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Original Article

Hypertension is an important predictor of recurrent colorectal adenoma after screening colonoscopy with adenoma polypectomy

Chung-Chi Lin [a,b,d,f], Kuang-Wei Huang [a,b,e], Jiing-Chyuan Luo [a,b,*], Ying-Wen Wang [a,b,f], Ming-Chih Hou [a,b,f], Han-Chieh Lin [a,b], Fa-Yauh Lee [a,b], Wan-Leong Chan [a,c,f]

[a] *Department of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC*
[b] *Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[c] *Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[d] *Department of Medicine, Taipei Municipal Gan-Dau Hospital, Taipei, Taiwan, ROC*
[e] *Shuang-Ho Hospital and Taipei Medical University, Taipei, Taiwan, ROC*
[f] *Healthcare and Management Center, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*

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Abstract

Background: The predictors of recurrent colorectal adenoma have not been fully examined. This study aimed to evaluate the predictors of recurrent colorectal adenoma after initial screening colonoscopy with adenoma polypectomy.
Methods: A retrospective cohort study was conducted at the Taipei Veterans General Hospital from 2003 to 2011. After screening, 356 patients who had undergone two consecutive colonoscopies with colorectal adenoma polypectomy at the initial colonoscopy were enrolled. The recurrence group was patients with recurrent colorectal adenoma at the second colonoscopy, whereas the nonrecurrence group was patients without recurrence. Anthropometric data, biochemical tests, metabolic comorbidities, and adenoma characteristics at initial colonoscopy were compared between the two groups. Cox proportional hazard regression analysis was conducted to identify the predictors of recurrent colorectal adenoma.
Results: During a mean follow-up interval of 3.07 ± 1.42 years, 94 patients (26.4%) were in the recurrence group, 262 patients (73.6%) were in the nonrecurrence group. The recurrence group was older, had a wider waist circumference, higher levels of serum alanine aminotransferase (ALT) and triglyceride, a higher prevalence of smoking, nonalcoholic fatty liver disease, metabolic syndrome, and hypertension, and a higher occurrence of initial multiply-located adenomas when compared with the nonrecurrence group ($p < 0.05$). Cox regression analysis showed that hypertension, smoking, higher ALT level (>40 IU/mL), and multiply-located adenomas were independent predictors for recurrent colorectal adenoma. The risk of recurrent adenoma increased when hypertension was combined with smoking, high ALT level, or multiply-located adenomas.
Conclusion: Hypertension is an important predictor for recurrent colorectal adenoma after screening colonoscopy with polypectomy.

Keywords: hypertension; metabolic syndrome; recurrent colorectal adenoma; smoking

1. Introduction

Colorectal cancer (CRC) is one of the most common malignancies in the world. Although CRC's mortality in the West is declining, it appears to have a rapidly rising trend in Asia among both males and females.[1] According to a report by the Bureau of Health Promotion in Taiwan, CRC is the most common cancer in Taiwan, with an age-standardized incidence

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* Corresponding author: Dr. Jiing-Chyuan Luo, Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: jcluo@vghtpe.gov.tw (J.-C. Luo).

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rate of 37.6 per 100,000 people in 2008. It also has the second highest total lifetime health expenditure among all malignancies because of its high incidence rate.[2,3] Based on the concept of the adenoma-carcinoma sequence, colorectal adenoma is considered a precursor of CRC. It has been believed that screening for CRC can reduce mortality and morbidity by detecting cancer at an earlier, curable stage and by removing colorectal adenomas.[4–6] Colonoscopic removal of colorectal adenomas not only decreases incidence of CRC but also significantly reduces the risk of death from CRC, as compared with that in the general population.[4,7] Therefore, several guidelines and consensus were established for clinical CRC screening and surveillance according to different stratified risks.[1,6,8] Current evidence supports the concept that patients who are obese, particularly those with abdominal obesity,[9] diabetes mellitus, or metabolic syndrome, are linked to insulin resistance, which plays an important role in development of CRC.[10–12] Similarly, colorectal adenoma has been closely associated with obesity, diabetes mellitus, metabolic syndrome, and insulin resistance in several studies.[13–15] The identification of risk patients has become important after colonoscopy screening in the general population and before surveillance in patients in whom adenoma has been previously detected. The current study attempted to clarify the predictors of recurrent adenoma after initial screening colonoscopy with adenoma polypectomy.

