

Association of Chinese sauerkraut consumption with esophageal cancer in Chinese populations: A meta-analysis

Dan Han

Minzu University of China

Shuang Liu

Minzu University of China

Kaige Liang

Minzu University of China

yaojiang huang (✉ yaojiangh@hotmail.com)

Minzu University of China <https://orcid.org/0000-0001-5409-5605>

Research

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Abstract

Background

With accumulating evidence showing that Chinese sauerkraut consumption may be associated with the developmental of Esophageal cancer.

Objective

We carried out a analysis by R to Evaluate whether the consumption of Chinese sauerkraut is associated with Esophageal cancer in Chinese populations.

Methods

Two independent investigators carry out a systematic search through Oct 8, 2019 for all studies. The search terms included Chinese sauerkraut, Chinese pickled vegetable, and Suancai, in combination with Esophageal cancer. Investigators extracted, pooled and analysed data from the included studies using a random-effects model in R.

Results

A random-effects meta-analysis of all 23 studies, including 32,259 unique participants, indicated that Chinese sauerkraut consumption is associated with a significantly increased risk of Esophageal cancer compared to controls (OR=1.81, 95% CI=1.50-2.19, P=0.00001). Sensitivity analysis showed that no single study significantly influenced the overall association. Most of the subgroup analyses, including those of subtype of EC, geographic area, publication language and year, demonstrated a statistically significant association between consuming Chinese sauerkraut and Esophageal cancer risk. Meta-regression indicated that gender and publication year is positively correlated with effect sizes. Furthermore, the trim-and-fill method used to adjust for funnel plot asymmetry in our meta-analysis confirmed that a positive outcome is unlikely to be due to publication bias.

Conclusion

The results of this meta-analysis provide evidence that consuming Chinese sauerkraut may increase the risk of Esophageal cancer.

Introduction

Esophageal cancer (EC) is the 8th most common cancer in the world and, with an estimated 456,000 new cases, ranked as the 6th leading of cancer death in 2012, with an estimated 400,000 cases [1]. In China, Esophageal cancer is the 5th most frequently diagnosed cancer with approximately 286,700 new cases in 2012, accounting for 62.87% of all EC cases worldwide. EC is the 4th most common cause of cancer-

related deaths in China, with approximately 211,000 deaths in 2012, according to the Chinese National Annual Cancer Registration Reports 5 [2].

Esophageal adenocarcinoma(EA) and Esophageal squamous cell carcinoma (ESCC) are the two predominant histological subtypes of Esophageal cancer. Esophageal adenocarcinoma is the predominant type of EC in North America and Europe, especially among white men [3]. Conversely, ESCC is the major subtype in China (more than 90% of all EC cases) [4]. Diet and environmental and genetic factors play important roles in the development of Esophageal cancer. Ecological studies have shown higher risks for EC in regions with a high intake of pickled food, Especially particularly the daily intake of pickled vegetables for 9–12 months in high-risk regions of China [5].

Suan Cai (also called suan tsai and Chinese sauerkraut) is a traditional Chinese pickled cabbage that is used for a variety of purposes. Suan cai is a unique form of pickled vegetable, and its production differs from that of other pickled vegetables (Pao cai, Jiang Cai, Yan Cai, Xian Cai, salted vegetable) due to the ingredients used and the method of production. Although Chinese sauerkraut may offer health benefits due to its fermentation process[6], many studies have reported that subjects who intake Chinese sauerkraut exhibit an increased risk for EC compared to controls in China, thus, the Intake of Chinese sauerkraut is considered a high risk factor for EC [7–16], but the epidemiological studies on this topic remain controversial. Therefore, we performed a systematic review and meta-analysis to investigate the association between consumption of Chinese sauerkraut and EC risk and performed meta-regression and subgroup analyses to adjust for possible confounders affecting the results.

