

The Association between Blood Pressure Status and Colorectal Polyps in a Taiwanese Population

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ABSTRACT

AIM: Colorectal cancer is the third most common cancer worldwide, especially in more developed countries. Colorectal adenomas can progress to malignant carcinoma based on the pathogenesis of adenoma-carcinoma sequence. This study was conducted to

investigate the association with colorectal polyps of blood pressure status after excluding the confounding effect of anti-hypertensive agents.

MATERIALS AND METHODS: A total of 8,700 eligible subjects with age ≥ 18 years were enrolled from the Health Examination Center of National Cheng Kung University Hospital (NCKUH) between June 2001 and August 2009. We categorized colonoscopic findings into four subgroups: polyp-free, non-neoplastic polyps, non-advanced adenomatous polyps, and advanced adenomatous polyps. Subjects were divided into normal blood pressure, prehypertension and hypertension.

RESULTS: The subjects were divided into polyp-free ($n = 6,773$), non-neoplastic polyps ($n = 806$), non-advanced adenomatous polyps ($n = 876$), and advanced adenomatous polyps ($n = 245$). With adjustments for other variables, hypertension was positively related to non-advanced adenomatous polyps (OR: 1.40, 95% CI: 1.14-1.73) and advanced adenomatous polyps (OR: 1.93, 95% CI: 1.37-2.72). Prehypertension was associated with a higher risk of non-neoplastic polyps (OR: 1.20, 95% CI: 1.01-1.43) and non-advanced adenomatous polyps (OR: 1.42, 95% CI: 1.21-1.68), but not associated with advanced adenomatous polyps.

CONCLUSION: Hypertension was positively related to an increased risk of non-advanced and advanced adenomatous polyps, but not non-neoplastic polyps. In contrast, prehypertension was associated with a less advanced stage of colon polyps, including non-neoplastic polyps and non-advanced adenomatous polyps, but not associated with advanced adenomatous polyps.

Key words: Non-neoplastic polyps; Non-advanced adenomatous polyps; Advanced adenomatous polyps; Hypertension; Prehypertension

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INTRODUCTION

Colorectal cancer is the third most common cancer worldwide, especially in more developed countries^[1], and it is also the third leading cause of cancer death in Taiwan^[2]. Colorectal adenomas may progress to malignant carcinoma based on the pathogenesis of the adenoma-carcinoma sequence^[3]. Some evidence suggests that it may take an average of about ten years for an adenomatous polyp to develop into invasive cancer^[4]. Colonoscopic polypectomy is thus thought to be helpful to decrease the incidence of colorectal cancer^[5]. Based on the histological classification, colorectal polyps can be divided into non-neoplasia and neoplasia. Non-neoplastic colorectal polyps, including hyperplastic polyps, hamartomas, lymphoid aggregates, or inflammatory polyps, do not have the potential to become malignant^[6]. On the other hand, neoplastic polyps can become malignant by the adenoma-carcinoma sequence, and they are further divided into non-advanced and advanced adenomatous polyps^[7].

Colorectal polyps have possible risk factors including age, sex, family history of colorectal cancer, smoking status or obesity^[8]. People with metabolic syndrome may face an increased risk of colorectal adenoma^[9-12]. To our surprise, elevated BP, one component of metabolic syndrome, was not found to be associated with colorectal adenoma^[9-12]. We found that the above studies did not exclude subjects with medication for hypertension and diabetes. As such, this study was conducted to investigate the association with colorectal polyps of blood pressure status, including normal blood pressure, prehypertension and hypertension, after excluding the confounding effect of anti-hypertensive agents and other possible factors.

METHODS

We enrolled a consecutive series of 9,536 adult subjects (≥ 18 years old) who received a voluntary health examination with colonoscopies at the Health Examination Center of National Cheng Kung University Hospital (NCKUH) between June 2001 and August 2009. Detailed histories included medical diseases, medication, smoking, alcohol consumption and exercise. The hospital ethics committee approved this study and informed consent was waived because this project was based on a secondary data analysis without any personal identification information (approval number: A-ER-105-083). Those subjects with a past history of colorectal cancer ($n = 13$), familial adenomatous polyposis ($n = 1$), Peutz-Jeghers syndrome ($n = 1$), colectomy (not due to colorectal cancer) ($n = 7$), and anti-hypertensive medication ($n = 778$), or with missing data ($n = 36$), were excluded from the study. Finally, a total of 8,700 subjects were included for the final analysis.

