



BRIEF ARTICLES

Risk factors for sporadic colorectal cancer in southern Chinese

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Abstract

AIM: To investigate the role of smoking, alcohol drinking, family history of cancer, and body mass index (BMI) in sporadic colorectal cancer in southern Chinese.

METHODS: A hospital-based case-control study was conducted from July 2002 to December 2008. There were 706 cases and 723 controls with their sex and age (within 5 years) matched. An unconditional logistic regression model was used to analyze the association between smoking, alcohol drinking, family history of cancer, BMI and sporadic colorectal cancer.

RESULTS: No positive association was observed between smoking status and sporadic colorectal cancer risk. Compared with the non alcohol drinkers, the current and former alcohol drinkers had an increased risk of developing sporadic colorectal cancer (CRC) (adjusted OR = 8.61 and 95% CI = 6.15-12.05; adjusted OR = 2.30, 95% CI = 1.27-4.17). Moreover, the increased risk of developing sporadic CRC was

significant in those with a positive family history of cancer (adjusted OR = 1.62, 95% CI = 1.12-3.34) and in those with their BMI ≥ 24.0 kg/m² (adjusted OR = 1.39, 95% CI = 1.10-1.75). Stratification analysis showed that the risk of developing both colon and rectal cancers was increased in current alcohol drinkers (adjusted OR = 7.60 and 95% CI = 5.13-11.25; adjusted OR = 7.52 and 95% CI = 5.13-11.01) and in those with their BMI ≥ 24.0 kg/m² (adjusted OR = 1.38 and 95% CI = 1.04-1.83; adjusted OR = 1.35 and 95% CI = 1.02-1.79). The risk of developing colon cancer, but not rectal cancer, was found in former alcohol drinkers and in those with a positive family history of cancer (adjusted OR = 2.51 and 95% CI = 1.24-5.07; adjusted OR = 1.82 and 95% CI = 1.17-2.82).

CONCLUSION: Alcohol drinking, high BMI (≥ 24.0 kg/m²) and positive family history of cancer are the independent risk factors for colorectal cancer in southern Chinese.

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Key words: Case-control; Colorectal cancer; Risk factors; Smoking; Alcohol drinking; Body mass index; Family history

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers in China. Although official statistic data are scanty, the reports from some regions indicate that the incidence of colorectal cancer increases^[1,2]. During 1974-1999 in Henan Province, the incidence of esophageal carcinoma was significantly decreased

whereas that of CRC has increased over the last two decades^[1]. In Guangdong Province, the incidence of CRC in Huidong County is getting close to that in the world^[2]. These data suggest that more attention should be paid to the prevention and control of CRC.

In recent years, the epidemiological factors for CRC in Chinese have been extensively studied^[3-8]. However, the results are uncertain. It has been reported that smoking is a risk factor for rectal cancer in Chinese^[3] and is associated with the increased risk of developing rectal cancer in Singapore Chinese^[4]. However, other studies showed that smoking is not a risk factor for CRC in Chinese^[5-7]. Similarly, the relation between alcohol drinking and colorectal cancer in Chinese is controversial^[3,6,8]. A population-based prospective cohort study showed that alcohol consumption is not significantly associated with the risk of developing CRC^[8], but is associated with the risk of developing CRC in northern Chinese^[6] and Hong Kong Chinese^[3].

The reports about the association between body mass index (BMI) and colorectal cancer in thin Chinese are scanty. A study comprising 931 cases and 1552 controls in Shanghai demonstrated that BMI is a risk factor for colorectal cancer in men and pre-menopausal women^[9]. Zhang *et al.*^[10] reported that family history is positively related with CRC. However, their data lack of multivariate analysis in unconditional logistic regression model adjusted by factors including age, sex, smoking status, alcohol consumption, family history of cancer, and BMI. Thus, the role of epidemiological factors for CRC in Chinese should be further investigated.

