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Research article

Ginseng consumption and risk of cancer: A meta-analysis

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ABSTRACT

Background: The findings of currently available studies are not consistent with regard to the association between the risk of cancer and ginseng consumption. Therefore, we aimed to evaluate this association by conducting a meta-analysis of different studies.
Methods: To systematically evaluate the effect of ginseng consumption on cancer incidence, six databases were searched, including PubMed, Ovid Technologies, Embase, The Cochrane Library, China National Knowledge Infrastructure, and Chinese VIP Information, from 1990 to 2014. Statistical analyses based on the protocol employed for a systematic review were conducted to calculate the summary relative risks (RRs) and 95% confidence intervals (CIs).
Results: We identified nine studies, including five cohort studies, three case-control studies, and one randomized controlled trial, evaluating the association between ginseng consumption and cancer risk; these studies involved 7,436 cases and 334,544 participants. The data from the meta-analysis indicated a significant 16% lower risk of developing cancer in patients who consumed ginseng (RR = 0.84, 95% CI = 0.76–0.92), with evidence of heterogeneity ($p = 0.0007$, $I^2 = 70\%$). Stratified analyses suggested that the significant heterogeneity may result from the incidence data for gastric cancer that were included in this study. Publication bias also showed the same result as the stratified analyses. In addition, subgroup analyses for four specific types of cancer (colorectal cancer, lung cancer, gastric cancer, and liver cancer) were also performed. The summary RRs for ginseng intake versus no ginseng consumption were 0.77 for lung cancer, 0.83 for gastric cancer, 0.81 for liver cancer, and 0.77 for colorectal cancer.
Conclusion: The findings of this meta-analysis indicated that ginseng consumption is associated with a significantly decreased risk of cancer and that the effect is not organ specific.

1. Introduction

Cancer imposes a global threat to public health. According to the Global Cancer Statistics estimates, there were about 14.1 million new cancer cases and 8.2 million cancer deaths in 2012 [1]. Importantly, these numbers have rapidly increased with increased population growth and environmental pollution. Malignancy results from complex interactions among multiple genes, the intracellular environment, and neighboring tissues [2]. The basic theory of tumorigenesis suggests that the process starts with a normal cell that is transformed through the activation of proto-oncogenes and the suppression of tumor suppressor genes. After the transformation, the cell does not behave like a normal cell, but instead begins to exhibit the properties of a cancer cell. These transformed cells acquire the capability to proliferate uncontrollably through self-sufficiency in growth signals and are insensitive to antigrowth signals. In addition, they are able to evade apoptosis, eventually resulting in tumor growth. As the tumor continues to develop, its growth is aided by the development of new blood vessels that provide it with nutrients, thereby allowing it to sustain itself and

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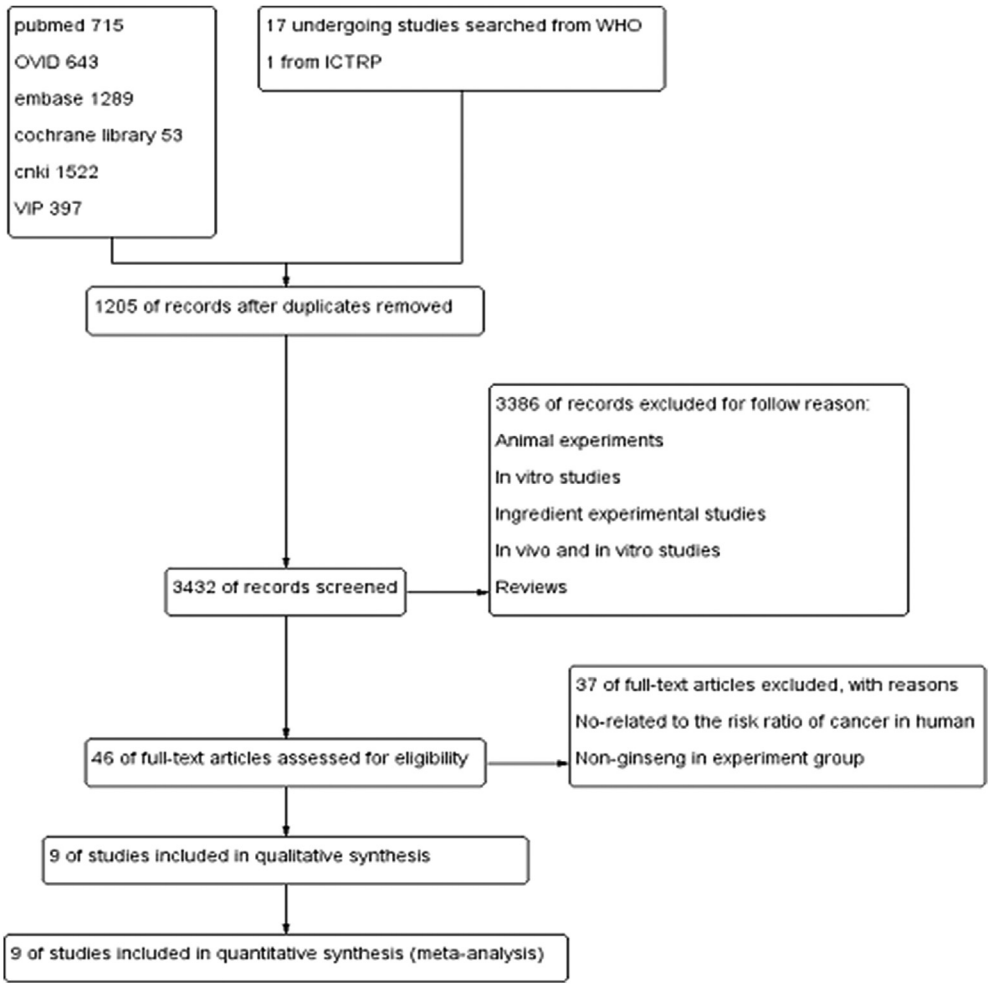

