Research Article

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Colorectal Cancer:Open Access
ISSN 2471-9943

2021
Vol.7 No.5:8308

Association between Serrated Polyps and the Risk of Synchronous Colorectal Cancer: A Community-Based Study

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Received Date:April 26, 2021;**Accepted Date**: September 17, 2021;**Published Date:**September 27, 2021

Citation: Saldana C(2021), Association between Serrated Polyps and the Risk of Synchronous Colorectal Cancer: A Community-Based Study , Colorec Cancer Vol: 7No:5.

Abstract

Objectives

Serrated polyps (SP), which include hyperplastic polyps (HP), sessile serrated adenomas/polyps (SSA/PS) and traditional serrated adenomas (TSA)), are considered premalignant lesions, but their association with synchronous colorectal cancer (sCRC) is not well known. Some features of SP are associated with increased risk of metachronous advanced colorrectal lesion, specially SP ≥ 10 mm or SP with dysplasia (SPwD), considering these lesions as high-risk serrated polyps (HRSP). The aim of this study was to evaluate the association of the different histological subtypes of SP and HRSP with sCRC.

Methods

A large, prospective crossectional multicenter, community-based study was conducted involving 8530 patients who underwent colonoscopy according to routine clinical practice between January 1 and December 31, 2011.

Results

Multivariate analysis associated the presence of TSA or SSA/PS with increased risk of sCRC (OR, 3.15; 95%CI: 1.42 - 6.99 and OR, 2.03; 95%CI, 1.27 - 3.24 respectively). According to the location of sCRC, the presence of TSA or SSA/PS was associated only with the presence of proximal sCRC. The presence of at least one HRSP was associated with increased risk of sCRC (OR 2.81, 95%CI 1.68 - 4.71; p<0.001), specially with proximal **location** (OR 3.72, 95%CI 1.91 – 7.23; p<0.001). We also found that the presence of at least one proximal SP or >2 SSA/PS were associated with sCRC (OR 2.12, 95%CI 1.47 - 3.06; p <0.001 and OR 4.34, 95%CI 1.14 – 13.14; p=0.01 respectively).

Conclusion:

The presence of TSA, SSA/PS, HRSP, proximal SP as well as multiple SSA/PS was associated with increased risk of sCRC, particularly with proximal location of sCRC and therefore, these features of SP should be considered as a marker of risk of sCRC.

KEY WORDS: Colorrectal cancer, Serrated polyp, High risk serrated polyps, Sessile serrated adenomas, Traditional serrated adenomas

Introduction

Colorectal cancer (CRC) is one of the most common cancers and the second leading cause of death related to cancer in the United States and Europe. 1 The advances made in recent decades in the detection and the molecular and genetic study of both preneoplastic lesions and CRC have led us to consider the CRC as a heterogeneous disease, regarding pathogenesis and clinical behavior. Currently, the existence of three colorectal neoplasia pathways are accepted: chromosomal instability; microsatellite instability and serrated neoplasia pathway (SNP). 2-4 Serrated pathway is thought to account for up to 15%- 30% of CRC.3-5 Historically, it was considered that serrated polyps (SP) did not have neoplastic potential. Nowadays, serrated polyps are considered precursor lesions that can progress to CRC through the serrated neoplasia pathway.

The classification of the World Health Organization (WHO) divides serrated polyps in three histological subtypes: Hyperplastic Polyps (HP), Sessil Serrated Polyps (SSA/PS) (with or without dysplasia) and Traditional Serrated Adenomas (TSA).6

Knowledge of SNP has important clinical implications in the management of CRC. However, most of the currently available scientific evidence of the natural history and malignant potential of SP, has derived from studies that do not distinguish serrated histological subtypes.

Not all SP will progress to CRC and currently we cannot discriminate what polyps will do. Different authors and scientific

societies highlight the importance of SP as precursor lesions of CRC and advise conducting a more intensive follow-up endoscopy in patients with large SP (size ≥ 10 mm) or SP with dysplasia, considering these lesions as high-risk serrated polyps (HRSP).

