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Authors

Casey, Yas

Demb, Joshua

Enwerem, Ngozi

et al.

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Risk of Incident and Fatal Colorectal Cancer after young-onset adenoma diagnosis: a national cohort study.

Yas Casey, MD, MAS[*,1,2,3], **Joshua Demb, PhD, MPH**[*,2,4], **Ngozi Enwerem, MD**[5], **Lin Liu, PhD**[2,4], **Christian Jackson, MD**[1,3], **Ashley Earles, MPH**[4], **Ranier Bustamante, MS**[2,4], **Sumana Mahata, BS**[6], **Shailja Shah, MD, MPH**[2,4], **Samir Gupta, MD, MSCS**[2,4]

[1]VA Loma Linda Healthcare System, Loma Linda, CA, USA

[2]Herbert Wertheim School of Public Health and Human Longevity Science.University of California, San Diego, La Jolla, CA, USA

[3]Loma Linda University School of Medicine, Loma Linda, CA, USA

[4]Jennifer Moreno VA San Diego Healthcare System, San Diego, CA, USA

[5]VA Dallas Healthcare System, Dallas, TX, USA

[6]UC San Diego School of Medicine, La Jolla, CA, USA

Abstract

Objectives: Colorectal cancer (CRC) incidence and mortality rates are increasing in adults ages <50 years. Young-onset adenoma (YOA)—adenoma detected in adults under 50—may signify increased CRC risk, but this association has not been widely studied. Our aim was to compare risk of incident and fatal CRC in adults age <50 years with YOA diagnosis compared to those with a normal colonoscopy.

Methods: We conducted a cohort study of US Veterans ages 18–49 years who received colonoscopy 2005–2016. Primary exposure of interest was YOA. Primary outcomes included incident and fatal CRC. We used Kaplan-Meier curves to calculate cumulative incident and fatal CRC risk and Cox models to examine relative CRC risk.

Results: The study cohort included 54,284 Veterans age <50 years exposed to colonoscopy, among whom 13% (n=7,233) had YOA at start of follow-up. Cumulative 10-year CRC incidence

Correspondence: Samir Gupta, MD, MSCS, AGAF, Address: 3350 La Jolla Village Drive, MC 111D, San Diego, CA 92161, s1gupta@health.ucsd.edu, UCSD Phone: 858.822.4499, VA Phone: 858.552.8585 ×3280.

*Drs. Casey and Demb contributed equally to this work and share first authorship

Specific author contributions:

Concept and Design: Casey, Demb, Enwerem, Liu, Bustamante, Gupta

Analysis and Interpretation of Data: Casey, Demb, Liu, Bustamante, Mahata, Shah, Gupta

Drafting of Manuscript: Casey, Demb, Gupta

Critical Revision of the Manuscript for Important Intellectual Content: Casey, Demb, Enwerem, Liu, Jackson, Earles, Bustamante, Mahata, Shah, Gupta

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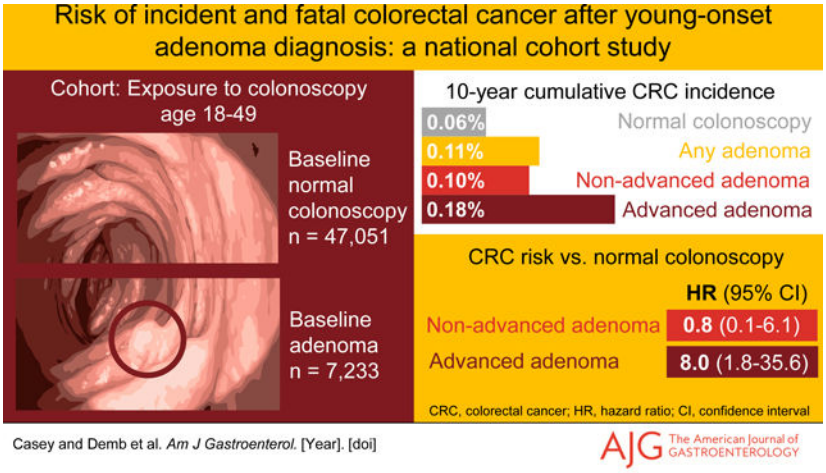
was 0.11% (95% CI: 0.00%−0.27%) after any adenoma diagnosis, 0.18% (95% CI: 0.02–0.53%) after advanced YOA diagnosis, 0.10% (95% CI: 0.00%−0.28%) after non-advanced adenoma diagnosis, and 0.06% (95% CI: 0.00–0.09%) after normal colonoscopy. Veterans with advanced adenoma had 8-fold greater incident CRC risk than those with normal colonoscopy (HR: 8.0; 95% CI: 1.8–35.6). Across groups, no differences in fatal CRC risk were observed.

