Screening by FIT**
CCI scores lacked a clear association with cumulative risk of CRC or CRC mortality (Tables 2 and 3), with no appreciable differences observed across CCI strata, unlike the clear association between higher CCI and higher risk of death from non-CRC causes (Tables S-2 and S-3). Cumulative risk of CRC incidence and mortality estimates stratified by encounter histories were nearly equivalent at two years after index date. By eight years after index date, patients with no encounters in the six months prior to index date were at higher risk of CRC than patients with recent primary care or institutional/inpatient visit. However, these differences were small, and no differences were observed in estimates of cumulative CRC mortality. For contrast, recent encounters had an expected association with competing risks: patients with a recent inpatient or institutional stay were far more likely to die from another cause of death (than individuals with only primary care encounters (Table S-2 and S-3).

Risk estimates were also stratified according to number of recent FIT (with negative result) in the five years preceding index date and age. Per eligibility criteria, all participants had one FIT exactly one year prior to index date so any further FIT occurred between one and five years prior to index date. No notable differences in CRC incidence or mortality were observed at two years, but incidence estimates were slightly higher among individuals with just one FIT compared to two or more by eight years. A sensitivity analysis that excluded patients missing a full five years of look-back (i.e., who were potentially misclassified as one FIT instead of two or more) indicated individuals with two or more FIT tests had lower CRC risk compared to just one FIT by eight years post index date, notwithstanding with wide confidence intervals: 0.91% (95% CI: 0.41-1.78%) vs. 1.26% (95% CI: 1.02-1.54%). This was also evident in risk estimates of CRC mortality: 0.19% (95% CI: 0.08-0.44%) vs. 0.28% (95% CI: 0.13-0.53%).

## Discussion

Screen-eligible adults aged 76-85 years with a negative FIT result one year prior were observed to be at low risk for incident CRC and for CRC mortality, with slight differences by age, race, and number of recent FITs. In a recent parallel study comparing screen-eligible adults in the same age group with a negative colonoscopy ten years ago (Aim 1), we also estimated low cumulative risk of CRC and CRC mortality.

SEER estimates for nearly the same age group (75-84 years) are much higher: CRC incidence is 0.58% (two-year) and 2.28% (eight-year); CRC mortality is 0.20% (two-year) and 0.78% (eight-

year). However, SEER estimates reflect the risks of a population that is, on average, higher risk than this study population, because the SEER population is not limited to screen-eligible individuals, nor does it restrict on the basis of prior screening history (e.g., limit to individuals with a negative FIT result one year ago).

The current results describe the natural history risk of CRC and CRC mortality in a population of screen-eligible older adults with recent negative FIT results. Selection of the population based on a negative test should lead to few prevalent cancers and thus lowered CRC risk for a limited period of time (51). Therefore, cancers diagnosed during follow-up were those that could potentially be detected and treated if screening were to continue between ages 76-85 years and thereby contribute to a reduction in CRC mortality. Given the moderate sensitivity of FIT (approximately 79%) (52), some cancers could potentially be missed by the recent FIT and would have been captured, albeit at a later stage, at a subsequent screening, if continued. Thus, the current cumulative risk estimates include cases that were either i) missed by a recent FIT or ii) emerged after screening cessation.

One limitation in the generalizability of these study results is the uneven distribution of index ages in the range of interest (i.e., high proportion of 76-year-olds). The age range available in the observational data are limited since the recommended age of CRC screening cessation is 75 years of age and (to a lesser extent) because we selected on the earliest test to occur in the observation period. This skewed age distribution should be carefully considered when applying these results in another setting. Furthermore, these estimates do not provide individual-level risk prediction, but rather offer empirical evidence of population-level CRC risk among screen-eligible older adults with recent negative FIT. Individuals undergoing surveillance due to prior CRC or high-risk findings will likely have much higher incidence than the population documented here. Another limitation is that despite the effort taken to include a diverse cohort, event counts in some race strata were insufficient to produce robust estimates when stratified by race and ethnicity.

This study benefits from the use of high-quality long-term data (including prior testing history) in a large and diverse screen-eligible cohort. One particular strength of this analysis is that these estimates account for a critical selection factor that may affect most disease risk estimates in older adults: death from other causes. Calculation of a cumulative risk estimate that accounts for competing risks of death acknowledges that lower life expectancy in an older population ultimately affects cumulative risk of CRC. This approach was validated by the similarity of CRC and CRC mortality estimates observed for individuals with a recent encounter, regardless of type, though rates of mortality from other causes were notably higher for individuals with a recent inpatient or institutional stay.

In summary, the results of this study suggest that for persons aged 76-85 years who had a negative FIT one year ago, the subsequent cumulative risks of CRC and CRC mortality are very low. Nonetheless, given the low risk of complications from FIT, as well as evidence suggesting sensitivity improves with repeated testing, screen-eligible older adults may wish to continue their FIT regimen beyond age 75.

Tables

Table 1: Characteristics at index date of screen-eligible patients aged 76-85 years.

| | Overall | | 76-80 | | 81-85 | |
|---|---|---|---|---|---|---|
| | N=114739 | | N=107222 | | N=7517 | |
| **Characteristic** | **N** | **%** | **N** | **%** | **N** | **%** |
| **Providing site** | | | | | | |
| KPWA | 4612 | 4.0% | 4140 | 3.9% | 472 | 6.3% |
| PHHS | 1714 | 1.5% | 1451 | 1.4% | 263 | 3.5% |
| KPNC | 63124 | 55.0% | 59458 | 55.5% | 3666 | 48.8% |
| KPSC | 45289 | 39.5% | 42173 | 39.3% | 3116 | 41.5% |
| **Age (years)** | | | | | | |
| 76 | 74722 | 65.1% | 74722 | 69.7% | 0 | 0.0% |
| 77 | 11142 | 9.7% | 11142 | 10.4% | 0 | 0.0% |
| 78 | 7605 | 6.6% | 7605 | 7.1% | 0 | 0.0% |
| 79 | 7121 | 6.2% | 7121 | 6.6% | 0 | 0.0% |
| 80 | 6632 | 5.8% | 6632 | 6.2% | 0 | 0.0% |
| 81 | 3050 | 2.7% | 0 | 0.0% | 3050 | 40.6% |
| 82 | 1439 | 1.3% | 0 | 0.0% | 1439 | 19.1% |
| 83 | 1223 | 1.1% | 0 | 0.0% | 1223 | 16.3% |
| 84 | 1109 | 1.0% | 0 | 0.0% | 1109 | 14.8% |
| 85 | 696 | 0.6% | 0 | 0.0% | 696 | 9.3% |
| **Age group** | | | | | | |
| 76-80y | 107222 | 93.4% | 107222 | 100.0% | 0 | 0.0% |
| 81-85y | 7517 | 6.6% | 0 | 0.0% | 7517 | 100.0% |
| **Sex** | | | | | | |
| Male | 49331 | 43.0% | 46294 | 43.2% | 3037 | 40.4% |
| Female | 65407 | 57.0% | 60927 | 56.8% | 4480 | 59.6% |
| Missing | 1 | 0.0% | 1 | 0.0% | 0 | 0.0% |
| **Ethnicity**[+] | | | | | | |
| Hispanic or Latinx | 19115 | 16.7% | 17868 | 16.7% | 1247 | 16.6% |
| Not Hispanic or Latinx | 37190 | 32.4% | 34330 | 32.02% | 2860 | 38.5% |
| Missing[++] | 58434 | 50.9% | 55024 | 51.3% | 3410 | 45.4% |
| **Race**[i] | | | | | | |
| White | 81646 | 71.2% | 76028 | 70.9% | 5618 | 74.7% |
| Black | 8907 | 7.8% | 8310 | 7.8% | 597 | 7.9% |
| Asian | 15202 | 13.2% | 14340 | 13.4% | 862 | 11.5% |
| Native American/Alaska Native | 652 | 0.6% | 615 | 0.6% | 37 | 0.5% |
| Native Hawaiian/Other Pacific Islander | 677 | 0.6% | 638 | 0.6% | 39 | 0.5% |
| Multiple or not otherwise specified | 394 | 0.3% | 363 | 0.3% | 31 | 0.4% |
| No race information | 8363 | 7.3% | 7953 | 7.4% | 410 | 5.5% |
| **Charlson Comorbidity Index (CCI) score**[ii] | | | | | | |
| 0 | 44297 | 38.6% | 42005 | 39.2% | 2292 | 30.5% |
| 1 | 20859 | 18.2% | 19853 | 18.5% | 1006 | 13.4% |
| 2 | 17184 | 15.0% | 16196 | 15.1% | 988 | 13.1% |
| 3 | 7899 | 6.9% | 7391 | 6.9% | 508 | 6.8% |
| 4 | 7409 | 6.5% | 6965 | 6.5% | 444 | 5.9% |
| ≥5 | 7702 | 6.7% | 7180 | 6.7% | 522 | 6.9% |
| Missing | 9148 | 8.0% | 7403 | 6.9% | 1745 | 23.2% |
| **Individual comorbid conditions** | | | | | | |
| Myocardial infarction | 5756 | 5.0% | 5333 | 5.0% | 423 | 5.6% |
| Congestive heart disease | 4634 | 4.0% | 4181 | 3.9% | 453 | 6.0% |
| Peripheral vascular disorder | 19244 | 16.8% | 18396 | 17.2% | 848 | 11.3% |
| Cerebrovascular disease | 5865 | 5.1% | 5432 | 5.1% | 433 | 5.8% |

