Meta-analysis of the association between dietary inflammatory index (DII) and upper aerodigestive tract cancer risk

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Abstract

Background: Epidemiological studies have reported an inconsistent relationship between dietary inflammatory index (DII) and upper aerodigestive tract (UADT) cancer risk. However, no systematic review or meta-analysis has been reported up to now. To quantify the association between DII and UADT cancer risk, we performed this meta-analysis.

Methods: The PubMed, EMBASE, Web of Science and Cochrane Library database were searched for relevant studies from inception December 2018. All case-control studies investigating the association between DII and UADT cancer risk were selected.

Results: A total of 9 case-control studies were identified, involving 13,714 participants. The adjusted pooled OR of UADT cancer for the highest (the most pro-inflammatory diet) vs lowest (the most anti-inflammatory diet) DII categories were 2.27 (95% CI: 1.89–2.73). Subgroup analysis showed that individuals with the highest category of DII score were independently associated with esophageal cancer (OR = 2.53, 95% CI: 1.74–3.68), oral cavity cancer (OR = 2.23, 95% CI: 1.73–2.86), pharyngeal cancer (OR = 2.02, 95% CI: 1.54–2.64), and laryngeal cancer (OR = 2.05, 95% CI: 0.85–4.93).

Conclusion: This meta-analysis suggested that the most pro-inflammatory diets (the highest DII scores) are associated with increased UADT cancer risk. However, the association between DII and laryngeal cancer risk need to be further investigated.

Abbreviations: BMI = body mass index, CI = confidence interval, CRP = C-reactive protein, DII = dietary inflammatory index, FFQ = food frequency questionnaire, G-CSF = Granulocyte-colony-stimulating factor, G-CSFR = granulocyte colony-stimulating factor receptor, HR = hazard ratio, IL-6 = Interleukin-6, NOS = Newcastle-Ottawa quality assessment scale, OR = odds ratio, RR = risk ratio, TNF-\textalpha = tumor necrosis factoralpha, UADT = upper aerodigestive tract.

Keywords: dietary inflammatory index, meta-analysis, squamous cell carcinoma, upper aerodigestive tract cancer

1. Introduction

Upper aerodigestive tract (UADT) cancer is the sixth most frequent cancer and the most common cancer-related deaths in the world.\textsuperscript{[1]} The cancer stage is advanced in 75% to 80% of the cases at the time of diagnosis,\textsuperscript{[2]} and with a mean mortality rate of 46% in 5 years.\textsuperscript{[3]} UADT cancers are found at various sites of the head and Neck and majority are squamous cell cancers, which including: the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, and esophagus. However, the exact cause is unknown, tobacco smoking and alcohol consumption were the main risk factors. In addition, diet also plays an important role in the generation and development of UADT cancer. It has been reported\textsuperscript{[4]} that eating more vegetables and fruits can reduce the risk of cancer, while eating more red and processed meat increase the risk of cancer. Current evidence also indicates that diet can regulate the expression of inflammatory cytokines [such as C-reactive protein (CRP), Interleukin-6 (IL-6), tumor necrosis factoralpha (TNF-\textalpha), etc]\textsuperscript{[5]} and regulate the inflammatory process of the body. Meanwhile, relevant studies have also proved that chronic inflammation mediated by inflammatory cytokines is involved in all the pathological processes of malignant tumor, including the generation, development, invasion and metastasis, so chronic inflammation is also known as the eighth feature of malignant tumor.\textsuperscript{[6]} Based on this, the literature-derived dietary inflammatory index (DII) was developed to measure the inflammatory potential of diet.\textsuperscript{[7]} The current research indicates that DII has relation with the level of inflammation in the body,\textsuperscript{[8]} higher DII score is closely associated with the onset and development of certain diseases.\textsuperscript{[9]} Although most studies have shown that DII is related to the risk of UADT cancer, the strength of the correlation varies. Up to now, no meta-analysis investigating the association between DII and UADT cancer risk as well. Therefore, to quantify the association between...
DII and UADT cancer risk, the current meta-analysis combined all published data up to December 2018.

2. Materials and methods

2.1. Ethics statement

As all analyses were based on previously published studies, and no ethical approval or patient consent was required.

