BRIEF ARTICLE

Multicenter case-control study of the risk factors for ulcerative colitis in China

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Abstract

AIM: To evaluate potential risk factors in the development of ulcerative colitis (UC) in China.

METHODS: A total of 1308 patients with UC and 1308 age-matched and sex-matched controls were prospectively studied in China. The UC cases were collected from 17 hospitals in China from April 2007 to April 2010. Uniform questionnaires were designed to investigate risk factors including smoking, appendectomy, stress, socio-economic conditions, nonsteroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, diet, breastfeeding, infections and family sanitary conditions. Group comparisons by each factor were done using simple logistic regression analysis. Conditional logistic regression was used for multivariate analysis.

RESULTS: By univariate analysis, the variables predictive of UC included feeling stress, light and heavy alcoholic drinking, spicy food, sugar consumption and infectious diarrhea, while heavy tea intake and tap water consumption were protective against UC. On multivariate analysis, the protective factor for UC was tap water consumption [odds ratios (OR) = 0.424, 95%CI: 0.302-0.594, $P < 0.001$]; while the potential risk factors for UC were heavy sugar consumption (OR = 1.632, 95%CI: 1.156-2.305, $P < 0.001$), spicy food (light intake: OR = 3.329, 95%CI: 2.282-4.857, $P < 0.001$; heavy intake: OR = 3.979, 95%CI: 2.700-5.863, $P < 0.001$), and often feeling stress (OR = 1.981, 95%CI: 1.447-2.711, $P < 0.001$). Other factors, such as smoking habit, appendectomy, breastfeeding, a history of measles, rural or urban residence, education, oral contraceptives, and NSAID use have not been found to have a significant association with the development of UC in the present study.

CONCLUSION: Our study showed tap water consumption was a protective factor for UC, while spicy food, heavy sugar consumption and often feeling stress were risk factors for UC in this Chinese population.

INTRODUCTION

The causes of inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), remain unknown. IBD is thought to arise in genetically predisposed individuals who mount an aberrant immune response to gut microbiota secondary to some environmental trigger[1]. Genetic susceptibility in the population should be relatively stable; it cannot account for the rapid rise of IBD incidence in China. Environmental factors may play an important role in the pathogenesis of IBD.

IBD has been primarily characterized as a disease of industrialized nations, emerging in the early 20th century in developed countries. In the past 20 years, incidence rates of traditionally high incidence areas such as North America and Europe have remained relatively stable or even decreased[2], while the diseases have become more prevalent in previously low incidence areas as they have become industrialized[3]. Recent surveys in China have also shown that IBD, especially UC, has been increasing in China[4-7].

A number of environmental risk factors have been explored in Western countries. There is no such epidemiologic study of large sample groups in Chinese populations. China presents an opportunity to study an environment that is evolving more to a Western-style based on changes in socioeconomics, diet habit, *etc*. The present study aims to assess the potential risk factors for the development of UC in the Chinese population by a multicenter case-control study.

MATERIALS AND METHODS

Patients and controls

A multicenter case-control study was undertaken in China during a 3-year period from April 2007 to April 2010. Patients were collected from 17 hospitals in 12 areas of China including Beijing and Dalian, which were chosen from Northern China; Shanghai, Nanjing and Hefei from Eastern China; Guangzhou from Southern China; Chengdu, Xian, Nanchong, Kunming from Western China; Wuhan and Changsha from Central China. The investigators were invited to take part in the program if their medical centers fulfilled the following requirements: (1) the medical center should be a university hospital or grade A tertiary hospital; and (2) diagnostic facilities for high-quality endoscopy, radiology and pathology should be available. The diagnosis of UC was made by clinical, laboratory, endoscopic, and histologic examinations in accordance with the suggested guidelines for the diagnosis and treatment of IBD, which were approved in China in 2007[8].

Controls were randomly selected in the same area as friends, neighbors or colleagues of the patients and matched by sex and age during the study. The controls were healthy volunteers with no bowel disease or other severe disease.