Conclusions: Young-onset advanced adenoma diagnosis was associated with 8-fold increased incident CRC risk compared to normal colonoscopy. However, cumulative CRC incidence and mortality at ten years were relatively low.

Graphical Abstract



Keywords

Colorectal cancer; early onset; adenoma; colonoscopy; risk

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and second leading cause of cancer mortality in the United States, with an estimated 153,020 new cases of CRC and 52,550 CRC deaths in 2023.[1] Overall, CRC incidence and mortality have decreased over the past two decades, but CRC incidence and mortality have increased in young adults ages 18–49, with cases often diagnosed at later stages requiring more intense treatment and having poorer prognosis[2–7].

Most CRCs emerge from adenomas, and while those developing in individuals younger than age 50 years-old, defined as young-onset adenomas (YOA), might contribute to early onset CRC risk, this risk has been incompletely defined. Likewise, strategies for colonoscopy surveillance are not well-defined for YOA and it is unclear whether individuals with YOA might benefit from altered colonoscopy surveillance strategies compared to those without YOA for the purpose of incident and fatal CRC risk reduction. Current surveillance recommendations developed by the U.S Multi-Society Task Force (USMSTF) are based on the findings at baseline colonoscopy, including number, size, and histology of

polyps[8]. Though these guidelines do not recommend differential application of surveillance recommendations based on age, they do note a paucity of data on whether cancer risks differ among individuals with young vs. older onset adenoma. Evidence on risks for incident and fatal CRC after YOA diagnosis could inform whether current USMSTF guidelines are appropriate for individuals diagnosed with YOA.

Prior studies that have compared CRC risk in young adults versus older adults have faced important limitations, including small sample size, limited generalizability of findings, limited follow-up time, lack of an appropriate comparison group and focus on advanced adenoma as an outcome rather than CRC[9–17]. Given these limitations, there is a gap in the evidence as to the risk of CRC following YOA diagnosis and whether surveillance guidelines should be tailored based on age. To address this knowledge gap, we examined incident and fatal CRC risk among Veterans ages <50 with versus without YOA.

METHODS

Study Design, Setting and Data Source

We conducted a cohort study of US Veterans ages 18–49 receiving care within the Veterans Health Administration (VHA) who received a colonoscopy between 2005–2016. VHA is one of the largest integrated healthcare providers in the US, providing care to over 6 million individuals annually[18]. Since 1999, all VHA sites have utilized an integrated Electronic Health Record (EHR) for documentation of clinical encounters, which can be accessed for research. The Department of Veterans Affairs Corporate Data Warehouse (CDW) provides access to discrete EHR data, including demographic characteristics, administrative claims-based diagnosis and procedure codes, prescriptions, and anthropometric measures (e.g., weight and height), as well as free-text data, including procedure notes and pathology reports, all of which were accessed for this research. We also used data from the VHA Vital Status file to ascertain follow-up time through the date of last visit, represented as the date and time the last vital record was taken by the healthcare provider[19]. Linked data from the National Death Index (NDI) were to assess vital status and cause of death. NDI offers the advantage of capturing cause of death within and outside VHA. Person-level linkage between VHA data and the NDI cause-specific mortality data was derived through collaboration between VA and Department of Defense partners, with matching based on social security number (SSN) or VA-scrambled SSN[20].

Study Sample and Selection Criteria

We included Veterans ages 18–49 within VHA with a documented completed colonoscopy between 2005–2016. The earliest colonoscopy within this period was considered the “baseline colonoscopy.” We excluded patients with a history of CRC or inflammatory bowel disease prior to or at time of baseline colonoscopy based on International Classification of Disease, Ninth Revision (ICD-9) diagnosis codes. Veterans whose colonoscopy reports noted an incomplete exam to the cecum or inadequate bowel preparation were also excluded, as were patients with missing data regarding exam extent or bowel prep quality. Veterans who had colonoscopies prior to 2005 were excluded due to inadequate quality of the colonoscopy and pathology reports.

