RESEARCH COMMUNICATION

Overview of Methodological Quality of Systematic Reviews about Gastric Cancer Risk and Protective Factors

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Abstract

Background and Objective: A comprehensive overall review of gastric cancer (GC) risk and protective factors is a high priority, so we conducted the present study. Methods: Systematic searches in common medical electronic databases along with reference tracking were conducted to include all kinds of systematic reviews (SRs) about GC risk and protective factors. Two authors independently selected studies, extracted data, and evaluated the methodological qualities and the quality of evidence using R-AMSTAR and GRADE approaches. Results: Beta-carotene below 20 mg/day, fruit, vegetables, non-fermented soy-foods, whole-grain, and dairy product were GC protective factors, while beta-carotene 20 mg/day or above, pickled vegetables, fermented soy-foods, processed meat 30g/d or above, or salty foods, exposure to alcohol or smoking, occupational exposure to Pb, overweight and obesity, helicobacter pylori infection were GC risk factors. So we suggested screening and treating *H. pylori* infection, limiting the amount of food containing risk factors (processed meat consumption, beta-carotene, pickled vegetables, fermented soy-foods, salty foods, alcohol), stopping smoking, avoiding excessive weight gain, avoidance of Pb, and increasing the quantity of food containing protective components (fresh fruit and vegetables, non-fermented soy-foods, whole-grain, dairy products). Conclusions: The conclusions and recommendations of our study were limited by including SRs with poor methodological bases and low quality of evidence, so that more research applying checklists about assessing the methodological qualities and reporting are needed for the future.

Keywords: Stomach neoplasms - etiology - environmental exposure - *Helicobacter pylori* - systematic reviews

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Introduction

Although the incidence and mortality rates of gastric cancer (GC) have decreased markedly in the past few decades, GC is the fourth most common cancer (accounted for 988,602, about 7.8% of all cancers) and the second leading cause of cancer-related death (accounted for 737,419, about 9.7% of all cancers) worldwide in 2008 (Jemal et al., 2002). As a result of trends in global aging and population growth, the potential incidence of GC for 2010 is estimated to achieve 1.1 million (Wang et al., 2010). So actions must be taken, in order to lower the chance of getting GC and the number of new GC cases. The best way is to avoid the risk factors associated with GC (any attribute, characteristic or exposure of an individual that increases the likelihood of developing GC) and increase GC protective factors (any attribute, characteristic or exposure of an individual that that prevents or reduces vulnerability for the development of GC). To prevent new GC from starting, risk factors and protective factors were needed to be found and recognized, and recommendations should be made at the same time. There were guidelines on nutrition and physical activity for GC prevention that produced by American Cancer Society (Byers et al., 2002) or the Asia-Pacific Gastric Cancer Consensus Conference (Fock et al., 2008), but these guidelines were not scientific enough using the best evidence, or comprehensive enough using all available evidence. So we conducted this study to review all available evidence about the GC etiology based on SRs or meta-analyses to present all GC risk and protective factors and give some recommendations by the way.

Materials and Methods

Data source and study selection

The Cochrane Library, PubMed, Embase, ISI Web of Knowledge, China Academic Journal Network Publishing Database, and Chinese Scientific Journals Full text Database and Chinese Biomedical Literature Database were searched with ("stomach cancer*" OR "stomach neoplasm*" OR "stomach tumor*" OR

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"stomach adenocarcinoma" OR "gastric cancer*" OR "gastric neoplasm*" OR "gastric tumor*" OR "gastric adenocarcinoma") and ("meta analys*" OR "review*") without language, publication year and publication status restrictions. All searches were conducted in March 2010 and updated in April 2011 by two independent reviewers (Lun Li & Tiantian Sun). Additional citations were identified by checking references of included studies and existing reviews of this topic.

Factors that were related to GC from available SRs or meta-analyses were divided into four categories (risk factor, protective factor, non-significant factor, unclear factor). The risk factor is any attribute, characteristic or exposure that increases the likelihood of developing GC and the protective factor is any attribute, characteristic or exposure that prevents or reduces vulnerability in the development of GC. Those factors that were not significant in the GC developing were defined as non-significant factors, and those factors whose effects in GC developing were unclear were called unclear factors. When there were more than one SRs or meta-analyses that focused on the same topic, we compared the differences among them and included the most comprehensive one.

Two reviewers (Lun Li & Tiantian Sun) independently selected studies according to predetermined inclusion criteria by screening titles and abstracts identified through all searches. If both reviewers believed that the abstracts were potentially relevant, we screened the full-text articles independently to determine whether the study was were eligible for inclusion.

Data collection and quality assessment

Two reviewers (Lun Li & Tiantian Sun) independently extracted data, assessed methodological quality, and evaluated the quality of evidence. Disagreements were resolved by consultations with a third reviewer (Kehu Yang). The data extraction form summarized key characteristics, including information on participants, exposures, outcomes, conclusions, and the quality assessment items.

The methodological qualities of included SRs were evaluated using assessment of multiple systematic reviews (AMSTAR), because it has good content validity, wide acceptance, recognized reliability and reproducibility (Shea et al., 2007; Shea et al., 2007; Shea et al., 2009; Kung et al., 2010). Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) was chosen in our study, as it could produce quantifiable assessments of SR quality (Kung et al., 2010).

For the evaluation of quality of evidence, we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach(Guyatt et al., 2010). The GRADE approach specifies four levels of quality: high, moderate, low, and very low after evaluating five factors (study quality, consistency, directness, precision, and reporting bias) which may lead to its downgrading and three factors (large effects, all plausible residual confounding and dose-response gradient) which can lead to upgrading quality of evidence (Nasser and Fedorowicz, 2011).

