Predictors of Metachronous Risk Polyps After Index Colonoscopy

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INTRODUCTION: **Guidelines for surveillance after polypectomy are lacking in strong evidence. Our aim was to identify some precursors of colorectal cancer lesions at 3 years after polypectomy to improve stratification and surveillance programs.**

METHODS: **We included patients with high-risk lesions (HRLs), defined as advanced adenoma (AA), large serrated polyps (SPs), and multiplicity (≥3 of any adenomas/SPs). Data on age, sex, cardiovascular risk factors, pharmacological treatment, and the histological characteristics in each individual, and mutations in genes involved in the most advanced index polyp, were collected. Parameters independently associated with a metachronous HRL diagnosis were evaluated through univariate and multivariate analyses. The results are reported as odds ratios and 95% confidence intervals along with *P* values.**

RESULTS: **A total of 537 cases (median age: 60.7 years; 66% male) were included. Dyslipidemia and smoking correlated with metachronous HRLs. Multivariate logistic regression analysis showed that the presence of multiplicity with ≥3 polyps on the index colonoscopy was significantly associated with metachronous HRL, AA, proximal AA, and ≥3 polyps at 3 years. In addition, independent predictors of metachronous proximal AA were increasing age, female sex, and the loss of expression of the MLH1 protein.**

DISCUSSION: **Multiplicity was a strong predictor of HRLs at 3 years, although the inclusion of other clinical variables (age, sex, smoking status, and dyslipidemia) improves surveillance recommendations. Without these risk factors, the surveillance could be extended to 5 years; we propose examining the somatic expression of MHL1 in all patients.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A498; http://links.lww.com/CTG/A499

Clinical and Translational Gastroenterology 2021;12:e00304. https://doi.org/10.14309/ctg.0000000000000304

INTRODUCTION

Advanced adenomas (AAs), defined as having more than 25% villous histology and/or a size ≥10 mm, and/or high-grade dysplasia, are the main precursor of colorectal cancer (CRC) (1,2). Moreover, large serrated polyps (SPs) (≥10 mm) are also considered equally premalignant lesions responsible for approximately 15% of CRC cases (3,4). Endoscopic polypectomy reduces the incidence and mortality of CRC and remains the key to successful population screening programs (2,5,6). Recent evidence confirms that individuals with AA and/or large SPs have a 3–4 times higher risk of mortality due to CRC than individuals without polyps (7,8). The risk of developing new lesions over time is associated with different factors (9,10). Individuals with low-risk adenomas (LRAs) (1–2 in number, tubular, <10 mm in size, and with low-grade dysplasia) diagnosed during their first colonoscopy have a 6.9% AA risk after 5 years from the procedure, whereas those with high-risk adenomas (HRAs) (AA and/or ≥3 synchronous adenomas) have a 15.5% risk after 5 years from the procedure (11). One analysis from a population-based colonoscopy registry showed that patients observed with large SPs at index colonoscopy had an increased risk of metachronous large SPs, and those with both HRAs and SPs had a considerably increased risk of metachronous HRAs (12). Colonoscopy remains the main strategy for surveillance after index polypectomy. The

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Received May 19, 2020; accepted December 18, 2020; published online February 18, 2021

intervals between colonoscopies are based on the size, number, and histopathology of the removed polyps. However, the current method of risk stratification is not accurate enough because of the lack of strong evidence (7,8,13,14).

Some research has pointed to other factors significantly related to metachronous lesions, such as a family history of CRC, sedentary lifestyle, smoking, and cardiovascular risk factors of metabolic syndrome (MetS) (15–17). Furthermore, some somatic molecular polyp characteristics have been linked to metachronous lesions. It is well known that molecular alterations occur during the progression of the adenoma-carcinoma sequence, which disturbs the cellular homeostasis. It has been postulated that these alterations can be a predisposition to new neoplasm development (18,19). In fact, the existence of the *KRAS* somatic mutation has been shown to be related to AA recurrences (20,21). For all of these reasons, applying the integrative concept of the "etiological field effect," which indicates that the interaction of multiple etiological and exogenous factors contribute to the initiation and progression of neoplasia, could help to improve the precision of risk stratification (22).

The goal of surveillance after polypectomy was to identify metachronous high-risk lesions (HRLs), which are defined as AA, large SPs, and/or having multiplicity (≥3 adenomas and/or SPs), for use as surrogate markers to signal the future risk of CRC (12). Thus, knowing the predictive factors of metachronous HRLs is essential and will improve stratification and surveillance programs.

Our aim was to identify the predictive factors for metachronous HRLs at 3 years after polypectomy. The study was conducted on a cohort drawn from a population-based CRC screening program at the index colonoscopy. We incorporated an evaluation of the environmental and clinical factors and the histopathological and somatic molecular changes based on the most advanced index polyp.

METHODS

We conducted a single-center retrospective study on a cohort that had an average risk of CRC (asymptomatic individuals between 50 and 69 years of age) from the Barcelona CRC Screening Program 2009–2011. The selected individuals had all been diagnosed with HRL through colonoscopy after a fecal immunochemistry test (OC-sensor ≥20 μg Hb/g of feces) and who had undergone surveillance colonoscopy at 3 years ± 6 months after polypectomy. We recorded which cases underwent more than one colonoscopy to ensure complete resection of polyps.

Informed consent was obtained from all patients. The biological samples were obtained from Barcelona Parc de Salut MAR Biobank (MARBiobanc), and the study was approved by the Hospital del Mar Clinical Research Ethics Committee (Ref. 2016S004). All colonoscopies fulfilled the standard quality policy (23), and all endoscopists adhered to the recommended adenoma detection rate standards.

Individuals with a personal and/or familial history of CRC or adenoma, inflammatory bowel disease, incomplete histopathological analysis of recovered polyps, and individuals who did not provide informed consent were excluded. Individuals who were observed to have SPs exclusively at the index colonoscopy were excluded because the number of SPs in such individuals was low.