In addition, some authors also recommend this same follow-up endoscopy in patients who have had multiple (more than two) SSA/PS. 7-11

Several studies have described the association between the presence of SP and presence of synchronous colorectal cancer (sCRC)12-17and synchronous advanced colorectal neoplasia (sACN).18-25 In these studies, some features of SP have been associated with an increased risk of sCRC, among which are size and location.

Large serrated polyps (size ≥ 10 mm) 13,17and proximal SP14 have been linked with an increased risk of synchronous and metachronous colorectal cancer. The possible association between SP with dysplasia or multiple SSA/PS with sCRC has not been investigated.

In addition to date no prospective community-based study has described the association between different histological subtypes of serrated polyps according to the new WHO classification with sCRC.

For these reasons we conducted this community-based study in a population of patients undergoing colonoscopy according to routine clinical practice, aimed at evaluating the association between histological subtypes of SP and high-risk serrated polyps with the risk of synchronous colorectal cancer.

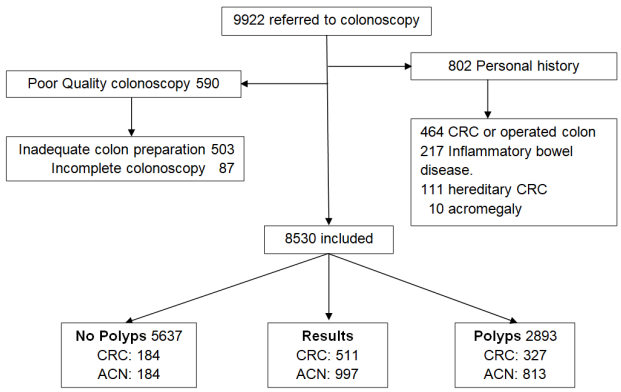
Methods

Study population

We included all consecutive patients who were referred to the endoscopy units of three hospitals (Hospital Complex of Navarra; Hospital Reina Sof a and Hospital García Orcoyen) in the network of public hospitals in the Autonomous Community of Navarra (Spain) for performing colonoscopy, according to routine clinical practice between January 1 2011 and December 31 2011.

Exclusion criteria were: age <15 years old, previous diagnosis of hereditary CRC syndrome with known genetic mutation or fulfilled the WHO criteria for serrated polyposis syndrome (SPS); patients with chronic inflammatory bowel disease or patients with acromegaly or ureterosigmoidostomy, patients with personal history of CRC or previous colon surgery, those with poor or inadequate colon preparation or with incomplete colonoscopy. In total, 9922 subjects were referred to endoscopy units to have a colonoscopy performed, out of which 8530 were finally included. (Figure 1)

Figure 1 Enrollment and outcomes of individuals included in the study



The reasons for the indication of the colonoscopy were screening of family history of CRC and surveillance polyps (37.7%), disturbed bowel habit (17.9%), rectal bleeding (15.6%), abdominal symptoms (13.1%), anemia (10.4%), constitutional syndrome (1.2%), positive fecal occult blood test (0.9%) and other reasons (3.2%).

We excluded 464 patients due to personal history of colorectal cancer and/or previously operated colon, 217 previously diagnosed with inflammatory bowel disease, 10 because of previous acromegaly diagnosis and 111 with the diagnosis of hereditary colorectal cancer (67 with Lynch syndrome, 10 with familial adenomatous polyposis, 2 with Peutz-Jeghers syndrome and 32 with Serrated Polyposis Syndrome (SPS)). We also excluded 590 patients due to poor quality colonoscopy, 503 with inadequate preparation of the colon and 87 with incomplete colonoscopy.

