

## Original Article

# The correlation between chili pepper consumption and gastric cancer risk: A meta-analysis

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**Background and Objectives:** The correlation between chili pepper intake and gastric cancer (GC) risk has been controversial. We conducted a meta-analysis of 16 studies to provide updated evidence for this uncertainty. **Methods and Study Design:** Medline, and China National Knowledge Infrastructure (CNKI) databases were searched to obtain all qualified literature related to pepper consumption and GC incidence before June 2020. Random effects models were adopted to integrate the relative risk of individual studies. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the literature of each included study. Dose response meta-analysis was implemented through the one-stage robust error meta-regression (REMR) approach. **Results:** 16 studies (8337 cases) were included in quantitative meta-analysis. The pooled odds ratio (OR) of GC for the highest versus the lowest category of chili consumption were 1.51 (95% confidence interval [CI]=1.02-2.00) for all countries, 2.05 (95% CI=1.15-2.95) for Mexican, 2.03 (95% CI =0.71-3.34) for Colombian, 1.92 (95% CI=1.21-2.64) for Asian and 0.48 (95% CI=0.24-0.72) for other countries. Dose-response meta-analysis showed that there was a positive linear correlation between the risk of GC and the daily frequency of chili consumption. **Conclusions:** Significantly increased consumption of chili pepper or capsaicin has the potential to increase the risk of gastric cancer, however, inconsistencies still exist in subgroup analysis between different regions.

**Key Words:** chili pepper, capsaicin, gastric cancer, dose response, meta-analysis

## INTRODUCTION

Gastric cancer is still the fifth most frequently diagnosed cancer (more than 1,000,000 new cases in 2018) and the third leading cause of cancer-related deaths (estimated 783,000 deaths) worldwide.<sup>1</sup> Differences in diet and lifestyle habits can, at least in part, explain the discrepancies in GC incidence among various geographic regions, according to several immigration-related studies.<sup>2</sup> High intake of alcohol, salt, salting, preserved foods and low intake of fresh fruits and vegetables have been increasingly reported as unfavorable dietary patterns for GC.<sup>3,4</sup>

The pepper plant is a solanaceous plant native to the tropical regions of the Americas and is currently widely cultivated in Asia, Africa and the Mediterranean region.<sup>5</sup> It is mainly composed of a variety of hot and sweet peppers, including a total of 27 species, about 3000 varieties.<sup>6</sup> As a dietary seasoning or food ingredient, chili peppers are loved by people all over the world, because of its variety, spicy taste, aroma and extended food deterioration time. Chili peppers are rich in various chemical nutrients that are beneficial to the human body, e.g., capsaicinoids (capsaicin, 6,7-Dihydrocapsaicin and nordihydrocapsaicin), phenolics and flavonoids, carotenoids, Vitamin C and Vitamin E, etc.<sup>7,8</sup> However, the significant differences in the proportions of various chemical components existing in the varieties of peppers may lead to

distinctive biological effects. For example, the pungency and red colouration of red peppers are mainly attributed to the higher proportion of capsaicin, carotenoids capsaanthin and capsorubin.<sup>9</sup> In addition, green and yellow pepper, also known as sweet pepper, are closely related to the large amount of beta-carotene, lutein, chlorophyll pigments and violaxanthin.<sup>9</sup>

However, there are still many inconsistencies and uncertainties regarding the safety of chili peppers. For example, several epidemiological studies have claimed that chili pepper consumption could increase the risk of GC,<sup>10-19</sup> while other studies observed a certain protective effect.<sup>20-22</sup> In addition, a meta-analysis also reported two opposite effects of capsaicin,<sup>23</sup> that is, low-dose capsaicin had the protective effect of GC, but high-dose significantly increased the risk of GC. Due to its limited number of included studies, in order to further clarify the correlation

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between pepper consumption and GC risk between various regions, we supplemented some high-quality clinical studies of other countries in our meta-analysis.<sup>10,16,17,20,22,24,25</sup>

## METHODS

### Search strategy

According to Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines, we conducted a meta-analysis of chili consumption and GC risk.<sup>26</sup> LL and YJ independently conducted systematic literature search through Medline and CNKI databases up to June 2020. Keywords used for retrieval mainly include: (“piper nigrum” or “piper” or “nigrum” or “chili” or “chillies” or “chilli “ or “pepper “ or “chili pepper “or “chillies” or “spiciness” or “spicy” or “food”) and (“stomach neoplasms” or “gastric cancer” or “gastric neoplasms” or “stomach cancer” or “gastric adenoma” or “ stomach adenoma”). Reference lists of high priority papers and reviews were also examined and searched to obtain more pertinent articles.

### Study selection

Studies were included according to the following inclusion criteria: (1) Case-control or cohort study of pepper consumption and GC risk; (2) Exposure factor was chili or capsaicin consumption; (3) GC incidence as an observation outcome. Studies were excluded according to the following exclusion criteria: (1) Republished articles; (2) Incomplete extractable data.

