Title

Baseline Characteristics and Longitudinal Outcomes of Traditional Serrated Adenomas: A Cohort Study.

Journal

Clinical Gastroenterology and Hepatology, 21(6)

Authors

Trivedi, Mehul

Godil, Suha

Demb, Joshua

et al.

Publication Date

2023-06-01

DOI

10.1016/j.cgh.2022.09.030

Peer reviewed

HHS Public Access

Author manuscript

Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2024 June 01.

Published in final edited form as:

Clin Gastroenterol Hepatol. 2023 June ; 21(6): 1637–1645. doi:10.1016/j.cgh.2022.09.030.

Baseline Characteristics and Longitudinal Outcomes of Traditional Serrated Adenomas: A Cohort Study

Mehul Trivedi[1,*], **Suha Godil**[2,3,4,*], **Joshua Demb**[5,6,*], **Ashley Earles**[3,7], **Ranier Bustamante**[6,7], **Olga V. Patterson**[8,9], **Andrew J. Gawron**[10,11], **Tonya Kaltenbach**[12,13], **Sumana Mahata**[14], **Lin Liu**[2,6,7], **Samir Gupta**[5,6,7]

[1]Department of Internal Medicine, University of California San Diego, San Diego, California

[2]Herbert Wertheim School of Public Health and Human Longevity Science, University of California San Diego, San Diego, California

[3]Veterans Medical Research Foundation, San Diego, California

[4]Western University of Health Sciences, Pomona, California

[5]Division of Gastroenterology, University of California San Diego, San Diego, California

[6]Moores Cancer Center, University of California San Diego, La Jolla, California

[7]Jennifer Moreno Veteran Affairs San Diego Healthcare System, San Diego, California

[8]Division of Epidemiology, University of Utah, Salt Lake City, Utah

[9]VA Salt Lake City Medical Center, Salt Lake City, Utah

[10]VA Salt Lake City Health Care System, Salt Lake City, Utah

[11]Division of Gastroenterology, Department of Internal Medicine, University of Utah, Salt Lake City, Utah

[12]San Francisco VA Medical Center, San Francisco, California

[13]School of Medicine, University of California, San Francisco, San Francisco, California

Correspondence: Address correspondence to: Samir Gupta, MD, 3350 La Jolla Village Drive, San Diego, California 92161. s1gupta@health.ucsd.edu; fax: (858) 552-4327.

*Authors share co-first authorship.

CRediT Authorship Contributions

Mehul Trivedi (Data curation: Equal; Formal analysis: Equal; Investigation: Equal; Writing – review & editing: Equal)
Suha Godil (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Writing – original draft: Equal)
Joshua Demb (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Writing – original draft: Equal)
Ashley Earles (Project administration: Supporting; Resources: Supporting)
Ranier Bustamante (Data curation: Supporting; Writing – original draft: Supporting; Writing – review & editing: Supporting)
Olga Patterson (Writing – review & editing: Supporting)
Andrew Gawron (Writing – review & editing: Supporting)
Tonya Kaltenbach (Writing – review & editing: Supporting)
Sumana Mahata (Writing – review & editing: Supporting; created graphical abstract: Equal)
Lin Liu (Formal analysis: Supporting)
Samir Gupta (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Investigation: Equal; Methodology: Equal; Supervision: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)

Conflicts of Interest

The authors disclose no conflicts.

[14]School of Medicine, University of California San Diego, San Diego, California

Abstract

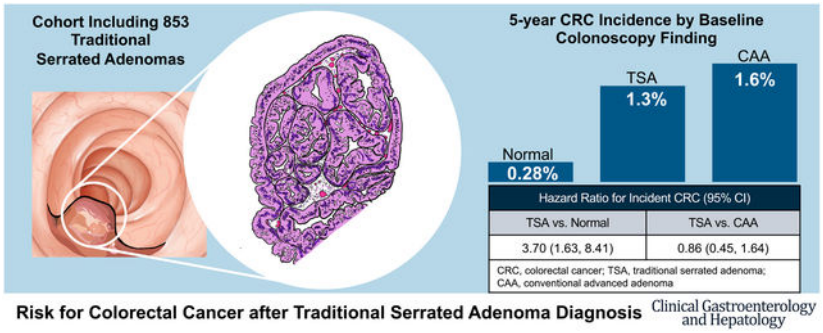
BACKGROUND AND AIMS: Traditional serrated adenomas (TSAs) may confer increased risk for colorectal cancer (CRC). Our objective with this study was to examine clinical characteristics and long-term outcomes associated with TSA diagnosis.

METHODS: We conducted a retrospective cohort study of U.S. Veterans ≥18 years of age with ≥1 TSA between 1999 and 2018. Baseline characteristics, colonoscopy findings, and diagnosis of incident and fatal CRC were abstracted. Advanced neoplasia was defined by CRC or adenoma with high-grade dysplasia, villous histology, or size ≥1 cm. Follow-up was through CRC diagnosis, death, or end of study (December 31, 2018).

RESULTS: A total of 853 Veterans with a baseline TSA were identified; 74% were ≥60 years of age, 96% were men, 14% were Black, and 73% were non-Hispanic White. About 64% were current or former smokers. Over 2044 total person-years at follow-up, there were 11 incident CRC cases and 1 CRC death. Cumulative CRC incidence was 1.34% (95% confidence interval [CI], 0.67%–2.68%), and cumulative CRC death was 0.12% (95% CI, 0.00%–0.35%). Among the subset of 378 TSA patients with ≥1 surveillance colonoscopy, 65.1% had high-risk neoplasia on follow-up. CRC incidence among TSA patients was significantly higher than in a comparison cohort of patients with normal baseline colonoscopy at baseline (hazard ratio, 3.70; 95% CI, 1.63–8.41) and similar to a comparison cohort with baseline conventional advanced adenoma (hazard ratio, 0.86; 95% CI, 0.45–1.64).