Materials And Methods

Search Strategy and Study Selection

Two investigators (D.J. and Y.L.) independently performed systematic searches of peer-reviewed English and Chinese literature, including comprehensive searches of Harvard's HOLLIS+ (Harvard's Hollis + includes databases such as PubMed, EMBASE, PsycINFO, and Web of Science), Open Grey, Clinicaltrials, the Wanfangdata and China National Knowledge Infrastructure databases (CNKI) through Oct 8, 2019, for all studies published in English and Chinese. The English database search consisted of the following terms: (esophageal OR esophageal OR esophagus OR oesophagus) AND (cancer OR carcinoma OR adenocarcinoma OR neoplasm OR neoplasia OR neoplastic) AND (pickle OR pickled OR Chinese sauerkraut OR Suan Cai OR pickled cabbage OR pickled vegetable OR Chinese pickled vegetable OR pickled Chinese cabbage OR northeast sauerkraut) AND (china OR chinese). The Chinese database search consisted of the following terms: (Suan Cai or Chinese sauerkraut), and (Xiao Huadao or digestive tract) or (Shi Guan, esophagus or esophageal), and (Ai, cancer or carcinoma), or (Zhong Liu or tumor). Original studies reporting data on Esophageal cancer with case–control or cohort designs were included. The exclusion criteria for this meta-analysis were as follows: no necessary data, no risk estimates or crude numbers of cases and controls; review or meta-analysis articles; the method of pickling vegetables differed from that used for Chinese sauerkraut (Suan Cai, a kind of pickled vegetable), such as vegetable,

Preserved food, Preserved vegetables, Dried vegetables and Salted Vegetables and Pao cai, Jiang Cai, Yan Cai, Xian Cai; and overlapping data [17–20]. This study followed the guidelines from the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [21].

Data Extraction

Data on sample sizes (users and non-users by case and control), crude and adjusted odds ratios (OR) or risk ratios (RR), 95% confidence intervals (CI), and P-values were extracted by two independent investigators from the included studies as primary outcomes to generate effect sizes. We also extracted details about the author, study design, method of selecting controls, place and publication year, and sample source (eTable in the Supplement).

Statistical analysis

We used Review Manager (RevMan) (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) [22], R and RStudio (Version 1.1.442– © 2009–2018 RStudio, Inc.) [23] to perform statistical analyses. Effect sizes were calculated as an OR, generated by sample sizes, RRs and ORs. We used a random-effects models to evaluate the ORs and 95% CIs for all studies combined. When an individual study presented both crude and adjusted ORs and 95% CIs, we used the maximally adjusted results. Within- and between-study confounders were assumed to result in a difference of the real effect size; therefore, we chose a random-effects model to perform a meta-analysis [24]. We used a sensitivity analysis via leave1out study (RStudio software, Version 1.1.442) to evaluate whether an individual study influenced the results of the meta-analysis. Heterogeneity among studies was evaluated by the Mantel–Haenszel Method and the I^2 statistic. The impact of heterogeneity among studies was calculated by the I^2 values, with I^2 values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. In addition, we evaluated the relevant covariates by a random-effects meta-regression (RStudio software, Version 1.1.442) of effect sizes [21], including publication year, sample size, and gender (Male%). We conducted subgroup analyses by subtype of EC, geographic area, publication language and publication year.

Publication Bias

The funnel plot used to assess publication bias was performed with R metabias (method.bias="peters") and matabin (Mantel-Haenszel method). Further, we examined publication bias using the trim-and-fill method (RStudio software, Version 1.1.442) [23], which calculates the number of missing studies that would need to be added to the analysis to produce statistically insignificant results. All statistical analyses were conducted with Review Manager (RevMan) (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) [22], R and RStudio (Version 1.1.442– © 2009–2018 RStudio, Inc. metabias (metaresult, method.bias="peters") [23].

