The association between dietary protein intake and colorectal cancer risk: a meta-analysis

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Abstract

Background: Association between dietary protein intake and colorectal cancer risk has not been fully quantified, while the results were controversial. This study aimed to evaluate the role of protein intake in the development of colorectal cancer.

Methods: PUBMED and EMBASE were searched up to December 2016. Two independent reviewers independently extracted data from eligible studies. Relative risk (RR) with 95% confidence intervals (CI) was pooled using random-effects model to estimate the result. Besides, publication bias and sensitivity analysis were conducted.

Results: Thirteen articles involving 21 studies comprising 8187 cases were included in this report. The pooled RR of colorectal cancer was 1.006 (95% CI = 0.857–1.179) indicating that there is no significant association between dietary protein intake and colorectal cancer risk. Furthermore, the pooled RRs for colon cancer and rectum cancer were 1.135(95% CI = 0.871–1.480) and 0.773(95% CI = 0.538–1.111), respectively, with the highest category of dietary protein intake. The association was not significant either in subgroup analysis of study design, protein type (animal protein or vegetable protein), sex, and or geographic locations.

Conclusions: The present study indicated that the highest category compared to the lowest category of protein intake had no significant association on colorectal cancer risk. Dose-response analysis was not conducted due to limited information provided. Therefore, more studies with large cases and participants as well as detailed amounts of dietary protein intake are wanted to confirm this result.

Keywords: Protein intake, Colorectal cancer, Meta-analysis, Relative risk

Background

Colorectal cancer is one of the high incidence of malignant tumors worldwide, with the morbidity and mortality ranking third among malignant tumors in the Western world [1]. Owing to economic development, air and water pollution, and changing lifestyle to high-protein, high-carbohydrate, and high-fat diet, the incidence and mortality of colorectal cancer has been on a rising trend in China [2]. In general, physical activity, low total energy intake such as dietary protein, low red and processed meat consumption, and limited alcohol drinking were known to give beneficial effect for cancer prevention [3]. Diet has long been regarded as the most important lifestyle risk factor for colorectal cancer. However, role of many dietary factors in colon carcinogenesis remains unresolved.

In animal and in vitro studies which investigated the effect of protein intake on colorectal cancer risk, high-protein diet could lead to DNA damage of colonocytes, decrease colonic mucosal thickness, and reduce the height of the colonocyte brushborder membrane [4–6]. Several epidemiologic studies have explored the relationship between dietary protein intake and the risk of colorectal cancer, but the results are inconsistent. A recent study by Tayyem RF et al. reported that the highest intake of protein could increase colorectal cancer risk [7]. However, Sun Z et al. found that colorectal cancer risk could be reduced with the highest category intake of protein [8]. Furthermore, Yang SY et al. failed to find any significant association between them [9]. So far,
there is no meta-analysis conclusively demonstrating the relationship between them. In this study, a comprehensive meta-analysis of observational studies was performed to assess the colorectal cancer risk associated with dietary protein intake. The aim of this report was also to assess the heterogeneity and publication bias.

**Methods**

**Search strategy**

This meta-analysis followed the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) guidelines [10]. We systematically searched PubMed and Embase (from their commencements to December 2016) for studies with the following format: (protein OR nutrition) AND (colorectal cancer OR colon cancer OR rectum cancer). In addition, the reference lists of relevant articles were also reviewed to find other suitable articles.

**Study selection**

Studies were included if they met all of the following criteria: (1) the study subjects were adults (≥ 18 years old) without specific diseases at study baseline; (2) the study was conducted with observational studies; (3) the exposure of interest was dietary intake of protein with two or more quantitative categories; (4) the outcome of interest was colorectal cancer, colon cancer, or rectum cancer; and (5) relative risk (RR) and 95% confidence intervals (CI) for dietary protein intake (or there are sufficient data to compute them was also acceptable).

**Data exaction and quality assessment**

The following data from each study were extracted independently by two authors: the first author’s name, publication year, study location, age and sex of the study population, outcomes of disease type, type of protein intake, number of cases and controls, variables adjusted in each original study, and RR with their 95% CI for dietary protein intake (or there are sufficient data to compute them was also acceptable).