Questionnaire survey

UC patients and controls were interviewed to complete a questionnaire. A uniform questionnaire was designed by the IBD collaborative group of the Chinese Digestive Association. The questionnaire included an exploration of dietary habits, smoking, alcohol use, oral contraceptives, nonsteroidal anti-inflammatory drugs (NSAIDs), previous appendectomy, breast-feeding in infancy, childhood measles virus infection, parasite infection, infectious gastroenteritis, education, employment, stress and family sanitary conditions (including lavatory and water conditions). Subjects were instructed to answer questions in such a way that the information reflected their behavior and characteristics prior to the appearance of disease symptoms. Participating investigators or supervised physicians were in charge of the questionnaire.

In the questionnaire, study subjects were asked about the consumption of milk, green tea, alcohol, spicy food,

Table 1 Social characteristics and household factors between ulcerative colitis and healthy controls

Variables	UC	Control	*P* value	OR	95%CI
Living area					
Rural	16.4%	15.7%			
Town	16.6%	12.9%	0.617	0.930	0.702-1.234
City	67.0%	71.4%	0.054	0.711	0.569-1.887
Education					
Primary or below	14.3%	13.2%			
Secondary	39.7%	36.8%	0.959	0.994	0.781-1.265
College or above	46.0%	50.0%	0.164	0.846	0.669-1.071
Feeling stress					
None	21.5%	21.3%			
Occasionally	55.6%	66.5%	0.056	0.828	0.682-1.005
Often	22.9%	12.2%	0.000	1.858	1.440-2.398
Water source					
Boiled well or tap water water	82.0%	68.5%			
Well water	3.4%	1.9%	0.118	1.494	0.903-2.471
Tap water	5.4%	21.6%	0.000	0.21	0.159-0.279
Mineral water	9.2%	8.0%	0.758	0.957	0.723-1.267
Lavatory					
Closestool	11.3%	9.8%			
Squat pan	39.4%	41.6%	0.173	0.829	0.634-1.085
Flush toilet	49.3%	48.6%	0.368	0.886	0.680-1.154
Refrigerator	78.7%	81.1%	0.181	0.86	0.690-1.073

UC: Ulcerative colitis; OR: Odds ratio.

and sugar in the year before the appearance of symptoms. Consumption degree of each food item was assessed using the following three categories: none or rare, light (1-2 times a week) and heavy (3-6 times a week or every day for a period of at least 2 mo). Consumption of meat and vegetables was classified into the following 3 categories: vegetarian, meat-eater, and balanced diet. Vegetarian was defined as eater of fruits and vegetables, and never or hardly eats meat or any animal products. Meat-eater was defined as eater of meat and never or hardly eats fruits and vegetables. Balanced diet was defined as consumption of both meat and vegetables.

Oral contraceptive use was defined as use for at least 1 mo for any indication including birth control, hormone replacement therapy, regulation of menstrual disorders, or other reasons. NSAID use was defined as taking related drugs at least twice per week for a period of at least one month.

The questionnaire ascertained whether subjects were non-smokers, current smokers and ex-smokers. Non-smokers were defined as those who never or rarely smoked. Current smokers were those who had smoked more than 1 cigarette per day within 6 mo before the diagnosis of UC. Ex-smokers were defined as patients who quit smoking more than 6 mo before the diagnosis of UC.

The frequency of feeling stress was classified into none, occasionally (feeling stress 1-2 times a week) and often (feeling stress 3-6 times a week or every day for a period of at least one month).

Statistical analysis

Statistical analyses were performed using SPSS17.0 software. We compared the background characteristics of UC with those of control subjects by two-sample *t* tests or χ^2 tests. Group comparisons by each factor were done using simple logistic regression analysis. Multiple logistic regression analysis was performed to propose a final set of independent risk factors for UC. Odds ratios (OR) and 95%CI were calculated. Odds ratios are provided for associations that were statistically significant at a *P* value < 0.05.

RESULTS

Demographic characteristics

A total of 1308 UC patients and 1308 age-matched and sex-matched controls were enrolled. The age of the patients at diagnosis ranged from 16 to 70 years. The average age was 41.6 ± 12.3 years for UC patients and 41.4 ± 13.5 years for healthy controls. The male to female ratio was 1.23:1 both for UC patients and controls. There were no statistically significant differences between UC and the controls in age and sex ratio (*P* > 0.05).