Results

We carry out a systematic search that produced 141 records from the English databases in HOLLIS+ (Harvard's Hollis + includes databases such as PubMed, PsycINFO, Embase and Web of Science), Open Grey and Clinicaltrials, 182 records from Chinese databases by Wanfang and CNKI, 16 dissertations from HOLLIS + and CNKI, and 3 additional records identified from the reference lists of retrieved articles. We examined abstracts of the selected articles and retrieved and reviewed the full text of those that were possibly eligible. Forty-five articles were identified for full-text analysis. We scrutinized these articles and excluded 22 due to a lack of necessary data [10, 15, 16], because the method of pickling vegetables differed from that of Chinese sauerkraut (Suan Cai) [25–27], or because the results were also reported in other publications [17–20]. Ultimately, 23 studies encompassing 8,223 cases and 24,036 controls [28–50] met the criteria for inclusion in our meta-analysis (Fig. 1).

Association of Chinese sauerkraut with Esophageal cancer

We carry out a meta-analysis using a random-effects model on the 23 extracted studies. A forest plot is shown in Fig. 2, illustrating that Chinese sauerkraut consumption correlates with a significantly increased risk for Esophageal cancer compared to controls (OR = 1.81, 95% CI = 1.50–2.19, $P = 0.00001$). No single study significantly influenced the overall association of Chinese sauerkraut consumption and risk of Esophageal cancer by sensitivity analysis (Fig. 3). Nevertheless, we observed significant heterogeneity among the studies in our meta-analysis ($\text{Tau}^2 = 0.17$; $\text{Chi}^2 = 161.02$; $\text{df} = 22$; $I^2 = 86\%$; $P < 0.00001$).

Investigation of Heterogeneity

We conducted subgroup analyses to explore the possible sources that explained the large heterogeneity. Six [33, 35, 36, 42, 47, 49] of the 23 studies in the meta-analysis were subtype ESCC, four [28, 38, 43, 48] studies were both subtype ESCC and EA, and the remaining 12 studies [29–32, 34, 37, 39–41, 44–46, 50] subtype were not available. Studies from subtype ESCC showed a marginally significant association (OR = 1.56; 95% CI, 1.39–1.76), Studies from both subtype ESCC and EA showed a highly significant association (OR = 2.02; 95% CI, 0.95–4.28), while the additional studies showed significant results (OR = 1.94; 95% CI, 1.46–2.57, Fig. 4a). Lowest heterogeneity among studies were found in 6 subtype ESCC studies ($\text{Chi}^2 = 0$; $I^2 = 0\%$), highly heterogeneity among studies were still found in 4 studies of both subtype ESCC and EA ($\text{Chi}^2 = 54.38$; $I^2 = 94\%$) and the other 13 studies ($\text{Chi}^2 = 20.29$; $I^2 = 88\%$). The summary ORs (95% CI) for studies from northern China [33, 34, 37, 43, 45, 46] and elsewhere were 2.22 (1.29–3.82) and 1.68 (1.37–2.06), and there was heterogeneity in northern China ($\text{Chi}^2 = 47.54$; $I^2 = 87\%$; $P < 0.00001$) and southern China ($\text{Chi}^2 = 110.98$; $I^2 = 86\%$; Fig. 4b). Then, the ORs (95% CIs) for studies retrieved from the English [29–32, 38, 40, 41, 47, 49, 50] and Chinese [28, 33–37, 39, 42–46, 48] literature was 1.47 (1.18–1.81) and 2.17 (1.62–2.91), respectively. We found high levels of heterogeneity among articles retrieved from English ($\text{Chi}^2 = 43.54$; $I^2 = 79\%$;) and Chinese literature ($\text{Chi}^2 = 83.88$; $I^2 = 86\%$;) (Fig. 5a). Further analysis of studies initiated in 2000 [35–50] or earlier [28–34] showed that compared to healthy controls, Chinese sauerkraut consumption significantly increased Esophageal cancer (Fig. 5b, OR = 1.5; 95% CI, 1.11–2.03 and OR = 1.93; 95% CI, 1.55–2.42). Again, we observed high levels of

heterogeneity among studies initiated in 2000 or earlier ($\text{Chi}^2 = 30.95$; $I^2 = 81\%$) or after 2000 ($\text{Chi}^2 = 92.05$; $I^2 = 84\%$).

To investigate the possible variables explaining the high levels of heterogeneity among studies, a meta-regression analysis was performed that included publication year, sample size, and gender (Male%) of each study. Of these possible variables, publication year and gender (Male%) positively correlated with effect sizes, but sample size has not moderating effects on the effect sizes by meta-regression analysis (Fig. 6).