Clinical and pathological data

We assessed the data on age, sex, the fecal immunochemistry test before colonoscopy, body mass index, smoking history, high blood pressure (25), type 2 diabetes mellitus, and dyslipidemia, defined as elevated plasma cholesterol, triglycerides, or both, or low HDL cholesterol. Data on the presence of MetS, as defined by the World Health Organization (26), administration of aspirin, nonsteroidal anti-inflammatory drugs, and statins and on any chronic treatment were also collected. Furthermore, the number of polyps, their size, location (distal or proximal to the splenic flexure), and histopathology at the basal and the surveillance colonoscopies were recorded.

Molecular markers

The molecular study was performed on the most advanced histological polyp in every patient. Two experienced pathologists selected the relevant section of the paraffin-embedded samples.

The genes most commonly involved in colorectal carcinogenesis that have been linked to the risk of advanced or metachronous polyps were studied based on the pathway, chromosomes, or microsatellite instabilities. These genes were *KRAS*, *NRAS*, *BRAF*, *APC*, *TP53*, *FBXW7*, *CTNNB1*, *SMAD4*, *Ki-67*, *MLH-1*, *CYTOKERATIN 7*, *CYTOQUERATIN 20*, and *CDX2*. DNA was extracted from formalin-fixed, paraffin-embedded blocks of the sample using the MagCore Genomic DNA FFPE One-Step Kit—MagCore HF 16 Plus (24,25).

Sequencing of the somatic mutation study. A sample library was generated with a QIAseq Targeted DNA panel (Qiagen) containing the coding region of the genes (see Supplementary Digital Contents 1 and 2, Supplementary Tables 1, http://links.lww.com/CTG/A498, and http://links.lww.com/CTG/A499). The resulting library was sequenced on the next-generation sequencing platform, MiSeq (Illumina, San Diego, CA), and analyzed with the QIASeq DNA pipeline. Variants obtained were filtered and annotated with Variant Studio v3.0 and visualized with Integrative Genomics Viewer v2.4. The average depth of coverage was 1559 x. The frequent CRC-associated variants in *KRAS*, *BRAF*, *NRAS*, *APC*, and *TP53* genes with variant allelic frequency <5% were considered true variants. Those variants with a variant allelic frequency >5% were considered less frequent variants to minimize the probability of false positive results.

All mutations identified were verified against a catalogue of somatic mutations in the cancer database and VarSome (27). The mutation nomenclature used follows the Human Genome Variation Society's recommendations.

Immunohistochemistry technique

Tissue microarray construction. Representative hematoxylin-eosin stained sections from polyps were prepared by 2 experienced gastrointestinal pathologists. The most histopathologically advanced polyp area was selected for the construction of the tissue microarray (TMA) blocks using a tissue arrayer. Each case was represented in the final TMA paraffin block by 2 tissue cores, each being 1.5 mm in diameter.

Immunohistochemistry tests were performed on the formalin-fixed paraffin-embedded TMA blocks. Sections were cut at 4 μm and then dewaxed and rehydrated. We used an

