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Smoking Is a Risk Factor of Colorectal Advanced Adenomas Compared to Nonadvanced Adenomas

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Abstract

Background: It is uncertain that whether smoking is a risk factor of colorectal advanced adenomas compared to nonadvanced adenomas, so we peformed the case-control study to explore this issue. **Material and Methods:** The cases were defined as patients with advanced adenomas and the controls were patients with nonadvanced adenomas. Clinical data were extracted from the hospital information system. Missing data were imputed with the multiple imputation of chained equations method, and the effect of smoking on the risk of advanced adenomas was calculated by binary logistic regression models to obtain odds ratios (ORs) and 95% confidence interval. **Results:** Current smoking rate in patients with advanced adenomas was significantly higher than that in patients with nonadvanced adenomas (31.6% VS 23.1%), the OR of advanced adenoma for current smoking compared with nonsmoking was 1.54 (1.09, 2.18), $P = 0.013$, and the weighted ORs ranged from 1.50 (1.01, 2.23) to 1.58 (1.09, 2.30), and the results of sensitivity analyses were still consistent. **Conclusion:** In adults with Han ethnicity in South China, current smoking is a risk factor of colorectal advanced adenomas compared to nonadvanced adenomas.

Keywords

Smoking, Colorectal Adenomas, Advanced Adenomas

1. Introduction

Smoking, as one of the most common unhealthy lifestyles, has been shown to

not only increase the risk of colorectal cancer and other malignant tumors [1] [2] [3], but also increase the risk of colorectal precancerous lesions, adenomatous polyps and serrated polyps [4] [5] [6]. It is well known that the traditional adenoma-carcinoma pathway leads to 70% - 90% of colorectal cancers [7]. And adenomas could be classified into nonadvanced adenomas (tubular adenomas ≤ 9 mm in size, without high-grade dysplasia) and advanced adenomas (adenomas with high-grade dysplasia, ≥10 mm in size, or villous histology), nonadvanced adenomas are low-risk polyps, and their risk of colorectal cancer has no significant difference compared with those without adenomas, while advanced adenomas are relatively high-risk, the risk of colorectal cancer could increase by about 3 times compared with those without adenomas [8].

However, it is uncertain that whether smoking is a risk factor of colorectal advanced adenomas compared to nonadvanced adenomas. We systematically searched Pubmed with "colorectal adenomas", "colorectal polyps" and "smoking" as keywords or titles, only found few studies with small sample sizes comparing smoking rates in patients with advanced adenomas and those with nonadvanced adenomas, and there was no significant difference [9].

Therefore, to further investigate this issue, we retrospectively analyzed patients with colorectal adenomas who were hospitalized in the Sixth Affiliated Hospital, Sun Yat-sen University in 2021.

2. Material and Methods

2.1. Study Design and Population

This retrospective case-control study was performed at the Sixth Affiliated Hospital, Sun Yat-sen University in 2022. And it was approved by the Ethics Committee of the Sixth Affiliated Hospital, Sun Yat-sen University. The ethical committee's reference number is 2022ZSLYEC-299.

All Han ethnicity adult patients with colorectal adenomas who were admitted to the Sixth Affiliated Hospital in 2021 were included in this study. Patients with a history of colorectal polyposis resection, serrated polyps, malignant or borderline tumors, inflammatory bowel disease, familial polyposis, Lynch syndrome, PJ syndrome, MUTYN-related polyposis, juvenile polyposis syndrome, Cowden syndrome, Li-Fraumeni syndrome, serrated polyposis syndrome, decompensated cirrhosis, or end-stage renal disease were excluded.

Cases were defined as patients with advanced adenomas and controls were defined as those with nonadvanced adenomas. Advanced adenomas were defined as adenomas with high-grade dysplasia, ≥10 mm in size, or villous histology. Nonadvanced adenomas were defined as tubular adenomas ≤ 9 mm, without high-grade dysplasia.