2. Methods

2.1. Patients

Asymptomatic patients who received two consecutive self-paid health check-ups and colonoscopies with colorectal adenoma polypectomy at first colonoscopy at Taipei Veterans General Hospital, Taipei, Taiwan between January 1, 2003 and December 31, 2010 were enrolled. There were 2255 patients who received two consecutive check-up colonoscopies, and there were 446 with colorectal adenoma polypectomy at first colonoscopy. After excluding patients with a history of CRC, inflammatory bowel disease, nonadenomatous polyp, and long-term use of aspirin or nonsteroidal anti-inflammatory drugs, 356 eligible patients were enrolled. This study complied with the standards of the Declaration of Helsinki and current ethical guidelines. The hospital's Institutional Review Board approved the study (#2011-08-010IC).

2.2. Anthropometric and laboratory measurements

Detailed chart review including smoking, alcohol consumption, and medical and family history, were recorded. Anthropometric measurements (i.e., body height, body weight, waist circumference, and blood pressure) were taken by experienced nursing staff. Waist circumference was measured based on the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition.[16,17] The body mass index (BMI) was calculated as weight (kg) divided by height (m) squared (kg/m^2). Laboratory data including sugar, alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride were checked. Metabolic syndrome was diagnosed if three or more of the following criteria were met: (1) abdominal obesity, waist circumference $\geq$90 cm in males and $\geq$80 cm in females; (2) high blood pressure, $\geq$130 mmHg systolic, $\geq$85 mmHg diastolic, or current medication for hypertension; (3) high serum fasting glucose, $\geq$100 mg/dL or current use of antidiabetic therapy; (4) low HDL cholesterol level, <40 mg/dL in males and <50 mg/dL in females; and (5) hypertriglyceridemia $\geq$150 mg/dL. Hypertension was diagnosed as systolic blood pressure $\geq$140 mmHg, or diastolic blood pressure $\geq$90 mmHg[18] or patients with hypertension and under antihypertension medication. Liver ultrasound examinations were performed using the Philips HD15 ultrasound system machine (Royal Philips Electronics, North Andover, MA, USA) by experienced radiologists. "Fatty liver" was considered if the contrast between the liver and parenchyma of the right kidney was increased, whereas nonalcoholic fatty liver disease (NAFLD) was diagnosed as the presence of fatty liver without viral (hepatitis B or hepatitis C), autoimmune or other liver diseases, or heavy alcohol consumption (>20 g/day).[3] All anthropometric and laboratory data, metabolic comorbidities, and the findings of screening colonoscopy were taken at the time of the first health check-up.

2.3. Colonoscopy

Colonoscopy was performed by experienced gastroenterologists and colorectal surgeons. The withdrawal time of colonoscopy was at least 6 minutes to minimize any chance of missing lesions. Detailed colonoscopy findings, including polyp size, number, and location and procedure of polypectomy were recorded. A lesion above the splenic flexure was defined as proximal and one in the left colon including the sigmoid and rectum was defined as distal adenoma.[3] Advanced adenoma was defined as adenoma size >10 mm, with villous or tubule-villous architecture, or with high-grade dysplasia.[3] Multiply-located adenomas was defined as at least two adenomas located at different sites (including ascending colon, transverse colon, descending colon, and sigmoid/rectum). Experienced pathologists confirmed the diagnosis of adenoma by histological examination after colonoscopic polypectomy. Among the 356 eligible patients, 94 patients were classified into the recurrence group (adenoma detected at the second colonoscopy after initial screening colonoscopy with adenoma polypectomy), whereas 262 patients were classified into the nonrecurrence group (absence of adenoma at the second colonoscopy after initial screening colonoscopy with adenoma polypectomy). The adenoma detection rate was 19.8% for the first-time colonoscopy and 26.4% for the second-time colonoscopy.

