Turk J Gastroenterol *2015; 26: 492-7*

Meat intake and risk of inflammatory bowel disease: A meta-analysis

INTESTINE

Jian Ge[1], Tian-Jie Han[2,4*], Jin Liu[1*], Jun-Shan Li[3], Xiao-Hua Zhang[1], Yu Wang[5], Qing-Yan Li[5], Qiang Zhu[1], Chong-Mei Yang[1]*

*These authors contributed to this work equally

[1]Department of Gastroenterology, Shandong Provincial Hospital, Shandong University, Jinan, Shandong, China
[2]Department of Hematology,Shandong Provincial Hospital, Shandong University, Jinan, Shandong, China
[3] Department of Gastroenterology, Tai'an Central Hospital, Tai'an, Shandong, China
[4]Department of Hematology, Tai'an Central Hospital, Tai'an, Shandong, China
[5]Department of Gastroenterology, Zhangqiu People's Hospital, Jinan, Shandong, China

Original Article

ABSTRACT

Background/Aims: This meta-analysis is designed to determine the association between meat consumption and the risk of inflammatory bowel disease.

Materials and Methods: Search relevant literature published in PubMed, Cochrane before July 2015 without restrictions. Studies were included if relative ratios and the corresponding 95% confidence intervals of the risk of inflammatory bowel disease were reported with respect to meat consumption.

Results: Nine studies were included in this meta-analysis. Relative to those who did not or seldom eat meat, meat consumers had a significantly greater risk of inflammatory bowel disease (pooled relative ratio: 1.50, 95% confidence interval: 1.15–1.95). The funnel plot revealed no evidence for publication bias.

Conclusion: Meat consumption may increase the risk of inflammatory bowel disease. Additional large prospective studies are warranted to verify this association.

Keywords: Case-control study, cohort study, inflammatory bowel disease, meat consumption, meta-analysis

INTRODUCTION

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), has significantly increased globally over the past several years, particularly in Europe and Asia. This increase in incidence is likely because of both the genetic and environmental causes, including infectious gastroenteritis (1), diet (2), medications (3), and smoking and drinking habits (4,5). For example, it is considered that a diet high in saturated fats and refined sugars changes the intestinal microenvironment and increases the risk for developing IBD (6,7).

Although diet and IBD have been investigated in many epidemiological studies, the association between meat consumption and IBD risk remains controversial. In contrast, a number of studies and meta-analyses have demonstrated that meat consumption is associated with an increased risk of coronary artery disease, hyperlipidemia, and prostate, esophageal, colorectal, and pancreatic cancers (8-10). With respect to IBD, some studies have suggested that meat intake is the causative factor, whereas other studies have suggested that the type of meat and cooking process may increase IBD risk (2,5). This meta-analysis was designed to assess the true association existing between IBD risk and meat consumption.

MATERIALS AND METHODS

Literature review and sources of data

We reviewed relevant studies from Pubmed and EMBASE databases that were published from July 1966 to July 2015 without language limitations. The inclusion criteria of the studies were as follows: inflammatory bowel disease, ulcerative colitis, Crohn's disease,

Address for Correspondence: Jian Ge, E-mail: 15168866758@163.com
Received: May 05, 2015 **Accepted:** June 26, 2015
 • Available online at www.turkjgastroenterol.org • DOI: 10.5152/tjg.2015.0106

and meat consumption (including red meat, processed meat, white meat, poultry, beef, pork, lamb, and goat). Red meat was defined as darker-colored meat from mammals, such as cows, sheep/lambs, pigs, and horses. White meat was defined as lighter-colored meat from poultry, such as chickens, and rabbits. The term "processed meat" referred to bacon, poultry sausage, luncheon meats (red and white meat), ham, hot dogs, etc.

Two investigators independently screened the results. Moreover, the reference lists of retrieved articles were reviewed to identify additional relevant studies. If the same data was present in different studies, the largest or latest study met the inclusion criteria.

Inclusion and exclusion criteria

Studies with the following criteria were included:
1) A case–control or cohort design; 2) an evaluation of the association between meat consumption (including total meat, red meat, processed meat, and white meat) and IBD risk; and 3) the availability of odds ratio, relative risk (RR), and hazard ratio estimates with 95% confidence interval (CI) statistical data.

Quality evaluation of included studies

The Newcastle–Ottawa Scale was adopted for quality assessment (11). A study is judged on three broad perspectives: the selection of the study groups, comparability of the groups, and ascertainment of either the exposure or outcome of interest for case–control or cohort studies, respectively. The maximum score is nine, and all studies included in this meta-analysis scored six or higher.

