High Spicy Food Intake and Risk of Cancer: A Meta-analysis of Case–control Studies

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Abstract

Background: Studies on the association between spicy food intake and cancer risk have reported inconsistent results. We quantitatively assessed this association by conducting a meta-analysis based on evidence from case–control studies.

Methods: PubMed, EMBASE, and the Cochrane Library were searched for eligible publications. Combined odds ratios (*OR*s) with their 95% confidence interval (*CI*) were calculated using a random- or fixed-effects model. The methodological quality of the included articles was assessed using the Newcastle–Ottawa scale (NOS). All data were analyzed using STATA 11.0 software (version 11.0; StataCorp., College Station, TX, USA). Subgroup analyses were also performed with stratification by region, sex, number of cases, cancer subtype, source of the control group, and NOS score.

Results: A total 39 studies from 28 articles fulfilled the inclusion criteria for the meta-analysis (7884 patients with cancer and 10,142 controls). Comparison of the highest versus lowest exposure category in each study revealed a significant *OR* of 1.76 (95% *CI* = 1.35–2.29) in spite of significant heterogeneity ($P < 0.001$). In the subgroup analyses, this positive correlation was still found for gastric cancer, different regions, different numbers of cases, different sources of the control group, and high-quality articles (NOS score of ≥ 7). However, no statistically significant association was observed for women, esophageal cancer, gallbladder cancer, or low-quality articles (NOS score of <7). No evidence of publication bias was found.

Conclusions: Evidence from case–control studies suggested that a higher level of spicy food intake may be associated with an increased incidence of cancer despite significant heterogeneity. More studies are warranted to clarify our understanding of the association between high spicy food intake and the risk of cancer.

Key words: Cancer Incidence; Case–control Studies; Meta-analysis; Spicy Food

Introduction

Cancer is a major health problem worldwide and the leading cause of death in both more and less economically developed countries.[1,2] Based on GLOBOCAN estimates, about 14.1 million new cancer cases and 8.2 million cancer-related deaths occurred in 2012 worldwide.[3] Although many risk factors contribute to the development of cancer, including genetic variants,[4,5] obesity,[6] smoking,[7] poor diet,[8] physical inactivity,[9] and reproductive factors[10] (including lower parity and higher age at first birth), such risk factors account for only a small proportion of cancer cases. Thus, other unknown risk factors still need to be identified.

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Capsaicin (trans-8-metil-vanillyl-6-nonenamida) is the main pungent active substance of spicy foods such as chili, pepper, and kimchi. Consumed worldwide, capsaicin has

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a long and controversial history with respect to whether its consumption or topical application is entirely safe.[11] Conflicting epidemiologic data and basic research study results suggest that capsaicin can act as a carcinogen, cancer preventive agent,[12,13] or tumor promoter,[14,15] while other data suggest that it has chemopreventive and chemotherapeutic properties.[16,17] Several animal studies have been conducted to identify the association between capsaicin and cancer risk. Researchers have found that approximately 60% of rats fed a semisynthetic diet containing 10% chilies developed neoplastic changes in the liver.[18] In another experiment, mice fed a ≤0.25% capsaicinoid mixture in the diet for 79 weeks showed no evidence of carcinogenicity.[19] In human studies, researchers from Korea proposed that capsaicin alters the metabolism of chemical carcinogens and might promote carcinogenesis at high doses.[20] Mahfouz *et al*. and Wu *et al*.[21,22] reported positive relationship between spicy food and the risk of digestive tract cancer, whereas other studies showed no such relationship.[23] In addition, in four case–control studies, researchers found negative relationships between spicy food intake and cancer risk.[24-27] To address these discrepancies, we performed a meta-analysis of the association between the consumption of spicy food and cancer risk.

Methods

Search strategy

Two of the authors (Yu-Heng Chen and Xiao-Nong Zou) independently performed a systematic search of published articles using the PubMed, EMBASE, and Cochrane Library databases up to June 2017.We used the following search terms: "spicy or chili or chilli or pepper or capsaicin" and "cancer or carcinoma." We also reviewed the reference lists from the retrieved articles and those from previous review studies to identify additional relevant studies that may not have been identified by our database searches.

