

ORIGINAL ARTICLE

Colorectal cancer risk factors in patients with serrated polyposis syndrome: a large multicentre study

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Background

- Conventional adenoma
 - Precursor lesion of the majority of CRCs
- **Serrated pathway**
 - Alternate mechanism of colorectal carcinogenesis
 - Up to 30% of all CRCs
 - Serrated polyps
 - ***Sessile serrated adenomas/polyps (SSA/Ps)***
 - Currently recognized as CRC precursors

Serrated polyp

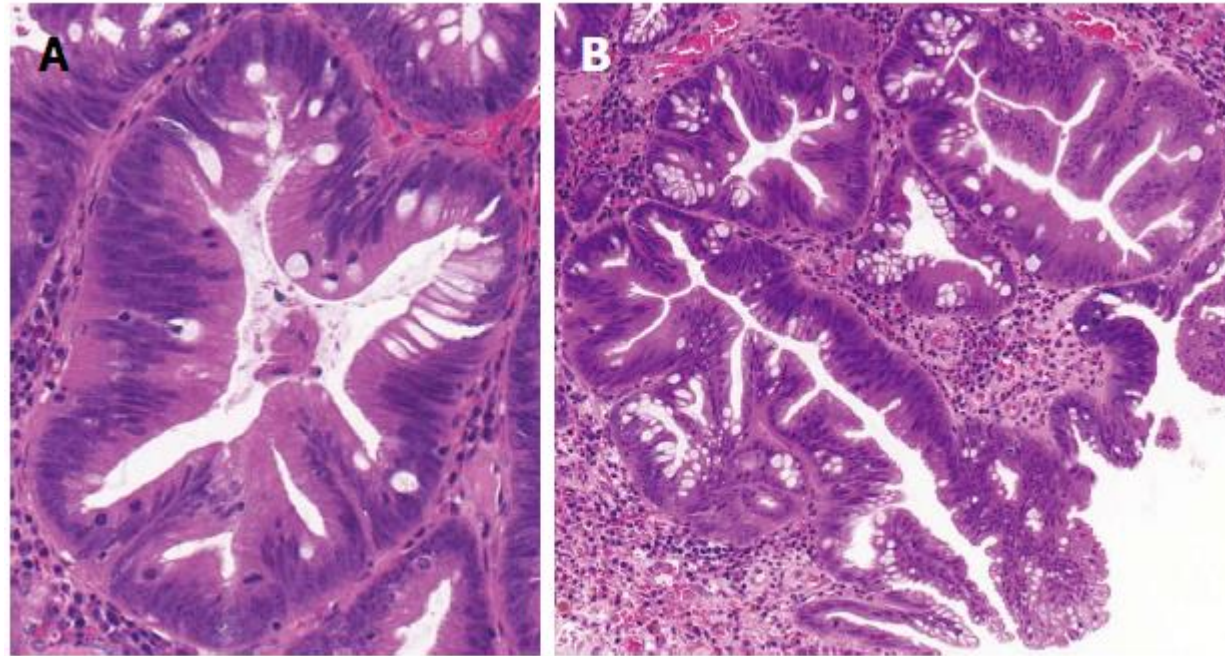


Figure 1 Microscopic features of serrated polyps. A: On cross section serrated crypt shows a stellate or starlike appearance; B: In longitudinal section a characteristic serrated or saw-toothed appearance can be seen.