### Data extraction

Three researchers (LL, JY and XHW) independently screened literature, extracted and cross-validated data. Differences and inconsistencies were eventually reached consensus through discussion. The following information were extracted from each article: last name of the first author, publication year, study design, country, number of subjects, follow up, evaluation method of chili consumption, estimates of the OR and their corresponding 95% confidence intervals (CIs) and covariates adjusted for in the analysis. If available, the OR with their corresponding 95% CIs for each classification of chili or capsaicin consumption were also extracted. Only the categories with the highest and lowest chili pepper consumption were retained for meta-analysis. Supplementary Table 1 shows the OR and 95% CIs of the highest category of chili consumption versus the lowest.

### Quality assessment

The risk of bias of included studies were independently evaluated by two reviewers (JY and XHW) using the NOS. Concisely, NOS was a 9-point scale, where 0-3, 4-6, and 7-9 points represented low, medium, and high quality studies, respectively.<sup>27</sup> The detailed evaluation process for each study was provided in supplementary materials.

### Statistical analysis

Random effects model was adopted to calculate ORs and 95% CIs for the comparison between the highest category of chili consumption versus the lowest. Heterogeneity between studies was assessed by Q-test (the significance

level of heterogeneous was  $p < 0.10$ ) and  $I^2$  statistic.  $I^2 < 50\%$  was considered that there was no significant heterogeneity between studies, and conversely, significant heterogeneity was existed. In order to identify the source of heterogeneity, we conducted a subgroup analysis based on the countries of studies. Publication bias was assessed by Egger’s and Begg’s tests ( $p < 0.05$  was considered representative of statistically significant) and by examination of funnel plots. The one-stage REMR approach was used for dose response meta-analysis due to its superiority compared with the currently widely used generalized least squares for trend (GLST) method.<sup>28</sup> Four studies consisting of the frequency of chili consumption were finally included in the dose-response meta-analysis. Detailed information (e.g., sample size, OR and 95% CIs) about the dose of pepper consumption is provided in Supplementary Table 2. All the statistical analyses were carried out with STATA software (version 14).

## RESULTS

### Search results

365 articles include 287 from Medline, 76 from CNKI and 2 from reference lists, which were finally identified according to the search strategy. 16 articles were considered eligible for quantitative meta-analysis after rigorous screening.<sup>10-18,20-22,24,25,29,30</sup> The detailed search steps and screening process are shown in Figure 1.

### Study characteristics

The characteristics of included studies are shown in Table 1. 16 studies consisting of 8337 cases were included in the meta-analysis of GC.<sup>10-18,20-22,24,25,29,30</sup> Of the 16 studies, 7 studies were conducted in Asia,<sup>10-12,15-17,30</sup> 4 in South America,<sup>20,22,24,25</sup> 4 in North America,<sup>13,14,18,29</sup> and 1 in Europe.<sup>21</sup> The FFQ was adopted by all studies to observe the basic demographic characteristics (name, age, gender, education, marriage, occupation and family history) and diet (chili consumption) of the subjects. The ORs with 95% CIs of 15 studies was about the effect of chili on the risk of GC incidence,<sup>10-13,15-18,20-22,24,25,29,30</sup> and only one study was about capsaicin.<sup>14</sup> Four studies reported the relationship between the frequency of chili intake and GC risk,<sup>12,17,18,29</sup> and they were further included in the dose-response meta-analysis. All included articles are of high quality with the NOS scores ranged from 7 to 9.

### Correlation between chili consumption and GC

In the current analysis, a significantly increased risk of GC was observed in the highest category of chili consumption, compared to the lowest category (OR=1.51, 95% CI=1.02–2.00) (Figure 2). Subgroup analysis based on geographic location was implemented due to significant heterogeneity in all studies ( $p=0$ ,  $I^2=71.9\%$ ). Subgroup analysis showed that there was a significant regional difference in the correlation between chili intake and GC risk. Among Asian and Mexican subpopulations, chili consumption was significantly positively correlated with GC risk with the pooled OR for GC risk comparing the highest versus lowest categories 1.92 (95% CI=1.21–2.64,  $I^2=48\%$ ,  $p=0.073$ ) for Asian, 2.05(95% CI=1.15–2.95,  $I^2=8.8\%$ ,  $p=0.349$ ) for Mexican (Figure 2). However, the other three regions suggested that chili consumption

