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*Original Article*

# A meta-analysis of case-control studies of high-fat diet and colorectal cancer

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**Abstract:** The association between high-fat diet and colorectal cancer (CRC) has been investigated for a few decades. Although animal studies have found a positive relationship between high-fat diet and CRC, it cannot be unequivocally confirmed in epidemiology studies. In this study, we performed a meta-analysis of epidemiology studies to examine the effects of high-fat diet and fat compositions on the risk of CRC. We systematically reviewed publications from Medline and China Knowledge Resource Integrated Database, and selected 10 case-control population studies that provided odds ratio or relative risk of different categories of fat diet intake. A total of 7989 CRC cases and 9854 controls met the inclusion criteria and were included in this meta-analysis. We found that the total fat was positively associated with CRC risk (odds ratio: 1.41, 95% confidence interval: 1.02-1.95). Further analysis of the fat subtypes using the data from 4 case-control studies did not find that the risk of CRC was associated with either saturated fat acid or unsaturated fat acid. Therefore, our meta-analysis confirmed that high-fat diet is associated with increased risk of CRC. A larger population-study is needed to determine which fat composition affects the cancer risk.

**Keywords:** High-fat diet, colorectal cancer, meta-analysis, case control study

## Introduction

Globally, cancer of the colorectum is the third most common cancer in men and the second most common in women. The incidence and mortality rates are highly associated with geographic region and country, wherein the higher number of cases are reported in developed countries than in developing countries [1]. In the United States, CRC is the third most common cancer and the third leading cause of cancer death in men and women [2]. In the last few decades, rapid increases of CRC cases have been observed in both developed and developing countries, a possible consequence of changing lifestyles in dietary and physical activity [3]. For example, the fact that CRC incidence rate in Japan has markedly increased over the past 40 years, which is generally ascribed to westernization of diet [3, 4]. In addition, the incidence and mortality of CRC increased substantially in South Asia immigrants in England when compared with the original South Asian records [5, 6].

Among all the lifestyle factors, diet is regarded as the most important factor to associate with CRC. It is suggested that CRC could be prevented with a proper diet consisting of small amounts of red meat and larger amounts of fruit, vegetables, and fiber [1]. A recent study using a mouse model has found that limiting caloric intake and reducing body weight could inhibit colon cancer induced by chemical factors [7]. Other animal studies suggested that high-fat diet consumption increases the risk for CRC via several possible mechanisms [8-12].

However, it is intriguing that the population studies have inconsistent or even contradictive results when studying the effect of high-fat diet on CRC. For example, while positive relation between high-fat diet and CRC risk has been found in several studies [13-20], other studies reported non-significant relation [12, 21, 22], or even negative relation [23, 24]. This inconsistence is possibly resulted from the difficulty of accurate diet measurement, the complicated

food compositions and the relative small sample size.

Meta-analysis has been proved to be an effective approach to achieve reliable conclusion by increasing the statistical power with pooled data and overcoming the variability and biases for individual studies [25]. Meta-analysis has been used to study the relationship of high-fat diet and CRC risk in a couple of early studies [26-29], but no significant association has been detected. For example, a recently report by Lee et al. investigated the link between fat, protein, and meat consumption and the risk of renal cancer using data from 13 prospective cohort studies, which include 530,469 women and 244,483 men with 7-20 years' follow up study. They reported positive associations or trends between renal cancer and intakes of total fat, saturated fat (SFA), monounsaturated fat (MUFA), polyunsaturated fat (PUFA) and cholesterol. However, these associations are weakened or disappear after adjusting by body mass index, fruit and vegetable intake, and alcohol intake [30]. To our knowledge, all the meta-analysis studies were based on pooling cohort studies, which has limited statistical power when investigating diseases with low incidence or with long-period of latency. The sample size and the time period of these cohort studies may not be sufficient for assessing the link of high-fat diet and CRC risk.

In view of the limitation for cohort studies, we conducted a meta-analysis using only well designed case-control studies. Case-control studies provided larger statistical power for association analysis of rare diseases. We aimed to test the association of CRC with various fat compositions, including total fat, saturated fatty acid, monounsaturated fatty acid and polyunsaturated fatty acid.