Serrated polyp



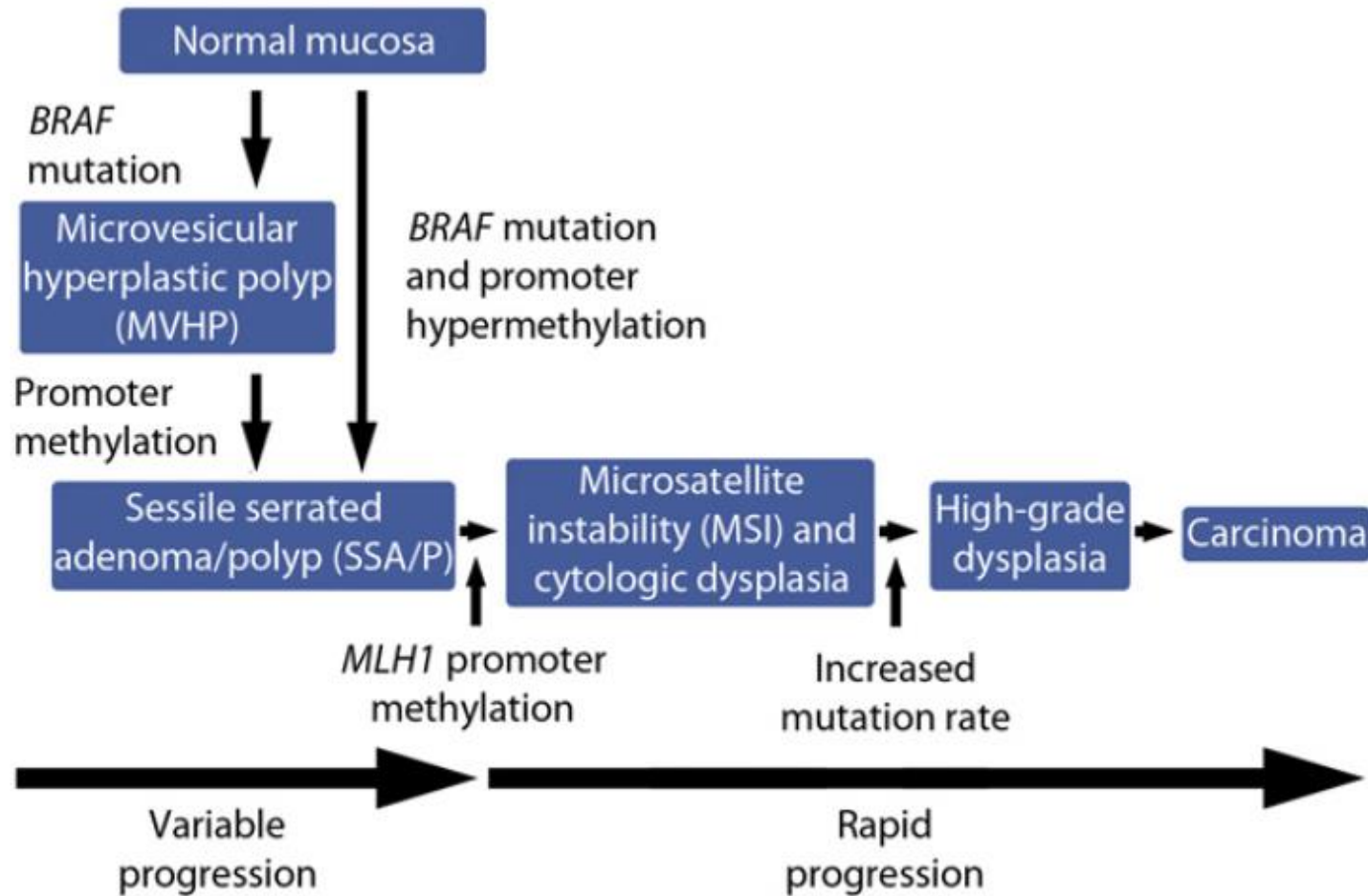
Figure 6. Typical serrated lesions in the proximal colon. (a–d) A sessile serrated adenoma/polyp in the cecum. Note the adherent mucus (a) in white light and (b) with narrow-band imaging. After removal of the cap by washing, the characteristic surface features are seen in (c) white light and (d) narrow-band imaging, including indistinct edges, color similar to the surrounding normal mucosa, and a paucity of blood vessels. (e–h) A flat sessile serrated adenoma/polyp in the transverse colon, with the mucus cap in (e) white light and (f) narrow-band imaging and with the cap washed off in (g) white light and (h) narrow-band imaging. Note the subtlety of the lesion after the cap is washed off.

Serrated polyp

TABLE 1. Serrated polyp classification scheme

Hyperplastic polyp	Microvesicular (MVHP) Goblet cell rich (GCHP) Mucin poor (MCHP)
Sessile serrated adenoma/polyp (SSA/P)	Without cytological dysplasia With cytological dysplasia
Traditional serrated adenoma (TSA)	Without conventional dysplasia With conventional dysplasia
Filiform serrated adenoma	
Serrated polyp, unclassifiable	

Serrated pathway



Serrated polyposis syndrome (SPS)

TABLE 5. WHO classification criteria for serrated polyposis²

I At least 5 serrated polyps proximal to the sigmoid colon, at least 2 polyps >10 mm, or

II Any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis, or

III >20 serrated polyps of any size distributed throughout the colon

WHO, World Health Organization.

