

## Dietary protein intakes and risk of ulcerative colitis

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### Abstract

**Background:** The incidence of ulcerative colitis (UC) is rising in populations with western-style diet, rich in fat and protein, and low in fruits and vegetables. In the present study, we aimed to evaluate the association between dietary protein intakes and the risk of developing incident UC.

**Methods:** Sixty two cases of UC and 124 controls were studied using country-specific food frequency questionnaire (FFQ). Group comparisons by each factor were done using  $\chi^2$  test, and significance level was set at  $\alpha=0.05$ . Logistic regression adjusted for potential confounding variables was carried out.

**Results:** Univariate analysis suggested positive associations between processed meat, red meat and organ meat with risk of ulcerative colitis. Comparing highest versus lowest categories of consumption, multivariate conditional logistic regression analysis accounting for potential confounding variables indicated that patients who consumed a higher amount of processed meat were at a higher risk for developing UC (P value for trend= 0.02). Similarly, patients who consumed higher amounts of red meat were at a higher risk for UC (P value for trend= 0.01). The highest tertile of intake of organ meat was associated with an increased risk of ulcerative colitis with a statistically significant trend across tertiles (P value for trend= 0.01) when adjusted.

**Conclusion:** In this case-control study we observed that higher consumptions of processed meat, red meat and organ meat were associated with increased risk for UC.

**Keywords:** Ulcerative colitis, Diet, Protein.

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### Introduction

Ulcerative colitis (UC) is a chronic relapsing mucosal disorder (1), leading to injure to the digestive tract (2-3). From the second half of the 20th century, incidence of the disease is growing speedily (4). This disease has adverse effects on the patient's quality of life (3, 5). The disease defects the regulation of the immune response to flora intestinal mucosa in genetically susceptible individuals and influenced by environmental factors (6). Although the etiology is not well understood, current hypotheses em-

phasize on a multifactorial disease model with both genetic and non-genetic risk factors (4, 7). While the genetic composition of the population has remained unchanged over the last several hundred years, the incidence and prevalence of UC in North-Western industrialized countries have steeply increased, which shows the effect of environmental factors (3-4, 8). Diet is one of the most modifiable environmental factors involved in UC pathogenesis, though limited information is available (9-11).

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Diet may be affected in different ways on the homeostasis of the gastrointestinal tract; directly with the effects on oxidative stress, the expression of transcription factors, which are involved in the regulation of intestinal inflammation, and the inflammatory response regulators and intestinal microflora (12-13). The incidence of UC is rising in populations that follow western-style diet, rich in fat and protein but low in fruits and vegetables. In the past two decades, for instance, the incidence of UC increased remarkably in Eastern Europe, Asia and Central America, where the lifestyle has become more 'westernized'. A recent study with a focus on specific compounds of the diet revealed that high meat intake, in particular, and red and processed meat increase the likelihood of relapse for colitis patients (14). Moreover, a cohort study has shown an association between high protein intake with an increased risk of incident UC (15); however, there is no case-control study in developing countries with different lifestyle patterns and UC risk factors to confirm the previous western cohort findings.

In the present study, we aimed to assess the relationship between dietary protein intake and risk of UC in a case-control design.

## Methods

### *Study Population*

A case-control study based on newly diagnosed patients (< 6 months) with UC was carried out. The study protocol was approved at Committee of Ethics of National Nutrition and Food Technology Institute, Shahid Beheshti University, Iran. Overall, 62 cases of UC and 124 controls in the age range of 20–80 years were studied. Participants were recruited from a referral hospital in Tabriz in 2013. The medical records of all cases were reviewed to confirm the UC diagnosis. Patients with history of any other gastro intestinal illness, carcinoma, autoimmune disease, and other inflammatory and infectious diseases were excluded. Controls were patients visiting the outpa-

tient orthopedic clinics of the same hospitals. Controls were frequency-matched with cases by sex and age (10-yr groups). Only those controls without a concurrent history of any gastro intestinal illness/symptoms (irritable bowel syndrome, gastroesophageal reflux, diarrhea, abdominal pain, etc.), diabetics, cardiovascular disease, gout, hyperlipidemia, likely to be related to dietary habits were recruited. Private face-to-face interviews were conducted by trained interviewers. Participants completed questionnaires on demography, medical history, medications, diet, alcohol, smoking, appendectomy, helicobacter pylori, education, and family history of UC. In terms of maximal education attained for analysis, we grouped participants to primary, secondary and high school and those attending university. Weight was measured with subjects standing without shoes and was recorded to the nearest 1kg. Height was measured while subjects were in a standing position without shoes, using a non-stretch tape meter fixed to a wall and was recorded to the nearest 1 cm. Body mass index (BMI) was then calculated by dividing weight in kilograms by square of height in meters.