Inclusion and exclusion criteria

The inclusion criteria were (1) original articles, (2) case–control studies, (3) inclusion of odds ratio (*OR*) estimates with the corresponding 95% confidence interval (*CI*) for the association between spicy food intake and cancer, (4) publication in English, and (5) inclusion of at least two comparison groups. For duplicate publications, we only included the one with the most detailed and latest information for both the exposure and outcome. The exclusion criteria were (1) reviews, reports, clinical trials, and genetic and cell studies and (2) insufficient data.

Data extraction

Two reviewers independently extracted the relevant information from the identified studies, and disagreements were discussed and resolved by consensus. The following information was collected from each eligible study: first author's surname, publication year, country, study period, sex, exposure, numbers of cases and controls, types of cancer, comparison of exposure level (highest versus lowest), multivariate-adjusted *OR* with corresponding 95% *CI* for the highest and lowest categories of spicy food intake, and covariates adjusted in the statistical analysis.

Among the 28 articles included in our meta-analysis, 19 articles reported the associations between the two-level of spicy food intake and cancer risk and 9 articles[14,15,23,26,28-32] reported the associations between the multi-level of spicy food intake and cancer risk. Therefore, we distinguished two levels of spicy food intake in our study: highest and lowest. The categories of intake levels for spicy food were defined in accordance with the definition in the original articles. The lowest category was defined as the lowest level of spicy food intake (reference group), and in 18 articles, it was defined as low, bland, medium, <75 $g \cdot cu^{-1} \cdot month^{-1}$, or <1 time/week and so forth, while 10 articles[14,21,22,25,28,30,33-36] defined as "no" or never. The highest category was defined as the highest level of spicy food intake, and in 21 articles, it was defined as high, hot, ≥2 times/day, or 90–250 mg/d and so forth, while 7 articles[14,22,25,33-36] defined as "yes."

Quality assessment of the studies

Two reviewers independently evaluated the quality of the included case–control studies using the Newcastle–Ottawa scale (NOS).[37] Each study was broadly assessed based on selection, comparability, and exposure and was assigned a score ranging from 0 to 9. Studies with a score of ≥7 were considered to be of high quality.

Statistical analysis

We summarized the study-specific *OR*s and 95% *CI*s and compared the highest and lowest categories of spicy food intake for each study. Heterogeneity among the studies was estimated using the I^2 statistic. Pooled *OR*s were obtained using either a fixed-effects model (used in the absence of heterogeneity, $I^2 < 50\%$) or random-effects model (used in the presence of heterogeneity, $I^2 > 50\%$).[38]

To explore the potential heterogeneity among studies, we conducted subgroup analyses for population regions (Asian and non-Asian), sex (female and combined male/female), cancer subtypes (gastric cancer, esophageal cancer, gallbladder cancer, and other cancers), number of cases (≥200 and <200), source of the control group (community-based and hospital-based), NOS score (≥7 and <7), and the definition of spicy food (chili pepper and all spicy food).

We visually inspected the funnel plot symmetry and performed the Begg regression test and Egger linear regression test[39] to assess the potential of publication bias.[40] All statistical analyses were performed with STATA software (version 11.0; StataCorp., College Station, TX, USA). $P < 0.05$ was considered statistically significant.

Results

Study selection and study characteristics

In this study, we investigated the cancer incidence associated with consumption of spicy food. Figure 1 outlines the

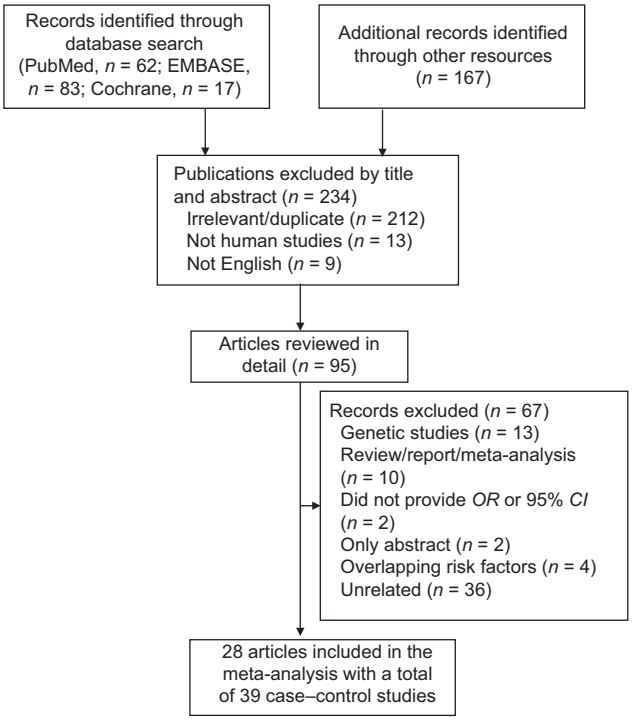

Figure 1: Flowchart of meta-analysis for exclusion or inclusion of individual articles. *OR*: Odds ratio; *CI*: Confidence interval.