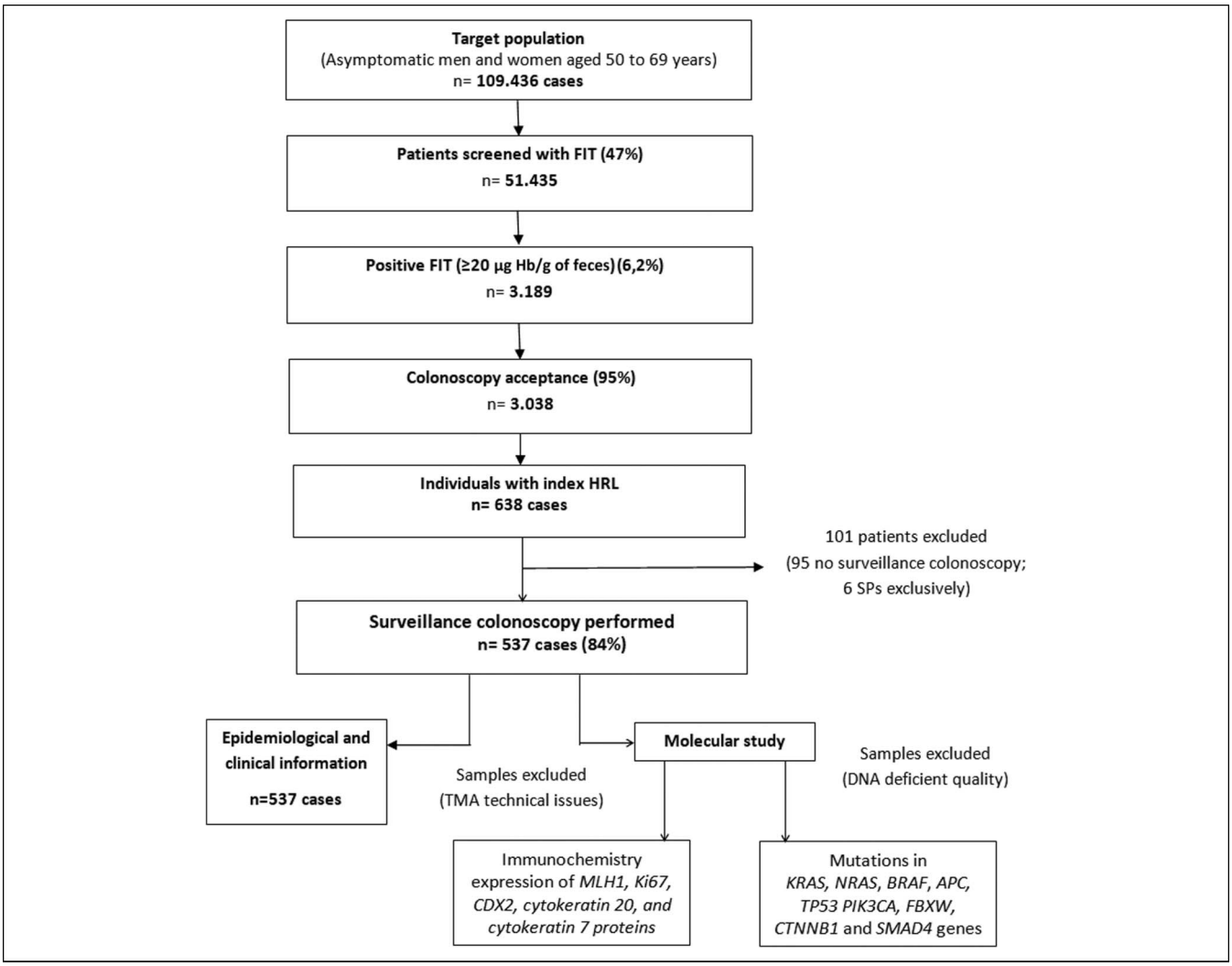

Figure 1. Study flow chart. Patients included in the analysis. FIT, fecal immunochemical test; HRL, high-risk lesions; SP, serrated polyps; TMA, tissue microarray.

automatized panel of Roche Ventana antibodies (Benchmarkt) (see Supplementary Digital Contents 1 and 2, Supplementary Tables 1, http://links.lww.com/CTG/A498, and 2 http://links.lww.com/CTG/A499). Each marker was semiquantitatively assessed and scored by estimating the percentage of tumor cells showing characteristic staining.

Membrane staining for CK7 and CK20 and nuclear staining for CDX-2 were considered positive when more than 5% of the tumor cells showed a positive reaction for each marker; Ki-67 was considered positive when more than 5% of the nonbasal located cells showed nuclear staining irrespective of intensity (28,29). Loss of MLH1 expression was considered when one or more clusters of tumor cells (minimal, focal, or multifocal) or all dysplastic cells showed ≥50% non-nuclear staining, compared with positive nuclear staining in normal epithelial cells (30).

Statistical analysis

Differences between demographic, clinical, and molecular data among patients with and without metachronous advanced lesions were tested with the χ^2 test. Multivariate logistic regression analysis was conducted to identify independent parameters associated with metachronous HRLs. The results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). SPSS version 25 (IBM, Armonk, NY) was used for the analyses.

RESULTS

We identified 638 individuals with HRLs at the baseline colonoscopy. We excluded 95 cases (14.8%) lacking surveillance colonoscopy and 6 cases with exclusively index SPs. A total of 537 cases (85.2%) that met the inclusion and exclusion criteria (median age 60.7 ± 5.2 years; 66% men) were analyzed. The median surveillance colonoscopy time was 38.8 months, and the study flow chart is presented in Figure 1.

Characteristics of the cohort included in the study are presented in Table 1. Half of the study population had had some exposure to tobacco, and 47% had been diagnosed with dyslipidemia. Of note, nearly 80% of the included individuals were overweight or obese (Figure 2).

Table 1. Baseline characteristics

Colonoscopy	Index	Surveillance at 3 yr	
Baseline characteristics	Patients	HRL	No HRL
Total no. of cases	N = 537 (%)	N = 103 (%)	N = 434 (%)
Age			
50–59 yr	229 (42.6)	39 (17.1)	190 (82.9)
60–69 yr	308 (57.4)	64 (20.8)	244 (79.2)
Sex			
Men	355 (66)	70 (19.7)	285 (80.3)
Woman	182 (44)	33 (18.2)	149 (81.8)
Cigarette smoking status			
Never	268 (49.9)	40 (15.6)	228 (84.4)
Smoker/former	269 (50.1)	61 (22.7)	208 (77.3)
High blood pressure			
Yes	273 (50.8)	59 (21.6)	214 (78.4)
Type 2 diabetes			
Yes	79 (15.9)	18 (22.8)	61 (77.2)
Dyslipidemia			
Yes	247 (46.7)	60 (24.4)	186 (75.6)
Body mass index (kg/m^2)			
<25	94 (19.6)	18 (19.8)	76 (80.9)
25–29	217 (45.2)	40 (18.4)	177 (81.6)
≥30	169 (35.2)	33 (19.5)	136 (80.5)
Metabolic syndrome			
Yes	53 (11)	14 (26.4)	39 (73.5)
Alcohol intake			
Yes	76 (17.2)	18 (23.7)	58 (76.3)
NSAID treatment			
Yes	65 (13.2)	13 (20)	52 (80)
Aspirin treatment			
Yes	75 (15.4)	14 (18.7)	61 (81.3)
Statins treatment			
Yes	201 (38.7)	42 (21)	158 (79)
More than one baseline colonoscopy			
Yes	137 (25.5)	38 (27.7)	99 (72.3)
Advanced adenoma			
Yes	463 (86.2)	89 (19.3)	373 (80.7)
Multiplicity (≥3 polyps)	282 (52.5)	71 (25.2)	211 (74.8)
Only adenomas	228 (42.5)	61 (26.8)	167 (73.2)
Adenomas and or serrated polyps	60 (11.2)	10 (1.6)	44 (1.6)
Adenoma size ≥10 mm	434 (80.8)	84 (19.4)	349 (80.6)
Villous component ≥25%	310 (57.7)	52 (16.8)	257 (83.2)
High grade dysplasia	111 (20.7)	22 (19.8)	89 (80.2)
Location of advanced adenomas			
Distal to the splenic flexure	327 (70.7)	55 (16.8)	271 (83.2)
Proximal splenic flexure	136 (29.3)	34 (25)	102 (75)

HRL, high-risk lesion; NSAID, nonsteroidal anti-inflammatory drug.

To achieve complete polyp resection, 137 cases (25.2%) required more than one colonoscopy, most of them because of control of the piecemeal removed lesions (70%) or for complete resection of the remaining polyps (30%).

The somatic molecular findings for the most histologically advanced polyps in every individual are provided in Table 2. As expected, most of the AAs had mutations in the *APC* gene. *KRAS* mutations were more frequent in AAs ($P < 0.05$). In addition, although they were not too frequent, *BRAF* mutations and loss of MLH1 expression were found in proximal AAs. The mutation data for the genes analyzed are presented in Supplementary Tables 1 and 2 (see Supplementary Digital Contents 1 and 2, http://links.lww.com/CTG/A498, and http://links.lww.com/CTG/A499).

