



Clinical characteristics and risk factors related to polyposis recurrence and advanced neoplasm development among patients with non-hereditary colorectal polyposis

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Background/Aims: Patients with more than 10 cumulative polyps might involve a greater genetic risk of colorectal neoplasia development. However, few studies have investigated the risk factors of polyposis recurrence and development of advanced neoplasms among patients with non-hereditary colorectal polyposis. **Methods:** This study included patients (n=855) with 10 or more cumulative polyps diagnosed at Severance Hospital from January 2012 to September 2021. Patients with known genetic mutations related to polyposis, known hereditary polyposis syndromes, insufficient information, total colectomy, and less than 3 years of follow-up were excluded. Finally, 169 patients were included for analysis. We collected clinical data, including colonoscopy surveillance results, and performed Cox regression analyses of risk factors for polyposis recurrence and advanced neoplasm development. **Results:** The 169 patients were predominantly male (84.02%), with a mean age of 64.19±9.92 years. The mean number of adenomas on index colonoscopy was 15.33±8.47. Multivariable analysis revealed history of cancer except colon cancer (hazard ratio [HR], 2.23; 95% confidence interval [CI], 1.23–4.01), current smoking (HR, 2.39; 95% CI, 1.17–4.87), and detection of many polyps (≥15) on index colonoscopy (HR, 2.05; 95% CI, 1.21–3.50) were significant risk factors for recurrence of polyposis. We found no statistically significant risk factors for advanced neoplasm development during surveillance among our cohort. **Conclusions:** The presence of many polyps (≥15) on index colonoscopy, history of cancer except colon cancer, and current smoking state were significant risk factors for polyposis recurrence among patients with non-hereditary colorectal polyposis. (Intest Res 2023;21:510-517)

Key Words: Colonic polyps; Polyposis; Recurrence; Adenoma; Smoking

INTRODUCTION

Colorectal cancer (CRC), the third most common cancer worldwide, is a significant cause of cancer-related morbidity and mortality, especially in developed countries.¹ Although most CRCs occur seemingly sporadically, up to a third of CRCs are likely to be related to heritable factors.² Despite this, only

5% to 6% of all CRCs are associated with germline mutations that confer an inherited predisposition to CRC.³ Timely identification of individuals at risk for hereditary CRC syndromes offers an opportunity to intervene in and prevent the development of cancer.³ Inherited CRC syndromes include Lynch syndrome (2%–3%), familial adenomatous polyposis (<1%), and hamartomatous polyposis syndrome (<0.1%), and so on.⁴ Among them, inherited CRC syndromes related to colon polyposis include familial adenomatous polyposis (APC mutation), MUTYH-associated polyposis (MYUHYH mutation), Cowden syndrome (PTEN mutation), and so on.⁵ However, in clinical practice, there are patients with polyposis (10 or more ade-

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nomatous polyps) with no family history of CRC or polyposis and negative genetic test results, which are indicative of non-hereditary polyposis, suggesting unknown polygenic genetic risk and interaction with environmental factors.

Colorectal polyp is considered to be a precancerous lesion, and colonoscopy screening with removal of a colorectal polyp is an effective strategy to reduce the incidence of CRC and related mortality.⁶⁻¹³ The surveillance interval is recommended based on the recurrence risk of polyps, such as 3 years for high-risk polyps (more than 1 cm in size, villous adenoma component, high-grade dysplasia, 3 or more adenoma in number, etc.).¹⁴ Moreover, colorectal polyposis, with more than 10 adenomas, may be a phenotype of genetic risk-associated neoplasia and is an indication for more frequent surveillance and genetic testing.¹⁵ Even if no genetic mutations have been identified, patients with more than 10 cumulative polyps may involve an increased genetic risk for colorectal polyp development. In the surveillance colonoscopy of these non-hereditary polyposis patients, some patients show continuous recurrence of polyposis, while others do not, which means that patients with continuous recurrence of polyposis may face a greater genetic risk than others.