Results

Search result

We found 2517 citations by searching and 43 citations by reference tracking. Finally, we included 80 papers for this overview of reviews, but in our article we only reviewed 55 etiological SRs/meta-analyses (Fu et al., 1995; Huang et al., 1998; Jacobs et al., 1998; Danesh et al., 1999; Eslick et al., 1999; Jia et al., 2000; Wu et al., 2000; Xue et al., 2001; Huang et al., 2003; Guo et al., 2004; Li et al., 2004; Botelho et al., 2006; Hu et al., 2006; Jakszyn et al., 2006; Larsson et al., 2006; Larsson et al., 2006; Liu et al., 2006; MacLean et al., 2006; Nishino et al., 2006; Tian et al., 2006; Xu et al., 2006; An et al., 2007; Kubo et al., 2007; Lunet et al., 2007; Merrill et al., 2007; Bae et al., 2008; Ladeiras-Lopes et al., 2008; Kuoppala et al., 2008; Shimazu et al., 2008; Zhou et al., 2008; Huang et al., 2009; La Torre et al., 2009; Liu et al., 2009; Liu et al., 2009; Mulholland et al., 2009; Myung et al., 2009; Yang et al., 2009; Zhang et al., 2009; Cavaleiro-Pinto et al., 2010; Gatto et al., 2010; Hussein et al., 2010; Kang et al., 2010; Kim et al., 2010; Noto et al., 2010; Shiota et al., 2010; Tian et al., 2010; Tong et al., 2010; Wang et al., 2010; Yang et al., 2010; Kim et al., 2011; Li et al., 2011; Tramacere et al., 2011; Tramacere et al., 2011; Wu et al., 2011; Zhou et al., 2011) that were related to GC factors and four SRs/meta-analyses (Bjelakovic et al., 2008; Fuccio et al., 2009; Druesne-Pecollo et al., 2010; Shimoyama et al., 2011) about preventing GC, as some of them were on the same condition (Figure 1).

Main results from SRs or meta-analyses (Table 1)

Available evidence showed that the relationships between diabetes, NSAIDs (aspirin), preserved fish, preserved vegetable, smoked food, green tea, red meat, beer intake, glycemic load, vitamin C, ham, sausage and GC were inconsistent. And there were not significant associations between occupational exposure to Cr and chrysotile fiber, dupA H. pylori positive strains, glycemic index, folate, coffee, fish, selenium or statins, omega-3 fatty acids, vitamin E, aspirin, onion leaf and GC.

Beta-carotene below 20 mg/d, fruit, vegetables, allium vegetables (onion, garlic, leek, Chinese chive, scallion, garlic stalk and Welsh onion), soybean products, tofu,

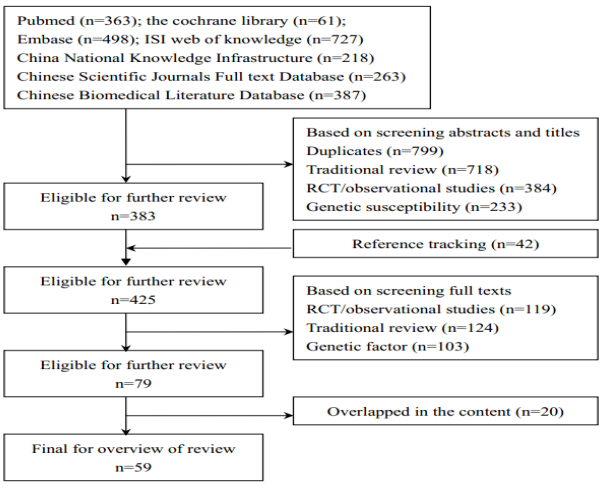

Figure 1. Flow Diagram

Table 1. Classifications of Factors Related to Gastric Cancer Based on Main Results from 55 SRs or Meta-Analyses of Observational Studies

Item	Included ID	Search time	Included study Cohort/CC	Results	R-AMSTAR Score	GRADE level
Helicobacter pylori infection	Hussein 2010, Shiota 2010	2010	0/12	Non-significant factor: duodenal ulcer promoting gene A dupA H. pylori	16-22	low
	Huang 2003	2003	3/13	Risk factors: CagA sero-prevalence H. pylori	24	low
	Xu 2006	2005	0/10		17	
	An 2007, Cavaleiro-Pinto 2010, Danesh 1999, Eslick 1999, Guo 2004, Hu and Dong 2006, Huang 1998, Jia 2000, Liu 2006, Tian 2006, Wang 2010, Xue 2001, Zhang 2009	1983-2009	-	Risk factors: Helicobacter pylori infection	13-27	low
Nitrosamine and related food intake	Jakszyn 2006	2005	10/24	Unclear factor: preserved fish, vegetable, smoked food, red meat, processed meat, beer intake	30	Low
	Larsson 2006	2006	3/10	Risk factors: processed meat consumption 30g/day above and bacon consumption	28	Low or moderate[1]
			1 RCT	Inconsistent factor: sausage, ham consumption		
Fruit and vegetables consumption	Zhou 2011	2010	2/19	Protective factors: allium vegetables onion, garlic, leek, Chinese chive, scallion, garlic stalk and Welsh onion non-significant factor: onion leaf	26	low
	Lunet 2007	2004	2/26	Protective factors: fruit and vegetables consumption	19	low
	Kim 2010	2008	1/7	Protective factors: fresh vegetables	27	low
			8/6	Risk factors: pickled vegetables		low
	Bae 2008	2007	2/12	Protective factors: citrus fruits	26	low
Soy-foods	Tong 2010	2008	12/16	Risk factors: miso protective factors: soybean products, tofu	18	low
	Wu 2000	1999	8/21	Risk factors: fermented soy-foods	16	low
	Kim 2011	2009	9/13	protective factors: non-fermented soy-foods	28	low
Whole-grain	Jacobs 1998	1997	0/7	Protective factors: Whole-grain	18	low
Dairy product	Huang 2009	2008	0/8	Protective factors: dairy product	25	low
Alcohol drinking	Tramacere 2011	2010	15/44	Non-significant factor: 10 g/day, 25g/day alcohol drinking risk factors: 50g/day, 75g/day, 100 g/day, 125g/day alcohol drinking	23	Moderate[2]
	Shimazu 2008	2007	11/11	Inconsistent factor: alcohol drinking in Japanese population	20	low
	Li 2011	2010	2/29	Risk factors: alcohol drinking in Chinese population	25	low
Smoking	Nishino 2006	2005	10/16	Risk factors: smoking in Japanese population	21	low
	Liu 2009	2009	8/22	Risk factors: smoking closest to 20 cigarettes per day, smoked closest to 10 years	16	Moderate[2]
	Tramacere 2011	2010	3/21	Risk factors: smoking	18	low
	Ladeiras-Lopes 2008	2007	5/27		23	low
	La Torre 2009	2006	0/46		26	low
Coffee	Botelho 2006	2004	7/16	Non-significant factor: coffee	29	low
Salty food	Liu 2009	2007	0/19	Risk factors: salty food	18	Very low[3]
Fish	Wu 2011	2009	2/15	Non-significant factor: fish consumption	27	low
Omega-3 fatty acids	MacLean 2006	2003	1/0	Non-significant factor: omega-3 fatty acids	26	Very low[4]
Green tea	Zhou 2008	2006	4/10	Non-significant factor: green tea	30	low
	Myung 2009	2007	5/8	Inconsistent factor: green tea	25	low
	Kang 2010	2007	7/11	Inconsistent factor: green tea	26	low
NSAIDs	Tian 2010	2009	8/13	Protective factors: NSAIDs, aspirin	30	low
	Yang 2010	2009	3/10	Non-significant factor: aspirin	28	low
Statins	Kuoppala 2008	2007	0/2	Non-significant factor: statins	20	low
Antioxidant intake	Kubo 2007	2006	1/3	Inconsistent factor: Vitamins E	30	Very low[5]
			1/3	Inconsistent factor: vitamins C		Very low[5]
			1/3	Protective factors: beta-carotene/vitamin A		Moderate[2]
Folate intake	Larsson 2006	2006	2/11	Non-significant factor: folate intake	25	very low[5]
GL and GI	Mulholland 2009	2008	1/1	Non-significant factor: GI	24	Very low[4]
				Inconsistent factor: GL		Very low[4,5]
Diabetes	Noto 2010	2010	2/1	Inconsistent factor: diabetes	27	Very low[4]
Overweight, obesity	Yang 2009	2009	10/0	Risk factors: overweight and obese, obese, overweight	27	Moderate[2]
Allergies	Merrill 2007	-	1/0	Protective factors: asthma	17	Very low[4]
Occupational exposure	Gatto 2010	2009	28/0	Non-significant factor: Cr	19	low
	Li 2004	2003	26/0	Non-significant factor: chrysotile fiber	22	low
	Fu 1995	1992	6/4	Risk factors: Pb	17	low