## Materials and methods

### *Literature search*

We conducted a search for Medline database and China Knowledge Resource Integrated Database (CNKI). We used the following key words for the literature search: high-fat diet, colorectal cancer (colon, rectum), and population study (case control). In addition, we conducted a broader search on diet and CRC aiming at identifying studies in which the aforementioned terms were not included in abstracts. Furthermore, we contacted investigators for unpublished results that might be useful for the analysis. The search was conducted through April 30, 2014. We systematically reviewed and examined whether the identified studies met the following criteria: (1) case-control; (2) having fat-consumption assessment; (3) the diet data were collected by the trained and certified interviewers using food frequency questionnaire or diet history questionnaire; (4) having risk estimates [relative risk (RR), or odds ratio (OR)] for colorectal, colon, or rectal cancer including its 95% confidence interval (95% CI) for the highest level of fat intake versus the lowest level; (5) assessed for confounding factors. When the studies used the same data series, the earliest published article or the article with the largest population was included. All data considered for inclusion in our meta-analysis originated from peer-reviewed published articles written in English language.

### *Statistical analysis*

The odds ratios from the study reports were used for meta-analysis. For the studies that only provided relative risks (RR) other than odds ratios (OR), we converted RR to OR by calculating the number of subjects in each group using the following equations given the total numbers of cases and control subjects.

$$RR = \frac{x_1 \bullet n_2}{x_2 \bullet n_1}, \quad (1)$$

$$SD = \sqrt{\frac{n_1 - x_1}{n_1 \bullet x_1} + \frac{n_2 - x_2}{n_2 \bullet x_2}}, \quad (2)$$

Where $n_1$ is the total number of cases, $n_2$ is the total number of control objects, $x_1$ is the number of high fat cases, $x_2$ is the number of high fat control subjects, and SD is the standard deviation for ln(RR). Because RR is given and SD can be calculated from 95% confidence interval of RR, we are able to obtain $x_1$ and $x_2$ values by solving the **Equations 1** and **2**. Thus, odds ratio can be obtained.

We targeted to estimate the risk of CRC by contrasting high-fat and low-fat diet. Homogeneity test for between study variance was first performed using Cochran's Q statistic. If all selected studies are homogeneous, a fixed effects model would be used for meta-analysis. If the

**Table 1.** Characteristics of the 10 selected case-control studies

| Study | Country | Total Case/ Control | Methods of assessment | Statistical adjustment |
|---|---|---|---|---|
| Sun 2012 | Canada | 1760/2481 | FFQ* | age, sex, BMI, physical activity (METs/week), family history of CRC, polyps, diabetes use of multivitamin supplements, regular use of folate supplement, regular use of calcium supplement, reported HRT (females only), province of residence, and intakes of fruits, vegetables, and red meat |
| Kurotani 2010 | Japan | 800/775 | FFQ | sex, age, residential area, smoking, alcohol use, BMI 10 years earlier, type of job, leisure-time physical activity, parental colorectal cancer and energy intake |
| Slattery 2010 | USA | 940/1189 | DHQ# | age, sex, recent aspirin or NSAID use, long-term activity level, pack-years of cigarette smoking, dietary calcium, and energy intake |
| Williams 2009 | USA | 720/800 | DHQ | age, sex, education, income, BMI 1 year ago, physical activity, family history, non-steroidal anti-inflammatory drug use, and total energy intake |
| Kimura 2007 | Japan | 782/793 | DHQ | age, sex, residential area, body mass index 10 years before, parental colorectal cancer, smoking, alcohol use, type of job, leisure-time physical activity, dietary calcium and dietary fiber |
| Rouillier 2005 | France | 171/309 | FHQ | age, sex, energy, body mass index, exercise, tobacco and alcohol energy, relative weight, and social class |
| Breuer 2001 | Germany | 184/184 | DHQ | energy, relative weight, and social class |
| Slattery 1997 | USA | 1993/2410 | DHQ | age at diagnosis or selection, total energy intake, dietary fiber, cholesterol, calcium, BMI, physical activity and use of NSAIDs |
| Bautista 1997 | USA | 286/295 | FFQ | age, physical activity, number of meals per day, and total caloric intake |
| Young 1988 | USA | 353/618 | DHQ | age, sex |

*FFQ: food frequency questionnaire, #DHQ: diet history questionnaire.