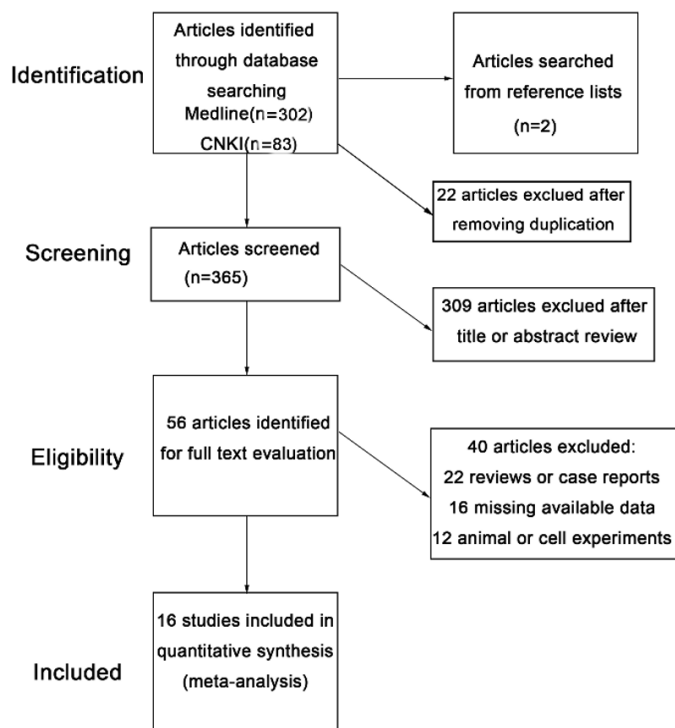


Figure 1. Flow chart of studies selection.

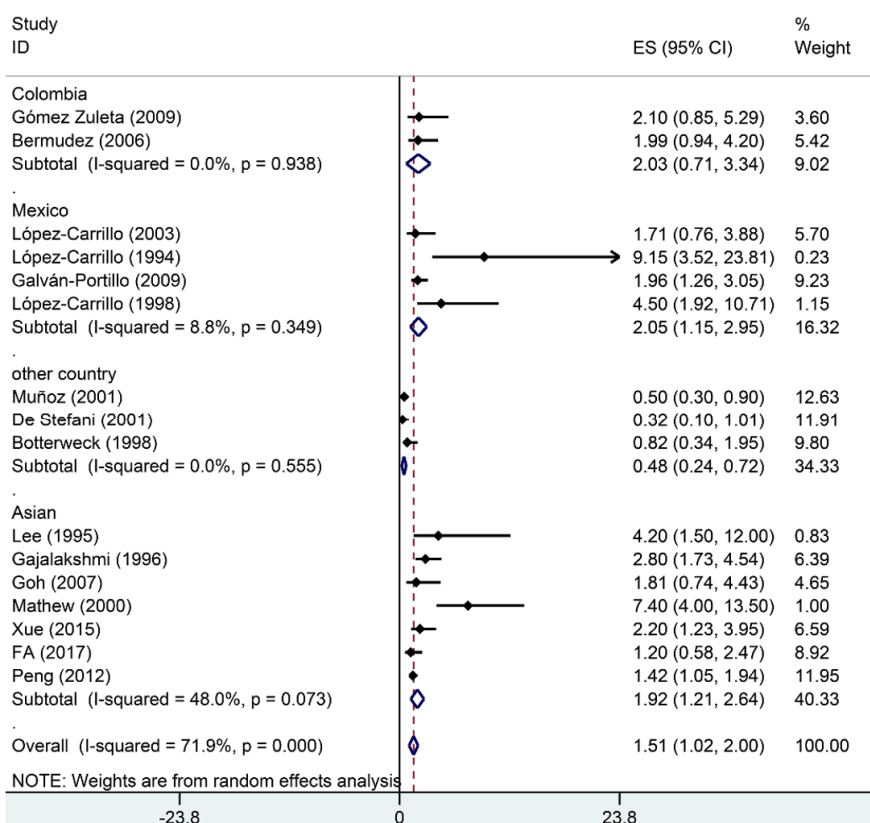


Figure 2. Forest plot for the pooled OR and 95% CI of studies investigating the effects of chili pepper consumption on gastric cancer according to different geographic region.

had a certain significant protective effect on the incidence of gastric cancer, with the pooled OR for GC risk comparing the highest versus lowest categories 0.48 (95% CI=0.24–0.72, I<sup>2</sup>=0%, p=0.555) (Figure 2). Although two Colombian studies showed a higher risk of GC in the highest chili consumption, no significant statistical differ-

ences were observed with the pooled ORs for GC risk comparing the highest versus lowest categories 2.03 (95% CI=0.71–3.34, I<sup>2</sup>=0%, p=0.938) (Figure 2). No significant publication bias was detected by Egger’s (p=0.594) and Begg’s test (p=0.753). No significant asymmetry was observed in Eggers funnel plots (Figure 3).