Fig. 1. Flowchart of study selection. ICTRP, International Clinical Trials Registry Platform; WHO, World Health Organization.

even invade other tissues, resulting in metastasis that is ultimately lethal [2–5].

Chemoprevention is defined as the use of natural, synthetic, or biological agents to prevent, suppress, and reverse the carcinogenic progression. It is ideally effective in prevention of the disease and should be nontoxic. Chemoprevention is characterized by the disruption of, or at least the delay of, multiple pathways and processes in the three stages of carcinogenesis, namely, initiation, promotion, and progression [6,7]. Chemicals or biomolecules that inhibit the initiation stage are necessary for the preservation of DNA [8,9]. In contrast to compounds that preserve DNA, compounds that affect the later stages of carcinogenesis (promotion and progression) are known for their ability to decrease the proliferative capacity of initiated cells. They interfere with cancer cell proliferation by downregulating the expression of the molecules involved in signal-transduction pathways, such as nuclear factor kappa-light-chain enhancer of activated B cells (NF-kB), mammalian target of rapamycin, and signal transducer and activator of transcription 3, and by inhibiting cytochrome P_{450} enzymes that modulate signal transduction to hormone-responsive elements [10]. In addition, suppressing agents are likely to reduce or delay the ability of cancer cells to acquire metastatic properties by promoting pathways leading to apoptosis [11] and inhibiting pathways leading to angiogenesis, epithelial mesenchymal transition, invasion, and dissemination [12].

Traditional herbal medicine used for thousands of years is advantageous in maintaining a balanced health status and help prevent further diseases in a safe and effective manner. Ginseng (*Panax ginseng* Meyer) is widely used and has been included in pharmacopoeias in China, Japan, Germany, France, Austria, and the United Kingdom. It is widely available as an over-the-counter drug and also commonly used as an adjuvant to increase human immunity [13,14]. Furthermore, the protective effect of ginseng in cancer chemoprevention has been shown by extensive laboratory and preclinical studies [15]. Ginseng is chemoprophylactic and often acts on its cellular and molecular targets through various signaling pathways, thereby inhibiting the tumor by regulation of the cell cycle, induction of apoptosis, and inhibition of angiogenesis and invasion [16,17]. The anticancer effects of ginseng involve modulation of diverse signaling pathways, including regulation of cell proliferation mediators (cyclin-dependent kinases and cyclins), growth factors (c-myc, epidermal growth factor receptor, and vascular endothelial growth factor), tumor suppressors (p53 and p21), oncogenes (*MDM2*), cell death mediators [B-cell lymphoma 2 (Bcl-2), B-cell lymphoma-extra large (Bcl-xL), X-linked inhibitor of apoptosis protein (XIAP), caspases, and death receptors], inflammatory response molecules (NF-κB and cyclooxygenase-2), and protein kinases (c-Jun N-terminal protein kinase, Akt, and adenosine monophosphate-activated protein kinase) [18]. During the past decade, although a series of epidemiologic studies had

