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Long-Term Colorectal Cancer Incidence After Adenoma and Serrated Polyp Removal: Results From the Colonprev Trial

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ABSTRACT

Background: The risk of colorectal cancer (CRC) after serrated polyp resection remains unclear, and current surveillance recommendations rely on limited evidence. We evaluated CRC incidence in individuals with advanced serrated lesions (ASL) detected at baseline colonoscopy and compared risk according to the most advanced lesion identified.

Methods: Participants undergoing colonoscopy within the COLONPREV trial (n = 8989) were included in this post hoc analysis. Individuals were classified according to the most advanced baseline lesion: no lesion, non-advanced adenoma, advanced adenoma, or ASL. The primary outcome was incident CRC. Cumulative incidence and hazard ratios (HR) were estimated using Cox proportional hazard models.

Results: At baseline colonoscopy, serrated polyps were detected in 19.8% of participants, including ASL in 2.5%. Over a mean follow-up of 9.5 years, 44 CRC cases were diagnosed (cumulative incidence 0.49%; incidence rate 0.52 per 1000 person-years). The 10-year cumulative incidence was 0.27% in individuals without baseline lesions (n = 5496), 0.57% in those with non-advanced adenomas (n = 2091), 1.23% in advanced adenomas (n = 1218), and 1.09% in ASL (n = 184). In multivariable analysis, CRC risk was increased for non-advanced adenomas (HR 3.25, 95% CI 1.48–7.16), advanced adenomas (HR 9.77, 95%

The complete list of the COLONPREV Study Investigators is provided in Supporting Information S1.

CI 4.24–22.50), and ASL (HR 6.37, 95% CI 1.42–28.54). Surveillance colonoscopy was associated with lower CRC incidence (HR 0.46, 95% CI 0.22–0.95 for one colonoscopy; HR 0.09, 95% CI 0.02–0.40 for ≥ 2 colonoscopies).

Conclusion: In this screening cohort, ASL were associated with increased CRC risk in the range of advanced adenomas. These findings provide risk estimates relevant to post-polypectomy management.

Trial registration number: NCT00906997.

1 | Introduction

Colorectal cancer (CRC) remains a leading cause of cancer-related morbidity and mortality worldwide despite substantial advances in screening and prevention strategies. Colonoscopy and faecal immunochemical testing (FIT) are the most widely implemented screening tools, and both have demonstrated effectiveness in reducing CRC incidence and mortality through the detection and removal of precursor lesions [1, 2]. Traditionally, adenomas have been regarded as the principal precursors of CRC, and surveillance guidelines have largely been based on adenoma characteristics such as size, histology, and multiplicity [1, 3–5].

In recent years, however, increasing recognition has been given to the serrated neoplasia pathway, which is thought to account for up to 20%–30% of all CRCs [6]. Sessile serrated lesions (SSL) and traditional serrated adenomas (TSA), in particular, have been implicated as potential precursors of CRC, especially in the proximal colon and those showing microsatellite instability. Our own results have shown that serrated polyps (SPs), particularly those larger than 10 mm, are associated with the detection of synchronous advanced neoplasia [7]. However, the available evidence regarding the natural history of SPs after resection, the risk of developing metachronous CRC, and the type of follow-up required remain limited. A recent meta-analysis demonstrated that the risk of CRC detection is increased in individuals who have undergone resection of an advanced serrated lesion (ASL), defined as ≥ 10 mm or with dysplasia [8]. Nevertheless, this meta-analysis is mainly based on case–control or cohort studies. To date, only one clinical trial with long-term follow-up (10 years) but with a limited sample size has provided data on this issue [9].

Current surveillance recommendations vary across international guidelines. The US Multi-Society Task Force and the European Society of Gastrointestinal Endoscopy propose relatively intensive surveillance for high-risk SPs (≥ 10 mm, with dysplasia, or proximal location), whereas smaller, non-dysplastic SPs are often considered lower risk [4, 10]. Nevertheless, such recommendations are based on limited evidence, and the long-term risk of CRC in individuals with SPs detected in population-based screening programmes remains to be clarified.

The COLONPREV trial, a large pragmatic study comparing one-time colonoscopy with biennial FIT in average-risk Spanish adults [11, 12], offers a unique opportunity to examine the long-term outcomes associated with SPs detected in a screening context. Thus, we aimed to evaluate the 10-year incidence of CRC among participants with ASL at baseline colonoscopy and compare them with those without such lesions.

2 | Patient and Methods

The current post hoc analysis was performed within the COLONPREV study (ClinicalTrials.gov NCT00906997), a pragmatic, non-inferiority, randomised controlled trial carried out in 8 Spanish regions with the participation of 15 tertiary hospitals. COLONPREV was designed to assess the effectiveness of one-time colonoscopy and biennial FIT to reduce CRC-related mortality at 10 years [11, 12]. The study was approved by the ethics committee at each hospital, and all subjects provided written informed consent.