The included patients were assessed for clinic-pathologic features, including age, gender, colonoscopy findings and pathology findings. Clinical data were anonymized and dissociated from personal data following country data protection law. The study was approved by the Ethics Committee for Clinical Research of Navarra (Project 70/11), which waived the need for informed written consent.

Colonoscopy evaluation

Colonoscopies were performed using conventional white light (with and without high definition), under deep sedation with propofol and with a standard preparative regimen (polyethylene glycol electrolyte with ascorbic acid or citric acid). The procedures were performed by 28 experienced endoscopist gastroenterologists at the endoscopy units of the three participating hospitals.

The polyp characteristics collected at colonoscopy were: number, location, size and shape. The location of the lesions was determined during withdrawal of the endoscope and a proximal location was considered when endoscopic findings were located proximal to descending colon or if its location was not specified when located at an endoscope insertion of ≥ 60 cm. All polyps were excised (including tiny <5 mm ones).

Histopathology evaluations

Colonic polyps were interpreted by six pathologists with expertise in the gastrointestinal tract. According to the WHO classification, serrated polyps were diagnosed by the presence of a saw-toothed appearance of the glands and were classified as HP; SSA/PS with or without dysplasia, and TSA. Following these recommendations for diagnostic SSA/PS, we used the presence of at least two irregular dilated crypts, including dilatation of the base of the crypts. Cytological dysplasia among SSA/PS and TSA was classified according to the Vienna criteria. 27.

High risk serrated polyps was defined by the presence of size ≥ 1 cm or dysplasia.

Colorectal cancer was defined according to the TNM classification28 which includes all invasive colorectal cancer and "carcinoma in situ" or intramucosal. Advanced adenoma (AA) was defined by the presence of at least one of the following features: adenoma ≥ 1 cm; adenoma with villous component or high-grade dysplasia. Adenomas that did not meet these criteria were considered not advanced adenomas (NAA). Advanced Colorectal Neoplasia (ACN) was defined as the presence of AA or CRC.

Statistical analysis

Patients' characteristics and health outcomes are summarized using frequencies for categorical variables, and mean and standard deviation (SD) for the quantitative ones. The association between categorical variables was assessed using the $\chi 2$ test and univariate and multivariate logistic models, by estimating the odds ratio (OR) and its confidence interval 95% (95% CI). For multivariate logistic regression analyses, we used age, gender and number of non advanced adenoma. In all cases, the values of $p < 0.05$ were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics 21.0 software (IBM Corporation, USA).

Results

The characteristics of individuals finally included are described in Table 1. Of the 8530 subjects enrolled, 4230 (49.6%) were male and the average age of the study population was 58.7 (SD: 14.92) years old.

The prevalence of the different polyp subtypes is summarized in Table 1. Colorectal polyps were found in 33.9% of subjects. Serrated polyps were found in 15.4%, including 14.2% of patients with HP, 2.1% with SSA/PS and 0.5% with TSA. High-risk SP was found in 1.4% of patients.

CRC and ACN were identified in 6% and 11.7% respectively and 20 patients presented 2 or more colorectal cancer simultaneously. Furthermore15 patients (0.18%) meet the diagnostic criteria for SPS. 6

Table 1: Characteristics of Study Population

	Patients (%) N = 8530	**Polyps (%) N = 8753**
Sex: Male	4230 (49.6%)	
Mean age (standard deviation)	58.7 (14.9)	
Colorectal Polyps	2893 (33.9%)	8753 (100%)
Colorectal Adenoma	2259 (26.5%)	5349 (61.1%)
NAA	1963 (23%)	4229 (48.3%)
AA	734 (8.56%)	1120 (12.8%)
SP	1313 (15.4%)	3385 (38.5%)
HP	1211 (14.2%)	3008 (34.4%)
SSA/PS	183 (2.1%)	325 (3.7%)
SSA/PS without dysplasia	167 (1.95%)	308 (3.5%)
SSA/PS with dysplasia	16 (0.19%)	17 (0.2%)
TSA	40 (0.5%)	52 (0.6%)
High-risk SP	117 (1,4%)	141 (1.6%)
Large SP	85 (1%)	124 (1,4%)
SP with dysplasia	56 (0,7%)	69 (0,8%)
Proximal SP	303 (3,6%)	539 (6,16%)
Multiple SSA/PS	23 (0,3%)	139 (1,6%)
SPS	15 (0.18%)	
CRC	511 (6%)	
Proximal CRC	199 (2.3%)	
Distal CRC	332 (3.9%)	
ANC	997 (11.7%)	
Proximal ANC	437 (5.1%)	
Distal ACN	685 (8%)	