Exposures, Outcomes and Covariates

The primary exposure was YOA identified at baseline colonoscopy. Colonoscopy occurrence was ascertained using a list of Current Procedural Terminology (CPT) codes derived from a prior study[21]. Colonoscopy details, including extent of exam and bowel preparation, and YOA details, including location, number, size, and histology were ascertained via a validated natural language processing-based approach for extracting colonoscopy and pathology findings from free-text reports. This NLP-based algorithm was able to identify a normal colonoscopy with 96.3% sensitivity, 97.5% specificity and a positive predictive value of 97%.[22] Ability to additionally predict location, size and histology of an adenoma had a positive predictive value of 90% or higher.[23] YOA exposure was defined as any histologically-confirmed adenoma at baseline colonoscopy. A "normal" colonoscopy was defined as a colonoscopy without any documented adenoma or no pathology report with a diagnosis of adenoma or malignancy. Veterans with YOA were categorized as having either: 1) advanced adenoma, defined as conventional adenoma ≥10 mm or adenoma with villous histology or high grade dysplasia of any size, or 2) non-advanced adenoma, defined as conventional adenoma <10 mm without any of the histological features of an advanced adenoma.

Primary outcomes included incident and fatal CRC. Incident CRC was ascertained by primary and secondary diagnoses identified through the VA Oncology Domain, which can accurately identify 90% of CRC cases, while fatal CRC was ascertained using National Death Index (NDI) data where CRC was listed as the primary cause of death[24]. We additionally conducted manual chart review of each suspected CRC case to confirm the date of diagnosis and that the case was identified at follow-up rather than present at baseline colonoscopy. Further, the suspected etiology for each CRC case was classified following the World Endoscopy Organization approach, noting that their categories of "detected lesion, not resected;" and "possible missed lesion, prior examination negative but inadequate" are not applicable since we excluded individuals from our cohort with lesions that were not removed at baseline or who had incomplete colonoscopy at baseline.[25]

Covariates potentially associated with YOA, and CRC risk were selected *a priori* based on prior literature. These included body mass index (BMI), race, ethnicity, aspirin use, diabetes, smoking status (current, former, never). We categorized race and ethnicity into five different categories: non-Hispanic White, non-Hispanic Black, Asian or Native Hawaiian, American Indian and Other. BMI and diabetes were characterized based on previous identified algorithms [26,27]. Aspirin use was defined based on whether two prescriptions were filled, or aspirin was mentioned in free-text notes up to one year prior to and including the date of baseline colonoscopy (start of follow-up). This methodology was found previously to have a positive predictive value and negative predictive value of 99.2% and 97.5%, respectively [28]. Smoking status (current, former, or never) was identified based on VHA Health Factors Structured data domain [29].

Statistical Analysis

We compared continuous and categorical variables between Veterans with vs. without YOA using Wilcoxon rank-sum tests and chi-square tests, respectively. We used Kaplan-Meier

curves to compare 10-year incident and fatal CRC risk among: 1) Veterans with YOA versus those without YOA on baseline colonoscopy, 2) Veterans with advanced YOA vs without YOA on baseline colonoscopy, and 3) non-advanced YOA vs without YOA on baseline colonoscopy. Follow up started at first (baseline) qualifying colonoscopy and continued until earliest of the following: 1) incident or fatal CRC, non-CRC related death, or end of study (12/31/16) for the incident CRC analysis or 2) fatal CRC, non-CRC related death, or end of the study (12/31/16) for the fatal CRC analysis. From these 10-year risk values, we also calculated risk difference and corresponding 95% confidence intervals. We used Cox models to calculate the incident and fatal CRC risk among adults with advanced YOA or non-advanced YOA diagnosis, compared to normal colonoscopy. Cox models were used to derive hazard ratios and corresponding 95% confidence intervals. The proportional hazards assumption was tested by examining the correlation between time and scaled Schoenfeld residuals for all exposure variables. The low number of CRC events precluded utilization of co-variate adjusted analyses. We additionally conducted a sensitivity analysis including all individuals who had inadequate bowel prep, incomplete extent of exam or missing data on bowel prep or extent of exam. We used R version 4.0.2 software to perform statistical analyses. Statistical significance was set at a two-tailed p-value <0.05. The study was approved by the VA San Diego Institutional Review Board.

RESULTS

Cohort Characteristics

There were 54,284 Veterans aged 18–49 years who met full study criteria and comprised the analytic cohort (Figure 1), of whom 7,233 (13.3%) had YOA at baseline. Overall, the median follow-up was 4.7 years (Quartile 1 – Quartile 3 [Q1-Q3]: 2.1–7.6 years), with the YOA group (median, 3.6 years, Q1-Q3: 1.6–6.4 years) having shorter median follow-up time than the non-YOA group (median 4.9 years, Q1-Q3: 2.2–6.2 years). The median age was 46 years for the adenoma group (Quartile 1 – Quartile 3 [Q1-Q3]: 42–48), compared to 43 years for the normal colonoscopy group (Q1-Q3: 35–47). Compared to the normal colonoscopy group, more Veterans in the adenoma group were ages 45–49 (adenoma vs. normal colonoscopy, 50% vs. 34%), men (89% vs. 80%), obese (50% vs. 44%), current smokers (41% vs. 33%), and diabetic (11% vs. 9%) (Table 1). Baseline polyp characteristics among those with YOA are shown in Supplementary Table 1.