Until now, numerous studies have investigated clinical risk factors for polyp development and recurrence. Old age, male sex, smoking, being overweight, excessive alcohol consumption, and family history of colon polyps are known risk factors related to colorectal neoplasia.¹⁶⁻¹⁸ However, no study has investigated risk factors related to the recurrence of multiple polyps in patients with more than 10 polyps without known hereditary polyposis syndrome. Also, there is no study on whether these patients are affected more by genetic factors or environmental factors. Thus, we aimed to investigate the clinical characteristics and risk factors of recurrence of polyposis and the development of advanced neoplasms among patients with non-hereditary colorectal polyposis.

METHODS

1. Patients

In this retrospective single center study, we reviewed the charts of patients (n=855) with 10 or more cumulative polyps observed on colonoscopies performed at Severance Hospital from January 2012 to September 2021. Of the total 855 patients, 308 patients underwent targeted next generation sequencing multigene panel.

Patients with genetic mutations related to colorectal polyp-

osis (n=209), insufficient information (n=68), total colectomy (n=8), and less than 3 years of follow-up (n=401) were excluded, leaving 169 patients with non-hereditary colorectal polyposis for analysis. Among final 169 patients, targeted next generation sequencing multigene panel was done in 16 (9.47%).

The study was approved by the Institutional Review Board (IRB) at the Severance Hospital, Seoul, Republic of Korea (IRB approval number: 4-2011-0671). This study is a retrospective study using medical record review and so informed consent was waived.

2. Data Collection

Clinical data were retrospectively collected from the patients' medical records. The data included information on age, sex, body mass index (BMI), family history of cancer, history of cancer other than colon cancer, surgery for colon cancer, comorbidities, regular use of medicine prescribed by a doctor for underlying diseases, and personal history of smoking cigarettes or drinking alcohol. BMI was calculated as weight in kilograms divided by height in meters squared. Family history of cancer was defined as cancer in one or more first-degree relatives. Smoking and drinking statuses were categorized as never, former, and current. If a patient underwent multiple colonoscopies, data from each examination were analyzed. The following data on polyps were recorded: number, size, and histological diagnosis. Polyp diameter in millimeter was measured by the endoscopist during the colonoscopy, and expert pathologists reviewed the histological characteristics of the polyps. In cases with multiple polyps, polyp size was defined as size of the largest polyp. Adenomas, serrated polyps, and hamartomatous polyps were included in the count, while hyperplastic polyps in the left colon and pseudo-polyps were excluded. If a surveillance colonoscopy was performed within 1 year from previous colonoscopy due to poor bowel preparation, the results of that colonoscopy were added to the results of the previous examination.

In this study, we defined index colonoscopy as the colonoscopy with a cumulative number of 10 or more polyps. Colonoscopy results prior to the index colonoscopy were cumulated.

We defined polyposis as the presence of 10 or more polyps. Polyposis recurrence was defined as the recurrence of 10 or more polyps again among patients with polyposis. Advanced neoplasm was defined as cancer or advanced adenoma with (1) a diameter of ≥ 10 mm, (2) a villous component, or (3) high-grade dysplasia.

3. Statistical Analysis

All statistical analyses were performed using the SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA). Continuous variables are presented as means with standard deviations or as medians (interquartile range), and categorical variables are presented as frequencies with percentages. We performed univariable and multivariable Cox regression analyses. Hazard ratios (HRs) were calculated along with 95% confidence intervals (CIs), and two-sided probability values <0.05 were considered statistically significant.

RESULTS

1. Baseline Patient Characteristics

At the time of index colonoscopy, the mean age was 64.19 ± 9.92 years, 84.02% of the patients were male, and the mean BMI was 24.32 ± 2.80 kg/m². There were 100 patients (59.17%) with comorbidities, such as hypertension, diabetes mellitus, etc., and 91 patients (53.85%) were taking medication for these chronic diseases. Among medications, 29 patients (17.16%) were taking aspirin and none were taking nonsteroidal anti-inflammatory drugs regularly. There were 48 patients (28.40%) with a family history of cancer and 28 patients (16.57%) with history of cancer other than colon cancer. There were 89 (52.66%) current smokers and 100 (59.17%) current alcohol drinkers. The baseline characteristics of the patients are shown in Table 1.