**Statistical analysis**

The pooled RR with 95% CI was calculated using random-effects models with the method of DerSimonian and Laird, which considers both within-study and between-study variation [12]. The between-study heterogeneity in the association between dietary protein intake and colorectal cancer was assessed using chi-square test and \( I^2 \) test, and < 25%, 25–50%, and > 75% represents low, moderate, and severe heterogeneity, respectively [13, 14]. Subgroup analyses were performed by disease type, study design, sex, protein type, and geographic locations. Sensitivity analysis was performed to assess whether the results could be affected while removing a single study [15]. The individual study is thought to produce excessive influence, if the point estimate lies outside the 95% CI of the combined analyses. Small study effect was assessed with visual inspection of the Egger's test and funnel plot [16]. We used STATA version 12.0 (Stata Corporation, College Station, TX, USA) for the meta-analysis. Two-tailed \( P \leq 0.05 \) was accepted as statistically significant for computed effects.

**Results**

**Characteristics of studies and data quality**

We have searched databases of PubMed and Embase and finally got 3069 articles. We then reviewed the titles and abstracts to exclude 3034 articles because of duplicates \( (n = 986) \), obvious irrelevance \( (n = 2022) \), and animal or cell studies \( (n = 26) \). Twenty-two of the remaining 35 articles are excluded due to the following reasons: review articles \( (n = 6) \), duplicate publications \( (n = 1) \), letter to the editors \( (n = 2) \), and paper provided insufficient data \( (n = 13) \). Finally, 13 articles [7–9, 17–26] were included in this study. Two articles [22, 25] reported colon cancer and rectum cancer, two articles [23, 24]...
| Study, year | Country   | Study design | Participants (cases) | Age (years) | Score quality | Protein type | Dietary assessment | Protein intake amounts (g) | RR (95% CI)    | Adjustment for covariates                                                                 |
|------------|-----------|--------------|----------------------|-------------|---------------|--------------|-------------------|--------------------------|----------------|------------------------------------------------------------------------------------------|
| Ghadiri P, 1997 | Canada    | Case-control | 1070 (402)           | 35–79       | 6             | Total animal  | Quantitative      | Colon                   | 0.81 (0.55–1.19) | Adjusted for gender, age, marital status, history of colon carcinoma in first-degree relatives, and total energy intake |
|            |           |              |                      |             |               | vegetable     | food frequency   | Quartile 1              | 0.91 (0.62–1.32)           |                |                                                                                           |
|            |           |              |                      |             |               |              | questionnaire    | Quartile 2              | 1.11 (0.77–1.61)           |                |                                                                                           |
|            |           |              |                      |             |               |              |                   | Quartile 3              |                           |                |                                                                                           |
|            |           |              |                      |             |               |              |                   | Quartile 4              |                           |                |                                                                                           |
| Goldbohm RA, 1994 | Netherlands | Cohort  | 120,852 (215)  | 55–69 | 8             | Animal        | Semiquantitative  | Colon                   | 1.10 (0.70–1.71) | Adjusted for quintiles of energy and energy-adjusted nutrient intakes, sex, and dietary fiber intake |
|            |           |              |                      |             |               |              | food frequency   | Quartile 1              | 1.05 (0.67–1.65)           |                |                                                                                           |
|            |           |              |                      |             |               |              | questionnaire    | Quartile 2              | 1.28 (0.82–2.00)           |                |                                                                                           |
|            |           |              |                      |             |               |              |                   | Quartile 3              | 0.90 (0.57–1.42)           |                |                                                                                           |