Rex et al. American Journal of Gastroenterology 2012

- **CRC risk in SPS**

- Patients with SPS and their relatives are at increased risk of CRC (7%–70%) (Small retrospective studies and selected bias)
- CRC can develop under colonoscopy surveillance
 - Annual endoscopic surveillance for all patients of SPS
 - Clinicopathological predictors of CRC development remain poorly understood

Aims of the study

- Current intensive surveillance for patients with SPS
 - Excessive
 - Optimized based on personalized CRC risk factors
- Describe CRC risk in a large cohort of patients with SPS
- Identify specific predictive factors for CRC development.

PATIENTS AND METHODS

- **Study population**

- From March 2013 to September 2014
- 18 Spanish centers
- Retrospectively recruited patients who fulfilled the SPS diagnostic criteria
- Clinical data was analyzed from 1993 to 2014

- **Exclusion**

- Hereditary CRC syndromes
- IBD

- **Endoscopic records**

- Polyp parameters ; number, size and location
- Polyp location definition
 - Proximal colon
 - Proximal to sigmoid or proximal to splenic flexure

- **Histopathological records**

- Hyperplastic polyp(HP), SSA/P, and Traditional serrated polyp(TSA)
- Cytological dysplasia
 - Low-grade and high-grade dysplasia
 - Intramucosal carcinoma and carcinoma in situ ; High grade dysplasia
- Advanced adenoma
 - ≥ 10 mm in diameters or with villous structure or with high grade dysplasia

Clinical features of patients with SPS

Table 1 Baseline characteristics of patients with SPS (n=296)

Demographic and clinical features

Age at diagnosis SPS (years), mean±SD	57.2±9.9
Female, n (%)	130 (43.9%)
BMI*, mean±SD	27.5±4.6
Overweight/obesity (BMI ≥25), n (%)	146 (69.5%)
Smoking history, n (%)†	207 (74.5%)
First-degree relative with CRC, n (%)	87 (29.4%)
First-degree relative with SPS, n (%)	13 (4.4%)
WHO criteria‡, n (%)	
I	79 (26.7%)
III	134 (45.3%)
I+III	83 (28%)
Follow-up since SPS diagnosis (months), median (IQR)	45 (26–79.7)
Number of total colonoscopies, median (IQR)	3 (2–4)

Cumulative number of serrated polyps (per patient)

Serrated polyps, median (IQR)	26 (18.2–40.7)
Location, median (IQR)	
Proximal to splenic flexure	7 (4–14)
Descending colon	3 (1–6)
Rectosigmoid	11 (5–23.5)
Size, median (IQR)	
Serrated polyps ≥10 mm	2 (0–4)
Histology, median (IQR)	
Serrated polyp subtypes	
Hyperplastic polyp	17.5 (6–30.2)
Sessile serrated adenoma/polyp	3 (0–9)
Traditional serrated adenoma	0 (0–0)
Serrated polyp with dysplasia§	
Any dysplasia	0 (0–1)
LGD	0 (0–1)
HGD	0 (0–1)
Adenoma features	
Patients with ≥1 adenoma, n (%)	238 (80.4%)
Patients with ≥1 advanced adenoma¶, n (%)	131 (44.2%)
Number of adenomas (per patient), median (IQR)	3 (1–6)
Number of advanced adenomas¶ (per patient), median (IQR)	0 (0–1)

Polyp features

Table 2 Characteristic of serrated polyps according to histological subtype

	Hyperplastic polyps	Sessile serrated adenomas/polyps	Traditional serrated adenomas
Total number, n (%)	6458 (72.5%)	2398 (27%)	47 (0.5%)
Size ≥ 10 mm, n (%)	359 (5.4%)	647 (28.7%)	27 (57.4%)
Location, n (%)			
▶ Proximal to splenic flexure	1520 (23.5%)	1330 (55.4%)	26 (55%)
▶ Descending colon	902 (14%)	446 (18.6%)	10 (21.2%)
▶ Rectosigmoid	4036 (62.5%)	622 (25.9%)	11 (23.8%)
Cytological dysplasia, n (%)			
▶ Any dysplasia		469 (19.5%)	15 (31.5%)
▶ Low-grade dysplasia		438 (18.2%)	12 (25.5%)
▶ High-grade dysplasia		31 (1.4%)	3 (6.4%)