**Table 1.** Characteristics of 16 studies included in the meta-analysis

| Author and publication year         | Country     | Number of case/control | Adjusted OR (95% CI) | Study design   | Age (mean)           | follow up (year) | Assessment method | Adjustment for confounders   | NOS score |
|-------------------------------------|-------------|------------------------|----------------------|----------------|----------------------|------------------|-------------------|--|-----------|
| Gómez Zuleta, 2009 <sup>24</sup>    | Colombia    | 90/93                  | 2.1 (0.85-5.29)      | case control   | G: 60.5<br>C: 57.1   | 1                | FFQ               | age, sex, oven cooked food and roasted food consumption, gastric cancer history  | 8         |
| Bermudez, 2006 <sup>25</sup>        | Colombia    | 108/307                | 1.99 (0.94-4.2)      | case control   | G: 61.43<br>C: 52.84 | 4                | FFQ               | age, sex, tumor localization, education, gastric cancer history  | 8         |
| López-Carrillo, 2003 <sup>14</sup>  | Mexico      | 234/468                | 1.71 (0.76-3.88)     | case control   | G: 58.07<br>C: 57.55 | 2                | FFQ/HPLC          | age, sex, energy, schooling, fruit, vegetable, processed meat and alcohol consumption  | 9         |
| López-Carrillo, 1994 <sup>18</sup>  | Mexico      | 218/739                | 9.15 (3.52-23.81)    | case control   | G: 57.2<br>C: 59.2   | 1                | FFQ               | age, sex, total calories, fruits, vegetables, processed meat, beans, alcohol and salt consumption, cigarette smoking, SES, history of peptic ulcer | 7         |
| Galván-Portillo, 2009 <sup>29</sup> | Mexico      | 247/478                | 1.96 (1.26-3.05)     | case control   | G: 58<br>C: 58       | 1                | FFQ               | age, sex, education  | 8         |
| Muñoz, 2001 <sup>22</sup>           | Venezuela   | 292/476                | 0.5 (0.3-0.9)        | case control   | NA                   | 6                | FFQ               | age, sex, alcohol, tobacco, total calories and SES   | 9         |
| De Stefani, 2001 <sup>20</sup>      | Uruguay     | 160/320                | 0.32 (0.1-1.01)      | case control   | NA                   | 3                | FFQ               | age, sex, residence, urbanrural status, education, body mass index, and total energy intake.   | 7         |
| Lee, 1995 <sup>12</sup>             | Korea       | 213/212                | 4.2 (1.5-12)         | case control   | NA                   | 1                | FFQ               | age, sex, education, SES, residence, and mutually adjusted for the other dietary factors.  | 8         |
| Gajalakshmi, 1996 <sup>11</sup>     | India       | 388/388                | 2.8 (1.73-4.54)      | case control   | NA                   | 2                | FFQ               | age, sex, chewing habit, income group, educational and area of residence   | 8         |
| Goh, 2007 <sup>30</sup>             | Malaysia    | 87/174                 | 1.812 (0.741-4.432)  | case control   | G: 61.4<br>C: 58.9   | 0.5              | FFQ               | age, sex, race, education, cigarette smoking, salted fish, fresh fruits and vegetables   | 7         |
| Mathew, 2000 <sup>15</sup>          | India       | 194/305                | 7.4 (4-13.5)         | case control   | NA                   | 3                | FFQ               | age, sex, religion, education, income, smoking, alcohol habits   | 9         |
| Xue, 2015 <sup>17</sup>             | China       | 307/308                | 2.202 (1.226-3.953)  | case control   | G: 57.57<br>C: 57.62 | 1                | FFQ               | age, sex, gastric cancer history, alcohol, length of meal, dietary taste, preserved food consumption   | 7         |
| FA, 2017 <sup>10</sup>              | Yemen       | 70/140                 | 1.2 (0.58-2.47)      | case control   | G: 57.9<br>C: 57.6   | 0.5              | FFQ               | age, sex, education, family history, tobacco chewing   | 7         |
| Botterweck, 1998 <sup>21</sup>      | Netherlands | 265/2953               | 0.82 (0.34-1.95)     | cohort studies | NA                   | 6.3              | FFQ               | age, sex, smoking, education, stomach disorders, gastric cancer history, fruit or vegetable consumption  | 8         |
| López-Carrillo, 1998 <sup>13</sup>  | Mexico      | 220/752                | 4.5 (1.92-10.71)     | case control   | G: 57.2<br>C: 59.2   | 1                | FFQ               | age, sex, total calories, fruits, vegetables, salt, and processed meats, cigarette smoking, socioeconomic status, and history of peptic ulcer      | 7         |
| Peng, 2012 <sup>16</sup>            | China       | 224/224                | 1.425 (1.046-1.94)   | case control   | NA                   | 1                | FFQ               | age, sex, education, gastric cancer history  | 8         |

FFQ: food frequency questionnaire; OR: odds ratio; 95%CI: 95% confidence intervals; SES: socioeconomic status; NA: not available; G: gastric cancer; C: control; HPLC: high pressure liquid chromatography.