| | | | | | | |
|---|---|---|---|---|---|---|
| Dementia | 1350 | 1.2% | 1231 | 1.1% | 119 | 1.6% |
| Chronic pulmonary disease | 16070 | 14.0% | 15133 | 14.1% | 937 | 12.5% |
| Rheumatic disease | 2274 | 2.0% | 2128 | 2.0% | 146 | 1.9% |
| Peptic ulcer | 351 | 0.3% | 317 | 0.3% | 34 | 0.5% |
| Mild liver disease | 294 | 0.3% | 281 | 0.3% | 13 | 0.2% |
| Diabetes | 22786 | 19.9% | 21638 | 20.2% | 1148 | 15.3% |
| Diabetes with chronic complications | 15074 | 13.1% | 14264 | 13.3% | 810 | 10.8% |
| Hemiplegia or paraplegia | 479 | 0.4% | 450 | 0.4% | 29 | 0.4% |
| Renal disease | 21081 | 18.4% | 19634 | 18.3% | 1447 | 19.2% |
| Malignancy (incl. leukemia and lymphoma) | 5217 | 4.5% | 4835 | 4.5% | 382 | 5.1% |
| Moderate or severe liver disease | 76 | 0.1% | 71 | 0.1% | 5 | 0.1% |
| Metastatic solid tumor | 825 | 0.7% | 784 | 0.7% | 41 | 0.5% |
| HIV/AIDS | 47 | 0.0% | 45 | 0.0% | 2 | 0.0% |
| **Encounters (<180 days prior to index date)**[iii] | | | | | | |
| Institutional or inpatient stay | 3822 | 3.3% | 3467 | 3.2% | 355 | 4.7% |
| Only primary care visit(s) | 72832 | 63.5% | 67839 | 63.3% | 4993 | 66.4% |
| None | 38085 | 33.2% | 35916 | 33.5% | 2169 | 28.9% |
| **Prior FIT (<5 years prior)** | | | | | | |
| 1 FIT (test 1y ago only)[iv] | 45277 | 39.5% | 37923 | 35.4% | 7354 | 97.8% |
| 1 FIT – Age 76-80y | 37923 | 33.1% | 37923 | 35.4% | 0 | 0.0% |
| 1 FIT – Age 81-85y | 7354 | 6.4% | 0 | 0.0% | 7354 | 97.8% |
| ≥2 FIT | 69462 | 60.5% | 69299 | 64.6% | 163 | 2.2% |
| ≥2 FIT – Age 76-80y | 69299 | 60.4% | 69299 | 64.6% | 0 | 0.0% |
| ≥2 FIT – Age 81-85y | 163 | 0.1% | 0 | 0.0% | 163 | 2.2% |

Index date was defined as date 365 days after a negative FIT.

+ Hispanic or Latinx ethnicity was considered distinct from race categories (and was selected in conjunction with race categories by some participants).

++KPNC recorded Hispanic or Latinx ethnicity as either present or missing. Not Hispanic or Latinx was not offered as an option.

i. Will not sum to 100% since some patients were identified with >1 race and/or ethnic group.

ii. Charlson Comorbidity Index score was calculated using patient-level administrative codes from 365 days preceding the start of the calendar quarter in which the index date occurred. For example, an index date of 2/15/10 would use a Charlson score calculated based on data collected between 1/1/09-12/31/09. Calendar quarters began January 1, April 1, July 1, and Oct 1 annually.

iii. Includes acute inpatient, institutional, and primary care encounters; does not include specialty or telemedicine encounters.

iv. Due to incomplete look-back, up to 24,713 patients could theoretically be misclassified as having one FIT instead of two or more in the five years prior to index date (i.e., underestimation of # prior FITs).

Table 2: Cumulative CRC incidence, stratified by patient characteristics at index date.

| | **Cumulative incidence of CRC, percent (95% confidence interval)** | | |
|---|---|---|---|
| | **2-year** | **5-year** | **8-year** |
| Overall | 0.19 (0.17,0.22) | 0.65 (0.59,0.70) | 1.17 (1.09,1.27) |
| Sensitivity analysis 1 (no censoring at subsequent screening colonoscopy) | 0.19 (0.17,0.22) | 0.64 (0.58,0.70) | 1.16 (1.07,1.26) |
| Kaplan-Meier approach[#] | 0.20 (0.17,0.22) | 0.67 (0.61,0.73) | 1.28 (1.18,1.38) |
| **Age (years) and sex** | | | |
| 76-80 | 0.18 (0.15,0.21) | 0.63 (0.57,0.69) | 1.14 (1.05,1.24) |
| 81-85 | 0.35 (0.23,0.51) | 0.82 (0.62,1.06) | 1.43 (1.15,1.75) |
| Male | 0.21 (0.17,0.26) | 0.67 (0.59,0.76) | 1.21 (1.08,1.36) |
| Female | 0.18 (0.15,0.22) | 0.63 (0.56,0.70) | 1.15 (1.03,1.27) |
| **Charlson Comorbidity Index (CCI)** | | | |
| 0 | 0.18 (0.11,0.29) | 0.73 (0.57,0.92) | 1.35 (1.12,1.62) |
| 1 | 0.20 (0.16,0.24) | 0.64 (0.56,0.74) | 1.15 (1.01,1.30) |
| 2 | 0.14 (0.09,0.20) | 0.59 (0.46,0.74) | 1.11 (0.90,1.36) |
| 3 | 0.21 (0.15,0.30) | 0.63 (0.50,0.79) | 1.24 (1.00,1.51) |
| 4 | 0.14 (0.07,0.26) | 0.61 (0.41,0.88) | 1.21 (0.85,1.67) |
| ≥5 | 0.20 (0.12,0.34) | 0.71 (0.51,0.99) | 1.05 (0.76,1.43) |
| **Encounters (<180 days prior to index date)** | | | |
| Institutional/inpatient stay | 0.18 (0.08,0.39) | 0.69 (0.43,1.06) | 1.08 (0.70,1.60) |
| Primary care only | 0.20 (0.17,0.24) | 0.60 (0.54,0.67) | 1.12 (1.02,1.24) |
| 0 encounters | 0.18 (0.14,0.24) | 0.73 (0.63,0.84) | 1.28 (1.13,1.45) |
| **Ethnicity and race** | | | |
| Hispanic or Latinx | 0.20 (0.14,0.28) | 0.53 (0.42,0.66) | 1.06 (0.87,1.29) |
| White | 0.22 (0.18,0.25) | 0.71 (0.64,0.78) | 1.26 (1.16,1.37) |
| Black | 0.21 (0.13,0.34) | 0.69 (0.51,0.93) | 1.23 (0.93,1.60) |
| Asian | 0.13 (0.08,0.21) | 0.51 (0.39,0.67) | 0.93 (0.72,1.18) |
| Native American/Alaska Native | 0.21 (0.02,1.13) | 0.44 (0.09,1.50) | 1.72 (0.60,3.94) |
| Native Hawaiian/Other Pacific Islander | * | 1.21 (0.46,2.71) | 1.68 (0.66,3.57) |
| **Recent FIT (<5 years prior to index date)** | | | |
| 1 FIT (test 1y ago only)[iii] | 0.19 (0.15,0.24) | 0.62 (0.55,0.70) | 1.19 (1.08,1.31) |
| 1 FIT – Age 76-80y | 0.16 (0.12,0.20) | 0.58 (0.50,0.67) | 1.14 (1.02,1.27) |
| 1 FIT – Age 81-85y | 0.36 (0.24,0.52) | 0.82 (0.62,1.06) | 1.44 (1.16,1.77) |
| ≥2 FIT | 0.19 (0.16,0.23) | 0.67 (0.59,0.76) | 1.12 (0.98,1.28) |
| ≥2 FIT – Age 76-80y | 0.20 (0.16,0.23) | 0.67 (0.59,0.75) | 1.13 (0.98,1.29) |
| ≥2 FIT – Age 81-85y | * | 0.82 (0.07,4.11) | 0.82 (0.07,4.11) |
| *Sensitivity analysis 3: Patients with complete data on FIT < 5y prior to index date (n=74,451)* | | | |
| 1 FIT (test 1y ago only) | 0.27 (0.20,0.36) | 0.70 (0.56,0.87) | 1.26 (1.02,1.54) |
| 1 FIT – Age 76-80y | 0.24 (0.17,0.33) | 0.68 (0.54,0.84) | 1.15 (0.91,1.44) |
| 1 FIT – Age 81-85y | 0.45 (0.25,0.77) | 0.82 (0.51,1.26) | 1.67 (1.11,2.44) |
| ≥2 FIT | 0.20 (0.05,0.63) | 0.69 (0.39,1.15) | 0.91 (0.41,1.78) |
| ≥2 FIT – Age 76-80y | 0.20 (0.16, 0.24) | 0.69 (0.57,0.82) | 0.91 (0.68,1.19) |
| ≥2 FIT – Age 81-85y | * | 1.73 (0.14,8.20) | 1.73 (0.14,8.20) |
| **Healthcare system** | | | |
| KPWA | 0.07 (0.01,0.24) | 0.22 (0.08,0.50) | 0.41 (0.17,0.87) |
| PHHS | * | 0.10 (0.01,0.56) | 0.10 (0.01,0.56) |
| KPNC | 0.01 (0.01,0.03) | 0.07 (0.05,0.10) | 0.22 (0.17,0.29) |
| KPSC | 0.01 (0,0.03) | 0.11 (0.06,0.18) | 0.38 (0.28,0.52) |

[#] Kaplan-Meier approach (1-KM estimator) provides an estimate of cumulative incidence that ignores (censors) at competing events (deaths from other causes); * Incident outcomes insufficient for statistical precision in this group.