Prevalence of CRC in patients with SPS

Table 3 Colorectal features of CRCs diagnosed in patients with SPS

N=47 (15%)	
Age at CRC diagnosis (years), mean±SD	53.9±12.8
WHO criteria*, n (%)	
▶ Criterion I	14 (29.7%)
▶ Criterion III	19 (40.6%)
▶ Criteria I+III	14 (29.7%)
Tumour location, n (%)	
▶ Caecum	3 (6.4%)
▶ Ascending colon	6 (12.8%)
▶ Hepatic flexure	3 (6.4%)
▶ Transverse colon	10 (21.3%)
▶ Descending colon	1 (2.1%)
▶ Sigmoid colon	18 (38.3%)
▶ Rectum	6 (12.8%)
TNM tumour stage, n (%)	
▶ I	24 (51%)
▶ II	12 (25.5%)
▶ III	6 (12.8%)
▶ IV	5 (10.7%)
Time at CRC diagnosis, n (%)	
▶ Before SPS diagnosis	8 (17%)
▶ At the time of SPS diagnosis	35 (74.5%)
▶ During SPS surveillance	4 (8.5%)

*WHO criteria: (I) patients who fulfil criterion I only; (III) patients who fulfil criterion III only; (I+III): patients who fulfil both I and III criteria.
CRC, colorectal cancer; SPS, serrated polyposis syndrome; TNM, tumour, node, metastases.

- Of the 296 patients included study
→ 47(15.8%) developed CRC

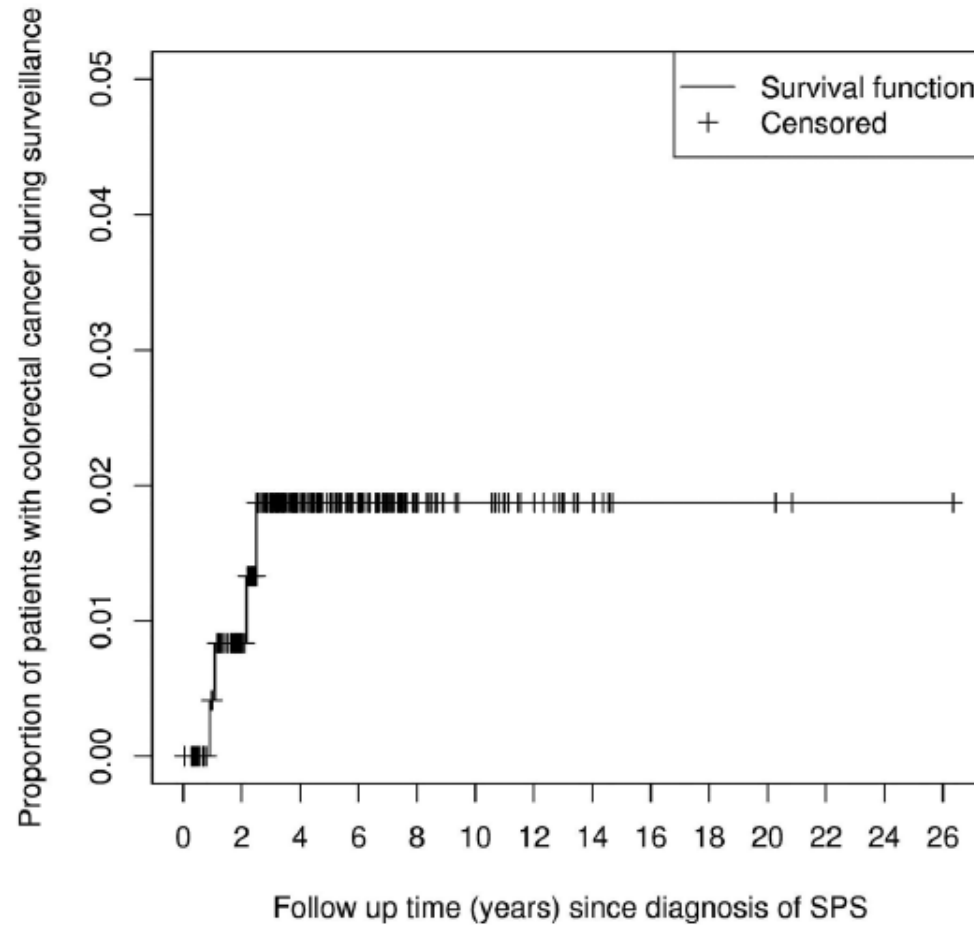


Figure 1 Proportion of patients with colorectal cancer during surveillance and follow-up time (years) since diagnosis of serrated polyposis syndrome (SPS).