initial search result of a total of 329 citations. After subjecting these citations to a series of exclusions, the meta-analysis included 28 articles.[14,15,21-36,41-50] In addition, since 7 articles[25,28,35,43,46,48,50] reported spicy food and cancer risk in different types of cancer, different types of spicy food, and different genders, they were considered as separate studies in the following data analysis. Therefore, a total 28 articles including 39 studies (7884 cases and 10,142 controls) were included in the final meta-analysis.

The characteristics of the 39 studies are shown in Table 1. All 39 studies involved case–control comparisons, including 17 community controls and 22 hospital controls. Twenty-eight studies were conducted among the residents of Asia, and 11 were from non-Asian regions. With respect to the number of cases, 18 studies included ≥200 subjects, and 21 included <200 subjects. In terms of cancer subtypes, 12, 9, 6, and 12 studies reported the association between spicy food and the risk of gastric cancer, esophageal cancer, gallbladder cancer, and other cancers, respectively. The NOS scores of all studies ranged from 5 to 9, and 29 studies had a score of ≥7.

Highest versus lowest intake of spicy food

Among the 39 studies included in the meta-analysis, 30 studies reported the associations between spicy food and cancer risk after adjustments and 9 studies[22,24,25,29,30,33,34,36] did not clarify whether adjustments have been done or not. Therefore, we extracted the adjusted data if possible and the data that was not specified as the crude or the adjusted in the 9 original studies was also extracted and included in the meta-analysis. The *OR* and 95% *CI* of each study in terms of the highest versus lowest spicy food intake is shown in Table 1. A forest plot of the 39 studies is shown in Figure 2. A random-effects model was applied, and it revealed a significantly positive association (*OR* = 1.76, 95% *CI* = 1.35–2.29). However, high heterogeneity was found among the studies (I^2 = 88.3%, *P* for heterogeneity <0.001).

Subgroup analyses

All spicy food

The categories of spicy food were defined in accordance with the definition in the original articles. In our study, "all spicy food" was defined as including chili pepper, undefined spicy food, spicy snacks, kimchi, spicy preserved meat, capsaicin, pepper-soybean in 39 studies. We conducted subgroup analyses for all spicy food. The highest category of spicy food intake was associated with cancer risk between the two different regions (Asian: *OR* = 1.66, 95% *CI* = 1.22–2.27; non-Asian: *OR* = 2.07, 95% *CI* = 1.25–3.43), numbers of cases (≥200: *OR* = 2.15, 95% *CI* = 1.45–3.18;<200: *OR* = 1.46, 95% *CI* = 1.03–2.08), and sources of the control group (community based: *OR* = 1.91, 95% *CI* = 1.19–3.07; hospital based: *OR* = 1.65, 95% *CI* = 1.20–2.29). We also found this positive association for gastric cancer (*OR* = 2.16, 95% *CI* = 1.26–3.71) and in high-quality studies (*OR* = 1.87, 95% *CI* = 1.40–2.48). There was no significant association between the highest category of spicy food intake and cancer in women (*OR* = 1.93, 95% *CI* = 0.72–5.23), esophageal cancer (*OR* = 1.43, 95% *CI* = 0.92–2.22), gallbladder cancer (*OR* = 1.78, 95% *CI* = 0.83–3.83), or low-quality studies (*OR* = 1.48, 95% *CI* = 0.74–2.97).

Chili pepper

The association between chili pepper consumption and the incidence of cancer was evaluated in 23 studies, which directly assessed chili peppers as a food item. Chili pepper included peppers, Hungarian sweet/hot pepper, red/green/undefined chili pepper, and chili/chillies. As shown in Table 2, chili pepper consumption showed a consistently positive association with both regions, case numbers of >200, esophageal cancer, community-based studies, and high-quality studies. However, no statistically significant association was observed between the highest category of spicy food consumption and cancer risk among women, a case number of <200, gastric cancer, gallbladder cancer, other cancer types, hospital-based studies, or low-quality articles.