NAA: Non Advanced Adenoma; AA: Advanced Adenoma; SP: Serrated Polyps; HP: Hyperplastic Polyps; SSA/PS: Sessile Serrated Adenoma/Polyp; TSA: Traditional Serrated Adenoma; SPS: Serrated Polyposis Syndrome; CRC: Colorectal Cancer; ACN: Advanced Colorectal Neoplasia

Association of histological subtypes of SP with sCRC and sACN

The analysis of associations between the presence of the different histological subtypes of serrated polyps and sCRC is shown in Table 2. The presence of at least one SP was associated with an increased risk of sCRC (OR, 1.60 95%CI 1.28 – 2.02; $p<0.001$). All analyzed risk factors (sex, age, NAA number, histological subtypes of SP) turned out to be significantly associated with the presence of sCRC in the univariate and multivariate analysis, except for the presence of HP in the multivariate analysis. Detection of TSA or SSA/PS was associated with the presence of proximal sCRC (OR 4.83, 95%CI 1.88 - 12.4; p=0.001 and OR 2.73, 95%CI 1.46 – 5.09; p=0.002, respectively).

Table 2: Multivariate analysis of the association between the presence of different histological subtypes of SP or HRSP and the presence of sCRC according to location.

	CRC								
Type of Polyp (n)	n	Total		n	Proximal	n	Distal		
	511	OR (CI 95 %)	p-value	199	OR (CI 95 %)	p-value	332	OR (CI 95 %)	p-value
Histological subtypes of SP									
SP (1313)	118	1.60 (1.28 – 2.02)	<0.001	53	1.94 (1.38 – 2.72)	<0.001	73	1.44 (1.1 – 1.9)	0.01
HP (1211)	97	1.25 (0.97 - 1.6)	0.079	40	1.25 (0.85 - 1.84)	0.25	62	1.23 (0.91 - 1.66)	0.17
SSA/PS (183)	24	2.03 (1.27 - 3.24)	0.003	13	2.73 (1.46 - 5.09)	0.002	13	1.58 (0.87 - 2.88)	0.134
TSA (40)	9	3.15 (1.42 - 6.99)	0.005	6	4.83 (1.88 - 12.4)	0.001	4	1.88 (0.65 - 5.5)	0.247
Features of SP associated with increased risk of CRC									
HRSP (117)	20	2.81 (1.68 - 4.71)	<0.001	11	3.72 (1.91 - 7.23)	<0.001	11	2.16 (1.13 - 4.14)	0.019
Large SP (85)	12	2.34 (1.23 - 4.46)	0.01	8	4.00 (1.85 - 8.68)	<0.001	6	1.65 (0.70 - 3.89)	0.25
SPwD (56)	12	3.28 (1.66 - 6.48)	0.001	7	4.40 (1.89 - 10.2)	0.001	7	2.68 (1.18 - 6.12)	0.019
Proximal SP (303)	40	2.12 (1.47 - 3.06)	<0.001	24	3.37 (2.11 - 5.38)	<0.001	20	1.47 (0.91 - 2.38)	0.119
Multiple SSA/P	4	4.34 (1.14 - 13.1)	0.01	1	2.65 (0.35 - 20.1)	0.346	3	4.55 (1.32 - 15.7)	0.016
S (23)									