Table 3: Cumulative CRC mortality, stratified by patient characteristics at index date

| | Cumulative mortality of CRC, percent (95% confidence interval) | | |
|---|---|---|---|
| | **2-year** | **5-year** | **8-year** |
| Overall | 0.02 (0.01,0.03) | 0.09 (0.06,0.12) | 0.28 (0.23,0.34) |
| Sensitivity analysis 1 (no censoring at subsequent screening colonoscopy) | 0.02 (0.01,0.03) | 0.09 (0.07,0.12) | 0.28 (0.22,0.34) |
| Sensitivity analysis 2 (no censoring at subsequent FIT) | 0.01 (0.01,0.02) | 0.10 (0.07,0.12) | 0.30 (0.25,0.35) |
| Via Kaplan-Meier approach[#] | 0.02 (0.01,0.02) | 0.09 (0.06,0.12) | 0.32 (0.25,0.38) |
| **Age and sex** | | | |
| 76-80 | 0.02 (0.01,0.03) | 0.09 (0.07,0.12) | 0.28 (0.23,0.35) |
| 81-85 | * | 0.06 (0.02,0.16) | 0.22 (0.11,0.40) |
| Male | 0.02 (0.01,0.04) | 0.07 (0.04,0.11) | 0.29 (0.21,0.39) |
| Female | 0.01 (0.01,0.03) | 0.10 (0.07,0.14) | 0.27 (0.21,0.35) |
| **Encounters (<180 days prior to index date)** | | | |
| Institutional/inpatient stay | * | 0.10 (0.02,0.36) | 0.36 (0.13,0.84) |
| Primary care only | 0.01 (0.01,0.03) | 0.08 (0.05,0.12) | 0.26 (0.20,0.34) |
| 0 encounters | 0.02 (0.01,0.04) | 0.10 (0.06,0.16) | 0.31 (0.22,0.42) |
| **Charlson Comorbidity Index (CCI)** | | | |
| 0 | * | 0.09 (0.04,0.19) | 0.42 (0.29,0.61) |
| 1 | 0.01 (0,0.03) | 0.07 (0.05,0.12) | 0.21 (0.14,0.30) |
| 2 | 0.02 (0.01,0.07) | 0.10 (0.05,0.19) | 0.29 (0.17,0.48) |
| 3 | * | 0.07 (0.03,0.17) | 0.23 (0.12,0.41) |
| 4 | * | 0.06 (0.01,0.20) | 0.38 (0.15,0.85) |
| ≥5 | 0.04 (0.01,0.15) | 0.11 (0.04,0.29) | 0.20 (0.07,0.50) |
| **Ethnicity and race** | | | |
| Hispanic or Latinx | 0.01 (0,0.03) | 0.07 (0.03,0.16) | 0.28 (0.17,0.47) |
| White | 0.02 (0.01,0.03) | 0.10 (0.07,0.14) | 0.30 (0.24,0.38) |
| Black | 0.02 (0,0.09) | 0.09 (0.03,0.23) | 0.30 (0.14,0.57) |
| Asian | * | 0.03 (0.01,0.12) | 0.24 (0.12,0.46) |
| Native American/Alaska Native | * | 0.30 (0.03,1.59) | 0.30 (0.03,1.59) |
| Native Hawaiian/Other Pacific Islander | * | * | * |
| **Recent FIT (<5 years prior to index date)** | | | |
| 1 FIT (test 1y ago only) | 0.01 (0,0.03) | 0.05 (0.03,0.09) | 0.26 (0.20,0.33) |
| 1 FIT – Age 76-80y | 0.01 (0,0.03) | 0.05 (0.03,0.09) | 0.27 (0.20,0.35) |
| 1 FIT – Age 81-85y | * | 0.06 (0.02,0.16) | 0.23 (0.12,0.41) |
| ≥2 FIT (incl. test 1y ago) | 0.02 (0.01,0.04) | 0.12 (0.08,0.17) | 0.26 (0.17,0.38) |
| ≥2 FIT – Age 76-80y | 0.02 (0.01,0.04) | 0.12 (0.08,0.17) | 0.26 (0.17,0.39) |
| ≥2 FIT – Age 81-85y | * | * | * |
| *Sensitivity analysis 3: Patients with complete data on FIT < 5y prior to index date (n=74,451)* | | | |
| 1 FIT (test 1y ago only) | 0.03 (0.01,0.08) | 0.09 (0.04,0.19) | 0.28 (0.13,0.53) |
| 1 FIT – Age 76-80y | 0.03 (0.01,0.08) | 0.10 (0.05,0.19) | 0.20 (0.11,0.33) |
| 1 FIT – Age 81-85y | * | 0.05 (0,0.26) | 0.12 (0.02,0.43) |
| ≥2 FIT (incl. test 1y ago) | 0.03 (0.03,0.03) | 0.13 (0.06,0.25) | 0.19 (0.08,0.44) |
| ≥2 FIT – Age 76-80y | 0.03 (0.01,0.05) | 0.13 (0.09,0.20) | 0.20 (0.11,0.33) |
| ≥2 FIT – Age 81-85y | * | * | * |
| **Healthcare system** | | | |
| KPWA | 0.33 (0.19,0.56) | 0.95 (0.65,1.34) | 1.23 (0.86,1.72) |
| PHHS | 0.30 (0.12,0.68) | 0.76 (0.40,1.32) | 0.86 (0.47,1.47) |
| KPNC | 0.17 (0.13,0.20) | 0.59 (0.52,0.67) | 1.14 (1.03,1.27) |
| KPSC | 0.21 (0.17,0.26) | 0.69 (0.60,0.79) | 1.23 (1.08,1.38) |

[#] Kaplan-Meier approach (1-KM estimator) provides an estimate of cumulative incidence that ignores (censors) at competing events (deaths from other causes); * Incident outcomes insufficient for statistical precision in this group.

Supplementary Material

Table S-1: Characteristics at index date of screen-eligible patients aged 76-85 years, stratified by healthcare system.

