Meta-analysis of the relationship between Dietary Inflammatory Index and esophageal cancer risk
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Abstract
Introduction: Diet is closely related to the occurrence of esophageal cancer (EC). Dietary Inflammatory Index (DII), as a novel index that describes the inflammatory potential of diet, was widely used in many diseases.
Objective: To systematically analyze the relationship between DII and the risk of esophageal cancer.
Methods: We mainly searched relative studies in PubMed, Cochrane library, Web of Science, and other literature database. The random-effect model was used for meta-analysis, and subgroup analysis and sensitivity analysis were used to detect the origin of heterogeneity.
Results: We finally obtained 6 articles (8 studies). All studies were case-control studies which consisted of 1961 cases and 3577 controls. In this study, compared with the lowest DII category, the highest DII category had a higher risk of esophageal cancer, and the pooled odds ratio (OR) of the 8 studies was 2.54 (95% confidence interval (CI): 1.90–3.40; \( I^2 = 65.7\% \), \( P = .005 \)). Furthermore, regardless of the differences in published year, DII components, geographic location, and study quality, there was still an increased risk of esophageal cancer in the highest DII category compared with the lowest DII category.
Conclusions: Our results inferred that DII was positively correlated with esophageal cancer risk and it could be used as a tool to predict the esophageal cancer risk and evaluate human health.
Abbreviations: DALYs = disability-adjusted life years, DII = dietary Inflammatory Index, EC = esophageal cancer, FFQ = Food Frequency Questionnaire.
Keywords: Dietary Inflammatory Index, esophageal cancer, inflammation, meta-analysis

1. Introduction
Esophageal cancer (EC), as the ninth most common cancer in the world, is a fatal disease. World Health Organization reported that 372,034 people developed esophageal cancer and 508,585 people died of EC in 2018.\cite{1} And about one third of disability-adjusted life years (DALYs) due to cancer were caused by EC, studies reported.\cite{2,3} These indicate that the incidence status, mortality status, and disease burden of EC are still very severe. Therefore, it is imperative to constantly study the etiology and find out the inducing factors of EC, and take this as a breakthrough point for prevention and treatment of EC.

To our knowledge, esophageal cancer is a disease caused by many factors. Except for genetic factors, environmental factors, nutrition and exercise factors, dietary factors are closely related to it.\cite{4} A scientific and reasonable diet is helpful to prevent the occurrence of esophageal cancer. Studies have shown that many food components can produce many bioactive substances related to chronic inflammation in the body.\cite{5-8} In recent years, an increasing number of studies have demonstrated that chronic inflammation plays an essential medium in the occurrence and development of tumor.\cite{9-12} We can use this as a pointcut to study the relationship between dietary factors and the esophageal cancer risk.

Dietary Inflammatory Index (DII), developed by Shivappa in 2014, could objectively describe the diet inflammatory potential, according to a large number of literatures, population data and the anti-inflammatory and pro-inflammatory effects of various dietary factors on 6 serum inflammatory markers.\cite{13} There are a total of 45 food components calculated for DII, including 9 pro-inflammatory components and 36 anti-inflammatory components.\cite{13} The calculation of DII needs to obtain dietary information from the Food Frequency Questionnaire (FFQ), to calculate the content of various food ingredients, and then calculate individual DII by specific formula according to the index of 45 Food ingredients. In a population, inflammatory potential of diet increased with the increase of DII score. Studies have identified that DII score is positively correlated with several
inflammatory factors, including TNF-α, CRP, homocysteine, and IL-6. Other studies have also indicated that serum inflammatory cytokines such as CRP and IL-6 are closely associated with several tumors risk. So we hypothesized that DII could be used to monitor dietary inflammation and health status.

Increasingly, researches were conducted on the connection between DII and esophageal cancer. And the relationship between DII and EC has not been reviewed. Therefore, our purpose is to conduct a systematic review on the relationship between DII score and esophageal cancer risk, to explore whether the DII could be used as a tool to predict the occurrence and development of esophageal cancer, and to determine the health status of people. It can provide theoretical basis for evaluating the status of dietary inflammation and predicting the occurrence and development of esophageal cancer.