Table 1
Characteristics of studies included in the meta-analysis

Study	Study design	Study population	Study period	Cases/control or cohort or RCT	Ginseng type and consumption	RR (95% CI)	Adjustments
Yun and Choi 1990 [26]	Case-control study	Seoul, Korean	1987–1988	905/905 Men 48%	Ginseng 562/905 vs. 674/905	0.83 (0.78,0.89)	Demographic characteristics (age, marital status, education, occupation, and income), lifestyle (cigarette smoking, alcohol consumption, and others), and ginseng consumption
Yun and Choi 1995 [28]	Case-control study	Seoul, Korean	1988–1990	1,987/1,987 Men 54%	Ginseng 1,066/1,987 vs. 1,382/1,987 Ginseng (colorectal cancer) 63/118 vs. 86/118 Ginseng (lung cancer) 156/276 vs. 195/276 Ginseng (gastric cancer) 158/300 vs. 224/300 Ginseng (liver cancer) 156/264 vs. 179/264	0.77 (0.73, 0.81) 0.73 (0.60, 0.90) 0.80 (0.70, 0.91) 0.71 (0.62, 0.80) 0.79 (0.70, 0.90)	Sociodemographic characteristics, lifelong occupational history, smoking habits, drinking habits, and ginseng intake
Yun and Choi 1998 [21]	Cohort study	Seoul, Korean	1987–1992	137/4,450 age was over 40 yr, followed for 5 yr Men 51%	Ginseng 75/137 vs. 3,167/4,450 Ginseng (lung cancer) 10/24 vs. 3,167/4,405 Ginseng (gastric cancer) 19/42 vs. 3,167/4,450 Ginseng (liver cancer) 10/14 vs. 3,167/4,450	0.77 (0.66, 0.90) 0.59 (0.36, 0.94) 0.64 (0.46, 0.89) 1.00 (0.72, 1.40)	Demographic characteristics, lifelong occupation, smoking and drinking habits, history of diseases, ginseng intake, etc.
Yun et al 2010 [29]	Randomized controlled trial	Hangzhou, Chinese	1997–2008	325/318 age was between 40 and 69 yr with chronic atrophic gastritis 1 g of ginseng every wk for 3 yr and followed up for 8 yr Men 61%	Red ginseng extract 8/24 vs. 317/616 Ginseng (colorectal cancer) 1/2 vs. 324/641 Ginseng (lung cancer) 2/8 vs. 323/635 Ginseng (gastric cancer) 3/6 vs. 322/637 Ginseng (liver cancer) 1/2 vs. 324/641	0.65 (0.37, 1.15) 0.99 (0.25, 3.96) 0.49 (0.15, 1.64) 0.99 (0.44, 2.21) 0.99 (0.25, 3.96)	Demographic characteristics, lifelong occupation, smoking and alcohol drinking patterns, history of diseases, and history of ginseng intake
Satia et al 2009 [23]	Cohort study	Western Washington State, American	2000–2007	665/76,460 age was between 50 and 76 yr, followed for a mean of 5.0 y at least once a wk for a yr	Ginseng (colorectal cancer) 29/428 vs. 6,309/76,084 Ginseng (lung cancer) 43/665 vs. 6,322/76,460	0.82 (0.57, 1.16) 0.78 (0.56, 1.05)	Duration in yr, frequency in d/wk, and usual dose of various supplements, including multivitamins, individual vitamin and mineral supplements, other mixtures, and herbal and specialty products
Kamangar et al 2007 [22]	Cohort study	Shanghai, Chinese	1997–2004	21,318/52,134 Women aged between 40 and 70 yr followed for 4 yr	Ginseng (gastric cancer) 56/153 vs. 21,318/73,452 At least five times a yr in the past 3 yr	1.26 (1.02, 1.55)	Demographic characteristics, education and income, lifestyle and habits, diet, taken ginseng, and several other factors
Rebbeck et al 2007 [27]	Case-control study	Philadelphia and Delaware Counties in Pennsylvania; Camden County in New Jersey, American	1999–2002	949/1,524 Women aged between 50 and 79 yr	Ginseng (breast cancer) 72/949 vs. 164/1,524 Use in European Americans 41/677 vs. 84/905 Use in African Americans 31/272 vs. 80/619 At least three times a wk for 1 mo or more any time	0.71 (0.54, 0.92) 0.65 (0.46, 0.94) 0.88 (0.60, 1.30)	Demographic characteristics; family history of breast, endometrial, and ovarian cancer; contraceptive history; fertility history; menstrual and menopausal history; medical history; detailed gynecologic screening history; use of exogenous hormones; and use of other medications

(*continued on next page*)

Table 1 (*continued*)