| | KPWA | | PHHS | | KPNC | | KPSC | |
|---|---|---|---|---|---|---|---|---|
| N= | 4612 | | 1714 | | 63124 | | 45289 | |
| **Characteristic** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| **Age (years)** | | | | | | | | |
| 76 | 2677 | 58.0% | 650 | 37.9% | 45144 | 71.5% | 26251 | 58.0% |
| 77 | 638 | 13.8% | 334 | 19.5% | 4989 | 7.9% | 5181 | 11.4% |
| 78 | 296 | 6.4% | 205 | 12.0% | 3460 | 5.5% | 3644 | 8.0% |
| 79 | 282 | 6.1% | 155 | 9.0% | 3086 | 4.9% | 3598 | 7.9% |
| 80 | 247 | 5.4% | 107 | 6.2% | 2779 | 4.4% | 3499 | 7.7% |
| 81 | 156 | 3.4% | 88 | 5.1% | 1472 | 2.3% | 1334 | 2.9% |
| 82 | 117 | 2.5% | 58 | 3.4% | 691 | 1.1% | 573 | 1.3% |
| 83 | 74 | 1.6% | 46 | 2.7% | 628 | 1.0% | 475 | 1.0% |
| 84 | 86 | 1.9% | 40 | 2.3% | 555 | 0.9% | 428 | 0.9% |
| 85 | 39 | 0.8% | 31 | 1.8% | 320 | 0.5% | 306 | 0.7% |
| 76-80 | 4140 | 89.8% | 1451 | 84.7% | 59458 | 94.2% | 42173 | 93.1% |
| 81-85 | 472 | 10.2% | 263 | 15.3% | 3666 | 5.8% | 3116 | 6.9% |
| **Ethnicity**[+] | | | | | | | | |
| Hispanic or Latinx | 131 | 2.8% | 862 | 50.3% | 6980 | 11.1% | 11142 | 24.6% |
| Not Hispanic or Latinx | 3036 | 65.8% | 848 | 49.5% | 0 | 0% | 33306 | 73.5% |
| Missing[++] | 1445 | 31.3% | 4 | 0.2% | 56144 | 88.9% | 841 | 1.9% |
| **Race**[i] | | | | | | | | |
| White | 4041 | 87.6% | 1007 | 58.8% | 45456 | 72.0% | 31142 | 68.8% |
| Black | 102 | 2.2% | 494 | 28.8% | 3791 | 6.0% | 4520 | 10.0% |
| Asian | 334 | 7.2% | 199 | 11.6% | 9394 | 14.9% | 5275 | 11.6% |
| Native American/Alaska Native | 53 | 1.1% | 6 | 0.4% | 303 | 0.5% | 290 | 0.6% |
| Native Hawaiian/Other Pacific Islander | 17 | 0.4% | 2 | 0.1% | 323 | 0.5% | 335 | 0.7% |
| Multiple or not otherwise specified | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 340 | 0.8% |
| Other | 54 | 1.2% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| No race information | 74 | 1.6% | 11 | 0.6% | 4057 | 6.4% | 4221 | 9.3% |
| **Sex** | | | | | | | | |
| Male | 2007 | 43.5% | 657 | 38.3% | 27140 | 43.0% | 19527 | 43.1% |
| Female | 2605 | 56.5% | 1057 | 61.7% | 35983 | 57.0% | 25762 | 56.9% |
| Missing | 0 | 0.0% | 0 | 0.0% | 1 | 0.0% | 0 | 0.0% |
| **Charlson Comorbidity Index (CCI)**[ii] | | | | | | | | |
| 0 | 2443 | 53.0% | 617 | 36.0% | 26841 | 42.5% | 14396 | 31.8% |
| 1 | 771 | 16.7% | 463 | 27.0% | 12659 | 20.1% | 6966 | 15.4% |
| 2 | 703 | 15.2% | 240 | 14.0% | 10001 | 15.8% | 6240 | 13.8% |
| 3 | 254 | 5.5% | 127 | 7.4% | 4521 | 7.2% | 2997 | 6.6% |
| 4 | 211 | 4.6% | 100 | 5.8% | 4299 | 6.8% | 2799 | 6.2% |
| ≥5 | 217 | 4.7% | 114 | 6.7% | 4543 | 7.2% | 2828 | 6.2% |
| *Missing* | 13 | 0.3% | 50 | 2.9% | 140 | 0.2% | 8945 | 19.8% |
| Myocardial infarction | 338 | 7.3% | 82 | 4.8% | 3231 | 5.1% | 2105 | 4.6% |
| Congestive heart disease | 227 | 4.9% | 148 | 8.6% | 2660 | 4.2% | 1599 | 3.5% |
| Peripheral vascular disorder | 223 | 4.8% | 89 | 5.2% | 11857 | 18.8% | 7075 | 15.6% |
| Cerebrovascular disease | 226 | 4.9% | 105 | 6.1% | 3468 | 5.5% | 2066 | 4.6% |
| Dementia | 46 | 1.0% | 72 | 4.2% | 581 | 0.9% | 651 | 1.4% |
| Chronic pulmonary disease | 517 | 11.2% | 225 | 13.1% | 10295 | 16.3% | 5033 | 11.1% |
| Rheumatic disease | 112 | 2.4% | 24 | 1.4% | 1427 | 2.3% | 711 | 1.6% |
| Peptic ulcer | 15 | 0.3% | 7 | 0.4% | 201 | 0.3% | 128 | 0.3% |
| Mild liver disease | 10 | 0.2% | 10 | 0.6% | 150 | 0.2% | 124 | 0.3% |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Diabetes | 673 | 14.6% | 675 | 39.4% | 12354 | 19.6% | 9084 | 20.1% |
| Diabetes with chronic complications | 462 | 10.0% | 204 | 11.9% | 8355 | 13.2% | 6053 | 13.4% |
| Hemiplegia or paraplegia | 19 | 0.4% | 7 | 0.4% | 276 | 0.4% | 177 | 0.4% |
| Renal disease | 659 | 14.3% | 225 | 13.1% | 12334 | 19.5% | 7863 | 17.4% |
| Malignancy (incl. leukemia and lymphoma) | 274 | 5.9% | 103 | 6.0% | 3085 | 4.9% | 1755 | 3.9% |
| Moderate or severe liver disease | 6 | 0.1% | 9 | 0.5% | 34 | 0.1% | 27 | 0.1% |
| Metastatic solid tumor | 36 | 0.8% | 11 | 0.6% | 511 | 0.8% | 267 | 0.6% |
| HIV/AIDS | 2 | 0.0% | 2 | 0.1% | 31 | 0.0% | 12 | 0.0% |
| **Encounters (<180 days prior)**[iii] | | | | | | | | |
| Institutional or inpatient stay | 156 | 3.4% | 59 | 3.4% | 2053 | 3.3% | 1554 | 3.4% |
| Only primary care visit(s) | 2717 | 58.9% | 1170 | 68.3% | 38615 | 61.2% | 30330 | 67.0% |
| None | 1739 | 37.7% | 485 | 28.3% | 22456 | 35.6% | 13405 | 29.6% |
| **Recent FIT (<5 years prior to index date)** | | | | | | | | |
| 1 FIT (test 1y ago only)[iv] | 1935 | 42.0% | 1107 | 64.6% | 21711 | 34.4% | 20524 | 45.3% |
| 1 FIT – Age 76-80y | 1476 | 32.0% | 847 | 49.4% | 18128 | 28.7% | 17472 | 38.6% |
| 1 FIT – Age 81-85y | 459 | 10.0% | 260 | 15.2% | 3583 | 5.7% | 3052 | 6.7% |
| ≥2 FIT | 2677 | 58.0% | 607 | 35.4% | 41413 | 65.6% | 24765 | 54.7% |
| ≥2 FIT – Age 76-80y | 2664 | 57.8% | 604 | 35.2% | 41330 | 65.5% | 24701 | 54.5% |
| ≥2 FIT – Age 81-85y | 13 | 0.3% | 3 | 0.2% | 83 | 0.1% | 64 | 0.1% |

Index date was defined as date 365 days after a negative FIT.

i. Will not sum to 100% since some patients were identified with >1 race and/or ethnic group.

+ Hispanic or Latinx ethnicity was considered distinct from race categories (and was selected in conjunction with race categories by some participants).

++KPNC recorded Hispanic or Latinx ethnicity as either present or missing. Not Hispanic or Latinx was not offered as an option.

ii. Charlson Comorbidity Index score was calculated using patient-level administrative codes from 365 days preceding the start of the calendar quarter in which the index date occurred. For example, an index date of 2/15/10 would use a Charlson score calculated based on data collected between 1/1/09-12/31/09. Calendar quarters began January 1, April 1, July 1, and Oct 1 annually.

iii. Includes acute inpatient, institutional, and primary care encounters; does not include specialty or telemedicine encounters.

Table S-2: Cumulative risk of death from other causes (competing risk to CRC *incidence* estimates), stratified by patient characteristics at index date

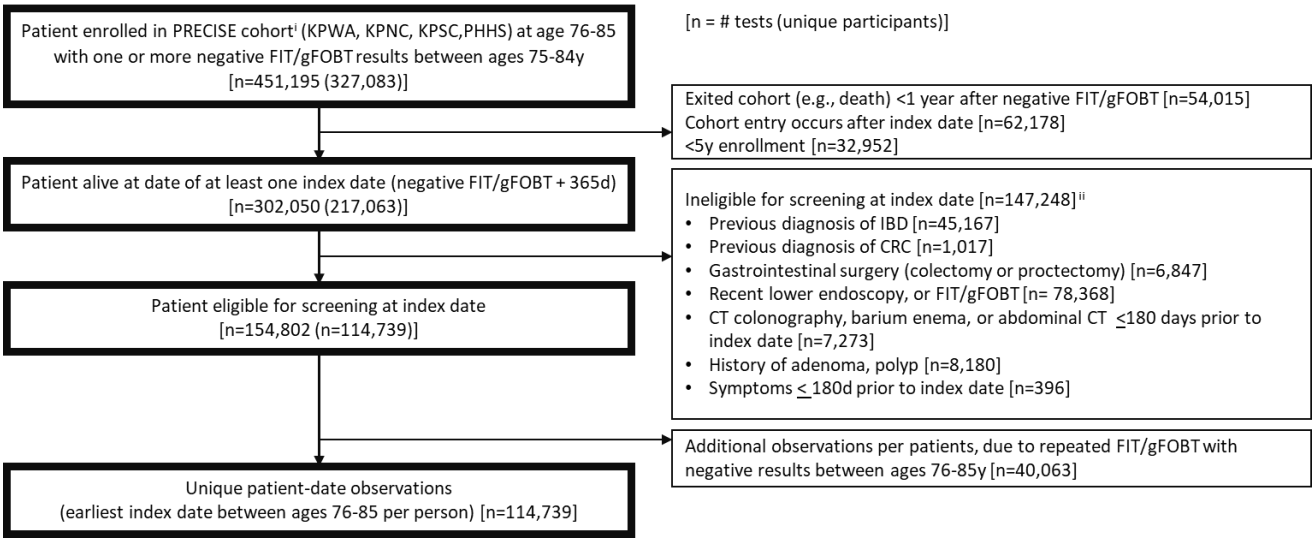
| | **Cumulative risk of death from other causes, percent (95% confidence interval)** | | |
|---|---|---|---|
| | **2-year** | **5-year** | **8-year** |
| Overall | 1.90 (1.82,1.98) | 7.44 (7.25,7.63) | 20.99 (20.62,21.36) |
| Sensitivity analysis 1 (no censoring at subsequent screening colonoscopy) | 1.90 (1.76,2.04) | 7.41 (7.20,7.63) | 20.85 (20.56,21.15) |
| **Age and sex** | | | |
| 76-80 | 1.97 (1.88,2.07) | 7.40 (7.17,7.64) | 20.55 (20.08,21.02) |
| 81-85 | 1.60 (1.32,1.92) | 8.88 (8.15,9.65) | 29.37 (28.04,30.7) |
| Male | 2.44 (2.30,2.59) | 9.23 (8.91,9.56) | 25.39 (24.78,26.01) |
| Female | 1.49 (1.39,1.59) | 6.10 (5.88,6.34) | 17.79 (17.34,18.25) |
| **Encounters (<180 days prior to index date)** | | | |
| Institutional/inpatient stay | 6.89 (6.08,7.77) | 17.54 (16.13,19.01) | 36.65 (34.42,38.89) |
| Primary care only | 1.82 (1.72,1.93) | 7.51 (7.27,7.76) | 21.24 (20.77,21.72) |
| None | 1.53 (1.40,1.67) | 6.22 (5.92,6.54) | 18.87 (18.26,19.48) |
| **Charlson Comorbidity Index (CCI)** | | | |
| 0 | 0.84 (0.75,0.93) | 4.55 (4.32,4.80) | 14.15 (13.63,14.67) |
| 1 | 1.40 (1.23,1.58) | 6.53 (6.08,6.99) | 20.09 (19.12,21.08) |
| 2 | 1.83 (1.62,2.06) | 8.49 (7.95,9.04) | 22.07 (21.03,23.13) |
| 3 | 3.16 (2.75,3.61) | 12.02 (11.05,13.04) | 28.91 (27.11,30.73) |
| 4 | 3.44 (3.01,3.91) | 13.41 (12.42,14.44) | 31.08 (29.25,32.93) |
| ≥5 | 9.06 (8.37,9.78) | 25.3 (23.96,26.66) | 46.94 (44.84,49.02) |
| **Ethnicity and race** | | | |
| Hispanic or Latinx | 1.68 (1.48,1.90) | 6.98 (6.45,7.54) | 20.73 (19.64,21.85) |
| White | 2.05 (1.94,2.17) | 7.89 (7.62,8.16) | 22.97 (22.45,23.50) |
| Black | 2.20 (1.87,2.56) | 9.15 (8.28,10.08) | 24.71 (23.02,26.43) |
| Asian | 1.60 (1.38,1.84) | 5.86 (5.32,6.42) | 16.25 (15.15,17.39) |
| Native American/Alaska Native | 2.18 (1.15,3.79) | 6.35 (4.11,9.25) | 15.74 (10.99,21.27) |
| Native Hawaiian/Other Pacific Islander | 1.57 (0.73,2.99) | 8.38 (5.31,12.33) | 21.88 (15.39,29.12) |
| **Recent FIT (<5 years prior to index date)** | | | |
| 1 FIT (test 1y ago only)[iii] | 1.16 (1.06,1.26) | 5.56 (5.32,5.79) | 20.52 (20.07,20.98) |
| 1 FIT – Age 76-80y | 1.09 (0.98,1.20) | 4.99 (4.75,5.24) | 18.75 (18.27,19.24) |
| 1 FIT – Age 81-85y | 1.50 (1.24,1.81) | 8.24 (7.58,8.93) | 28.62 (27.42,29.82) |
| ≥2 FIT | 2.45 (2.33,2.58) | 9.13 (8.83,9.43) | 19.58 (18.93,20.24) |
| ≥2 FIT – Age 76-80y | 2.45 (2.32,2.58) | 9.09 (8.80,9.40) | 19.41 (18.76,20.07) |
| ≥2 FIT – Age 81-85y | 3.78 (1.55,7.62) | 18.18 (12.05,25.34) | 43.67 (33.70,53.20) |
| **Healthcare system** | | | |
| KPWA | 2.57 (2.07,3.16) | 11.50 (10.12,12.99) | 26.43 (23.85,29.07) |
| PHHS | 0.59 (0.28,1.13) | 2.97 (2.02,4.20) | 6.72 (4.97,8.81) |
| KPNC | 1.67 (1.56,1.78) | 6.72 (6.45,6.98) | 19.77 (19.23,29.31) |
| KPSC | 2.38 (2.22,2.56) | 9.23 (8.79,9.69) | 26.30 (25.45,27.15) |