2.4. Statistical analysis

All statistical analyses were performed using SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). Demographic data

were expressed as frequency (percentage) or as mean ± standard deviation. Continuous variables were compared using the Student *t* test, whereas categorical data were compared by Chi-square test and Yates correction or Fisher's exact test, as appropriate. Multivariate regression analysis was conducted using Cox proportional hazard regression analysis to identify the predictors of recurrent adenoma, including age, sex, smoking, anthropometric data, biochemical tests, metabolic comorbidities, and adenoma characteristics. A two-sided $p < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

Among the 356 enrolled patients, 262 (73.6%) were male and 94 (26.4%) female, and the mean age was 55.1 ± 9.0 years old. Eighty-three (23.3%) patients had a history of smoking. Eighty-two (23.0%) patients had hypertension, including 55 patients taking antihypertension medication, thirty-nine (11%) patients had diabetes, 92 (25.8%) patients had received a diagnosis of metabolic syndrome, and 150 (42.1%) patients had NAFLD. The mean BMI was 24.53 ± 3.09 kg/m^2. During the initial screening colonoscopy with adenoma occurrence and polypectomy, the most common locations of adenomas were the sigmoid colon ($n = 125$, 35.1%), followed by the rectum ($n = 90$, 25.3%) and ascending colon ($n = 88$, 24.7%). Sixty-four patients (18.0%) had advanced adenomas, 125 (35.1%) patients had proximal adenoma, and 60 (16.9%) patients had multiply-located adenomas.

3.2. Comparison between nonrecurrence group and recurrence group

During a mean follow-up interval of 3.07 ± 1.42 years between the two consecutive colonoscopic examinations, all enrolled patients were divided into a nonrecurrence group ($n = 262$, 73.6%) and recurrence group ($n = 94$, 26.4%). Comparison between the two groups showed that the recurrence group was older, had a wider waist circumference, higher serum ALT, GGT, and triglyceride, and higher prevalence of smoking, NAFLD, metabolic syndrome, and hypertension than the nonrecurrence group ($p < 0.05$, Table 1). The recurrence group also had a higher occurrence of initial multiply-located adenomas. However, there was no significant difference in sex, BMI, diabetes, serum total cholesterol, LDL, HDL, the occurrence of proximal adenoma, and advanced adenoma between the two groups (Table 1).

3.3. Independent predictors for colorectal adenoma

Cox proportional hazard regression model analyses for predictors of recurrent adenoma are shown in Table 2. Smoking, hypertension, ALT >40 IU/mL, and multiply-located adenomas but not metabolic syndrome were independent predictors for developing recurrent colorectal adenoma after initial colonoscopy with adenoma polypectomy. For 262 male patients, smoking [hazard ratio (HR): 2.559, 95% confidence interval (CI): 1.560–4.198], hypertension (HR: 2.372, 95% CI: 1.399–4.022), advanced adenoma (HR: 2.109, 95% CI: 1.219–3.647), and multiply-located adenomas (HR: 2.207, 95% CI: 1.306–3.731) were independent predictors for developing recurrent colorectal adenoma after initial colonoscopy with adenoma polypectomy. For 94 females, only ALT >40 IU/mL (HR: 4.992, 95% CI: 1.166–21.37) and multiple-located adenomas (HR: 37.071, 95% CI: 8.710–157.773)

Table 1
Demographic characteristics between patients with or without recurrence of colorectal adenomas.