In this post hoc analysis, we included all subjects who underwent a colonoscopy within the trial. We excluded subjects who underwent procedures other than colonoscopy, had incomplete data, or presented with polyposis, CRC, or inflammatory bowel disease at baseline colonoscopy.

2.1 | Colonoscopy Findings

All colonoscopies were performed by experienced endoscopists (individual experience > 200 colonoscopies per year) and findings were documented in a standardized report form. Bowel cleansing and sedation were performed according to the standardized COLONPREV protocol, as previously described [11–13]; specifically, in accordance with the clinical practice guidelines on quality of colonoscopy in CRC screening [13] Colonoscopy was considered complete if caecal intubation was achieved and visualization of at least 90% of the colonic mucosa was accomplished, as assessed by the Aronchick scale [11–13]. Macroscopic appearances of polyps were registered in the database. In individuals requiring more than one procedure to achieve complete removal of detected lesions or full mucosal assessment, all findings were grouped as a single baseline colonoscopy. Follow-up time was calculated beginning at the date of the final procedure included within this baseline assessment.

2.2 | Pathological Findings

As previously described [7], histological studies were conducted on all polyps taken by polypectomy by board-certified pathologists at each participating hospital. Adenomas ≥ 10 mm in size or with villous architecture, high-grade dysplasia, or intramucosal carcinoma (pTis) were classified as advanced adenomas. In contrast, adenomas < 10 mm in size without villous architecture or high-grade dysplasia were classified as non-advanced adenomas. SPs included SSL, TSA and hyperplastic polyps (HP) [14]. ASL were defined as those SPs ≥ 10 mm in diameter or with dysplasia [8, 15]. Proximal SPs were defined as any lesion proximal to the descending colon [8]. For this analysis, patients were classified according to the most advanced SPs identified at baseline colonoscopy. Accordingly, subjects were

Key Summary

- Summarise the established knowledge on this subject
  - Serrated lesions contribute substantially to colorectal carcinogenesis.
  - Long-term colorectal cancer (CRC) risk after resection of advanced serrated lesions (ASL) remains insufficiently defined.
  - Surveillance recommendations are largely extrapolated from adenoma cohorts.
- What are the significant and/or new findings of this study?
  - In this population-based screening cohort with 10-year follow-up, CRC incidence after ASL resection (1.09%) was comparable to that observed after advanced adenomas (1.23%).
  - Multivariable analyses confirmed increased CRC risk of ASL and adenomas, whereas endoscopic surveillance was associated with lower CRC incidence.

categorised as having ASL, non-advanced SPs, or a normal colonoscopy (no SPs).

2.3 | Surveillance Recommendations

Surveillance recommendations after colorectal lesion resection were based on the American and Spanish guidelines [5, 16]. In subjects meeting high-risk criteria (i.e., at least one advanced adenoma or more than two adenomas of any characteristic), the first surveillance colonoscopy was scheduled at 3 years. Conversely, in those meeting low-risk criteria (i.e., one to two non-advanced adenomas), the first surveillance colonoscopy was scheduled at 5 years. Subsequent colonoscopies were scheduled according to the lesions detected during follow-up. In contrast, no specific surveillance recommendation was established on the basis of the SPs detected. For this analysis, we recorded all colonoscopies performed during follow-up, irrespective of adherence to guideline recommendations, together with their indications. Colonoscopies leading to CRC detection were excluded unless undertaken as part of endoscopic surveillance.

2.4 | Outcomes

The primary outcome was incident CRC, defined as any histologically confirmed adenocarcinoma diagnosed after completion of the baseline evaluation. All CRCs detected within 6 months of baseline colonoscopy were considered prevalent cases. Follow-up started at the date of baseline colonoscopy and ended at the earliest of CRC diagnosis, last available contact, or study censoring date. The CRC incidence was expressed as cumulative incidence and incidence rate (number of cases per 1000 patient-years).

Among participants in the study, any colorectal examination for screening, surveillance and diagnostic purposes was registered in an online electronic case-report form and stored at a central database, and their findings were considered for this analysis. This information was confirmed by consultation of both regional screening programs and hospital databases, as previously stated [11]. Diagnostic colonoscopies were defined as those performed outside the screening or surveillance context, typically prompted by the onset of symptoms or other clinical indications.

2.5 | Dependent Variables

To identify variables associated with the CRC incidence and to control for potential confounders, we collected data on age, sex, COLONPREV arm and the characteristics of adenomas and SPs detected at baseline colonoscopy. In an exploratory analysis, CRC incidence was first estimated across all combinations of adenomatous and serrated lesions at baseline. Based on these incidence patterns, a post hoc classification was derived to facilitate clinically interpretable risk stratification.