Publication Bias

The funnel plots for assessment of publication bias by R metabias (method.bias="peters") and matabin (Mantel-Haenszel method) are shown in Fig. 7a. Visual inspection of dots appeared to be non-symmetric, which suggested publication bias. We further investigated publication bias using the trim-and-fill method to adjust for funnel plot asymmetry in our meta-analysis, which yielded significantly results (OR = 1.344; 95% CI, 1.10–1.63, Fig. 7b), thus confirming the positive outcome is unlikely to be caused by publication bias.

Discussion

Our overall analysis included a large body of studies, and we found significant associations between Chinese sauerkraut consumption and EC risk (OR = 1.81, 95% CI 1.50 to 2.19). Sensitivity analysis indicated that our results were not significantly influenced by any individual study. We investigated publication bias using R metabias, matabin and the trim-and-fill method and did not find a significant influence of publication bias, indicating that our outcome is unlikely to be caused by publication bias.

Despite the large heterogeneity between studies found in this meta-analysis, the strength of this work lies in the use of meta-regression analyses and subgroup analyses to adjust for possible moderators. Subgroup analyses that included subtype of EC, geographic area, publication language and publication year showed that none of our multiple subgroups essentially reduced heterogeneity. Although all subgroup analyses showed stronger associations of Chinese sauerkraut consumption and Esophageal cancer, we performed a meta-regression analysis that included gender (Male%), publication year, and sample size. As a result, publication year might have correlated with the effect sizes, which is reasonable because recent studies may be more rigorous and may have obtained richer data. Gender (Male%) have correlated with the effect sizes, because male sex is a well-known risk factors for EC.

The production of suan cai (Chinese sauerkraut) differs from that of other kinds of pickled vegetables in that the vegetable is compressed in the former. This is accomplished by placing a heavy weight such as a large rock on top of the cover of the container so that the Chinese cabbage inside the container is slowly pressed and anaerobically fermented over several weeks. Although pickled vegetables may offer health benefits due to the fermentation process [6], they may have adverse effects on EC risk due to the loss of

key nutrients such as antioxidants [51–53], thus allowing growth of fungi and yeasts [5, 54] that potentially generate N-nitroso compounds and mycotoxins [5, 55, 56], which are carcinogens. A number of studies have demonstrated the mutagenicity and carcinogenicity of Chinese sauerkraut [57–59]. All of Study explains why intake of Chinese sauerkraut may increase the risk of Esophageal cancer.

Regardless of its significant strengths, there are several limitations to this meta-analysis.

First, we chose a random effects model to mitigate the huge heterogeneity between studies in this meta-analysis, but this model has a limitation in that it does not strictly exclude the influence of heterogeneity [60]. In fact, the statistical significance of the results of the fixed-effect model and the random effect model was unchanged (OR = 1.81, 95% CI 1.50 to 2.19 in random effect model; OR = 1.51, 95% CI 1.41 to 1.60 in fixed-effect model) in this meta-analysis.

Second, in this study, we chose sauerkraut as the research object and excluded other types of pickled vegetables, which may have led to some limitations. Because China is home to a huge variety of pickled vegetables, including suan cai, la baicai, paocai, zhacai, Yan Cai, and Xian Cai, among many others, that are all considered "pickled vegetables". However, the production of Suan cai (also called suan tsai and Chinese sauerkraut) differs from that of other pickled vegetables due to the ingredients used and the method of production, It also means that Chinese sauerkraut and other types of pickled foods have different health effects; thus, they are difficult to group as a single food type to study the risk of Esophageal cancer.

Finally, as most of the data in this analysis come from case-control studies, the food intake data may be subject to recalls and interviewer bias. Due to the above limitations and biases, the summary statistics derived from this meta-analysis should be regarded cautiously.