### Dose–response meta-analysis

Dose-response meta-analysis showed a significant linear and positive correlation between daily frequency of chili consumption and GC risk (Figure 4). The risk of GC increased by approximately 10% as the daily frequency of chili consumption increased to more than 2.1 times with estimated OR 1.10 (95% CI=0.11- 2.09).

### DISCUSSION

The current meta-analysis showed that a large amount of chili or capsaicin consumption significantly increased the overall incidence of GC by 1.51 times, but significant differences and even reverse trends appeared in individual regions in the subgroup analysis. Differences in genetic susceptibility and dietary preferences (different varieties of chili) between different regions could, at least partly, explain the completely opposite research outcome. The difference is observable in the type of pepper consumed by subjects in different regions, although the type of pep-

per in some studies is unknown (Supplementary table 1). For example, the subjects in Mexico prefer jalapenos and manzano (rich in capsaicin),<sup>13,14,18</sup> while sweet peppers (lack of capsaicin) are more popular in Netherlands.<sup>21</sup> In addition, the category criteria of high chili peppers consumption between the 16 studies are significantly different. For example, some studies define the criteria of high pepper consumption as more than once a day,<sup>22</sup> while 3-4 times a week in other studies.<sup>30</sup> Furthermore, distinctive methods for evaluating the magnitude of pepper consumption are also responsible for the conflicting results between studies. For example, compared with the high pressure liquid chromatography technology adopted by Mexico,<sup>13,14,18</sup> while other countries prefer a more subjective interview or questionnaire approach to classify the chili consumption of subjects into low, medium and high.<sup>10-13,15-18,20-22,24,25,29,30</sup>

In order to clarify the dose-effect relationship between chili consumption and GC risk, we implemented a dose-

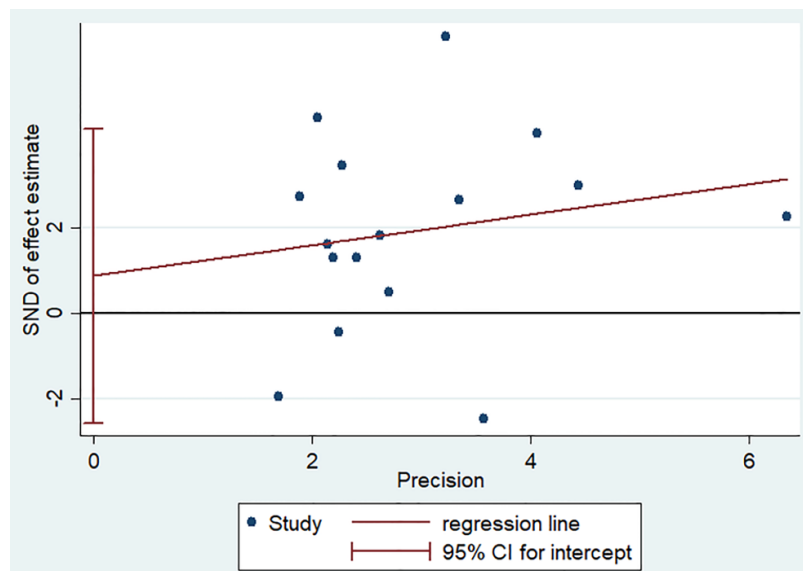


Figure 3. Publication bias was checked through Eggers funnel plots ( $p=0.594$ ).

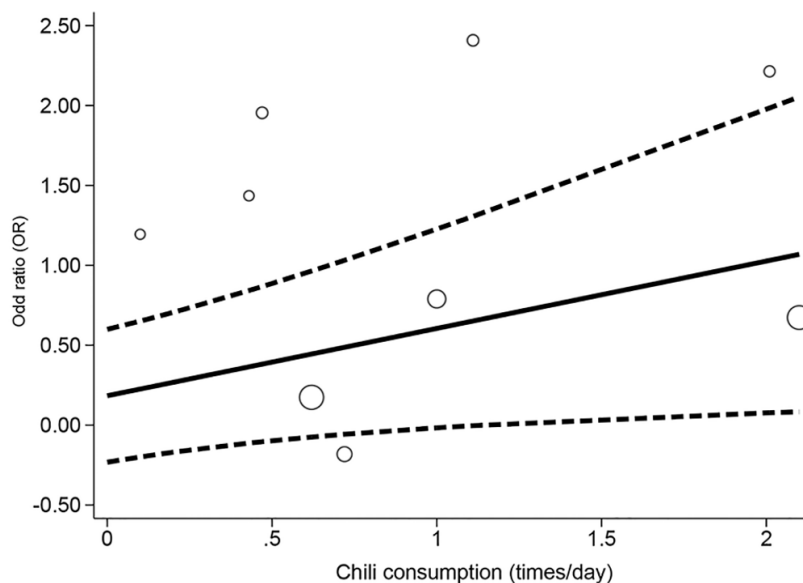


Figure 4. Linear dose-response meta-analysis model of chili pepper consumption (times/day) and gastric cancer risk ( $p$  linearity  $<0.05$ ). Solid line and long dashed lines represent OR and 95%CI, respectively.