2. Index Colonoscopy Findings

The mean number of polyps detected on index colonoscopy was 15.33 ± 8.47 . The number of advanced neoplasms was 1.93 ± 1.87 , and the mean size of maximal polyp of index colonoscopy was 16.54 ± 10.45 mm. Thirty-five patients underwent partial colectomy because of advanced CRC on the index colonoscopy. The worst pathological findings of index colonoscopy are shown in Table 1.

3. Colonoscopy Surveillance

The median follow-up time was 4.13 years (interquartile range, 3.60–5.26 years). Surveillance colonoscopy of all 169 patients revealed that 59 patients (34.91%) had recurrence of 10 or more polyps. Thirty-five patients (20.71%) developed advanced neoplasms during follow-up. Among 35 patients, there were 1 patient with intramucosal cancer, 3 patients with high-grade dysplasia, 2 patients with villous component, and the rest 29 patients with adenoma larger than 10 mm in size.

Table 1. Baseline Clinical Characteristics of the Patients (n = 169)

Characteristic	Value
Age (yr)	64.19 ± 9.92
Body mass index (kg/m ²)	24.32 ± 2.80
Sex	
Male	142 (84.02)
Female	27 (15.98)
Comorbid disease	100 (59.17)
Family history of cancer	48 (28.40)
Past history of cancer (except colon cancer)	28 (16.57)
Current smoker	89 (52.66)
Current alcohol drinker	100 (59.17)
Medication use	91 (53.85)
Aspirin	29 (17.16)
Worst pathological findings	
Adenocarcinoma	44 (26.04)
High-grade dysplasia, and intramucosal carcinoma	24 (14.20)
Villous adenoma	10 (5.92)
Tubular adenoma	91 (53.85)

Values are presented as a mean ± standard deviation or number (%).

4. Comparison of Clinical Characteristics and Index Colonoscopy Findings Based on Surveillance Colonoscopy Results

1) Polyposis Recurrence During Surveillance

We divided patients according to the recurrence of polyposis on surveillance colonoscopy (≥ 10 polyp recurrence [n = 59] and < 10 polyp recurrence [n = 110]) and compared the total number of polyps and number of advanced neoplasms on index colonoscopy, as well as the following 10 clinical characteristics: age, sex, BMI, comorbidities, family history of cancer, history of cancer other than colon cancer, surgery of colon cancer, current smoking, current alcohol drinking, and medication use. The results of the comparison are shown in Table 2. There were significant differences between the 2 groups in terms of sex, family history of cancer, history of cancer except colon cancer, and current smoking.

2) Advanced Neoplasm Development During Surveillance

We divided patients according to the presence/absence of advanced neoplasms on surveillance colonoscopy (with advanced neoplasms [n = 35] and without advanced neoplasms [n = 134]) and compared the 10 clinical characteristics, as well as the total number of polyps and the number of advanced neoplasms on index colonoscopy. The results of the comparison are shown in Table 2.

Table 2. Clinical Characteristics and Index Colonoscopy Findings of Patients with and without Polyposis Recurrence on Surveillance Colonoscopy

Characteristic	Polyp ≥ 10 recurrence (n = 59)	Polyp < 10 recurrence (n = 110)	P-value
Age (yr)	64.37 \pm 11.10	64.09 \pm 9.28	0.488
Male sex	55 (93.22)	87 (79.09)	0.017 ^a
Body mass index (kg/m ²)	24.41 \pm 2.61	24.27 \pm 2.90	0.758
Comorbid disease	38 (64.41)	62 (56.36)	0.311
Family history of cancer	26 (44.07)	22 (20.00)	0.001 ^a
History of cancer (except colon cancer)	16 (27.12)	12 (10.91)	0.007 ^a
Surgery of colon cancer	9 (15.25)	26 (23.64)	0.200
Current smoking	42 (71.19)	47 (42.73)	< 0.001 ^a
Current alcohol drinking	40 (67.80)	60 (54.55)	0.095
Medication use	35 (59.32)	56 (50.91)	0.296
Total number of polyps on index colonoscopy	16.90 \pm 9.49	14.49 \pm 7.79	0.076
No. of advanced neoplasms on index colonoscopy	1.97 \pm 2.03	1.91 \pm 1.79	0.750

Values are presented as a mean \pm standard deviation or number (%).

