Research Article

Gastroenterology, Hepatology & Digestive Disorders

# Investigating the Prevalence and Progression of Serrated Polyps – Tampa VA Experience

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## ABSTRACT

***Background:*** *Adenomatous polyps have historically been considered the sole precursor lesions that lead to colorectal cancer (CRC) via the adenoma-carcinoma sequence. It is increasingly recognized that CRC is not a single disease, but rather a heterogeneous disorder with various distinct molecular pathways. A recently recognized emerging pathway in colorectal carcinogenesis involves "serrated polyps", which until recently were considered to be innocuous lesions. The WHO classification system divides serrated polyps into sessile serrated adenomas (SSA), traditional serrated adenomas (TSA) and serrated adenomas (SA). Despite the serrated neoplastic pathway accounting for up to 10-20% of all sporadic colorectal cancers, these polyps remain under-diagnosed and poorly understood. We sought to identify the prevalence and potential progression of serrated polyps in our veteran population.*

***Methods:*** *We conducted a retrospective analysis of all patients who underwent all-cause colonoscopies at James A Haley Veterans' Hospital over a 10-year period from January 1, 2004 through December 31, 2014. Our primary outcome was to analyze the change in prevalence of serrated polyps in the veteran population. Secondary outcomes were to correlate prevalence of serrated polyps with modifiable lifestyle factors, and attempt to correlate if the previous presence of serrated polyps leads to the development of colorectal cancer. Low risk adenomas were categorized as tubular adenoma and high risk adenomas were categorized as tubulo-villous adenomas.*

***Results:*** *An electronic databank was created using keyword search "polyps," "colonoscopy." A retrospective analysis of pathology reports 14593 all cause colonoscopies was conducted over 10-year period. The individual cases were categorized as SSA, TSA, SA, SSA + high risk adenoma, SSA + low risk adenoma, SA + high risk adenoma, SA + low risk adenoma, TSA + high risk adenoma, TSA + low risk adenoma and TA (Control). There was a progressive increase in the percentage of serrated polyps per all lesions identified on colonoscopy over the 10 year period, with the most exponential increase occurring between 2010 through 2014. There was no significant correlation between HgA1c, Total cholesterol, HLD, LDL and Triglycerides between TA vs. TSA and SA. There was a statistical significance between TA vs. SSA in regards to LDL ($p<0.03$).*

***Discussion:*** *Serrated polyps are increasingly being recognized as lesions with malignant potential. It is therefore essential that these lesions are properly removed and classified. In this study, a large database of serrated polyps in the veteran population undergoing all-cause colonoscopy was created. Temporal trends in the detection of these lesions and variables that may affect their prevalence were identified and analyzed. To our knowledge, this is the first study to date to investigate the prevalence of serrated polyps in the veteran population.*

**Keywords**
Colorectal cancer, Polyps, Tubulovillous adenomas.

## Introduction

Typically, colorectal polyps have been divided in to two main groups: traditional adenomas and serrated adenomas/polyps. Traditional adenomas have been considered to have malignant potential and are classified as tubular adenomas (TA), tubulovillous adenomas, and villous adenomas on the basis of their architecture. Tubular adenomas have closely packed tubular crypts with less than 25% villous component. Tubulovillous adenomas share both tubular and villous features, with anywhere from 25% to 75% villous components, and villous adenomas are predominated with more than 75% villous components on pathology [1-3].

Serrated adenomas/polyps are a heterogeneous group of lesions that include hyperplastic polyps, sessile serrated adenomas (SSA), and traditional serrated adenomas (TSA) by the WHO classification. The terms sessile serrated polyp and sessile serrated adenoma can be used interchangeably per the WHO. SSAs account for 15%-20% of all serrated polyps. These adenomas have a high frequency in the often poorly-prepped proximal colon, making them easy to miss on colonoscopy. Additionally, the sessile morphology of many of these adenomas may make them difficult to detect, further explaining variability in detection rates. They are frequently covered with a mucus cap and indistinct edges, and tend to have paler mucosa than traditional adenomas. Histologically, SSAs are noted to have mature goblet cells at the base of crypts. Traditional serrated adenomas constitute up to 5% of serrated adenomas identified in Western countries but have a higher prevalence in Asia. Unlike SSAs, TSAs are more frequently found on the left side of the colon and are more prevalent in patients greater than 50 years of age [1-6].