During surveillance

→ 4 (8.5%) individuals developed CRC

The cumulative CRC risk for patients with SPS with no prior history of CRC

→ 1.9% with a mean follow up of 4.9 years

Table 4 Characteristics of patients with SPS with CRC diagnosed during surveillance

	Patient 1	Patient 2	Patient 3	Patient 4
Patient characteristics				
Age at SPS diagnosis, years	64	53	64	60
Age at CRC diagnosis, years	68	54	66	62
Gender	Male	Female	Male	Female
Endoscopic characteristics				
WHO criteria for SPS diagnosis	III	I+III	I+III	I+III
Number of serrated polyps/proximal* serrated polyps ≥ 10 mm	26/0	42/2	60/20	36/2
Number of SSA/P/proximal* SSA/P	1/1	33/28	58/58	32/31
Serrated polyps with high-grade dysplasia	No	No	Yes	Yes
Number of adenomas/advanced adenomast	11/0	5/3	0/0	6/0
Number of surveillance colonoscopies (before CRC diagnosis)	3	2	2	7
Interval between previous surveillance colonoscopy and CRC diagnosis (months)	26	13	6	11
Indication for diagnostic colonoscopy	Surveillance	Surveillance	Surveillance	Surveillance
Tumour features				
Histology	Adenocarcinoma	MANEC	SSA/P+adenocarcinoma	Adenocarcinoma
Mucinous component	No	Yes	Yes	No
Lesion size (mm)	10	25	18	4
Location	Transverse colon	Transverse colon	Ascending colon	Sigmoid colon
Morphology‡	Ulcerated lesion	0-IIa+IIc	0-Is+IIa	0-IIa
Tumour staging (TNM)	I	IV	I	I

*Referred to the splenic flexure.

†Advanced adenoma: ≥ 10 mm in diameter or with villous structure or with high-grade dysplasia.

‡Based on the Paris classification.

CRC, colorectal cancer; MANEC, mixed adenoneuroendocrine carcinoma; SPS, serrated polyposis syndrome; SSA/P, sessile serrated adenoma/polyp; TNM, tumour, node, metastases.

Variables associated with CRC in patients with SPS

(Univariate analysis)

Table 5 Clinicopathological features associated with CRC in patients with SPS (univariate analysis)

Variable	CRC N=47 (15.8%)	No CRC N=249 (84.2%)	p value
Demographic and clinical features			
Age at SPS diagnosis: years, mean±SD	56.8±8.8	56.9±10.2	0.342
Female, n (%)	22 (46.8)	108 (43.4)	0.664
BMI*, mean±SD	27.1±5.1	27.7±4.5	0.425
Overweight/obesity (BMI ≥25), n (%)	22/39 (56.4)	124/171 (72.5)	0.051
Smoking history†, n (%)	30/45 (66.7)	177/233 (76)	0.193
First-degree relative with CRC, n (%)	9 (19)	78 (31)	0.097
First-degree relative with SPS, n (%)	1 (2)	12(4)	0.376
SPS WHO criteria‡, n (%)			
▶ Patients who fulfil criterion I	28 (59.6)	134 (46.2)	0.468
▶ Patients who fulfil criterion III	33 (70.2)	185 (74.3)	0.560
▶ Patients who fulfil criteria I and III	14 (29.8)	70 (28.1)	0.815
Follow-up time (months), median (IQR)	48 (24–79)	44 (26–80)	0.843
Number of colonoscopies, median (IQR)	3 (2–4)	3 (2–4)	0.315
Cumulative number of polyps (per patient), median (IQR)			
<i>Serrated polyps</i>			
Serrated polyps	26 (13–42)	26 (19–40)	0.326
Location			
▶ Proximal to splenic flexure	9 (4–16)	7 (4–13)	0.107
▶ Proximal to sigmoid colon	12 (5–28)	11 (6–19)	0.169
▶ Rectosigmoid	7 (4–21)	12 (5–24)	0.396
Size ≥10 mm	3 (0–6)	2 (0–4)	0.054
Specific subtype of serrated polyp			
▶ Sessile serrated adenoma/polyp	4 (1–14)	2 (0–8)	0.040
▶ Hyperplastic polyp	8 (0–24)	19 (8–33)	0.277
▶ Traditional serrated adenoma	0 (0–0)	0 (0–0)	0.516
Serrated polyps with dysplasia			
▶ Any dysplasia	0 (0–1)	0 (0–1)	0.496
▶ Low-grade dysplasia	0 (0–1)	0 (0–1)	0.961
▶ High-grade dysplasia	0 (0–0)	0 (0–0)	0.075
Combined features§			
▶ SSA/Ps proximal to splenic flexure	3 (0–11)	1 (0–4)	0.005
▶ SSA/P with high-grade dysplasia	0 (0–0)	0 (0–0)	0.041
▶ Proximal (to splenic flexure) SSA/P with high-grade dysplasia	0 (0–0)	0 (0–0)	0.016
Adenomas			
Number of adenomas	3 (1–6)	3 (1–6)	0.906
Number of advanced adenomas¶	1 (0–1)	0 (0–1)	0.910