We performed an additional exploratory analysis restricted to individuals who underwent at least one surveillance colonoscopy during follow-up. In this subset, we evaluated the detection of post-polypectomy recurrence according to the histological characteristics of the baseline lesions. For this analysis, all colonoscopies performed after baseline, irrespective of indication, were included unless they led directly to CRC diagnosis.

2.6 | Statistical Analysis

Baseline demographic and clinical characteristics were summarized descriptively. CRC incidence was expressed as cumulative incidence and incidence rate per 1000 person-years (PY). Incidence rate ratios were estimated using Poisson regression models. Kaplan–Meier curves were generated to illustrate cumulative incidence across study groups, and proportional hazard assumptions were assessed graphically. Hazard ratios (HR) and 95% confidence intervals (CI) were obtained using Cox proportional hazards regression models adjusted for age, sex, study arm, completeness of baseline colonoscopy, baseline lesion group, and surveillance exposure during follow-up. The number of covariates was restricted to preserve model stability given the limited number of events. All analyses were performed using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA). Two-sided p-values < 0.05 were considered statistically significant.

3 | Results

Within the COLONPREV study, 9415 subjects underwent at least one colonic examination. As shown in Figure 1, 426 individuals were excluded. Therefore, a total of 8989 subjects were included in this analysis. The mean age at baseline colonoscopy was 61.9 $\pm$ 6.2 years, and 51.7% were female. The colonoscopy was performed as primary screening in 5314 individuals, as a work-up examination after a positive FIT in 2015 subjects, and for diagnostic purposes in the remaining 1660 patients. Of the 8989 subjects included, 331 (3.7%) required more than one baseline colonoscopy. The characteristics of the baseline lesions detected are shown in Table 1. ASL were detected in 231 individuals (2.6%), most frequently due to the presence of dysplasia ($n = 223$; 2.5%), followed by lesions $\geq$ 10 mm ($n = 74$; 0.8%). A total of 125 participants (1.4%) had ASL located in the proximal colon. The distribution of adenomatous and SPs across

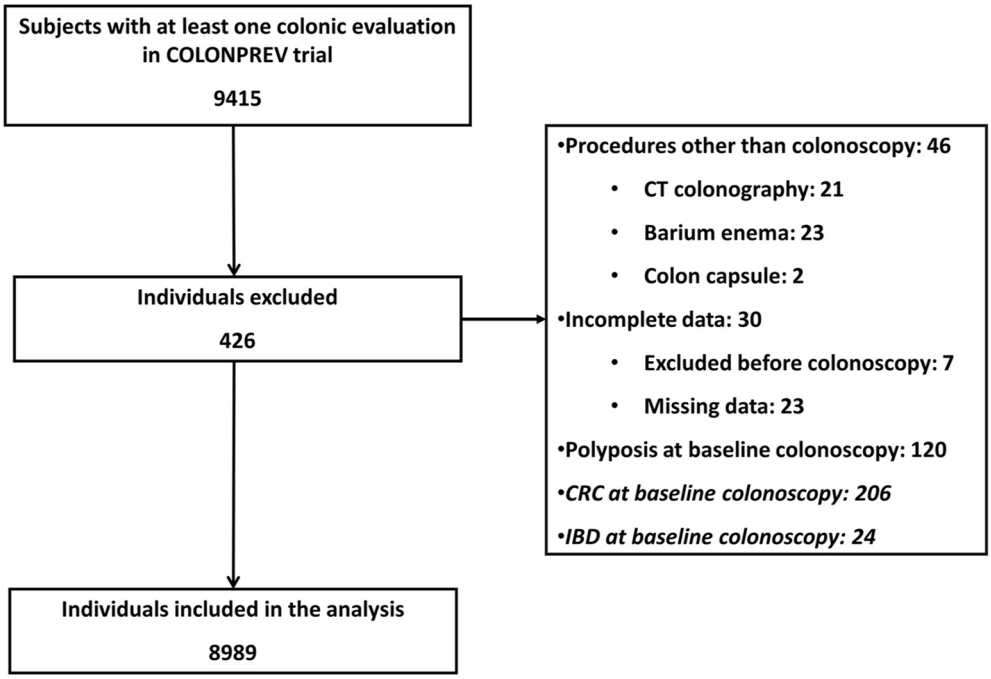


FIGURE 1 | Flowchart of individuals included in the analysis. Footnote: CT colonography, Computed tomography colonography; CRC, colorectal cancer; IBD, inflammatory bowel disease.

TABLE 1 | Baseline characteristics of the study population and colorectal cancer incidence (n = 8989).