* Adjusted Odds ratio by age, gender and number of non advanced adenoma. n: number of patients; CRC: Colorectal Cancer; SP: Serrated Polyps; HP: Hyperplastic Polyps; SSA/PS: Sessile Serrated Adenoma/Polyp; TSA: Traditional Serrated Adenoma; HRSP: High-Risk Serrated Polyps; SPwD: Serrated Polyp with dysplasia

Afterwards, we conducted a sub-analysis of associations between the location of the different histological subtypes of SP and location of sCRC, whose results are shown in Table 3. We found that the presence of proximal TSA and proximal SSA/PS were associated with the presence of sCRC (OR 4.05, 95%CI 1.24 - 13.26; p=0.021 and OR 2.2, 95%CI 1.22 – 3.97; p=0.009, respectively), particularly with the proximal location of sCRC (OR 7.04, 95%CI 1.87 – 26.5; p=0.004 and OR 4.64, 95%CI 2.3 – 9.36; p<0.001, respectively).

We also analyzed the association of the presence of PS and sACN with similarly results to the previously observed for sCRC that are shown on the supplementary material.

Association of HRSP with sCRC and sACN

The analysis of the association between HRSP and sCRC is described in Table 2. Multivariate analysis showed an increased risk of CRCs in patients with at least one HRSP compared with patients without HRSP (OR 2.81, 95%CI 1.68 - 4.71; p<0.001). Analysis of this association according to sCRC location showed that HRSP was associated with proximal and distal location, although this association was stronger for the proximal location (OR 3.72, 95%CI 1.91 – 7.23; p<0.001 and OR 2.16, 95%CI 1.13 - 4.14; p=0.019 respectively). We conducted a sub-analysis of this association between the different subtypes of HRSP (Large SP and SPwD) with sCRC. We showed an increased risk of sCRC for both subtypes of HRSP, being stronger in those patients with PSwD (OR 3.28, 95%CI 1.66 – 6.48; p=0.001 vs OR 2.34, 95%CI 1.23 - 4.46; p=0.01).

The subanalysis or the association of the presence of HRSP and sACN is presented on supplementary material.

Association of proximal SP and multiple SSA/PS with sCRC and sACN

The analysis of associations between the presence of proximal SP and multiple SSA/PS with sCRC is shown in the Table 2. In the multivariate analysis, the presence of at least one proximal SP was associated with sCRC (OR 2.12, 95%CI 1.47 - 3.06; p <0.001), especially with the proximal location of cancer (OR 3.37, 95%CI 2.11 – 5.38; p <0.001). Similarly, the multivariate analysis showed an increased risk of CRCs in patients with multiple SSA/PS (OR 4.34, 95%CI 1.14 – 13.14; p=0.01), especially with the distal location of sCRC (OR 4.55, 95%CI 1.32 –15.7; p=0.016).

The association between the presence of proximal SP and multiple SSA/PS with sACN is shown on supplementary material.

Discussion

In this large, prospective crossectional multicenter, community-based study conducted in a population of patients undergoing colonoscopy according to routine clinical practice, we found that the presence of TSA, SSA/PS, HRSP, proximal SP as well as multiple SSA/PS was associated with increased risk of sCRC. To our knowledge, this is the first population-based study that has shown the association between the presence of different histological subtypes of SP according to the WHO classification and the presence of sCRC. A study that included only patients with SP recruited from pathology archives of one hospital, found that the presence of large SP and the presence of SSA/PS or TSA compared with HP's presence were associated with sCRC17. Ipsjeert et al published a study with a cross-sectional design using data retrieved from a prospectively collected database of general colonoscopy practice, observed an association between SSA/PS and the presence of sACN, especially in patients with high-risk SSA/PS 29.