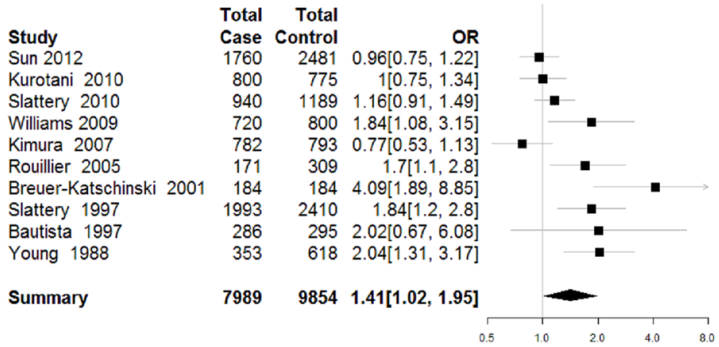


**Figure 1.** Meta-analysis of the case-control studies of total fat consumption and CRC. Cochran's homogeneity test *P*-value=0.000069 (df=9), *Q*=34.6. OR: odds ratio. 95% confidence interval is presented for each odd ratio.

studies are heterogeneous, we would estimate the CRC risk using a random-effects model in which the effect measures were log OR-weighed by the method of DerSimonian and Laird (DSL) [31], giving greater weight in the summary measure to studies with smaller standard error of estimate. The overall OR and the 95% confidence interval were obtained using the method proposed by Hartung and Knapp [32]. We used the methods of Begg and Mazumdar [33] and Egger et al. [34] to detect publication bias. Both methods test for funnel plot asymmetry, the former being based on the rank correlation between the effect estimates and their sampling variances, and the latter on a linear regression of a standard normal deviate on its precision. If a potential bias was detected, we further conducted a sensitivity analysis to assess the robustness of combined effect estimates and the possible influence of the bias and to have the bias corrected. All statistical analyses were performed using R programing language. All reported *P* values are from two-sided statistical tests, and differences with $P < 0.05$ were considered significant.

## Results

### *Characteristics of studies*

We searched two publication databases, Medline and China Knowledge Resource Integrated Database (CNKI), up to April 21, 2014. The titles of 8767 papers from Medline, 124 papers from CNKI were selected by searching the key words: high-fat diet, colorectal cancer, population study, case-control. The selection and exclusion process was performed in the following steps. First, a total of 8830 papers were excluded due to the following reasons: 1) The topics of 8381 papers were not relevant; 2) 449 were not research papers, including 393 reviews, 13 editorials, 26 comments and 17 communication letters. Second, the abstracts of the remaining 61 papers were reviewed and 36 papers were further filtered: 1) 32 were obviously irrelevant; 2) 3 were for the combined effect of fat with other nutritional elements; 3) 1 paper studied the association between fatty acids and the risk of colorectal polyps and adenomas. Third, the full texts of the 25 papers were reviewed. Fifteen additional papers were excluded because: 1) eight did not provided OR (or RR) and 95% CI; 2) two papers had no comparison between the high and low fat intakes; 3) three papers analyzed the same dataset, so two of them were excluded; 4) two were for cohort study. Finally, we found a total of 10 case-control studies [12, 13, 15-17, 19-22, 35] met the selection criteria and were included in this study.

The final 10 selected studies were published between 1994 and 2012, including a total of 7,989 cases and 9,854 controls. The characteristics of the selected studies were summarized in **Table 1**. All of the studies provided explicit inclusion and exclusion criteria. Among those 10 studies, 6 were performed in America, 2 in Europe (one in France, the other in Germany), and 2 in Asia (two in Japan). These studies had CRC in either the colon or the rectum, including 6 studies for both colon and rectum cancers, 2 for only rectal cancer, 1 for only colon cancer and 1 for colorectal adenoma. All studies have taken into account the potential effects of confounding factors, such as age, sex, energy, dietary calcium and dietary fiber in their analyses of the risk of CRC as summarized in **Table 1**. Publication bias was not observed for the selected case-control studies.

### *Total dietary fat*

Out of the 10 case-control studies, 6 found total dietary fat was positively correlated with the risk of CRC (**Figure 1**). All the studies except Breuer-Katschinski 2001 [16] had provided the odds ratios and their corresponding 95% confi-

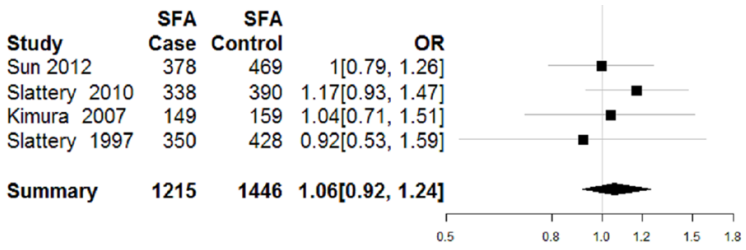


**Figure 2.** Meta-analysis of the case-control studies of saturated fat acid consumption and CRC. Cochran's homogeneity test *P*-value > 0.05 (df=3), *Q*=1.25. OR: odds ratio. 95% confidence interval is presented for each odd ratio.