response meta-analysis. As the daily frequency of chili consumption increased, we observed a significant increase in the incidence of gastric cancer. However, this result should be considered carefully because the daily frequency of chili consumption could not fully represent the daily consumption of capsaicin. Unfortunately, a dose-response meta-analysis of capsaicin consumption and GC risk could not be performed, as only one study provided clear capsaicin consumption.<sup>14</sup>

Chili is a crop originating from Mexico in South America, which is loved by people all over the world, but its safety, especially for gastric cancer, is currently receiving much attention.<sup>19</sup> For example, studies in Mexico by López-Carrillo et al. unanimously believe that chili consumption can be considered an independent risk factor for gastric cancer.<sup>13,14,18</sup> However, three studies suggested that chili consumption has no significant correlation with GC risk, and even has a protective effect.<sup>20,22</sup> The conflicting reports may be mainly due to differences in the scales of capsaicin consumption measurement used by subjects in each study. A meta-analysis also reported that low-dose capsaicin can reduce the risk of GC by 45%, while high-dose capsaicin consumption can increase GC by 1.9 times.<sup>23</sup> Contradictory results about the cocarcinogenic effect of capsaicin had also been found in experimental studies. In 2010, a study by cancer research showed that capsaicin could act as an adjunct cancer promoter through the EGFR dependent pathway to promote the development of skin cancer.<sup>31</sup> However, the accumulated evidence indicated that remarkable tumor suppressive effect of capsaicin had been observed in studies of various types of tumor cells, such as oral squamous cell carcinoma,<sup>32</sup> gastric cancer,<sup>33</sup> liver cancer<sup>34</sup> and bladder cancer cells.<sup>35</sup> Together, both clinical and experimental evidence indicate that the tumor-promoting effects of capsicum and capsaicin are still uncertain.

Some neglected confounding factors are worth pointing out in our meta-analysis. *Helicobacter pylori* (*H. pylori*) was considered to be a potential synergistic carcinogen for increased GC risk.<sup>36</sup> Therefore, a subgroup analysis based on *H. pylori* should be performed to confirm whether chili consumption is a risk factor for GC independent of *H. pylori* infection. However, only two studies tested *H. pylori* antibodies in the serum of subjects.<sup>14,30</sup> In addition, chili consumption had a certain correlation with the pathological type of gastric cancer, especially diffuse GC.<sup>14</sup> However, only 3 studies reported the relationship between different GC pathological types and chili consumption.<sup>13,14,29</sup> Due to these confounding factors, our conclusions should be drawn carefully.

In conclusion, our study confirmed that high-dose chili consumption is a potential risk factor for gastric cancer, but substantial differences exist in the subgroup analysis between different geographic regions. However, due to the potential confounding factors between the various studies, such as the inconsistency of the capsaicin detection method and the classification of chili consumption, which may reduce the credibility of the research results. Therefore, in order to further clarify the complex interaction relationship between chili consumption and GC risk, more and more well-designed large-scale epidemiological

studies that take into account the above-mentioned confounding factors need to be carried out all over the world.

#### AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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**Supplementary table 1.** Supplementary information of the 16 studies included in the meta-analysis

| Study                | OR    | Low 95%CI | Up 95%CI | T           | Type of chili pepper                                | Category criteria of high chili consumption |
|----------------------|-------|-----------|----------|-------------|---|---|
| Gómez Zuleta-2009    | 2.1   | 0.85      | 5.29     | Colombia    | unknown   | A   |
| Bermudez -2006       | 1.99  | 0.94      | 4.2      | Colombia    | unknown   | A   |
| López-Carrillo-2003  | 1.71  | 0.76      | 3.88     | Mexico      | 14 types including Jalapeno, Manzano, Serrano, etc. | 90-250mg/day(capsaicin)                     |
| López-Carrillo-1994  | 9.15  | 3.52      | 23.81    | Mexico      | 14 types including Jalapeno, Manzano, Serrano, etc. | >2.01 times/day                             |
| Galván-Portillo-2009 | 1.96  | 1.26      | 3.05     | Mexico      | unknown   | A   |
| Muñoz-2001           | 0.5   | 0.3       | 0.9      | Venezuela   | home-made   | ≥1 times/week                               |
| De Stefani-2001      | 0.32  | 0.1       | 1.01     | Uruguay     | red pepper  | A   |
| Lee-1995             | 4.2   | 1.5       | 12       | Korea       | red and black pepper                                | >2 times/day                                |
| Gajalakshmi-1996     | 2.8   | 1.73      | 4.54     | India       | unknown   | ≥1 times/day                                |
| Goh-2007             | 1.812 | 0.741     | 4.432    | Malaysia    | unknown   | >3-4 times/week                             |
| Mathew-2000          | 7.4   | 4         | 13.5     | India       | hot pepper  | B   |
| Xue-2015             | 2.202 | 1.226     | 3.953    | china       | local chili pepper                                  | ≥1 times/day                                |
| FA-2017              | 1.2   | 0.58      | 2.47     | Yemen       | sweet and chilli pepper                             | ≥1 times/day                                |
| Botterweck-1998      | 0.82  | 0.34      | 1.95     | Netherlands | sweet pepper  | >3-7 times/week                             |
| López-Carrillo-1998  | 4.5   | 1.92      | 10.71    | Mexico      | 14 types including Jalapeno, Manzano, Serrano, etc. | B   |
| Peng-2012            | 1.425 | 1.046     | 1.94     | china       | local chili pepper                                  | ≥4 times/week                               |