SPVariables	n (%)	CRC (n)	Cumulative incidence[a]	P[b]	Incidence rate[c]	P[d]
Age (years)						
50–59	3611 (40.2%)	12	0.36% (0.18–0.62)	0.08	0.33 (0.17–0.58)	0.04
60–69	5378 (59.8%)	32	0.57% (0.39–0.80)		0.66 (0.45–0.93)	
Gender						
Male	4345 (48.3%)	20	0.46% (0.28–0.71)	0.7	0.49 (0.30–0.75)	0.7
Female	4644 (51.7%)	24	0.52% (0.33–0.77)		0.54 (0.35–0.81)	
Study arm						
Colonoscopy	6010 (66.9%)	25	0.42% (0.27–0.61)	0.1	0.39 (0.25–0.58)	0.008
FIT	2979 (33.1%)	19	0.64% (0.38–0.99)		0.88 (0.53–1.37)	
Baseline colonoscopy						
Complete[e]	8262 (91.9%)	40	0.48% (0.35–0.66)	0.7	0.51 (0.36–0.69)	0.5
Incomplete	727 (8.1%)	4	0.55% (0.15–1.40)		0.67 (0.18–1.72)	
SPs						
No SPs	7206 (80.2%)	36	0.50% (0.35–0.69)	0.5	0.53 (0.37–0.74)	0.5
Non-advanced SP	1552 (17.3%)	6	0.39% (0.14–0.84)		0.39 (0.14–0.85)	
Advanced SP[f]	231 (2.6%)	2	0.87% (0.11–3.09)		0.87 (0.10–3.14)	
Adenoma						
No adenoma	5632 (62.7%)	17	0.30% (0.18–0.48)	< 0.001	0.31 (0.18–0.50)	< 0.001
Non-advanced adenoma	2139 (23.8%)	12	0.56% (0.29–0.98)		0.61 (0.31–1.06)	
Advanced adenoma[g]	1218 (13.5%)	15	1.23% (0.69–2.02)		1.34 (0.75–2.21)	

[a]Cumulative incidence is expressed as percentage with 95% CI from the exact binomial distribution (Clopper–Pearson).
[b]Comparisons between groups were assessed using Pearson's chi-square test. A $p < 0.05$ is considered statistically significant.
[c]Incidence rates are expressed per 1000 person-years with 95% confidence interval (CI) from the Poisson distribution.
[d]Comparisons were performed using Poisson regression. A $p < 0.05$ is considered statistically significant.
[e]Colonoscopy was considered complete if cecal intubation was achieved and visualization of at least 90% of the colonic mucosa was accomplished.
[f]SP $\geq$ 10 mm or with dysplasia.
[g]Adenoma $\geq$ 10 mm with villous histology or high-grade dysplasia.
Abbreviations: CRC, colorectal cancer; FIT, faecal immunochemical test; SP, serrated polyp.

the eight participating regions is presented in Supporting Information S1.

With respect to endoscopic surveillance, 68.4% of participants (6147) did not undergo any colonoscopy, 21.1% had one follow-up colonoscopy, and 10.5% had two or more procedures (Table 2). Surveillance distribution varied significantly according to baseline characteristics: participants with advanced adenomas or ASL were substantially more likely to undergo repeated colonoscopies, whereas those without adenomas or SPs seldom received surveillance ($p < 0.001$).

During a mean follow-up of 9.45 ± 3.26 years, 604 (6.7%) subjects died and 44 incident CRC cases were identified. CRC was diagnosed after a mean follow-up of 6.39 ± 3.23 years, most commonly during symptomatic evaluation ($n = 32$), followed by surveillance colonoscopy ($n = 9$) and work-up after a positive FIT ($n = 3$). The overall cumulative incidence was 0.49% (95% CI 0.36–0.66). The corresponding incidence density was 0.52 cases per 1000 person-years (95% CI 0.38–0.70). Incidence rates varied across participant and procedural subgroups as shown in Table 1. At 10 years of follow-up, the cumulative incidence of CRC in participants with baseline SPs remained low and did not differ significantly from that in those without such lesions. The 10-year cumulative incidence was 0.39% (95% CI 0.14–0.84) for individuals with non-advanced SPs and 0.87% (95% CI 0.11–3.09) for those with ASL, compared with 0.50% (95% CI 0.35–0.69) in participants without SPs (global comparison across SP categories, $p = 0.4$). In contrast, the presence of adenomas at baseline, particularly advanced adenomas (1.23%, 95% CI 0.69–2.02), was strongly associated with an increased risk of CRC detection during follow-up. Based on the incidence

TABLE 2 | Endoscopic surveillance was performed according to the most advanced baseline findings.