CONCLUSION: Individuals with TSA have substantial risk for CRC based on their cumulative CRC incidence, as well as significant risk of developing other high-risk neoplasia at follow-up surveillance colonoscopy. These data underscore importance of current recommendations for close colonoscopy surveillance after TSA diagnosis.

Graphical Abstract



Risk for Colorectal Cancer after Traditional Serrated Adenoma Diagnosis Clinical Gastroenterology and Hepatology

Keywords

Colonoscopy; Traditional Serrated Adenoma; Conventional Advanced Adenoma; Colorectal Cancer

Colorectal cancer (CRC) is the second leading cause of cancer death among men and women combined in the United States.[1] Traditional serrated adenomas (TSAs) are one of several

precursor epithelial polyps that can develop into CRC.[2] TSAs are the least common type of serrated polyp, making up only 5% of all serrated polyp diagnoses, but are thought to be lesions that have high risk for CRC progression.[2–4]

The U.S. Multi-Society Task Force on Colorectal Cancer recommends individuals with a TSA receive a repeat colonoscopy in 3 years.[5] However, the quality of evidence supporting that recommendation is low, mainly because long-term outcomes after TSA diagnosis have not been well established.[6] Due in part to their rarity, few studies have been conducted to characterize TSAs further, and have been limited by sample size or longitudinal follow-up.[7,8] To address this knowledge gap, we conducted a retrospective observational cohort study of individuals with a TSA diagnosis within the Veterans Health Administration (VHA) to describe baseline characteristics and outcomes on subsequent surveillance exams.

Materials and Methods

Cohort Inclusion and Exclusion Criteria

We conducted a retrospective cohort study of Veterans exposed to colonoscopy between 1999 and 2018 receiving care within the VHA—the Veterans Affairs (VA) Colonoscopy cohort—to identify veterans ≥18 years of age with TSA diagnosis. Prior to initiation, approval to conduct our study was obtained from the VA San Diego Institutional Review Board.

The primary data source used was the VA's Corporate Data Warehouse (CDW), a repository of usual care structured and unstructured health care data that have been captured from clinical encounters throughout the VHA.[9] To assemble the primary study cohort, we first identified individuals exposed to colonoscopy with any TSA diagnosis.

TSA diagnosis was identified using a previously developed natural language processing (NLP)–based search strategy of pathology reports demonstrated to have 95% sensitivity and specificity for identifying microscopic diagnoses based on polyp histology. The NLP strategy was developed through an iterative process that included clinical annotation of free text notes, development of search pipelines to extract key concepts of interest such as histology, and validation of the accuracy of NLP output results through manual chart reviews of a random sample of notes. Post-NLP processing, summary variables (such as for TSA diagnosis) were created. The first colonoscopy associated with a TSA diagnosis was defined as the baseline (index) exam. A stepwise process was implemented to assemble the primary analytic cohort. First, using discrete data available through queries of the VA CDW, we excluded patients with a history of CRC based on International Classification of Diseases–Ninth Revision diagnosis codes. Next, using manual chart review, we excluded individuals with evidence of CRC prior to baseline, CRC diagnosis within 60 days of baseline exam, missing documentation of TSA in a pathology report, or documentation that the TSA was incompletely resected at time of baseline colonoscopy. Thus, all individuals included had manual chart-review confirmed TSA diagnosis, and ascertainment of outcomes using manual chart review.

Exposures, Outcomes, and Covariates

Colonoscopy exposure was defined by data queries which identified the date for baseline and surveillance exams. Manual chart reviews were performed to abstract data associated with baseline colonoscopy and subsequent surveillance colonoscopies. Follow-up continued until the time of death, CRC diagnosis, or through December 31, 2018, whichever came first.

We ascertained demographic characteristics of patients with TSA, as well as body mass index (BMI), smoking status, and aspirin exposure from CDW data, using date of TSA diagnosis as the reference date. Discrete data such as demographic characteristics, procedure and diagnostic codes, and anthropometric measurements, as well as free-text procedure and pathology reports, are included.[9]

Clinical notes 30 days before and 60 days after baseline colonoscopy were manually reviewed to ascertain exam data, as well as to confirm and address any missing data on demographics or baseline characteristics found through our CDW query. For baseline and surveillance exams, colonoscopy and pathology reports were reviewed to abstract the number, location, shape, size, and histology of polyps. Due to variabilities in clinical documentation on colonoscopy reports, pathology reports were used to determine polyp size. Data were abstracted for up to 10 polyps from each report. If an individual had multiple microscopic histologic diagnoses listed due to pooling of multiple polyp specimens in a single pathology specimen jar, each diagnosis was abstracted at least once to ensure all outcomes were captured. Of note, findings at follow-up colonoscopy performed within 6 months of baseline were counted as part of baseline findings.