In the United States and worldwide, colorectal cancer (CRC) is the third most frequently diagnosed cancer and the third leading cause of cancer-related death in both men and women. In the United States alone, it is estimated that there will be more than 135,000 new diagnoses and greater than 50,000 deaths from colon cancer annually; globally, there are approximately 600,000 deaths from CRC each year [7]. It is widely accepted that the process by which most CRCs arise is via the adenoma carcinoma sequence, first described by Vogelstein et al. as the classical pathway of tumorigenesis [8,9]. Of the identified CRCs, over 90% are adenocarcinomas arising from traditional adenomas. Via the classical pathway, CRCs are produced when oncogene activation is coupled with the inactivation of tumor suppressor genes. The ras oncogene, identified in more than 50% of colonic carcinomas and many adenomas, is one of the key oncogenes identified in the adenoma-carcinoma sequence. Similarly, suppression of the APC gene, notably in familial CRCs, and the p53 gene on chromosome 17, identified in a large portion of not only CRCs but also many other human solid tumors, have been established as integral parts of the classical pathway [10-12].

In recent years, though, a new "alternative" pathway for colorectal carcinogenesis suggests that CRC may actually be a heterogeneous process with various molecular pathways involving more than one precursor lesion. First described by Drs. Jass and Smith, this alternative pathway suggests the development of CRCs via serrated adenomas [13]. It is estimated that approximately 10% to 30% of all CRCs are a result of this alternative pathway with distinct genetic profiles [14]. While precise pathogenetic pathways have not been clearly defined, it appears the serrated pathway of tumorigenesis is driven by inhibition of apoptosis and inactivation of DNA repair genes. Mutations in the BRAF oncogene appear to play a large part in this process. Additionally, it is hypothesized that CRC may develop via microsatellite instability and silencing of DNA repair genes mediated by aberrant methylation of the gene's promoter region, notably of hMLH1 and MGMT genes and particularly in those with the CpG island methylator phenotype (CIMP) [9,15-18].

Despite the serrated neoplastic pathway accounting for up to one-third of all sporadic colorectal cancer, these polyps remain under-diagnosed and poorly understood. There is a notable lack of data regarding serrated adenomas and their potential progression in the veteran population, which is unique due to its multiple comorbidities. As such, we sought to identify the prevalence and potential progression of serrated adenomas in our veteran population. In addition, we aimed to identify any correlation between these adenomas and modifiable lifestyle factors including Hemoglobin A1C (HgA1C), body mass index (BMI), total cholesterol, high-density lipoproteins (LDL), low density lipoproteins (HDL), and triglycerides.

## Methods

We performed a retrospective analysis of all patients who underwent all cause colonoscopies at James A Haley Veteran's Hospital over a 10-year period from January 1, 2004 through December 31, 2014. The study was approved by the Institutional Review Boards for Human Research at the University of South Florida. A databank was created using a search criteria that included "colonoscopy, polyps, cecum, colon, rectum, anal, sigmoid, descending, transverse, [and] ascending." A cohort of 14593 pathology reports from all cause colonoscopies in patients 18 years of age and above was electronically generated. Pathology from those patients with inflammatory bowel disease, familial adenomatous polyposis, and non-polyposis colorectal cancer were excluded.

Individual polyp pathologies were identified and classified as sessile serrated adenoma (SSA), SSA and high risk adenoma, SSA and low risk adenoma, serrated adenoma (SA), SA and high risk adenoma, SA and low risk adenoma, traditional serrated adenoma (TSA), TSA and high risk adenoma, and TSA and low risk adenoma, with TA serving as the control in line with the primary study outcome of identifying the change in prevalence of serrated polyps in the veteran population. Low risk adenomas were categorized as tubular adenoma and high risk adenomas were categorized as tubulovillous adenomas.

Secondary outcomes were to correlate prevalence of serrated

polyps with modifiable lifestyle factors, and attempt to correlate if the previous presence of serrated polyps leads to the development of colorectal cancer. As such, data were further extracted on the following modifiable lifestyle factors: HbA1c, total cholesterol, HDL, LDL, and triglycerides. Total cholesterol, triglycerides, HDL, and LDL were classified as low, normal, or high based on standardized guidelines. BMI was categorized for this population as <25, 26-29, 30-34, 35-39, and >40.