^aStatistically significant, $P < 0.05$.

Table 3. Clinical Characteristics and Index Colonoscopy Findings of Patients with and without Advanced Neoplasms on Surveillance Colonoscopy

Characteristic	With advanced neoplasms (n = 35)	Without advanced neoplasm (n = 134)	P-value
Age (yr)	65.11 \pm 7.90	63.95 \pm 10.40	0.975
Sex (male)	29 (82.86)	113 (84.33)	0.833
Body mass index (kg/m ²)	24.76 \pm 2.79	24.2 \pm 2.80	0.293
Comorbid disease	22 (62.86)	78 (58.21)	0.618
Family history of cancer	7 (20.00)	41 (30.60)	0.216
History of cancer (except colon cancer)	9 (25.71)	19 (14.18)	0.102
Surgery of colon cancer	10 (28.57)	25 (18.66)	0.197
Current smoking	20 (57.14)	69 (51.49)	0.551
Current alcohol drinking	20 (57.14)	80 (59.70)	0.784
Medication use	22 (62.86)	69 (51.49)	0.230
Total number of polyps on index colonoscopy	17.80 \pm 10.19	14.69 \pm 7.88	0.094
No. of advanced neoplasms on index colonoscopy	2.17 \pm 1.98	1.87 \pm 1.84	0.382

Values are presented as a mean \pm standard deviation or number (%).

son are shown in Table 3. There was no significant difference between the 2 groups.

5. Analyses for Risk Factors for Polyposis Recurrence and the Development of Advanced Neoplasms

Univariable analysis was performed with clinical characteristics (age, sex, BMI, comorbid disease, family history of cancer, history of cancer other than colon cancer, history of colon cancer surgery, current smoking and drinking state, and medication use) and index colonoscopy results (≥ 15 polyps on in-

dex colonoscopy and presence of advanced neoplasm on index colonoscopy). Multivariable analysis was then performed on factors with P -value of less than 0.2 on univariable analysis.

1) Risk factors for Recurrence of Polyposis during Surveillance

In univariable analysis, history of cancer, current smoking, and 15 or more polyps on index colonoscopy were significant, with P -values less than 0.05. Multivariable analysis was then performed on 4 factors (history of cancer other than colon

cancer, current smoking, current alcohol drinking, 15 or more polyps on index colonoscopy) with a *P*-value of less than 0.2 in univariable analysis (Table 4). History of cancer other than colon cancer (HR, 2.23; 95% CI, 1.23–4.01) and current smok-

ing (HR, 2.39; 95% CI, 1.17–4.87) were significant risk factors for the recurrence of 10 or more polyps. Fifteen or more polyps on index colonoscopy (HR, 2.05; 95% CI, 1.12–3.50) was also a significant risk factor for polyposis recurrence, com-

Table 4. Cox Regression Analysis of Risk Factors for Polyposis Recurrence

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
Age (≥ 65 yr)	0.98 (0.58–1.66)	0.952		
Sex (male)	1.71 (0.61–4.76)	0.308		
Body mass index (≥ 25 kg/m ²)	0.74 (0.43–1.28)	0.281		
Comorbid disease	0.89 (0.52–1.53)	0.673		
Family history of cancer	1.29 (0.76–2.20)	0.350		
History of cancer (except colon cancer)	2.01 (1.13–3.60)	0.018 ^a	2.23 (1.23–4.01)	0.008 ^a
Gastric cancer	1.73 (0.84–3.56)	0.136		
Lung cancer	1.50 (0.36–6.20)	0.573		
Prostate cancer	0.43 (0.06–3.10)	0.399		
Surgery of colon cancer	0.99 (0.48–2.03)	0.973		
Current smoking	2.55 (1.44–4.53)	0.001 ^a	2.39 (1.17–4.87)	0.016 ^a
Current alcohol drinking	1.77 (1.02–3.09)	0.043 ^a	1.03 (0.52–2.05)	0.933
Medication use	0.86 (0.51–1.47)	0.587		
Aspirin	0.76 (0.37–1.55)	0.452		
Total number of polyps (≥ 15) on index colonoscopy	2.00 (1.18–3.38)	0.010 ^a	2.05 (1.12–3.50)	0.008 ^a
Advanced neoplasm on index colonoscopy	0.75 (0.42–1.34)	0.339		

HR, hazard ratio; CI, confidence interval.