### *Assessment of Diet*

Information on usual diet was measured by a country-specific food frequency questionnaire that was modified to include national food items (16). This FFQ is a semi quantitative questionnaire acquiring information on 168 foods with relative validity and reproducibility for several nutrient intakes among Iranian adults. Consumption frequency of food items was obtained on a daily, weekly, or monthly basis, and the portion sizes for each food item in the FFQ were specified according to the USDA portion sizes (e.g., apple, 1 medium; bread, 1 slice; dairy, 1 cup); whenever using the USDA portion sizes was not possible, household measures (e.g., beans 1 tablespoon; chicken meat 1 leg or wing; rice 1 large, medium, or small plate) were used alternatively. Dietary habits of cases 1 yr prior to diagnosis and controls 1 yr before

the interview were collected. Nutrient intake was calculated by multiplying the frequency of consumption of relevant foods by their protein content as determined from national databases of food content. The protein intakes which were calculated were: total protein, processed meat, red meat, fish, organ meat, poultry, bean, nuts egg and dairy product.

### Statistical Analysis

Group comparisons by each factor were done using  $\chi^2$  test, and significance level was set at  $\alpha=0.05$ . Logistic regression analysis adjusting for potential confounding variables was carried out. The dietary intakes of each item were transformed into the average daily intake, distributed into approximate marginal tertiles with the lowest category serving as the reference category. Odds ratios (ORs) and their respective 95% confidence intervals (95% CIs) were estimated.

### Results

Table 1 shows sociodemographic characteristics and distribution of potential confounding variables in cases and controls. By design, age and sex distributions were similar in cases and controls. Each identified case of UC was clinically confirmed by a physician. The data were 100% complete for all cases and controls. Education, cigarette smoking, family history of UC and BMI were similar between UC and

controls. The history of appendectomy and *Helicobacter pylori* infection was higher in cases in comparison to controls. None of the cases or controls had alcohol intake.

Table 2 shows the association of protein intake with risk of UC. Univariate analysis suggested positive associations between processed meat, red meat and organ meat with risk of UC. When comparing highest versus lowest categories of consumption, multiple conditional logistic regression analysis accounting for potential confounding variables indicated that patients who consumed a higher amount of processed meat were at a higher risk of developing UC (P value for trend= 0.02). Similarly, patients who consumed higher amounts of red meat had a higher risk of UC (P value for trend= 0.01). Moreover, the highest tertile of intake of organ meat was associated with an increased risk of UC with a statistically significant trend across tertiles (P value for trend= 0.01) when adjusted. In this case-control study, none of total protein, fish, poultry, egg, bean, nuts and dairy products showed a significant impact on UC. The results were similar when adjusted for total energy intake and total protein intake.

### Discussion

The main finding of this study is that higher meat intake was associated with an increased risk of UC. Among animal protein sources, red meat, processed meat, and

Table 1. Sociodemographic characteristics and distribution of potential confounding variables in cases and controls

Characteristic	Cases	Controls	p
Number	62	124	
Sex			
Males (%)	27(44)	54(44)	
Females (%)	35(56)	70(56)	
Age (yr)	37.43	36.23	
BMI (kg/m <sup>2</sup> )	24.81	25.68	0.15
Total energy intake (kcal/day)	2590	2902	0.00
Education			0.17
Primary(%)	7(11)	6(5)	
Secondary and high school(%)	28(45)	69(55)	
University(%)	27(43)	49(40)	
Family history(%)	2(3)	0(0)	0.11
Smoking(%)	6(10)	10(8)	0.71
h-pylori(%)	7(11)	1(0.8)	0.00
Appendectomy	4(6)	0(0)	0.01

Table 2. Odds Ratios and 95% CI for Tertiles of dietary protein intakes as risk factors for UC<sup>1</sup>