YOA Exposure and CRC Incidence and Mortality Risk

Among 7,233 Veterans with a baseline diagnosis of any adenoma, 3 (0.08%) developed CRC during the follow-up period. Among 47,051 Veterans with normal colonoscopy, 13 (0.03%) Veterans developed CRC during the follow up period. Cumulative 10-year CRC incidence was 0.11% (95% CI: 0.00%−0.27%) among adults with YOA at baseline compared to 0.06% (95% CI: 0.02%−0.09%) among adults without baseline YOA. Based on KM curves, the risk of CRC was not significantly different in Veterans with advanced YOA vs. no YOA (log-rank p = 0.27) (Figure 2). Cumulative 10-year CRC incidence among Veterans with advanced YOA was 0.18% (95% CI: 0.02%−0.53%), 0.10% (95% CI: 0.00% −0.28%) among Veterans with non-advanced adenoma (Table 2; Figure 3). Cumulative 10-year CRC mortality was 0.11% (95% CI: 0.00%−0.32%) among Veterans with advanced

YOA and 0.04% (95% CI: 0.01%−0.07%) among Veterans with normal colonoscopy. There were no fatal cases among adults with non-advanced YOA during the follow-up period. Characteristics of CRC cases found during follow-up are found in Supplementary Table 2. Among the 3 patients with CRC who had baseline adenoma, 2 were categorized as having likely new CRC, and 1 as a possibly missed CRC. Among the 13 patients with no adenoma at baseline and subsequent CRC, 3 were categorized as likely new, and 8 as possibly missed with adequate baseline exam; suspected etiology could not be classified for 2 subjects.

In unadjusted Cox models (Table 2), Veterans with advanced adenoma had 8-fold greater incident CRC risk compared to Veterans with normal colonoscopy (HR: 8.0, 95% CI: 1.8–35.6). Having a non-advanced adenoma was not significantly associated with increased CRC risk compared to those with normal colonoscopy in unadjusted Cox models (HR: 0.8, 95% CI: 0.1–6.1). There was no statistically significant association between advanced adenoma (HR: 6.3, 95% CI: 0.8–50.1) and fatal CRC risk, compared to those with normal colonoscopy, though the confidence interval surrounding this risk estimate was wide. Sensitivity analyses including procedures excluded due to inadequate bowel prep, incomplete extent of exam or missing information about bowel prep and extent of exam did not produce qualitatively different results (data not shown).

DISCUSSION

Based on this nationwide cohort study of Veterans aged 18–49 who completed a colonoscopy within the VHA, we report a low overall 10-year cumulative risk of incident or fatal CRC among Veterans with YOA, especially non-advanced YOA. While absolute CRC risk was low, Veterans with advanced YOA, but not non-advanced YOA, have a significantly increased CRC risk compared to Veterans without YOA. Notably, YOA was not associated with fatal CRC risk, although we acknowledge the potential for insufficient power related to the low number of fatal CRC events in this age group. The findings illustrate that while Veterans under age 50 with advanced adenoma might be at increased risk for CRC, the low absolute incidence might not necessitate more intense surveillance than recommended for older individuals.

Our study is one of the largest studies to examine CRC risk in adults with versus without YOA. Prior studies limited by small sample size have analyzed metachronous adenoma(s) as an outcome instead of CRC given the rarity of the latter [9,15,30]. A systematic review and meta-analysis conducted by our group included 24 studies and found that prevalence of YOA was 9%, and prevalence of metachronous advanced neoplasia after baseline young-onset adenoma was low, at 6% [31]. Further, studies conducted by Nagpal et al. and Hemmasi et al. found no statistically significant difference in risk of metachronous adenoma between <50 and ≥50 year-old age groups, though these studies included 128 and 737 total participants, respectively, potentially leading to type II error related to insufficient power[9,13]. Our large study sample enabled us to detect if a difference in risk existed between those with versus without YOA, filling a critical knowledge gap. That said, the cumulative risk for incident and fatal CRC after YOA diagnosis is low, even among individuals with conventional advanced adenoma (0.18%). For context, based on a study by Lee et al. of

more than 60,000 patients age ≥50 years, ten-year CRC risk among patients with advanced adenoma diagnosis was estimated to be 1.2% [32].