MATERIALS AND METHODS

Subjects and data collection

From July 2002 to December 2008, a hospital-based case-control study was conducted in Guangzhou City. Patients with sporadic CRC were recruited in our study with a response rate of about 95%. A total of 513 patients were recruited as a test group between July 2002 and April 2008 at the Sixth Affiliated Hospital (Gastrointestinal and Anal Hospital) of Sun Yat-Sen University (Guangzhou, China), Sun Yat-Sen University Cancer Center (Guangzhou, China), the First Affiliated Hospital of Sun Yat-Sen University (Guangzhou, China) and the Affiliated Tumor Hospital of Guangzhou Medical College (Guangzhou, China). To validate our findings, 193 patients were recruited as a validation group between May 2008 and December 2008 at Guangdong Provincial People's Hospital and Panyu People's Hospital (Guangzhou, China). Cancer-free controls were randomly selected from about 10000 individuals in Guangzhou City during the same period, with a response rate of about 85%. Five hundred and twenty-three controls were recruited as an original test group and 200 controls as a validation group. Cases of familial adenomatous polyposis and those fulfilling the criteria of Amsterdam for hereditary non-polyposis colorectal cancer were excluded. Thus, 706 sporadic CRC patients and 723 cancer-free controls were included in this study. All subjects were genetically-

unrelated Han nationality Chinese from Guangzhou City and its surrounding regions. The control subjects were sex and age (within 5 years) matched to the patients. The study was approved by the Review Board of Sun Yat-Sen University.

Exposure assessment

Each participant was scheduled for an interview after he or she gave his or her written informed consent, and a structured questionnaire was designed by the interviewers to collect data on smoking status, alcohol consumption and other factors including BMI, family history of cancer, menstrual history, sex and age. The participants who smoked < 100 cigarettes in their lifetime were defined as non smokers. Otherwise, they were defined as smokers. Smokers who were quitted with smoking for > 1 year prior to enrollment were considered former smokers, and the remaining were defined as current smokers. Similarly, participants who consumed alcohol at least once a week for ≥ 1 year were defined as alcohol drinkers and the remaining as non alcohol drinkers. Alcohol drinkers who were quitted with drinking for ≥ 1 year were defined as former alcohol drinkers, and the others as current drinkers. Those with a positive family history of cancer were defined as the first- or second-degree relatives or both. This study used the BMI cutoff points recommended by the Cooperative Meta-Analysis Group on Obesity in China^[11]. Subjects with their BMI ≤ 23.9 kg/m² were categorized as underweight and normal body weight, while those with their BMI ≥ 24.0 kg/m² were categorized as overweight and obese.

Statistical analysis

Two-sided chi-square test was performed to assess differences in age, sex, smoking status, alcohol consumption, family history of cancer and BMI between patients and controls. An unconditional logistic regression model was used to estimate the association between case-control status and factors including smoking status, alcohol consumption, BMI, and family history of cancer, measured by odds ratio (OR) and corresponding 95% confidence interval (CI). Logistic regression modeling was used in trend test. Statistical analysis was performed using SPSS for Windows (version 13.0). All statistical analyses were 2-sided and $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of studied Chinese

A total of 706 sporadic CRC cases and 723 cancer-free controls were included in statistical analysis. The differences in distribution of age, sex, menstrual history between the cases and controls were not statistically significant ($P = 0.992, 0.937, 0.883$, respectively) (Table 1). Compared with the controls, the cases were more likely to be current smokers and current drinkers (current smokers: 44.8% *vs* 30.3%, $P < 0.0001$ and current drinkers: 52.8% *vs* 19.4%, $P < 0.0001$). Moreover, the cases tended to have a higher BMI ($P = 0.002$) and a positive family history of cancer ($P = 0.018$). Therefore, these variables were further

Table 1 Distributions of selected variables in colorectal cancer patients and cancer-free controls *n* (%)