The sample size of this study was calculated by PASS 11.0 software, the smoking rate in the control group was estimated to be 0.2, the estimated odds ratio (OR) of clinical observations was 2.0, α was 0.05, β was 0.1, and the case-control sample size ratio was 1:1, the minimum required sample size was calculated to be 460.

2.2. Data Sources

The clinical data were obtained from the hospital information system, including: gender, age, education level, polyp size, histology, family history of colorectal cancer, height, weight, smoking, history of diabetes, plasma glucose, glycosylated hemoglobin, creatinine, urine protein, urine glucose, serum uric acid, lipids, liver function, alcohol consumption, hypertension, hyperlipidemia, hyperuricemia, chronic kidney disease, liver disease, atherosclerotic cardiovascular disease, etc.

2.3. Definitions and Assessments of Exposures

Current smoking was defined as current smoking for ≥1 year or smoking for ≥1 year and quitting for <6 months. Past smoking was defined as smoking for ≥1 year and quitting for ≥6 months. Nonsmoking was defined as never smoking or smoking for <6 months.

Glucose metabolism status was classified according to diabetes classification criterion of the American Diabetes Association [10].

Chronic kidney disease was defined as decreased kidney function shown by glomerular filtration rate (GFR) of less than 60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, or markers of kidney damage, or both, of at least 3 months duration, regardless of the underlying cause.

Definition of atherosclerotic heart disease: including acute coronary syndromes, myocardial infarction, stable angina, coronary/other arterial revascularization, stroke, transient ischemic attack, and peripheral arterial disease of atherosclerotic origin.

2.4. Statistical Analyses

Missing data in the study such as educational level (2.5%), weight (0.2%) and chronic kidney disease (1.3%), were imputed by with the multiple imputation of chained equations method using the baseline characteristics, outputting 5 imputation datasets for follow-up analyses [11].

ORs with 95% confidence intervals (CIs) for associations between smoking and advanced adenomas were obtained using binomial logistic regression models. Sex, age, body mass index (BMI), family history and other confounders that could change the odds ratios >10% were included in logistic regression models, while intermediary factors such as atherosclerotic cardiovascular disease (ASCVD) were pre-excluded.

In addition, we modified the inclusion criteria to include patients admitted to hospital with the complaint of colorectal polyps or mass, and performed sensitivity analyses to assess the robustness of the main results.

All statistical tests were 2-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using SPSS Statistics software for mac version 26.0 (IBM, Armonk, NY, USA).

3. Results

Table 1 shows that 666 patients including 316 cases and 350 controls were included

Table 1. Baseline characteristics of patients with colorectal adenomas.

Characteristics	Cases (n = 316)	Controls (n = 350)	P value
Male	234 (74.1)	249 (71.1)	0.401
Age, mean (SD), y	58.29 (10.92)	57.28 (11.71)	0.251
Educational level			0.531
Illiteracy	10 (3.2)	11 (3.1)	
Primary school	55 (17.4)	56 (16.0)	
Secondary school	158 (50.0)	173 (49.4)	
University and above	85 (26.9)	101 (28.9)	
Unknown	8 (2.5)	9 (2.6)	
Family history	9 (2.8)	5 (1.4)	0.202
BMI (Kg/m^2)			0.259
<18.5	16 (5.1)	17 (4.9)	
18.5 - 23.9	154 (48.7)	154 (44.0)	
24.0 - 27.9	112 (35.4)	141 (40.3)	
28.0 - 31.9	30(9.5)	33 (9.4)	
>32	3 (0.9)	5 (1.4)	
Unknown	1 (0.3)	0 (0)	
Glucose metabolism status			0.033
Normal	216 (68.4)	209 (59.7)	
Prediabetes	68 (21.5)	85 (24.3)	
Diabetes	32 (10.1)	56 (16.0)	
Alcoholism			0.041
No	281 (88.9)	329(94.0)	
Past	2 (0.6)	1 (0.3)	
Current	33 (10.4)	20 (5.7)	
Dyslipidemia	183 (57.9)	184 (52.6)	0.167
Hypertension	68 (21.5)	98 (28.0)	0.054
Hyperuricemia	55 (17.4)	58 (16.6)	0.775
CKD	20 (6.3)	22 (6.3)	0.970
Unknown	5 (1.6)	4 (1.1)	
ASCVD	22 (7.0)	22 (6.3)	0.726