[1]The quality of evidence for the result of processed meat consumption on GC risk is moderate, as there is evidence of dose-response gradient; the qualities of evidence for the other results were low; [2]There is evidence of dose-response gradient; [3]Significant heterogeneities and publication bias were found among all studies; [4]The total number of events is less than 300; [5]Significant heterogeneities were found among all studies

non-fermented soy-foods, whole-grain, or dairy product, and asthma could decrease GC risk, while beta-carotene 20 mg/d or above, pickled vegetables, fermented soy-foods (miso), processed meat 30 g/d or above, or bacon, or salty foods, exposure to alcohol (50 g/day, 75 g/day, 100 g/day, 125 g/day) or smoking, occupational exposure to Pb, overweight and obesity, helicobacter pylori (including cagA-positive strains) infection could increase GC risk. The methodological quality of included SRs or meta-analyses (Table 2).

For 55 included SRs or meta-analyses that evaluated the gastric cancer etiology, the R-AMSTAR score ranges from 13 to 30 (median 22, mean ± SD 22.13 ± 4.65). 31 achieved 22-30 score using R-AMSTAR checklist, and 23 achieved 13-21 score with a maximum possible total score of 44. Very few studies conducted all contents of item 2 (27.27%), item 8 (1.82%), item 10 (1.82%), item 11 (3.64%). And 9.09% (five studies) to 92.73% (51 studies) did not conduct any contents of item 2 to item 11, especially for item 2, 4, 7, 8, which were conducted in less than half of studies.

Of 52 small items from the R-AMSTAR (Kung et al., 2010), seven small items were not conducted in all included studies, seventeen small items were conducted in more than half of all included studies (five small items were conducted in more than 75% of all included studies), twenty-seven small items were conducted in less than half of all included studies (eleven small items were conducted in less than 25% of all included studies).

For item 1, none of these 55 SRs or meta-analyses conducted 'a priori' design, as all of them were published in regular journals. 96.36% of all studies stated inclusion criteria and 65.45% raised their research questions using PICO format.

For item 2, 27.27% studies did duplicate study selection and data extraction and 56.36% showed that they conducted none of three small items in item 2. All these three small items were conducted in less than half of all included studies (32.73%).

For item 3, which was operationalized into five small items, none of all studies conducted all and only five studies conducted none. 52.73% searched at least two electronic sources, 49.09% told the search time, 83.64% mentioned search strategy or key words they used to search, 67.27% also searched by reviewing the references in the studies found or consulting current contents,

Table 2. Methodological Quality of Included 55 Systematic Reviews/Meta-analyses of Observational Studies