Variables	Test group		Validation group		Merged group		<i>P</i> ¹
	Case	Control	Case	Control	Case	Control	
Age (yr)							0.992
≤ 49	120 (23.4)	122 (23.3)	36 (18.7)	36 (18.0)	156 (22.1)	158 (21.9)	
50-60	146 (28.5)	149 (28.5)	39 (20.2)	42 (21.0)	185 (26.2)	191 (26.4)	
> 60	247 (48.2)	252 (48.2)	118 (61.1)	122 (61.0)	365 (51.7)	374 (51.7)	
Sex							0.937
Male	300 (58.5)	300 (57.4)	137 (71.0)	149 (74.5)	437 (61.9)	449 (62.1)	
Female	213 (41.5)	223 (42.6)	56 (29.0)	51 (25.5)	269 (38.1)	274 (37.9)	
Smoking status							< 0.0001
Current	228 (44.4)	142 (27.2)	88 (45.6)	77 (38.5)	316 (44.8)	219 (30.3)	
Former	59 (11.5)	79 (15.1)	20 (10.4)	24 (12.0)	79 (11.2)	103 (14.3)	
Non	226 (44.1)	302 (57.7)	85 (44.0)	99 (49.5)	311 (44.1)	401 (55.5)	
Drinking status							< 0.0001
Current	275 (53.6)	83 (15.9)	98 (50.8)	57 (28.5)	373 (52.8)	140 (19.4)	
Former	14 (2.7)	25 (4.8)	12 (6.2)	10 (5.0)	26 (3.7)	35 (4.8)	
Non	224 (43.7)	415 (79.4)	83 (43.0)	133 (66.5)	307 (43.5)	548 (75.8)	
Family history of cancer							0.018
Yes	71 (13.8)	57 (10.9)	20 (10.4)	8 (4.0)	91 (12.9)	65 (9.0)	
No	442 (86.2)	466 (89.1)	173 (89.6)	192 (96.0)	615 (87.1)	658 (91.0)	
BMI (kg/m ²)							0.002
≤ 23.9	297 (57.9)	346 (66.2)	92 (47.7)	118 (59.0)	389 (55.1)	464 (64.2)	
24.0-27.9	169 (32.9)	139 (26.6)	77 (39.9)	66 (33.0)	246 (34.8)	205 (28.4)	
≥ 28.0	47 (9.2)	38 (7.3)	24 (12.4)	16 (8.0)	71 (10.1)	54 (7.5)	
Menstrual history							0.881
Premenopause	43 (20.2)	41 (18.4)	10 (17.9)	11 (21.6)	53 (19.7)	52 (19.0)	
Menopause	170 (79.8)	182 (81.6)	46 (82.1)	40 (78.4)	216 (80.3)	222 (81.0)	

¹*P* value for two-sided χ^2 test.

Table 2 Comparison of epidemiological factors for colorectal cancer

Variables	Adjusted OR (95% CI) ¹		
	Test group	Validation group	Merged group
Smoking status			
Non	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Former	0.97 (0.52-1.80)	0.66 (0.30-1.46)	0.78 (0.49-1.23)
Current	1.41 (0.82-2.43)	0.79 (0.45-1.38)	1.01 (0.69-1.48)
Trend test <i>P</i> value	< 0.00001	0.187	< 0.00001
Drinking status			
Non	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Former	2.02 (0.93-4.41)	2.84 (1.03-7.81)	2.30 (1.27-4.17)
Current	14.69 (9.41-22.94)	3.82 (2.23-6.56)	8.61 (6.15-12.05)
Trend test <i>P</i> value	< 0.00001	0.023	< 0.00001
Family history of cancer			
Negative	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Positive	1.43 (0.94-2.18)	3.21 (1.31-7.84)	1.62 (1.12-3.34)
BMI (kg/m ²)			
≤ 23.9	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
≥ 24.0	1.34 (1.00-1.78)	1.60 (1.05-2.44)	1.39 (1.10-1.75)

¹Adjusted for age, sex, smoking status, alcohol drinking, family history of cancer, BMI.

adjusted in multivariate logistic regression model for controlling any residual effect of possible confounding on the main effect of studied factors.

Risk factors for sporadic colorectal cancer

Logistic regression analysis showed that compared with the non alcohol drinkers, current and former alcohol drinkers had a significantly increased risk of developing sporadic CRC (adjusted OR = 8.61 and 95% CI = 6.15-12.05; adjusted OR = 2.30 and 95% CI = 1.27-4.17) (Table 2).