The low absolute CRC risk observed among individuals with young onset adenoma in our study may suggest that these individuals do not need more aggressive surveillance than what is already recommended for adults ages ≥50: 7 to 10 year follow up after diagnosis of 1–2 non-advanced adenomas <10 mm in size; 3 to 5 year follow up after diagnosis of 3–4 non-advanced adenomas <10 mm in size; and 3 year follow up after diagnosis of an advanced adenoma.[8] A decision to engage in more aggressive surveillance should also take into account issues of resource utilization, access, and overall healthcare cost. An editorial in response to the Kim et al. 2018 study even argued that surveillance intervals could be lengthened given the low rates of advanced neoplasia in this younger population compared to average risk adults[33]. Our data may be especially relevant to individuals age 45 to 49 who are newly eligible for screening based on US Preventive Service and US Multi-Society Task Force on colorectal cancer recommendations to initiate screening at age 45 instead of 50[34], and have adenomas detected, as our findings would suggest that these individuals do not require more aggressive surveillance than recommended by current polyp surveillance guidelines. This is particularly notable given that 36% of our study population was ages 45–49, with half of the group with YOA being ages 45–49.

A key strength of our study was utilization of a large national sample, which is markedly higher than prior studies restricted to adults <50 years old. The use of National Death Index data, which ascertains cause-specific death data regardless of where adults receive care, also enabled greater confidence in our ascertainment of both incident and fatal CRC cases.

Some limitations should be noted in interpreting this work. The study population is entirely comprised by US Veterans, who were majority non-Hispanic White, with 18.7% female, which may raise concerns about generalizability that can be addressed by future studies assessing risk utilizing non-VA data. Despite our large sample size, the outcomes of incident and fatal CRC in our study population were still very rare, leading to small event numbers and possibly limited power to detect differences between groups. Further, the limited number of CRC cases hindered our ability to adjust for key confounders in our models. Thus, important measured confounders, such as age, sex, and race/ethnicity and unmeasured covariates, such as diet, family history, alcohol use, baseline procedure indication, and environmental/military exposures, could not be accounted for in our risk estimates. The available sample size also precluded subgroup analyses stratified by characteristics such as age group. Our NLP algorithm to ascertain colonoscopy-related information relied on high quality reports that may have not been as sensitive for collection of data on bowel prep and extent of exam, leading to a high number of individuals with missing information. To account for this, we conducted a sensitivity analysis including all excluded individuals with either missing bowel prep, inadequate bowel prep or incomplete extent of exam, finding results that were not qualitatively different from the primary analyses. Our study did not examine exposure to colonoscopy after baseline, which might have provided greater context about follow-up of baseline findings and natural history of CRC in younger adults. Future studies should examine how polyp surveillance might impact CRC incidence and mortality, particularly among adults found to have an adenoma at their initial colonoscopy.

CONCLUSION

Among adults under age 50 with YOA diagnosis, the risk for incident and fatal CRC is low, even among individuals with baseline advanced adenoma. Compared to individuals with normal colonoscopy, risk for incident CRC was similar for patients with non-advanced YOA, and higher for patients with advanced YOA. Taken together, these data suggest that patients with YOA are unlikely to account for a substantial proportion of early onset CRC diagnoses, and that individuals with YOA may not need to have surveillance that is more aggressive than currently recommended for older individuals with adenomas.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights:

WHAT IS KNOWN?

- Colorectal cancer incidence is increasing in adults ages <50 years.
- Adenomas are often incidentally diagnosed among adults <50 undergoing usual care colonoscopy
- Adenoma under age 50 years may be a risk factor for early onset colorectal cancer, but this has not been well defined, and management of individuals with young onset adenoma diagnosis remains uncertain.

HAT IS NEW HERE?

- Individuals under age 50 with any adenoma have low incident and fatal colorectal cancer risk.
- Adults ages <50 with advanced adenoma have higher CRC risk compared to those with normal colonoscopy.