	1	2	3	4	5	6	7	8	9	10	11	Total score
Hussein 2010	B	NO	C	NO	AD	ABC	NO	NO	NO	NO	NO	16
	2	1	1	1	2	4	1	1	1	1	1	
Shiota 2010	BC	NO	NO	NO	AD	ABC	NO	NO	C	ABC	AB	22
	3	1	1	1	2	4	1	1	1	4	3	
Huang 2003	BC	ABC	CD	NO	ACD	AC	AB	NO	C	AC	NO	24
	3	4	2	1	3	3	2	1	1	3	1	
Xu and Bi 2006	B	NO	AD	NO	D	AC	NO	NO	NO	AC	NO	17
	2	1	2	1	1	3	1	1	1	3	1	
Xue 2001	BC	NO	C	NO	AD	AC	NO	NO	NO	NO	A	17
	3	1	1	1	2	3	1	1	1	1	2	
Tian 2006	B	NO	NO	NO	AD	ABC	NO	NO	CD	NO	NO	17
	2	1	1	1	2	4	1	1	2	1	1	
Jia 2000	B	NO	CD	NO	NO	NO	NO	NO	C	NO	NO	13
	2	1	2	1	1	1	1	1	1	1	1	
An 2007	B	NO	C	NO	AD	AC	NO	NO	NO	NO	NO	15
	2	1	1	1	2	3	1	1	1	1	1	
Zhang 2009	BC	NO	ACD	NO	AD	AC	NO	NO	CD	AB	NO	21
	3	1	3	1	2	3	1	1	2	3	1	
Wang 2010	BC	ABC	AC	NO	AD	ABC	NO	NO	CD	AB	NO	24
	3	4	2	1	2	4	1	1	2	3	1	
Liu 2006	BC	NO	AC	NO	CD	NO	NO	NO	NO	NO	A	16
	3	1	2	1	2	1	1	1	1	1	2	
Hu 2006	BC	NO	NO	NO	AD	ABC	NO	NO	CD	NO	NO	18
	3	1	1	1	2	4	1	1	2	1	1	
Guo 2004	BC	NO	NO	NO	ACD	AC	NO	NO	C	NO	A	18
	3	1	1	1	3	3	1	1	1	1	2	
Huang 1998	BC	A	C	NO	ACD	ABC	AB	NO	BC	NO	NO	21
	3	2	1	1	3	4	2	1	2	1	1	
Eslick 1999	BC	NO	ABCD	AD	AD	ABC	AB	AB	CD	AB	NO	27
	3	1	4	3	2	4	2	2	2	3	1	
Danesh 1999	B	NO	CD	NO	D	NO	NO	NO	BC	NO	NO	14
	2	1	2	1	1	1	1	1	2	1	1	
Cavaleiro-Pinto 2010	B	ABC	BCD	NO	ACD	ABC	NO	NO	BC	AB	A	26
	2	4	3	1	3	4	1	1	2	3	2	
Jakszyn 2006	BC	NO	ABCD	NO	D	NO	NO	NO	NO	NO	A	17
	3	1	4	1	1	1	1	1	1	1	2	
Larsson 2006	BC	NO	BC	NO	D	ABC	NO	NO	BCD	ABC	A	25
	3	1	4	1	1	4	1	1	3	4	2	
Zhou 2011	B	ABC	BCD	NO	ACD	ABC	NO	NO	BC	AC	B	26
	2	4	3	1	3	4	1	1	2	3	2	
Lunet 2007	BC	ABC	BCD	NO	NO	NO	NO	NO	B	NO	A	19
	3	4	3	1	1	1	1	1	1	1	2	
Kim 2010	BC	ABC	ABC	NO	CD	ABC	NO	NO	BCD	AC	A	27
	3	4	3	1	2	4	1	1	3	3	2	
Bae 2008	BC	NO	ABCD	NO	ACD	ABC	NO	NO	BC	ABC	A	26
	3	1	4	1	3	4	1	1	2	4	2	
Tong 2010	BC	NO	AC	NO	NO	ABC	NO	NO	NO	NO	A	18
	3	1	2	1	1	4	1	1	1	1	2	
Wu 2000	B	NO	D	NO	D	ABC	NO	NO	NO	NO	A	16
	2	1	1	1	1	4	1	1	1	1	2	
Kim 2011	BC	ABC	ACD	NO	ACD	ABC	NO	NO	BCD	AC	B	28
	3	4	3	1	3	4	1	1	3	3	2	
Jacobs 1998	C	NO	CD	NO	AD	ABC	NO	NO	NO	NO	A	18
	2	1	2	1	2	4	1	1	1	1	2	
Huang 2009	BC	NO	ACD	NO	ACD	ABC	NO	NO	BC	ABC	A	25
	3	1	3	1	3	4	1	1	2	4	2	
Tramacere 2011	B	A	BCD	NO	AD	NO	NO	NO	ABC	ABC	AB	23
	2	2	3	1	2	1	1	1	3	4	3	
Shimazu 2008	B	NO	ABCD	NO	AD	ABC	NO	NO	NO	NO	B	20
	2	1	4	1	2	4	1	1	1	1	2	
Li 2011	B	ABC	ABD	NO	ACD	AC	AB	NO	BCD	NO	B	25
	2	4	3	1	3	3	2	1	3	1	2	
Tramacere 2011	B	A	BCD	NO	NO	NO	NO	NO	ABC	NO	A	18
	2	2	3	1	1	1	1	1	3	1	2	
Nishino 2006	B	NO	BCD	NO	AD	ABC	NO	NO	BCD	NO	A	21
	2	1	3	1	2	4	1	1	3	1	2	
Liu 2009	B	NO	ACD	NO	D	NO	NO	NO	CD	AC	A	18
	2	1	3	1	1	1	1	1	2	3	2	
Ladeiras-Lopes 2008	B	ABC	ABC	NO	CD	NO	NO	NO	BCE	ABC	NO	23
	2	4	3	1	2	1	1	1	3	4	1	
La Torre 2009	BC	ABC	BC	NO	AD	ABC	AB	AB	BC	AB	NO	26
	3	4	2	1	2	4	2	2	2	3	1	
Botelho 2006	BC	ABC	BCD	D	AD	ABC	NO	NO	BCE	ABC	A	29
	3	4	3	2	2	4	1	1	3	4	2	
Liu 2009	BC	NO	ABC	NO	AD	ABC	NO	NO	NO	AB	A	22
	3	1	3	1	2	4	1	1	1	3	2	
Wu 2011	BC	ABC	CD	NO	ACD	ABC	AB	NO	BC	AB	B	28
	3	4	2	1	3	4	2	1	2	3	2	
MacLean 2006	BC	A	ABCD	AD	AD	ABC	AB	AB	B	NO	A	26
	3	2	4	3	2	4	2	2	1	1	2	
Zhou 2008	BC	ABC	ABCD	NO	ACD	ABC	NO	NO	BCD	ABC	B	30
	3	4	4	1	3	4	1	1	3	4	2	
Myung 2009	BC	NO	ABCD	NO	ACD	ABC	NO	NO	BC	ABC	NO	25
	3	1	4	1	3	4	1	1	2	4	1	
Kang 2010	BC	NO	ACD	NO	ACD	ABC	NO	NO	BCD	ABC	B	26
	3	1	3	1	3	4	1	1	3	4	2	
Tian 2010	BC	ABC	ABCD	NO	BCD	ABC	NO	NO	BCD	ABC	B	30
	3	4	4	1	3	4	1	1	3	4	2	
Yang 2010	BC	ABC	ACD	B	AD	ABC	NO	NO	BCD	AB	B	28
	3	4	3	2	2	4	1	1	3	3	2	
Kuoppala 2008	C	NO	ABCD	NO	ACD	ABC	A	AB	NO	NO	B	22
	2	1	4	1	3	4	1	2	1	1	2	
Kubo 2007	BC	ABC	ABCD	NO	ACD	ABC	A	NO	BCD	ABC	A	30
	3	4	4	1	3	4	1	1	3	4	2	
Larsson 2006	BC	NO	BCD	D	D	ABC	NO	NO	BC	AC	A	23
	3	1	3	2	1	4	1	1	2	3	2	
Mulholland 2009	BC	NO	ACD	D	AD	ABC	NO	NO	BC	AB	B	24
	3	1	3	2	2	4	1	1	2	3	2	
Noto 2010	BC	ABC	ABCD	NO	AD	ABC	A	NO	BC	AB	A	27
	3	4	4	1	2	4	1	1	2	3	2	
Yang 2009	BC	ABC	ABCD	NO	ACD	ABC	NO	NO	BCD	NO	B	27
	3	4	4	1	3	4	1	1	3	1	2	
Merrill 2007	B	NO	AD	NO	NO	ABC	NO	NO	NO	NO	A	17
	2	1	2	1	1	4	1	1	1	1	2	
Gatto 2010	BC	A	C	NO	AD	ABC	NO	NO	C	NO	B	19
	3	2	1	1	2	4	1	1	1	1	2	
Li 2004	B	A	ABCD	NO	AD	ABC	NO	NO	BC	NO	A	22
	2	2	4	1	2	4	1	1	2	1	2	
Fu 1995	B	NO	NO	NO	AD	ABC	NO	NO	NO	NO	A	17
	2	1	1	1	2	4	1	1	1	1	2	