Conclusion

This meta-analysis provides evidence that the risk of EC is associated with Chinese sauerkraut consumption. This result suggests that consumption of fresh vegetables rather than pickled vegetables is healthier. Furthermore, methods to improve the production process of Chinese sauerkraut are warranted to avoid the formation of carcinogens, such as N-nitroso compounds and mycotoxins.

Abbreviations

HOLLIS:The Harvard Library launched a new search tool; CNKI:National Knowledge Infrastructure; OR:odds ratios; EC:Esophageal cancer; EA:Esophageal adenocarcinoma; ESCC:Esophageal squamous cell carcinoma; RR:risk ratios; CI:95% confidence intervals.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

The authors agree for publication.

Availability of data and material

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

DH and SL contributed equally to this work. YH had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: DH, YH. Acquisition, analysis, or interpretation of data: DH, SL and KL. Drafting of the manuscript: DH, SL and KL. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: DH, YH. Obtained funding: YH.

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Figures



Figure 1

PRISMA Flowchart for the Literature Search. 23 studies encompassing 8,223 cases and 24,036 controls met the criteria for inclusion in our meta-analysis.



Figure 2

Forest Plot for Random-effects Meta-analysis. Forest plot for association between consumption of Chinese sauerkraut and esophageal cancer. Squares sizes are proportional to study weights. The diamond marker indicates pooled effect size.



Figure 3

Sensitivity Analysis. No single study significantly influenced the overall association of Chinese sauerkraut consumption and risk of esophageal cancer by sensitivity analysis.

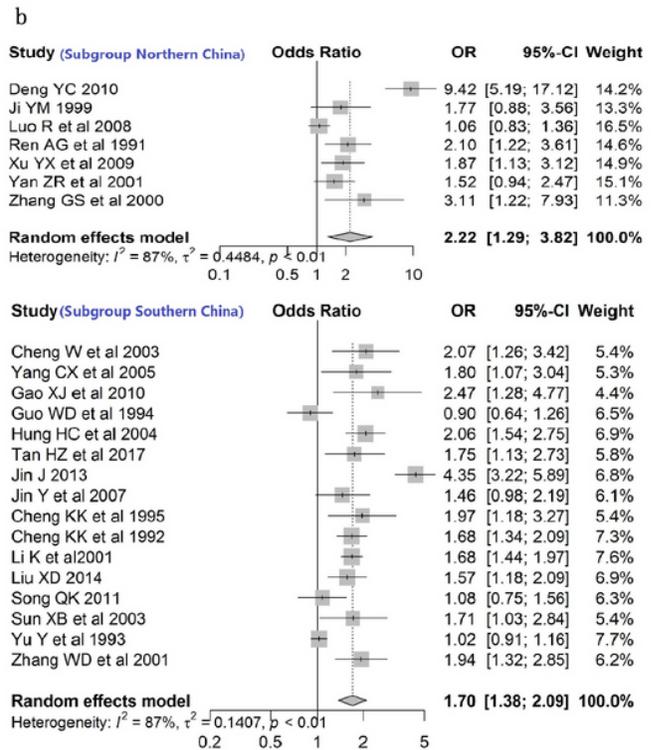
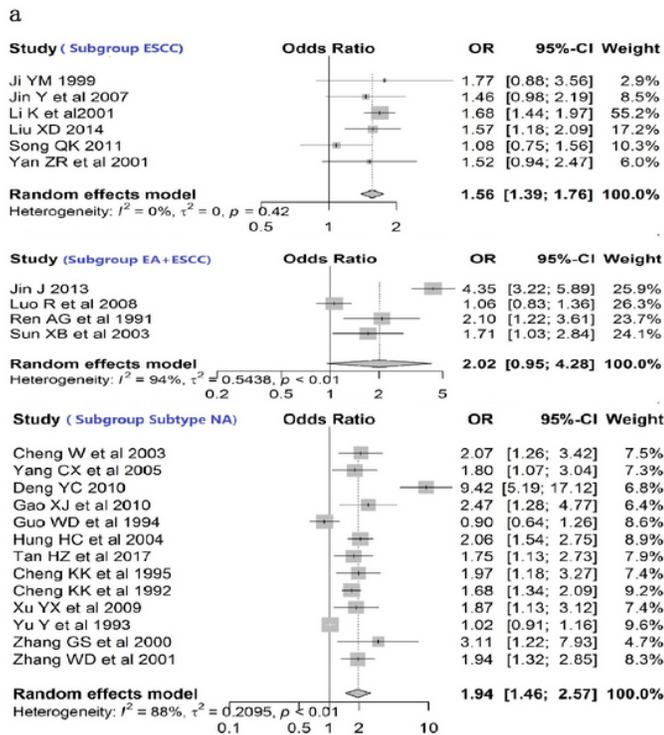