2. Methods

2.1. Search strategy
The relative studies were searched mainly in PubMed, Cochrane library, Web of Science and other literature database. The main search strategy terms were as follows: (((dietary inflammatory index OR inflammatory diet OR the potential inflammatory of diet OR anti-inflammatory diet OR dietary score) AND (esophagus OR oesophagus)) AND (cancer OR carcinoma OR neoplasm OR tumor)). In addition, when we reviewed abstracts and full texts of relevant studies in the database, we searched for similar articles recommended by the database and the references of relevant studies. There were no restrictions on country and type of design, but only English articles published after 2014 (DII was proposed in 2014) were considered.

2.2. Inclusion and exclusion criteria
Inclusion criteria:
1. The literatures are retrospective studies or prospective studies.
2. The DII in the literature is measured by the original data.

Exclusion criteria:
1. The full text of the literature cannot be obtained.
2. Literature is a review.
3. The original text does not contain the descriptions of DII and esophageal cancer.

Studies that meet both of these inclusion criteria will be included. However, if the study met one of the exclusion criteria, they would be excluded.

2.3. Quality evaluation of included articles
Two authors (Liang Ou and Kai Li) reviewed the quality of selected articles by using Newcastle-Ottawa Scale (NOS) tool, including selection, comparability, and outcome assessment. Studies with a NOS score above 7 were considered as high-quality studies.

2.4. Data extraction
The information of included articles were extracted as follows:
First author, publication year, country, sample of size, sex, age, Food Frequency Questionnaire (FFQ) items, DII components, adjustments, Odds ratios (ORs), 95% confidence intervals (CIs).

In this study, we extracted the multivariate adjusted ORs and 95%CIs. For different ORs and 95%CIs levels, we only extracted the ORs and 95%CIs of the comparison between the highest and the lowest category of DII. When there were no overall ORs and 95%CIs in the article, only the classified ones could be obtained, then the ORs and 95%CIs of each related category were extracted respectively.

2.5. Ethical approval
Because this study is a meta-analysis and the data are based on previously published literature, ethical approval is not necessary.

2.6. Statistical analysis
The ORs and 95% CIs were combined by meta-analysis to evaluate the relationship between DII and risk of EC. The results of meta-analysis were presented by forest plot. Because DII score was used as continuous variables or categorical variables in studies and only 2 studies included continuous variables, we mainly performed statistical analysis on categorical variables. For articles containing multiple categories, the relevant categories were analyzed as independent studies. In this study, Cochrane’s Q test was used to identify the heterogeneity, P < .1 was regarded as significant heterogeneity. Inconsistency (I²) was used to evaluate the size of heterogeneity. I² ≤ 50% indicates low heterogeneity, using fixed-effect model. 50% < I² ≤ 75% suggests significant heterogeneity, utilizing random-effect model. And we had better to find out the sources of heterogeneity. I² > 75% meant that there was considerable heterogeneity among the studies, and it was rather necessary to explore and analyze the origins of heterogeneity.

To explore the origin of heterogeneity, subgroup analyses were carried out on published year, DII components, geographical location and study quality of relevant researches. In addition, sensitivity analysis was performed by removing the studies one by one, and new heterogeneity should be recorded when the studies were removed. Egger or Begger test should be used to detect the publication bias when ten or more researches were included, and P > .05 could be considered as no publication bias.

All of the statistical analyses and results display of this study were performed using STATA version 11.0.

3. Results

3.1. Study search and characteristics
In this study, 126 documents were retrieved according to the retrieval strategy. Among that, 34 articles were retrieved from PubMed, 39 articles from Cochrane Library, 23 articles from Web of Science, 30 articles from other databases. Twenty two duplicate articles were eliminated and 91 articles were excluded based on the title and abstract of literatures. Then, 13 literatures were obtained for full-text evaluation. Other 7 literatures unmatched the inclusion criteria were excluded (4 were reviews, 3 did not contain the description of esophageal cancer). Finally, 6 articles (8 studies) were obtained, all of which were case-control studies. The detailed process was displayed in Figure 1.