Similarly, the increased risk of developing sporadic CRC was significantly greater in those with a positive family history of cancer (adjusted OR = 1.62, 95% CI = 1.12-3.34) and in those with their BMI ≥ 24.0 kg/m² (adjusted OR = 1.39, 95% CI = 1.10-1.75). There was a significant trend to develop CRC (*P*_{trend} < 0.00001) due to alcohol drinking. However, smoking status was not positively correlated with the risk of developing sporadic CRC.

Stratification analysis of colon and rectal cancer

We further performed a stratification analysis of the association between selected variables and risk of developing colon and rectal cancer in subgroups (Table 3). The risk of developing both colon and rectal cancers was increased in current alcohol drinkers (adjusted OR = 7.60 and 95% CI = 5.13-11.25; adjusted OR = 7.52 and 95% CI = 5.13-11.01) and in those with their BMI ≥ 24.0 kg/m² (adjusted OR = 1.38 and 95% CI = 1.04-1.83; adjusted OR = 1.35 and 95% CI = 1.02-1.79). The risk of developing colon cancer, but not rectal cancer, was found in former alcohol drinkers (adjusted OR = 2.51 and 95% CI = 1.24-5.07) and in those with a positive family history of cancer (adjusted OR = 1.82 and 95% CI = 1.17-2.82). However, smoking status was not significantly associated with the risk of developing CRC.

DISCUSSION

In our study, smoking status was not positively associated with the risk of developing sporadic CRC. Compared with the non alcohol drinkers, current and former alcohol drinkers had an increased risk of developing sporadic

Table 3 Stratification analysis of colon and rectal cancer

Variables	Adjusted OR (95% CI) ¹					
	Test group		Validation group		Merged group	
	Colon cancer (n = 253)	Rectal cancer (n = 260)	Colon cancer (n = 95)	Rectal cancer (n = 98)	Colon cancer (n = 348)	Rectal cancer (n = 358)
Smoking status						
Non	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Former	0.71 (0.34-1.49)	1.26 (0.59-2.69)	1.09 (0.44-2.72)	0.41 (0.14-1.18)	0.83 (0.48-1.43)	0.79 (0.45-1.38)
Current	1.34 (0.72-2.51)	1.87 (0.96-3.65)	1.03 (0.53-2.03)	0.78 (0.40-1.51)	1.22 (0.78-1.91)	1.17 (0.75-1.83)
Drinking status						
Non	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Former	2.28 (0.90-5.76)	1.32 (0.48-3.64)	2.51 (0.78-8.06)	3.10 (0.88-10.92)	2.51 (1.24-5.07)	1.71 (0.80-3.65)
Current	13.24 (7.78-22.51)	11.91 (7.14-19.87)	3.46 (1.83-6.53)	3.61 (1.94-6.74)	7.60 (5.13-11.25)	7.52 (5.13-11.01)
Family history of cancer						
Negative	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Positive	1.67 (1.01-2.75)	1.26 (0.76-2.09)	3.26 (1.12-9.45)	3.52 (1.26-9.85)	1.82 (1.17-2.82)	1.51 (0.97-2.35)
BMI (kg/m ²)						
≤ 23.9	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
≥ 24.0	1.48 (1.05-2.09)	1.22 (0.86-1.73)	1.18 (0.70-1.99)	2.00 (1.18-3.36)	1.38 (1.04-1.83)	1.35 (1.02-1.79)

¹Adjusted for age, sex, smoking status, alcohol drinking, family history of cancer, BMI.

CRC. The increased risk of developing sporadic CRC was found in those with their BMI ≥ 24.0 kg/m² and in those with a positive family history of cancer. The stratification analysis showed that the risk of developing both colon and rectal cancers was increased in current alcohol drinkers and in those with their BMI ≥ 24.0 kg/m². The increased risk of developing colon cancer but not rectal cancer was found in former alcohol drinkers and in those with a positive family history of cancer.