Protein-containing food groups	Tertile 1	Tertile 2	Tertile 3	P for Trend
<b>Total protein</b>				
No. Cases/No. Controls	19/41	21/42	22/41	
Minimal Model <sup>2</sup>	1.00	1.02(0.45-2.30)	1.90(0.86-4.20)	0.11
Full Model <sup>3</sup>	1.00	1.01(0.24-2.22)	1.70(0.75-3.15)	0.23
<b>Processed meat</b>				
No. Cases/No. Controls	15/41	20/42	27/41	
Minimal Model <sup>2</sup>	1.00	1.24(0.52-2.92)	2.44(1.10-5.39)	0.02
Full Model <sup>3</sup>	1.00	1.13(0.41-2.51)	2.65(1.12-5.34)	0.03
<b>Organ meat</b>				
No. Cases/No. Controls	14/41	20/42	28/41	
Minimal Model <sup>2</sup>	1.00	2.50(1.05-5.95)	3.02(1.27-7.18)	0.01
Full Model <sup>3</sup>	1.00	2.32(1.10-5.65)	2.93 (1.24-6.67)	0.02
<b>Red meat</b>				
No. Cases/No. Controls	14/41	20/42	28/41	
Minimal Model <sup>2</sup>	1.00	1.29(0.55-3.02)	2.81(1.25-6.30)	0.01
Full Model <sup>3</sup>	1.00	1.52(0.45-3.14)	2.52(1.40-6.24)	0.02
<b>fish</b>				
No. Cases/No. Controls	20/41	21/42	21/41	
Minimal Model <sup>2</sup>	1.00	1.59(0.71-3.50)	1.24(0.54-2.86)	0.40
Full Model <sup>3</sup>	1.00	1.62(0.92-3.44)	1.22(0.47-2.53)	0.44
<b>poultry</b>				
No. Cases/No. Controls	20/41	21/42	21/41	
Minimal Model <sup>2</sup>	1.00	1.58(0.68-3.70)	1.39(0.62-3.12)	0.46
Full Model <sup>3</sup>	1.00	1.62(0.57-3.65)	1.24(0.54-3.23)	0.51
<b>egg</b>				
No. Cases/No. Controls	20/41	21/42	21/41	
Minimal Model <sup>2</sup>	1.00	1.00(0.42-2.40)	0.66(0.31-1.40)	0.27
Full Model <sup>3</sup>	1.00	1.12(0.33-2.36)	0.85(0.41-1.54)	0.32
<b>bean</b>				
No. Cases/No. Controls	20/41	20/42	22/41	
Minimal Model <sup>2</sup>	1.00	0.77(0.35-1.72)	0.89(0.41-1.93)	0.77
Full Model <sup>3</sup>	1.00	0.75(0.34-1.53)	0.91(0.32-1.54)	0.82
<b>nuts</b>				
No. Cases/No. Controls	20/41	21/42	21/41	
Minimal Model <sup>2</sup>	1.00	1.55(0.66-3.61)	2.01(0.88-4.61)	0.09
Full Model <sup>3</sup>	1.00	1.79(0.56-3.74)	1.97(0.91-4.54)	0.12
<b>Dairy product</b>				
No. Cases/No. Controls	20/41	22/42	20/41	
Minimal Model <sup>2</sup>	1.00	2.02(0.91-4.49)	1.15(0.50-2.66)	0.73
Full Model <sup>3</sup>	1.00	2.13(0.81-4.56)	1.54(0.48-2.73)	0.86

<sup>1</sup> an unconditional logistic regression model

<sup>2</sup> adjusted for total energy intake, H.pylori infection, and history of appendectomy

<sup>3</sup> adjusted for total energy intake, H.pylori infection, history of appendectomy, dietary fat, carbohydrate, and food groups intakes

organ meat were associated with UC risk, whereas poultry, fish, egg and dairy products were not associated with the UC risk. Some studies have previously examined the role of protein intake (15, 17) in the etiology of UC. Evidence across studies has been inconsistent; however, many studies have reported positive associations with protein intake, in particular animal protein, and UC risk. A national cohort consisted of women living in France, aged 40–65 years, showed that high total protein intake, specifically animal proteins, was associated with a significantly increased risk of UC; among

sources of animal protein, high consumption of meat or fish but not eggs or dairy products were associated with IBD risk (15). Similarly, the European Prospective Investigation into Cancer and Nutrition (EPIC) suggested a role for processed meat including sausage in the etiology of UC (7). Moreover, a prospective cohort study on UC patients in remission reported high meat intake is associated with an increased likelihood of relapse of the disease (14). However, Hart et al. detected no significant association between diet and UC risk, apart from a possible increased risk with a higher

total polyunsaturated fatty acid (PUFA) intake (12).