Study	Study design	Study population	Study period	Cases/control or cohort or RCT	Ginseng type and consumption	RR (95% CI)	Adjustments
Walter et al 2011 [25]	Cohort study	Western Washington State, American	2000–2008	586/65,429 Men and women aged between 50 and 76 yr, followed for 6 yr Men 49%	Ginseng (< 4 d/wk or < 3 yr, hematologic malignancies) 37/586 vs. 5,507/65,429	0.75 (0.55, 1.03)	For each vitamin, mineral, and specialty supplement taken at least once a wk for 1 yr, we ascertained intake from single supplements and multivitamins, including the duration in yr and frequency of use in d/wk during the 10-yr period prior to baseline. For individual vitamin and mineral supplements, we also ascertained the average dose taken each d.
Brasky et al 2011 [24]	Cohort study	Western Washington State, American	2000–2008	1,602/33,637 Men aged between 50 and 76 yr (follow-up time was 6.1 yr)	Ginseng (≥ 1 d/wk for ≥ 1 yr, prostate cancer) 76/1,602 vs. 1,821/33,637 10-yr average use Low use [< 4 d/wk or any use < 3 yr] 106/1,602 vs. 2,091/33,637 High use [≥ 4 d/wk for ≥ 3 yr] 25/1,602 vs. 714/33,637	0.88 (0.70, 1.10) 1.07 (0.88, 1.29) 0.74 (0.49, 1.09)	Specialty supplement use during the 10-yr period prior to baseline, in addition to use of vitamin and mineral supplements, inquired about current and past regular use (≥ 1 d/wk for ≥ 1 yr) of 18 specialty supplements including frequency of use (d/wk) and duration of use (yr) over the previous 10 yr.

CI, confidence interval; RCT, randomized controlled trial; RR, relative risk.

indicated that ginseng consumption affects cancer incidence, the results of the studies are inconsistent. Therefore, a quantitative analysis of the associations between ginseng consumption and risk of cancer was necessary to expound the existing inconsistency in the literature.

Thus, a meta-analysis aimed at reviewing and summarizing the relationship between ginseng consumption and risk of cancer was performed, and different relative risk (RR) ratios of cancer were determined by performing subgroup analyses.

2. Materials and methods

2.1. Search strategy

We conducted a literature search for relevant articles in PubMed, Ovid Technologies, Embase, Cochrane Library, China National Knowledge Infrastructure, and Chinese VIP Information for published papers from 1990 to July 2014 using the following search terms without language restrictions: “ginseng,” “fresh ginseng,” “white ginseng,” “red ginseng,” “ginseng supplement,” “ginseng or fresh ginseng or white ginseng or red ginseng or ginseng supplement,” “Neoplasms” (Mesh), “randomized controlled trial,” “cohort,” “case control,” “randomized controlled trial or cohort or case control,” “ginseng or fresh ginseng or white ginseng or red ginseng or ginseng supplement and neoplasms (Mesh) and randomized controlled trial or cohort or case control.”

In addition, the reference lists of the selected articles were also reviewed to identify other relevant articles. The research was conducting by two authors on their own account.

2.2. Study selection

The following criteria were chosen to identify the studies for this meta-analysis: studies comprising a randomized controlled trial or observation study with the exposure factor being ginseng intake, studies with risk of cancer being the end point of interest, and studies in which risk estimates were reported. If data were included more than once, the latest and complete research was chosen.

2.3. Data extraction and quality assessment

The data were charted as follows: first author, publication year, study design, region, study period, case and control, ginseng type and consumption, RR, and confounding factors of interest. The included studies were independently evaluated by two authors using the methodological quality assessment system in RevMan 5.3. Discrepancies in evaluation were resolved by a third author, and potential publication bias was examined using Begg’s test. A linear regression approach was used to measure the funnel plot asymmetry on the natural logarithm scale of the RR ratios [19].

2.4. Statistical analysis

The main analyses were focused on the associations between consumption of ginseng and cancer incidence. In addition, the RR of lung cancer, colorectal cancer (cancer of the colon and rectum), gastric cancer (cancer of the stomach), and liver cancer was determined in relation to ginseng consumptions in a subgroup analysis.

All analyses were performed using Review Manager version 5.3 (Cochrane Collaboration software) and GRADE profiler version 3.6. All p values are two-sided and $p < 0.1$ was considered significant.

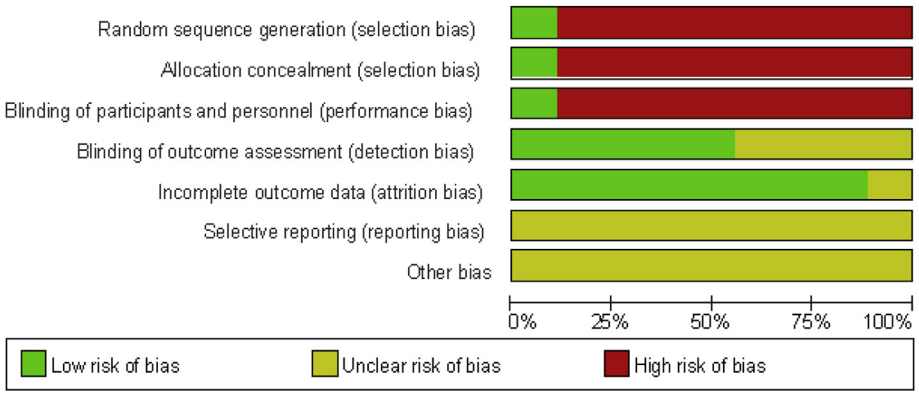

Fig. 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

Furthermore, the I^2 index, a quantitative measure of inconsistency, across studies was calculated [20].