At surveillance colonoscopies, 103 cases (19%) were classified as HRLs. There were 54 patients with AAs (10.1%), with 29 of the AAs (5.4%) located in the proximal colon. In 73 cases (13.6%), we found multiplicity (63 cases with ≥3 adenomas and 10 cases with ≥3 adenomas plus large SPs). Nine patients (1.7%) had large SPs in the proximal colon. The remaining 435 individuals (81.0%) had normal colonoscopy findings at 3 years (48.9%) or had low-risk lesions (32.0%). No CRCs were diagnosed.

Risk of advanced lesions at the surveillance colonoscopy

The univariate analysis results are reported in Tables 3 and 4. When we evaluated the clinical factors, the patients who were current or former smokers had a slightly but statistically significantly increased metachronous HRL risk (OR = 1.58, 95% CI: 1.01–2.46) as did those with dyslipidemia (OR = 1.74, 95% CI: 1.12–2.70). A history of dyslipidemia or high blood pressure correlated with multiplicity at the surveillance colonoscopy (OR = 2.20, 95% CI: 1.32–3.67; OR = 1.74, 95% CI: 1.05–2.91, respectively). In addition, those presenting with multiplicity at the index colonoscopy were more than twice as likely to develop metachronous AAs (OR = 2.54, 95% CI: 1.36–4.74), proximal AAs (OR = 2.46, 95% CI: 1.07–5.66), repeated multiplicity (OR = 2.49, 95% CI: 1.45–4.28), and HRLs (OR = 2.36, 95% CI: 1.48–3.75). The need for additional colonoscopies after the index colonoscopy correlated with increased occurrence of metachronous AAs, multiplicity, and HRLs (OR = 1.99, 95% CI: 1.10–3.57; OR = 1.86, 95% CI: 1.10–3.14; OR = 1.91, 95% CI: 1.20–3.04, respectively). Of all the studied baseline characteristics, large metachronous SPs were only significantly associated with the need for more than one index colonoscopy (OR = 6.56, 95% CI: 1.18–36.46), although the number of metachronous large SPs was small. We evaluated the mutations individually and in groups from the same polyp for the power to predict metachronous lesions at 3 years, which turned out to be poor in both cases. Loss of nuclear expression of the *MLH1* gene at the time of baseline colonoscopy resulted in an 8-fold increased risk of proximal AAs (OR = 8.68, 95% CI: 2.44–30.89) and up to a 5-fold increased risk of multiplicity (OR = 5.02, 95% CI: 1.54–16) and HRLs (OR = 4.59, 95% CI: 1.44–14.62) at the follow-up colonoscopy.

Multivariate analysis

Multivariate logistic regression analysis (Table 5) confirmed that older individuals and women had a higher risk of being diagnosed with metachronous proximal AAs (OR = 3.59, 95% CI: 1.29–9.93; OR = 3.12, 95% CI: 1.31–7.69, respectively). Dyslipidemia and smoking history were associated with a higher risk of developing HRLs (OR = 1.68, 95% CI: 1.00–2.79; OR = 1.69, 95% CI: 1.00–2.86, respectively). Individuals with index multiplicity were 3 times more likely to be diagnosed at the 3-year surveillance of HRL (OR = 2.35, 95% CI: 1.35–4.10), AA (OR = 3.01, 95% CI: 1.44–6.27), proximal AA (OR = 4.42, 95% CI: 1.66–11.75), and multiplicity (OR = 2.93, 95% CI: 1.48–5.81) than those with no multiplicity. From the molecular somatic analysis, the multivariable analysis showed that the expression of the MLH1 protein was significantly associated with proximal AAs at surveillance (OR = 15.21, 95% CI: 3.07–76.58) and the mutation in *NRAS* was significantly associated with any size of SP at surveillance 4.42 (95% CI: 1.31–14.91).

DISCUSSION

This study confirms that multiplicity is a strong predictor of metachronous HRLs and also highlights the importance of factors such as a history of smoking, dyslipidemia, older age, female sex, and loss of MLH1 protein expression. These results reveal the need to optimize current surveillance guideline strategies.

At the 3-year follow-up, 19% of patients with HRL at the index colonoscopy had metachronous HRLs. These results were comparable with those of other studies (31). However, the variability in HRL recurrence in published studies is high because it depends not only on individual risk factors but also on the colonoscopy quality and the subsequent polyps' miss rate (MR) (9,32,33). In our cohort, we estimated a 13% MR for AAs, a

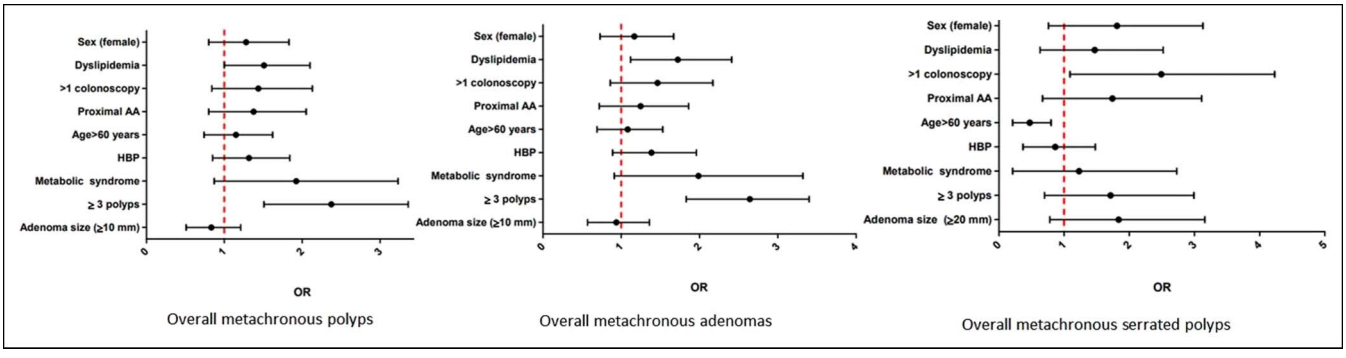

Figure 2. Predictive factors of metachronous overall lesions. Multivariate analysis. AA, advanced adenoma; HBP, high blood pressure; OR, odds ratio.

