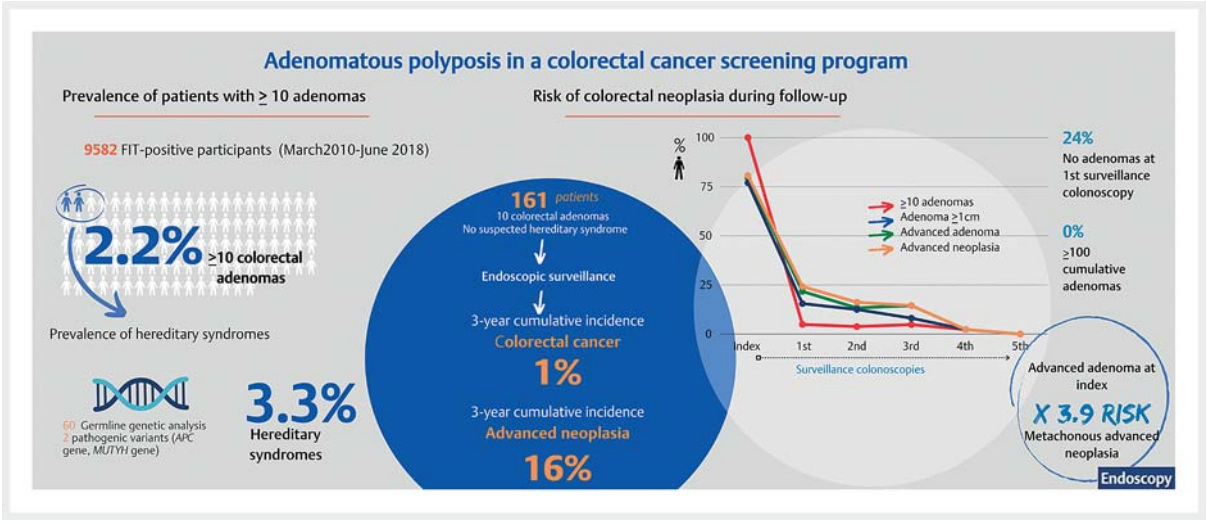
Prevalence of adenomatous polyposis in a fecal immunochemical test-based colorectal cancer screening program and risk of advanced neoplasia during follow-up

GRAPHICAL ABSTRACT



Authors
Sabela Carballal[1], Ariadna Sánchez[1], Leticia Moreira[1], Jesús Eduardo Cuellar-Monterrubio[1,2], Julio Bernuy[1,3], Maria Daca[1], Oswaldo Ortiz[1], Teresa Ocaña[1], Liseth Rivero-Sánchez[1], Gerhard Jung[1], Anna Serradesanferm[4], Angels Pozo[4], Jaume Grau[4], Isabel Torá[4], Diana Zaffalon[1], Antoni Castells[1], María Pellisé[*,1], Francesc Balaguer[*,1], on behalf of the PROCOLON Group

Institutions
1 Department of Gastroenterology, Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), University of Barcelona, Barcelona, Spain
2 Department of Gastroenterology, Dr. José Eleuterio González University Hospital, Autonomous University of Nuevo León, Monterrey, Mexico
3 Department of Gastroenterology, Hospital of Zumarraga, Guipuzkoa, Spain
4 Preventive Medicine and Hospital Epidemiology Department, Hospital Clinic, Barcelona, Spain

submitted 14.5.2021
accepted after revision 4.10.2021
published online 4.10.2021

Bibliography
Endoscopy 2022; 54: 688–697
DOI 10.1055/a-1660-5353
ISSN 0013-726X

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Scan this QR-Code for the author commentary.

Supplementary material
Supplementary material is available under https://doi.org/10.1055/a-1660-5353

* Joint senior authors

Corresponding author
Francesc Balaguer, MD, PhD, Department of Gastroenterology, Hospital Clínic of Barcelona, Villarroel 170, 08036 Barcelona, Spain
fprunes@clinic.cat

ABSTRACT

Background Current guidelines recommend genetic counseling and intensive colonoscopy surveillance for patients with ≥10 colorectal adenomas based on scarce data. We investigated the prevalence of this condition in a fecal immunochemical test (FIT)-based colorectal (CRC) screening program, and the incidence of metachronous lesions during follow-up.

Methods We retrospectively included all FIT-positive participants with ≥10 adenomas at index colonoscopy between 2010 and 2018. Surveillance colonoscopies were collected until 2019. Patients with inherited syndromes, serrated polyposis syndrome, total colectomy, or lacking surveillance data were excluded. The cumulative incidence of CRC and advanced neoplasia were analyzed by Kaplan–Meier analysis. Risk factors for metachronous advanced neoplasia were investigated by multivariable logistic regression analysis.

Results 215 of 9582 participants (2.2%) had ≥10 adenomas. Germline genetic testing was performed in 92% of patients with ≥20 adenomas, identifying two inherited syndromes (3.3%). The 3-year cumulative incidence of CRC and advanced neoplasia were 1% and 16%, respectively. In 39 patients (24.2%), no polyps were found on first surveillance colonoscopy. The presence of an advanced adenoma was independently associated with a higher risk of advanced neoplasia at first surveillance colonoscopy (odds ratio 3.91, 95%CI 1.12–13.62; $P=0.03$). Beyond the first surveillance colonoscopy, the risk of metachronous advanced neoplasia was lower.

Conclusions The prevalence of ≥10 adenomas in a FIT-based CRC screening program was 2.2%; a small proportion of inherited syndromes were detected, even amongst those with ≥20 adenomas. A low rate of post-colonoscopy CRC was observed and the risk of advanced neoplasia beyond the first surveillance colonoscopy tended to progressively decrease throughout successive follow-ups.

Introduction

The definition of attenuated adenomatous polyposis has traditionally been based on the occurrence of 10–99 cumulative lifetime adenomas in the colorectum [1]. This definition, regardless of family history, is known to cover a wide spectrum of situations, from patients with multiple sporadic adenomas to those with genetically inherited polyposis syndromes due to *APC* or *MUTYH* pathogenic germline variants [2].