Figure 4

Forest Plot for Subtype and Geographic area Subgroup Analysis. The sizes of the squares are proportional to study weights. Diamond marker indicates pooled effect size.



Figure 5

Forest Plot for Publication language and year Subgroup Analysis. The sizes of the squares are proportional to study weights. Diamond marker indicates pooled effect size.

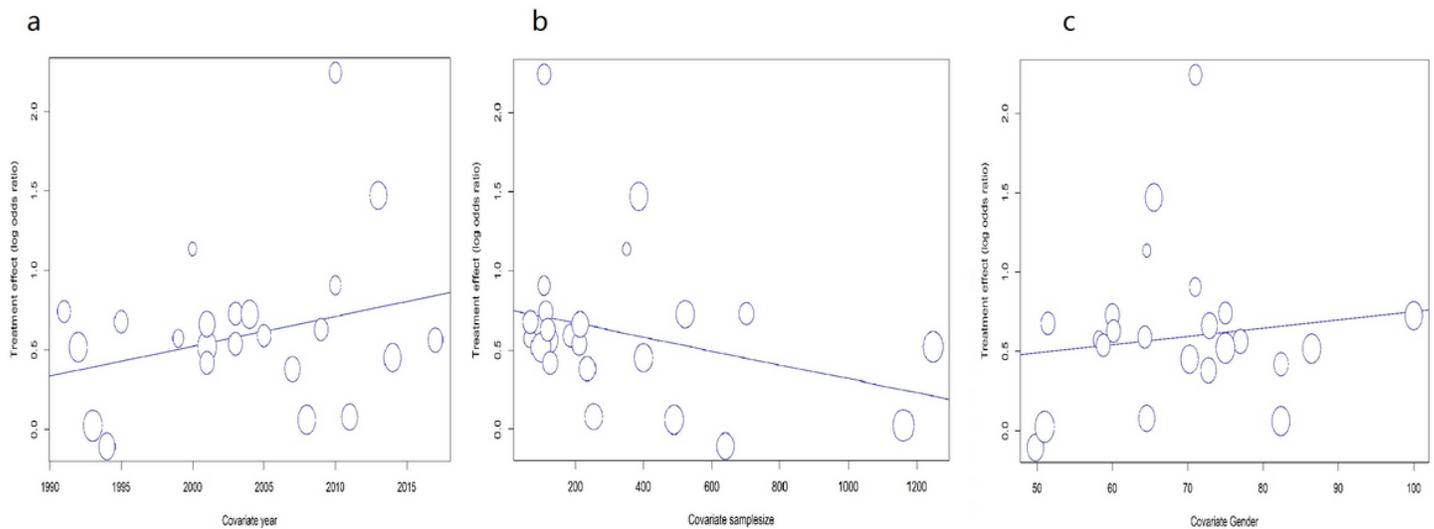


Figure 6

Meta-regression in all studies. Association between publication year (a), sample size (b), or gender (Male%) (c) and effect size (OR). The sizes of the circles are proportional to study weights.



Figure 7

Funnel Plots for assessment of publication bias. Visual inspection of dots appeared to be non-symmetric, which suggested publication bias in Figure 7a. We used the trim-and-fill method to adjust for funnel plot asymmetry in our meta-analysis, which yielded significantly results (OR = 1.344; 95% CI, 1.10-1.63, Figure 7b), thus confirming the positive outcome is unlikely to be caused by publication bias.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [eTable.Characteristics.pdf](#)