Table 2. Molecular baseline characteristics

Mutation	Patients	%
KRAS (n = 441)		
Wild type≤5%	278	63
Mutation >5%	163	37
BRAF (n = 444)		
Wild type≤5%	425	95.7
Mutation >5%	19	4.3
NRAS (n = 444)		
Wild type≤5%	429	96.6
Mutation >5%	15	3.4
APC (n = 434)		
Wild type≤5%	50	11.5
Mutation >5%	384	88.5
TP53 (n = 436)		
Wild type≤5%	345	79.1
Mutation >5%	91	20.9
CTNNB1 (B-catenin) (n = 408)		
Wild type≤5%	391	95.8
Mutation >5%	17	4.2
SMAD4 (n = 411)		
Wild type≤5%	400	97.3
Mutation >5%	11	2.7
FBXW7 (n = 407)		
Wild type≤5%	364	89.4
Mutation >5%	43	10.6
MLH1 (n = 455)		
Normal expression	443	97.4
Loss nuclear expression ≥50%	12	2.6
CDX2 (n = 455)		
Normal expression	259	56.9
Loss of any nuclear expression	196	36.5
Cytokeratin 7 (n = 446)		
Normal expression	396	88.8
Cytoplasmatic expression	50	11.2
Cytokeratin 20 (n = 440)		
Normal expression	377	85.7
Loss of cytoplasmatic expression	63	14.3
Ki-67 (n = 332)		
Normal expression	2	0.6
Nuclear expression	330	99.4
APC + *KRAS*	142	32.7
APC + *KRAS* + *TP53*	37	8.5
APC + KRAS + NRAS	5	1.1

proportion higher the 9% MR published in the meta-analysis by Zhao et al. (34). Our MR was likely overestimated because we obtained it from surveillance colonoscopies performed to ensure complete resection (46).

Older age and female sex were robust predictors of metachronous proximal AAs (OR = 3.59, 95% CI: 1.29–9.93; OR = 3.12, 95% CI: 1.31–7.69, respectively). Older age has been identified as an independent HRL risk factor (9,35), especially for HRLs in the proximal colon (36). This might be because of decreased immunity and genetic variations that occur with advancing age (35). The Clinical Outcomes Research Initiative endoscopy database provides the opportunity to study the differences in polyps and tumors with differences in age and sex. Using this, we found that women have a greater tendency of developing right-sided polyps. Indeed, hormonal factors may explain a large percentage of the metachronous right-sided AAs observed in women (37) because estrogen exposure is a protective factor against the Microsatellite Instable high phenotype, which often accompanies right-sided tumors (38). Therefore, it is necessary to emphasize that special attention must be given in the detection of proximal lesions in women older than the age of 60 years.

There is limited information about the role of each of the components of MetS in metachronous HRL development (16). Nevertheless, we found a higher proportion of new HRLs at surveillance colonoscopy in patients with dyslipidemia; up until now, the molecular mechanism behind this is not well understood (38,39).

Likewise, carcinogenic compounds in tobacco, mainly aromatic amines, can cause mutations in genes implicated in CRC, such as *KRAS* and *BRAF* (40). In a retrospective study, higher nicotine levels between the index and follow-up colonoscopies were correlated with metachronous colorectal neoplasia risk (41). These findings have important public health implications because they show that improving the plasma levels of cholesterol/triglycerides and giving up cigarette smoking would be effective measures for preventing colorectal metachronous polyps.

In our series, exposure to tobacco and the presence of dyslipidemia had a higher risk of global metachronous HRL, whereas older age, female sex, and loss of *MLH1* expression were significantly associated with HRLs on the right side (36,42). Thus, our results could suggest that genetic factors have a greater effect on the proximal colon, whereas environmental factors have a more global effect (36,42).

Some characteristics found in index polyps are indicative of an increased risk of metachronous lesions. However, these findings are sufficiently helpful for planning early surveillance strategies, most likely because their effect could depend on latency time. We did not find any histological characteristics that increased metachronous HRL risk. Nonetheless, we report that multiplicity on index colonoscopy was a powerful predictor of HRL recurrence, possibly owing to genetic imbalance of cell proliferation in some individuals, which could lead to accelerated carcinogenesis on normal mucosa. Therefore, it is important to ensure that proper surveillance is performed on these individuals(43,44,46).

In addition, we found that *NRAS* mutations predicted the risk of SPs of any size 3 years after the polypectomy, and the loss of

Table 3. Predictive factors of metachronous overall lesions (univariate analysis)