Current guidelines recommend that patients with 10 or more cumulative adenomatous colorectal polyps should receive genetic counseling, as well as intensive endoscopic surveillance in specialized colorectal cancer (CRC) high risk units [1, 3–9]. Given the growing volume of screening colonoscopies and the increasing improvements in technology and polyp detection [10, 11], more and more individuals are being diagnosed with multiple colorectal adenomas, representing a meaningful burden for high risk clinics [12].

The diagnostic yield of genetic testing in this population (especially in those with 10–19 adenomas) is very low [2, 13]. Moreover, in the setting of organized CRC screening programs aimed at individuals ≥50 years of age without a relevant family history of this neoplasia, the yield of germline genetic testing is likely to be even lower. With this in mind, Spanish guidelines for CRC diagnosis and prevention establish the lower limit for genetic testing as 20 lifetime adenomas, except in those cases diagnosed at a young age or where a family history of CRC or polyposis is documented [14].

On the other hand, there is scarce information to support the efficacy of intensive surveillance in patients with non-hereditary attenuated adenomatous polyposis. Some of these patients may carry a low risk of metachronous neoplasia and are currently over-surveilled, representing a significant burden on endoscopy units.

The prevalence of patients with ≥10 adenomas and the proportion of inherited polyposis syndromes in fecal immunochemical test (FIT)-based CRC screening programs remain unclear [15]. More importantly, for those patients without a hereditary cause, the risk of metachronous neoplasia has been poorly described. Given the above mentioned uncertainties, the aims of the current study were: (i) to evaluate the prevalence of patients with ≥10 adenomas in a FIT-based CRC screening program; (ii) to describe the prevalence of hereditary syndromes; and (iii) to investigate the incidence of CRC and advanced neoplasia during follow-up of non-inherited cases.

Methods

Study design and patients

This observational retrospective cohort study included individuals from the FIT-based organized Barcelona–Eixample–Esquerra population CRC Screening Program, in which all individuals aged 50–69 are invited to participate. A personal history of CRC, adenoma, or inflammatory bowel disease; a family history of CRC (defined as those individuals with two first-degree relatives [FDRs] with CRC or one diagnosed before the age of 60); known hereditary CRC syndromes; severe coexisting illness; colonoscopy performed within the last 5 years; previous colectomy; or contraindication for colonoscopy are considered definitive or temporary exclusion criteria for screening.

For the present study, participants from the first to fourth screening round of the program (from January 2010 to June

2018) who had a positive FIT result (cutoff ≥ 20 µg hemoglobin/g feces) followed by a complete colonoscopy with ≥ 10 adenomas found and who had undergone at least one surveillance colonoscopy at an interval consistent with current recommendations were considered eligible to enter the study [3, 4, 9, 14]. Individuals with ≥ 10 adenomas who met either the WHO 2010 or 2019 criteria of serrated polyposis syndrome (SPS) [16] were also excluded.

All colonoscopies were performed at the Hospital Clinic of Barcelona, a tertiary academic center that follows high quality standards [17, 18]. All participating endoscopists had an adenoma detection rate ≥ 40 % in FIT-positive patients. In the setting of the screening program, all colonoscopies and pathology reports were reviewed weekly by a committee composed of expert gastroenterologists, endoscopists, and nurses before follow-up recommendations were given.

Participants' baseline demographic data were prospectively recorded in the CRC screening program database. Other clinical data, such as cigarette smoking history, body mass index (BMI) or cardiovascular disease (i. e. diabetes, hypertension, dyslipidemia, ischemic heart disease), were obtained, when available, from hospital medical records and Catalonia's National Health Service database.

Only histologically confirmed adenomas were counted for diagnosis. Patient selection was based on endoscopic and histopathological reports from all polyps removed at baseline screening colonoscopy.

Patients with ≥ 10 adenomas were offered an appointment at the CRC high risk unit. Based on Spanish Guidelines, genetic testing was offered in the following situations: (i) individuals with ≥ 20 lifetime adenomas; (ii) individuals with ≥ 10 adenomas detected before the age of 40; (iii) individuals with ≥ 10 adenomas and a personal or family history of CRC before the age of 60; (iv) ≥ 10 adenomas and a family history of adenomatous polyposis [14].

Germline genetic testing was carried out by Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA) of *APC* and *MUTYH* genes until 2016, and afterwards by a multigene cancer panel that included the *APC* and *MUTYH* genes (Trusight Cancer v1; Illumina Inc., San Diego, California, USA). All germline genetic reports from both the hospital medical records and the high risk clinic's database were reviewed. Patients with germline pathogenic variants were excluded for the analysis of the risk of CRC and advanced neoplasia during surveillance.

The study was approved by the institutional review board (IRB) of our Institution and was carried out respecting the fundamental principles established in the Declaration of Helsinki.

Endoscopic characteristics and treatment

Data on the baseline and surveillance colonoscopies, such as the number and size of adenomas and serrated lesions detected, and the grade of dysplasia, were retrieved from endoscopy and pathology reports.

When several baseline colonoscopies were needed, for example for inadequate bowel preparation, a high burden of polyps, or complex polypectomy, the baseline colonoscopy was set as the date of the last colonoscopy that completely scrutinized the entire colon and/or achieved a clear colon. For analysis purposes, the findings of any repeated colonoscopies were compiled into one and the date of the last colonoscopy was used. After a first surveillance colonoscopy, all consecutive surveillance procedures performed were counted until October 2019. Incomplete procedures and those with inadequate colon cleansing, as well as those performed outside of the recommended interval, were excluded.

The type of any colorectal surgery and cause for referral were documented. Patients referred for surgery after baseline colonoscopy owing to CRC, an unresectable polyp, or the polyp burden were included if a segmental colectomy had been performed, while those who underwent a total colectomy were excluded.

Data was registered and stored in an anonymous database.