Statistical analysis

The χ^2-based Q statistic (12) was used to estimate the heterogeneity among the included studies; a significant Q statistic means heterogeneity ($p<0.10$). Fixed or a random effect model (using the Mantel–Haenszel method or the DerSimonian and Laird method) was used to calculate the pooled OR. Using Begg's funnel plot and Egger's test, we evaluated publication bias ($p<0.05$ means statistically significant) (13). Analyses were performed using Stata software, version 12.0 (Stata Corp LP.; College Station, TX, USA). A two-sided p value of <0.05 was considered statistically significant (14).

RESULTS

Literature review and study characteristics

A flow chart depicting the selection of eligible studies from the literature review using the inclusion criteria is shown in Figure 1. The characteristics of the final nine studies selected for analysis are shown in Table 1 (15-23). Two cohort and seven case–control studies were included. The nine studies reported a total of 2,019 cases of UC, 683 of CD, and 160 of IBD. Data was obtained from Asian (n=4) (15-17,21) and European (n=5) populations (18-20, 22, 23). Of the nine studies, five examined total meat consumption (15-17,19,21,23), three only examined red meat consumption (18,20,22), two examined processed meat consumption (22,23), and two only examined white meat consumption (18,20). Four studies divided meat consumption into lowest intake, medium intake, and high intake (15,18,20,22); two studies defined high intake as meat consumption for >7 times/week, medium consumption as 3–5 times/week, and low consumption as <1 time/month (18,20). Two studies classified meat consumption into three groups by quartiles (T1–T3) of energy-adjusted intake among controls (19,23), and one study classified consumption into four groups by quartiles (Q1–Q4) (17). Among these studies, the confirmation of outcome was obtained from the cancer registry. Potential confounders (at least for age) were controlled in all studies.

Meta-analysis

The summary RRs for esophageal cancer in the highest versus lowest consumption groups were 1.50 (95% CI: 1.15–1.95) for total meat, 2.37 (95% CI: 1.40–3.99) for red meat, 1.60 (95% CI: 0.53–4.78) for processed meat, and 1.20 (95 % CI: 0.73–1.97) for white meat (Table 2). There was significant evidence of heterogeneity among studies ($Q=45.31$, $p<0.001$, $I^2=60.3\%$).

Subgroup meta-analyses were conducted using geographic area, study design, and type of meat consumed. The summary RRs (95% CI) of the association between total meat consumption and IBD risk were 2.92 (1.59–5.34) in cohort studies and 1.33 (1.02–1.72) in case–control studies (Figure 2, Table 2). Significant heterogeneity existed among the case–control studies ($Q=30.51$, $p=0.010$, $I^2=50.8\%$) but not among the cohort studies ($Q=3.44$, $p=0.179$, $I^2=41.9\%$).

Stratification of data by geographic area (Figure 3) identified a significant association between total meat consumption and IBD risk in studies that were conducted in European populations (summary RR: 1.61; 95% CI: 1.16–2.21) with statistical heterogeneity among studies ($Q=28.71$, $p=0.007$, $I^2=54.7\%$) and

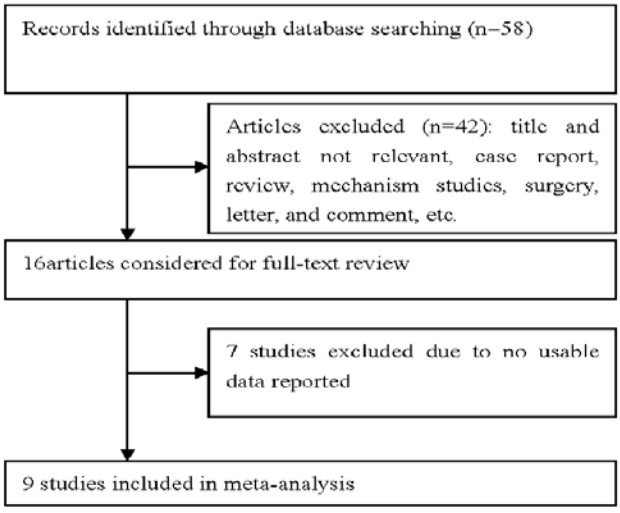

Figure 1. Flow chart depicting the selection of eligible studies.