2.2. Protocol and registration

According to the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P),\[10\] the systematic review protocol was prepared and registered at the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42019119430.\[11\]

2.3. Search strategy

PubMed, EMBASE, Cochrane Library and Web of Science are going to be searched for studies published up to December 2018, and with using the keywords of (((case- control OR cohort OR prospective OR retrospective OR epidemiologic))) AND (((inflammatory potential of diet OR dietary inflammatory index OR anti-inflammatory diet OR pro-inflammatory diet)))) AND (((osphag* OR head and neck OR oral OR pharyn* OR laryn*))))) AND (((cancer OR tumor OR carcinoma OR squamous cell carcinoma)))).

Reference lists of reviews are also manually searched. No language restrictions.

2.4. Study selection

Studies meeting the following inclusion and exclusion criteria were applied.

Inclusion:
1. all cohort and case-control studies that reported on the association between dietary inflammatory index and upper aerodigestive tract cancer risk;
2. those provided the multivariable-adjusted risk ratio (RR), hazard ratio (HR), or odds ratio (OR) with corresponding 95% confidence intervals (CI) of upper aerodigestive tract cancer.

Exclusion:
1. studies that did not investigate the association between dietary inflammatory index and upper aerodigestive tract cancer risk;
2. reviews, case-reports, protocols, short-communications, personal opinions, letters, posters, conference abstracts, and laboratory research (in vivo and in vitro studies).

2.5. Data extraction and quality assessment

From each article, the following data was extracted in standard format: first author's surname, publication year, country of the study origin, cancer site, study design, sample sizes, number of cases/control studies), gender, age range or mean age, source of controls (for case-control studies), method of diet assessment, comparison of DII score, most fully adjusted risk estimate, during of follow-up (for cohort studies), and adjustment for confounding factors in the statistical analysis.

Study selection, extraction of study characteristics and quality assessment were independently performed by two reviewers (Hua and Liang). The selection process was performed in two phases. Phase-1 two blinded reviewers (Hua and Liang) screened the title and abstracts of all identified references. Phase-2, the same 2 reviewers applied the eligibility criteria to full-text articles, any disagreements were mutually discussed, and if necessary, a third reviewer was involved (Yang) to make a final decision. The methodological quality of the included studies was evaluated using a 9-star NOS.\[12\] This scale judges a study quality based on selection, comparability, and ascertaining of outcome. A study achieving 7 or more stars was considered to be high quality.

2.6. Statistical analysis

The multivariate-adjusted risk estimates were selected if they were reported in the original publication, otherwise the unadjusted risk estimates were calculated using the original data. ORs and 95%CI were considered as the effect size for all studies. We pooled OR estimates for the highest vs the lowest DII score. One study providing only the continuous OR was also included. The heterogeneity among studies was assessed using Cochrane Q and I-squared (I^2) statistic, defining a significant heterogeneity as Cochrane Q < 0.10 and /or I^2 > 50%. The fixed-effects model was selected when there is no significant heterogeneity was observed; otherwise the random-effects model was applied. Subgroup analyses were conducted by cancer site and region. Publication bias was assessed by funnel plots and the tests proposed by Egger linear regression\[13\] and Begg rank correlation\[14\] when more than 10 studies were retrieved.\[11\] A sensitivity analysis was conducted by removing individual studies each time to analyze the robustness of the pooling risk estimate. All statistical analyses were carried out in STATA version 12.0 (Stata Corp, College Station, TX).

3. Results

3.1. Search results

A total of 9 eligible studies\[16-24\] from 225 relevant articles were identified in this meta-analysis. After duplicates removed, 162 studies remained and needed to be further evaluated. After reviewing the title and abstract, 15 studies were retrieved. Six studies were subsequently excluded after reviewing the full text, for the following reasons: 1 study did not report the relevant outcome; 4 studies were reviews; and 1 study was esophageal adenocarcinomas, not squamous cell cancers. For the final meta-analysis, 9 studies met the inclusion criterion and were included. Flow chart of the study selection is presented in Figure 1.

3.2. Studies characteristics

The detailed characteristics of the 9 studies are showed in Table 1. All of these studies were case-control studies and published from 2015 to 2018, including 13,714 individuals at baseline with ages ranging from 19 to 80 years old. Of the included studies, seven studies were hospital-based controls, the other 2 studies were Swedish and North Carolina populations respectively. Most studies reported effects for mixed sex participants, whereas one study not available. Four studies were conducted in Italy,\[17-19\] and the other in Iran,\[16\] Sweden,\[25\] Japan,\[22\] USA,\[23\] and China.\[24\] The cancer types were represented in the included studies: 5 studies reported on esophagus cancer, 7 on pharyngeal
cancers (including 2 nasopharyngeal cancers, 2 hypopharyngeal cancers, 3 oropharyngeal cancers), 3 on oral cavity cancers, and 3 on laryngeal cancers. All of these studies used validated food frequency questionnaires (FFQs) to calculate DII score. The Newcastle-Ottawa Quality Assessment Scale (NOS) of 9 studies ranged from 6 to 8 stars and a mean score was 6.56, suggesting moderate methodological quality.