Variables	No surveillance ($n = 6147$)	One colonoscopy ($n = 1901$)	≥ 2 colonoscopies ($n = 941$)	p[a]
Age (years)				
50–59	2442 (67.6%)	794 (22.0%)	375 (10.4%)	0.2
60–69	3705 (68.9%)	1107 (20.6%)	566 (10.5%)	
Gender				
Male	2781 (64.0%)	1002 (23.1%)	562 (12.9%)	< 0.001
Female	3366 (72.5%)	899 (19.4%)	379 (8.2%)	
Study arm				
Colonoscopy	4122 (68.6%)	1304 (21.7%)	584 (9.7%)	0.002
FIT	2025 (68.0%)	597 (20.0%)	357 (12.0%)	
Baseline colonoscopy				
Complete[b]	5630 (69.1%)	1773 (21.5%)	859 (10.4%)	0.05
Incomplete	517 (71.1%)	128 (17.6%)	82 (11.3%)	
SPs				
No SPs	5143 (71.4%)	1374 (19.1%)	689 (9.6%)	< 0.001
Non-advanced SP	923 (59.5%)	444 (28.6%)	185 (11.9%)	
Advanced SP[c]	81 (35.1%)	83 (35.9%)	67 (29.0%)	
Adenoma				
No adenoma	4775 (84.8%)	705 (12.5%)	152 (2.7%)	< 0.001
Non advanced adenoma	1059 (49.5%)	736 (34.4%)	344 (16.1%)	
Advanced adenoma[d]	313 (25.7%)	460 (37.8%)	445 (36.5%)	
Study group				
No adenoma or ASL	4720 (85.9%)	655 (11.9%)	121 (2.2%)	< 0.001
Non-advanced adenoma[e]	1033 (50.7%)	692 (34.0%)	313 (15.4%)	
Advanced adenoma[f]	325 (25.4%)	490 (38.3%)	466 (36.4%)	
ASL[g]	71 (39.7%)	66 (36.8%)	47 (23.6%)	

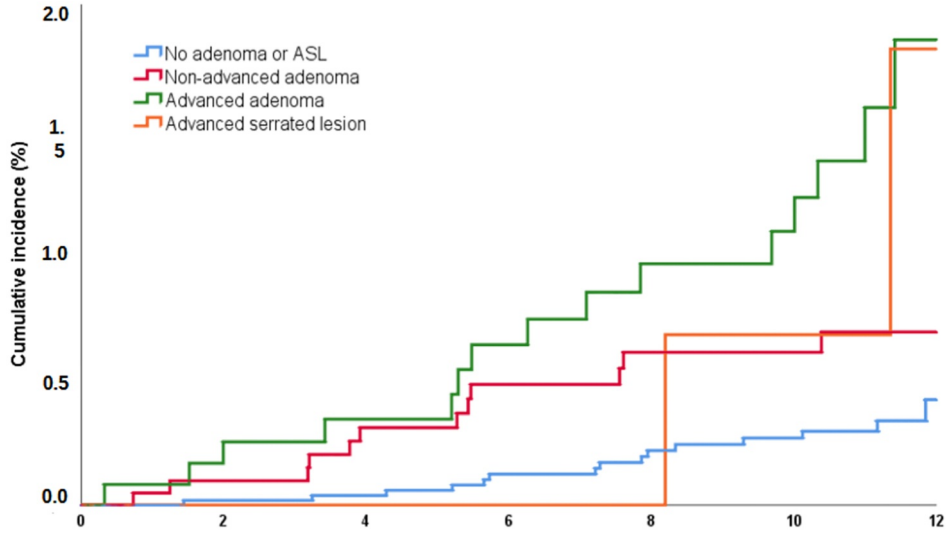
[a]Comparisons between groups were assessed using Pearson's chi-square test. A $p < 0.05$ is considered statistically significant.
[b]Colonoscopy was considered complete if cecal intubation was achieved and visualization of at least 90% of the colonic mucosa was accomplished.
[c]SP ≥ 10 mm or with dysplasia.
[d]Adenoma ≥ 10 mm with villous histology or high-grade dysplasia.
[e]Adenoma < 10 mm, tubular and with low-grade dysplasia. No synchronous advanced SPs.
[f]Adenoma ≥ 10 mm with villous histology or high-grade dysplasia irrespective of the characteristics of the synchronous SP.
[g]SP ≥ 10 mm or with dysplasia. No synchronous advanced adenoma.
Abbreviations: ASL, advanced serrated lesion; CRC, colorectal cancer; FIT, faecal immunochemical test; SP, serrated polyp.

patterns observed across combinations of adenomatous and serrated lesions (Supporting Information S1), participants were classified into four groups: no lesion (no adenoma or ASL), non-advanced adenoma (non-advanced adenomas without ASL), advanced adenoma (irrespective of the presence of ASL), and ASL (Figure 2 and Table 3). Participants with advanced adenomas had the highest incidence of CRC, with an incidence rate of 1.34/1000 person-years and a more than four-fold increased risk compared with those without adenomas or ASL (incidence rate ratio-IRR 4.67, risk ratio-RR 4.53; both $p < 0.001$). Non-advanced adenomas were associated with a borderline increase in risk (IRR 2.14, RR 2.12; both $p = 0.05$). Subjects with ASL had incidence rates comparable to those with non-advanced adenomas (1.07/1000 person-years), with point estimates suggesting a three-to four-fold higher risk compared with the reference group (IRR 3.65, RR 3.99), although these differences did not reach statistical significance ($p \approx 0.07$–0.08).