Pathology and lifestyle variables were correlated via chi-squared analysis. Statistical significance was set at 5% for all comparisons along with 95% confidence intervals (CI). All analyses were performed using the SPSS statistical analysis software.

## Results

A total of 14,593 polyp pathology reports met inclusion criteria and were initially analyzed. Of these, 11,458 (78.5%) had only tubular adenomas and fell in to the control group. Of the remaining qualifying pathology reports, 180 were identified as SSA, 221 as SSA with low risk adenoma, and 7 as SSA with high risk adenoma as illustrated in Figure 1. Similarly, 78 SA were identified, 5 SA with high risk adenoma, and 61 SA with low risk adenoma in addition to 40 TSA, 16 TSA with low risk adenoma, and 1 TSA with high risk adenoma.

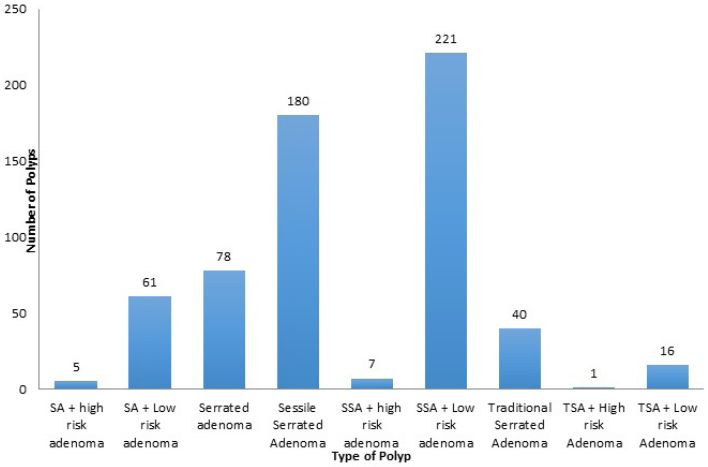


**Figure 1:** Distribution of polyp pathologies.

The temporal trend of all serrated polyps identified on all cause colonoscopy over the 10 year period showed a progressive increase (Figure 2). The range in serrated patients identified annually in this population was 85 patients, with 15 total patients identified in 2005 and 101 patients identified in 2014. The most exponential increase in the detected number of serrated polyps occurred between the years 2010 and 2014, with a nearly 100% increase in serrated polyp detection in that time.

Of those patients in the control group with tubular adenomas identified, the greatest proportion was noted to have BMI in the range of 26 kg/m$^2$ – 29 kg/m$^2$. When analyzed based on cholesterol, HbA1c, HDL, LDL, and triglycerides, a majority of patients fell within the normal range with no patients noted to have low total cholesterol, low HbA1c, high HDL, low LDL, or low triglycerides. No statistically significant correlation was established between BMI, HbA1c, total cholesterol, HDL, LDL, and triglycerides and the presence of tubular adenomas. Similarly, there was no notable correlation between these modifiable risk factors and TSA and SA compared to TA. There was a statistical significance, however, between TA vs SSA with regard to LDL ($p<0.03$).

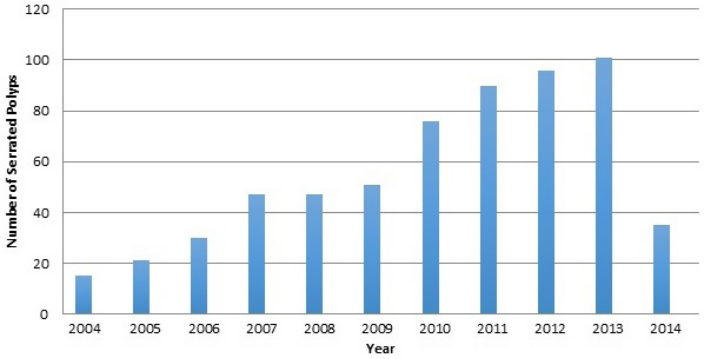


**Figure 2:** Prevalence of serrated polyps over 10 years.

| TA vs. SA | HgA1c | Total Chol | HDL | LDL | Trig |
|---|---|---|---|---|---|
| p Value | 0.869 | 0.89 | 0.79 | 0.581 | 0.375 |
| OR<br>95 % CI | 1.124<br>(0.58-2.17) | 0.974<br>(0.56-1.6) | 1.07<br>(0.65-1.77) | 1.21<br>(0.69-2.1) | 1.2<br>(0.77-2.1) |