	Nonrecurrence group ($n = 262$)	Recurrence group ($n = 94$)	*p*
Male	186 (71)	76 (80)	0.076
Age (y)	54.4 ± 8.9	57.2 ± 8.9	0.010
Smoking	46 (17.6)	37 (39.4)	<0.001
Body mass index (kg/m^2)	24.4 ± 3.1	24.9 ± 3.2	0.144
Waist circumference (cm)	86.2 ± 8.9	88.9 ± 9.9	0.018
NAFLD	99 (37.8)	51 (54.3)	0.007
Metabolic syndrome	59 (22.5)	33 (35.9)	<0.001
Hypertension	46 (17.6)	36 (38.3)	<0.001
Diabetes	26 (9.9)	13 (13.8)	0.196
Total cholesterol (mg/dL)	206 ± 37	211 ± 39	0.280
Low-density lipoprotein (mg/dL)	135 ± 33	139 ± 32	0.245
High-density lipoprotein (mg/dL)	50 ± 14	47 ± 13	0.058
Alanine aminotransferase (IU/mL)	32 ± 24	46 ± 58	0.025
Gamma-glutamyltransferase (mg/dL)	27 ± 26	35 ± 36	0.040
Triglyceride (mg/dL)	143 ± 83	172 ± 107	0.019
Advanced adenoma in initial colonoscopy[a]	41 (15.6)	23 (24.5)	0.062
Proximal adenoma in initial colonoscopy[b]	99 (37.8)	26 (27.7)	0.080
Multiply-located adenoma in initial colonoscopy	25 (9.5)	35 (37.2)	<0.001

Data are presented as *n* (%) or mean ± SD.
NAFLD = nonalcoholic fatty liver disease.
[a] Advanced adenoma: lesion >10 mm, with villous or tubulovillous architecture or high-grade dysplasia.
[b] Proximal adenoma: adenoma proximal to the splenic flexure.

Table 2
Independent risk factors or predictors of recurrent colorectal adenomas, analyzed by multivariate Cox regression model.

	Adjusted HR[a]	95% CI	*p*
Male	1.084	0.597–1.969	0.791
Age (y)	1.024	0.996–1.053	0.088
Smoking	2.161	1.343–3.476	0.001
NAFLD	1.260	0.813–1.954	0.301
Metabolic syndrome	0.839	0.503–1.402	0.503
Hypertension	2.311	1.421–3.760	0.001
Alanine aminotransferase > 40 (IU/mL)	1.644	1.002–2.698	0.049
Gamma-glutamyltransferase > 30 (mg/dL)	0.988	0.621–1.572	0.961
Advanced adenoma in initial colonoscopy	1.540	0.934–2.539	0.091
Proximal adenoma in initial colonoscopy	1.023	0.627–1.668	0.929
Multiply-located adenoma in initial colonoscopy	3.289	2.060–5.249	<0.001

CI = confidence interval; HR = hazard ratio; NAFLD = nonalcoholic fatty liver disease.
[a] Each variable was adjusted for every other variable listed.

Table 3
Risk for recurrent colorectal adenoma by the presence of hypertension and other predictors.

	HR[a]	95% CI	p
Hypertension and smoking	5.013	2.372–10.597	<0.001
Hypertension and multiply-located adenoma	6.038	2.806–12.994	<0.001
Hypertension and ALT >40 IU/mL	4.182	1.939–9.018	<0.001

ALT = alanine aminotransferase; CI = confidence interval; HR = hazard ratio.
[a] Adjusting factors including age, sex, smoking, nonalcoholic fatty liver disease, metabolic syndrome, hypertension, serum ALT, serum gamma-glutamyltransferase, advanced adenoma, proximal adenoma, and multiple-located adenoma.

were independent predictors for recurrent colorectal adenoma after Cox proportional hazard regression analyses.

3.4. Risk of recurrent colorectal adenoma by the presence of hypertension with other predictors

The risk of recurrent adenoma in hypertension patients with other predictors are shown in Table 3. By adjusting for other confounding factors, the HR of recurrent adenoma increased when hypertension was associated with smoking, high ALT, and multiply-located adenomas, respectively (Table 3).