3.3. DII and UADT cancer risk
The adjusted pooled OR of UADT cancer for the highest (the most pro-inflammatory diet) vs lowest (the most anti-inflammatory diet) DII categories was 2.27 (95% CI: 1.89–2.73) in a random effect model. Meanwhile, significant heterogeneity between studies was revealed ($I^2 = 60.2\%$, $P<.001$) (Fig. 2).

3.4. Subgroup meta-analysis
Subgroup analysis stratified by cancer site and region. The pooled OR for the highest vs lowest DII score was 2.53 (95% CI: 1.74–3.68, $I^2 = 71.7\%$, $P = .007$) in esophagus cancer, 2.23 (95% CI: 1.73–2.86, $I^2 = 0.0\%$, $P = .844$) in oral cavity cancer, 2.02 (95% CI: 1.54–2.64, $I^2 = 20.3\%$, $P = .275$) in pharyngeal cancer, 2.05 (95% CI: 0.85–4.93, $I^2 = 85.6\%$, $P = .001$) in laryngeal cancer (Fig. 2); When stratified by region, the pooled OR was 2.11 (95% CI: 1.52–2.93, $I^2 = 61.9\%$, $P = .010$) in Asia, 2.19 (95% CI: 1.69–2.82, $I^2 = 46.8\%$, $P = .080$) in Europe, and 3.01 (95% CI: 2.23–4.05, $I^2 = 0.0\%$, $P = .690$) in USA (Fig. 3).

3.5. Sensitivity and publication bias analysis
Sensitivity analysis was performed for UADT cancer by omitting one study each time; the results showed that the overall pooled ORs were not influenced by any individual study (Fig. 4), suggesting that the results of this meta-analysis are stable. The Begg funnel plot and Egger test ($P = .025$) showed publication bias in the analyses between DII and UADT cancer (Fig. 5).

4. Discussion
Diet and chronic inflammation of the UADT have been suggested to be risk factors in the development of UADT cancer.$^{26–28}$ Therefore, the DII was developed to measure the inflammatory potential of individuals’ overall diet, and this meta-analysis indicates that there is a significant association between DII and UADT cancer risk (pooled OR = 2.27, 95% CI: 1.89–2.73). Participants with the highest DII score (the most pro-inflammatory diets) had a UADT cancer risk compared with those in the lowest DII score (the most anti-inflammatory diets). Furthermore, when the results were stratified by cancer site, a positive association was observed between DII score and increased the risk of esophagus cancer (pooled OR = 2.53, 95% CI: 1.74–3.68), oral cavity cancer (pooled OR = 2.23, 95% CI: 1.73–2.86), pharyngeal cancer (pooled OR = 2.02, 95% CI: 1.54–2.64), respectively. Our overall findings are in accordance with prior
### Table 1
Characteristics of studies included in the meta-analysis.