Histopathological records

Polyp histology was evaluated by expert pathologists dedicated to gastrointestinal oncology. Adenomas were histologically classified according to the Vienna classification [19]. Advanced adenomas were defined as adenomas ≥ 1 cm in size, and/or with villous component, and/or showing high grade dysplasia. Serrated lesions were classified as hyperplastic polyps, sessile serrated lesions [SSLs], and traditional serrated adenomas [TSAs], based on the current WHO classification criteria [20]. Cytological dysplasia among serrated lesions was analyzed both as the presence/absence of dysplasia, and as the presence of low and high grade dysplasia. Advanced serrated lesions were defined as serrated lesions ≥ 1 cm in size, and/or with dysplasia (i. e. SSLs with dysplasia and TSAs). Neoplastic extension vertically into the submucosal layer or beyond was classified as invasive cancer. Advanced neoplasia was defined as CRC, advanced adenoma, or advanced serrated lesion.

Outcome measures during surveillance

The main outcome was the detection during surveillance of: (i) CRC; and (ii) advanced neoplasia. CRCs detected at baseline screening colonoscopy were classified as prevalent and those diagnosed during surveillance as post-colonoscopy CRC. Post-colonoscopy CRC was defined as a CRC diagnosed after the performance of a colonoscopy without cancer. Following World Endoscopy Organization (WEO) consensus, post-colonoscopy CRC was subdivided into "interval CRC" (detected before the recommended surveillance interval) and "non-interval CRC" (detected at the recommended surveillance interval [non-interval type A], after the recommended surveillance interval [non-interval type B], or when no surveillance interval had been recommended [non-interval type C]) [21].

Statistical analysis

A description of colorectal lesions per patient identified at baseline and during colonoscopy surveillance is presented (per-patient analysis). Percentages were used for categorical data, using median and interquartile range (IQR) for non-normally distributed variables, and mean and SD for normally dis-

tributed variables. When information was missing, the denominator accounted for patients with available data.

The cumulative incidences of CRC, advanced adenoma, and advanced neoplasia were calculated by Kaplan-Meier survival analysis. Because the surveillance times were different for each patient, the incidence rate, expressed in new cases per 100 person-years under surveillance, was also calculated to describe the risk of post-colonoscopy CRC and metachronous lesions. The denominator of this rate was obtained from the sum of the time each person was observed, totaled for all persons. This denominator represents the total time the population was at risk of and being watched for each event.

We performed bivariable analyses to explore baseline factors potentially associated with metachronous advanced neoplasia at first surveillance endoscopy. Quantitative variables were analyzed using Student's *t* test, and qualitative variables were analyzed using the chi-squared test. Next, a multivariable logistic regression analysis was performed, including clinically relevant variables and those with *P* values of < 0.10 obtained on bivariable analysis. We included odds ratios (ORs) with 95 %CIs to quantify the magnitude of the association. Statistical analysis was performed using SPSS 22.0 (IBM Corp., Armonk, New York, USA).

Results

Prevalence of adenomatous polyposis and hereditary syndromes

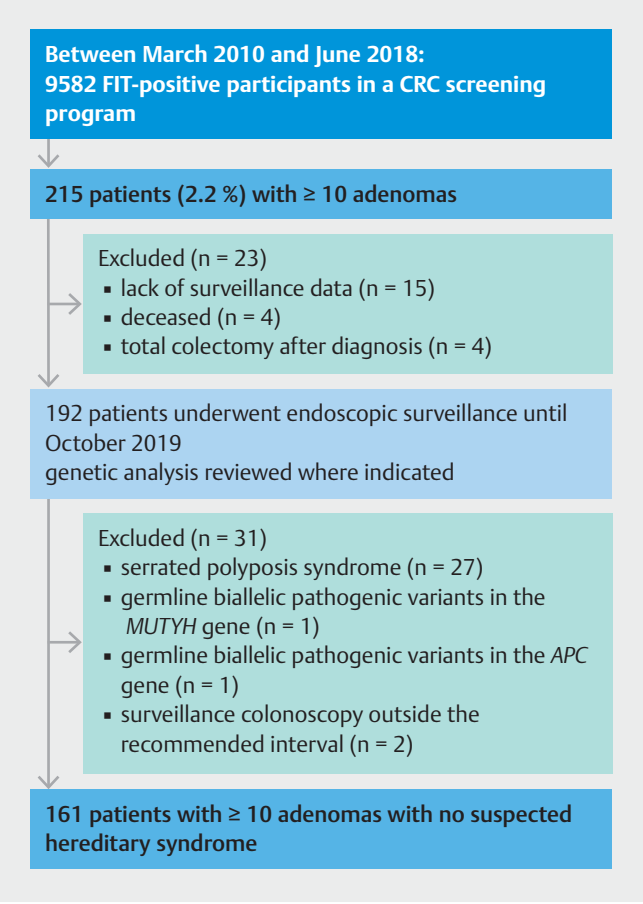
A total of 215 of 9582 FIT-positive individuals (2.2 %) had 10–99 adenomas on their baseline screening colonoscopy (▶ **Fig. 1**). Of these, 23 patients were excluded owing to incomplete surveillance data, but this group did not differ from the patients who did undergo surveillance (**Table 1s**, see online-only Supplementary material).

Germline genetic analysis was performed in 60 cases (27.9%), comprising 57 of 62 individuals with ≥ 20 adenomas (92 %) and three patients with 10–19 adenomas. The indications for germline testing in the latter group were: a family history of CRC in a second-degree relative younger than 60 years (n = 2); and a family history of CRC in an FDR < 60 years who was diagnosed after the inclusion of the patient in the screening program (n = 1).

Pathogenic mutations were found in two of the 60 individuals (3.3 %): a biallelic pathogenic variant in the *MUTYH* gene – Y179C (573A > G) and G396 D (1187 G > A) – detected in a 57-year-old woman with 52 adenomas; and a pathogenic variant in the *APC* gene (c.6742A > T; *P.* K2248X) found in a 68-year-old man with > 70 adenomas.