Univariate analysis of risk factors for UC

Sociodemographic characteristics and family sanitary conditions for both UC patients and controls are shown in Table 1. Patients with UC were more likely to feel stress (22.9%) than controls (12.2%) (OR = 1.858, 95%CI: 1.440-2.398, *P* < 0.001). However, UC patients tended to be less likely to have used tap water as their primary water source compared with boiled well or tap water *vs* controls (OR = 0.210, 95%CI: 0.159-0.279, *P* < 0.001). There were no statistically significant differences between UC and the controls in living area in recent 5 years, educational status, lavatory and refrigerator details.

Dietary factors between the two groups are shown in Table 2. Compared with the group of none or rare tea intake, heavy tea intake before the diagnosis seemed to have a protective effect on the development of UC (OR = 0.738, 95%CI: 0.591-0.922, *P* = 0.007). In contrast to nonalcoholic drinkers, light and heavy alcoholic drinkers before the diagnosis were at a higher risk of developing the disease (light drinkers: OR = 1.264, 95%CI: 1.073-1.490, *P* = 0.005; heavy drinkers: OR = 1.453, 95%CI: 1.122-1.882, *P* = 0.005). Compared with the group of none or rare spicy food intake, UC patients were significantly more likely to ingest spicy food than controls (light intake: OR = 2.432, 95%CI: 1.943-3.043, *P* < 0.001; heavy intake: OR = 3.189; 95%CI: 2.513-4.046, *P* < 0.001). Compared with the group of none or rare sugar intake, subjects with UC were also significantly more likely to ingest sugar than controls (light intake: OR = 3.162, 95%CI: 2.480-4.032, *P* < 0.001; heavy intake: OR = 3.390, 95%CI: 2.921-5.288, *P* < 0.001). There were no significant differences in milk, vegetable and meat consumption between two groups. Medical histories and

Table 2 Dietary factors between ulcerative colitis and healthy controls

Variables	UC	Control	P value	OR	95%CI
Milk					
None or rare	23.9%	24.5%			
Light	55.8%	58.5%	0.845	0.981	0.806-1.293
Heavy	20.3%	16.9%	0.096	1.237	0.963-1.590
Tea intake					
None or rare	18.5%	17.7%			
Light	50.5%	42.3%	0.231	1.139	0.921-1.409
Heavy	30.9%	40.0%	0.007	0.738	0.591-0.922
Alcohol					
None or rare	40.5%	47.0%			
Light	46.9%	43.0%	0.005	1.264	1.073-1.490
Heavy	12.5%	10.0%	0.005	1.453	1.122-1.882
Spicy food consumption					
None or rare	11.1%	25.2%			
Light	50.6%	47.4%	0.000	2.432	1.943-3.043
Heavy	38.3%	27.4%	0.000	3.189	2.513-4.046
Sugar			0.000	1.989	1.718-2.301
None or rare	12.3%	31.8%			
Light	64.8%	53.1%	0.000	3.162	2.480-4.032
Heavy	23.0%	15.2%	0.000	3.390	2.921-5.288
Vegetable and meat					
Vegetarian	13.3%	12.4%			
Meat-eaters	10.4%	9.4%	0.421	0.909	0.720-1.147
Balanced diet	76.3%	78.2%	0.848	1.032	0.745-1.432

UC: Ulcerative colitis; OR: Odds ratio.

Table 3 Smoking, breast feeding and medical history between ulcerative colitis and healthy controls

Variables	UC	Control	P value	OR	95%CI
Smoking					
Nonsmoker	74.8%	74.5%			
Current smoker					
< 10 cigarettes per day	13.5%	13.4%	0.982	1.003	0.798-1.259
> 10 cigarettes per day	7.7%	8.9%	0.292	0.859	0.648-1.139
Ex-smoker	4.0%	3.2%	0.272	1.264	0.832-1.922
Breast feeding	46.5%	53.5%	0.628	1.080	0.790-1.477
Infectious diarrhea	14.1%	9.3%	0.000	1.610	1.256-2.064
Appendectomy	3.4%	3.2%	0.737	0.929	0.602-1.432
NSAIDs	9.0%	7.2%	0.209	1.269	0.875-1.841
Measles	9.4%	8.2%	0.286	1.162	0.882-1.532
Parasite	15.7%	11.2%	0.053	1.486	0.946-1.926
Oral contraceptive	6.3%	5.2%	0.082	2.734	0.880-8.495

UC: Ulcerative colitis; NSAIDs: Nonsteroidal anti-inflammatory drugs; OR: Odds ratio.

other issues between the two groups are shown in Table 3. As shown in Table 3, UC patients (14.1%) were more likely to report that they had ever had infectious diarrhea than controls (9.3%) (OR = 1.610, 95%CI: 1.256-2.064, P < 0.001). There were no significant differences in smoking status, breast feeding during infancy, appendectomy, measles and parasite infection, NSAID and oral contraceptive use between the two groups.