Sensitivity analysis and publication bias

Sensitivity analyses were conducted to evaluate the effect of excluding any individual study. The pooled *OR* was not altered by exclusion of one study at a time in turn (data not shown). No publication bias was detected for spicy food (Egger's test: *P* = 0.714; Begg's test: *P* = 0.942) in the selected studies. The funnel plot was symmetrical [Figure 3].

Discussion

To the best of our knowledge, the current study represents the most comprehensive and up-to-date meta-analysis (39 case–control studies) of the association between high spicy food intake and cancer risk. The results showed that a

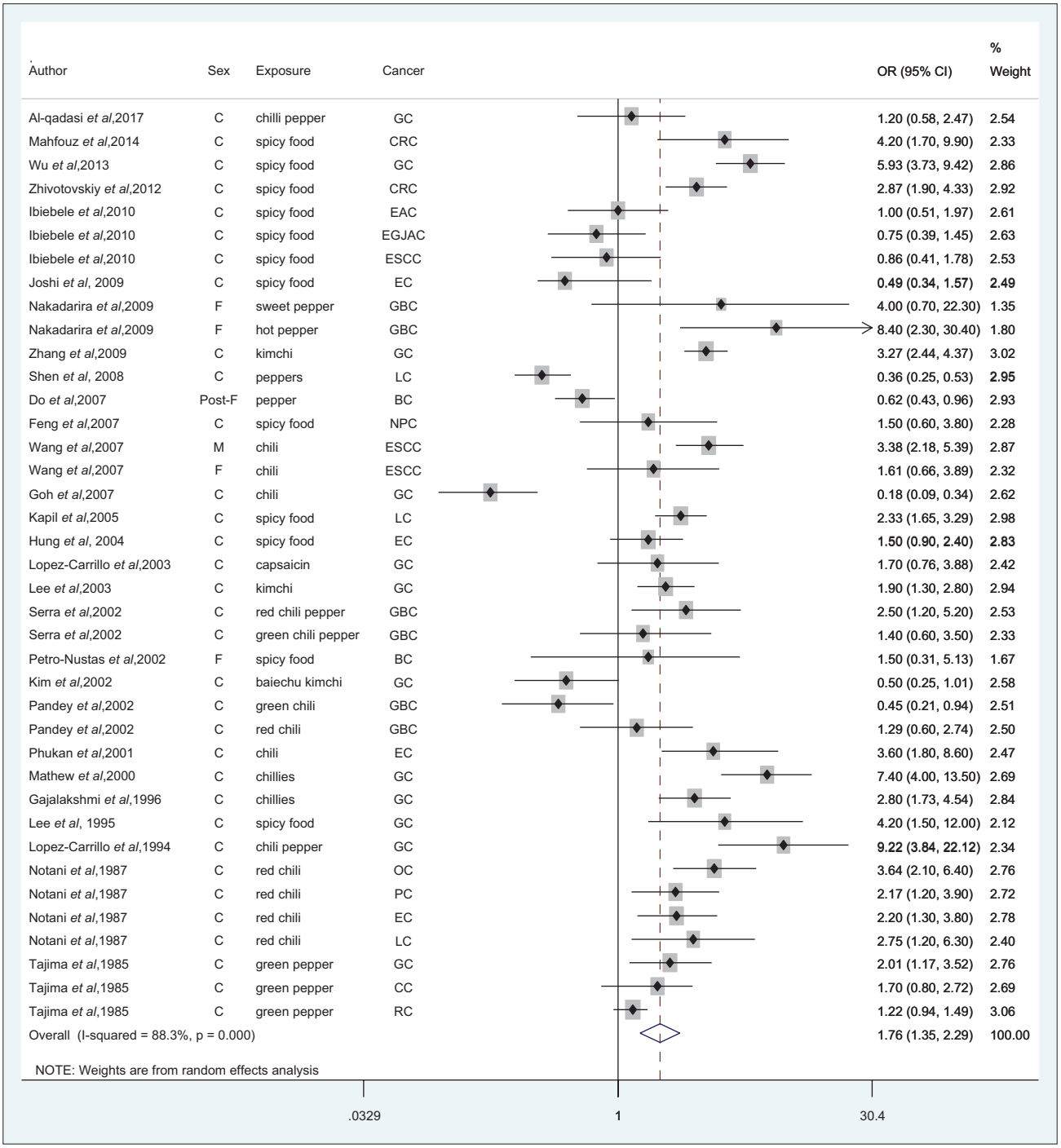

Figure 2: Forest plot of association between high spicy food intake and cancer risk.