Among the two CRC cases observed in patients with baseline ASL, both were located in the proximal colon and were diagnosed following the onset of new symptoms. One case required surgical treatment (TNM stage II), whereas the second was treated endoscopically and corresponded to a low-risk pT1 carcinoma. Regarding their relationship with baseline lesions, the index ASL was located in the proximal colon in one case and in the sigmoid colon in the other.

Kaplan–Meier curves showed clear separation by study group (Figure 2). Log (–log) plots did not indicate major violations of proportionality. Based on the univariant analysis, we developed a model adjusted for age, sex, study arm, completeness of the baseline colonoscopy, and surveillance exposure during follow-up. In the Cox regression analysis (Table 4) model, non-advanced adenomas, advanced adenomas, and ASL were all associated with an increased risk of CRC. The association was stronger for advanced adenomas (HR 9.77, 95% CI 4.24–22.50; $p < 0.001$) than for non-advanced adenomas (HR 3.25, 95% CI 1.48–7.16; $p = 0.003$), while ASL were also associated with an increased risk of CRC (HR 6.37, 95% CI 1.42–28.54; $p = 0.01$). In contrast, sex and baseline colonoscopy completeness showed no significant relationship with CRC incidence. Older age (60–69 years) showed a borderline association (HR 1.91, 95% CI 0.97–3.74; $p = 0.06$), as did assignment to the FIT arm (HR 1.91, 95% CI 1.02–3.59; $p = 0.04$). Endoscopic surveillance strongly reduced CRC risk, with a single surveillance colonoscopy associated with nearly halved risk (HR 0.46, 95% CI 0.22–0.95; $p = 0.03$) and two or more examinations conferring a marked protective effect (HR 0.09, 95% CI 0.02–0.40; $p = 0.002$).

Among participants undergoing surveillance colonoscopy, recurrence was frequent and varied significantly according to baseline findings ($p < 0.001$). Individuals without baseline lesions had the lowest recurrence rates, with high-risk lesions detected in only 1.8%. In contrast, those with advanced adenomas or ASL at baseline showed substantially higher recurrence burdens, with high-risk lesions identified in approximately 27% of cases. Participants with non-advanced adenomas exhibited an intermediate risk profile. Detailed findings are presented in Supporting Information S1.



Number at risk							
No adenoma or ASL	5496	5268	4912	4562	4147	3730	873
Non-advanced adenoma	2091	2014	1838	1680	1508	1307	252
Advanced adenoma	1218	1170	1056	984	864	730	174
Advanced serrated lesion	184	175	166	162	149	139	49

FIGURE 2 | Colorectal cancer cumulative incidence (1—survival) estimated using the Kaplan–Meier method according to the study group classification. The table shows the number of individuals at risk. Footnote: Non-advanced adenoma group: Adenoma < 10 mm, tubular and with low-grade dysplasia. No synchronous advanced serrated lesions. Advanced adenoma group: Adenoma ≥ 10 mm with villous histology or high-grade dysplasia irrespective of the characteristics of the synchronous SP. Advanced serrated lesion: SP ≥ 10 mm or with dysplasia. No synchronous advanced adenoma. ASL, advanced serrated lesion; SP, serrated polyp.

TABLE 3 | Colorectal cancer incidence according to the study group.

Study group	CRC incidence rate[a]	Incidence rate ratio[b]	p[c]	Cumulative incidence[d]	Risk ratio[e]	p[f]
No adenoma or ASL ($n = 5496$)	0.29 (0.16–0.48)	Ref	—	0.27 (0.15–0.45)	Ref	—
Non advanced adenoma[g] ($n = 2091$)	0.62 (0.32–1.08)	2.14 (0.99–4.63)	0.05	0.57 (0.29–0.99)	2.12 (0.99–4.54)	0.05
Advanced adenoma[h] ($n = 1218$)	1.34 (0.75–2.21)	4.67 (2.33–9.34)	< 0.001	1.23 (0.69–2.02)	4.53 (2.27–9.03)	< 0.001
ASL[i] ($n = 184$)	1.07 (0.13–3.87)	3.65 (0.82–16.2)	0.08	1.09 (0.13–3.90)	3.99 (0.89–17.9)	0.07