3. Results

3.1. Literature search

A flowchart showing the study selection process is presented in Fig. 1. In brief, a total of 4,619 publications and 18 studies that are currently underway were identified. A total of 1,205 duplicates were then removed. After screening the abstracts, we excluded the duplicates, studies involving animal experiments and *in vitro* analyses, ingredient experimental studies, and reviews, etc. for not meeting the inclusion criteria. After evaluating the full manuscripts of the 46 potentially relevant articles, 37 potentially relevant studies were excluded further because they were not related to the to the risk ratio of cancer in humans and nonginseng use in experimental group. Finally, nine studies were selected for analysis [21–29].

3.2. Study characteristics

The included studies were identified with regard to ginseng consumption, and risk of cancer in this meta-analysis is presented in Table 1. The eight observation studies, including five cohort studies [21–25] and three case-control studies [26–28], were published between 1990 and 2014. Only one randomized controlled trial [29] was reported. Of these studies, four involved research on lung cancer [21,23,28,29] and gastric cancer [21,22,28,29], three assessed colorectal cancer [21,23,28,29] and liver cancer [21,28,29], and one study each assessed prostate cancer [24], hematologic malignancies [25], and breast cancer [27].

3.3. Quality assessment of the included studies

The Cochrane risk of bias tool was used to assess risk bias (Figs. 2 and 3). Because eight of the studies were observation studies, the random sequence generation, allocation concealment, and blinding of participants and personnel all showed high risk. Most of the studies involved questionnaire analysis, and the participants were

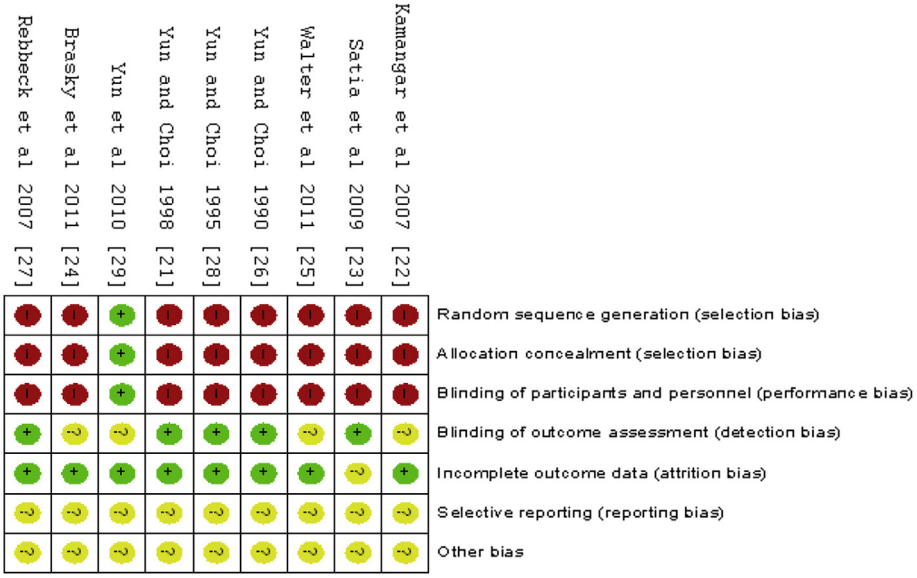

Fig. 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Table 2
Grading of recommendations assessment results

Quality assessment							No of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ginseng	Control	Relative (95% CI)	Absolute		
9	Observational studies ($n = 8$) and randomized controlled trial ($n = 1$)	Very serious[1)]	No serious inconsistency	No serious indirectness	No serious imprecision	Reduced effect for RR >> 1 or RR << 1[2)] Dose–response gradient[3)]	2,031/7,436 (27.3%)	14%	RR 0.84 (0.76–0.92)	22 fewer/1,000 (from 11 fewer to 34 fewer)	Low	Critical

[1)] Most were observational studies.
[2)] Other factor may affect the results.
[3)] Some of studies described the dose-response.
CI, confidence interval; RR, relative risk.

diagnosed in different hospitals by randomized doctors. Therefore, blinding of outcome assessment showed low risk. In addition, outcome data loss was less than 20%, and therefore, incomplete outcome data presented a low risk. Because the protocols of all the trials were not accessible, selective reporting was generally unclear. Therefore, the grading of recommendations assessment results is shown with a low quality of evidence (Table 2).