Conventional advanced adenoma (AA) was defined as an adenoma ≥10 mm in size, an adenoma with tubulovillous or villous histology, an adenoma with high-grade dysplasia, or carcinoma in situ. Conventional advanced neoplasia was defined as conventional AA or adenocarcinoma. A large serrated polyp (LSP) was defined as any serrated polyp ≥10 mm in size. For characterization of LSPs, the definition of serrated polyp included hyperplastic polyps; sessile serrated adenomas (SSAs), sessile serrated polyps (SSPs), or sessile serrated lesions (SSLs); and TSAs. High-risk neoplasia was defined by us as having LSP, TSA, or conventional AA, as these are lesions that increase risk of subsequent CRC. The worst baseline finding at index colonoscopy was noted for each patient based on the following order of lesion severity: conventional AA, LSP, and conventional nonadvanced adenoma (NAA). For the subset of individuals who had 2 surveillance colonoscopies subsequent to baseline TSA diagnosis, we characterized findings at second surveillance colonoscopy stratified by findings at first surveillance exam, as previously described.[5]

CRC diagnosis was confirmed with the presence of an adenocarcinoma diagnosis in a pathology report resulting from a biopsy or polypectomy, or using the Oncology Domain, a resource available in VHA to identify incident cancer cases.[10] Deaths were ascertained using VA Vital Status files, which have high sensitivity for capture of mortality. CRC death was ascertained via linkage to National Death Index cause-specific mortality data.

Statistical Analysis

Subject demographic and clinical characteristics were summarized for the study population using descriptive statistics. Colonoscopy exposure, as well as findings at follow-up among patients with ≥1 surveillance colonoscopy, were estimated using proportions and median values, as appropriate.

Cumulative incidence of CRC and fatal CRC was estimated using Kaplan-Meier estimation, and bootstrapped 95% confidence intervals (CIs) among all individuals, with follow-up through CRC diagnosis, death, or end of study period (December 31, 2018).

In a secondary analysis, we compared cumulative risk for incident and fatal CRC among patients with TSA with 2 matched cohorts without baseline TSA: one cohort comprised patients with normal baseline colonoscopy and one cohort of patients with conventional AA at baseline. Normal colonoscopy and conventional AA were identified using previously developed NLP algorithms. TSA patients were age and sex matched at a 1:4 ratio to non-TSA patients. The baseline exams for these matched cohorts occurred over the same observation window used to identify individuals with baseline TSA (1999–2018). For the matched cohorts, incident and CRC on follow-up were ascertained using the methods described previously, or cause-specific mortality data indicating CRC. Hazard ratios (HRs) were used to compare CRC incidence and CRC mortality between the TSA group and the normal colonoscopy or conventional AA groups. We used R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) to conduct all statistical analyses. This study was approved by the VA San Diego Institutional Review Board.

Results

Baseline Characteristics

A cohort of 853 Veterans with TSA meeting inclusion criteria were identified from a pool of 972 Veterans initially suspected to have a baseline colonoscopy with TSA diagnosis (Figure 1). Reasons for exclusion were presence of baseline CRC (n = 69), absence of confirmed TSA at baseline colonoscopy (n = 32), incomplete TSA resection at baseline colonoscopy (n = 17), or absence of colonoscopy report for review (n = 1). Table 1 shows the baseline characteristics of the study cohort. Of 853 patients with TSA, 74% were ≥60 years of age, 96% were men, 72.7% were non-Hispanic White, 13.8% were Black, and 13.5% were other. Median BMI was 29.6 kg/m^2, 64% were current or former smokers, and 45% had documented aspirin exposure at baseline TSA diagnosis. The average size of TSA was 8.5 mm, and 28.3% were diagnosed in the proximal colon, 44.9% in the distal colon, and 25.7% in the rectum.

Over 4036 total person-years at follow-up there were 10 cases of incident CRC, 1 case of fatal CRC, and 60 non-CRC deaths; the remaining 793 individuals included in the cohort were alive at end of study follow-up. Median follow-up time was 2.0 (interquartile range, 0.6–3.5) years. Exposure to ≥1 surveillance colonoscopy was observed for 44% (n = 378) of the cohort. The most significant baseline findings were TSA, AA, and LSP for 3.6% of patients; TSA and AA for 19.2%; TSA and LSP for 6.3%; TSA and NAA for 46%; and TSA only for 24.7% (Table 1).

CRC and Neoplasia Outcomes

Among the 853 patients with TSA at baseline, 3-year cumulative CRC incidence was 0.83% (95% confidence interval [CI], 0.40%–1.74%) (Table 2) and 5-year cumulative incidence was 1.3% (95% CI, 0.67%–2.7%), with all observed CRC cases occurring within the first 5 years of follow-up. Both the 3-year and 5-year cumulative rates of fatal CRC were 0.12% (95% CI, 0.00%–0.35%), with the only fatal case occurring within the first 3 years of follow-up.

There were 378 patients that had ≥1 follow-up surveillance colonoscopy. Among individuals with surveillance, the most significant finding was adenocarcinoma for 1.9%, TSA for 5.6%, conventional AA for 45.2%, LSP for 12.4%, conventional NAA for 7.4%, small SSL for 10.1%, and no significant neoplasia for 17.4% (Table 3). High-risk neoplasia (adenocarcinoma, TSA, serrated polyp ≥10 mm, villous or tubulovillous adenoma, adenoma with high-grade dysplasia, or conventional adenoma ≥10 mm) was found among 65.1% of individuals at follow-up based on all surveillance exams recorded.

Table 4 shows the follow-up findings at the first and second surveillance examinations among individuals who had surveillance. Of 378 patients with surveillance exams, 56.3% (n = 213) were found to have high-risk neoplasia at first surveillance. Among these 213 patients, 47.4% (n = 101) received a second surveillance exam. Proportion with high-risk neoplasia at second surveillance was 65.3% for those with high-risk neoplasia at first surveillance, 68.8% among those with low-risk neoplasia at first surveillance, and 47.7% among those with no neoplasia at first surveillance.