A: “yes” or “no” respectively represent the high or low category of chili peppers consumption; B: The high, middle and low categories of pepper consumption were assessed by the subjects themselves.

**Supplementary table 2.** Details of 4 studies used for dose response meta-analysis

| Id | Study                 | Dose (times/day) | Cases | Control | n   | OR    | Low 95% CI | Up 95% CI |
|----|-----------------------|------------------|-------|---------|-----|-------|------------|-----------|
| 1  | López-Carrillo -1994  | 0                | 9     | 145     | 154 | 1     |            |           |
| 1  | López-Carrillo -1994  | 0.47             | 68    | 220     | 288 | 7.06  | 2.84       | 17.54     |
| 1  | López-Carrillo -1994  | 1.11             | 82    | 204     | 286 | 11.11 | 4.43       | 27.84     |
| 1  | López-Carrillo -1994  | 2.01             | 59    | 170     | 229 | 9.15  | 3.52       | 23.81     |
| 2  | Lee-1995              | 0                | 18    | 49      | 67  | 1     |            |           |
| 2  | Lee-1995              | 0.1              | 93    | 126     | 219 | 3.3   | 1.2        | 9.9       |
| 2  | Lee-1995              | 0.43             | 102   | 37      | 139 | 4.2   | 1.5        | 12        |
| 3  | Galván-Portillo -2009 | 0.21             | 49    | 140     | 189 | 1     |            |           |
| 3  | Galván-Portillo -2009 | 0.62             | 95    | 203     | 298 | 1.19  | 0.77       | 1.84      |
| 3  | Galván-Portillo -2009 | 2.1              | 103   | 135     | 238 | 1.96  | 1.26       | 3.05      |
| 4  | Xue-2015              | 0.43             | 98    | 150     | 248 | 1     |            |           |
| 4  | Xue-2015              | 0.72             | 44    | 75      | 119 | 0.834 | 0.41       | 1.696     |
| 4  | Xue-2015              | 1                | 165   | 83      | 248 | 2.202 | 1.226      | 3.953     |



**Supplementary table 3.** Newcastle-Ottawa Quality Assessment Scale of case-control studies

| Study                | Is the case definition adequate? | Selection                       |                       | Definition of controls | Comparability   |   |
|----------------------|----------------------------------|---------------------------------|-----------------------|------------------------|---|---|
|                      |                                  | Representativeness of the cases | Selection of controls |                        | Comparability of cases and controls on the basis of the design or analysis (study adjusts for age, sex) |   |
| Gómez Zuleta-2009    | 1                                | 1                               | 0                     | 1                      | 2   | 2 |
| Bermudez-2006        | 1                                | 1                               | 1                     | 1                      | 2   | 2 |
| López-Carrillo- 2003 | 1                                | 1                               | 1                     | 1                      | 2   | 2 |
| López-Carrillo- 1994 | 1                                | 1                               | 0                     | 1                      | 2   | 2 |
| Galván-Portillo 2009 | 1                                | 1                               | 0                     | 1                      | 2   | 2 |
| Muñoz-2001           | 1                                | 1                               | 1                     | 1                      | 2   | 2 |
| Stefani-2001         | 1                                | 1                               | 0                     | 1                      | 2   | 2 |
| Lee-1995             | 1                                | 1                               | 0                     | 1                      | 2   | 2 |
| Gajalakshmi- 1996    | 1                                | 1                               | 1                     | 1                      | 2   | 2 |
| Goh-2007             | 1                                | 1                               | 0                     | 1                      | 2   | 2 |
| Mathew-2000          | 1                                | 1                               | 1                     | 1                      | 2   | 2 |
| Xue-2015             | 1                                | 1                               | 1                     | 1                      | 2   | 2 |
| FA-2017              | 1                                | 1                               | 0                     | 1                      | 2   | 2 |
| López-Carrillo-1998  | 1                                | 1                               | 0                     | 1                      | 2   | 2 |
| Peng-2012            | 1                                | 1                               | 0                     | 1                      | 2   | 2 |