Baseline characteristics	Polyps		Adenoma		Serrated lesion	
Variable	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
Age >60 yr	164	1.25 (0.89–1.77)	151	1.21 (0.86–1.72)	18	**0.49 (0.26–0.91)**
Gender (female)	90	0.90 (0.63–1.29)	80	0.82 (0.57–1.17)	17	1.24 (0.65–2.35)
Smoker/former	145	1.23 (0.88–1.74)	133	1.19 (0.84–1.68)	28	1.85 (0.96–3.55)
High blood pressure	151	**1.39 (0.99–1.95)**	142	**1.47 (1.04–2.07)**	19	0.70 (0.37–1.31)
Type 2 diabetes	45	1.28 (0.79–2.07)	43	1.36 (0.84–2.20)	7	1.11 (0.47–2.58)
Dyslipidemia	142	**1.61 (1.14–2.27)**	136	**1.80 (1.27–2.55)**	22	1.18 (0.63–2.19)
Body mass index ≥30	88	1.03 (0.80–1.32)	79	1.00 (0.78–1.29)	15	1.10 (0.69–1.73)
Metabolic syndrome	35	**1.92 (1.05–3.5)**	34	**2.14 (1.18–3.87)**	3	0.64 (0.19–2.16)
>1 colonoscopy	85	**1.80 (1.21–2.68)**	80	**1.82 (1.23–2.70)**	18	**2.13 (1.13–4.02)**
≥3 polyps	173	**2.41 (1.70–3.42)**	164	**2.60 (1.83–3.69)**	28	1.62 (0.85–3.07)
AA	228	0.61 (0.37–1.01)	210	0.62 (0.38–1.02)	37	0.83 (0.35–1.93)
Proximal AA	82	**1.70 (1.14–2.54)**	76	**1.65 (1.11–2.45)**	16	1.78 (0.93–3.42
Adenoma size						
≥10 mm	208	**0.51 (0.33–0.80)**	192	**0.55 (0.35–0.85)**	33	0.68 (0.33–1.39)
≥20 mm	67	1.10 (0.73–1.64)	60	1.01 (0.67–1.51)	16	**1.96 (1.02–3.75)**
Villous component≥25%	172	0.82 (0.58–1.17)	138	0.78 (0.55–1.10)	25	0.95 (0.51–1.76)
High grade dysplasia	56	0.95 (0.63–1.45)	52	0.97 (0.64–1.48)	10	1.12 (0.54–2.35)
KRAS mutation	86	1.04 (0.70–1.54)	80	1.07 (0.73–1.58)	11	0.73 (0.35–1.53)
NRAS mutation	8	1.05 (0.37–2.96)	7	0.95 (0.34–2.65)	4	3.96 (1.20–13.07)
BRAF mutation	10	1.03 (0.41–2.59)	9	0.98 (0.39–2.47)	3	2.21 (0.61–7.99)
APC mutation	198	1.07 (0.59–1.94)	182	0.98 (0.54–1.77)	31	1.01 (0.34–3.01)
TP53 mutation	45	0.87 (0.55–1.39)	42	0.91 (0.57–1.45)	7	0.94 (0.39–2.21)
CTNNB1 mutation	11	1.71 (0.62–4.72)	10	1.57 (0.58–4.22)	3	2.47 (0.67–9.08)
SMAD4 mutation	5	0.74 (0.22–2.48)	4	0.61 (0.17–2.10)	2	2.38 (0.49–11.46)
MLH1	8	1.92 (0.57–6.46)	8	2.26 (0.67–7.61)	2	2.39 (0.50–11.37)
CDX2	127	0.82 (0.57–1.20)	118	0.87 (0.59–1.25)	15	0.52 (0.26–1.03)
Cytokeratin 7	25	0.95 (0.52–1.71)	23	0.93 (0.51–1.68)	4	1.13 (0.38–3.37))
Cytokeratin 20	195	1.19 (069–203)	180	1.15 (0.67–1.97)	31	1.80 (0.53–6.08)
Ki67	161	—	151	—	21	0.07 (0.004–1.13)
APC and KRAS	74	1.01 (0.67–1.51)	68	1.00 (0.67–1.50)	9	0.67 (0.31–1.47)
APC, KRAS, and p53	19	0.97 (0.49–1.91)	19	1.16 (0.59–2.28)	2	0.62 (0.14–2.68)
APC, KRAS, and NRAS	2	0.60 (0.10–3.67)	2	0.71 (0.11–4.33)	1	2.89 (0.31–26.59)

Significant values are represented in bold.
AA, advanced adenoma; CI, confidence interval; OR, odds ratio.

MLH1 protein expression was associated with proximal AA. Limited data exist about the molecular profile of index polyps as a predictive factor of metachronous lesions. Because several such polyps represent early mutational changes, they could prove useful in histological classification efforts, apart from their conventional use as carcinogenesis predictors. As expected, *BRAF* mutations were uncommon, although no patients with SPs were analyzed. Nevertheless, we found that 4% of patients exhibited *BRAF* mutation and loss of MLH1 protein expression. These polyps could reflect mixed polyps or serrated polyps mistakenly classified as adenomas. Three years may have been a too short of a period to identify molecular changes to predict recurrence (19). Juarez et al. found that polyps with *KRAS* mutations had a 2-fold higher risk of metachronous advanced lesions. Although we could not replicate this finding in our series, we found that *KRAS* mutations were useful for diagnosing HRL. This discrepancy could be because the cohort was different and that they analyzed all polyps, whereas we analyzed the most advanced polyp of each individual.

This study has several strengths. The cohort was homogenous, drawn from a CRC population screening program, and although this was a retrospective study, baseline colonoscopies were

Table 4. Predictive factors of metachronous risk lesions characterized by AA, multiplicity (≥3 polyps), high-risk lesion (AA and/or multiplicity), and advanced serrated polyps (univariate analysis)