The included articles were published between 2015 and 2018, 8 case-control studies had 1961 cases and 3577 controls (Males:...
Table 1
Characteristics of 6 articles in the meta-analysis.

| First author [references], year, country | Study design | Cases, n | Total participants, n | Age | DII components (FFQ items) OR (95%CI) | Adjustments | NOS score |
|------------------------------------------|--------------|----------|-----------------------|-----|---------------------------------------|-------------|-----------|
| Shivappa,[24] 2015, Italy                | Case-control | 304      | 1047                  | 39–77 | Overall: High vs low: 2.46 (1.40–4.36); Continuous: 1.39 (1.25–1.54) | Age, Sex, Year of interview, Area of residence, Alcohol intake, Smoking status, BMI, Physical activity, Aspirin use | 7          |
| Shivappa,[25] 2015, Iran                 | Case-control | 47       | 143                   | 40–75 | Overall: High vs low: 8.24 (2.03–33.47); Continuous: 3.58 (1.76–7.26) | Age, Sex, Education, Physical activity, BMI, Smoking status, Gastroesophageal reflux | 7          |
| Lu,[26] 2015, Sweden                     | Case-control | 594      | 1155                  | 19–80 | Oesophageal squamous cell cancer: High vs low: 4.35 (2.24–8.43); Oesophageal adenocarcinoma: High vs low: 3.59 (1.87–6.89); Gastroesophageal junctional adenocarcinoma: High vs low: 2.04 (1.24–3.36) | Age, Sex, Total energy intake, Education, Smoking status, Alcohol intake, Physical activity, Gastroesophageal reflux, Helicobacter pylori infection | 6          |
| Shivappa,[27] 2017, USA                  | Case-control | 224      | 405                   | 64.3±11.2 | Overall: High vs low: 2.29 (1.32–3.96) | Age, Sex, Total energy intake, Smoking status, BMI, Occupation, Alcohol intake, NSAIDs use, Helicobacter pylori infection | 8          |
| Tang,[28] 2018, China                    | Case-control | 359      | 739                   | 61.0±11.4 | Overall: High vs low: 2.55 (1.61–4.06) | Age, Sex, Education, BMI, Total energy intake, Smoking status, Alcohol intake, Family history of cancer in first-degree relatives | 7          |
| Abe,[29] 2018, Japan                     | Case-control | 433      | 1729                  | 60±10.9  | Overall: High vs low: 1.71 (1.54–1.90) | Smoking status, Alcohol intake, flushing, phenotype, Number of teeth, occupation | 8          |

OR = odds ratio, CI = confidence interval, DII = Dietary Inflammatory Index, FFQ = Food Frequency Questionnaire, High vs low = the highest DII category compared with the lowest DII category, Continuous = DII is used as a continuous variable, NOS = Newcastle-Ottawa Scale.
All of the studies used Food Frequency Questionnaire (FFQ) to evaluate the dietary intake status, and 23 to 36 components of diet were used to calculate DII by using the method of Shivappa. The 6 articles were from 6 countries, including 1 from Iran, 1 from Italy, 1 from Sweden, 1 from USA, 1 from China and 1 from Japan. The detailed characteristics of relevant articles were shown in Table 1.

### 3.2. Quality assessment

The NOS score of 6 literatures ranged from 6 to 8 points, among which 5 articles with the NOS score ≥7 points were of high quality. The detailed NOS score of all relevant articles is shown in Table 1.

### 3.3. DII and esophageal cancer risk

As shown in the forest plots (Fig. 2). The risk of EC in the highest category of DII was 2.54 times higher than that in the lowest. The pooled OR of 8 studies was 2.54 (95% CI: 1.90–3.40; $I^2=65.7\%$, $P=.005$; Fig. 2).

### 3.4. Subgroup analysis and sensitivity analysis

Subgroup analyses were carried out to detect the sources of the heterogeneity in this study ($I^2=65.7\%$, $P=.005$). Subgroup analysis of published year showed significant heterogeneity in studies published in 2018 ($I^2=63.3\%$, $P=.099$) and no significant heterogeneity in studies published in 2015 ($I^2=35.7\%$, $P=.183$). There were significant heterogeneity in studies with <30 DII components ($I^2=63.8\%$, $P=.041$) and no significant heterogeneity in studies with ≥30 DII components ($I^2=25.1\%$, $P=.261$). Studies in Asia showed significant heterogeneity ($I^2=63.8\%$, $P=.041$), while studies in Europe showed no significant heterogeneity ($I^2=25.1\%$, $P=.261$). There were significant heterogeneity in studies of NOS score ≥7 ($I^2=58.0\%$, $P=.049$) and no significant heterogeneity in studies of NOS score <7 ($I^2=46.9\%$, $P=.152$). The detailed results of subgroup analysis were shown in Table 2. The results of subgroup analyses implied that the differences in published year, DII components, geographic location, study quality were not the source of heterogeneity in this study.