^aStatistically significant, *P* < 0.05.

Table 5. Cox Regression Analysis of Risk Factors for Advanced Neoplasm Development

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
Age (≥ 65 yr)	1.22 (0.62–2.42)	0.563		
Sex (male)	0.77 (0.32–1.86)	0.557		
Body mass index (≥ 25 kg/m ²)	0.78 (0.38–1.59)	0.489		
Comorbid disease	0.97 (0.48–1.94)	0.927		
Family history of cancer	0.46 (0.19–1.11)	0.085	0.47 (0.20–1.15)	0.099
History of cancer (except colon cancer)	1.89 (0.88–4.05)	0.103	2.14 (0.99–4.62)	0.054
Surgery of colon cancer	1.88 (0.90–3.94)	0.096	1.76 (0.83–3.73)	0.143
Current smoking	1.21 (0.62–2.39)	0.579		
Current alcohol drinking	0.88 (0.45–1.74)	0.718		
Medication use	1.24 (0.62–2.49)	0.537		
Aspirin	0.79 (0.31–2.04)	0.622		
Total number of polyps (≥ 15) on index colonoscopy	1.76 (0.90–3.47)	0.101	1.73 (0.86–3.45)	0.122
Advanced neoplasms on index colonoscopy	1.62 (0.67–3.92)	0.284		

HR, hazard ratio; CI, confidence interval.

pared with detection of less than 15 polyps on index colonoscopy (Table 4). The other factors were not statistically significant.

History of cancer other than colon cancer was found as a risk factor, so we analyzed each type of cancer separately. In total, 28 patients had a history of accompanying cancer other than colon cancer, including gastric cancer (n = 15), lung cancer (n = 6), and prostate cancer (n = 4), and so on. In univariable analysis, only the *P*-value of gastric cancer was less than 0.2; the others were not. When multivariable analyses were performed for gastric cancer, gastric cancer alone was not statistically significant for polyposis recurrence.

2) Risk Factors for Development of Advanced Neoplasms during Surveillance

Univariable analysis was performed on the same 10 clinical characteristics and 2 index colonoscopy findings. There was no significant factor in the univariable analysis. Among the 12 factors, multivariable analysis was performed on 4 factors (family history of cancer, history of cancer other than colon cancer, history of colon cancer surgery, and 15 or more polyps on index colonoscopy) with a *P*-value of less than 0.2 in univariable analysis (Table 5). Multivariable analysis showed no statistically significant risk for any of the 4 factors (Table 5).

DISCUSSION

We investigated the clinical characteristics and the risk factors of polyposis recurrence or advanced neoplasm development among patients with non-hereditary polyposis. To the best of our knowledge, this study is the first study to investigate risk factors for polyposis recurrence or advanced neoplasm development among patients with colorectal polyposis without known hereditary polyposis syndrome.

As in other studies on development of colorectal polyps,^{17,19,20} there were more males than females with polyposis in our cohort. However, we found that male sex was not a risk factor for polyposis recurrence during surveillance. Our results indicate that the presence of many (≥ 15) polyps on index colonoscopy is a risk factor for polyposis recurrence. Although there is a possibility of incomplete removal of polyps on index colonoscopy, this is a limitation of a retrospective study on polyposis. The risk of polyposis recurrence is also identified in patients with a history of cancer other than colon cancer. In total, 28 patients had a history of accompanying cancer other than colon cancer, including gastric cancer (n = 15), lung cancer (n = 6),