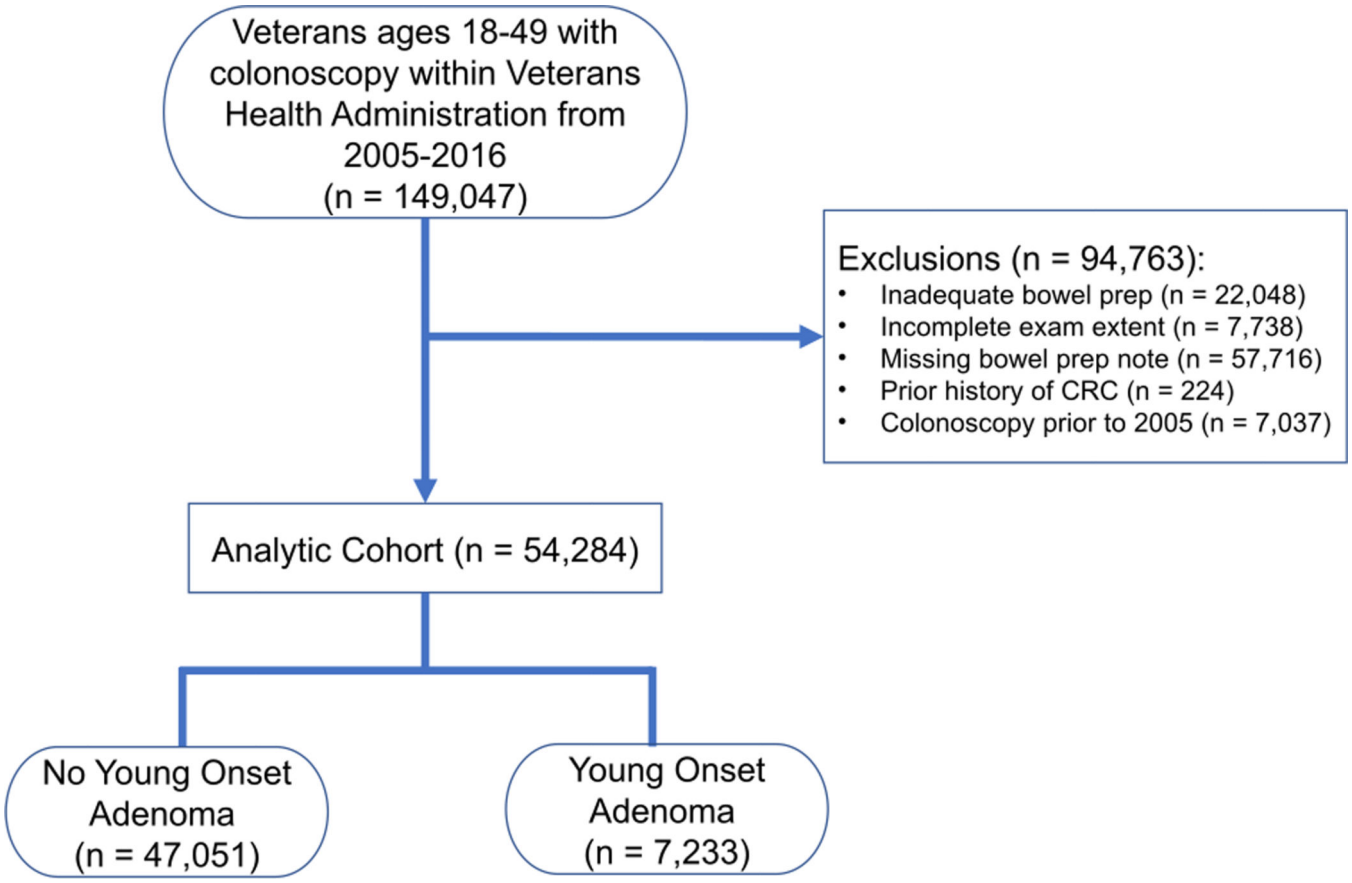

Figure 1. Flowchart of study population with inclusion and exclusion criteria.
Abbreviations: Colorectal cancer, CRC.