Sensitivity analysis was carried out to further identify the source of heterogeneity. We removed relevant studies one by one and recorded changes in heterogeneity. When Abes study was removed, the heterogeneity reduced ($I^2=12.8\%$, $P=.332$), while the heterogeneity did not change much when other studies were removed. The heterogeneity of meta-analysis after removal of a certain study is shown in Table 3. In the multivariate adjustment analysis, Abes study failed to include age and gender into the multivariate adjustment model and only 6 variables were included into the multivariate adjustment model. In addition,
the Food Frequency Questionnaire (FFQ) of the study was only 47 items, which was the least among the 8 studies. And Abes\cite{24} study was a gray literature, considering the result of sensitivity analysis, the study might be the source of heterogeneity in the meta-analysis.

Since less than 10 studies were included, publication bias could not be assessed.

4. Discussion

In this study, meta-analysis was performed on the relationship between DII and esophageal cancer risk in 6 articles (8 studies).\cite{24-28} The results suggested that the risk of esophageal cancer in the highest DII category was 2.54 times higher than that in the lowest (OR: 2.54, 95% CI: 1.90–3.40). Besides, regardless of the differences in published year, DII components, geographic location and study quality, the highest DII group had a higher risk of esophageal cancer than the lowest group. The results of our study are consistent with the meta-analysis on other cancers.\cite{29}

Nevertheless, in Abes study, DII was positively correlated with the risk of esophageal cancer.\cite{28} Therefore, we inferred that DII could be used as a tool to predict the risk of esophageal cancer and to evaluate the state of human health.

Dietary Inflammatory Index (DII) is an updated, low-consumption, novel, and readily available index, which can describe the state of dietary inflammation. DII has been shown to be positively correlated with some inflammatory factors such as CRP, TNF-α, IL-6, and homocysteine.\cite{14-16} Recently, a Japanese research also showed a similar correlation between DII and CRP levels.\cite{32} These inflammatory factors were closely related to the occurrence of chronic inflammation, which could promote the development of tumors.\cite{19,33}

A series of bioactive substances produced by diet could induce the occurrence of chronic inflammation in the body.\cite{5-8} Some rational explanations have been proposed for diet-induced inflammation. In the DII system, energy, carbohydrates, and total fats are considered as pro-inflammatory components that could induce system inflammation through increasing body weight.\cite{34} Saturated fatty acids (SFAs) could induce worse inflammation by promoting the activation and proliferation of NF-κB, protein kinase C, mitogen-activated protein kinases, and the induction of inflammatory genes.\cite{35} Trans fatty acids (TFAs) can increase the activation of TNF system\cite{36} and promote the production of CRP, IL-6 and other inflammatory factors, leading to systemic inflammation.\cite{37,38} Cholesterol promotes inflammation through accumulation in immune cells. And its mechanisms include activation of inflammasome, enhancement of toll-like receptor (TLR) signaling, production of monocytes and neutrophils in bone marrow and spleen.\cite{39} To our knowledge,

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**Table 2**

| Subgroup | Studies, n | Model | Pooled OR (95% CI) | Heterogeneity |
|----------|------------|-------|-------------------|---------------|
| All studies | 8 | Random | 2.54 (1.90–3.40) | 65.7 | .005 |
| Published year | | | | | |
| 2015 | 5 | Fixed | 3.06 (2.11–4.43) | 35.7 | .183 |
| 2017 | 1 | Fixed | 2.29 (1.32–3.97) | NA | NA |
| 2018 | 2 | Random | 1.95 (1.35–2.83) | 63.3 | .090 |
| DII components | | | | | |
| ≥30 | 4 | Fixed | 2.03 (2.01–3.97) | 25.1 | .261 |
| <30 | 4 | Random | 2.26 (1.54–3.31) | 63.8 | .041 |
| Geographic location | | | | | |
| Asia | 3 | Random | 2.38 (1.39–4.06) | 73.0 | .024 |
| North America | 1 | Fixed | 2.29 (1.32–3.97) | NA | NA |
| Europe | 4 | Fixed | 2.83 (2.01–3.97) | 25.1 | .261 |
| Study quality | | | | | |
| NOS score ≥7 (high quality) | 5 | Random | 2.25 (1.64–3.10) | 58.0 | .049 |
| NOS score <7 | 3 | Fixed | 3.04 (1.87–4.88) | 46.9 | .152 |

**OR** = odds ratio, **CI** = confidence interval, **DII** = Dietary Inflammatory Index, **NA** = not available, **NOS** = Newcastle-Ottawa Scale.