high level of spicy food intake was significantly associated with cancer risk, and the association was consistent in most subgroup analyses. We found no association in women, esophageal cancer, or gallbladder cancer because of the limited numbers of such studies. Interestingly, in terms of cancer subtypes, high spicy food intake was only found to be associated with gastric cancer. We also assessed chili pepper as a food item to identify the association between chili pepper consumption and cancer risk. Consistent associations were found in different regions, case numbers of >200, esophageal cancer, community-based studies, and high-quality articles.

Several possible underlying mechanisms may link the consumption of spicy food and the incidence of cancer. Capsaicin is a primary pungent and irritating agent found in chilies and red peppers, which are widely used as spices in many cultures worldwide.[16] Several animal studies have shown a carcinogenic dose–effect relationship. For example, chili extract has been shown to promote the development of stomach and liver tumors in BALB/c mice initiated by methyl (acetoxymethyl) nitrosamine and benzene hexachloride. Capsaicin also has a cocarcinogenic effect on TPA-promoted skin

Table 1: Characteristics of studies included in the meta-analysis

Author, year	Country	Study period	Sex*	Exposure (all spicy food)	Number of cases/ controls	Types of cancer†	Comparison (highest vs. lowest)	Adjusted *OR* (95% *CI*)	Adjusted variables	NOS score
Al-Qadasi *et al*., 2017	Yemen	2014	C	Chili pepper	70/140	GC	Yes versus no	1.20 (0.58–2.47)	No description	6
Mahfouz *et al*., 2014	Egypt	2010–2011	C	Consumption of spicy food (e.g., chili)	150/300	CRC	Higher versus no	4.2 (1.7–9.9)	Red meat, preserved food, artificial sweeteners, fast foods, smoking, soft drinks, processed meat, pickles, tea, obesity, alcohol	8
Wu *et al*., 2013	China	2009–2011	C	Frequent ingestion of spicy food	501/523	GC	Yes versus no	5.93 (3.73–9.42)	No description	5
Zhivotovskiy *et al*., 2012	Siberia	2011–2012	C	Spicy food	185/210	CRC	Yes versus no	2.87 (1.9–4.33)	No description	5
Ibiebele *et al*., 2010	Australia	2001–2005	C	Frequency of consumption of spicy food (e.g., chili, curry, tabasco peppers)	286/1472 320/1472 238/1472	EAC EGJAC ESCC	1 per week versus never	1.00 (0.51–1.97) 0.75 (0.39–1.45) 0.86 (0.41–1.78)	Age, gender, cumulative history of smoking in pack-years, lifetime mean alcohol intake, heartburn and acid reflux symptoms, BMI in previous year, education status, aspirin use in previous 5 years, total fruit and vegetable intake, total energy intake in kilojoules	9
Joshi *et al*., 2009	India	2005–2006	C	Spicy food/snacks, etc.	94/94	EC	Too spicy versus mild or almost nil	0.49 (0.34–1.57)	No description	5
Nakadarira *et al*., 2009	Hungary		F	Hungarian sweet pepper	41/30	GBC	Yes versus no	4.0 (0.7–22.3)	Age	6
				Hungarian hot pepper	41/30			8.4 (2.3–30.4)		
Zhang *et al*., 2009	Korea	2000–2005	C	Kimchi (containing red pepper power)	471/471	GC	High versus low	3.27 (2.44–4.37)	Age, sex, total energy intake	7
Shen *et al*., 2008	China	1985–1990	C	Peppers	498/498	LC	Frequently versus rarely and sometimes	0.36 (0.25–0.53)	Age, sex, literacy, lung cancer in first-degree relatives, hours spent at home per day, nonmalignant lung disease history, coal mine work history, ever smoking, passive smoking, coal type at birth, having enough food	9
Do *et al*., 2007	Korea	1999–2003	Post-F	Pepper	163/316	BC	High versus low	0.62 (0.43–0.96)	Age, education, age at menarche, family history of breast cancer, age at first live birth, age at menopause, total duration of breastfeeding, physical activity,	7

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Table 1: Contd...