A significant positive association was detected between the risk of UC and an increasing percentage of red meat intakes. Carcinogenic byproducts such as heterocyclic amines and polycyclic aromatic hydrocarbons, created during high temperature cooking of meat; animal fat and heme iron from red meat; and hormone residues of the exogenous hormones for growth stimulation in beef cattle are some of the mechanisms that may explain the positive association between high intake of red meat and risk of UC (3). Also, a variable proportion of heme and amino acids contained in animal proteins, are not absorbed by the small bowel and reach the colonic lumen, where they are metabolized by the microflora. This results in a number of end products, which include hydrogen sulfide, phenolic compounds, and amines and ammonia, some of which are potentially toxic to the colon. For instance, it has been suggested that sulfide, in the presence of nitric oxide produced by anaerobic bacteria, may alter the cell membrane of the colonocyte, and lead to the loss of barrier function and the immune cascade as observed in UC (15,17). Other mechanisms, such as the impact of animal protein intake leading dysbiosis or inflammatory response, can also be supposed (15).

This investigation also found a statistically significant positive association between processed meat and risk of UC. Corn and soybean oils often used for preparing fast foods contain high amounts of linoleic acid that is an n-6 PUFA. Linoleic acid undergoes carbon chain elongation and desaturation to form arachidonic acid which is incorporated into cell membranes. A high dietary intake of PUFAs, particularly n-6-derived would lead to a source of pro-inflammatory molecules which could hypothetically predispose to UC (12). In general, these lipid types are proinflammatory, propagating their signaling actions via receptor-mediated mechanisms and are responsible for many incidence of inflamma-

tion, including fever, increased vascular permeability, chemotaxis, edema, and tissue damage (4).

In this case-control study no association with total protein, bean, nut, fish, poultry, egg and dairy products was found, maybe because larger numbers of subjects need to be studied and also due to measurement error inherent in the food-frequency questionnaires.

The study had some limitations; the small patient sample size, which prevented the division of dietary factors into quartiles or quintiles to present stronger data on dose-response effects. Other potential limitations of this study include reliability and validity of the estimation of average food intakes which were based on the relatively limited number of food items (168 items). As with other case-control studies, a recall bias was inevitable. In case-control studies, there is the possibility that cases may recall their diets differently after UC diagnosis. However, the recall bias is unlikely because we interviewed with those patients who were diagnosed during the last six months. Also, using the same clinic controls and administering validated FFQs by trained interviewers might have further reduced the recall bias and improved the comparability of information of cases and controls. A measurement bias was unavoidable, because of using FFQ to assess dietary intake. This might have led us to underestimate the associations. However, we used a validated FFQ and excluded the participants who were misreporting their energy intake. As in most case-control studies, a selection bias is also possible. Among the possible limitations of the present study is the use of the same clinic controls, who may have different dietary habits and lifestyles when compared with the general population. Furthermore, we are not entirely able to rule out residual confounding due to imprecise measurement or the omission of important covariates. Also, non-significant associations may have been declared significant by chance alone.

The strength of our study is the high par-

participation rate of individuals in our research (more than 95%). This might be of particular importance since food intakes could be associated with factors such as the BMI, smoking and socioeconomic status. Besides, where economic resources have been severely limited, food intake is closely linked to income, so that even small economic inequalities directly influence the diet. This relevance might increase discrepancy among people.

In conclusion, this study reinforces previous findings linking dietary meat intake and the risk of UC. This study found that a higher intake of meat including red meat, processed meat, and organ meat is significantly associated with higher risk of UC, whereas we could not find any association between other protein sources intakes and risk of UC. We recommend that more studies with higher sample size should be done to confirm the results and address the mechanism of action of these dietary factors in pathogenesis of UC.

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### Conflict of interest

None of the authors had a conflict of interest.

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