**Table 1:** TA vs. SA – risk factors.

| TA vs. SSA | HgA1c | Total Chol | HDL | LDL | Trig |
|---|---|---|---|---|---|
| p Value | 0.60 | 0.85 | 0.44 | 0.03 | 0.67 |
| OR<br>95 % CI | 1.12<br>(0.74-1.70) | 0.96<br>(0.67-1.34) | 0.86<br>(0.61-1.21) | 0.69<br>(0.49-0.97) | 1.03<br>(0.77-1.51) |

**Table 2:** TA vs SSA – risk factors.

| TA vs. TSA | HgA1c | Total Chol | HDL | LDL | Trig |
|---|---|---|---|---|---|
| p Value | 1.0 | 0.41 | 0.227 | 0.26 | 1.00 |
| OR<br>95 % CI | 0.937<br>(0.40-2.17) | 0.858<br>(0.41-1.76) | 1.54<br>(0.79-2.99) | 1.23<br>(0.78-3.87) | 0.99<br>(0.50-1.9) |

**Table 3:** TA vs. TSA – risk factors.

## Discussion

Emerging data has demonstrated that serrated polyps are not as benign as they were once believed to be, and these polyps are being increasingly recognized as lesions that progress to cancer. In light of compelling evidence that these polyps account for a rising percentage of CRCs globally, the detection and management of serrated adenomas poses a novel challenge to gastroenterologists and pathologists. At this time, limited data is available regarding the natural history of serrated polyps; and the current guidelines defer from the traditional adenoma surveillance protocol [6,19-21].

Compounding the complex, heterogeneous nature of CRC pathogenesis is the unique constellation of comorbidities found in the veteran population, frequently including type 2 diabetes mellitus, hyperlipidemia, hypertension, and obesity. Through this study, we were able to develop a large database of serrated

polyps detected in the James A. Haley VA population undergoing all-cause colonoscopy. Furthermore, a computerized algorithm was developed to collect data at any point from the VA electronic medical records system via which the database can be expanded on a yearly basis and further information on prevalence and temporal trends can be garnered.

As described previously, temporal trends in the detection of these lesions and variables that may affect their prevalence were identified. Consistent with global trends, our study too revealed increased reporting of serrated adenomas over the 10 year period. This may be in part due to increased identification of these lesions during endoscopic inspection by gastroenterologists, despite the challenges posed by their innate morphologic features and location. Identification of serrated polyps during endoscopy can be further improved by ensuring adequate bowel preps, particularly in the proximal colon, as well as increased training in their identification. Increased serrated adenoma reporting is likely also reflective of increased understanding of pathologic interpretation of these serrated lesion, and improved knowledge of terminology and training in differentiation of serrated polyp subtypes [1,6,22,23].

Advanced age, personal history of inflammatory bowel disease or adenomatous polyps, and family history of colorectal cancer or adenomatous polyps have long been established as non-modifiable risk factors for colorectal cancer. Colon cancer has also been considered to be heavily impacted by modifiable risk factors. Cigarette smoking and heavy alcohol use been implicated in the development of colorectal cancer. Dietary practices, particularly diets high in animal fats, obesity, and sedentary lifestyle with limited physical activity are also known to be risk factors for colorectal cancer in the general population [24-27]. This may be of particular importance in the veteran population with its significant comorbidity profile, frequently inclusive of type 2 diabetes mellitus, hyperlipidemia, hypertension, obesity, and often tobacco and/or alcohol abuse.

No significant correlation, though, was established in the veteran population at the James A. Haley VA from 2004 through 2014 between laboratory studies reflective of these disease processes and tubular adenomas. Furthermore, statistical significance was noted only with regard to LDL in comparing TA and SSA prevalence. With this in mind, it may be of benefit to assess further modifiable known risk factors for CRC in the context of serrated adenomas, particularly in the veteran population.

To our knowledge, this is the first analysis to date investigating the prevalence of and trends in serrated polyps in the veteran population undergoing all cause colonoscopy. There has been a limited understanding of the natural history of serrated polyps up to this point. In our veteran population with multiple significant medical comorbidities, increased identification and proper management of these high risk lesions is imperative.

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