|            |           |              |                      |             |               |              |                   | Quartile 4              |                           |                |                                                                                           |
| Iscovich JM, 1992 | Argentina | Case-control | 330 (110)           | NA          | 7             | Total          | Food-frequency     | Colon                   | 0.81 (0.46–1.90) | Adjusted for fiber at 19.02 g per day, other sources of energy intake |
|            |           |              |                      |             |               |              | questionnaire    | Quartile 1              | 0.63 (0.26–1.49)           |                |                                                                                           |
|            |           |              |                      |             |               |              |                   | Quartile 2              | 1.03 (0.33–3.21)           |                |                                                                                           |
| Levi F, 2002 | Switzerland | Case-control  | 836 (286)           | ≤ 74        | 7             | Total          | Food-frequency     | Colorectal               | 0.80 (0.50–1.30) | Adjusted for age, sex, education, physical activity, and residual energy |
|            |           |              |                      |             |               |              | questionnaire    | Lowest                  | 1.10 (0.70–1.70)           |                |                                                                                           |
|            |           |              |                      |             |               |              |                   | Middle                  |                           |                |                                                                                           |
|            |           |              |                      |             |               |              |                   | Highest                 |                           |                |                                                                                           |
| Pietinen P, 1999 | Finland  | Cohort   | 27,111 (185)        | 50–69       | 8             | Total          | Food-frequency     | Colorectal               | 1.20 (0.80–1.70) | Adjusted for age, supplement groups, smoking years, body mass index, alcohol, education, and physical activity at work, and calcium intake (except for milk protein and milk products) |
|            |           |              |                      |             |               | Animal         | questionnaire    | Quartile 1              | 0.90 (0.60–1.40)           |                |                                                                                           |
|            |           |              |                      |             |               | Vegetable      |                   | Quartile 2              | 0.90 (0.50–1.50)           |                |                                                                                           |
|            |           |              |                      |             |               |              |                   | Quartile 3              |                           |                |                                                                                           |
|            |           |              |                      |             |               |              |                   | Quartile 4              |                           |                |                                                                                           |
| Prentice RL, 2009 | American | Cohort   | 59,105 (280)        | 50–89       | 8             | Total          | Food-frequency     | Colon                   | 0.97 (0.70–1.34) | NA                                                                                      |
|            |           |              |                      |             |               |              | questionnaire    | Quartile 1              | 1.11 (0.76–1.61)           |                |                                                                                           |
|            |           |              |                      |             |               |              |                   | Quartile 2              | 0.96 (0.64–1.44)           |                |                                                                                           |
| Prentice RL, 2009 | American | Cohort   | 59,105 (280)        | 50–89       | 8             | Total          | Food-frequency     | Rectum                  | 1.22 (0.56–2.65) | NA                                                                                      |