Current smoking was defined as at least one pack per month for more than half a year. Alcohol drinking was defined as at least one alcoholic drink per week for more than half a year. Regular exercise was defined as vigorous exercise for a minimum of 20 minutes each time, three times or more per week. BMI was calculated as the weight (kg) divided by the square of the height in meters (kg/m^2). Brachial blood pressure was measured using a DINAMAP vital signs monitor (Model 1846SX DINAMAP Monitor, Critikon, Florida, USA) in a supine position after a 5-minute rest period in a quiet room. Hypertension was defined as blood pressure of $\geq 140/90$ mm Hg or participants who reported a history of hypertension. Normal blood pressure was defined as blood pressure of $< 120/80$ mm Hg without a history of hypertension. Prehypertension was defined as blood pressure of 120-139/80-89 mm Hg without a history of

hypertension^[13].

Blood samples were collected from all subjects after overnight fasting for at least 12 hours. The laboratory tests included the following parameters: total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG), and 2-hour postload plasma glucose (2h PG). Subjects were considered to have diabetes mellitus (DM) if they had a FPG ≥ 6.9 mmol/L (126 mg/dL), 2h-PG ≥ 11.0 mmol/L (200 mg/dL), glycosylated hemoglobin $\geq 6.5\%$ or a positive DM history.

After bowel preparation, the colonoscope (CFTYPE Q260AL, OLYMPUS, Japan) was inserted from the anus to the ileocecal area and operated by an experienced gastroenterologist. We categorized colonoscopic findings into four subgroups: polyp-free, non-neoplastic polyps (including hyperplastic polyps, hamartomas, lymphoid aggregates, inflammatory polyps, xanthoma), non-advanced adenomatous polyps (including low-grade adenoma, such as tubular adenoma), and advanced adenomatous polyps (including tubulovillous adenoma, villous adenoma, and high-grade dysplasia). The largest one was measured if there were two or more adenomatous polyps.

Statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA), with the data presented as the mean \pm standard deviations or numbers/percentages. Subjects were divided into four groups, including polyp-free, non-neoplastic polyps, non-advanced adenomatous polyps, and advanced adenomatous polyps. Pearson Chi square tests were used for comparison of categorical variables, and independent samples *t*-tests for continuous variables among groups. Multinomial regression was used to assess the independent association between colon polyps (including polyp-free, non-neoplastic polyps, non-advanced adenomatous polyps, and advanced adenomatous polyps) and blood pressure statuses (including hypertension, pre-hypertension, and normal blood pressure) after adjusting for other variables, including age (< 40 , 40 to 64, and ≥ 65 years), sex, body mass index (< 24 , 24-26.9 and $\geq 27\text{kg}/\text{m}^2$), hypertriglyceridemia (triglyceride > 150 mg/dL), TC/HDL-C > 5 , diabetes, current smoking, current drinking, and regular exercise. The odds ratios (ORs) and 95% confidence intervals (CIs) of the independent variables were derived from the regression model. Statistical significance was defined as $p < 0.05$.

RESULTS

A total of 8,700 subjects were included in the study, and they were divided into four groups, including polyp-free ($n = 6,773$), non-neoplastic polyps ($n = 806$), non-advanced adenomatous polyps ($n = 876$), and advanced adenomatous polyps ($n = 245$). Table 1 shows the demographic and clinical parameters in these four groups. Significant differences in the prevalence of hypertension and prehypertension were found among the groups. There were also significant differences in age, gender, body mass index, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, HDL-C, HbA1c, FPG, 2h-PG, and the prevalence of diabetes mellitus and current smoking.

The odds ratios (OR) and 95% confidence intervals (CI) of clinical variables for the risk of colon polyps are presented in Table 2. With adjustments for other variables, hypertension was positively related to non-advanced adenomatous polyps (OR: 1.40, 95% CI: 1.14-1.73) and advanced adenomatous polyps (OR: 1.93, 95% CI: 1.37-2.72). Prehypertension was associated with a higher risk of non-neoplastic polyps (OR: 1.20, 95% CI: 1.01-1.43) and non-advanced adenomatous polyps (OR: 1.42, 95% CI: 1.21-1.68), but not advanced

adenomatous polyps. Moreover, age ≥ 65 years (OR: 9.87, 95% CI: 4.93-19.79), age 40-64.9 years (OR: 4.42, 95% CI: 2.32-8.43), and male gender (OR: 1.84, 95% CI: 1.34-2.51) were independently associated factors of all types colorectal polyps. DM was positively associated with non-advanced adenomatous polyps and advanced adenomatous polyps. Current smoking was significantly related to non-neoplastic polyps, and regular exercise was inversely associated with non-neoplastic polyps and non-advanced adenomatous polyps.