Author, year	Country	Study period	Sex*	Exposure (all spicy food)	Number of cases/ controls	Types of cancer†	Comparison (highest vs. lowest)	Adjusted *OR* (95% *CI*)	Adjusted variables	NOS score
									total menstruation period, BMI, alcohol consumption, cigarette smoking, frequency of exercise, total energy intake, fat intake, fruit intake, vegetable intake, Vitamins A, C, E, and vitamin supplementation	
Feng *et al*., 2007	Maghreb	2002–2005	C	Spicy preserved meet	636/615	NPC	≥10 times/ year versus <10 times/ year	1.5 (0.6–3.8)	Age, socioeconomic status, exposure to toxic substances	8
Wang *et al*., 2007	China	2004–2006	M F	Chili intake	223/252 132/156	ESCC	Often versus seldom	3.38 (2.12–5.39) 1.61 (0.66–3.89)	Age, marital status, education years	8
Goh *et al*., 2007	Malaysia		C	Chili intake	87/174	GC	Heavy versus low/none	0.18 (0.09–0.34)	No description	5
Kapil *et al*., 2005	India	2000–2002	C	Spicy food	305/305	LC	Yes versus no	2.33 (1.65–3.29)	No description	5
Hung *et al*., 2004	China	1996–2002	C	Spicy condiments (containing red pepper) at age ≥40 years	266/443	EC	≥1 time/week versus <1 time/week	1.5 (0.9–2.4)	Age, education levels, ethnicity, source of hospital, smoking, alcohol drinking, areca nut chewing	9
Lopez-Carrillo *et al*., 2003	Mexico	1994–1996	C	Capsaicin intake (mg/d)	234/468	GC	90–250 versus 0–29.9	1.7 (0.76–3.88)	Age, sex, energy, schooling, fruit intake, vegetable intake, processed meat consumption, tobacco smoking, alcohol consumption, other variables	8
Lee *et al*., 2003	Korea	1999	C	Kimchi (containing red pepper)	69/199	GC	≥2/day versus <2/day	1.9 (1.3–2.8)	Age, sex, education, family history of gastric cancer, smoking, drinking, *Helicobacter pylori* infection	7
Serra *et al*., 2002	Chile	1992–1995	C	Red chili pepper Green chili pepper	114/114 114/114	GBC GBC	>20 g/day versus <20 g/day	2.5 (1.2–5.2) 1.4 (0.6–3.5)	Low socioeconomic status, fried foods, schooling	8
Petro-Nustas *et al*., 2002	Jordan	1996	F	Spicy food	100/100	BC	Always versus never	1.5 (0.31–5.13)	No description	8
Kim *et al*., 2002	Korea	1997–1998	C	Baechu kimchi	136/136	GC	High versus low	0.50 (0.25–1.01)	Sex, age, socioeconomic status, family history, refrigerator use	7
Pandey *et al*., 2002	India		C	Green chili Red chili	64/101 64/101	GBC	Yes versus no	0.45 (0.21–0.94) 1.29 (0.6–2.74)	No description	5
Phukan *et al*., 2001	India	1997–1998	C	Chili intake	502/1004	EC	Very high versus moderate chili intake	3.6 (1.8–8.6)	Education, income, chewing betel nuts and tobacco, smoking, alcohol use	9

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Table 1: Contd...

Author, year	Country	Study period	Sex*	Exposure (all spicy food)	Number of cases/ controls	Types of cancer†	Comparison (highest vs. lowest)	Adjusted *OR* (95% *CI*)	Adjusted variables	NOS score
Mathew *et al*., 2000	India	1988–1991	C	Chillies	194/305	GC	Very hot versus bland	7.4 (4.0–13.5)	Age, sex, religion, education, smoking, alcohol habits	9
Gajalakshmi *et al*., 1996	India	1988–1990	C	Chillies	388/388	GC	Hot versus medium	2.8 (1.73–4.54)	Chewing habit, factors significant in the multivariate model of dietary item analysis, income group, educational level, area of residence	7
Lee *et al*., 1995	Korea	1990–1991	C	Hot pepper-soybean paste stew	213/213	GC	≥2–3 times/ week versus none or 4–5 times/ year	4.2 (1.5–12.0)	Age, sex, education, economic status, residence, mutually adjusted for the other dietary factors	8
Lopez-Carrillo *et al*., 1994	Mexico	1989–1990	C	Chili pepper consumption	220/752	GC	Yes versus no	9.22 (3.84–22.12)	Age, sex, fruit, vegetables, processed meat, beans, alcohol, salt added after cooking food, cigarette smoking, socioeconomic status, history of peptic ulcer, chili pepper consumption variable of internet	9
Notani *et al*., 1987	India	1976–1984	C	Red chili powder use, $g \cdot cu^{-1} \cdot month^{-1}$	278/177	OC	≥75 versus <75	3.64 (2.1–6.4)	Age, tobacco habits	8
					225/177	PC		2.17 (1.2–3.9)		
					80/177	EC		2.20 (1.3–3.8)		
					215/177	LC		2.75 (1.2–6.3)		
Tajima *et al*., 1985	Japan	1981–1983	C	Green pepper	93/186	GC	≥1 per week versus <1 per week	2.01 (1.17–3.52)	Age, sex	7
					42/186	CC		1.70 (0.80–2.72)		
					51/186	RC		1.22 (0.94–1.49)		