|            |           |              |                      |             |               |              | questionnaire    | Quartile 1              | 1.57 (0.72–3.41)           |                |                                                                                           |
|            |           |              |                      |             |               |              |                   | Quartile 2              | 1.08 (0.48–2.41)           |                |                                                                                           |
| Slattery ML, 1994 | American | Case-control | 623 (231)          | 40–79       | 7             | Total          | Food-frequency     | Colon                   | 2.30 (1.10–4.70) | Adjusted for age, religion, body mass index, crude fiber, and separate logistic models were used for each variable. Calcium as continuous variables in multiple logistic regression models. |
|            |           |              |                      |             |               |              | questionnaire    | Quartile 1              | 2.40 (1.00–5.70)           |                |                                                                                           |
|            |           |              |                      |             |               |              |                   | Quartile 2              | 3.70 (1.30–10.50)          |                |                                                                                           |
| Slattery ML, 1994 | American | Case-control | 623 (231)          | 40–79       | 7             | Total          | Food-frequency     | Colon                   | 0.90 (0.40–1.90) | Adjusted for age, religion, body mass index, crude fiber, and separate logistic models were used for each variable. Calcium as continuous variables in multiple logistic regression models. |
|            |           |              |                      |             |               |              | questionnaire    | Quartile 1              | 1.90 (0.90–4.00)           |                |                                                                                           |
| Study          | Country   | Study Design | N (Cases) | Age Range | Total Energy Intake | Food-frequency Questionnaire | Colon (kcal) | Adjusted for: |
|---------------|-----------|--------------|-----------|------------|---------------------|----------------------------|--------------|---------------|
| Slattery ML, 1997 | American | Case-control | 2389 (1099) | 30–79 | 7 Total | Total Food-frequency questionnaire | Colon (men) 1 < 263 264–331 332–407 408–512 > 512 | 1.25(0.95–1.65) 1.35(1.01–1.81) 1.33(0.95–1.84) 1.73(1.11–2.68) | age, body mass index, and family history of first-degree relative with colorectal cancer, use of aspirin and/or nonsteroidal anti-inflammatory drugs, physical activity, and dietary intake of fiber, cholesterol, and calcium |
| Slattery ML, 1997 | American | Case-control | 2014 (894) | 30–79 | 7 Total | Total Food-frequency questionnaire | Colon (women) 1 ≤ 209 210–259 260–316 317–399 > 399 | 1.00(0.74–1.35) 1.02(0.74–1.40) 1.00(0.70–1.43) 0.91(0.56–1.48) | age, body mass index, and family history of first-degree relative with colorectal cancer, use of aspirin, and/or nonsteroidal anti-inflammatory drugs, physical activity, and dietary intake of fiber, cholesterol, and calcium |
| Sun Z, 2012    | Canada    | Case-control | 4241 (1760) | 20–74 | 7 Total | Total Food-frequency questionnaire | Colorectal Quintile 1 Quintile 3 Quintile 5 | 0.88(0.70–1.11) 0.85(0.69–1.00) | total energy intake. Other potential confounders included age, sex, BMI, physical activity, family history of CRC, polyps, diabetes, reported colon screening procedure, cigarette smoking, alcohol drinking, education attainment, household income, marital status, regular use of NSAID, regular 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. Variables were included in the final model based on a ≥ 10% alternation in the parameter coefficients of interest |
| Tayyem RF, 2015 | Jordan    | Case-control | 417 (169)  | 53.8 ± 12.2 | 6 Total | Quantitative food frequency questionnaire | Colorectal Quartile 1 Quartile 2 Quartile 3 Quartile 4 | 1.66(0.74–3.69) 1.74(0.78–3.90) 3.62(1.63–8.04) | total energy intake normality of the distributions of dietary intake variables was assessed by the Shapiro-Wilk test. Non-normally distributed variables were log transformed. Other potential confounders included age, gender, BMI, physical activity (METs/week), family history (beyond the second degree) of CRC, education attainment, household income, marital status, and tobacco use |
### Table 1 Characteristics of the included studies (Continued)