Table 3. Classifications of Factors Related to Gastric Cancer Based on Main Results from Four SRs or Meta-Analyses of Randomization Controlled Studies

Item	Included ID	Search tiem	Included study Cohort/CC	Results	R-AMSTAR Score	GRADE Level
H. pylori eradication	Fuccio 2009	Jan.-Sep.	2 RCTs	H. pylori eradication could reduce GC risk.	31	Moderate[1]
Antioxidant intake	Druesne-Pecollo 2010	Apr.-Sep.	7 RCTs	Non-significant factor: beta-carotene Beta-carotene below 20 mg/d could reduce GC risk. Beta-carotene 20 mg/d and above could increase GC risk	23	High
	Bjelakovic 2008	Oct.-Jul.	4 RCTs	Non-significance: beta-carotene	36	Moderate[1]
			1 RCT	Non-significance: vitamin E		Moderate[1]
			1 RCT	Non-significance: selenium		Moderate[1]
Statins	Shimoyama 2011	2008	3 RCTs	Non-significance: statins	20	Moderate[1]

[1]The total number of events is less than 300

Table 4. Methodological Quality of Four Systematic Reviews/Meta-Analyses of Randomization Controlled Studies

	1	2	3	4	5	6	7	8	9	10	11	Total score
Fuccio 2009	BC	A	ABCD	AD	AD	ABC	AB	NO	NO	NO	B	31
	3	2	4	3	2	4	2	1	1	1	2	
Druesne-Pecollo 2010	BC	A	BCD	NO	AD	ABC	NO	NO	BCD	NO	A	23
	3	2	3	1	2	4	1	1	3	1	2	
Bjelakovic 2008	ABC	ABC	ABCD	A	ABCD	ABC	AB	AB	BCDE	ABC	B	36
	4	4	4	2	4	4	2	2	4	4	2	
Shimoyama 2011	BC	NO	BCD	NO	AD	ABC	NO	NO	BC	NO	NO	20
	3	1	3	1	2	4	1	1	2	1	1	

reviews, textbooks, specialized registers, or experts in the particular field, none hand-searched relevant journals.

For item 4, 89.09% studies did not use the status of publication (i.e. grey literature) as an inclusion criterion, and no study conducted all four small items operationalized from item 4. 3.64% stated that they searched for reports regardless of their publication type, 1.82% stated they excluded any reports based on their publication status, none mentioned "Non-English papers were translated", and 9.09% said no language restriction.

For item 5, 9.09% did not provide a list of studies (included and excluded), and none conducted all four small items operationalized from item 5. 70.91% gave a table of included studies, 1.82% mentioned excluded studies in a supplemental source, 36.36% stated the reason for exclusion of the seriously considered studies, and 90.91% supplied a table or reference list of included or excluded studies.

For item 6, 16.36% provided the characteristics of the included studies, and none conducted all three small items operationalized from item 6. 83.64% provided a table that presented the original data about PICO, 70.91% provided the ranges of relevant characteristics in the studies analyzed, and 83.64% provided complete information.

For item 7, 81.82% did not assess the scientific quality of the included studies, and none conducted all four small items operationalized from item 7. 18.18% provided 'a priori' methods of assessment, 12.73% provided the assessment results, and none discussed level of evidence and ranked quality of evidence.

For item 8, 92.73% did not use the scientific quality of the included studies in formulating conclusions, and 1.82% conducted all four small items operationalized from item 8. 7.27% considered the results of the methodological rigor and scientific quality, and 7.27% stated the results of the methodological rigor and scientific quality.

For item 9, 25.45% did not tell how to combine the findings of studies, and none conducted all five small items operationalized from item 9. None stated criteria that the studies analyzed were similar enough to be pooled, 50.91% did a test to assess their homogeneity, 67.27% recognized heterogeneity, and 30.91% supplied the methods to deal with high heterogeneity.

For item 10, 47.27% did not assess the likelihood of publication bias, and 1.82% conducted all three small items operationalized from item 8. 56.36% recognized publication bias, 43.64% assessed publication bias using graphical aids, and 38.18% used statistical tests.

Recommendations produced by available evidence

Only four SRs/meta-analyses of randomized controlled studies for preventing GC were found (Bjelakovic et al., 2008; Fuccio et al., 2009; Druesne-Pecollo et al., 2010; Shimoyama et al., 2011) (Table 3 and 4), but there were 55 SRs/meta-analyses (Fu et al., 1995; Huang et al., 1998; Jacobs et al., 1998; Danesh et al., 1999; Eslick et al., 1999; Jia et al., 2000; Wu et al., 2000; Xue et al., 2001; Huang et al., 2003; Guo et al., 2004; Li et al., 2004; Botelho et al., 2006; Hu et al., 2006; Jakszyn et al., 2006; Larsson et al., 2006; Larsson et al., 2006; Liu et al., 2006; MacLean et al., 2006; Nishino et al., 2006; Tian et al., 2006; Xu et al., 2006; An et al., 2007; Kubo et al., 2007; Lunet et al., 2007; Merrill et al., 2007; Bae et al., 2008; Ladeiras-Lopes et al., 2008; Kuoppala et al., 2008; Shimazu et al., 2008; Zhou et al., 2008; Huang et al., 2009; La Torre et al., 2009; Liu et al., 2009; Liu et al., 2009; Mulholland et al., 2009; Myung et al., 2009; Yang et al., 2009; Zhang et al., 2009; Cavaleiro-Pinto et al., 2010; Gatto et al., 2010; Hussein et al., 2010; Kang et al., 2010; Kim et al., 2010; Noto et al., 2010; Shiota et al., 2010; Tian et al., 2010; Tong et al., 2010; Wang et al., 2010; Yang et al., 2010; Kim et al., 2011; Li et al., 2011; Tramacere et al., 2011; Tramacere et al., 2011; Wu et al., 2011; Zhou et al., 2011) about etiological factors. Available evidence showed that the