*M: Male; F: Female; Post-F: Postmenopausal females; C: Combined males and females. †Types of cancer: BC; GC; CRC; EAC; EGJAC; ESCC; EC; GBC; NPC; LC; OC; PC; CC; RC. BC: Breast cancer; GC: Gastric cancer; CRC: Colorectal cancer; EAC: Esophageal adenocarcinoma; EGJAC: Esophagogastric junction adenocarcinoma; ESCC: Esophageal squamous cell carcinoma; EC: Esophageal cancer; GBC: Gallbladder cancer; NPC: Nasopharyngeal carcinoma; LC: Laryngeal cancer; OC: Oral cancer; PC: Pharyngeal cancer; CC: Colon cancer; RC: Rectal cancer; BMI: Body mass index; NOS: Newcastle–Ottawa scale; *CI*: Confidence interval; *OR*: Odds ratio.

carcinogenesis *in vivo*; this is mediated through the transient receptor potential vanilloid subfamily number 1 and the tyrosine kinase epidermal growth factor receptor. In the present meta-analysis, 19 studies indicated that high-level consumption of capsaicin-containing foods was associated with an increased risk of cancer. We believe that these results are credible because the pooled *OR*s from 39 articles and subgroup analyses indicated a significantly positive association between high spicy food intake and cancer risk.

In past decades, the anticancer activity of capsaicin has been broadly investigated for a variety of cancer types. Briefly, the anticancer mechanisms of capsaicin include activation of apoptosis,[51] cell growth arrest,[52] and inhibition of angiogenesis[53] and metastasis.[54] Capsaicin stimulates the anti-tumorigenic/tumor-suppressive signaling pathway and related transcription factors, whereas it inhibits oncogenic signaling pathways and tumor promoters. In addition, capsaicin synergistically interacts with other cancer-preventive agents, providing the possibility for the use of capsaicin in cancer therapy with other chemotherapeutic agents.[55] In the population-based prospective cohort study in China by Lv *et al*.,[56] compared with those who ate spicy food less than once a week, those who consumed spicy food almost every day had a 14% lower risk of death, and inverse association was also observed for deaths due to cancer. Among the 39 studies included in our meta-analysis, 4 studies reported a negative association; however, when we summarized the estimate of high spicy food intake and cancer risk, this negative association was no longer present. These intrinsic differences in different populations and different research emphases may partly explain the above controversies.

Table 2: Subgroup analyses of association between high spicy food intake and cancer risk