| Study | Country | Design | Cases (Controls) | Age Range | Sex | Questionnaire Type | Measurement | Reference |
|-------|---------|--------|-----------------|-----------|-----|--------------------|-------------|-----------|
| Wakai K, 2006 | Japan | Case-control | 3042 (507) | 20–79 | 7 | Total | Food-frequency questionnaire | Colon Quartile 1: 0.74 (0.52–1.07), Quartile 2: 0.65 (0.45–0.95), Quartile 3: 0.74 (0.51–1.07); Adjusted for age, sex, year of first visit, season of first visit to the hospital, reason for the visit, family history of colorectal cancer, body mass index, exercise, alcohol drinking, smoking, multivitamin use, and energy intake. | Wakai K, 2006 Japan Case-control 3042 (507) 20–79 7 Total Food-frequency questionnaire Colon 1: 0.74 (0.52–1.07), Quartile 2: 0.65 (0.45–0.95), Quartile 3: 0.74 (0.51–1.07). Adjusted for age, sex, year of first visit, season of first visit to the hospital, reason for the visit, family history of colorectal cancer, body mass index, exercise, alcohol drinking, smoking, multivitamin use, and energy intake. |
| Wakai K, 2006 | Japan | Case-control | 3042 (507) | 20–79 | 7 | Total | Food-frequency questionnaire | Rectum Quartile 1: 0.83 (0.57–1.22), Quartile 2: 0.91 (0.62–1.32), Quartile 3: 0.71 (0.47–1.06). Adjusted for age, sex, year of first visit, season of first visit to the hospital, reason for the visit, family history of colorectal cancer, body mass index, exercise, alcohol drinking, smoking, multivitamin use, and energy intake. | Williams CD, 2010 American Case-control 1520 (720) 59.6 ± 10.3 8 Total Food-frequency questionnaire Colorectal Quartile 1: 0.90 (0.64–1.27), Quartile 2: 0.86 (0.57–1.30), Quartile 3: 0.57 (0.32–1.01). Adjusted for age, sex, education, body mass index, family history, nonsteroidal anti-inflammatory drug use, physical activity, calcium, fiber, and total energy. |
| Williams CD, 2010 | American | Case-control | 384 (225) | 58.0 ± 10.0 | 8 | Total | Food-frequency questionnaire | Colorectal Quartile 1: 0.90 (0.64–1.27), Quartile 2: 0.86 (0.57–1.30), Quartile 3: 0.57 (0.32–1.01). Adjusted for age, sex, education, body mass index, family history, nonsteroidal anti-inflammatory drug use, physical activity, calcium, fiber, and total energy. | Williams CD, 2010 American Case-control 1520 (720) 59.6 ± 10.3 8 Total Food-frequency questionnaire Colorectal (whites) Quartile 1: 0.90 (0.64–1.27), Quartile 2: 0.86 (0.57–1.30), Quartile 3: 0.57 (0.32–1.01). Adjusted for age, sex, education, body mass index, family history, nonsteroidal anti-inflammatory drug use, physical activity, calcium, fiber, and total energy. |
| Yang SY, 2016 | Korea | Case-control | 1056 (406) | 30–70 | 8 | Animal | Food-frequency questionnaire | Colorectal Tertile 1: 0.71 (0.47–1.07), Tertile 2: 1.25 (0.88–1.78). Adjusted for total energy intake, waist circumference, BMI, HDL cholesterol, fasting glucose, alcohol intake, smoking status, and family history of colorectal adenoma. | Yang SY, 2016 Korea Case-control 1056 (406) 30–70 8 Animal Food-frequency questionnaire Colorectal (men) Tertile 1: 0.71 (0.47–1.07), Tertile 2: 1.25 (0.88–1.78). Adjusted for total energy intake, waist circumference, BMI, HDL cholesterol, fasting glucose, alcohol intake, smoking status, and family history of colorectal adenoma. |
| Yang SY, 2016 | Korea | Case-control | 658 (151) | 30–70 | 8 | Animal | Food-frequency questionnaire | Colorectal Tertile 1: 0.71 (0.47–1.07), Tertile 2: 1.25 (0.88–1.78). Adjusted for total energy intake, waist circumference, BMI, HDL cholesterol, fasting glucose, alcohol intake, smoking status, and family history of colorectal adenoma. | Yang SY, 2016 Korea Case-control 1056 (406) 30–70 8 Animal Food-frequency questionnaire Colorectal (women) Tertile 1: 0.71 (0.47–1.07), Tertile 2: 1.25 (0.88–1.78). Adjusted for total energy intake, waist circumference, BMI, HDL cholesterol, fasting glucose, alcohol intake, smoking status, and family history of colorectal adenoma. |
| Yang SY, 2016 | Korea | Case-control | 658 (151) | 30–70 | 8 | Vegetable | Food-frequency questionnaire | Colorectal Tertile 1: 0.87 (0.52–1.46). Adjusted for total energy intake, waist circumference, BMI, HDL cholesterol, fasting glucose, alcohol intake, smoking status, and family history of colorectal adenoma. | Yang SY, 2016 Korea Case-control 1056 (406) 30–70 8 Vegetable Food-frequency questionnaire Colorectal (men) Tertile 1: 0.87 (0.52–1.46). Adjusted for total energy intake, waist circumference, BMI, HDL cholesterol, fasting glucose, alcohol intake, smoking status, and family history of colorectal adenoma. |
| Yang SY, 2016 | Korea | Case-control | 658 (151) | 30–70 | 8 | Vegetable | Food-frequency questionnaire | Colorectal Tertile 1: 0.54 (0.27–1.11). Adjusted for total energy intake, waist circumference, BMI, HDL cholesterol, fasting glucose, alcohol intake, smoking status, and family history of colorectal adenoma. | Yang SY, 2016 Korea Case-control 1056 (406) 30–70 8 Vegetable Food-frequency questionnaire Colorectal (women) Tertile 1: 0.54 (0.27–1.11). Adjusted for total energy intake, waist circumference, BMI, HDL cholesterol, fasting glucose, alcohol intake, smoking status, and family history of colorectal adenoma. |