risk factors of GC included H. pylori infection (especially for CagA-positive strains), and Helicobacter pylori eradication was associated with decreased GC cases, so H. pylori infection should be screened and eradicated based on these SRs/meta-analyses (Bjelakovic et al., 2008; Fuccio et al., 2009; Druesne-Pecollo et al., 2010; Shimoyama et al., 2011). Processed meat consumption (30g/d or below), beta-carotene (20 mg/d or below), pickled vegetables, fermented soy-foods (including miso), and salt or salty foods were also associated increased GC risk, so their consumption amount should be limited. Alcohol and smoking were two main risk factors of GC, so their quantities should be lowered or stopped. Overweight or obese, as co-morbid conditions, they should be also increase GC risk, so excessive weight gain must be avoided, and a healthy weight should be achieved and maintained. Occupational exposure to Pb was found to be related with GC, so we must keep away from it, or take enough protective actions when you have to. Our study demonstrated that fresh fruit and vegetables (including allium vegetables), non-fermented soy-foods (including soybean products, tofu), whole-grain consumption, dairy product consumption in dietary food could decrease GC risk, so more should be taken in daily life.

Discussion

Diet and lifestyle are thought to be involved in the development of GC. The American Cancer Society recommends a diet that is high in fresh fruit, fresh vegetables, and whole grain foods and low in processed food and red meat. This is similar to our results, namely intake of food containing protective factors (fruit, vegetables, soybean products, non-fermented soy-foods, whole-grain, and dairy product) could prevent GC. Certainly, some food that contains chemical carcinogenic compounds may be involved in increasing the risks of developing GC, such as nitrites and nitrates, which could be transformed to carcinogenic compounds nitrosamines inside the human body. In our study, intake of food containing risk factors (pickled vegetables, fermented soy-foods, processed meat 30 g/d or above, and bacon, or salted foods), might be associated with increased GC risk. Recent study has showed that increased consumption of vegetables, fruit and vitamin C and a decrease in salt consumption could result the decline of GC incidence in Poland for about forty years (Jarosz et al., 2011). So in the future, increasing intake of food containing protective factors, and limiting or avoiding intake of food containing risk factors might help to prevent GC. As a result, diet that contains more protective factors and less or no risk factors should be recommended for GC prevention. Lifestyle exposure to alcohol and smoking were associated with increased GC risks (Tredaniel et al., 1997; Corrao et al., 1999; Bagnardi et al., 2001; Bagnardi et al., 2001; Liu and Wang, 2002; Zeka et al., 2003; Corrao et al., 2004; Inoue et al., 2005; Nishino et al., 2006; Gandini et al., 2008; Ladeiras-Lopes et al., 2008; Shimazu et al., 2008; La Torre et al., 2009; Li et al., 2011; Liu et al., 2009; Tramacere et al., 2011; Tramacere et al., 2011), and other studies have showed that cigarette smoking may play the most harmful role in the initial development of GC, and that drinking alcohol may promote the process (Chen et al., 2000, Sauvaget et al., 2005, Yamaji et al., 2009). So smoking and alcohol should be avoided or diminished in order to prevent GC incidence. For other diet and lifestyle factors, available evidence showed that the relationships between preserved fish, preserved vegetable, smoked food, green tea, red meat, beer, glycemic load, vitamin C, ham, sausage and GC were inconsistent, and there were not significant associations between glycemic index, folate, coffee, fish, omega-3 fatty acids, onion leaf and GC.

However, for some factors, such as omega-3 fatty acids, the number of studies that evaluated their relationships to GC was few and the conclusion could not be drawn. And for inconsistent factors, such as green tea and glycemic load, the different results from several SRs or meta-analyses or primary studies (cohort or CC studies) were found. There are two SRs (Borrelli et al., 2004; Boehm et al., 2009) and three meta-analyses (Zhou et al., 2008; Myung et al., 2009; Kang et al., 2010), which evaluated the association between green tea consumption and GC risk. There were discrepancies in the effects of green tea consumption on GC risk between CC and cohort studies in three meta-analyses (Zhou et al., 2008; Myung et al., 2009; Kang et al., 2010), as well as between the crude and adjusted data in the pooled results (Myung 2009; Kang 2010). So we have to pay attention to several things. Firstly, these three meta-analyses (Zhou et al., 2008; Myung et al., 2009; Kang et al., 2010) included both case control (CC) and cohort studies, but their pooled results of these two kinds of studies were not consistent. In this condition, among the pooled results of CC studies, or cohort studies, or all studies, which one should we believe? We suggested that if there was no heterogeneity between all studies, and across the subgroup analyses of these two study designs, we believed the pooled results of all studies. If not, we believed the pooled results of cohort studies, as in the evidence pyramid cohort studies were more believable than CC studies, and further cohort studies were needed to confirm the results of meta-analysis. Secondly, the first meta-analysis (Myung et al., 2009), which used both crude and adjusted data, showed differences between these results. However, which result should be trusted? We suggested the pooled results of adjusted data should be more believable if the adjusted data was right, as confounders in included studies were adjusted. But the discrepancies in the effects of green tea consumption on GC risk between CC and cohort studies, or between the crude data and adjusted data make us confused, so further meta-analyses with rigor methodological ways and comprehensive studies included were needed. Also, further cohort studies were needed to confirm the results of these meta-analyses. As a result, more studies (including SRs, meta-analyses, cohort or CC studies) were needed to provide more information.