It has been reported that smoking is related with the risk of developing invasive colorectal cancer and current smokers have a significantly increased risk of developing rectal cancer but not colon cancer compared with non smokers^[12]. In a population-based case-control study recruiting 540 cases of colorectal cancer and 614 controls in Germany, current smokers had a significantly increased risk of developing colorectal cancer compared with non smokers^[13]. Another report including 852 patients demonstrated that tobacco smoking is a risk factor for early colorectal cancer^[14]. Inconsistent with the above reports, in our study, smoking was not associated with the risk of developing colorectal cancer. However, our results are consistent with the reported findings^[7]. The different results might be due to the different time of smoking between mainland Chinese and other populations. The main increase in cigarette consumption in various Chinese communities occurred a few decades later than that of the Western countries^[15]. Similarly, the prevalence of cigarette smoking reached its peak in Hong Kong about 20 years earlier than in mainland China^[15]. Giovannucci *et al.*^[16,17] demonstrated that smoking is related to the risk of developing colorectal cancer only after allowing for an induction period of at least 35 years. It has been shown that long-term smoking is associated with the elevated risk of developing colorectal cancer^[13,18].

Our results suggest that alcohol drinking was an independent risk factor for sporadic CRC, which is consistent with the findings in Japan, American, French, and Hong Kong^[3,19-21]. However, the OR value in our

study was much higher than the reported data, which may be due to the selection bias in our study. In our study, the cases were recruited from 6 hospitals, whereas the controls were enrolled from communities in Guangzhou City. Thus, the percentage of current alcohol drinkers in the controls was relatively low (Table 1).

Our study found that there was an independent association between BMI and sporadic CRC risk in Chinese. Insulin action decreases with increasing obesity^[22]. Insulin resistance develops as a metabolic adaptation to increased levels of circulating non-esterified fatty acids released from adipose tissues. Because non-esterified fatty acids force the liver, muscles, and other tissues to store and oxidize fats for energy, the pancreas would secrete more insulin to prevent elevated concentrations of glucose in blood^[23]. Increased blood insulin levels decrease insulin-like growth factor binding protein 1 levels, thus increasing free insulin-like growth factor 1 (IGF-1) levels^[24]. It has been shown that insulin resistance is related with hyperinsulinaemia, IGF-1 and colorectal cancer^[25-27]. In this study, the increased risk of developing colon cancer but not rectal cancer was associated with a positive family history of cancer, indicating that genetic susceptibility may play a more important role in the pathogenesis of colon cancer than in that of rectal cancer.

However, our study had several limitations, such as a small sample size, hospital-based case control, Chinese subjects, and lack of food intake information, which might result in improper findings.

In conclusion, in our study, we found that alcohol drinking and greater BMI (≥ 24.0 kg/m²) are the independent risk factors for colon and rectal cancer in southern Chinese. The risk of developing colon cancer but not rectal cancer increases in former alcohol drinkers and in those with a positive family history of cancer. Because of the uncontrolled bias in selection of participants and retrospective design, our findings need to be further evaluated in well-designed larger epidemiological studies with different ethnic populations.

COMMENTS

Background

The incidence of colorectal cancer in China is growing. More attention should be paid to the prevention and control of colorectal cancer. However, the epidemiological factors for colorectal cancer are controversial.

Research frontiers

Although the association between the epidemiological factors and sporadic colorectal cancer has been studied, the relation between smoking, alcohol drinking, family history of cancer, body mass index (BMI) and sporadic colorectal cancer still remains uncertain. It is important to investigate the role of these factors in the development of sporadic colorectal cancer.

Innovations and breakthroughs

In this study, the authors found that current alcohol drinking and greater BMI ($\geq 24.0 \text{ kg/m}^2$) are the independent risk factors for colon and rectal cancer, while former alcohol drinking and positive family history of cancer are the independent risk factors for colon cancer in southern Chinese.

Peer review

In the case-control study, smoking, alcohol consumption, BMI and family history of cancer were evaluated in patients with sporadic colorectal cancer. The study showed that alcohol drinking, higher BMI ($\geq 24.0 \text{ kg/m}^2$) and positive family history of cancer were the independent risk factors for sporadic colorectal cancer in a southern Chinese. Its findings may contribute to the prevention and control of sporadic colorectal cancer.

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