Original Article

Table 1. Characteristics of the nine studies included in this meta-analysis

Author	Year	Country	No. of cases	Controls or cohort size (n)	Meat type	Meat consumption	Risk estimate (95% CI)		Adjustments
Cohort studies									
Jowett et al. (22)	2004	UK	UC: 191	463	Meat and meat products Red and processed meat	Lowest intake Medium intake High intake Lowest intake Medium intake High intake	Meat and meat products 1.0 1.37 (0.60–3.13) 3.20 (1.31–7.79) Red and processed meat 1.0 2.16 (0.93–4.98) 5.19 (2.09–12.90)		Age, sex, smoking, triglycerides, alcohol consumption
Jantchou et al. (23)	2010	France	IBD: 77	67,581	Meat	T1 T2 T3	Meat 1.0 1.45 (0.76–2.75) 1.87 (1.00–3.49)		Age, sex, smoking, HR for energy
Case–control studies									
Higashi et al. (15)	1991	Japan	UC: 50	50	Meat	Lowest intake Medium intake High intake	Meat 1.0 NA 1.4 (0.4–5.06)		Age, sex
Akihiro et al. (16)	1994	Japan	UC: 101	143		1–2 times/week 3–5 times/week >7 times/week	Meat 1.0 2.0 (1.0–3.8) 1.3 (0.6–3.0)		Age, sex, smoking
Sakamoto et al. (17)	2004	Japan	UC: 111 CD: 128	219	Meat	Q1 Q2 Q3 Q4	Meat UC 1.0 0.93 (0.44–1.97) 1.27 (0.62–2.61) 1.35 (0.66–2.74)	CD 1.0 1.63 (0.81–3.30) 1.61 (0.79–3.26) 1.90 (0.95–3.78)	Age, sex, smoking, study area
Bernstein et al. (18)	2006	Canada	UC: 217 CD: 364	433	Pork (red meat) Chicken (white meat)	Lowest intake Medium intake High intake Lowest intake Medium intake High intake	Pork UC 1.0 NA 2.62 (1.37–5.03) CD 1.0 NA 2.48 (1.40–4.40)	Chicken UC 1.0 NA 1.58 (0.97–2.59) CD 1.0 NA 1.42 (0.92–2.19)	Age, sex, smoking, drinking
D'Souza et al. (19)	2008	Canada	CD: 149	251	Meat	T1 T2 T3	Meat CD 1.0 0.7 (0.3–1.7) 0.8 (0.4–1.9)		Age, sex
Maconi et al. (20)	2010	Italy	IBD: 83 UC: 41 CD: 42	160	Red meat White meat Processed meat	Lowest intake Medium intake High intake Lowest intake Medium intake High intake Lowest intake Medium intake High intake	Red meat UC 1.0 1.22 (0.45–3.32) 0.63 (0.20–1.94) White meat 1.0 2.04 (0.69–6.05) 0.75 (0.19–3.04) Processed meat 1.0 0.82 (0.28–2.36) 0.63 (0.21–1.91)	CD 1.0 1.25 (0.38–4.07) 2.42 (0.85–6.85) 1.0 1.33 (0.50–3.52) 0.25 (0.05–1.27) 1.0 7.80 (1.61–37.89) 1.97 (0.35–11.03)	Age, sex
Wang et al. (21)	2013	China	UC: 1308	1308	Meat	Meat-eaters	Meat	0.909 (0.720–1.147)	Age, sex

CI: confidence interval; IBD: inflammatory bowel diseases; UC: ulcerative colitis; CD: Crohn's disease; NA: not applicable; Lowest intake: <1 times/month, Medium intake: 1–3 times/month or 1–2 times/week, High intake: 3–6 times/week or every day.

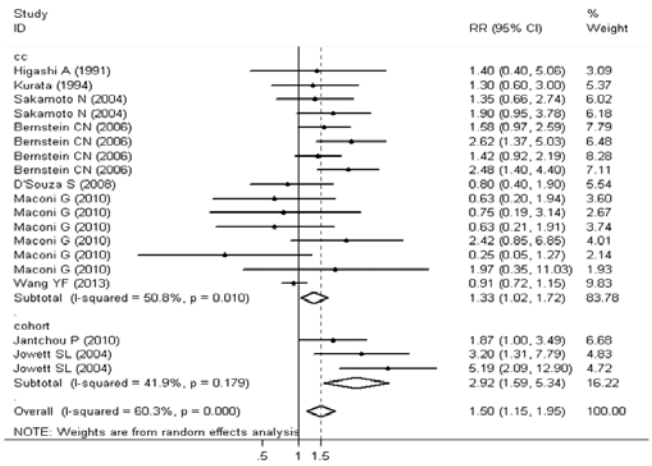

Figure 2. Funnel plot of the association between meat intake and the risk of inflammatory bowel disease stratified by study design.