Comparison of Risk With Patients With Baseline Normal Colonoscopy or Conventional AA

The matched cohort of individuals with baseline normal colonoscopy included 3412 patients. Over 26,781 total person-years at follow-up, there were 17 cases of incident CRC and 8 cases of fatal CRC. The matched cohort of individuals with baseline conventional AA included 3405 patients. Among these individuals over 20,049 total person years at follow-up, 57 cases of incident CRC and 6 cases of fatal CRC were identified.

Among the 3412 patients with normal colonoscopy at baseline, cumulative CRC incidence was 0.28% (95% CI, 0.10%–0.46%) at both 3 and 5 years of follow-up and cumulative fatal CRC was 0.09% (95% CI, 0.00%–0.19%) at both 3 and 5-years of follow-up. Compared with patients with a normal baseline colonoscopy, patients diagnosed with TSA were more likely to be diagnosed with CRC (HR, 3.70, 95% CI, 1.63–8.41); however, no significant difference in mortality was noted (HR, 1.16, 95% CI, 0.10–7.26) (Table 5).

Among the 3405 patients with conventional AA at baseline colonoscopy, 3-year cumulative CRC incidence was 1.32% (95% CI, 0.93%–1.71%) and 5-year cumulative incidence was 1.61% (95% CI, 1.16%–2.06%). The 3-year cumulative rate of fatal CRC was 0.07% (95% CI, 0.00%–0.16%), and the 5-year rate was 0.22% (95% CI, 0.02%–0.43%). Compared with patients with conventional AA on baseline colonoscopy, there was no significant difference in CRC incidence or mortality when compared with patients diagnosed with TSA (incidence: HR, 0.86, 95% CI, 0.45–1.64; mortality: HR, 0.78, 95% CI, 0.09–6.53) (Table 5).

Discussion

In a cohort of 853 TSA patients with 4036 person-years at follow-up, cumulative 5-year CRC incidence was 1.3% and cumulative CRC mortality was 0.12%. Of 378 patients who received follow-up surveillance colonoscopy, proportion with high-risk neoplasia was 65.1% overall. Further, proportion with high-risk neoplasia at second surveillance remained very substantial (≥47%) even among individuals with no neoplasia at first surveillance exam, suggestive of persistent high risk for CRC. We also found a high proportion of individuals with potential risk factors for TSA such as older age, BMI ≥25 kg/m^2, and smoking. TSA patients were found to have significantly higher risk of incident CRC when compared with patients with normal colonoscopy at baseline, and similar risk when compared with patients with conventional AA at baseline.

Few studies have examined risk for CRC among patients with TSA. A previous case cohort study from patients seen at Mayo Clinic estimated 1.67% developed CRC within a group of 1390 patients with advanced SSAs or SSPs or TSA at incident colonoscopy.[11] One large longitudinal cohort study found that among 5918 participants with serrated polyps, defined by having any hyperplastic polyp, TSA, or SSAs or SSPs, with or without cytological dysplasia, the cumulative CRC incidence at 10 years was 0.4% among those with serrated polyps <10 mm and 1.1% among those with serrated polyps ≥10 mm.[12] In another large longitudinal study, Li et al[13] reported cumulative CRC incidences at 10 years of 14.8, 30.2, and 5.9 per 1000 persons for individuals with proximal serrated polyps <10 mm, proximal serrated polyps ≥10 mm, and distal serrated polyps, respectively, with serrated polyps defined as having any hyperplastic polyp, SSA or SSP, TSA, or unspecified serrated polyp. In all 3 of these studies, analyses restricted to individuals with only TSA at baseline polypectomy were not reported. In contrast to these studies, we focused on characterizing outcomes among individuals with confirmed TSA and found that 5-year cumulative CRC incidence was 1.3% and 5-year cumulative CRC mortality was 0.12%.

We compared CRC incidence among patients with TSAs with matched cohorts of patients with baseline findings of no adenoma and conventional AAs. The incidence of CRC that we found in these groups was similar to those described in a large U.S. cohort study by Click et al,[14] which demonstrated a 5-year CRC incidence of 0.28% among patients with no adenomas and 0.94% among patients with conventional AAs at baseline. These values fell within our reported ranges of CRC incidence at 5 years of 0.28% for patients with a normal colonoscopy at baseline and 1.6% for patients with conventional AAs at baseline. We also found an increased risk of incident CRC among patients with TSAs compared with those with no adenomas at baseline, with an HR of 3.70. These findings were consistent with Erichsen et al's study[7] demonstrating that patients with TSAs were nearly 5 times as likely to develop CRC at 10 years when compared with those with no adenomas (odds ratio, 4.84; 95% CI, 2.36–9.93).