Baseline characteristics	Surveillance colonoscopy									
	AA		Proximal AA		Multiplicity		HRL		Large SPs (≥10 mm)	
Variable	n	OR (95% CI)	n	OR (95%CI)	n	OR (95%CI)	n	OR (95% CI)	n	OR (95% CI)
Age >60 yr	34	1.29 (0.72–2.31)	23	3.01 (1.18–7.40)	45	1.22 (0.73–2.03)	64	1.36 (0.87–2.12)	3	0.85(0.17–4.28)
Gender (female)	22	1.40 (0.78–2.5)	15	**2.22 (1.04–4.76)**	22	0.82 (0.48–1.40)	33	0.90 (0.48–1.44)	9	2.12 (0.57–1.44)
Smoker/former	31	1.45 (0.81–2.61)	12	0.70 (0.32–1.52)	42	1.44 (0.87–2.40)	61	**1.58 (1.01–2.46)**	10	1.44 (0.53–3.87)
High blood pressure	23	0.68 (0.38–1.20)	13	0.76 (0.36–1.63)	46	**1.74 (1.05–2.91)**	58	1.36 (0.87–2.10)	4	2.00 (0.36–11.05)
Type 2 diabetes	7	0.83 (0.36–1.92)	1	0.19 (0.02–1.46)	13	1.28 (0.66–2.47)	18	1.31 (0.73–2.33)	1	1.23 (0.14–10.81)
Dyslipidemia	27	1.18 (0.67–2.07)	14	1.1 (0.52–2.32)	46	**2.20 (1.32–3.67)**	60	**1.74 (1.12–2.70)**	1	0.24 (0.02–2.10)
Body mass index ≥30	17	1.03 (0.68–1.58)	8	0.94 (0.53–1.66)	24	1.05 (0.73–1.51)	33	1.00 (0.72–1.37)	1	0.72 (0.21–2.44)
Metabolic syndrome	40	1.23 (0.49–3.07)	1	0.34 (0.46–2.60)	11	1.77 (0.86–3.65)	14	1.69 (0.87–3.26)	0	—
>1 colonoscopy	21	**1.99 (1.10–3.57)**	12	2.12 (0.99–4.58)	27	**1.86 (1.10–3.14)**	38	**1.91 (1.20–3.04)**	4	**6.56 (1.18–36.46)**
≥3 polyps	39	**2.54 (1.36–4.74)**	21	**2.46 (1.07–5.66)**	52	**2.49 (1.45–4.28)**	71	**2.36 (1.48–3.75)**	5	5.32 (0.61–46.03)
AA	45	0.76 (0.35–1.64)	24	0.74 (0.27–2.02)	63	0.99 (0.48–2.04)	89	1.08 (0.57–2.06)	5	0.76 (0.08–6.65)
Proximal AA	16	1.26 (0.68–2.35)	9	1.33 (0.59–3.00)	24	1.53 (0.89–2.60)	34	1.56 (0.97–2.49)	2	1.75 (0.31–9.72)
Adenoma size										
≥10 mm	42	1.00 (0.53–1.88)	21	0.72 (0.25–1.40)	57	1.44 (0.79–2.59)	84	1.25 (0.99–1.57)	4	0.36 (0.07–1.83)
≥20 mm	15	1.28 (0.68–2.41)	21	1.02 (0.42–2.46)	19	1.16 (0.66–2.05)	27	1.23 (0.75–2.02)	4	1.60 (0.28–8.88)
Villous component≥25%	29	0.83 (0.47–1.46)	14	0.66 (0.31–1.39)	34	**0.59 (0.36–0.97)**	52	0.69 (0.45–1.07)	4	1.31 (0.23–7.27)
High grade dysplasia	13	1.23 (0.63–2.40)	6	0.99 (0.39–2.49)	13	0.80 (0.42–1.52)	22	1.08 (0.63–1.82)	2	1.86 (0.33–10.35)
KRAS mutation	15	0.81 (0.42–1.55)	8	0.66 (0.28–1.55)	21	0.88 (0.50–1.56)	34	1.21 (0.74–1.97)	3	2.58 (0.42–15.68)
NRAS mutation	2	1.34 (0.29–6.14)	2	2.37 (0.50–11.07)	2	0.96 (0.21–4.37)	3	1.07 (0.25–3.38)	0	—
BRAF mutation	3	1.70 (0.47–6.09)	3	3.11 (0.84–11.43)	4	1.75 (0.56–5.46)	5	1.58 (0.55–4.52)	3	—
APC mutation	39	1.02 (0.38–2.72)	22	0.70 (0.23–2.13)	51	0.80 (0.35–1.81)	74	1.05 (0.49–2.26)	35	0.44 (0.04–4.10)
TP53 mutation	8	0.77 (0.34–1.72)	5	0.80 (0.29–2.19)	12	0.83 (0.18–3.73)	14	0.73 (0.39–1.38)	8	—
CTNNB1 mutation	1	0.51 (0.06–4.00)	0	—	2	0.93 (0.47–1.84)	2	0.56 (0.12–2.54)	3	6.72 (0.68–67.77)
SMAD4 mutation	2	1.94 (0.40–9.28)	1	1.49 (0.18–12.12)	2	1.39 (0.29–6.60)	2	0.96 (0.20–4.53)	1	—
MLH1	3	3.09 (0.80–11.8)	**4**	**8.68 (2.44–30.89)**	5	**5.02 (1.54–16)**	6	**4.59 (1.44–14.62)**	3	—
CDX2	25	0.89 (0.48–1.65)	14	0.74 (0.34–1.59)	35	1.07 (0.61–1.86)	48	0.92 (0.57–1.48)	18	0.44 (0.07–2.66)
Cytokeratin 7	6	1.28 (0.51–3.20)	4	1.39 (0.46–4.22)	4	0.51 (0.17–1.48)	8	0.77 (0.34–1.71)	4	—
Cytokeratin 20	39	1.09 (0.44–2.71)	2	2.17 (0.50–9.43)	53	1.31 (0.56–3.03)	73	1.00 (0.51–1.98)	4	—
Ki67	0	—	0	—	1	0.12 (0.01–1.94)	56	0.19 (0.01–3.18)	1	—
APC and KRAS	14	0.93 (0.48–1.82)	7	0.71 (0.29–1.72)	19	0.96 (0.53–1.72)	30	1.25 (0.76–2.07)	12	3.04 (0.50–18.52)
APC, KRAS, and p53	4	1.04 (0.35–3.08)	2	0.82 (0.18–3.62)	5	0.98 (0.36–2.64)	7	1.00 (0.42–2.37)	3	—
APC, KRAS, and NRAS	1	2.20 (0.24–20.1)	1	3.82 (0.41–35.4)	2	4.31 (0.70–26.38)	2	2.91 (0.48–17.74)	2	—

Significant values are represented in bold.
AA, advanced adenoma; CI, confidence interval; OR, odds ratio; HRL, high-risk lesion; SP, serrated polyps.

performed following an identical protocol of quality standards. Moreover, the integrity of both resections and polyp pathology analyses was ensured via second-look colonoscopies when it was deemed necessary, and the surveillance colonoscopy was performed at 3 years using the same quality standards. Finally, clinical information was obtained from computerized medical records. Thus, ours is a study with reliable results involving exhaustive analyses of clinical, endoscopic, and molecular factors associated with advanced metachronous lesions at 3 years after polypectomy.