Study population baseline characteristics

A total of 161 patients with at least one surveillance colonoscopy and no suspicion of a hereditary syndrome were included as the study population (▶ **Fig. 1**). The median age at index colonoscopy was 61 years, with a male predominance (124/161 [77 %]). With regard to environmental risk factors, 65 % (87/134) were either active (60/134 [44.8 %]) or former (27/134 [20.1 %]) smokers, and 82 % of patients (132/161) had at least one cardiovascular risk factor (including being overweight, or having dyslipidemia, hypertension, diabetes, or a history of ischemic heart disease). Detailed demographic and clinical characteristics are represented in ▶ **Table 1**.



▶ **Fig. 1** Study flowchart showing the inclusion and exclusion of individuals from a fecal immunochemical test (FIT)-positive colorectal cancer (CRC) screening program, which resulted in data being analyzed from a final group of 161 patients.

A family history of an FDR with CRC ≤ 60 years was reported in only one case, which occurred after the patient had entered the screening program. In 14 individuals (8.7 %), a CRC history in FDRs older than 60 was notified. A personal history of extracolonic malignancy was reported in 23 individuals (14.3 %), with lung and prostate cancers being the most frequent.

Findings at baseline colonoscopy

At baseline colonoscopy, a median of 10 adenomas (IQR 10–13) and one serrated lesion (IQR 0–2) were detected per patient. The majority of patients had 10–19 adenomas (147; 91.3 %), 13 (8.0 %) had 20–29 adenomas, and one patient (0.6 %) had 30 adenomas. Advanced adenomas, advanced serrated lesions, and advanced neoplasia were found in 128 (79.5 %), 17 (10.6 %), and 130 patients (80.7 %), respectively (▶ **Table 2**).

Prevalent CRCs were detected in eight patients (5.0 %) at a median age of 62.5 years (range 51–67), with six patients (75%) being male. Most tumors were diagnosed at early stages

▶ **Table 1** Clinical features and colonic phenotype in the 161 patients with ≥ 10 adenomas.

Demographic and clinical features	
Age at baseline colonoscopy, median (IQR), years	61 (57–65)
Sex, female, n (%)	37/161 (23.0)
BMI, median (IQR), kg/m^2	28.7 (26.1–32.4)
Cardiovascular risk factors present, n (%)	
▪ Smoking history	87/134 (64.9)
▪ Overweight/obese (BMI ≥ 25 kg/m^2)	44/53 (83.0)
▪ Diabetes	40/137 (29.2)
▪ Dyslipidemia	60/140 (42.9)
▪ Hypertension	66/141 (46.8)
Ischemic heart disease, n (%)	11/132 (8.3)
Any cardiovascular risk factor[1], n (%)	132/161 (82.0)
Family history of colorectal cancer in a first- or second-degree relative, n (%)	27/161 (16.8)
Personal history of any extracolonic cancer, n (%)	23/161(14.3)
▪ Prostate	6 (26.1 %)
▪ Lung	5 (21.7 %)
▪ Lymphoma	3 (13.0 %)
▪ Breast	2 (8.7 %)
▪ Kidney	1 (4.3 %)
▪ Other	6 (26.1 %)
Endoscopic phenotype at index colonoscopy (per patient)	
Colorectal cancer, n (%)	8/161 (5.0)
At least one advanced adenoma, n (%)	128/161 (79.5)
Any serrated lesion, n (%)	84/161 (52.2)
At least one sessile serrated lesion, n (%)	34/161 (21.1)
At least one advanced serrated lesion, n (%)	17/161 (10.6)
At least one advanced neoplasia, n (%)	130/161 (80.7)

IQR, interquartile range; BMI, body mass index.
[1] Cardiovascular risk factors: diabetes, dyslipidemia, hypertension, smoking history, and BMI ≥ 25 kg/m^2.

(six stage I–II [75 %]), including four pT1 CRCs. Two of these pT1 CRCs (50 %) were able to be successfully managed by endoscopic resection owing to the absence of pathological risk factors for lymph node metastasis.

With regard to the clinical management, 10 patients (6.2 %) were referred for surgery after their baseline colonoscopy because of either severe polyposis (n = 1), an unresectable polyp (n = 2), or CRC (n = 6); the remaining patient underwent surgery owing to a post-colonoscopy perforation (n = 1). Right hemicolectomy was performed in six patients and sigmoidectomy in four patients.

Findings during surveillance

Polyposis phenotype

A total of 427 surveillance colonoscopies (median 2 per patient [IQR 2–4]) were performed at a median follow-up time of 3 years (IQR 1–5). The median interval time between procedures was 14 months (IQR 12–17). Only eight patients (5.0 %) showed ≥ 10 adenomas at first surveillance colonoscopy. Cumulatively, 110 individuals (68.3 %) displayed 10–19 adenomas and 51 (31.7 %) developed ≥ 20 adenomas. None of the 161 patients displayed a classic phenotype (≥ 100 adenomas).

Incidence of post-colonoscopy colorectal cancer

During follow-up, 48 individuals (29.8 %) developed advanced adenomas (3-year cumulative incidence 15.7 %, 95 %CI 12.3 %–19.1 %); and nine (5.6 %) developed advanced serrated lesions (3-year cumulative incidence 5.0 %, 95 %CI 3.0 %–7.2 %). The corresponding incident rate figures were 8.3 and 1.5 new cases per 100 person-years under surveillance for advanced adenomas and advanced serrated lesions, respectively.