We found similar CRC incidence among patients with TSAs at baseline and those with conventional AAs at baseline, supporting the current same 3-year surveillance recommendation for patients with TSAs and conventional AA after baseline polypectomy.[5]

Within our cohort, almost 2 in 3, or 65.1%, individuals with baseline TSA developed high-risk neoplasia on follow-up. Few other studies have examined risk for metachronous advanced neoplasia among individuals with TSA at baseline. One study with 200 TSA patients estimated the incidence of high-grade dysplasia or carcinoma to be 9.3%.[15] Yoon et al[16] compared follow-up outcomes of 186 individuals with TSAs with an age- and sex-matched group of 372 individuals with conventional adenomas and found that proportion with a high-risk polyp (defined as having 3 or more conventional adenomas or any conventional AA) was 47.3% among those with TSA and 32% among those with conventional adenoma. Our study demonstrates a higher rate of developing high-risk neoplasia following a diagnosis of a TSA than seen in prior studies, further supporting current guideline recommendations for surveillance colonoscopy 3 years after TSA diagnosis, and may indicate that an even shorter follow-up interval may be needed to address ongoing risk during follow-up.[6]

Our study provides novel insights regarding the potential yield of serial surveillance colonoscopy among patients with TSA. In the subset of patients who underwent 2 surveillance colonoscopies, the proportion with high-risk neoplasia at the second surveillance colonoscopy was 47.7% among individuals with no neoplasia at first surveillance, 68.8% among individuals with low-risk neoplasia at first surveillance, and 65.3% among individuals with high-risk neoplasia at first surveillance. These findings suggest that regardless of findings at first surveillance, patients with a baseline TSA may remain at persistently increased risk for high-risk neoplasia on follow-up and merit continued close (eg, 3-year) surveillance after a first surveillance exam.

Importantly, we observed that fewer than 45% of patients with TSA at baseline had a surveillance exam, despite significant rates of high-risk neoplasia on follow-up among those who did complete surveillance. This suggests a need to promote greater awareness and adherence to current guideline recommendations for patients with TSA to receive surveillance colonoscopy at most 3 years from baseline.

Our findings confirm and extend results from prior studies regarding characteristics of patients with TSA. Other studies have identified ≥50 years of age and current smoking as being prevalent among patients with TSA, similar to our findings.[17,18] Kim et al[17] reported that compared with individuals with conventional adenoma, those with TSA were more likely to be ≥50 years of age, have hypertension, and be current smokers. A case-control study by Pyo et al[18] reported that individuals with TSA, compared with those with normal colonoscopy, were more likely to be ≥50 years of age, have obesity, and have higher triglyceride levels; smoking was not associated with a statistically significant increased risk. In our study, we did not collect data on hypertension or triglyceride levels, precluding an analysis of the association of these factors with TSAs. Older age represents a greater time for potential carcinogenic exposures.[17] The carcinogenic effects of cigarette smoking may affect the development of polyps like TSAs.[17] Obesity, indicated by a BMI ≥30 kg/m^2, and more specifically adiposity, have been previously identified as a risk factor for colon cancer and adenoma, with adiposity theorized to promote adenoma growth or the existence of some central metabolic characteristics associated with adiposity and colon cancer risk.[19] The observed association of hypertension, obesity, and elevated triglycerides may point

to involvement of pathophysiologic factors such as decreased insulin sensitivity in the development of TSAs, as has been previously postulated.[17] Further research is necessary to investigate the mechanisms by which age, smoking, obesity, elevated triglycerides, and hypertension may be associated with risks for TSA.

Limitations of this study include a focus on a mostly male and White population of Veterans. Pathologic diagnoses were based on usual care reports, and could be subject to interobserver variability, which could have resulted in both under- and overdiagnosis of serrated lesions. Polyp size was obtained from gross measurements from pathology reports, which may have resulted in both under- or overestimation of polyp size. Variability in serrated lesion diagnosis or polyp size estimation could impact the precision of our estimates of baseline characteristics and follow-up outcomes, though we postulate that any variability would reflect what is seen in usual clinical practice, given that this was a national sample. Strengths include inclusion of one of the largest cohorts of TSA patients to date (N = 853), with over 2044 total person-years at follow-up, an analysis that included rigorous ascertainment and reporting of CRC specific incidence and mortality, sampling from a large, nationally representative cohort of Veterans, and use of manual chart review to ensure accurate capture of polyp, colonoscopy, and other key data.[16]

In conclusion, we found having a TSA was associated with substantial cumulative risk for incident and fatal CRC, and that approximately 2 in 3 individuals with baseline TSA had high-risk neoplasia at surveillance colonoscopy. These findings support close colonoscopic surveillance of patients with TSA.

Acknowledgments

The authors formally acknowledge all the entities that made this research possible, including but not limited to the VA Central Cancer Registry, Mortality Data Repository, and VA Informatics and Computing Infrastructure. The study was approved by the VA San Diego's Institutional Review Board and included a waiver of informed consent for data access and use. The authors thank Dr Scott DuVall, Director of the VA Informatics and Computing Infrastructure, for assistance with facilitating the development of the VA Colonoscopy Cohort utilized for this research.

Funding

Research reported in this publication was supported by VA Health Services Research and Department awards I01HX001574 (Samir Gupta, principal investigator) and 1I01HX002778 (Andrew Gawron, Tonya Kaltenbach co-principal investigators), and by the National Cancer Institute of the National Institutes of Health under award numbers R37CA222866 (Samir Gupta, principal investigator) and 5F32CA239360 (Joshua Demb, principal investigator).