Abbreviations: SD, standard deviation; BMI, body mass index; CKD, chronic kidney disease; ASCVD, arteriosclerotic cardiovascular disease.

in this study. Colorectal adenomas were more common in men (72.5%), and patients with an average age of 58 years old, half of the patients were overweight or

obese (48.6%), and current drinking rate of patients with advanced adenomas was higher than that of patients with nonadvanced adenomas (10.4% VS 5.7%), while the prevalence of diabetes and hypertension was lower in patients with advanced adenomas than that in patients with nonadvanced adenomas (10.1% VS 16.0% and 21.5% VS 28.0%).

Table 2 shows that current smoking rate in patients with advanced adenomas was significantly higher than that in patients with nonadvanced adenomas (31.6% VS 23.1%), the OR of advanced adenoma for current smoking compared with nonsmoking was 1.54 (1.09, 2.18), $P = 0.013$. After adjusting for some confounders, the weighted ORs ranged from 1.50 (1.01, 2.23) to 1.58 (1.09, 2.30).

Table 3 and Table 4 show that sensitivity analyses in patients admitted to hospital with the complaint of colorectal polyps or mass, current smoking rate in patients with advanced adenomas was still significantly higher than that in patients with nonadvanced adenomas (28.7% VS 18.0%), the OR of advanced adenoma was 1.80 (1.13, 2.87), $P = 0.013$, the weighted OR was 1.78 (1.06, 2.99), $P = 0.030$, similar to the results in Table 2.

Table 2. Association between smoking and advanced adenomas.

Smoking	Cases ($n = 316$)	Controls ($n = 350$)	OR (95% CI) *P* value	Weighted OR (95% CI) *P* value[a]	Weighted OR (95% CI) *P* value[b]
No	212 (67.1)	265 (75.7)	Reference	Reference	Reference
Past	4 (1.3)	4 (1.1)	1.25 (0.31, 5.06) 0.754	1.29 (0.31, 5.36) 0.726	1.67 (0.38,7.38) 0.496
Current	100 (31.6)	81 (23.1)	1.54 (1.09, 2.18) 0.013	1.58 (1.09, 2.30) 0.016	1.50 (1.01, 2.23) 0.047

Abbreviations: OR, odds ratio; CI, confidence interval. [a]adjusted for sex, age, BMI and family history. [b]adjusted for sex, age, BMI, family history, alcoholism and glucose metabolism status.

Table 3. Baseline characteristics of patients with colorectal adenomas in sensitivity analysis.

Characteristics	Cases ($n = 258$)	Controls ($n = 183$)	*P* value
Male	185 (71.7)	131 (71.6)	0.978
Age, mean (SD), y	57.72 (10.73)	56.88 (10.31)	0.412
Educational level			0.125
Illiteracy	8 (3.1)	3 (1.6)	
Primary school	45 (17.4)	25 (13.7)	
Secondary school	128 (49.6)	90 (49.2)	
University and above	71 (27.5)	59 (32.2)	
Unknown	6 (2.3)	6 (3.3)	
Family history	9 (3.5)	3 (1.6)	0.379