Abbreviations: NA not available, BMI body mass index, CRC colorectal cancer, CI confidence interval, RR relative risk.
reported male populations and female populations, one article [26] reported Whites and African Americans, and one article [9] reported animal protein and vegetable protein, respectively. Therefore, 21 studies involving 8187 cases were used for the analysis. And the screening process was showed by Fig. 1. The average NOS score was 7.23, and all included studies were with high quality (over six stars). The details of the quality score for every study are shown in Additional file 1: Table S1. The characteristics of included studies are listed in Table 1.

**Dietary protein intake and risk of colorectal cancer**

To assess if the intake of protein could influence the colorectal cancer risk, we used random-effect model to pool the study-specific RR. Compared with the lowest category of protein intake, the pooled RR of colorectal cancer for the highest category was 1.006 (95% CI = 0.857–1.179) indicating that highest category of dietary protein intake had no significant association on colorectal cancer risk (Fig. 2). Heterogeneity was found to be significant ($I^2 = 53.4\%$, $p = 0.002$).

**Sources of heterogeneity and subgroup analysis**

In the pooled results of the overall studies, significant heterogeneity was demonstrated for the associations between dietary protein intake and colorectal cancer risk. Thus, we used univariate meta-regression to explore the reason of causing with the covariates of publication year, disease type, study design, protein type (animal protein or vegetable protein), sex, and geographic locations. No significant findings were found contributing significantly to the between-study heterogeneity.

Subgroup analyses were also conducted to explore the potential relationship and heterogeneity. For the subgroup of disease type, the pooled RRs for colon cancer and rectum cancer were 1.135 (95% CI = 0.871–1.480) (Fig. 3) and 0.773 (95% CI = 0.538–1.111) with the highest category of dietary protein intake, respectively. As different types of proteins could influence the risk of colorectal cancer, a subgroup analysis has been conducted. The results showed that no evidence of significance was found between dietary animal protein or vegetable protein intake and colorectal cancer risk. When we conducted the subgroup analysis by study...
design, the highest dietary protein intake levels had non-
significant association for colorectal cancer risk either in cohort studies or in case-control studies. In a stratified
analysis by sex and geographic locations, the association
was consistent with the overall result. The detailed
results are shown in Table 2.

Sensitive analysis
In a sensitivity analysis excluding a single study at a
time, no individual study would affect the whole result.

Publication bias
The Egger’s test ($P = 0.201$) and Begg’s funnel plot (Fig. 4) detected no obvious publication bias.

Discussion
Findings from this report of observational studies indi-
cated that no evidence of significant association was
found on colorectal cancer risk with the highest category
of dietary protein intake. The association was not signifi-
cant either in the colon cancer risk or in the rectum
cancer risk with the highest category of dietary protein
intake. The results of subgroup analyses by study design,
protein type, sex, and geographic locations were consist-
ent with the overall pooled result. To our knowledge,
this is the first comprehensive report conducted to as-
sess the relation between dietary protein intake and
colorectal cancer risk. Although we did not find any
positive result between them, a large number of colorec-
tal cancer cases could allow a much greater possibility of
reaching reasonable conclusions.

Significant between-study heterogeneity was found in the
process of merging results ($I^2 = 53.4\%, P_{\text{heterogeneity}} = 0.002$). However, heterogeneity is common in the meta-analysis
[27]. Meta-regression was used to explore the potential co-
variates that cause between-study heterogeneity. All the co-
variates of publication year, disease type, study design,
protein type, sex, and geographic locations were not found
any significant contributed to the heterogeneity. Furthe-
more, subgroup analyses by disease type, study design, pro-
tein type, sex, and geographic locations were performed to
explore the high heterogeneity. To our attention, the
heterogeneity was not significant either in the animal
protein studies ($I^2 = 0.0\%, P_{\text{heterogeneity}} = 0.624$) or vege-
table protein studies ($I^2 = 49.9\%, P_{\text{heterogeneity}} = 0.112$).
Therefore, the protein type may increase the heterogeneity
to the whole results.