Table S-3: Cumulative risk of death from other causes (competing risk to CRC *mortality* estimates), stratified by patient characteristics at index date

| | **Cumulative risk of death from another cause^^, percent (95% confidence interval)** | | |
|---|---|---|---|
| | **2-year** | **5-year** | **8-year** |
| Overall | 1.94 (1.85,2.04) | 7.61 (7.38,7.83) | 21.84 (21.39,22.29) |
| Sensitivity analysis 1 (no censoring at subsequent screening colonoscopy) | 1.94 (1.94,1.94) | 7.58 (7.52,7.64) | 21.65 (21.51,21.79) |
| Sensitivity analysis 2 (no censoring at subsequent FIT) | 1.90 (1.90,1.90) | 7.45 (7.39,7.51) | 21.00 (20.86,21.15) |
| **Age and sex** | | | |
| 76-80 | 1.97 (1.88,2.07) | 7.40 (7.17,7.64) | 20.55 (20.08,21.02) |
| 81-85 | 1.60 (1.32,1.92) | 8.88 (8.15,9.65) | 29.37 (28.04,30.70) |
| Male | 2.49 (2.34,2.65) | 9.55 (9.17,9.94) | 26.22 (25.49,26.96) |
| Female | 1.53 (1.42,1.64) | 6.17 (5.90,6.44) | 18.67 (18.12,19.33) |
| **Encounters (<180 days prior to index date)** | | | |
| Institutional/inpatient stay | 7.00 (6.15,7.92) | 18.09 (16.49,19.75) | 37.96 (35.38,40.54) |
| Primary care only | 1.85 (1.74,1.96) | 7.66 (7.37,7.95) | 22.19 (21.62,22.77) |
| None | 1.59 (1.45,1.74) | 6.36 (6.01,6.73) | 19.41 (18.68,20.15) |
| **Ethnicity and race** | | | |
| Hispanic or Latinx | 1.64 (1.46,1.85) | 6.72 (6.28,7.17) | 19.73 (18.84,20.64) |
| White | 2.01 (1.91,2.12) | 7.76 (7.53,7.99) | 22.11 (21.67,22.55) |
| Black | 2.16 (1.86,2.50) | 8.89 (8.17,9.65) | 22.99 (21.63,24.37) |
| Asian | 1.50 (1.30,1.72) | 5.57 (5.12,6.05) | 15.71 (14.78,16.66) |
| Native American/Alaska Native | 1.98 (1.05,3.42) | 6.58 (4.47,9.22) | 15.91 (11.70,20.70) |
| Native Hawaiian/Other Pacific Islander | 1.37 (0.65,2.59) | 8.44 (5.86,11.60) | 23.07 (17.67,28.92) |
| **Charlson Comorbidity Index (CCI)** | | | |
| 0 | 0.84 (0.75,0.95) | 4.60 (4.31,4.90) | 14.89 (14.25,15.53) |
| 1 | 1.43 (1.25,1.63) | 6.82 (6.29,7.38) | 20.97 (19.80,22.17) |
| 2 | 1.87 (1.64,2.12) | 8.94 (8.29,9.62) | 23.02 (21.75,24.32) |
| 3 | 3.18 (2.74,3.66) | 12.06 (10.92,13.26) | 30.06 (27.86,32.29) |
| 4 | 3.65 (3.18,4.16) | 13.56 (12.41,14.76) | 31.91 (29.71,34.12) |
| ≥5 | 9.20 (8.47,9.97) | 25.35 (23.82,26.91) | 47.75 (45.26,50.20) |
| **Recent FIT** | | | |
| 1 FIT (test 1y ago only)[iii] | 1.14 (1.04,1.25) | 5.61 (5.35,5.88) | 21.09 (20.57,21.62) |
| 1 FIT – Age 76-80y | 1.05 (0.95,1.17) | 4.91 (4.64,5.19) | 19.23 (18.67,19.80) |
| 1 FIT – Age 81-85y | 1.55 (1.27,1.87) | 8.63 (7.90,9.40) | 29.04 (27.71,30.39) |
| ≥2 FIT | 2.55 (2.41,2.69) | 9.63 (9.25,10.02) | 20.33 (19.46,21.22) |
| ≥2 FIT – Age 76-80y | 2.54 (2.41,2.69) | 9.57 (9.19,9.96) | 20.07 (19.20,20.95) |
| ≥2 FIT – Age 81-85y | 3.91 (1.60,7.87) | 21.91 (14.45,30.38) | 46.98 (35.40,57.71) |
| **Healthcare system** | | | |
| KPWA | 2.23 (1.80,2.73) | 9.57 (8.52,10.69) | 24.87 (22.92,26.86) |
| PHHS | 0.50 (0.24,0.95) | 3.06 (2.23,4.10) | 7.28 (5.79,9.00) |
| KPNC | 1.61 (1.50,1.71) | 6.46 (6.22,6.71) | 19.07 (18.59,19.55) |
| KPSC | 2.34 (2.19,2.49) | 8.80 (8.47,9.13) | 24.03 (23.40,24.66) |

^^Small deviations between competing risk estimates corresponding to CRC incidence vs. CRC mortality (S-2 vs. S-3) are due to differences in censoring events for each of these outcomes. Specifically, the occurrence of a fecal testing during follow-up was treated as a censoring event for the mortality outcome analysis but not in the incidence analysis (affecting 362 participants who were counted as having had a competing event in the incidence analysis but instead censored prior to that time in the mortality analysis due to the occurrence of a fecal test).

Figure S-1: Selection of eligible study population from PRECISE cohort




i. PRECISE cohort eligibility requirements: living at least one day between 1/1/2010-12/30/20, aged 40-95 years, and enrolled in KPNC, KPSC, or KPWA health plan, or residing in catchment area of PHHS. KPWA patients were also required to have selected or be assigned/attributed to a KPWA primary care provider (to ensure more complete data availability), reside in the Seattle-Puget Sound SEER Registry catchment area (to ensure capture of CRC occurrence), not be insured via Medicaid, and not be on any study exclusion lists.
ii. Exclusions were counted incrementally, in the order presented

# Conclusion

Ultimately, the findings of this dissertation do not offer an explicit answer to any of the clinical patients profiled in the introduction. These results are population-level estimates and, as the guidelines indicate, decisions regarding re-screening are highly individual. Two patients reviewing the same evidence may arrive at different conclusions regarding re-screening after age 75 years. Risk assessment for an individual is inexorably a personal assessment.