Two CRCs were diagnosed during surveillance (3-year cumulative incidence 1.0 %, 95 %CI 0.89 %–1.9 %); incidence rate 0.3 new cases per 100 person-years under surveillance. In one case, an interval-type post-colonoscopy CRC, TNM stage IIIa (T3N2M0), was detected in a 69-year-old man who had undergone colonoscopy because of weight loss and increased carcinoembryonic antigen 14 months after a previous high quality surveillance procedure. An ulcerated lesion of 5 cm in size, with infiltrative appearance, was observed in the hepatic flexure. In this patient, 11 non-advanced adenomas had been previously removed: 10 at baseline colonoscopy and only one diminutive adenoma in the previous surveillance procedure. The other case of CRC was a pT1 CRC detected in a 63-year-old woman who had accumulated 60 adenomas over 7 years. A slightly elevated polyp of 1 cm was detected over a scarred base in the sigmoid colon during scheduled surveillance colonoscopy (a non-interval type A post-colonoscopy CRC).

Incidence of advanced neoplasia in subsequent colonoscopies

With regard to the incidence of polyps during follow-up, 122 patients (75.8 %) had adenomas at their first surveillance colonoscopy, whereas 39 (24.2 %) showed no polyps. Advanced neoplasia during follow-up was detected in 52 patients (32.3%) The 3-year cumulative incidence rate was 16 % (95 %CI 12.6 %–19.4 %), with an incidence rate of nine new cases per 100 person-years under surveillance, the great majority of these being found at the first surveillance colonoscopy (39 [75%]). In 28 patients (53.8 %), advanced neoplasia was found only once during surveillance.

The proportion of patients with advanced adenomas, advanced serrated lesions, and advanced neoplasia progressively decreased throughout successive follow-up colonoscopies. The per-patient distribution of lesions at each surveillance colonoscopy is shown in ▶ **Table 2** and ▶ **Fig. 2**.

▶ **Table 2** Colorectal lesions identified during colonoscopy surveillance (per-patient analysis).

	Index colonoscopy	Surveillance colonoscopy number				
		1	2	3	4	5
Number of patients	161	161	106	62	43	34
Time since previous colonoscopy, median (IQR), months	–	14 (12–17)	13 (12–24)	13 (12–18.5)	13 (12–20.7)	15 (12–24)
Patients with invasive CRC[1]	8 (5.0)	0 (0)	0 (0)	0 (0)	1 (2.3)	0 (0)
Patients with ≥ 1 adenoma, n (%)	161 (100)	122 (75.8)	82 (78.8)	49 (79.0)	26 (60.0)	12 (35.3)
Number of adenomas, total; median (IQR)	1946; 10 (10–13)	461; 2 (1–4)	315; 2 (1–4)	200; 2 (1–4)	85; 1 (1–3)	38; 1 (0–2.7)
Patients with ≥ 10 adenomas, n (%)	161 (100)	8 (5.0)	4 (3.8)	3 (4.8)	1 (2.3)	0 (0)
Patients with at least one advanced adenoma, n (%)	128 (79.5)	35 (21.7)	14 (13.3)	9 (14.5)	1 (2.3)	0 (0)
Patients with at least one adenoma ≥ 1 cm, n (%)	124 (77)	25 (15.5)	13 (12.5)	5 (8.1)	1 (2.3)	0 (0)
Patients with at least one adenoma ≥ 2 cm, n (%)	46 (28.6)	6 (3.1)	1 (0.9)	1 (1.6)	0 (0)	0 (0)
Patients with at least one serrated lesion, n (%)	84 (52.2)	62 (38.5)	45 (43.3)	25 (40.3)	12 (27.9)	5 (141)
Patients with at least one SSL, n (%)	34 (21.1)	10 (6.2)	12 (11.3)	6 (9.6)	1 (2.3)	3 (8.8)
Patients with at least one advanced serrated lesion, n (%)	17 (10.6)	7 (4.3)	3 (2.9)	3 (4.8)	0 (0)	0 (0)
Patients with at least one advanced neoplasia, n (%)	130 (80.7)	39 (24.2)	17 (16.2)	9 (14.5)	1 (2.3)	0 (0)

CRC, colorectal cancer; SSL, sessile serrated lesion.
[1] Only endoscopic data from surveillance procedures are shown in this table. For this reason, only one of two post-colonoscopy CRCs is included (the other case was diagnosed at a colonoscopy performed because of symptoms).

In terms of the clinical management, six patients (3.7 %) were referred for surgery during surveillance: four for unresectable polyps and two because of CRC.

Risk factors of advanced neoplasia at first surveillance colonoscopy

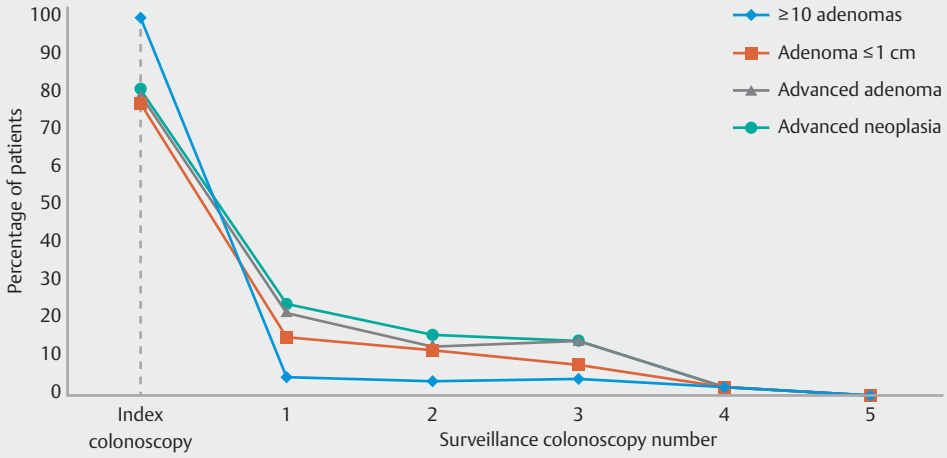
At first surveillance colonoscopy, advanced neoplasia was diagnosed in 39 patients (24.2 %). Clinical and phenotypical characteristics of the patients with and without advanced neoplasia at first surveillance colonoscopy are summarized in ▶ **Table 3**. Bivariable analysis and subsequent multivariable regression analysis revealed that the presence of an advanced adenoma at baseline was independently associated with a higher risk of advanced neoplasia at first surveillance colonoscopy (OR 3.91, 95 %CI 1.12–13.62; $P = 0.03$).