3.4. Main analysis

A total of nine studies were included in this meta-analysis to evaluate the association between ginseng intake and the risk of cancer. There was a significant 16% lower cancer risk associated with ginseng consumption in comparison with the risk associated with no ginseng consumption for all studies combined [RR = 0.84, 95% confidence interval (CI) = 0.76–0.92], with evidence of heterogeneity ($p = 0.0007$, $I^2 = 70\%$) in Fig. 4.

3.5. Publication bias

There was no significant combined publication bias in all studies assessing the relationship between ginseng intake and cancer incidence, as suggested by Begg's rank correlation test in Fig. 5 (p for Begg's test was 0.596). However, the study by Kamangar et al [22] may have had a high bias. When this study was excluded from this meta-analysis, we observed a significant 19% lower risk of developing cancer after ginseng consumption in comparison with the risk without ginseng consumption (RR = 0.81, 95% CI = 0.76–0.85), with low heterogeneity ($p = 0.20$, $I^2 = 28\%$).

3.6. Subgroup and sensitivity analyses

The subgroup analyses according to the type of cancer are presented in Table 3. When the analyses were stratified by cancer site, the summary RRs for ginseng intake versus no ginseng consumption were 0.77 for lung cancer, 0.83 for gastric cancer, 0.81 for liver cancer, and 0.77 for colorectal cancer. Evidence of heterogeneity was observed only in the gastric cancer subgroup (Fig. 6). In addition, sensitivity analysis indicated that the summary estimates (RR = 0.81, 95% CI = 0.76–0.85) showed low heterogeneity ($p = 0.20$, $I^2 = 28\%$) when the study by Kamangar et al [22] was excluded. Meanwhile, in the gastric cancer subgroup, the sensitivity analysis also indicated that when the Kamangar et al [22] study was excluded, the summary estimates changed (RR = 0.70, 95% CI = 0.62–0.79), with no significant heterogeneity ($p = 0.59$, $I^2 = 0\%$).

4. Discussion

The present meta-analysis, based on the latest published results, is the first quantitative systematic analysis of the association between ginseng consumption and cancer risk in 7,436 cases and 334,544 participants. The meta-analysis of the studies identified indicated that ginseng consumption may be associated with a reduced risk of cancer. We found substantial heterogeneity in the association between ginseng consumption and cancer risk across studies. This is not surprising given the variation in study designs and characteristics of the study populations. However, the stratified analysis by cancer type showed significant heterogeneity only for gastric cancer. It indicated that gastric cancer may be the major source of heterogeneity. Furthermore, when we separated the population in Shanghai, China [22] from others in Seoul, Korea [21,28,29], the results indicated no significant inverse association between ginseng consumption and gastric cancer risk. Because the

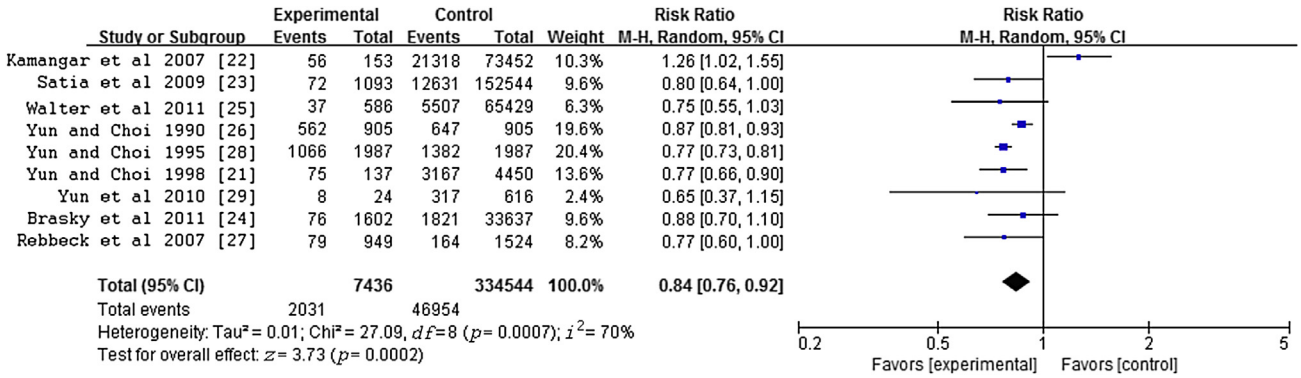

Fig. 4. Meta-analysis of studies examining association between ginseng consumption and risk of cancer. CI, confidence interval.

chemical components of ginseng differ by region, the inclusion of studies from different regions may have been responsible for the heterogeneity. Moreover, the exposure factor may be greater, because patient information obtained after diagnoses in an observation study could also result in systematic errors. However, the fact that large numbers of cases and controls were involved in this meta-analysis also means that the findings about association between ginseng consumption and the risk of cancer are more reliable. In addition, we found a significant association between ginseng intake and reduction of cancer incidence, which further strengthened our result.