Multivariate analysis of risk factors for UC

The multivariate analysis by logistic regression analysis showed that consumption of tap water was a protective factor for UC (OR = 0.424, 95%CI: 0.302-0.594, P < 0.001); while the potential risk factors for UC were often feeling stress (OR = 1.981, 95%CI: 1.447-2.711, P < 0.001), spicy food consumption (light intake: OR = 3.329, 95%CI: 2.282-4.857, P < 0.001; heavy intake: OR = 3.979, 95%CI: 2.700-5.863, P < 0.001), and heavy sugar consumption (OR = 1.632, 95%CI: 1.156-2.305, P < 0.001).

DISCUSSION

This is the first multicenter study to investigate the risk factors of UC patients in the Chinese population. We conducted a case-control study during a 3-year period and evaluated a number of potential risk factors in a group of UC patients and a group of age-matched and sex-matched controls.

The major finding of the present study (on multivariate analysis) was to demonstrate that some dietary habits

including sugar consumption, spicy food and tap water consumption were related to UC development.

First of all, our study confirmed that sugar consumption was related to an increased risk of UC. Previous studies have found strong positive associations between foods with a relatively high amount of sugar and CD[9,10]. Tragnone *et al*[11] confirmed that both UC and CD patients had a higher intake of total carbohydrate, starch, and refined sugar than did healthy controls. Russel *et al*[12] reported consumption of cola drinks and chocolate were positively associated with developing ulcerative colitis. However, a negative relationship was found for carbohydrate consumption in a Canadian study[13]. The possible reasons for this finding were studied in CD. Rashid *et al*[14] report that high dietary starch intake increases the growth of intestinal microflora, among which *Klebsiella* microbes constituted an important part. Increased exposure to *Klebsiella* in the gut leads to high production of anti-*Klebsiella* antibodies as well as autoantibodies to the cross-reactive self-antigens with resultant inflammation at the pathological sites. Another study[15] shows that translocation of *Escherichia coli* is reduced by soluble non-starch polysaccharide, but increased by the emulsifier Polysorbate-80. Although all studies above were related to CD, perhaps sugar is having the same deleterious effects in UC as it does in CD through effects on the composition of intestinal microflora or on the permeability of the gastrointestinal mucosa.

Secondly, spicy food is confirmed to be a risk factor for UC in our study. Another study from China also shows spicy food may contribute to the progress of UC[16]. Capsaicin is the spicy component of hot peppers. Capsaicin can promote intestinal vasodilation, stimulate mucus secretion, and sometime even lead to diarrhea. Therefore, capsaicin may lead to changes in mucosal barrier function or colonic motility. Some studies also show capsaicin can modulate the lymphocyte prolifera-

tive response and induce tumor necrosis factor-alpha secretion[17,18]. There is no such study about spicy food and UC. The exact effect and mechanism still needs further study.

Thirdly, our study shows consumption of tap water has a protective effect for UC. A systematic environmental factor study from the EPIMAD registry reported that the regular consumption of tap water decreased the risk of CD[19]. Another two case-control studies revealed a more frequent hot water supply among patients presenting with CD than among controls[20,21], but failed to find such an association with UC. Although findings are inconsistent, consumption of tap water may have the same protective effect in UC as it does in CD.

This is consistent with the hygiene hypothesis of IBD, which theorizes that a lack of exposure to enteric pathogens makes one susceptible to IBD. A possible explanation is that tap water may contain non-pathogenic bacteria which thrive in untreated water, but are absent from boiled water. This kind of bacteria may play an immunoregulatory role and reduce the risk of UC or CD by helping to establish the body's normal intestinal flora.

The data above showed that some dietary habits are related to UC development. Diet is probably the single most important factor influencing the composition and metabolic behavior of the microbiota. Some dietary habits may have a consistent impact on the gut microbiome or gastrointestinal mucosa permeability, and maybe trigger an aberrant immune response in genetically predisposed individuals.