prostate cancer (n = 4), and so on. When analyses for risk factor of polyposis recurrence were performed separately for each type of cancer, any type of cancer was not statistically significant. This result may be because accurate statistical analysis was difficult due to the small number of patients diagnosed with each type of cancer. However, it should be also considered that there would be a possibility of sharing some common risk factors of cancer development. We also found that current smoking was a risk factor for recurrence of polyposis, while past smoking history was not a significant risk factor. Neither were alcohol drinking, old age (≥ 65 years), obesity (BMI ≥ 25 kg/m²), CRC history, presence of comorbidities, medications use. When analyses were performed separately for each type of medication, aspirin and nonsteroidal anti-inflammatory drugs were not significant related factor. Previously reported risk factors for polyp development and recurrence (old age, excess alcohol use, obesity, etc.)^{16-18,21} were not correlated with an increased risk of polyposis recurrence in our cohort. In a previous report analyzing colonoscopy data of patients with more than 10 adenomas,¹⁹ the authors focused only on development of advanced colorectal neoplasia and found a higher risk of advanced colorectal neoplasia in patients with more than 10 adenomas, compared to that in patients with 3 to 10 adenomas, but did not evaluate the risk factors of the recurrence of polyposis and advanced neoplasia. In our study, we focused on polyposis recurrence and advanced neoplasm development, and their risk factors among non-hereditary polyposis patients.

Numerous studies have reported that many polyps at baseline is an important risk factor for the development of advanced colorectal neoplasm on surveillance.^{8,19,22-25} However, the results of our study do not support these previous findings. We did not identify any distinct risk factors for the development of advanced neoplasms among our cohort. Clear identification of risk factors for the development of advanced neoplasms may have been hindered by frequent surveillance colonoscopy and short intervals of surveillance due to polyposis.

The results of the current study indicate that both genetic and environmental risk factors may have a role in polyposis recurrence in non-hereditary polyposis patients. We presumed that genetic factors would have a greater influence on polyposis recurrence than clinical characteristics, including environmental factors and lifestyles. This is because most of the known environmental and lifestyle factors related to polyp development were not clearly shown in this study. In addition, the risk of recurrence of polyposis is high when there are accompany-

ing cancers, which means that patients with polyposis recurrence have polygenic risks associated with cancer.

Our study has several limitations. First, this is a retrospective study and the number of patients was not sufficiently large. Because we thought that at least 3 years would be required to evaluate cumulative recurrence of polyposis, 401 patients were excluded according to the exclusion criteria of a follow-up period of less than 3 years. In addition, patients underwent surveillance colonoscopy with different intervals, and the follow-up period was different. To complement this, we excluded patients with a follow-up period of less than 3 years and conducted statistical analysis with survival analysis. We expect that the number of patients with a follow-up period of more than 3 years will increase with time, and therefore, it will be possible to analyze more patients in the near future. Second, although genetic tests were performed on our cohort to exclude patients with polyposis-related germline genetic mutations, it was not performed in some patients who refused genetic test or were not indicated. However, despite negative germline genetic test results, patients with well-known phenotypes of hereditary CRC syndromes or family history were excluded in this study. In addition, there may be limitations caused by the omission of gene mutations that have not yet been identified, and multifactor inheritance may be involved.

In conclusion, we found that the risk of polyposis recurrence is high when the number of polyps in the index colonoscopy is 15 or more, the patient has a history of cancer other than colon cancer, and the patient is a current smoker. We presume that both polygenic risks associated with cancer and environmental factors influence the recurrence of polyposis. Further prospective studies are needed to discover the potential interactions between genetic and environmental risk factors associated with non-hereditary polyposis.

ADDITIONAL INFORMATION

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Conflict of Interest

Park J and Cheon JH are editorial board member of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Data Availability Statement

Data are available upon reasonable request by contacting the corresponding author. The de-identified participant data are available.

Author contributions

Conceptualization: Kim TI. Data curation: all authors. Formal analysis: Jang J. Investigation: Jang J, Kim TI. Methodology: Kim TI. Project administration: Kim TI. Resource: Park J, Park SJ, Park JJ, Cheon JH, Kim TI. Supervision: Kim TI. Validation: Kim TI. Writing - original draft: Jang J. Writing - review & editing: Park J, Park SJ, Park JJ, Cheon JH, Kim TI. Approval of final manuscript: all authors.

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