The basic mechanism of cancer development is now known to result from an accumulation of genetic and epigenetic alterations in cells [30]. Although diagnosis and treatment are the major strategies for controlling cancer, the importance of cancer chemoprevention has gradually increased because advanced cancer is difficult to cure [31,32].

Ginseng, a famous traditional Chinese medicine, has been used for thousands of years [33]. Its usefulness in cancer prevention and therapy has been shown by extensive preclinical and epidemiological studies [34–36]. The main active ingredients of ginseng are often thought to be ginsenosides. The anticancer effects of ginseng involve diverse molecular mechanisms of action, which in turn involve the regulation of most known modulators of carcinogenesis [19]. Because ginsenosides cause tumor cell death through various mechanisms, it may be difficult for cells to develop resistance to ginsenoside-induced death. Furthermore, the ability of ginsenosides to kill tumor cells and relative non-toxicity to normal cells make them attractive candidates for drug development [37]. The diverse properties of ginseng are attributable to the diversity in both chemical structure and biological activity.

The study by Kamangar et al [22] showed opposite effects. The types of ginseng used by the participants in their study were similar to those used in other studies. However, the group and its extension were selected from among patients who were also referred to other studies included in this meta-analysis. Therefore, the sex of the patients included was significantly different from others. The prevalence of sex differences might have led to greater bias in this group than in the general population because of the differences in lifestyle and genetic constitution of female participants. Therefore, further evaluation of the association between ginseng consumption and sex may be needed to clarify ginseng's role in cancer.

Several potential limitations of our meta-analysis should be considered while interpreting the results. First, most of the studies included were observational studies, and the presence of cohort and case-control studies may have introduced confounding factors and biases as a result of the different methods used in the studies. Second, studies included were mainly conducted in Korea, China, and the United States; therefore, the data should be extrapolated to other populations with caution. Third, the apparent protective effect of ginseng against cancer may be also attributable to genetic and other environmental factors. Finally, the articles included in our meta-analysis were published in journals. Unpublished studies and original data were not included. However, our meta-analysis also has several strengths. In particular, it allowed us to directly address the association between ginseng consumption and cancer risk in humans, avoiding the uncertainties derived from the use of animal data and mathematical models, and to assess the public

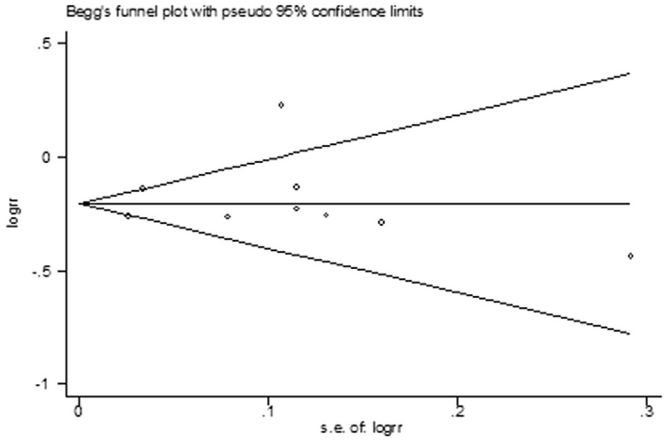

Fig. 5. Begg's funnel plot of ginseng consumption and risk of cancer incidence. RR, relative risk; s.e., standard error.

Table 3
Subgroup analyses of the risk ratio of different kinds of cancer

Group	Number of studies	Risk ratio (95% confidence interval)	$p_{heterogeneity}$	I^2, %
All	9	0.84 (0.76, 0.92)	0.0007	70
Type of cancer				
Colorectal cancer	3	0.76 (0.64, 0.90)	0.78	0
Lung cancer	4	0.78 (0.70, 0.87)	0.53	0
Gastric cancer	4	0.83 (0.75, 0.92)	< 0.0001	88
Liver cancer	3	0.82 (0.73, 0.91)	0.41	0
Breast cancer	1	0.71 (0.54, 0.92)	—	—
Hematologic 35372 malignancies	1	0.75 (0.55, 1.03)	—	—
Prostate cancer	1	0.88 (0.70, 1.10)	—	—