CC: case–control study; CI: confidence interval; RR: relative risk

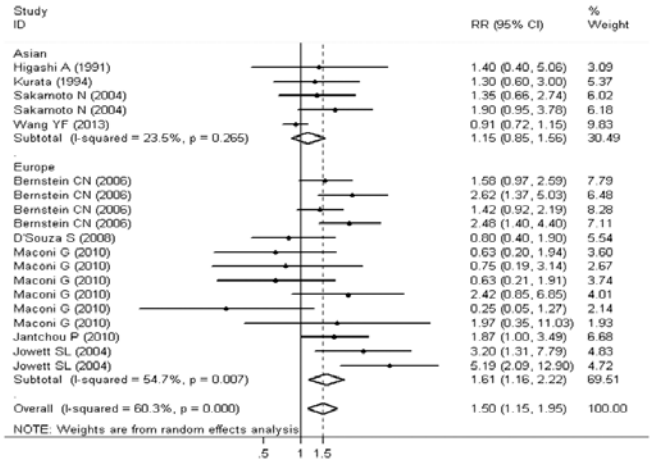

Figure 3. Funnel plot of the association between meat intake and the risk of inflammatory bowel disease stratified by race.

CI: confidence interval; RR: relative risk

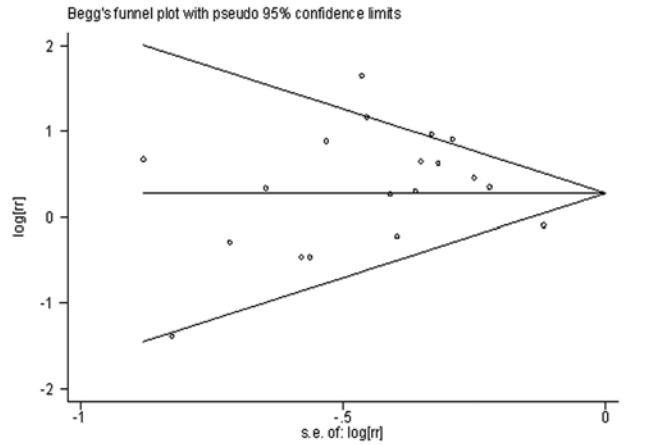

Figure 4. Funnel plot of studies evaluating the association between meat intake and the risk of inflammatory bowel disease.

Table 2. Meta- and sub-analyses of studies evaluating the association between meat and IBD risk

Groups	No. of studies	SRRE (95% CI)	p[a]	p value for heterogeneity
Design				
Cohort	2	2.92 (1.59–5.34)	0.001	0.179
Case–control	7	1.33 (1.02–1.72)	0.032	0.010
Race				
Asian	4	1.15 (0.85–1.56)	0.362	0.265
Europe	5	1.61 (1.16–2.22)	0.004	0.007
IBD type				
UC	7	1.47 (1.01–2.15)	0.046	0.001
CD	4	1.50 (0.98–2.28)	0.059	0.074
Meat				
Red meat	3	2.37 (1.40–3.99)	0.001	0.086
White meat	2	1.20 (0.73–1.97)	0.465	0.151
Processed meat	2	1.60 (0.53–4.78)	0.401	0.079

[a]DerSimonian and Laird random-effects model

SRRE: summary relative risk estimates; CI: confidence interval; IBD: inflammatory bowel diseases; UC: ulcerative colitis; CD: Crohn's disease

Asian populations (summary RR: 1.15, 95% CI: 0.85–1.56) with no statistical heterogeneity among studies (Q=5.23, p=0.265, I^2=23.5%). Only red meat consumption was associated with IBD risk (RR: 2.37, 95% CI: 1.40–3.99). No significant association between white meat (RR: 1.20, 95% CI: 0.73–1.97) or processed meat (RR: 1.60, 95% CI: 0.53–4.78) and IBD risk was found. A significant association between total meat intake and UC risk was found (summary RR: 1.47; 95% CI: 1.01–2.15), whereas no association was detected between total meat intake and CD risk (summary RR: 1.50, 95% CI: 0.98–2.28). However, there was significant heterogeneity among studies conducted on UC (Q=29.98, p=0.001, I^2=66.6%) and CD (Q=11.51, p=0.074, I^2=47.9%).