Discussion

In this study, we have shown that the prevalence of ≥ 10 adenomas (i. e. adenomatous polyposis) in a FIT-based CRC screening program is 2.2 %, with a very low frequency of germline pathogenic variants among the patients with an indication for germline genetic testing. A considerable percentage of individuals (32 %) develop advanced neoplasia during follow-up, most of them (75 %) found at the first surveillance colonoscopy. On the other hand, post-colonoscopy CRC is rare (1 %) in our series and both the percentage of patients with advanced and non-advanced neoplasia tends to progressively decrease throughout the successive follow-up colonoscopies. Overall, our results suggest that adenomatous polyposis within a FIT-based program is mainly sporadic and surveillance intervals could probably be lengthened after the first surveillance colonoscopy.

This work is, to our knowledge, the first study that describes the rate of polyposis within a FIT-based CRC screening cohort. Our results suggest a minor occurrence of hereditary polyposis in CRC screening populations, given the low rate of germline pathogenic variants detected. However, germline genetic testing was not performed in the whole cohort, in line with the current guidelines. Moreover, only adenomatous polyposis genes were investigated in the majority of cases (mainly *APC* and *MUTYH*). Previous evidence has suggested that the diagnostic yield of testing for pathogenic variants in patients with 10–19 adenomas is low and always influenced by a referral bias [2].

Recently, Stanich et al. [13] described the prevalence of polyposis- and CRC-associated inherited gene mutations in patients with ≥ 10 colorectal polyps (including adenomas and ha-



	n = 161	n = 161	n = 106	n = 62	n = 43	n = 34
▪ ≥ 10 Adenomas, n (%)	161 (100)	8 (4.9)	4 (3.8)	3 (4.8)	1 (2.3)	0 (0)
▪ any advanced adenoma, n (%)	128 (79.5)	35 (21.7)	14 (13.3)	9 (14.5)	1 (2.3)	0 (0)
▪ any adenoma ≥ 1 cm, n (%)	124 (77)	25 (15.5)	13 (12.5)	5 (8.1)	1 (2.3)	0 (0)
▪ any advanced neoplasia, n (%)	130 (80.7)	39 (24.2)	17 (16.2)	9 (14.5)	1 (2.3)	0 (0)

▶ **Fig. 2** Colorectal lesions identified during colonoscopy surveillance (per-patient analysis).

martomas) who underwent multigene panel testing. Within the adenoma cohort (almost 3200 patients [median age 58.7 years]), the prevalence of pathogenic mutations in adenomatous polyposis genes (*APC,* bi-allelic *MUTYH, POLE, POLD1*) was only 2.3 % in individuals with 10–19 adenomas, 8.5 % in those with 20–99 adenomas, and 41 % in patients with ≥ 100 adenomas. Nevertheless, a key limitation of the Stanich et al. study was the referral bias, because patients with ≥ 10 polyps were selected from a database of individuals who had undergone genetic testing for several reasons (personal and/or family history of CRC or other tumors), meaning not all patients with ≥ 10 colorectal adenomas were tested. Accordingly, considering the average-risk population of our study, we expected the true prevalence of inherited syndromes to be very low. Furthermore, we found a strong association with clinical and environmental factors in our cohort. A clear predominance of male sex (77 %) was observed and both smoking history and cardiovascular risk factors (65 % and 82 %, respectively) were common, reinforcing the involvement of these factors in colorectal carcinogenesis [14].

Our results provide evidence reinforcing the recommendation of a 1-year surveillance colonoscopy in individuals with ≥ 10 adenomas within a FIT-based screening program. Nearly 25 % of this population displayed an advanced neoplasia at 1 year, and the 3-year risk of CRC was up to 1 % (0.3 new cases per 100 person-years under surveillance). A previous Korean study evaluated the incidence of advanced adenoma in a cohort of 214 individuals with ≥ 10 adenomas within a colonoscopy-based screening program [22]. In this work, no post-colonoscopy CRC was observed and a 3-year cumulative incidence of 7 % was reported for advanced adenoma. This lower percentage could be explained because, in the Asian study, lesions detected within 2.5 years following the index colonoscopy were counted as prevalent and merged to the date of screening colonoscopy. Therefore, the authors only considered advanced adenoma as incident when it occurred afterwards.

Taking into account our results, the consideration of individuals with ≥ 10 adenomas as a high risk population, after (if indicated) hereditary causes have been ruled out, is basically justified by the meaningful risk of advanced neoplasia at the 1-year surveillance colonoscopy. However, it should be kept in mind that the risk of advanced neoplasia remains high (> 10 %) until the third surveillance colonoscopy. Afterwards, the risk of advanced neoplasia considerably decreases, suggesting that surveillance intervals could be lengthened.

These data are interesting as no surveillance recommendation has been established in patients with non-hereditary polyposis after the first surveillance colonoscopy. Actually, in patients with < 10 adenomas who require surveillance, evidence of the benefit of a second surveillance colonoscopy in terms of CRC risk is still unclear. Even in the updated European guidelines, for the high risk group (≥ 5 polyps or size ≥ 2 cm), surveillance recommendations after the first surveillance colonoscopy are based on low quality evidence [9]. Our results suggest that, after the first surveillance colonoscopy, the follow-up could be reassessed on the basis of what was found during that examination.

In our work, the presence of an advanced adenomas at baseline was a clear independent risk factor for developing advanced neoplasia at first surveillance colonoscopy. This finding is not unexpected, taking into account that both the incidence and mortality of CRC is higher in individuals with advanced adenomas [23, 24]. In our opinion, given the scarce evidence to tailor colonoscopy surveillance intervals in patients with ≥ 10 ade-

▶ **Table 3** Factors associated with advanced neoplasia at first surveillance colonoscopy in patients with ≥ 10 baseline adenomas on bivariable and multivariable analysis.