All available evidence from meta-analyses showed that *Helicobacter pylori* infection increased GC risk, regardless of languages or publication time of studies they included (Huang et al., 1998; Danesh et al., 1999; Eslick et al., 1999; Jia et al., 2000; Xue et al., 2001; Guo et al., 2004; Hu et al., 2006; Liu et al., 2006; Tian et al., 2006;

An et al., 2007; Zhang et al., 2009; Cavaleiro-Pinto et al., 2010; Wang et al., 2010). For different *H. pylori* strains, cagA-positive strains were associated with increased GC risk (Huang et al., 2003; Xu et al., 2006), but not dupA positive strains (Hussein et al., 2010; Shiota et al., 2010). A meta-analysis (Fuccio et al., 2009) based on two RCTs showed that the pooled result of *H. pylori* eradication in the prevention of GC was 0.46 (95%CI 0.26 to 0.82), suggesting that H. pylori eradication reduced GC risk. So we suggested that patients with *H. pylori* infection should be screened and treated, especially for CagA-positive strains of *H pylori* infection.

For co-morbid conditions, overweight or obese could increase GC risk, asthma could decrease GC risk (one study), and the relationship between diabetes (two studies) and GC was inconsistent. So suggestions about avoiding excessive weight gain, achieving and maintaining a healthy weight if currently overweight or obese, were made. But for the other two factors, we could not conclude any conclusions and make any suggestions.

For drug use, available evidence showed that there was not a significant relationship between statins use and GC risk, and the relationships between NSAIDs use (including aspirin) and GC risk were inconsistent. Two meta-analyses (Tian et al., 2010; Yang et al., 2010) evaluated the relationships between aspirin use and GC risk, but they were different in their ORs, as one meta-analysis included one RCT (Cook et al., 2005) and another PCC study (Figueroa et al., 2009). So the other meta analysis (Yang et al., 2010) were much more comprehensive than the first one (Tian et al., 2010). That is the two studies, which might change OR between aspirin and GC. So we are not sure that they may change the conclusion of the first meta-analysis, if the two studies (Cook et al., 2005; Figueroa et al., 2009) mentioned above were included. Why did these happen? The first review (Tian et al., 2010) searched three common medical databases (Medline, Embase, and Web of science) in March 2009, but it did not find the PCC study (Figueroa et al., 2009), which was epub 2008 Nov 7. We searched PubMed for this paper (Figueroa et al., 2009), and found this paper was indexed in PubMed and free to download. We thought it is not included as omitting by the study selectors and that might be the reason why the authors of this paper did not mention the process of study selection. So in the future, more rigor methods and comprehensive searches should be applied in SRs/meta-analyses making.

For occupational factors, available evidence showed that Pb could increase GC risk, and there were not significant associations between occupational exposure to Cr, chrysotile fiber and GC. So we suggested keeping away from occupational exposure to Pb, or taking enough protective actions when you have to.

Regarding methodological qualities of included SRs/meta-analyses, for 55 included SRs or meta-analyses that evaluated the GC etiology, their methodological qualities of included SRs or meta-analyses were not so good and nearly half of them were low quality. Very few studies conducted all contents of item 2, item 8, item 10, and item 11. And 9.09% to 92.73% studies did not conduct any contents of item 2 to item 11, especially for item 2, 4, 7, 8, which were not conducted in more than half of studies. Of 52 small items which were operationalized from the R-AMSTAR (Kung et al., 2010), seven small items were not conducted in all included studies , twenty-seven small items were conducted in less than half of all included studies (eleven small items were conducted in less than 25% of all included studies). Even though, meta-analyses/SRs of observational studies about the etiology have been developed for about twenty years, their methodological quality were still low.

One terrible problem that exists in meta-analyses/SRs of observational studies about the etiology of GC was the search, study selection, and data extract. Nearly half of studies searched only one electronic source, such as Pubmed. Till now, we could not know whether only searching in Pubmed could find all available studies about one topic or not. But we know that, only searching in Pubmed might lose to find some studies that were only indexed in other databases, such as Embase. Also given that articles are often misclassified, this study also highlights the importance of searching various databases in addition to other methods such as snowballing reference list of included studies (Anne). However, 47.26% only searched Pubmed to provide evidence, and 32.73% did not search by reviewing the references in the studies found or consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field. We could not say that this search of one database without tracking reference list must miss some studies in their review, but the kind of search strategy might loss some studies that met their inclusion criteria. 56.36% studies did not do duplicate study selection and data extraction, while only 27.27% studies did duplicate study selection and data extraction. This is so terrible. One person or two dependent persons might make some mistakes during data extracting, which is the reason why well conducting SRs/meta-anslyses need two independent persons to select studies and abstract data. Even though, high prevalence of data extraction and reporting errors were found in Cochrane systematic reviews (Jones et al., 2005). We compared the search strategy, study selection, data abstraction of three SRs/meta-anslyses about the relationships between green tea and GC risk (Zhou et al., 2008; Myung et al., 2009; Kang et al., 2010). Three meta-analyses (Zhou et al., 2008; Myung et al., 2009; Kang et al., 2010) we reviewed did not include the same studies, even though their results were similar. These three meta-analyses (Zhou et al., 2008; Myung et al., 2009; Kang et al., 2010) searched PubMed and the Cochrane library after 2006, and the inclusion criteria of both meta-analyses were similar, but all failed to include some studies before 2006. We wondered how it happened. One meta-analysis (Myung et al., 2009) reported that all of the studies retrieved from the databases were independently evaluated by 3 evaluators, but the other two (Zhou et al., 2008; Kang et al., 2010) did not mention who selected the studies for eligibility. Each meta-analysis (Zhou et al., 2008; Myung et al., 2009) has one study missing to be found. Although the third meta-analysis (Kang et al., 2010) included both Chinese and Japanese studies, but it failed to include some studies the previous two meta-analyses included (Zhou et al., 2008;

Myung et al., 2009). Why did this happen? This might be because they failed to search them or excluded them during selecting. At the same time, we could find some mistakes about data abstracting in one meta-analysis. This also happened in the topic about the relationships between aspirin use and GC risk (Tian et al., 2010; Yang et al., 2010). One meta-analysis (Yang et al., 2010) included one RCT (Cook et al., 2005) and another PCC study (Figueroa et al., 2009) than the first one (Tian et al., 2010). That is the two studies, which changed OR between aspirin and GC. So we are not sure that they may change the conclusion of the first meta-analysis, if the two studies (Cook et al., 2005; Figueroa et al., 2009) mentioned above were included. Why did these happen? The first review (Tian et al., 2010) searched three common medical databases (Medline, Embase, and Web of science) in March 2009, but it did not find the PCC study (Figueroa et al., 2009), which was epub 2008 Nov 7. We searched PubMed for this paper (Figueroa et al., 2009), and found this paper was indexed in PubMed and free to download. We thought it is not included as omitting by the study selectors and that might be the reason why the authors of this paper did not mention the process of study selection. So in the future, more rigor methods and comprehensive searches should be applied during SRs/meta-analyses making. So how to prevent mistakes in finding some studies and data abstraction from happening again deserves thinking and needs actions, such as search more electronic sources and reference tracking, discussing the disagreements among reviewers again and again. We suggested that it is better to search at least electronic sources along with reference tracking, and select studies, extract data by two independent persons in the process of conducting SRs/meta-analyses of observational studies.