Variables associated with CRC in patients with SPS (Multivariate analysis)

Table 6 Multivariate logistic regression of variables associated with colorectal cancer in patients with SPS

Variable	Adjusted OR	95% CI	Adjusted p value
Age at SPS diagnosis	1.02	0.98 to 1.05	0.256
Gender (female)	0.83	0.42 to 1.61	0.586
Number of SSA/Ps	0.97	0.91 to 1.02	0.267
Number of SSA/Ps with HGD	0.76	0.29 to 2.92	0.678
Number of SSA/Ps proximal to the splenic flexure (per polyp)	1.04	1.01 to 1.07	0.016
Number of proximal (to splenic flexure) SSA/Ps with HGD (per polyp)	2.12	1.01 to 4.50	0.049

Statistically significant results are represented in bold.

HGD, high-grade dysplasia; SPS, serrated polyposis syndrome; SSA/P, sessile serrated adenoma/polyp.

- The number of SSA/Ps proximal to the splenic flexure
 - The number of SSA/Ps with high grade dysplasia proximal to the splenic flexure
- Independently associated with CRC in patients with SPS

Variables associated with CRC in patients with SPS

Using the most meaningful cut-off, two independent CRC predictors

≥ 2 proximal SSA/Ps

≥ 1 proximal SSA/P with high grade dysplasia

Table 7 CRC risk groups in patients with SPS according to independent CRC risk factors

Variable	OR	95% CI	p value
No proximal SSA/P with HGD and ≤2 proximal SSA/Ps	1*	–	–
Any proximal SSA/P with HGD or >2 proximal SSA/Ps	1.98	1.02 to 3.81	0.04†
Any proximal SSA/P with HGD and >2 proximal SSA/Ps	4.27	1.30 to 14.03	0.01†
No proximal SSA/P with HGD and ≤2 proximal SSA/Ps	0.45	0.24 to 0.86	0.01‡

Proximal location refers to the splenic flexure.

*Reference category.

†Compared with the reference category.

‡Compared with patients fulfilling either of the two risk factors.

CRC, colorectal cancer; HGD, high-grade dysplasia; SPS, serrated polyposis syndrome; SSA/P, sessile serrated adenoma/polyp.

- Patients with no risk factors
- Patients with either of the two risk factors
- Patients with both risk factors
- Patients with SPS with no risk factors
 - 55% CRC risk reduction

Conclusion

- SPS is associated with an increased CRC risk (15.8%)
 - Although the magnitude of this risk is lower than previously published.
- Annual colonoscopy surveillance in experienced centers
 - Low risk of developing CRC (1.9% in 5 years).
- Specific polyp features
 - **SSA/P histology, proximal location and presence of high-grade dysplasia**
 - **Stratify the CRC risk of patients with SPS**
 - **Tailored surveillance according to the risk factors**
 - **Offer longer surveillance intervals (1–3 years) in low-risk patients**
- Both serrated and conventional pathways of carcinogenesis coexist
 - 50% of patients, tumors occurred in the rectosigmoid colon
- Future studies should focus on patients with SPS
 - Standardized treatment and surveillance protocols