[a]Incidence rates are expressed per 1000 person-years with 95% confidence interval (CI) from the Poisson distribution.
[b]Incidence rate ratios are expressed with 95% confidence interval.
[c]Comparisons were performed using Poisson regression. A $p < 0.05$ is considered statistically significant.
[d]Cumulative incidence is expressed as percentage with 95% CI from the exact binomial distribution (Clopper–Pearson).
[e]Risk ratio is expressed as an absolute number with 95% confidence interval.
[f]Comparisons between groups were assessed using Pearson's chi-square test. A $p < 0.05$ is considered statistically significant.
[g]Adenoma < 10 mm, tubular and with low-grade dysplasia. No synchronous advanced serrated lesions.
[h]Adenoma ≥ 10 mm with villous histology or high-grade dysplasia irrespective of the characteristics of the synchronous serrated polyp.
[i]Serrated polyp ≥ 10 mm or with dysplasia. No synchronous advanced adenoma.
Abbreviations: ASL, advanced serrated lesion; CRC, colorectal cancer.

TABLE 4 | Hazard ratios for incident colorectal cancer according to baseline characteristics.

Variables	Hazard ratio (95% CI)	p[a]
Age (years)		
50–59	1	0.06
60–69	1.91 (0.97–3.74)	
Gender		
Male	1	0.2
Female	1.41 (0.77–2.60)	
Study arm		
Colonoscopy	1	0.04
FIT	1.91 (1.02–3.59)	
Endoscopic surveillance		
No colonoscopy	1	
One colonoscopy	0.46 (0.22–0.95)	0.03
≥ 2 colonoscopies	0.09 (0.02–0.40)	0.002
Study group		
No adenoma or ASL	1	
Non-advanced adenoma[b]	3.25 (1.48–7.16)	0.003
Advanced adenoma[c]	9.77 (4.24–22.50)	< 0.001
ASL[d]	6.37 (1.42–28.54)	0.01

[a]Comparisons were performed using Cox proportional hazard regression. A $p < 0.05$ is considered statistically significant.
[b]Adenoma < 10 mm, tubular and with low-grade dysplasia. No synchronous advanced SPs.
[c]Adenoma ≥ 10 mm with villous histology or high-grade dysplasia irrespective of the characteristics of the synchronous SP.
[d]Serrated polyp ≥ 10 mm or with dysplasia. No synchronous advanced adenoma.
Abbreviations: ASL, advanced serrated lesion; CRC, colorectal cancer; FIT, faecal immunochemical test.

4 | Discussion

This post hoc analysis of the COLONPREV trial evaluated long-term CRC risk after ASL in a population-based screening setting and compared it with the risk observed after advanced adenomas. ASL were associated with increased CRC incidence, at a magnitude in the range of advanced adenomas, whereas non-advanced serrated polyps were not independently associated with risk. Endoscopic surveillance was associated with lower CRC incidence; however, as follow-up was not randomized, this association should not be interpreted as definitive evidence of causality.

The key finding in our study is that, after resection of ASL, the long-term risk is similar to the risk after advanced adenoma resection. The hazard ratios observed are comparable to those reported for advanced adenomas, positioning ASL within the group of post-polypectomy patients who remain at risk of subsequent CRC. This finding is aligned with the results from nationwide and population-based cohorts [8, 9, 17, 18], which reported that large, proximal, or dysplastic SPs substantially increase CRC risk, especially when synchronous adenomas are present. In addition, a recent large prospective study by Polychronidis et al. [19] further supports this concept, showing that both high-risk adenomas and high-risk serrated polyps are associated with an increased risk of CRC, with the highest risk observed in the early post-polypectomy period.

The prevalence of ASL in our cohort (2.6%) is aligned with population-based studies across different screening eras. In the Norwegian randomized screening trial, large SPs ≥ 10 mm represented less than 1% of findings [20], and more recently, in the Dutch FIT-based programme [21] ASL accounted for approximately 2% of the screened individuals. These data underline that ASL remain rare even with improved recognition, dedicated training, and uniform diagnostic criteria. The low prevalence is therefore intrinsic to serrated neoplasia epidemiology rather than solely related to detection practice, although it inevitably limits the statistical power of long-term risk estimates. For this reason, our estimates may be conservative and reinforce, rather than weaken, the observed association between ASL and future CRC risk.