Another terrible problem is that 81.82% did not assess the scientific quality of their included studies, and 92.73% did not use the scientific quality of the included studies in formulating conclusions. We all know, observational studies began with low quality (Balshem et al., 2011). If we evaluated the scientific quality of the included studies without any other downgrading factors, we could be more confident with the results. If the methodological quality of included studies was not evaluated, we could not judge the results could be changed if there were limitations. So the results of assessment could influence the confidence of the conclusions. However, available evidence showed that almost all SRs/meta-analyses of observational studies about the etiology did not evaluate the scientific quality their included studies. Why could it be like that? There may be several reasons: first, more instruments were used to evaluate the methodological quality of observational studies, such as the Newcastle-Ottawa Scale (NOS), or methodological index for non-randomized studies (MINORS) (Wells et al., 2000; Slim et al., 2003; Stang et al., 2010), and it is hard to choose an appropriate one. Second, it is difficult to use them, as the authors did not have the ability to understand the contents or it will add the burden of working. Third, the authors were not aware of evaluating the scientific quality of their included studies or they did not know that there were these instruments. So in the future, we suggested using appropriate instrument to assess the methodological quality and implant the assessment results in formulating conclusions.

Overall, the methodological qualities of included SRs/meta-analyses were not so good, as some did not report necessary items. So the validities of the results of these SRs/meta-analyses were questionable, as some serious methodological flaws might lead to a high risk of bias (Lundh and Knijnenburg, 2009). In the future, checklists about assessing the methodological qualities and reporting SRs/meta-analyses were needed to follow (Stroup et al., 2000; Shea et al., 2007; Kung et al., 2010).

Rearding strengths and limitations, our overview is the first one that comprehensively reviewed all available SRs/meta-analyses about the risk and protective factors of GC using rigor evidence based medicine methods: employ objective searches of the literature, apply predetermined inclusion criteria, critical appraisal of all relevant studies. Also we used GRADE approach to evaluate the quality of evidence and gave recommendations about GC prevention, which was the first paper to give recommendations based on SRs and meta-analyses using evidence based methods and GRADE approach. Even though, our work has potential limitations. Firstly, we just included SRs or meta-analyses, which means we did not review the factors of GC in primary studies (such as cohort studies, CC studies, etc). As a result, we might miss some factors of GC. Secondly, we just reviewed the single factor of GC, so the interactions between two or more factors for GC were not included. Thirdly, the methodological qualities of included SRs/meta-analyses were not so good, as some did not report necessary items, such as data extracting process. So the validities of the results of these SRs/meta-analyses were questionable, and some serious methodological flaws might lead to a high risk of bias (Lundh and Knijnenburg, 2009). Fourthly, there were so few primary studies about one topic that the conclusion about it was less confirmable. The last limitation was the big problem of our study. Only four SRs/meta-analyses of preventing GC were found (Bjelakovic et al., 2008; Fuccio et al., 2009; Druesne-Pecollo et al., 2010; Shimoyama et al., 2011), but there were 55 SRs/meta-analyses about etiological factors. Here we must make clear an important distinction between evidence on the GC etiology and evidence supporting the effectiveness of preventive actions. The results from etiological research or addressing the impact of interventions cannot be taken as equivalent in terms of their support to preventive actions. For example, the evidence that H. pylori infection is associated with GC does not necessarily translate into the conclusion that its eradication will prevent GC. The consequences of such an intervention should also be taken into account when making a recommendation. However, we also gave recommendations when there were not any preventive SRs/meta-analyses, as everyone knows that it is not ethical to expose one group people to the GC risk factors in RCTs.

Regarding implications, for practice, although little evidence was provided, we must pay more attention to how to prevent GC cancer from such small clues. The GC inconsistent factors included diabetes, NSAIDs (aspirin), preserved fish, preserved vegetables, smoked

food, green tea, red meat, beer, glycemic load, vitamin C, ham, sausage, the GC non-significant factors included occupational exposure to Cr and chrysotile fiber, dupA H. pylori positive strains, glycemic index, folate, coffee, fish, selenium or statins, omega-3 fatty acids, vitamin E, aspirin, onion leaf. Beta-carotene below 20 mg/d, fruit, vegetables, allium vegetables, soybean products, tofu, non-fermented soy-foods, whole-grain, or dairy product, and asthma were the protective factors of GC, while beta-carotene 20 mg/d or above, pickled vegetables, fermented soy-foods (miso), processed meat 30 g/d or above, or bacon, or salty foods, exposure to alcohol (50 g/day, 75 g/day, 100 g/day, 125 g/day) or smoking, occupational exposure to Pb, overweight and obesity, helicobacter pylori (including cagA-positive strains) infection were GC risk factors. So we suggested screening and treating H. pylori infection, and limiting the amount of intake of processed meat consumption (30 g/d or below), beta-carotene (20 mg/d and below), pickled vegetables, fermented soy-foods (including miso), and salt or salty foods, lowering alcohol consumption, stopping smoking, avoiding excessive weight gain, keeping away from occupational exposure to Pb, and increasing the quantity of consumption of fresh fruit and vegetable (including allium vegetables), non-fermented soy-foods (including soybean products, tofu), whole-grain consumption, dairy product consumption in dietary food could decrease GC risk in daily life.

For research, the methodological qualities of included SRs/meta-analyses were not so good, and some necessary items were not well conducted, so it needs to be improved according some checklists, such as AMSTER. And there were so few primary studies about one topic that made the conclusion less confirmable, as a result more primary studies about the factors related to GC and how to prevent GC should be conducted. Another terrible thing we have discussed above is the conflicted results of different SRs/meta-analyses on the same topic as some of them were missed during searching and study selecting. That is why future similar researches need more rigorous methods and ways during systematic review making.

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