Abbreviations:

AA	advanced adenoma
BMI	body mass index
CDW	Corporate Data Warehouse
CI	confidence Interval
CRC	colorectal cancer

HR	hazard ratio
LSP	large serrated polyp
NAA	nonadvanced adenoma
NLP	natural language processing
SSA	sessile serrated adenoma or polyp
SSL	sessile serrated lesion
SSP	sessile serrated polyp
TSA	traditional serrated adenoma
VA	Veterans Affairs
VHA	Veterans Health Administration

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7–30. [PubMed: 31912902]
2. Kalimuthu SN, Chelliah A, Chetty R. From traditional serrated adenoma to tubulovillous adenoma and beyond. World J Gastrointest Oncol 2016;8:805–809. [PubMed: 28035250]
3. Chetty R Traditional serrated adenoma (TSA): morphological questions, queries and quandaries. J Clin Pathol 2016;69:6–11. [PubMed: 26553935]
4. Toll AD, Fabius D, Hyslop T, et al. Prognostic significance of high-grade dysplasia in colorectal adenomas. Colorectal Dis 2011;13:370–373. [PubMed: 20718835]
5. Gupta S, Lieberman D, Anderson JC, et al. Recommendations for follow-up after colonoscopy and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc 2020;91:463–485.e5. [PubMed: 32044106]
6. Short MW, Layton MC, Teer BN, Domagalski JE. Colorectal cancer screening and surveillance. Am Fam Physician 2015; 91:93–100. [PubMed: 25591210]
7. Erichsen R, Baron JA, Hamilton-Dutoit SJ, et al. Increased risk of colorectal cancer development among patients with serrated polyps. Gastroenterology 2016;150:895–902.e5. [PubMed: 26677986]
8. Bettington ML, Chetty R. Traditional serrated adenoma: an update. Hum Pathol 2015;46:933–938. [PubMed: 26001333]
9. Demb J, Earles A, Martínez ME, et al. Risk factors for colorectal cancer significantly vary by anatomic site. BMJ Open Gastroenterol 2019;6:e000313.
10. Earles A, Liu L, Bustamante R, et al. Structured approach for evaluating strategies for cancer ascertainment using large-scale electronic health record data. JCO Clin Cancer Inform 2018;2: 00072:CCI.17.
11. Mouchli MA, Ouk L, Scheitel MR, et al. Colonoscopy surveillance for high risk polyps does not always prevent colorectal cancer. World J Gastroenterol 2018;24:905–916. [PubMed: 29491684]
12. He X, Hang D, Wu K, et al. Long-term risk of colorectal cancer after removal of conventional adenomas and serrated polyps. Gastroenterology 2020;158:852–861.e4. [PubMed: 31302144]
13. Li D, Liu L, Fevrier HB, et al. Increased risk of colorectal cancer in individuals with a history of serrated polyps. Gastroenterology 2020;159:502–511.e2. [PubMed: 32277950]
14. Click B, Pinsky PF, Hickey T, Doroudi M, Schoen RE. Association of colonoscopy adenoma findings with long-term colorectal cancer incidence. JAMA 2018;319:2021–2031. [PubMed: 29800214]

15. Song SY, Kim YH, Yu MK, et al. Comparison of malignant potential between serrated adenomas and traditional adenomas. J Gastroenterol Hepatol 2007;22:1786–1790. [PubMed: 17914951]
16. Yoon JY, Kim HT, Hong SP, et al. High-risk metachronous polyps are more frequent in patients with traditional serrated adenomas than in patients with conventional adenomas: a multicenter prospective study. Gastrointest Endosc 2015; 82:1087–1093.e3. [PubMed: 26117178]
17. Kim J, Lee JY, Hwang SW, et al. Risk factors of traditional serrated adenoma and clinicopathologic characteristics of synchronous conventional adenoma. Gastrointest Endosc 2019; 90:636–646.e9. [PubMed: 31063737]
18. Pyo JH, Ha SY, Hong SN, et al. Identification of risk factors for sessile and traditional serrated adenomas of the colon by using big data analysis. J Gastroenterol Hepatol 2018;33:1039–1046. [PubMed: 29087626]
19. Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. Gastroenterology 2007;132:2208–2225. [PubMed: 17498513]

What You Need to Know

Background

Traditional serrated adenomas (TSAs) are understudied lesions that may confer a high risk of progression to colorectal cancer (CRC). We conducted a retrospective cohort study of U.S Veterans diagnosed with a TSA over a 17-year span to determine long-term outcomes after diagnosis.

Findings

Cumulative CRC incidence was 1.34%, significantly higher than in patients with a normal baseline colonoscopy, and similar to patients with baseline conventional advanced adenoma. A total of 65.1% of patients with a subsequent surveillance colonoscopy were diagnosed with high-risk neoplasia on follow-up.

Implications for patient care

Patients diagnosed with TSAs are at significant risk for development of CRC and high-risk neoplasia, underscoring the importance of current recommendations for close surveillance in this population.