4. Discussion

About 20–50% of patients with colorectal adenomas will experience recurrence in a 3- to 5-year period.[19–21] However, only a limited number of studies have discussed the risk factors or predictors of recurrent colorectal adenomas.[22–24] In the current study, we found that hypertension, smoking, higher ALT (>40 IU/mL), and multiply-located adenomas were independent predictors for developing recurrent colorectal adenoma after initial colonoscopy with adenoma polypectomy. Also, the risk of recurrent adenoma increased when hypertension coexisted with smoking, high ALT level (>40 IU/mL), or multiply-located adenomas, respectively.

Hypertension was found to be a predictor for colorectal adenoma formation in previous studies,[3,25] but other studies reported conflicting findings[26,27] and some did not include hypertension as a predictor for analysis.[28,29] However, studies that evaluated the risk factors or predictors for recurrent colorectal adenoma did not pay any attention to hypertension as a potential predictor.[22,23] The finding in this study that hypertension rather than metabolic syndrome was a key predictor for recurrent colorectal adenoma should remind all researchers to pay attention to this important factor in evaluating the predictors of primary or recurrent colorectal adenoma. However, the possible mechanisms or interactions between hypertension and recurrent colorectal adenoma remain uncertain and need further clarification. Whether there is a dose-response relationship between BP and recurrence of adenoma is an interesting question. Because 55 of the 82 hypertension patients in this study had taken antihypertension drugs, the baseline blood pressure values without taking medication could not be obtained exactly in two-thirds of the hypertension patients. Therefore, we did not analyze whether a dose-response relationship existed between blood pressure level and recurrence of adenoma.

Smoking has been a known risk factor of recurrent colorectal adenomas,[24,30] and exposure to smoking significantly increases the prevalence of distal, tubular, larger, and multiple adenomas.[29] Several previous studies also supported that smoking increases the size of colorectal polyps.[31,32] However, we did not observe that smoking was correlated to adenoma number or size (data not shown). Previous studies have also shown that smoking is an important risk factor of primary colorectal adenoma after an initial negative screening colonoscopy.[3] Therefore, smoking is a convenient and important indicator for clinicians to assess primary or recurrent colorectal adenomas in their daily practice.

Metabolic syndrome is composed of a cluster of cardiovascular risk factors including insulin resistance, dyslipidemia, central obesity, and prehypertension. Several previous studies have shown that metabolic syndrome is associated with increased risk of colorectal adenoma,[13,25,27,33] but others do not support this theory.[34,35] Evidence concerning the relationship between recurrent colorectal adenoma and metabolic syndrome is relatively limited. Our study demonstrated that metabolic syndrome was not a predictor of recurrent colorectal adenoma by multivariate Cox regression analysis.

According to the updated guidelines for colonoscopy surveillance after screening and polypectomy by the US Multi-Society Task Force on Colorectal Cancer,[8] the recommended surveillance interval for multiply-located adenoma and advanced adenoma is 3 years. About one-third of the patients in our study had multiply-located or advanced adenoma at the initial colonoscopy. The mean follow-up interval in this study was 3.07 years between the two consecutive colonoscopic examinations. Only 26.4% of patients had recurrent adenoma, and none of them developed CRC. The updated guideline is in line with our study findings and general clinical practice.

4.1. Limitations

The current study has several limitations that are worth noting. First, it was a retrospective study with observations based on patients who came in for a health check-up. Certain selection biases indeed exist therefore caution must be exercised in extrapolating the results. Second, the socioeconomic status of our study group was relative higher in Taiwan society, and this may be another confounding factor in data analysis. Third, a missed polyp is inevitable for each experienced colonoscopist during examination and decreases the accuracy of this kind of study. However, all screening or surveillance studies of colon adenoma-carcinoma have the same inevitable problems. Finally, though patients taking long-term aspirin or nonsteroidal anti-inflammatory drugs were excluded, patients taking statins, which might be chemoprotective for colorectal adenoma, were not excluded.

In conclusion, after adjusting for age, sex, anthropometric data, biochemical tests, metabolic comorbidities, and adenoma characteristics at initial colonoscopy by Cox regression analysis, hypertension was an important predictor for recurrent

colorectal adenoma after screening colonoscopy with adenoma polypectomy.

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