Publication bias

As shown in Figure 4, there was no publication bias as determined by either the Egger's test (p=0.245) or Begg's funnel plot (p=0.327).

DISCUSSION

The results suggest that high meat intake increases IBD risk, and this association varies by the type of meat consumed. Summary associations for red meat consumption are slightly greater compared with processed meat and white meat consumption.

Several possible underlying mechanisms exist linking the consumption of meat, particularly red meat, and the incidence of IBD. Research has revealed that cooking meat at high temperatures creates chemical by-products with mutagenic or carcino-

Original Article

genic properties that may influence the digestive tract once ingested (24). Other postulated mechanisms involve heme iron and N-nitroso compounds. Heme iron, derived from red meat, can promote the formation of N-nitroso compounds, which influence cell proliferation in the digestive tract. Under acidic gastric conditions, nitrites, which are mainly found in processed meats (25), create nitrosylating agents that react with amines or amides (8). Fat intake from animal sources has also been hypothesized to increase IBD risk (6,7). Indeed, a high intake of meat correlates with UC incidence and relapse (26). Furthermore, studies have demonstrated that a high intake of linoleic acid, a polyunsaturated omega-6 fatty acid present in meat, increases IBD risk (26,27). Previous meta-analyses have also revealed that consumption of processed meat increases cancer risk (7,9,10). However, this meta-analysis found no correlation between processed meat and IBD; to confirm this, additional studies are required.

Heterogeneity is a common concern in meta-analysis. A certain degree of heterogeneity was observed in this study, which is not surprising given the inter-study variation in factors, such as race and study type. In this analysis, one source of heterogeneity may have been the inclusion of both cohort and case–control studies. The degree of heterogeneity was slightly attenuated among the studies conducted in Asian populations, suggesting that race is an influential factor. However, meta-regression analysis did not detect any variables as potential contributors to heterogeneity.

The results from this study may have been confounded by the influence of several environmental risk factors, such as aging and smoking. However, the analyses determined that risk was only marginally attenuated after adjustment for a wide range of potential confounders. Moreover, there was no evidence of publication bias as determined by either the Egger's test or Begg's funnel plot.

This meta-analysis has potential limitations that should be taken into consideration. First, many of the analyzed studies did not extensively describe the study characteristics; some studies categorized meat consumption on the basis of amount consumed, whereas others did not specify consumption levels. Consequently, dose-response analysis was not possible. Many studies did not analyze the type of meat consumed. Third, the number of analyzed studies requires to be increased. The inclusion of additional cohort studies is required to confirm the results obtained in this study.

In conclusion, the results of this meta-analysis indicate that high intake of meat is associated with an increased IBD risk. Further cohort studies are warranted to confirm this association.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Shandong Provincial Hospital, Shandong University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Q.Z., C.M.Y.; Design - J.G., T.J.H., J.L.; Supervision - Q.Z., C.M.Y.; Resource - J.L., J.S.L.; Materials - X.H.Z., Y.W.; Data Collection and/or Processing - Y.W., Q.Y.L.; Analysis and/or Interpretation - J.G., J.S.L.; Literature Search - T.J.H., J.L.; Writing - J.G., J.S.L.; Critical Reviews - Q.Z., C.M.Y.