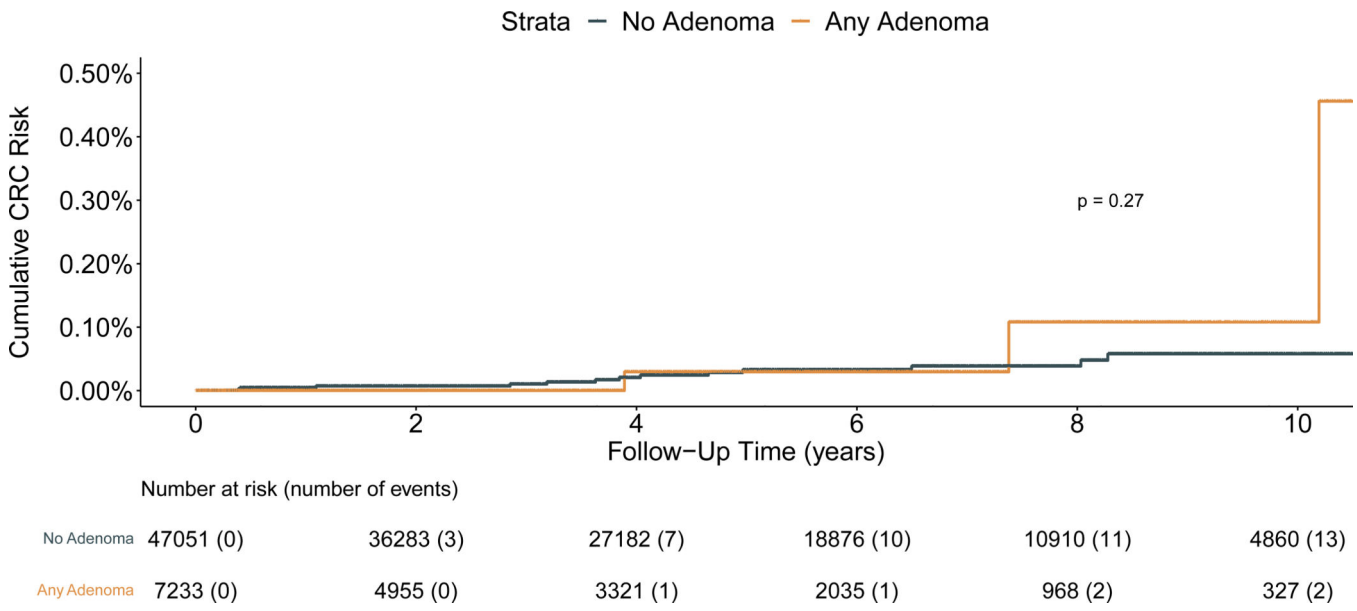

Figure 2. Cumulative incidence curves of CRC risk among adults with versus without any adenoma.

Abbreviations: Colorectal cancer, CRC.

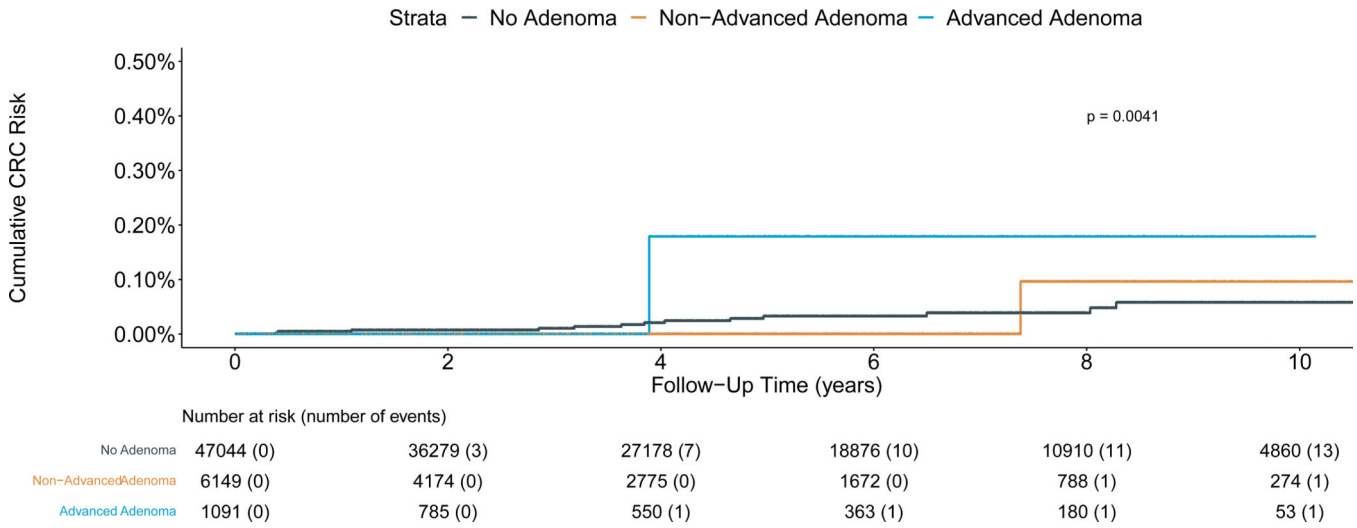

Figure 3. Cumulative incidence curves of CRC risk among adults with normal colonoscopy, non-advanced adenoma or advanced adenoma.

Abbreviations: Colorectal cancer, CRC.

Table 1:

Baseline characteristics of individuals with no adenomas vs. young onset adenoma at colonoscopy under age 50 years