This study also has certain limitations. Some clinical factors associated with the risk of metachronous lesions, such as diet and physical activity, were not studied, and they may be relevant. Furthermore, the CpG island methylator phenotype and microsatellite instability were not determined. Although these results would have been interesting, we instead analyzed BRAF mutations and MLH1 expression that also reflect the serrated pathway, although the correlation is not always 100%. Likewise, a greater number of cases included in the study could have helped to obtain more relevant results.

Table 5. Predictive factors of metachronous risk lesions (multivariate analysis)

	Surveillance colonoscopy				
Basal characteristics	AAs OR (95% CI)	Proximal AA OR (95% CI)	≥3 polyps OR (95% CI)	High risk lesions (AA and/or multiplicity) OR (95% CI)	Large serrated lesions OR (95% CI)
Age 60–69	1.55 (0.76–3.14)	3.59 (1.29–9.93)	1.34 (0.71–2.54)	1.51 (0.87–2.60)	0.91 (0.27–3.21)
Gender (female)	2 (1–4)	3.12 (1.31–7.69)	1.21 (0.60–2.45)	1.40 (0.77–2.53)	2.84 (0.73–11.05)
Smoker/former	1.74 (0.85–3.58)	0.95 (0.38–2.33)	1.64 (0.85–3.20	1.69 (1.00–2.86)	4.82 (1.05–22.02)
Dyslipidemia	1.03 (0.53–2.02)	0.86 (0.37–2.01)	2.47 (1.33–4.57)	1.68 (1.00–2.79)	0.71 (0.20–2.45)
≥3 polyps	3.01 (1.44–6.27)	4.42 (1.66–11.75)	2.93 (1.48–5.81)	2.35 (1.35–4.10)	3.70 (0.81–16.83)
>1 colonoscopy	1.21 (0.56–2.57)	1.82 (0.72–4.64)	1.74 (0.90–3.38)	1.64 (0.92–2.93)	3.64 (1.16–11.34)
Adenoma size ≥20 mm	0.92 (0.41–2.09)	0.69 (0.23–2.02)	0.94 (0.46–1.94)	1.04 (0.56–1.93)	2.33 (0.68–8.8.03)
NRAS	1.23 (0.25–6.07)	1.87 (0.35.9.93)	1.05 (0.18–5.96)	1.08 (0.26–4.49)	4.45 (0.43–46.51)
MLH1	3.06 (0.57–16.21)	15.21 (3.07–76.58)	4.09 (0.88–18.95)	4.03 (0.99–16.43)	

AA, advanced adenoma; CI, confidence interval; OR, odds ratio.

In conclusion, these results suggest that the ability to identify groups at risk of metachronous lesions remains challenging, as does the formulation of best follow-up recommendations.

Older age, female sex, smoking status, dyslipidemia, and baseline multiplicity significantly increased the risk of new advanced lesions at 3 years after polypectomy. The clinical guidelines for patient surveillance after index polypectomy should consider incorporating these clinical factors to personalize surveillance recommendations. Because no cancer was diagnosed at surveillance, we suggest that follow-up should be performed at 5 years after the procedure if the individuals do not present with risk predictive factors. Regarding MLH1 expression, we suggest examining it in all patients when conducting proximal HRL surveillance because it would be a cost-effective strategy because of the low price of the MLH1 immunohistochemistry technique.

Future studies involving larger cohorts could further confirm these findings.

Study Highlights

WHAT IS KNOWN

- ✓ The risk of developing new advanced lesions is associated with different factors.
- ✓ Clinical follow-up recommendations are lacking in strong evidence, and surveillance strategies are based only on the size, number, and pathologic characteristics of the removed index polyps.
- ✓ Knowing clinical and molecular predictive factors of metachronous risk lesions would provide better risk stratification and improve surveillance programs.

WHAT IS NEW HERE

- ✓ Results regarding clinical, endoscopic, and molecular factors associated with risk metachronous lesions at 3 years.
- ✓ This study confirms that multiplicity is a strong predictor of metachronous HRLs, besides the relevance such factors as a history of smoking, dyslipidemia, older ager, female sex, and loss of MLH1 protein expression.
- ✓ These results expose the need to optimize current surveillance guidelines strategies.

TRANSLATIONAL IMPACT

- ✓ We suggest following up at 5 years if individuals do not present with clinical risk predictive factors.
- ✓ We propose examining patients with HRLs considering that it would be a cost-effective strategy because of low price of the MLH1 immunohistochemistry technique.

CONFLICTS OF INTEREST

Guarantor of the article: Alvarez-Urturi Cristina, MD, PhD.

Specific author contributions: M.A.: conceived and designed this study. M.A., C.A.-U., L.C., and A.B.: gathered the data. A.S.-U.: contributed to the performance and evaluation of colonoscopies. G.N., D.N.-H., M.I.-C., A.D., L.F., and B.B.: processed the samples and carried out and analyzed the histopathological and molecular studies. M.A., C.A.-U., L.C., and X.B.: analyzed and interpreted the data. M.A., C.A.-U., and L.C.: drafted the article. All authors critically reviewed the draft and approved the final version of the article.

Financial support: This work was supported by grants from the Instituto de Salud Carlos III-FEDER (PI14/00441) and (PT17/0015/0011); the Singular Project AECC (PS14152544ANDR); and the Xarxa de Bancs de Tumors sponsored by Pla Director d'Oncologia de Catalunya (XBTC). AGAUR Research scholarship 2017SGR80.

Potential competing interests: None to report.

Ethics approval: The study was approved by The Hospital del Mar Clinical Research Ethics Committee (Ref. 2016S004).

ACKNOWLEDGMENTS

We thank Xavier Duran for statistical analysis support. In addition, we are deeply grateful to the patients who participated in this investigation. We would like to thank Editage (www.editage.com) for English language editing. This study will be part of Laura Carot Bastard's doctoral thesis.

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