The Golfer seems especially interested in the short to mid-term risks (<5 years) and may be reassured by the low population-level risks for someone in his age group, especially in comparison to much higher risks of death from many other causes. He may choose to celebrate his 81$^{st}$ birthday as a big one with his round-the-world cruise, even if he's planning to see his 85$^{th}$ birthday and regardless of the low CRC risk, because he is instead motivated by the risk of his osteoarthritis worsening over time.

The Gardener might be reassured by the low population-level risks for someone in her age group with a recent negative colonoscopy, and also be encouraged to continuing to screen with a lower burden test (e.g., FIT) that could further lessen her risk of CRC death over time.

Finally, the Baker might be inspired by the presence of some risk of CRC to continue screening by FIT if not too burdensome, but she should ultimately be reassured that the average risk for someone with a recent history of negative tests is quite low for the near future.

Based on the results of this dissertation, all three patients, and their providers, have additional empirical information on risk of CRC and CRC mortality in the context of their experience with CRC testing modalities. These estimates also may provide benchmarks for the building of predictive models that could eventually offer more personalized screening recommendations based on individuals' health status and screening histories.

# Appendix: Comparing screen-eligible populations with recent history of colonoscopy vs. recent history of FIT (Aim 1 vs. Aim 2)

The prior chapters describe cumulative incidence and mortality for populations that can be collectively referred to as screen-eligible adults aged 76-85 years with a history of adequate screening. The distinction between the two populations, however, emerges in the details of defining "prior adequate screening" and the subsequent results. These similarities and differences merit discussion.

**Colonoscopy (Aim 1) vs. FIT (Aim 2) populations**

In general, the two populations of older adults share many similar characteristics since they both restrict to patients eligible for screening between the ages 76-85 years: individuals need to have survived until they reach the age range of interest, without diagnosis of CRC, IBD, or gastrointestinal surgeries such as colectomy or proctectomy; to not have a screening exam or other medical procedure within the relevant time frame prior to index date that would make a person ineligible for screening on the index date (e.g., sigmoidoscopy in the prior 5 years, FIT in the 364 days prior, CT colonography/barium enema/abdominal CT in the 180 days prior, etc.); to not have symptoms within six months of index date.

However, the two populations diverge in certain demographic characteristics when the definition of "prior adequate screening" is defined based on colonoscopy (i.e., negative colonoscopy result ten years ago) vs. FIT (i.e., negative FIT result one year ago). This observational cohort uses electronic health data during a time when age 75 years is the cutoff for recommended universal screening. As a result, screening activity in the cohort drops off sharply in prevalence (both FIT and colonoscopy) after age 75 years, whereas screening rates are relatively constant across the ages within the universal screening range (at the time, 50-75 years), and especially between ages 66-75 years (when prior colonoscopy was required for eligibility in the present). This means patients with a colonoscopy ten years ago are more uniformly distributed in age across the cohort than patients with a FIT one year ago. In both populations, the proportion of 76–80-year-olds is larger than 81-85-year-olds, but the "prior FIT" population is much more skewed towards younger ages (93.4% aged 76-80y) than the "prior colonoscopy" population (53.7% aged 76-80y). The difference is especially obvious when comparing population proportions that are a single year of age: 65.1% of the prior FIT population is aged 76y vs. 11.8% of the colonoscopy population. The prior FIT population is on average much younger than the prior colonoscopy population (median age: 76y vs. 80y).

Perhaps related to this age skew, the distribution of Charlson Comorbidity Index scores (CCI) is also different for the prior colonoscopy vs. FIT populations: 23.8% CCI=0 and 14.6% CCI$\geq$5 vs. 38.6% CCI=0 and 6.7% CCI$\geq$5, respectively. Given the overwhelming difference in age distribution for the two observational cohorts, I compared each population by year of age at index date and present side-by-side descriptive statistics [Table 1] to illustrate the similarities and differences in characteristics for prior FIT and prior colonoscopy populations of the same age (ages 76 and 77 years).

Within year of age at index (screen-eligibility) the colonoscopy-defined group has slightly higher representation from KPSC and lower KPNC, compared to the FIT-defined group. The colonoscopy group also has higher comorbidity burden compared to FIT: overall CCI score is higher (among 76-year-olds: 29.3% of the colonoscopy cohort has CCI=0 compared to 40.2% of FIT). Prevalence of peripheral vascular disease, chronic pulmonary disease, diabetes, and renal disease were higher in the colonoscopy populations compared to FIT. One hypothesis is that individuals with more serious disorders are getting removed from the FIT population by behaviors or health system protocols that are not captured in electronic data (e.g., dementia patients may not be offered FIT testing once diagnosed or patients with serious chronic health conditions do not prioritize completion of their FIT tests).

**Colonoscopy vs. FIT populations cumulative incidence**

The cumulative incidence estimates from these two populations are also different, both for the outcomes of interest (CRC incidence and mortality) as well as death from other causes (competing risks) (Table 2). The difference in cumulative mortality from non-CRC causes confirms our suspicion that the population defined by recent FIT is, on average, younger and healthier.

The colonoscopy cohort is defined on an event from ten years ago and relies solely on billing codes to confirm screening eligibility (i.e., absence of diagnoses that would make them ineligible for screening) whereas the FIT population is based on a more recently performed test. Perhaps providers are "selecting" a healthier population to screen by FIT because they have information gathered closer to the index date (1 year prior) and thus at an older age compared to the qualifying colonoscopy that occurred ten years before the index date. The impact of this sort of differential practice was *a priori* expected to be low because of the routine CRC screening recommendations across all four health systems for all up to age 75 years but perhaps underestimated the influence of chronologic age on offerings.

An additional aspect of the differential time between prior test and index date is the sensitivity of each test. FIT would not be expected to prevent CRC incidence to a measurable degree (44, 45, 53, 54). However, the CRC incidence estimate in the colonoscopy population was double that in the FIT population at two years after the index date. By eight years following index date, the difference had declined until it was no longer appreciable in the full age range, though still nearly double in the 76- and 77-year-old age strata. This may be, in part, a recency issue where people in the FIT group were determined to be cancer-free more recently than in the colonoscopy group.

The approximately doubled risk of CRC mortality is more easily attributable to differences in the testing modalities. While estimates of CRC incidence and mortality after a prior negative test do not offer any inference about the efficacy of subsequent screening, selecting on a negative test should lead to few prevalent cancers and thus lowered CRC mortality risk for a limited period of time (51) and would depend on both the sensitivity of the test and time since test (for a cancer to grow). Lee et al. (55) found CRC incidence rates after negative colonoscopy increased from 16.6 per 100,000 person-years (95% CI, 6.7-26.6) one year later to 133.2 per 100,000 person-years (95% CI,70.9-227.8) ten years later, and CRC mortality rates increased from 6.8 per 100,000 person-years (95% CI, 0.8-12.7) one year later to 92.2 per 100,000 person-years (95% CI, 19.0-165.4) ten years later. Although comparable values are not available for FIT, the sensitivity of the

test (using a standard of CRC diagnosis within 2 years) is high [0.87, CI: 0.75-0.93]. Therefore, cumulative risk estimates in the FIT and colonoscopy cohort included cases that were either i) missed by a recent FIT or colonoscopy or ii) emerged after screening cessation. I would hypothesize the former cause is a source of more cancers in the FIT cohort while the latter cause is responsible for a higher proportion of colonoscopy cohort cancer cases.

Appendix Tables

Table 1: Characteristics of screen-eligible patients aged 76 and 77 at index date, stratified by both age group and prior negative test