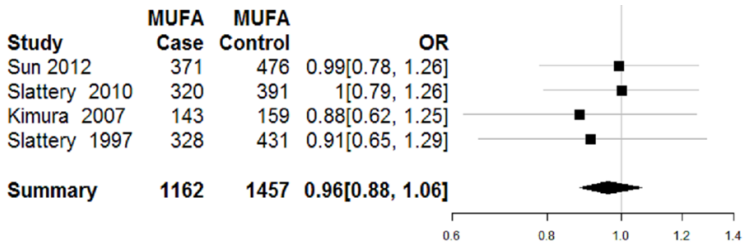


**Figure 3.** Meta-analysis of the case-control studies of monounsaturated fat acid consumption and CRC. Cochran's homogeneity test *P*-value > 0.05 (df=3), *Q*=0.51. OR: odds ratio. 95% confidence interval is presented for each odd ratio.

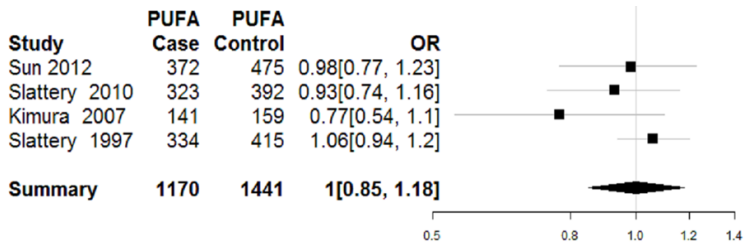


**Figure 4.** Meta-analysis of the case-control studies of polyunsaturated fat consumption and CRC. Cochran's homogeneity Chi-squared test *P*-value > 0.05 (df=3), *Q*=3.38. OR: odds ratio. 95% confidence interval is presented for each odd ratio.

dence intervals, but only 5 studies had provided the numbers of cases and control subjects for each group. Thus, we performed all analysis based on odds ratios. For Breuer-Katschinski 2001 study, we converted the relative risk to the odds ratio by solving the **Equations 1** and **2**.

Cochran's homogeneity statistic was Q=34.6, compared with 16.9, the 5% cut-off point of the chi-square distribution with 9 (10 studies) degree of freedom. Thus, the homogeneity hypothesis of no between study variance was rejected with a *P*-value of 0.000069. Our meta-analysis was performed using a random effect model. The between-study variance was estimated using DSL estimator [31]. The overall odds ratio of meta-analysis, 1.41 with 95% confidence interval (1.02, 1.95), indicated that total dietary fat is positively correlated with the risk of CRC.

*Saturated fatty acids*

Only four case-control studies provided data for analysis of the sub-types of fatty acids, including saturated fatty acids (SFA), monounsaturated fatty acids (MUFA) and polyunsaturated fatty acid (PUFA). The four studies were Slattery 1997, Kimura 2007, Slattery 2010 and Sun 2012. The two Slattery studies recruited different sets of subjects, so we included both studies. Slattery 1997 study provided odds ratios and 95% confidence interval by sex. In order to obtain the overall odds ratio regardless of sex, we used a fixed model for a meta-analysis for the Slattery 1997 data, obtaining the resulting uni-sex odds ratio, 0.92 with 95% confidence interval [0.53, 1.59] (**Figure 2**).

The Cochran's homogeneity statistic Q was 1.21, not significant when compared with 7.81, the 5% cutoff value for chi-square statistic with 3 degrees of freedom. Thus, a fixed model is used to estimate the overall odds ratio of meta-analysis. The resulting odds ratio was 1.06 with 95% confidence interval [0.92, 1.24] (**Figure 2**).

*Monounsaturated fatty acid*

A fixed effect model was used to merge the data by sex in the Slattery 1997 study. The resulting uni-sex odds ratio was 0.92 with 95% confidence interval [0.53, 1.59] (**Figure 3**). The Cochran's homogeneity statistic Q was 0.51, not significant when compared with 7.81, the 5% cutoff value for chi-square statistic with 3 degrees of freedom. Thus, a fixed model is used to estimate the overall odds ratio of meta-

analysis. The resulting odds ratio was 0.96 with 95% confidence interval [0.88, 1.06] (**Figure 3**).

*Polyunsaturated fatty acid*

By fitting a mixed effect model, we found the uni-sex odds ratio for PUFA for the Slattery 1997 to be 1.06 with 95% confidence interval [0.94, 1.20] (**Figure 4**). The Cochran's homogeneity statistic Q was 3.38, not significant when compared with 7.81, the 5% cutoff value for chi-square statistic with 3 degrees of freedom. Thus, a fixed model is used to estimate the overall odds ratio of meta-analysis. The resulting odds ratio was 1 with 95% confidence interval [0.85, 1.18] (**Figure 4**).