Acknowledgements: The authors thank Medjaden Bioscience Limited for assisting in the preparation of this manuscript.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Porter CK, Tribble DR, Aliaga PA, Halvorson HA, Riddle MS. Infectious gastroenteritis and risk of developing inflammatory bowel disease. Gastroenterology 2008; 135: 781-6. [CrossRef]
2. de Silva PS, Olsen A, Christensen J, et al. An association between dietary arachidonic acid, measured in adipose tissue, and ulcerative colitis. Gastroenterology 2010; 139: 1912-7. [CrossRef]
3. Ananthakrishnan AN, Higuchi LM, Huang ES, et al. Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn disease and ulcerative colitis: a cohort study. Ann Intern Med 2012; 156: 350-9. [CrossRef]
4. Calkins BM. A meta-analysis of the role of smoking in inflammatory bowel disease. Dig Dis Sci 1989; 34: 1841-54. [CrossRef]
5. Miner PB, Jr. Factors influencing the relapse of patients with inflammatory bowel disease. Am J Gastroenterol 1997; 92: 1-4.
6. John S, Luben R, Shrestha SS, Welch A, Khaw KT, Hart AR. Dietary n-3 polyunsaturated fatty acids and the aetiology of ulcerative colitis: a UK prospective cohort study. Eur J Gastroenterol Hepatol 2010; 22: 602-6. [CrossRef]
7. Franceschi S, Favero A, Conti E, et al. Food groups, oils and butter, and cancer of the oral cavity and pharynx. Br J Cancer 1999; 80: 614-20. [CrossRef]
8. Sinha R, Kulldorff M, Curtin J, Brown CC, Alavanja MC, Swanson CA. Fried, well-done red meat and risk of lung cancer in women (United States). Cancer Causes Control 1998; 9: 621-30. [CrossRef]
9. Gonzalez CA, Jakszyn P, Pera G, et al. Meat intake and risk of stomach and esophageal adenocarcinoma within the European Prospective Investigation Into Cancer and Nutrition (EPIC). J Natl Cancer Inst 2006; 98: 345-54. [CrossRef]
10. Jakszyn P, Gonzalez CA. Nitrosamine and related food intake and gastric and oesophageal cancer risk: a systematic review of the epidemiological evidence. World J Gastroenterol 2006; 12: 4296-303.
11. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of non randomized studies in meta-analyses. Euro J Epidemiol 2010; 25: 603-5. [CrossRef]
12. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-48.
13. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-88. [CrossRef]
14. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-34. [CrossRef]

15. Higashi A, Watanabe Y, Ozasa K, et al. [A case-control study of ulcerative colitis]. Nihon Eiseigaku Zasshi 1991; 45: 1035-43. **[CrossRef]**
16. Akihiro M, Hikara W, Takashi S, et al. Dietary and other risk factors of ulcerative colitis. A case-control study in Japan. Epidemiology Group of the Research Committee of Inflammatory Bowel Disease in Japan. J Clin Gastroenterol 1994; 19: 166-71. **[CrossRef]**
17. Sakamoto N, Kono S, Wakai K, et al. Dietary risk factors for inflammatory bowel disease: a multicenter case-control study in Japan. Inflamm Bowel Dis 2005; 11: 154-63. **[CrossRef]**
18. Bernstein CN, Rawsthorne P, Cheang M, Blanchard JF. A population-based case control study of potential risk factors for IBD. Am J Gastroenterol 2006; 101: 993-1002. **[CrossRef]**
19. D'Souza S, Levy E, Mack D, et al. Dietary patterns and risk for Crohn's disease in children. Inflamm Bowel Dis 2008; 14: 367-73. **[CrossRef]**
20. Maconi G, Ardizzone S, Cucino C, Bezzio C, Russo AG, Bianchi Porro G. Pre-illness changes in dietary habits and diet as a risk factor for inflammatory bowel disease: a case-control study. World J Gastroenterol 2010; 16: 4297-304. **[CrossRef]**
21. Wang YF, Ou-Yang Q, Xia B, et al. Multicenter case-control study of the risk factors for ulcerative colitis in China. World J Gastroenterol 2013; 19: 1827-33. **[CrossRef]**
22. Jowett SL, Seal CJ, Pearce MS, et al. Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study. Gut 2004; 53: 1479-84. **[CrossRef]**
23. Jantchou P, Morois S, Clavel-Chapelon F, Boutron-Ruault MC, Carbonnel F. Animal protein intake and risk of inflammatory bowel disease: The E3N prospective study. Am J Gastroenterol 2010; 105: 2195-201. **[CrossRef]**
24. Sugimura T, Wakabayashi K, Nakagama H, Nagao M. Heterocyclic amines: Mutagens/carcinogens produced during cooking of meat and fish. Cancer Sci 2004; 95: 290-9. **[CrossRef]**
25. Mirvish SS. Role of N-nitroso compounds (NOC) and N-nitrosation in etiology of gastric, esophageal, nasopharyngeal and bladder cancer and contribution to cancer of known exposures to NOC. Cancer Lett 1995; 93: 17-48. **[CrossRef]**
26. Richman E, Rhodes JM. Review article: Evidence-based dietary advice for patients with inflammatory bowel disease. Aliment Pharmacol Ther 2013; 38: 1156-71. **[CrossRef]**
27. Vagianos K, Clara I, Carr R, et al. What are adults with inflammatory bowel disease (ibd) eating? A closer look at the dietary habits of a population-based canadian ibd cohort. JPEN J Parenter Enteral Nutr 2014. pii: 0148607114549254. **[CrossRef]**