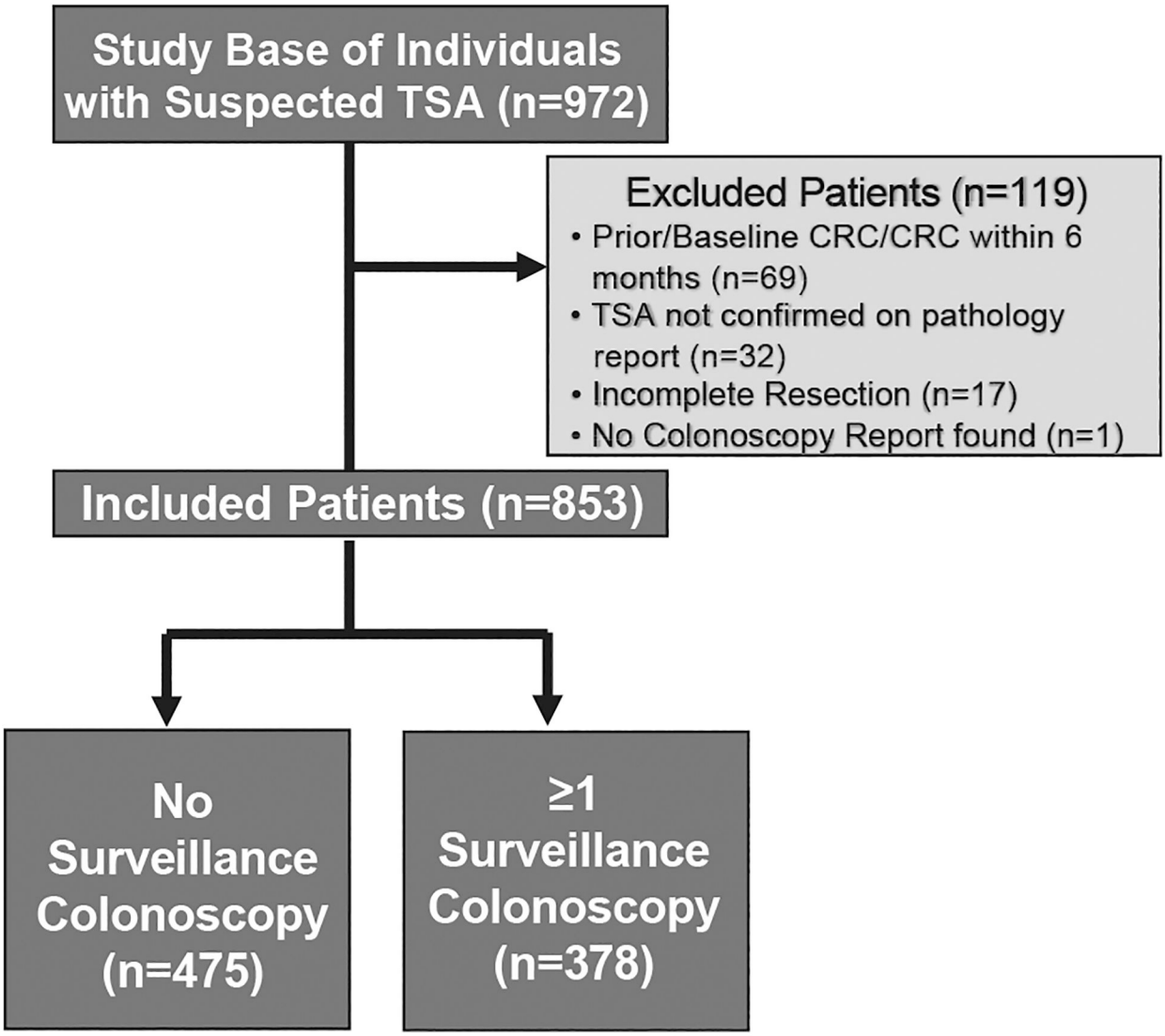


Figure 1.
Study flow.

Table 1.

Baseline Characteristics Individuals With TSA, Veterans Affairs Colonoscopy Cohort, 1999–2018

	Overall (N = 853)	Baseline TSA, No Surveillance Colonoscopy (n = 475)	Baseline TSA, >1 Surveillance Colonoscopy (n = 378)
Number of procedures	1 (1–2)	1 (1–1)	2 (2–3)
Follow-up, person-years	2.0 (0.6–3.5)		2.3 (1.0–3.6)
Age, y	65 (59–69)	66 (60–70)	64 (59–68)
30–39 y	4 (0.47)	3 (0.63)	1 (0.27)
40–49 y	28 (3.3)	11 (2.3)	17 (4.5)
50–59 y	187 (21.9)	99 (20.8)	88 (23.3)
60–69 y	425 (49.9)	231 (48.6)	194 (51.5)
70–79 y	183 (21.5)	110 (23.2)	73 (19.4)
80+ y	25 (2.9)	21 (4.4)	4 (1.1)
Sex			
Male	819 (96.0)	457 (96.2)	362 (95.8)
Female	34 (4.0)	18 (3.8)	16 (4.2)
Race/Ethnicity			
White	620 (72.7)	342 (72.0)	278 (73.5)
Black	118 (13.8)	68 (14.3)	50 (13.2)
Asian	13 (1.5)	8 (1.7)	5 (1.3)
Native American	9 (1.1)	4 (0.84)	5 (1.3)
Hispanic	1 (0.12)	1 (0.21)	0 (0.00)
Missing	92 (10.8)	52 (10.9)	40 (10.6)
Body mass index, kg/m^2	29.6 (26.3–33.9)	29.5 (26.3–34.3)	29.9 (26.3–33.6)
Underweight	6 (0.70)	5 (1.1)	1 (0.26)
Normal	120 (14.1)	72 (15.2)	48 (12.7)
Overweight	290 (34.0)	160 (33.7)	130 (34.4)
Obese	376 (44.1)	204 (42.9)	172 (45.5)
Missing	61 (7.2)	34 (7.16)	27 (7.1)
Smoking status			
Never	239 (28.0)	132 (27.8)	107 (28.3)
Former	200 (23.4)	117 (24.6)	83 (22.0)

	Overall (N = 853)	Baseline TSA, No Surveillance Colonoscopy (n = 475)	Baseline TSA, >1 Surveillance Colonoscopy (n = 378)
Current	348 (40.8)	189 (39.8)	159 (42.1)
Missing	66 (7.7)	37 (7.8)	29 (7.7)
Aspirin exposure	385 (45.1)	214 (45.1)	171 (45.2)
Most significant finding at baseline colonoscopy			
TSA and AA and LSP	31 (3.6)	16 (3.4)	15 (4.0)
TSA and AA	164 (19.2)	79 (16.6)	85 (22.5)
TSA and LSP	54 (6.3)	31 (6.5)	23 (6.1)
TSA and NAA	393 (46.0)	225 (47.4)	168 (44.3)
TSA only	211 (24.7)	124 (26.1)	87 (23.0)

Values are median (interquartile range) or n (%).