## Discussion

The population studies for the effect of high-fat diet on CRC often have controversial and even contradictive results, which promotes meta analyses for a more accurate estimation by pooling the data from all studies up to date. Two meta-analysis studies have been reported in the last few years [27-30]. They didn't find any significant association between high-fat diet and the risk of CRC. However, both studies performed meta-analyses for the studies completed before 1997, while there are a large number of population studies for diet and CRC conducted after 1997. More importantly, both meta-analysis studies were exclusively focused on cohort studies. Colorectal carcinoma takes many years to develop and the incidence of CRC is relative low. A cohort study for CRC may only obtain a small number of cases that barely provide sufficient power for statistical analysis, while cohort study may examine the risk link between the factors and outcomes. On the other hand, case-control study has balanced number of subjects in both cancer and control group, which allows more rigorous statistical analysis, and only assesses associations. Therefore, our meta-analysis was limited to all the case-control studies despite their relatively fewer limitations.

In this meta-analysis study, we found a positive association between consumption of total fat and the risk of CRC (OR: 1.41 [1.02, 1.95]). Although laboratory studies showed that a high-fat intake increases the incidence of colorectal carcinoma in experimental animals [36, 37], the human epidemiology studies cannot always confirm the link with statistical significance. Among the 10 case-control studies included in the meta-analysis, only 5 reported a positive relationship between total fat and CRC and the other 5 did not find any significant association. For the prospective cohort studies, a study in female nurses found a positive association between red meat consumption and the risk of colon cancer [38], but no increase in cancer risk was observed in CPS II and the Iowa Women's Health Study (IWHS) [39, 40]. The conflicting results may come from the limitations of cohort studies and insufficient number of subjects, or from variations in study design such as confounding factors, food composition, etc. Meta-analysis is an effective way to control the study variations. In our analysis, we found that the 10 case-control studies were highly heterogeneous in variance, and we were able to take into account the heterogeneity using a random effect model. Our analysis confirmed an increased risk of CRC associated with total fat consumption.

Further meta-analysis of the subtypes of fatty acids, SFA, MUFA and PUFA, did not find any significant association with CRC. These results are conservative considering only 4 studies, with the total number of subjects in the case or control group less than 1,500, were included in the analysis of fatty acid subtypes. Plant fats have higher concentrations of unsaturated fatty acids, whereas animal fats consist of larger amounts of SFA. Various compositions of fatty acids have been previously reported to have association with CRC. Two case-control studies in Russia found that a higher ratio of PUFA to SFA was associated with decreased risk of CRC [41]. An increased risk of CRC was found to associate with arachidonic acid, a polyunsaturated fatty acid, in male, and with the PUFA ratio of ω6/ω3 (n6/n3) in female [42]. Deceased intake of n-6 PUFAs and saturated fats and increased intake of n-3 PUFAs have been reported to be beneficial to colon cancer control [43]. In our meta-analysis, no association of cancer risk was found for the different types of fatty acids. Given the relative small sample size for each study, these results need to be confirmed with a larger population study or a meta-analysis of larger number of studies.

Meta-analysis of population studies has a few limitations in general, and to this study specifically. Firstly, the selected studies usually have variations in study design. For examples, different ages of the populations were recruited, different dietary questionnaires were used, and

the categories of fat were inconsistent. Our homogeneity test found the 10 studies for total fat were highly heterogeneous. Although the heterogeneity between studies can be largely controlled by robust meta-analysis, it decreases the statistical power and may even bias the results. Secondly, the sample size for several studies might be too small for reliable analysis. As discussed previously, the small sample size for fatty acid subtypes may lead inconclusive results. Thirdly, the confounding factors, such as race, age and consumption of other foods such as vegetables, were not uniformly controlled for all studies. Some studies may fail to adjust some or all the confounding factors. Finally, it is unclear whether patterns of associations vary by anatomic tumor sites within the colorectum. Not all studies reported the actual tumor sites, so analysis of association with CRC subtypes cannot be conducted.

In conclusion, our meta-analysis found that high-fat diet is positively related to the risk of colorectal cancer. It suggests that the reduction of high-fat diet consumption is beneficial for prevention of CRC. We didn't found specific subtype(s) of fatty acids were associated with CRC using current limited sample sizes. Further investigations with well-designed case-control studies are recommended to evaluate the potentially pathogenic role of SFA and n6 PUFA in colorectal cancer etiology.

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