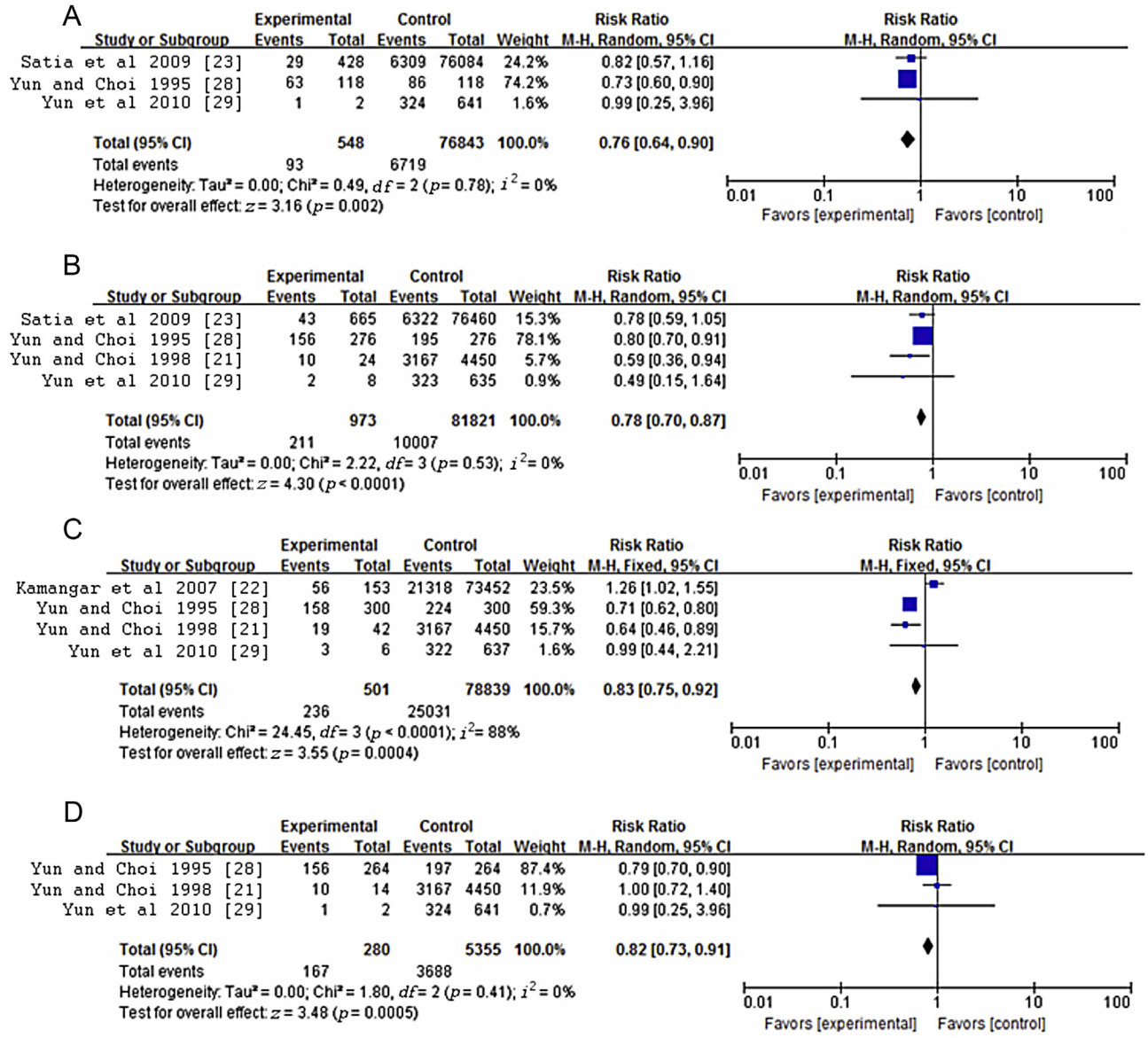

Fig. 6. Meta-analysis of studies examining association between ginseng consumption and risk of (A) colorectal cancer, (B) lung cancer, (C) gastric cancer, and (D) liver cancer. CI, confidence interval.

health relevance of such a relation. Previous epidemiological studies have already identified several dietary and nutritional factors associated with the risk of various cancers, particularly those of the digestive tract. This weighs in favor of the capability of epidemiological studies included in this meta-analysis to assess the association of cancer with ginseng consumption.

5. Conclusion

To the best of our knowledge, this review is the first to systematically perform a quantitative evaluation of the chemopreventive effect of ginseng on the incidence of cancer, addressing the lack of this type of research. In summary, ginseng consumption was associated with a significantly lower risk of developing cancer. However, the findings should be interpreted with caution due to the low quality of the included trials. Rigorous multicenter, large-scale clinical trials should be carried out to reveal the exact effectiveness in the future.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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