Continued

BMI (Kg/m^2)			0.874
<18.5	14 (5.4)	7 (3.8)	
18.5 - 23.9	121 (46.9)	87 (47.5)	
24.0 - 27.9	96 (37.2)	73 (39.9)	
28.0 - 31.9	25 (9.7)	15 (8.2)	
>32	2 (.08)	1 (0.5)	
Glucose metabolism status			0.179
Normal	188 (72.9)	124 (67.8)	
Prediabetes	51 (19.8)	37 (20.2)	
Diabetes	19 (7.4)	22 (12.0)	
Alcoholism			0.049
No	235 (91.1)	176(96.2)	
Past	1 (0.4)	1 (0.5)	
Current	22 (8.5)	6 (3.3)	
Dyslipidemia	149 (57.8)	87 (47.5)	0.034
Hypertension	51 (19.8)	40 (21.9)	0.593
Hyperuricemia	45 (17.4)	31 (16.9)	0.891
CKD	13 (5.0)	6 (3.3)	0.366
Unknown	5 (1.9)	3 (1.6)	
ASCVD	13 (5.0)	9 (4.9)	0.954

Abbreviations: SD, standard deviation; BMI, body mass index; CKD, chronic kidney disease; ASCVD, arteriosclerotic cardiovascular disease.

Table 4. Association between smoking and advanced adenomas in sensitivity analysis.

Smoking	Cases (n = 258)	Controls (n = 183)	OR (95% CI) P value	Weighted OR (95% CI) P value[a]
No	183 (70.9)	147 (80.3)	Reference	Reference
Past	1 (0.4)	3 (1.6)	0.27 (0.03, 2.60) 0.256	0.28 (0.02, 3.28) 0.312
Current	74 (28.7)	33 (18.0)	1.80 (1.13, 2.87) 0.013	1.78 (1.06, 2.99) 0.030

Abbreviations: OR, odds ratio; CI, confidence interval. [a]adjusted for sex, age, BMI, family history and alcoholism.

4. Discussion

Data from our study showed that current smoking rate in patients with advanced adenomas was significantly higher than that in patients with nonadvanced adenomas, suggesting that current smoking was associated with an increased risk of advanced adenomas compared to nonadvanced adenomas. If replicated in other populations, it might suggest that smoking could be an impor-

tant risk factor of colorectal precancerous lesions. Smokers might need to adjust colorectal cancer screening strategies, and the indications for colorectal polypectomy in smokers might also need to be appropriately relaxed.

To our knowledge, there was no study to clarify whether smoking rates differ between patients with nonadvanced adenomas and those with advanced adenomas. Smoking may increase the risk of colorectal adenomas and advanced adenomas compared to healthy people or patients with hyperplastic polyps [4] [12]. However, the effect of smoking on risk of advanced adenomas compared to nonadvanced adenomas was unclear [9]. In this case-control study, for the first time, we found that current smoking may be one of the risk factors of the advanced adenomas compared to nonadvanced adenomas.

The study has several strengths. Firstly, the patients included in the study came from a large gastrointestinal disease center, the patient composition might be closer to reality due to larger number of visits. Secondly, the study conducted a double survey of smoking status from admission records from doctors and questionnaires from nurses, which increased the accuracy of smoking prevalence estimates. Finally, in terms of statistical analyses, the multiple imputation was used to deal with missing data, and the effect of current smoking was repeatedly assessed through multiple logistic regression models and sensitivity analysis to ensure the robustness of the conclusions.

The study has a few limitations. Firstly, as a single-center study, only the Han ethnicity population in South China was included, the finding is difficult to extrapolate to other regions and populations. Therefore, further studies are needed to confirm the finding in other regions and populations. Secondly, as a retrospective study, due to the limited content of medical records, data such as red meat intake and drugs use were not collected in this study, and further prospective studies covering more information are needed to strengthen the conclusions. Finally, the missing of smoking status in medical records might also lead to misclassification, and smoking prevalence might be underestimated. However, we do not have evidence to support that misclassification occurred differently for cases and controls. If the misclassification was nondifferential by case-control status, current smoking may actually have a more significant effect increasing risk of advanced adenomas in this study.

5. Conclusion

This study provides evidence that in adults with Han ethnicity in South China, current smoking was a risk factors of colorectal advanced adenomas compared to nonadvanced adenomas.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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