	Advanced neoplasia at first surveillance colonoscopy				
	No (n = 122)	Yes (n = 39)	*P* value	Adjusted odds ratio (95 %CI)	Adjusted *P* value
Baseline characteristics					
Age at baseline colonoscopy, median (IQR), years	61 (56.6–65)	62 (59–65)	0.23		
Sex, female, n (%)	28 (22.9)	9 (23)	0.98		
BMI, median (IQR), kg/m^2 (n = 58)	29.4 (26.8–33.6)	26.8 (24.8–31.5)	0.19		
Cardiovascular risk factors present, n (%)					
Smoking history	66 (54.1)	21 (53.8)	0.65		
Overweight/obese (BMI ≥ 25 kg/m^2)	31 (86)	13 (33.3)	0.38		
Diabetes (n = 154)	31 (29.5)	9 (25.5)	0.87		
Dyslipidemia (n = 159)	46 (43.4)	14 (35.8)	0.82		
Hypertension (n = 159)	47 (43.9)	19 (48.7)	0.22		
Ischemic heart disease, n (%) (n = 150)	9 (9.0)	2 (5.1)	0.62		
Any cardiovascular risk factor, n (%)	101 (82.7)	31 (79.4)	0.64		
Family history of CRC, n (%)	19 (15.5)	8 (20.5)	0.47		
Personal history of extracolonic tumor, n (%)	18 (14.2)	5 (12.8)	0.76		
Phenotype at the index colonoscopy					
Number of adenomas, median (IQR)	10 (10–13)	10 (10–13)	0.97		
Patients with at least one advanced adenoma; n (%)	92 (75.4)	36 (92.3)	**0.03**	3.91 (1.12–13.62)	**0.03**
Patients with at least one adenoma ≥ 1 cm, n (%)	90 (73.7)	34 (87.1)	0.08	0.54 (0.09–2.97)	0.48
Patients with at least one adenoma ≥ 2 cm, n (%)	33 (27.0)	13 (33.3)	0.45		
Patients with at least one serrated lesion, n (%)	59 (48.3)	25 (64.1)	0.08	1.79 (0.84–3.81)	0.13
Patients with at least one SSL, n (%)	24 (19.6)	10 (25.6)	0.42		
Patients with at least one advanced serrated lesion, n (%)	12 (9.8)	5 (12.8)	0.59		
Patients with advanced adenoma and advanced serrated lesions, n (%)	11 (9.0)	5 (12.8)	0.48		
Interval time between procedures, median (IQR), months	14 (12–17)	14 (12–17)	0.65		

IQR, interquartile range; BMI, body mass index; CRC, colorectal cancer; SSL, sessile serrated lesion.

nomas, this factor becomes quite relevant and could be considered in the design of future prospective studies comparing different personalized surveillance strategies.

Lastly, no association was observed in relation to the number of baseline adenomas, consistent with the current evidence suggesting the minor role of multiplicity by itself in post-colonoscopy CRC risk [23–25]. This is an important point owing to increasing colonoscopy screening activity and the improvement in endoscopy equipment and ancillary techniques, which result in more and more individuals who are diagnosed with many diminutive polyps and are then referred for surveillance.

Our study has several strengths. First, this is the first work to estimate the prevalence of inherited and non-inherited adenomatous polyposis syndromes within a FIT-based CRC screening program; second, although retrospective, we focused on an unselected population of individuals with a shared surveillance program.

Nevertheless, several limitations should be acknowledged. First, as pointed out previously, germline genetic analysis testing was not performed in the whole cohort, so the percentage of patients with hereditary syndromes could have been underestimated. It is important to note that the figures observed in our cohort cannot be generalized to the average risk population, because they are restricted to FIT-based CRC screening cohorts.

Second, the number of patients decreased from the second surveillance colonoscopy onwards, so the incidence of lesions described during follow-up could be overestimated. To mini-

mize this bias, only the findings at the first surveillance colonoscopy were included when analyzing the potential risk factors of advanced neoplasia. Taking into account that 75% of patients who developed advanced neoplasia in the follow-up did so by their first surveillance colonoscopy, our observations are probably an adequate estimate of reality.

Finally, advanced neoplasia was selected as an end point instead of CRC owing to the small number of post-colonoscopy CRCs detected. Nevertheless, surveillance should aim to prevent, rather than detect, CRCs and the recent recommendations from the WEO [10] recognized the need for possible surrogate measures in surveillance studies. In this regard, the rate of "advanced colorectal polyps" (defined as an advanced adenoma or advanced serrated lesion) represents an acceptable surrogate outcome that is less prone to overdiagnosis or lead-time bias, as compared with using any polyp as an outcome [12]. Given all of this, we think that there is enough evidence to support advanced neoplasia, as a precursor condition of invasive cancer, being a good surrogate end point.

In conclusion, in a FIT-based CRC screening scenario, 10 or more adenomas are found in a small proportion of patients and inherited adenomatous polyposis syndromes seem to be rare within this population. A low rate of post-colonoscopy CRC is observed, but there is a substantial risk of advanced neoplasia, especially at the first surveillance colonoscopy in those individuals with advanced adenomas on their baseline colonoscopy. It is important to point out that, after the first surveillance colonoscopy, the proportion of patients with advanced neoplasia tends to progressively decrease through successive follow-up colonoscopies.

Based on our findings, in patients with ≥10 baseline adenomas, we therefore recommend genetic counseling to assess the indication for genetic testing and 1-year interval endoscopic surveillance. Once an inherited cause has been ruled out, the following surveillance intervals may be based on the findings of each successive colonoscopy, as is recommended for those patients with<10 adenomas. Future studies should focus on patients with ≥10 adenomas undergoing standardized protocols in order to define the best management and surveillance strategies for these patients.