| Author/year | Country (Region) | Cases/Controls | Cancer Site | OR (95%CI) | DI score | % Female | Mean or Age Range | Source of Control | Dietary Assessment Tool | Adjustment Confounders | NOS Stars |
|-------------|------------------|----------------|-------------|------------|----------|----------|-------------------|-------------------|------------------------|------------------------|-----------|
| Shivpasha et al [16] 2015 | Iran (Asia) | 47/96 | Esophagus | 3.58 (1.76–7.26) | Cases: 1.81 ± 1.23 Controls: 0.76 ± 1.50 | Case: 62 Control: 60 | 40–75 | Hospital based | FFQ (125 items) | Age, energy, sex, BMI, education, physical activity, smoking gastroesophageal reflux, area of residence, education, smoking, alcohol drinking, BMI, physical activity, aspirin use | 6 |
| Shivpasha et al [17] 2015 | Italy (Europe) | 304/743 | Esophagus | 2.47 (1.40–4.36) | Cases: 0.47 ± 1.50 Controls: 0.19 ± 1.40 | Case: 9.50 Control: 20.20 | 39–77 | Hospital based | FFQ (78 items) | Age, sex, year of interview, education, smoking, alcohol drinking, BMI, physical activity, aspirin use | 6 |
| Lu et al [25] 2016 | Sweden (Europe) | 167/820 | Esophagus | 4.35 (2.24–8.43) | Cases: 1.04 to 1.46 | Not available | 19–80 | Swedish population | FFQ (63 items) | Age, sex, center, place of living, education, smoking, alcohol drinking, BMI, physical activity, aspirin use | 6 |
| Shivpasha et al [18] 2016 | Italy (Europe) | 460/1088 | Larynx | 3.30 (2.06–5.28) | Cases: 0.44 ± 1.41 Controls: 0.17 ± 1.41 | Case: 9.80 Control: 21.0 | 30–80 | Hospital based | FFQ (78 items) | Age, sex, center, education, BMI, tobacco smoking, alcohol consumption, non-alcohol energy intake | 6 |
| Shivpasha et al [19] 2016 | Italy (Europe) | 198/594 | Nasopharynx | 1.64 (1.06–2.55) | Cases: 0.28 ± 1.49 Controls: 0.09 ± 1.40 | Case: 20.70 Control: 20.70 | 52 | Hospital based | FFQ (78 items) | Study center, place of living, education, smoking, alcohol drinking, BMI, physical activity, aspirin use | 7 |
| Shivpasha et al [21] 2017 | Italy (Europe) | 946/2492 | Oral cavity, pharynx | 1.17 (1.10–1.25) | Cases: 0.45 ± 1.46 Controls: 0.17 ± 1.43 | Case: 20.10 Control: 39.90 | 58 | Hospital based | FFQ (78 items) | Age, sex, energy intake, center, place of living, education, BMI, physical activity, aspirin use | 6 |
| Guests et al [22] 2018 | Japan (Asia) | 506/1515 | Oral cavity | 2.08 (1.47–2.92) | Controls: 0.62 ± 1.25 | Case: 19.20 Control: 20.0 | 60 | Hospital based | FFQ (47 items) | Smoking, ethanol consumption, alcohol drinking, BMI, energy intake, occupation group | 7 |
| Guests et al [23] 2018 | USA | 50/153 | Nasopharynx | 4.99 (1.14–21.29) | Controls: 0.62 ± 1.10 | Case: 19.20 Control: 20.0 | 60 | North Carolina | FFQ (72 items) | Education, income, smoking, education, alcohol drinking, BMI, energy intake, occupation group | 8 |
| Guests et al [24] 2018 | China (Asia) | 359/380 | Esophagus | 2.55 (1.61–4.06) | Cases: 21.86 Control: 21.86 | Case: 20.10 Control: 39.90 | 58 | Hospital based | FFQ (137 items) | Age, sex, ethnic group, education, BMI, total energy intake, smoking status, alcohol drinking, family history of cancer in first-degree relatives | 7 |

95%CI = 95% confidence interval, OR = odds ratio, FFQ = food frequency questionnaire, BMI = body mass index, NOS = Newcastle–Ottawa Quality Assessment Scale.
reports showing that the highest DII score, as indicated by a pro-inflammatory diet, was associated with UADT cancer risk. However, the highest DII score is not related to laryngeal cancer risk (pooled OR = 2.05, 95% CI: 0.85–4.93), in contrast to the conclusions of previous studies.[18,23] This difference among studies may be the result of small sample sizes, region (Japan,[22] Italy,[18] and USA[23]) or other factors, the association between DII and laryngeal cancer risk need to be further investigated. And we found significant differences subgroups stratified by region, a stronger association among people between DII and UADT cancer risk from USA than those in Asia and Europe. One possible explanation is that the USA populations tend to Western dietary patterns, including the consumption of high fat, sweetened soft drinks, red meat, and fried foods, the European prone to relatively less red or processed meat and more vegetables intake.[29,30] Another possible reason is that the number of studies from USA is very limited.