DISCUSSION

Studies have shown that people with metabolic syndrome have an increased risk of colorectal polyps^[9-12], but high blood pressure, one component of metabolic syndrome, with the definition of systolic and diastolic blood pressure $\geq 130/85$ mmHg, or current medication for hypertension, were not found to have a positive relationship with the colorectal polyps^[9-12]. In addition, all these earlier studies

Table 1 Comparison of clinical parameters among subgroups with different status of colorectal polyps.

	Polyp-free (n = 6773)	Non-neoplastic (n = 806)	Neoplastic polyps		P value
			Non-advanced (n = 876)	Advanced (n = 245)	
Age, year	49.4 ± 11.8	51.6 ± 10.9	54.9 ± 10.5	57.3 ± 10.8	< 0.001
Male gender	3857 (56.9)	557 (69.1)	612 (69.9)	178 (72.7)	< 0.001
Body weight, kg	65.2 ± 12.2	68.4 ± 12.2	67.7 ± 11.8	67.2 ± 12.2	< 0.001
Body mass index, kg/m ²	24.3 ± 3.49	25.0 ± 3.3	25.1 ± 3.3	25.0 ± 0.23	< 0.001
Body mass index					
≥ 27 kg/m ²	1343 (19.8)	199 (24.7)	217 (24.8)	68 (27.8)	< 0.001
24 - 26.9 kg/m ²	2145 (31.7)	288 (35.7)	318 (36.3)	78 (31.8)	
< 24 kg/m ²	3285 (48.5)	319 (39.6)	341 (38.9)	99 (40.4)	
SBP, mmHg	116.3 ± 17.1	120.5 ± 17.1	122.0 ± 17.2	125.8 ± 19.5	< 0.001
DBP, mmHg	68.7 ± 10.6	71.8 ± 10.7	73.0 ± 10.7	73.9 ± 11.1	< 0.001
Blood pressure status					
Hypertension	856 (12.6)	134 (16.6)	173 (19.7)	73 (29.8)	< 0.001
Pre-HTN	1762 (26.0)	253 (31.4)	305 (34.8)	73 (29.8)	< 0.001
Normal blood pressure	4155 (61.3)	419 (52.0)	398 (45.4)	99 (40.4)	< 0.001
Total cholesterol, mg/dL	196.6 ± 37.3	200.2 ± 39.0	202.5 ± 38.3	204.0 ± 37.0	< 0.001
Triglyceride, mg/dL	128.8 ± 82.2	142.9 ± 82.0	143.7 ± 98.1	154.3 ± 98.2	< 0.001
HDL-C, mg/dL	48.0 ± 13.4	45.5 ± 13.2	46.6 ± 13.3	45.3 ± 13.1	< 0.001
HbA1c, %	5.7 ± 1.0	5.9 ± 0.9	5.9 ± 1.0	6.1 ± 1.2	< 0.001
FPG, mg/dL	92.5 ± 25.5	94.0 ± 25.0	96.7 ± 27.1	101.6 ± 33.2	< 0.001
2h-PG, mg/dL	128.4 ± 54.8	133.6 ± 53.4	135.6 ± 55.8	152.6 ± 75.2	< 0.001
Diabetes mellitus	945 (14.0)	154 (19.1)	189 (21.6)	73 (29.8)	< 0.001
Alcohol drinking	1052 (15.5)	159 (19.7)	152 (17.4)	43 (17.6)	0.013
Smoking	1216 (18.0)	211 (26.2)	189 (21.6)	56 (22.9)	< 0.001
Regular exercise	600 (8.9)	55 (6.8)	58 (6.6)	18 (7.3)	0.038

Data are expressed as n (%) or mean ± standard deviations; HDL-C: high density lipoprotein-cholesterol; FPG: Fasting plasma glucose.

Table 2 Adjusted odds ratios (OR) and 95% confidence intervals (CI) of clinical variables on the risk of non-neoplastic polyps, non-advanced and advanced adenomatous polyps based on multinomial logistic regression