| | **Age = 76y** | | **Age = 77y** | |
|---|---|---|---|---|
| | Colonoscopy/Aim 1 N=3059 | FIT/ Aim 2 N=74722 | Colonoscopy/ Aim 1 N=2981 | FIT/ Aim 2 N=11142 |
| **Providing Site** | | | | |
| KPWA | 122 (4.0) | 2677 (3.6) | 128 (4.3) | 638 (5.7) |
| PHHS | 0 (0.0) | 650 (0.9) | 0 (0.0) | 334 (3.0) |
| KPNC | 1241 (40.6) | 45144 (60.4) | 1161 (38.9) | 4989 (44.8) |
| KPSC | 1696 (55.4) | 26251 (35.1) | 1692 (56.8) | 5181 (46.5) |
| **Race and Ethnicity** | | | | |
| Hispanic or Latinx | 430 (14.1) | 11915 (15.9) | 370 (12.4) | 2053 (18.4) |
| White | 2270 (74.2) | 52682 (70.5) | 2194 (73.6) | 7836 (70.3) |
| Black | 290 (9.5) | 5618 (7.5) | 283 (9.5) | 955 (8.6) |
| Asian | 368 (12.0) | 10241 (13.7) | 410 (13.8) | 1463 (13.1) |
| Native American/Alaska Native | 22 (0.7) | 420 (0.6) | 11 (0.4) | 68 (0.6) |
| Native Hawaiian/Other Pacific Islander | 14 (0.5) | 453 (0.6) | 19 (0.6) | 66 (0.6) |
| Multiple/NOS | 12 (0.4) | 182 (0.2) | 3 (0.1) | 50 (0.4) |
| Other | 2 (0.1) | 30 (0.0) | 2 (0.1) | 10 (0.1) |
| **Sex** | | | | |
| Male | 1267 (41.4) | 32496 (43.5) | 1273 (42.7) | 4794 (43.0) |
| Female | 1792 (58.6) | 42226 (56.5) | 1708 (57.3) | 6347 (57.0) |
| Missing | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| **Charlson Comorbidity Index Score** | | | | |
| Missing | 0 (0.0) | 2103 (2.8) | 0 (0.0) | 1469 (13.2) |
| 0 | 878 (29.3) | 29980 (40.2) | 835 (28.6) | 4410 (39.7) |
| 1 | 676 (22.6) | 14704 (19.7) | 618 (21.2) | 1840 (16.6) |
| 2 | 549 (18.3) | 11718 (15.7) | 554 (19.0) | 1507 (13.6) |
| 3 | 304 (10.1) | 5427 (7.3) | 301 (10.3) | 654 (5.9) |
| 4 | 265 (8.8) | 5195 (7.0) | 237 (8.1) | 624 (5.6) |
| ≥5 | 324 (10.8) | 5448 (7.3) | 370 (12.7) | 603 (5.4) |
| **Individual Comorbid Conditions** | | | | |
| Myocardial infarction | 198 (6.5) | 3795 (5.1) | 202 (6.8) | 550 (5.0) |
| Congestive heart disease | 174 (5.7) | 2960 (4.0) | 173 (5.8) | 435 (3.9) |
| Peripheral vascular disorder | 996 (32.6) | 14686 (19.7) | 970 (32.6) | 1230 (11.1) |
| Cerebrovascular disease | 201 (6.6) | 3862 (5.2) | 207 (6.9) | 515 (4.6) |
| Dementia | 85 (2.8) | 854 (1.1) | 105 (3.5) | 117 (1.1) |
| Chronic pulmonary disease | 646 (21.1) | 11234 (15.1) | 565 (19.0) | 1386 (12.5) |
| Rheumatic disease | 83 (2.7) | 1569 (2.1) | 94 (3.2) | 194 (1.7) |
| Peptic ulcer | 9 (0.3) | 204 (0.3) | 13 (0.4) | 37 (0.3) |
| Mild liver disease | 19 (0.6) | 200 (0.3) | 18 (0.6) | 27 (0.2) |
| Diabetes | 724 (23.7) | 16091 (21.6) | 733 (24.6) | 1471 (13.2) |
| Diabetes with chronic complications | 520 (17.0) | 10644 (14.3) | 518 (17.4) | 1291 (11.6) |
| Hemiplegia or paraplegia | 25 (0.8) | 347 (0.5) | 14 (0.5) | 35 (0.3) |

| | | | | |
|---|---|---|---|---|
| Renal disease | 710 (23.2) | 14334 (19.2) | 747 (25.1) | 1795 (16.2) |
| Malignancy (incl. leukemia and lymphoma) | 188 (6.2) | 3479 (4.7) | 205 (6.9) | 429 (3.9) |
| Moderate or severe liver disease | 3 (0.1) | 52 (0.1) | 4 (0.1) | 6 (0.1) |
| Metastatic solid tumor | 41 (1.3) | 596 (0.8) | 51 (1.7) | 72 (0.6) |
| HIV/AIDS | 0 (0.0) | 34 (0.0) | 4 (0.1) | 1 (0.0) |
| **Encounters (<180 days prior to index date)** | | | | |
| Inpatient or Institutional | 135 (4.4) | 2357 (3.2) | 153 (5.1) | 350 (3.1) |
| Primary Care Only | 2283 (74.6) | 47547 (63.6) | 2192 (73.5) | 6852 (61.5) |
| None | 641 (21.0) | 24818 (33.2) | 636 (21.3) | 3940 (35.4) |

NOS = Not otherwise specified

Table 2: Cumulative incidence and mortality (CRC and other causes), from aims 1 and 2 and age subsets (ages 76 and 77 years old)

| **Age at index** | **Outcome** | **Past negative FIT** | **Past negative Colonoscopy** |
|---|---|---|---|
| 76-85 | 2-year CRC incidence | 0.19 (0.17,0.22) | 0.39 (0.31,0.48) |
| 76 | 2-year CRC incidence | 0.19 (0.16,0.23) | 0.50 (0.26,0.92) |
| 77 | 2-year CRC incidence | 0.21 (0.13,0.33) | 0.16 (0.04,0.48) |
| 76-85 | 8-year CRC incidence | 1.17 (1.09,1.27) | 1.29 (1.02,1.61) |
| 76 | 8-year CRC incidence | 1.69 (1.48,1.92) | 3.86 (2.17,6.29)[1] |
| 77 | 8-year CRC incidence | 1.04 (0.80,1.34) | 3.13 (1.29,6.36)[1] |
| 76-85 | 2-year CRC mortality | 0.02 (0.01,0.03) | 0.04 (0.02,0.08) |
| 76 | 2-year CRC mortality | 0.02 (0.01,0.04) | * |
| 77 | 2-year CRC mortality | * | * |
| 76-85 | 8-year CRC mortality | 0.28 (0.23,0.34) | 0.46 (0.30,0.70) |
| 76 | 8-year CRC mortality | 0.28 (0.20,0.39) | 1.09 (0.26,3.23) |
| 77 | 8-year CRC mortality | 0.16 (0.07,0.32) | 0.39 (0.04,2.03) |
| 76-85 | 2-year other-cause mortality[2] | 1.94 (1.85,2.04) | 8.24 (7.83,8.66) |
| 76 | 2-year other-cause mortality[2] | 2.25 (2.13,2.38) | 5.77 (4.69,7.01) |
| 77 | 2-year other-cause mortality[2] | 1.39 (1.16,1.66) | 5.83 (4.70,7.13) |
| 76-85 | 8-year other-cause mortality[2] | 21.84 (21.39,22.29) | 41.45 (39.74,43.16) |
| 76 | 8-year other-cause mortality[2] | 19.47 (18.78,20.17) | 28.95 (24.08,33.99) |
| 77 | 8-year other-cause mortality[2] | 18.40 (17.29,19.53) | 28.15 (23.42,33.06) |

* Incident outcomes insufficient for statistical precision in this group.

[1]Although the 76- and 77-year-old group estimates seem high compared to the overall age group, it's a reflection of lower estimates in other age groups (78-85)

[2]Estimates correspond to CRC mortality estimates, but are nearly identical to those corresponding to CRC incidence.

Appendix Figures

Figure 1: Cumulative incidence (A) and mortality (B) curves for population subsets defined by index age (76 or 77 years) and prior CRC test (colonoscopy 10y ago or FIT 1y ago).