AA, advanced adenoma; LSP, large serrated polyp; NAA, nonadvanced adenoma; SSL, sessile serrated lesion; TSA, traditional serrated adenoma.

Table 2.

Cumulative Incidence of CRC and CRC-Related Death After TSA diagnosis, Veterans Affairs Colonoscopy Cohort, 1999–2018 (n = 853)

	Follow-Up (Days)	Number of CRC Cases	3-Year Cumulative Incidence (95% CI)	5-Year Cumulative Incidence (95% CI)
CRC incidence	1543 (1104–2299)	10	0.83% (0.40%–1.7%)	1.30% (0.67%–2.7%)
CRC mortality	1557 (1112–2299)	1	0.12% (0.00%–0.35%)	0.12% (0.00%–0.35%)

Values are median (interquartile range), unless otherwise indicated.

CI, confidence interval; CRC, colorectal cancer; TSA, traditional serrated adenoma.

Table 3.

Most Significant Neoplasia on Follow-Up Among TSA Patients With ≥1 Surveillance Colonoscopy (n = 378)

Variable	n	%
Most advanced finding by histology and size[a]		
Adenocarcinoma	7	1.9
TSA	21	5.6
Conventional AA	171	45.2
LSP	47	12.4
Conventional NAA	28	7.4
SSL <10 mm	38	10.1
No finding	66	17.4
Aggregate most advanced finding[a]		
High-risk neoplasia[b]	246	65.1
Low-risk neoplasia[c]	66	17.5
No finding	66	17.5

AA, advanced adenoma; LSP, large serrated polyp; NAA, nonadvanced adenoma; SSL, sessile serrated lesion; TSA, traditional serrated adenoma.

[a]Categories are mutually exclusive, and listed in descending order of severity.

[b]Adenocarcinoma, TSA, serrated polyp ≥10 mm, villous or tubulovillous adenoma, adenoma with high-grade dysplasia, or conventional adenoma 10 mm.

[c]Conventional adenoma <10 mm or sessile serrated adenoma, sessile serrated polyp, or SSL <10 mm.

Table 4.

Neoplasia Yield at First and Second Colonoscopy Surveillance Examinations After Initial TSA Diagnosis

Findings at First Surveillance Exam (n = 378)		Received Second Surveillance Exam	Findings at Second Surveillance Exam (n = 161)	
High-risk neoplasia	213 (56.3)	101 (47.4)	High-risk neoplasia	66 (65.3)
			Low-risk neoplasia	20 (19.8)
			No neoplasia	15 (14.9)
Low-risk neoplasia	70 (18.5)	16 (22.9)	High-risk neoplasia	11 (68.8)
			Low-risk neoplasia	1 (6.3)
			No neoplasia	4 (25.0)
No neoplasia	95 (25.1)	44 (46.3)	High-risk neoplasia	21 (47.7)
			Low-risk neoplasia	7 (15.9)
			No neoplasia	16 (36.4)

Values are n (%). High-risk neoplasia was defined as adenocarcinoma, TSA, large serrated polyp, or advanced adenoma. Low-risk neoplasia was defined as nonadvanced adenoma or sessile serrated lesions <10 mm.

TSA, traditional serrated adenoma

Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2024 June 01.

Table 5.

Cumulative Risk for Incident and Fatal CRC for Individuals With Baseline TSA vs Normal Colonoscopy, and Baseline TSA vs Conventional Adenoma: Matched Cohort Analysis

		Follow-Up (Days)	Number of CRC Cases	3-Year Cumulative Event Rate (95% CI)	5-Year Cumulative Event Rate (95% CI)	CRC Incidence HR (95% CI)	CRC Mortality HR (95% CI)
TSA vs normal colonoscopy (n = 4265)[a]	CRC incidence: TSA	1543 (1104–2299)	10	0.83% (0.22%-1.5%)	1.3% (0.40%-2.3%)	3.70 (1.63–8.41)	1.16 (0.10–7.26)
	CRC incidence: normal	2882 (1818–3964)	17	0.28% (0.10%-0.46%)	0.28% (0.10%-0.46%)		
	CRC mortality: TSA	1557 (1112–2299)	1	0.12% (0.00%-0.35%)	0.12% (0.00%-0.35%)		
	CRC mortality: normal	2882 (1818–3964)	8	0.09% (0.00%-0.19%)	0.09% (0.00%-0.19%)		
TSA vs conventional AA (n = 4257)[b]	CRC incidence: TSA	1540 (1103–2301)	11	0.95% (0.29%-1.6%)	1.5% (0.49%-2.4%)	0.86 (0.45–1.64)	0.78 (0.09–6.53)
	CRC incidence: AA	1956 (1196–3042)	57	1.3% (0.93%-1.7%)	1.6% (1.2%-2.06%)		
	CRC mortality: TSA	1548 (1110–2301)	1	0.12% (0.00%-0.35%)	0.12% (0.00%-0.35%)		
	CRC mortality: AA	1956 (1196–3042)	6	0.07% (0.00%-0.16%)	0.22% (0.02%-0.43%)		

Values are median (interquartile range), unless otherwise indicated.

AA, advanced adenoma; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; TSA, traditional serrated adenoma.

[a]Includes 853 TSA patients and 3412 matched patients with normal colonoscopies.

[b]Includes 852 TSA patients and 3405 matched patients with conventional advanced adenomas (1 TSA patient could not be successfully matched).