Variables	Non-neoplastic polyps vs Polyp-free OR (95% CI)	Non-advanced adenomatous polyps vs Polyp-free OR (95% CI)	Advanced adenomatous polyps vs Polyp-free OR (95% CI)
Age, years			
≥ 65 vs < 40	1.84 (1.35 - 2.50)***	4.70 (3.40 - 6.51)***	9.87 (4.93 - 19.79)***
40 - 64.9 vs < 40	1.65 (1.32 - 2.06)***	3.04 (2.31 - 4.00)***	4.42 (2.32 - 8.43)***
Male vs female	1.37 (1.15 - 1.64)***	1.57 (1.32 - 1.86)***	1.84 (1.34 - 2.51)***
Body mass index, kg/m²			
≥ 27 vs < 24	1.17 (0.95 - 1.43)	1.16 (0.95 - 1.41)	1.10 (0.78 - 1.54)
24 - 26.9 vs < 24	1.11 (0.93 - 1.32)	1.09 (0.92 - 1.30)	0.82 (0.60 - 1.12)
Blood pressure status			
HTN vs normal BP	1.20 (0.96 - 1.50)	1.40 (1.14 - 1.73)**	1.93 (1.37 - 2.72)***
Pre-HTN vs normal BP	1.20 (1.01 - 1.43)*	1.42 (1.21 - 1.68)***	1.26 (0.92 - 1.74)
Diabetes, yes vs no	1.16 (0.95 - 1.41)	1.21 (1.00 - 1.45)*	1.56 (1.15 - 2.12)**
Hypertriglyceridemia, yes vs no	1.18 (0.98 - 1.41)	1.08 (0.91 - 1.29)	1.33 (0.98 - 1.81)
TC/HDL-C > 5, yes vs no	1.14 (0.95 - 1.36)	1.08 (0.91 - 1.29)	1.05 (0.77 - 1.42)
Smoking, yes vs no	1.44 (1.17 - 1.76)**	1.15 (0.93 - 1.41)	1.18 (0.82 - 1.70)
Alcohol drinking, yes vs no	0.99 (0.80 - 1.23)	0.96 (0.77 - 1.20)	0.93 (0.63 - 1.38)
Regular exercise, yes vs no	0.71 (0.53 - 0.95)*	0.69 (0.52 - 0.91)*	0.79 (0.48 - 1.30)

NGT: normal glucose tolerance; TC: total cholesterol; HDL-C: high density lipoprotein-cholesterol; HTN: hypertension; BP: blood pressure; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

included subjects using an antihypertensive agent and they did not classify colorectal polyps into polyp-free, non-neoplastic polyps^[6], non-advanced adenomatous polyps, and advanced adenomatous polyps^[6,7]. In this study, we excluded subjects with antihypertensive agent and found that prehypertension was associated with a higher risk of non-neoplastic polyps and non-advanced adenomatous polyps, but not advanced adenomatous polyps. In addition, hypertension was positively related to an increased risk of non-advanced and advanced adenomatous polyps. This is the first study to show that different blood pressure statuses, from normal blood pressure, prehypertension, to hypertension, had a parallel relationship with the progression of colorectal polyps. In this work, by mapping different stages of colorectal polyps, from polyps free to non-neoplastic, non-advanced and advanced adenomatous polyps, across the different blood pressure statuses, from normal blood pressure, then to prehypertension, and finally to hypertension, we perceived that the colorectal polyps may progress from non-neoplastic polyps toward non-advanced and advanced adenomatous polyps during the development from normal blood pressure, then to prehypertension, and finally to hypertension.

The mechanisms underlying the association between elevated blood pressure/hypertension and the colorectal polyps are still not well known. Insulin resistance may be the major mechanism for the parallel relationship between the progression of blood pressure and colorectal polyps, because hypertension and colorectal polyps share the same mechanism of insulin resistance (IR)^[14-18]. One study showed that the prevalences of insulin resistance, defined by a homeostatic model assessment (HOMA), in normotensive, prehypertensive and hypertensive individuals, were 23.6, 40.5, and 54.9%, respectively. Compared with persons with normal blood pressure, those with prehypertension/hypertension were more likely to have insulin resistance^[16]. Although studies of IR in colorectal non-neoplastic polyp are available^[14-18], IR in non-advanced and advanced adenoma has not been examined. There are three studies which showed an association of IR with colorectal adenomas^[14,15,17], while one study did not^[18]. In addition, elevated insulin has been found to be positively associated with adenoma risk and decreased apoptosis in normal rectal mucosa^[14]. Furthermore, spontaneous apoptosis can remove damaged colonic crypt cells and avoid more proliferation^[19]. Subjects with low apoptosis are more predisposed to develop colorectal adenoma in the normal colonic mucosa^[20, 21]. Elevated insulin has been found to stimulate cell division and inhibit apoptosis^[22] by interacting with IGF-I receptors, enhancing nuclear factor- κ B activation or decreasing peroxisome proliferator-activated receptor- γ activation^[23,24]. To the best of our knowledge, although IR and low apoptosis seem to be a link between prehypertension/hypertension and non-advanced/advanced colorectal adenoma, mechanisms other than IR and low apoptosis need more studies to reveal the mechanism between elevated blood pressure and different stages of colorectal polyps.