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**Table 3**

The heterogeneity of the meta-analysis after the following studies was removed.

| Studies | I² (%) | P value |
|---------|--------|---------|
| Shivappa,\cite{27} 2015, Italy | 69.2 | .000 |
| Shivappa,\cite{27} 2015, Iran | 62.7 | .013 |
| Lu,\cite{26} 2015, Sweden, Oesophageal squamous cell cancer | 57.1 | .030 |
| Lu,\cite{26} 2015, Sweden, Oesophageal adenocarcinoma | 63.5 | .012 |
| Lu,\cite{26} 2015, Sweden, Gastroesophageal junctional adenocarcinoma | 70.4 | .002 |
| Shivappa,\cite{27} 2017, USA | 69.8 | .003 |
| Tang,\cite{28} 2018, China | 67.7 | .005 |
| Abe,\cite{29} 2018, Japan | 12.8 | .332 |
saturated fats (SFAs) could be found in animal fats, palm oil, cocoa butter, coconut oil, etc. Trans fatty acids (TFAs) are widely found in margarine, cakes, cookies, fried foods, cheeses, etc. Cholesterol is present in meat, eggs and fish, especially in animal livers and egg yolk. We can reduce the occurrence of chronic inflammation by controlling our weight and decreasing the intake of these pro-inflammatory food components. What should remind especially is, we should take scientific and effective method when controlling weight, cannot be blind.

In the DII system, some possible explanations of some anti-inflammatory food components have also been proposed. Vitamin E and vitamin C could decrease system inflammation by reducing pro-inflammatory cytokine expression and decreasing oxidative stress.[16,40] N-3 fatty acids could increase anti-inflammatory effects by reducing the production of hydrogen peroxide and activation of NF-κB.[43] Zinc, an anti-inflammatory mineral, could decrease activation of NF-κB, TNF-α and IL-1β and increase the gene expression of double zinc finger protein, A20 and PPAR-α, which have anti-inflammatory effects.[42] Polyunsaturated fatty acids (PUFAs) can achieve anti-inflammatory effects through inhibiting the production of TNF-α and NO.[41] To take an example, the Mediterranean diet contains a great many of anti-inflammatory components such as monounsaturated fatty acids (MUFAs), omega-3, omega-6 polyunsaturated fatty acids (PUFAs), many vegetables, beans, and grains rich in various vitamins, which have anti-inflammatory effects on human body.[13,44–46] So we can increase the intake of such food components to make our body more anti-inflammatory.

There are some strengths in the study. This study is the first systematic review on the relationship between DII and esophageal cancer risk. Moreover, DII is used to describe dietary inflammation, which is more comprehensive and objective than a single nutrient. And DII could be used as a tool to screen esophageal cancer and conduct public nutrition interventions in the future. And it has important guiding significance to predict the risk of esophageal cancer and evaluate human health. However, there are several limitations in the study. First, all researches included in this study were case-control studies. DII was extracted from the FFQ based on participants self-reports, which might lead to a degree of recall bias. Second, there was substantial heterogeneity in this study, and it might be caused by the Abes study.[28] It might because Abes study[28] failed to include age and gender into the multivariate adjustment model and only 6 variable were included into the multivariate adjustment model. Besides, FFQ items in the study were the least among all the included studies and the study was a gray literature. Third, there were only 6 articles (8 studies) included in the study. Further research is required to include more studies in the future.

In conclusion, our results suggested that DII was positively correlated with esophageal cancer risk, that is, people with relatively high dietary inflammatory potential were more likely to develop esophageal cancer. Therefore, DII could be used as a tool to predict the risk of esophageal cancer and evaluate human health. We believe that, on the premise of ensuring reasonable nutrition, reducing the intake of pro-inflammatory food ingredients and increasing anti-inflammatory food ingredients have important guiding significance for preventing the occurrence of esophageal cancer.

**Author contributions**

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**Supervision:** Kai Li.
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**Writing – review & editing:** Liang Ou, Fengrong Ou.

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