Diet represents a complex set of exposures that often interact, and cumulative effects may modify both inflammatory responses and health outcomes.[31] Previous reports revealed protective effect of vegetable, fruits,[32,33] whole grains,[34] olive oil,[35] vitamin,[36,37] and fiber[18] whereas there appears to be a carcinogenic effect of red and processed meat,[39] fat[40] and carbohydrate[41] for UADT cancer. These foods and nutrients, all components of DII, have the potential to contributes to the excessive production of pro-inflammatory biomarkers such as CRP,[42] IL-6 and homocysteine.[43] Lee et al.[44] studied an adult population indicated that the individuals with a higher score for the “vegetable pattern” displayed a lower CRP concentration, as well as a higher antioxidant intake. Schwedhelm et al.[45] found processed meat consumption was positively associated with TNF-α, even after adjusting for fruit, green vegetable, and dairy consumption. Previous study indicated an enhancing effect of dietary n-3 polyunsaturated fatty acids on resolution of inflammation.[46] Vitamin C, as a regulator of cytokine redox-signal transduction in host defense cells and a possible role in controlling inflammatory responses.[47]

In the tumor microenvironment, inflammatory cells, inflammatory chemokines and cytokines regulate tumor growth, metastasis and differentiation.[48] Recent studies have pointed towards a role of tumor-infiltrating neutrophils in cancer biology, the study showed different degrees of neutrophil infiltration between T1-T2 and T3-T4 oral cancers, with higher indexes in the advanced lesions.[49] The balance between neutrophil survival and clearance is crucial to the resolution of inflammation. A major regulator of neutrophil production and survival is the cytokine granulocyte colony-stimulating factor (G-CSF).[50] G-CSF, a hematopoietic cytokine, regulates the proliferation and differentiation of granulocytic progenitor cells and functionally activated mature neutrophils.[51] and G-CSF can play a role in...
Figure 3. Forest plots showing OR with 95% CI of UADT cancer risk comparing the highest to the lowest DII score by region. CI = confidence interval, OR = odds ratio, DII = dietary inflammatory index, UADT = upper aerodigestive tract.

Figure 4. Sensitivity analysis was performed by omitting one study each time and recalculating the pooled OR estimates.
inflammation. Many studies have demonstrated the expression of G-CSFR in tumor cells or autocrine secretion of G-CSF in hematopoietic or non-hematopoietic tumors such as acute myeloid leukemia, squamous cell cancer. Chronic inflammation and tumor development form the inflammatory-cancer transformation chain, which influences and promotes each other. However, specific dietary components may reduce UADT cancer risk by influencing chronic inflammation.

In practice, it is important to know whether UADT cancer can be prevented by changing dietary patterns. The current meta-analysis plays an important part in clinical practice. The results of this analysis suggest that promoting diets rich in anti-inflammatory food components such as vegetables, fruits, whole grains, and low fats should help in preventing UADT cancer. Meanwhile, avoid consuming foods with pro-inflammatory properties, for example, High intake of refined carbohydrates, sweetened soft drinks, red and processed meats, and fried foods. The same is true for diagnosed UADT cancer patients to limit pro-inflammatory diets may contribute to reduce the recurrence. Therefore, future medical and social advice should focus on increasing the awareness of lifestyle changes, such as diet habits, and their effects on UADT cancer.

4.1. Limitations
There are several limitations to this meta-analysis. First, all included studies were case-control design. Case-control studies are subject to recall bias, selection bias, and reverse causation bias. These biases must be considered. Second, DII score is calculated using a validated food frequency questionnaire (FFQ), these were based on self-report questionnaire, therefore, it is difficult to rule out potential sources of information bias. Third, most of the control participants were selected from the hospital, the dietary habits of hospital controls may differ from those of general population or changes in dietary habits will be occurred. Fourth, the Begg funnel plot and Egger test (P = .025) suggested that publication bias was present in the results which may due to the limited studies in the current meta-analysis. Finally, statistically significant heterogeneity among studies was observed, which was likely to be attributed to the variation in cancer site and region. As a result, the use of random-effects model was allowed to take into account the heterogeneity among studies.

5. Future directions
Pro-inflammatory diet can induce persistent inflammation in the body, which may promote the development of cancer to some extent, and may also increase the risk of specific cancers in some parts of the body, while a proper diet can reduces chronic inflammatory response. Dietary patterns based on dietary inflammatory index can provide a direction for cancer prevention and control. However, it should also be noted that most of the current studies are limited to case-control studies, and there are few related intervention studies, so there are still many problems to be explored and deepened. It is expected that the future research will transition from etiology exploration to interventional research to examine etiology.

6. Conclusions
In conclusion, this is the first meta-analysis to examine DII and UDAT cancer risk. Significant positive associations were observed between higher DII and UDAT cancer risk. However, further large sample size and prospective epidemiological studies are needed to confirm the findings.

Author contributions
Conceptualization: Rongyu Hua.
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