Competing interests

FB received endoscopic equipment on loan of Fujifilm, received an honorarium for consultancy from Sysmex (2017–2020) and CPP-FAP (2018), speaker's fee from Norgine Iberia, and editorial fee from Elsevier as editor of Gastroenterologia y Hepatologia. M. Pellisé has received consultancy and speaker's fees from Norgine Iberia (2015–2020), a consultancy fee from GI Supply (2019), speaker's fees from Casen Recordati (2016–2019), Olympus (2018), and Jansen (2018), and research funding from Fujifilm Spain (2019), Fujifilm Europe (2020), and Casen Recordati (2020); her department has received loan material from Fujifilm Spain (from 2017 ongoing), a research grant from Olympus Europe (2005–2019), and loan material and a research grant from Fujifilm Europe (2020–2021); she is a Board member of ESGE and SEED; and receives a fee from Thieme as an Endoscopy Co-Editor.

Funding

"Instituto de Salud Carlos III" co-funded by European Regional Development Fund/European Social Fund; "A way to make Europe"/"Investing in your future"
PI16/00766
"Instituto de Salud Carlos III" co-funded by European Regional Development Fund/European Social Fund; "A way to make Europe"/"Investing in your future"
PI19/01050
"Instituto de Salud Carlos III" co-funded by European Regional Development Fund/European Social Fund; "A way to make Europe"/"Investing in your future"
PI19/01867
Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR)2017 SGR 653
Beca de la Marató de TV3 2020201932-30

References

[1] Syngal S, Brand RE, Church JM et al. ACG Clinical Guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 2015; 110: 223–262

[2] Grover S, Kastrinos F, Steyerberg EW et al. Prevalence and phenotypes of *APC* and *MUTYH* mutations in patients with multiple colorectal adenomas. JAMA 2012; 308: 485–492

[3] Rutter MD, East J, Rees CJ et al. British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland/Public Health England post-polypectomy and post-colorectal cancer resection surveillance guidelines. Gut 2020; 69: 201–223

[4] 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

[5] Hampel H, Bennett RL, Buchanan A et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: Referral indications for cancer predisposition assessment. Genet Med 2015; 17: 70–87

[6] Stoffel EM, Mangu PB, Gruber SB et al. Hereditary colorectal cancer syndromes: American society of clinical oncology clinical practice guideline endorsement of familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines. J Clin Oncol 2015; 33: 209–217

[7] Monahan KJ, Bradshaw N, Dolwani S et al. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). Gut 2020; 69: 411–444

[8] van Leerdam ME, Roos VH, van Hooft JE et al. Endoscopic management of polyposis syndromes: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2019; 51: 877–895

[9] Hassan C, Antonelli G, Dumonceau J-M et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2020. Endoscopy 2020; 52: 687–700

[10] Kaminski MF, Robertson DJ, Senore C et al. Optimizing the quality of colorectal cancer screening worldwide. Gastroenterology 2020; 158: 404–417

[11] Castaneda D, Popov VB, Verheyen E et al. New technologies improve adenoma detection rate, adenoma miss rate, and polyp detection rate: a systematic review and meta-analysis. Gastrointest Endosc 2018; 88: 209–222.e11

[12] Rutter MD, Bretthauer M, Hassan C et al. Principles for evaluation of surveillance after removal of colorectal polyps: Recommendations from the World Endoscopy Organization. Gastroenterology 2020; 158: 1529–1533.e4

[13] Stanich PP, Pearlman R, Hinton A et al. Prevalence of germline mutations in polyposis and colorectal cancer–associated genes in patients with multiple colorectal polyps. Clin Gastroenterol Hepatol 2019; 17: 2008–2015.e3

[14] Cubiella J, Marzo-Castillejo M, Mascort-Roca JJ et al. Clinical practice guideline. Diagnosis and prevention of colorectal cancer. 2018 update. Gastroenterol Hepatol 2018; 41: 585–596

[15] Lee TJW, Nickerson C, Goddard AF et al. Outcome of 12-month surveillance colonoscopy in high-risk patients in the national health service bowel cancer screening programme. Colorectal Dis 2013; 15: e435–e42

[16] Dekker E, Bleijenberg A, Balaguer F et al. Update on the World Health Organization criteria for diagnosis of serrated polyposis syndrome. Gastroenterology 2020; 158: 1520–1523

[17] Kaminski MF, Thomas-Gibson S, Bugajski M et al. Performance measures for lower gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) Quality Improvement Initiative. Endoscopy 2017; 49: 378–397

[18] Rembacken B, Hassan C, Riemann JF et al. Quality in screening colonoscopy: Position statement of the European Society of Gastrointestinal Endoscopy (ESGE). Endoscopy 2012; 44: 957–968

[19] Rubio CA, Nesi G, Messerini L et al. The Vienna classification applied to colorectal adenomas. J Gastroenterol Hepatol 2006; 21: 1697–1703

[20] Crockett SD, Nagtegaal ID. Terminology, molecular features, epidemiology, and management of serrated colorectal neoplasia. Gastroenterology 2019; 157: 949–966.e4

[21] Rutter MD, Beintaris I, Valori R et al. World Endoscopy Organization consensus statements on post-colonoscopy and post-imaging colorectal cancer. Gastroenterology 2018; 155: 909–925.e3

[22] Park SK, Hwang SW, Kim KO et al. Risk of advanced colorectal neoplasm in patients with more than 10 adenomas on index colonoscopy: A Korean Association for the Study of Intestinal Diseases (KASID) study. J Gastroenterol Hepatol 2017; 32: 803–808

[23] Click B, Pinsky PF, Hickey T et al. Association of colonoscopy adenoma findings with long-term colorectal cancer incidence. JAMA 2018; 319: 2021–2031

[24] Wieszczy P, Kaminski MF, Franczyk R et al. Colorectal cancer incidence and mortality after removal of adenomas during screening colonoscopies. Gastroenterology 2020; 158: 875–883.e5

[25] Atkin W, Wooldrage K, Brenner A et al. Adenoma surveillance and colorectal cancer incidence: a retrospective, multicentre, cohort study. Lancet Oncol 2017; 18: 823–834