Our findings contribute specifically to the debate regarding surveillance after resection of ASL, rather than serrated polyps in

general. Non-advanced SPs were not associated with a significant increase in CRC incidence in our cohort, and therefore our conclusions should be interpreted primarily in the context of ASL. Recent population-based studies have demonstrated that patients with high-risk SPs present an increased risk of early post-polypectomy CRC or advanced metachronous neoplasia [21]. Likewise, large SPs have been shown to confer equal or even greater short-term risk of metachronous advanced neoplasia than high-grade adenomas [19, 22], and the combination of clinically significant SPs with synchronous adenomas has been identified as a particularly high-risk scenario [23]. However, in contrast to these observations, we did not identify an increased short-term risk in our cohort, with CRC cases occurring predominantly during long-term follow-up. This pattern is consistent with previous long-term prospective data, including the study by Holme et al., in which CRC diagnoses in individuals with large serrated polyps occurred after a median of more than 7 years of follow-up [9]. As highlighted in the most recent meta-analysis, the long-term evidence on post-polypectomy CRC risk after SPs remains scarce, with few studies reaching more than 10 years of follow-up [8]. Within this context, our study provides long-term prospective data on incident CRC and supports the hypothesis that surveillance may exert a protective effect in patients with high-risk serrated neoplasia.

A major contribution of this study is the demonstration that surveillance colonoscopy is strongly protective. Participants who underwent surveillance had a markedly reduced risk of CRC compared with those who did not, with the lowest hazards observed among those with repeated follow-up examinations. This supports a causal protective effect, as the benefit increased with the intensity of surveillance. Previous studies of adenoma cohorts have demonstrated that surveillance reduces CRC incidence and mortality [20, 24]. Until now, evidence for SPs has been limited, and surveillance recommendations were largely extrapolated from adenoma studies [5, 10].

The strengths of this study include its large prospectively followed screening cohort, detailed characterization of baseline colonoscopic findings, and follow-up extending beyond 10 years. These features enabled the estimation of long-term CRC incidence after lesion resection within an organized population-based programme, a setting in which robust outcome data remain limited. However, the small number of CRC events in the ASL group. The limited number of individuals with concomitant advanced adenomas and ASL and the absence of consistent anatomical correspondence with baseline lesions limit causal inference and result in imprecise regression estimates.

Pathological classification was performed according to the criteria available at the time of the study, prior to publication of the currently applicable WHO classification for serrated lesions [25], and without central pathology review. Substantial inter-regional variability in serrated lesion detection was observed, likely reflecting differences in pathological interpretation and endoscopic practice, including bowel preparation quality, lesion recognition, and withdrawal time. Variability in training and reporting practices across centres may also have contributed. Although some degree of non-differential misclassification cannot be excluded, such misclassification would be expected to attenuate rather than exaggerate risk estimates.

In addition, surveillance colonoscopy was not randomly assigned but was conducted according to clinical practice and guideline recommendations. Residual confounding by indication may therefore persist despite multivariable adjustment, as individuals undergoing surveillance could differ systematically from those who did not. Another limitation of this study relates to the historical period of recruitment. Baseline examinations were performed more than 15 years ago, when standardized endoscopic quality metrics were not routinely collected in a systematic way. As a consequence, neither validated bowel preparation scales (e.g., BBPS) [26] nor endoscopist-level adenoma detection rates could be applied retrospectively. Besides, withdrawal time was not systematically recorded at the individual level for all baseline colonoscopies, particularly in symptom-driven examinations, and the heterogeneity in colonoscopy indications precluded a reliable assessment of its association with adenoma detection. Furthermore, detailed information on endoscopic resection techniques and histological margin assessment was not recorded, which precludes an evaluation of the potential impact of incomplete resection on CRC risk.

In conclusion, in this population-based screening cohort, individuals with advanced adenomas and ASL exhibited higher CRC risk than those without lesions. Surveillance colonoscopy was associated with lower CRC incidence; however, given the observational nature of follow-up, causal inference cannot be firmly established. Although the number of ASL cases and CRC events was limited, these findings provide long-term risk estimates that are consistent with current surveillance strategies and underscore the importance of considering absolute risk in post-polypectomy management. Ongoing randomised surveillance trials, including the European Polyp Surveillance Study [27], will be essential to determine the optimal follow-up intervals for both adenomas and SPs.

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authors remain solely responsible for the accuracy and integrity of the manuscript and all accompanying materials.

Ethics Statements

As previously described, the study was approved by the ethics committee at each hospital, and all subjects provided written informed consent [11, 12].

Consent

Patients were not directly involved in data collection, analysis, or interpretation, but their priorities and advocacy were fundamental in guiding the study and maximizing its impact for the public. The Spanish Association Against Cancer contributed decisively to disseminating information about the study to the general public, increasing awareness and engagement with colorectal cancer screening. Furthermore, they provided essential financial support that made the execution of the trial feasible. The study team maintained regular dialog with their representatives throughout the project to ensure that patient perspectives and societal needs were appropriately incorporated.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information S1: ueg270245-sup-0001-suppl-data.docx.