	Overall	No Young Onset Adenoma	Young Onset Adenoma
	N=54,284	*N=47,051 (86.6%)*	*N=7,233 (13.3%)*
Follow-up time (years), median [Q1-Q3]	4.7 [2.1–7.6]	4.9 [2.2–6.2]	3.6 [1.6–6.4]
Age, median [Q1-Q3]	43.0 [36.0–47.0]	43.0 [35.0–47.0]	46.0 [42.0–48.0]
Ages 18–29 (N, %)	6,598 (12.1%)	6,332 (13.5%)	266 (3.7%)
Ages 30–34 (N, %)	6,385 (11.8%)	5,898 (12.5%)	487 (6.7%)
Ages 35–39 (N, %)	7,422 (13.7%)	6,667 (14.2%)	755 (10.4%)
Ages 40–44 (N, %)	14,094 (26.0%)	11,989 (25.5%)	2,105 (29.1%)
Ages 45–49 (N, %)	19,784 (36.4%)	16,164 (34.4%)	3,620 (50.0%)
Sex (N, %):			
Female	10,136 (18.7%)	9,318 (19.8%)	818 (11.3%)
Male	44,148 (81.3%)	37,733 (80.2%)	6,415 (88.7%)
Race/Ethnicity (N, %):			
Asian/Pacific Islander	1,019 (1.9%)	909 (1.9%)	110 (1.5%)
American Indian/Alaska Native	411 (0.8%)	363 (0.8%)	48 (0.7%)
Hispanic	4,813 (8.9%)	4,201 (8.9%)	612 (8.5%)
Multiracial/Other	1,105 (2.0%)	967 (2.1%)	138 (1.9%)
Non-Hispanic Black	12,849 (23.7%)	11,119 (23.6%)	1,730 (23.9%)
Non-Hispanic White	31,595 (58.2%)	27,315 (58.1%)	4,280 (59.2%)
Missing	2,518 (4.6%)	2,194 (4.7%)	324 (4.5%)
BMI, median [Q1-Q3]	29.8 [26.3–33.7]	29.6 [26.2–33.6]	30.5 [26.9–34.5]
Underweight (N, %)	234 (0.4%)	204 (0.4%)	30 (0.4%)
Normal (N, %)	8,297 (15.3%)	7,386 (15.7%)	911 (12.6%)
Obese (N, %)	24,274 (44.7%)	20,684 (44.0%)	3,590 (49.6%)
Overweight (N, %)	17,569 (32.4%)	15,394 (32.7%)	2,175 (30.1%)
Missing (N, %)	3,910 (7.2%)	3,383 (7.2%)	527 (7.3%)
Smoking (N, %):			
Never	21,203 (39.1%)	18,732 (39.8%)	2,471 (34.2%)
Former	6,506 (12.0%)	5,687 (12.1%)	819 (11.3%)
Current	18,502 (34.1%)	15,545 (33.0%)	2,957 (40.9%)
Missing	8,073 (14.9%)	7,087 (15.1%)	986 (13.6%)
Diabetes Prevalence (N, %):	4,835 (8.9%)	4,027 (8.6%)	808 (11.2%)
Aspirin Use (N, %):	6,761 (12.5%)	5,788 (12.3%)	973 (13.5%)

All comparisons significant at $p<0.05$

Abbreviations: Body Mass Index, BMI; Quartile 1-Quartile 3, Q1-Q3.

Table 2.

Risk for incident and fatal CRC among individuals with any YOA, non-advanced YOA, and advanced YOA compared to normal colonoscopy under age 50.

	Cases (Total Person-Years Follow up)	HR (95% CI)	10-year Cumulative Incidence% (95% CI)	10-year Risk Difference% (95% CI)
Incident CRC				
Baseline Colonoscopy Finding				
Normal Colonoscopy (ref)	13 (241,956 PY)	1.00 (Ref)	0.06% (0.02%−0.09%)	Ref
Any YOA	3 (30,081 PY)	2.0 (0.6–7.0)	0.11% (0.00%−0.27%)	0.05% (−0.02%−0.18%)
Non-Advanced YOA	1 (25,232 PY)	0.8 (0.1–6.1)	0.10% (0.00%−0.28%)	0.04% (−0.02%−0.19%)
Advanced YOA	2 (4,872 PY)	8.0 (1.8–35.6)	0.18% (0.02%−0.53%)	0.12% (0.00%−0.44%)
Fatal CRC				
Baseline Colonoscopy Finding				
Normal Colonoscopy (ref)	8 (242,027 PY)	1.00 (Ref)	0.04% (0.01%−0.07%)	Ref
Any YOA	1 (30,124 PY)	1.1 (0.1–8.4)	0.02% (0.00%−0.05%)	−0.02% (−0.02%, −0.01%)
Non-Advanced YOA	0 (25,250 PY)	No Cases	No Cases	No Cases
Advanced YOA	1 (4,905 PY)	6.3 (0.8–50.1)	0.11% (0.00%−0.32%)	0.07% (−0.01%−0.25%)

Abbreviations: Colorectal cancer, CRC; Hazard Ratio, HR; Referent group, Ref; Young onset adenoma, YOA; 95% Confidence Interval, 95% CI

*Model failed proportional hazards assumption (Schoenfeld residuals p-value=0.03)