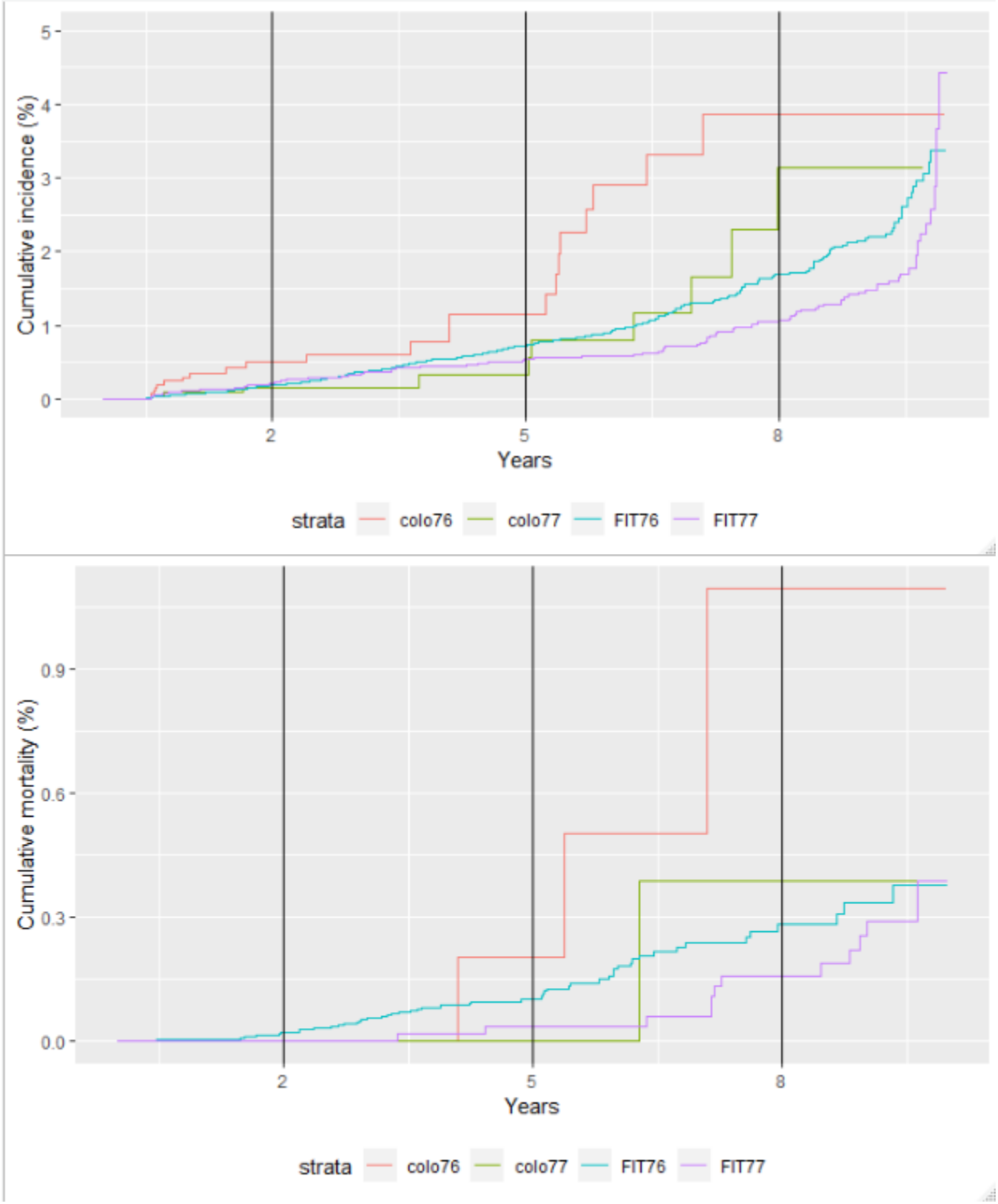
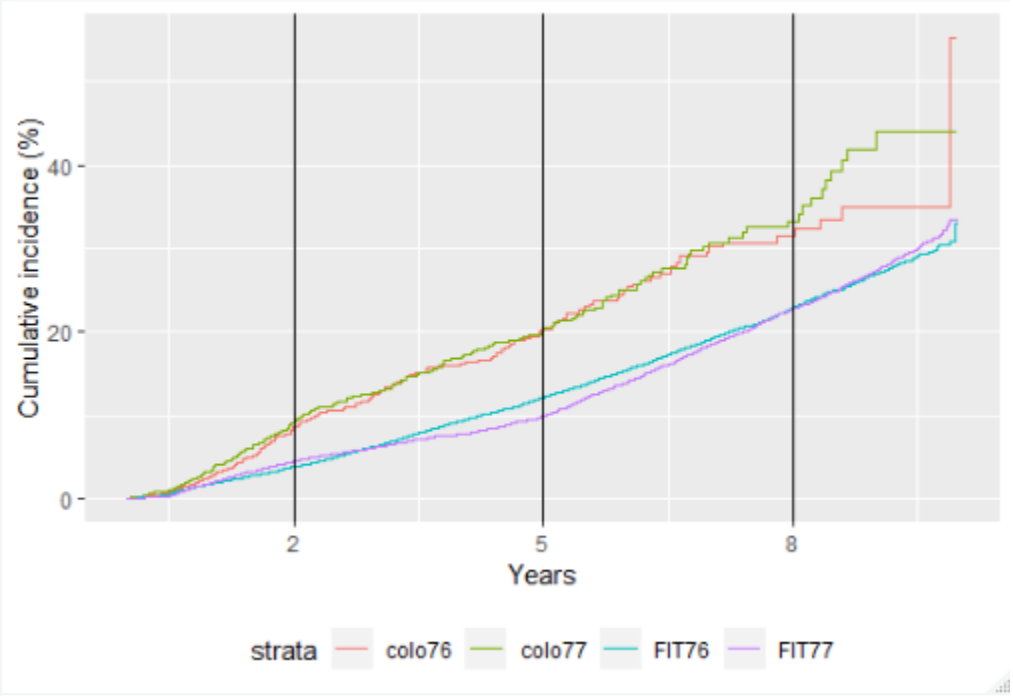


Figure 2: Cumulative risk of death from other causes [(A) competing risks curves corresponding to mortality estimates in Figure 1A and B) mortality estimates in 1B] for population subsets defined by index age (76 or 77 years) and prior CRC test (colonoscopy 10y ago or FIT 1y ago).



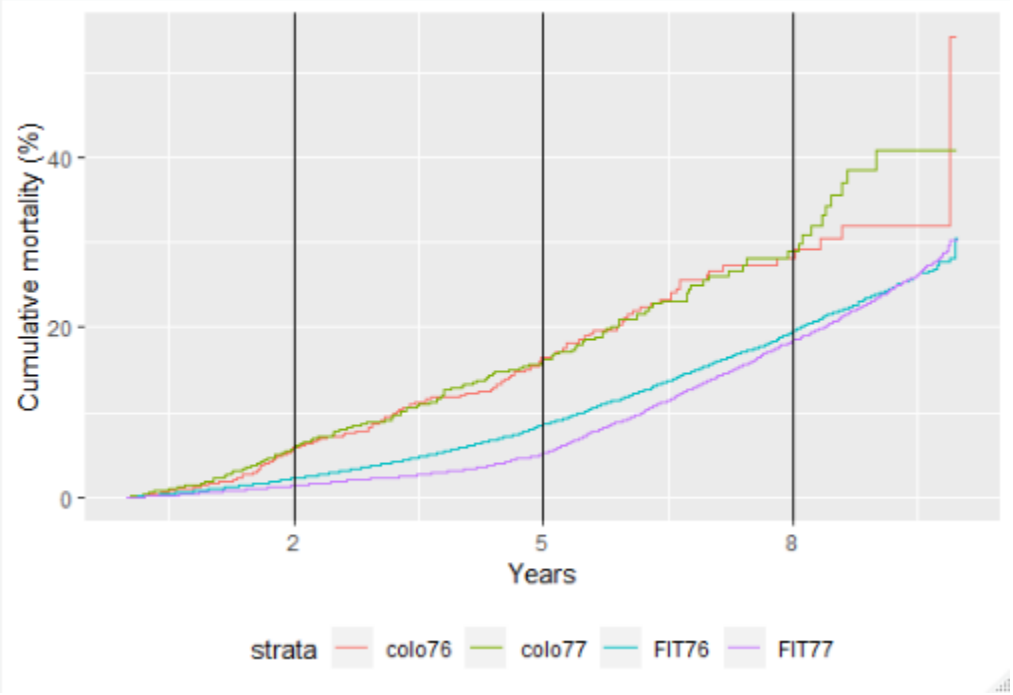
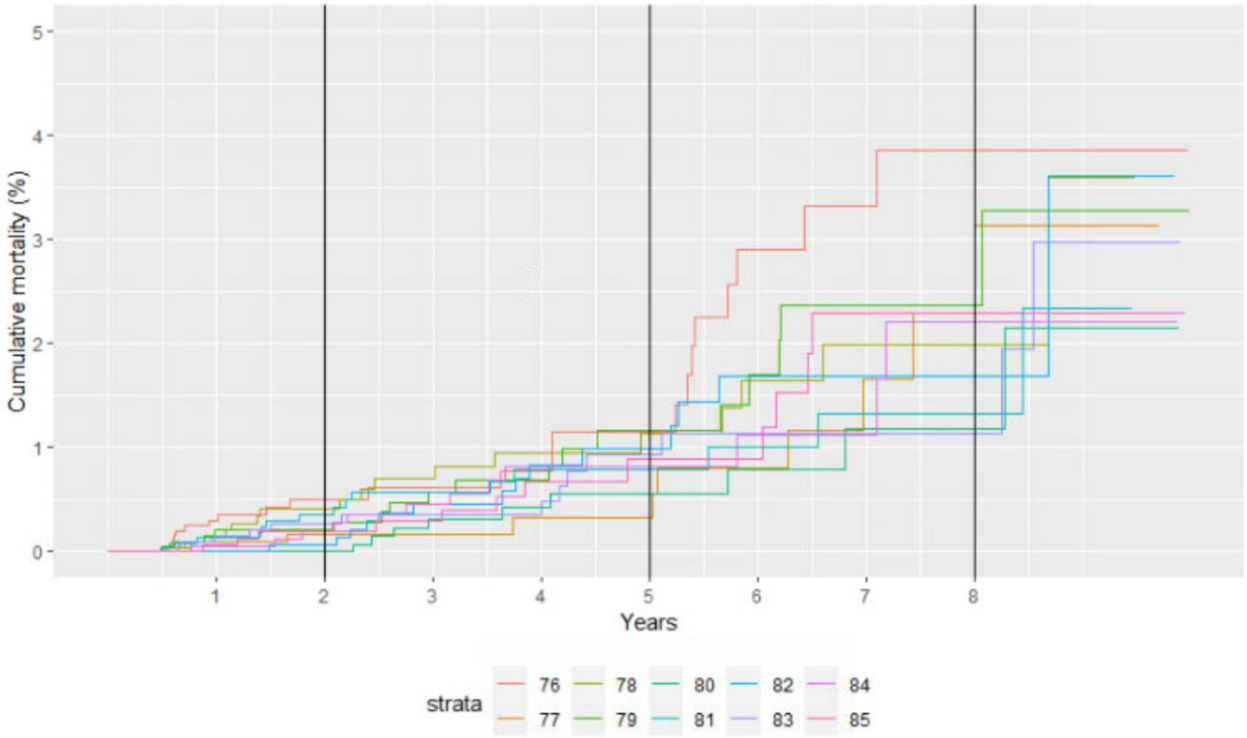



Figure 3: Cumulative CRC incidence, stratified by age at index date to illustrate the outlier status of estimates for individuals aged 76 years at index, especially >5 years later.




Individual years of age have major heterogeneity (no clear pattern of cumulative incidence by year of age).

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