In our study, the presence of SSA/PS and TSA was strongly correlated with proximal sCRC. And what is more, proximal location of SSA/PS or TSA was correlated with sCRC. These results suggest that the presence of SSA/PS or TSA may serve as a marker of sCRC, especially of proximal sCRC. Accumulating histological and molecular evidence suggests that both SSA/PS and TSA are more advanced lesions in the serrated neoplasia pathway.2-4,9 Some molecular alteration such as mutant BRAF are more prevalent on serrated pathway 2,9,30-36 . In our study precursor lesions (SSA/PS or TSA), which have a higher risk of harboring the molecular alterations described especially in its proximal location, was closely associated with the presence of proximal sCRC. One potential explanation of this association could be related to the progressive accumulation of genetic and epigenetic changes in normal colonic mucosa which results in a polyp-to-cancer progression sequence and promotes the development of SP and concomitant CRC from the same field of cancerization.37 Consequently, we consider it of interest to conduct further studies in order to find out if these lesions which coincide on location and time also share the same molecular profile.

Another finding of our study was the high prevalence (22.5%) of sCRC in patients with at least one TSA. Similar to that recently published by Zhu et al17 which included 56 patients with TSA, out of which 11 (19.6%) had sCRC. Furthermore, although TSA in our study had a predominantly distal location (62.5%) in line with the previously published, the presence of TSA was correlated with the presence of sCRC, especially proximal location. 38

Another remarkable finding of our study was to show the association between the presence of HSRP with sCRC, that was maintained for both sCRC locations. Several studies have described the association between the presence of large SP and sCRC with similar results as our study. 12-17 Regarding the presence of SPwD, although it was not very frequent (0.18%), it nevertheless presented a strong association with the presence of sCRC (OR 3.28 (1.66 - 6.48)) in both locations SPwD are considered very advanced preneoplastic lesions in the serrated pathway of carcinogenesis. This strong association supports the consideration of SPwD as a risk marker of sCRC. 3,4,9

In the same way, we also found an increased risk of sCRC in patients with proximal SP or with multiple SSA/PS. These features have been associated with an increased risk for development of metachronous CRC/ANC 18-25 y sANC, 14,15, 19-22 . The association with sCRC has not been described. We found association between proximal SP and sCRC (OR 2.12, 95%CI 1.47 - 3.06; p <0.001), especially with the proximal location (OR 3.37, 95%CI 2.11 – 5.38; p <0.001). Similarly, our study notably describes an increased risk of sCRC in patients with multiple SSA/PS (OR 4.34, 95%CI 1.14 – 13.14; p=0.01). Four of 23 patients with multiple SSA/PS (17%) presented sCRC. Multiplicity of SP is associated with increased risk of metachronous CRC as shown on SPS. We consider that multiplicity of SSA/PS should be considered a risk factor of sCRC.

The major strengths of this study are the large size and its community-based design. The study size provided power to reliably estimate the association between sCRC and the different features of SP. The community-based design facilitates the extrapolation of the results to clinical practice.

Our results performed by standard endoscopists, with standard endoscopes and usual indications of colonoscopy, were similar to those previously described in the literature. 39 We also describe for the first time, the prevalence of HRSP (1.4%) and multiple SSA/PS (0.3%) on a clinical practice population colonoscopy.

The prevalence of SP was 15.4% patients (serrated polyp detection rate) similar to those described in the literature 19, 21-24,29,40-43 ranging between 5.4% and 27.2%. We identified at least one SSA/PS in 2.1% and at least one TSA in 0.5%. These data are similar to the prevalence reported in previous studies that ranged between 0,6% and 14%12,23,29, 41,44-51 and between 0.004% and 0.5%12,20,23,24,29,41,50-52 respectivily. Adenoma detection rate in our series was 26.5% (32.4% for male and 20.7% for female patients). This figure falls within the margins recently proposed by the ASGE as an indicator of quality of colonoscopy in asymptomatic, average-risk individuals.39

Our prevalence data of serrated polyps and their association with sACN consistent with data recently published by Gao et al in their meta-analysis25.

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