| Study                | Ascertainment of exposure | Outcome   |   | Non-response rate | Score |
|----------------------|---------------------------|---|---|-------------------|-------|
|                      |                           | Same method of ascertainment for cases and controls |   |                   |       |
| Gómez Zuleta-2009    | 1                         | 1   | 1 | 1                 | 8     |
| Bermudez-2006        | 1                         | 1   | 1 | 0                 | 8     |
| López-Carrillo- 2003 | 1                         | 1   | 1 | 1                 | 9     |
| López-Carrillo- 1994 | 1                         | 1   | 1 | 0                 | 7     |
| Galván-Portillo 2009 | 1                         | 1   | 1 | 1                 | 8     |
| Muñoz-2001           | 1                         | 1   | 1 | 1                 | 9     |
| Stefani-2001         | 1                         | 1   | 1 | 0                 | 7     |
| Lee-1995             | 1                         | 1   | 1 | 1                 | 8     |
| Gajalakshmi- 1996    | 1                         | 1   | 1 | 0                 | 8     |
| Goh-2007             | 1                         | 1   | 1 | 0                 | 7     |
| Mathew-2000          | 1                         | 1   | 1 | 1                 | 9     |
| Xue-2015             | 1                         | 0   | 1 | 0                 | 7     |
| FA-2017              | 1                         | 1   | 1 | 0                 | 7     |
| López-Carrillo-1998  | 1                         | 1   | 1 | 0                 | 7     |
| Peng-2012            | 1                         | 1   | 1 | 1                 | 8     |

**Supplementary table 4.** Newcastle-Ottawa Quality Assessment Scale of cohort studies

| Study           | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis (study adjusts for age*, sex*) |
|-----------------|--|-------------------------------------|---------------------------|--|--|
| Botterweck-1998 | 1  | 0                                   | 1                         | 1  | 2  |

| Study           | Assessment of outcome | Outcome   |                                  | Total |
|-----------------|-----------------------|---|----------------------------------|-------|
|                 |                       | Was follow-up long enough for outcomes to occur | Adequacy of follow up of cohorts |       |
| Botterweck-1998 | 1                     | 1   | 1                                | 8     |

**Supplementary table 5.** The keywords and subject headings used to search

| Search number | Query   | Search Details   |
|---------------|---|--|
| 1             | (((((("piper nigrum") OR ("piper")) OR ("nigrum")) OR ("chili")) OR ("chilies")) OR ("chilli ") OR ("pepper ") OR ("chili pepper")) OR ("chillies")) OR ("spiciness")) OR ("spicy") | "piper nigrum"[All Fields] OR "piper"[All Fields] OR "nigrum"[All Fields] OR "chili"[All Fields] OR "chilies"[All Fields] OR "chilli"[All Fields] OR "pepper"[All Fields] OR "chili pepper"[All Fields] OR "chillies"[All Fields] OR "spiciness"[All Fields] OR "spicy"[All Fields]  |
| 2             | (((((("stomach neoplasms") OR ("gastric cancer")) OR ("gastric neoplasms")) OR ("stomach cancer")) OR ("gastric adenoma")) OR ("stomach adenoma"))                                  | "stomach neoplasms"[All Fields] OR "gastric cancer"[All Fields] OR "gastric neoplasms"[All Fields] OR "stomach cancer"[All Fields] OR "gastric adenoma"[All Fields] OR (("stomach"[MeSH Terms] OR "stomach"[All Fields] OR "stomachs"[All Fields] OR "stomach s"[All Fields] OR "stomachal"[All Fields] OR "stomaches"[All Fields]) AND ("adenoma"[MeSH Terms] OR "adenoma"[All Fields] OR "adenomas"[All Fields] OR "adenoma s"[All Fields]))   |
| 3             | #1 AND #2   | ("piper nigrum"[All Fields] OR "piper"[All Fields] OR "nigrum"[All Fields] OR "chili"[All Fields] OR "chilies"[All Fields] OR "chilli"[All Fields] OR "pepper"[All Fields] OR "chili pepper"[All Fields] OR "chillies"[All Fields] OR "spiciness"[All Fields] OR "spicy"[All Fields]) AND ("stomach neoplasms"[All Fields] OR "gastric cancer"[All Fields] OR "gastric neoplasms"[All Fields] OR "stomach cancer"[All Fields] OR "gastric adenoma"[All Fields] OR (("stomach"[MeSH Terms] OR "stomach"[All Fields] OR "stomachs"[All Fields] OR "stomach s"[All Fields] OR "stomachal"[All Fields] OR "stomaches"[All Fields]) AND ("adenoma"[MeSH Terms] OR "adenoma"[All Fields] OR "adenomas"[All Fields] OR "adenoma s"[All Fields]))) |