Another finding of this study on multivariate analysis was to demonstrate that often feeling stress was a risk factor for UC. A case-control study observed an excess of life events in the 6-mo period prior to the onset of CD and UC[22]. However, results remain controversial. The different results may be attributed to no standard method to measure stress and recall bias. Quantification and identification of stress remains a difficult task. Our study quantified "stress" by the frequency of feeling stress. As in most case-control studies, recall bias may be also a concern in this study.

In the present univariate analysis, a prior episode of infectious gastroenteritis and alcohol use were related to an increased risk of UC, while heavy tea consumption was shown to be a protective factor for UC. However, these positive associations failed to be demonstrated in the multivariate analysis.

Two large-scale case-control studies have also shown that IBD risk is higher in patients with a prior episode of infectious gastroenteritis, but specific pathogenic agents cannot be found in IBD[23,24]. The hypothesis is that an enteric infection may trigger an initial change in the gut epithelial barrier resulting in exposure to microflora and disturbed adaptive and innate immune responses, leading to disease in a genetically susceptibility individual. Another possible reason for this finding may be related to antibiotics. Other studies[25,26] have shown that exposure to antibiotics in childhood could hypothetically interfere with the normal process of developing tolerance to enteric bacteria and may lead to IBD. However, we could not include this possible factor in the present study. Thus, further such studies are necessary to be done in China.

Alcohol has been shown to disrupt gut barrier function and increase intestinal permeability[27,28]. However, another study reported an inverse relation between alcohol use and UC[29]. Some studies also showed potential anti-inflammatory properties of green tea[30,31]. It is likely that these factors are simply cofactors with other variables. Further studies are needed to examine these findings.

Other factors, such as smoking habit, appendectomy, breast-feeding in infancy, a history of measles, rural or urban residence, education, oral contraceptives, and NSAID use have not been found to have a significant association with the development of UC in the present study.

A main disadvantage of the study is that it is retrospective, relying on recall of childhood events and ingestions. There is a potential recall bias on some variables such as dietary ingestions. However, the recall issues should equally apply to cases with IBD and to controls. These data should be tested prospectively.

Exploring UC risk factors in China will be a great opportunity to advance our understanding of disease pathogenesis by investigating this aspect when the disease is newly emerging. Our study showed that often feeling stress, and a high intake of spicy food and sugar may enhance the risk of developing UC, while consumption of tap water may reduce the rate of presenting with UC. Smoking and appendectomy, which have been demonstrated to be associated with the development of UC in western studies, could not be confirmed in our study. These differences provide further evidence that environmental factors may influence development of UC and may give us some valuable clues to the cause of the disease. Thus, further studies are necessary to better understand the environmental determinants of IBD.

ACKNOWLEDGMENTS

COMMENTS

Background

Ulcerative colitis (UC) and Crohn's disease (CD) are collectively referred to as inflammatory bowel disease (IBD). The etiology of IBD has been extensively studied; however, causative factors are not yet fully understood. IBD is thought to arise in genetically predisposed individuals who mount an aberrant immune response to gut microbiota secondary to some environmental triggers. Genetic susceptibility in the population should be relatively stable, it cannot account for the rapid rise of IBD incidence in China. Environmental factors may play an important role in the pathogenesis of IBD. A number of environmental risk factors have been explored in western countries. However, there is a lack of such epidemiologic study in Chinese populations.

Research frontiers
A number of environmental risk factors of UC and CD have been explored in Western countries, including smoking, appendectomy, stress, socio-economic conditions, nonsteroidal anti-inflammatory drugs, oral contraceptives, diet, breastfeeding, infections/vaccinations, antibiotics, and childhood hygiene. However, most of these factors have demonstrated inconsistent findings.

Innovations and breakthroughs
The relationship between the risk of UC and environmental factors has been well studied, but the results are inconsistent in different racial populations. To date, there is no such epidemiologic study of large samples in Chinese populations. China presents an opportunity to study an environment that is evolving more to a Western-style based on changes in socioeconomics, diet habit, *etc*.

Applications
This study shows consumption of tap water is a protective factor for UC, while spicy food, heavy sugar consumption, and stress are risk factors for UC in Chinese populations.

Peer review
This is well done article. A great deal of work went into this study and should not be wasted. It is a clear paper with convincing results.

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