Subgroups	All spicy food				Chili pepper			
	Number of studies	*OR* (95% *CI*)	I^2 (%)	$P_{Heterogeneity}$	Number of studies	*OR* (95% *CI*)	I^2 (%)	$P_{Heterogeneity}$
Regions								
Asian	28	1.66 (1.22–2.27)	90.6	<0.001	18	1.53 (1.01–2.32)	91.1	<0.001
Non-Asian	11	2.07 (1.25–3.43)	73.7	<0.001	5	3.84 (1.77–8.33)	65.1	0.022
Sex*								
F	5	1.93 (0.72–5.23)	79.7	0.001	4	2.10 (0.63–6.97)	84.4	<0.001
C	33	1.71 (1.29–2.27)	88.8	<0.001	18	1.72 (1.12–2.65)	90.6	<0.001
Number of cases								
≥200	18	2.15 (1.45–3.18)	89.4	<0.001	8	2.59 (1.19–5.61)	93.3	<0.001
<200	21	1.46 (1.03–2.08)	86.0	<0.001	15	1.48 (0.96–2.28)	86.8	<0.001
Cancer type†								
GC	12	2.16 (1.26–3.71)	91.3	<0.001	6	2.07 (0.73–5.91)	94.0	<0.001
EC	9	1.43 (0.92–2.22)	77.1	<0.001	4	2.75 (2.04–3.70)	9.6	0.345
GBC	6	1.78 (0.83–3.83)	75.0	0.001	6	1.78 (0.83–3.83)	75.0	0.001
Others	12	1.67 (1.07–2.60)	90.0	<0.001	7	1.34 (0.75–2.40)	91.7	<0.001
Controls								
Community-based	17	1.91 (1.19–3.07)	89.4	<0.001	10	2.69 (1.34–5.38)	92.6	<0.001
Hospital-based	22	1.65 (1.20–2.29)	87.9	<0.001	13	1.30 (0.85–1.99)	84.9	<0.001
NOS score								
≥7	29	1.87 (1.40–2.48)	86.9	<0.001	17	2.13 (1.42–3.19)	90.1	<0.001
<7	10	1.48 (0.74–2.97)	91.9	<0.001	6	1.12 (0.41–3.09)	87.5	<0.001

*F: Females; C: Combined males and females. †Cancer type: GC; EC; GBC; Others included breast cancer, colorectal cancer, laryngeal cancer, oral cancer, and pharyngeal cancer. GC: Gastric cancer; EC: Esophageal cancer; GBC: Gallbladder cancer; *OR*: Odds ratio; *CI*: Confidence interval; NOS: Newcastle–Ottawa scale.

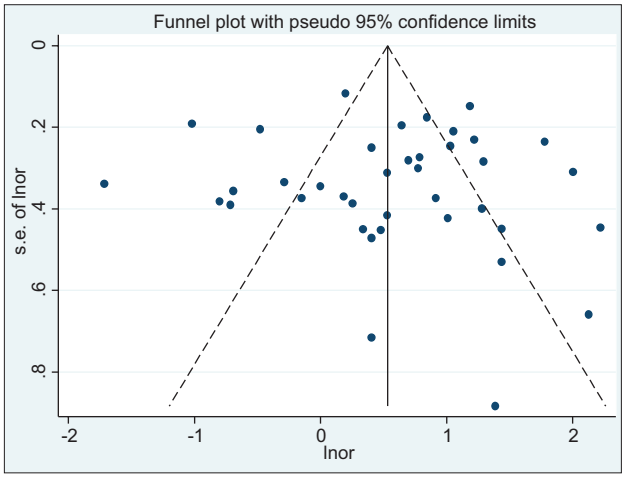

Figure 3: Funnel plot of studies evaluating the association between high spicy food intake and cancer risk. Dotted lines indicate 95% pseudo-confidence interval. SE: Standard error; *OR*: Odds ratio. Egger's test ($P = 0.714$) Begg's test ($P = 0.942$).

Our meta-analysis has several limitations. First, because the data were obtained from case–control studies, confounding bias may be present, such as selection bias and recall bias due to the contribution of different results obtained from different populations or hospital designs. Although we attempted to include adjusted estimates from multivariate models from each contributing study and apply a stratified analysis, we still cannot explain the potential effects of other dietary habits or behavior or the etiologic relationship between spicy food intake and cancer events. Second, the definition of spicy food and the highest and lowest categories of spicy food intake were inconsistent. People of different races and dietary cultures have eating preferences, such as kimchi in Korea or spicy preserved meat in the Maghreb. Third, 9 studies did not adjust for confounding factors, confounders that were adjusted for in each study were different, and there were some unknown confounders. Fourth, relatively low sample sizes were included in the subgroup analyses by sex, region, and cancer subtype, which may have rendered chance effects more likely. In addition, only 7 articles (including 11 studies) with subgroup analyses conducted in non-Asian regions were included in our meta-analysis. The small sample size may have contributed to the heterogeneity.

In conclusion, our meta-analysis suggests a positive association between a high level of spicy food or chili pepper intake and cancer risk. Furthermore, no statistically significant effect was observed among females after application of a stratified analysis by sex because of the limited number of studies. Studies with larger sample sizes, longer follow-up periods, more cancer types, and more detailed measures of spicy food intake are necessary to confirm these results.

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Conflicts of interest

There are no conflicts of interest.

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