Some studies suggest that age has a positive association with a higher prevalence of adenomatous polyps^[9,10,25-27]. The current study found that age also has a positive association with adenomatous polyps. Increasing age is a risk factor for the development of colorectal adenomatous polyps by the accumulation of dysplastic changes^[28,29]. With regard to gender difference, one meta-analysis showed that men had higher detection rates of adenomatous polyps than women when screening colonoscopy was arranged for an asymptomatic group^[30], and another study found that non-neoplastic polyps were more common in men than women^[31]. In the current work we found that men had a higher risk of adenomatous polyps

and non-neoplastic polyps compared to women. The underlying mechanism for the association of adenomatous polyps with male gender remains unclear, but the possible explanation may be related to sex hormones and chronic inflammation^[32,33].

Some studies found a positive association of DM with non-advanced and advanced adenomatous polyps^[26,34], while other studies found that DM has no association with non-neoplastic polyps^[27]. The current work found that DM is another important risk factor for non-advanced and advanced adenomatous polyps, while not for non-neoplastic polyps. The possible mechanism for the association between DM and adenomatous polyps is not well unknown, but may be related with diabetic subjects exhibiting hyperinsulinemia status^[35,36] and the production of more inflammatory cytokines^[37], which may result in the formation or progression of colorectal adenomatous polyps. Some studies found a link between hypertriglyceridemia and colorectal adenomatous polyps^[25,38,39], but others found no such relationship^[9,10]. This work found no association between hypertriglyceridemia and colorectal polyps. One explanation for the insignificant association of adenomatous polyps with hypertriglyceridemia may be the collinear effects of hyperinsulinemia, such as diabetes and hypertension. In addition, the difference in the definition of hypertriglyceridemia may be another reason for these inconsistent results^[9,10,38,39].

Although cigarette smoking has been more consistently associated with colorectal adenomatous polyps^[40], the association between cigarette smoking and polyps was inconsistent in advanced ones^[27,41]. In our study, smoking was positively associated with non-neoplastic polyps, but not non-advanced or advanced adenomatous polyps. The relationship between colorectal adenomatous polyps and alcohol drinking showed inconsistent results in previous studies^[9,10,42,43]. Two works found a positive association between colorectal adenomatous polyps and alcohol drinking^[42,43], while two others found no association between them^[9,10]. The current study found no association between alcohol drinking and colorectal adenomatous polyps. Two recent works found that physical activity is negatively associated with colorectal adenoma^[44,45], but another suggested that physical activity is not associated with colorectal polyps^[46]. Our study found that regular exercise had a negative association with non-neoplastic polyps and non-advanced adenomatous polyps, while not for advanced adenomatous polyps. The inconsistent results for the association of lifestyle factors, such as smoking, alcohol drinking and exercise, with colorectal polyps in the above studies may be related to subject selection, different classifications of adenomatous polyps and lifestyle.

There are some limitations in the present study that should be noted. First, this study adopted a cross-sectional design, and we cannot draw a causal relationship between elevated blood pressure and colorectal polyps. Second, this study was based on a Taiwanese population, and it might not be representative of other ethnic groups. Third, we did not have the subjects' dietary data, although diet plays an important role in colorectal polyps. In addition, since insulin resistance has been suggested as the possible mechanism between blood pressure status and colorectal polyps, insulin resistance levels and inflammatory markers might be needed for further analysis.

In summary, this study shows that hypertension was positively related to an increased risk of non-advanced and advanced adenomatous polyps, but not non-neoplastic polyps. In contrast, prehypertension was associated with a less advanced stage of colon polyps, including non-neoplastic polyps and non-advanced adenomatous polyps, but not associated with advanced adenomatous polyps. These results suggest that colorectal polyps may progress

from non-neoplastic polyps, shifting toward non-advanced and advanced adenomatous polyps during the development from normal blood pressure, then to prehypertension, and finally to hypertension, but further studies are needed to prove this inference.

The authors' responsibilities were as follows

NYS, JSW, and CJC designed the research; YCY, FHL, HEH, JSW, and CJC recruited the subjects and conducted the research; NYS and HCY analyzed the data; NYS wrote the paper; JSW and CJC critically reviewed the manuscript; CJC had primary responsibility for the final content. All the authors read and approved the final manuscript. None of the authors reported a conflict of interest related to the study. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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