| Author      | Year | Sex  | RR (95% CI) | Weight(%) |
|-------------|------|------|-------------|-----------|
| Ghadriar P  | 1997 | Both | 1.11 (0.77, 1.61) | 15.61     |
| Goldbohm RA | 1994 | Both | 0.90 (0.57, 1.42) | 13.44     |
| Iscovitch JM| 1992 | Both | 1.03 (0.33, 3.21) | 4.36      |
| Prentice RL | 2009 | Women| 0.96 (0.64, 1.44) | 14.68     |
| Slattery ML | 1994 | Men  | 3.70 (1.30, 10.50) | 4.99      |
| Slattery ML | 1994 | Women| 2.70 (0.90, 7.70)  | 4.76      |
| Slattery ML | 1997 | Men  | 1.73 (1.11, 2.68)  | 13.81     |
| Slattery ML | 1997 | Women| 0.91 (0.56, 1.48)  | 12.76     |
| Wakai K     | 2006 | Both | 0.74 (0.51, 1.07)  | 15.56     |
| Overall     |      |      | 1.14 (0.87, 1.48)  | 100.00    |

NOTE: Weights are from random effects analysis

Fig. 3 The forest plot between the highest versus the lowest categories of dietary protein intake and colon cancer risk
To our attention, various studies showed an opposite correlation (some positive and others inverse) between dietary intake of protein and colorectal cancer. The methods of dietary assessment in all the included studies are food frequency questionnaire (FFQ). Subgroup analysis by geographic locations was conducted to find the opposite correlation between dietary intake of protein and colorectal cancer, but there is no significant association among American populations, Asian populations, or European populations. The detailed amounts of dietary protein intake are not provided in most studies. Then, we did not consider the influences of dietary intake considerations to the colorectal cancer risk. Furthermore, the results are unstable due to the small sample size in each independent study. Therefore, this meta-analysis was performed to obtain a comprehensive result of this issue.

Several restrictions in this report should be attended. Firstly, our study included 21 individual studies; therefore, many diversification such as adjustments and quality that may influence the whole result. Secondly, although most of the included studies have adjusted for potential confounding factors, such as age, sex, and BMI, we cannot rule out the possibility that some other un-measured factors, such as intake of other energy, might have been partly responsible for the observed association. Thirdly, due to the limited information in the reported studies, dose-response analysis was not performed for dietary protein intake and colorectal cancer risk. Therefore, detailed information for each category of protein intake is wanted to assess the relationship between protein intake and colorectal cancer. Fourthly, dietary protein intake was collected via food-frequency questionnaires (FFQs), recall bias, and measurement bias.
could not be eliminated. Finally, significant heterogeneity was observed across studies included in the present meta-analysis. And the between-study heterogeneity was not resolved by meta-regression, the results of subgroup analyses were also with high heterogeneity in some groups except in the subgroup of protein type. Therefore, dietary protein type (animal protein or vegetable protein) may be the potential contributor to the between-study heterogeneity, and it would be further affecting the heterogeneity.

Conclusions
In summary, this study suggested that the highest category of dietary protein intake had no significant association for the risk of colorectal cancer. Therefore, further studies with large cases and participants as well as detailed amounts of dietary protein intake are wanted to confirm this result, during some limitation that existed in our study.

Additional file

**Additional file 1: Table S1.** The details of quality score for the included study. (DOCX 12 kb)

Abbreviations
CI: Confidence intervals; HR: Hazard ratio; NOS: Newcastle-Ottawa Scale; OR: Odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RR: Risk ratio

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Availability of data and materials
Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Authors’ contributions
RLX and ZB conceived of the study. RLX, ZB, and HL carried out the literature searching. RLX, ZB, and HL are responsible for the data extraction. JNR and HILZ analyzed the data. RLX drafted the manuscript. RLX, ZB, HL, JNR, HILZ, and HXG did the final approval of the version to be submitted.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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