Pre-existing diabetes mellitus increases the risk of gastric cancer: A meta-analysis

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Abstract

AIM: To systematically assess the association between diabetes and incidence of gastric cancer.

METHODS: We searched MedLine (PubMed), EMBASE, and the Cochrane Library without any limitations with respect to publication date or language, we also searched the references of qualifying articles. Case-control studies and cohort studies comparing the risk of gastric cancer between diabetic patients and control subjects were included. We excluded studies reporting only standardized incidence ratios without control groups and those that investigated only mortality but not incidence. Seventeen studies met our criteria, and the qualities of these studies were assessed using the Newcastle-Ottawa Quality Assessment Scale. We performed a meta-analysis of pre-existing diabetes and gastric cancer incidence using the DerSimonian-Laird method for random-effects. For subgroup analyses, we separated the studies by study type, region, sex and method to determine confounding factors and reliability. We also conducted subgroup analyses to examine the effects of smoking, *Helicobacter pylori* (*H. pylori*) infection, and cancer site. Publication bias was evaluated using Begg's test.

RESULTS: A random-effects model meta-analysis showed an increased gastric cancer risk in diabetic patients [relative risk (RR) = 1.19; 95%CI: 1.08-1.31]. Subgroup analyses indicated that this result persisted in cohort studies (RR = 1.20; 95%CI: 1.08-1.34), in studies on populations of both Western (RR = 1.18; 95%CI: 1.03-1.36) and Eastern countries (RR = 1.19; 95%CI: 1.02-1.38), in a female subgroup (RR=1.24; 95%CI: 1.01-1.52), and in highly qualified studies (RR = 1.17; 95%CI: 1.05-1.31). Moreover, these results persisted when the analysis was confined to studies adjusted for well-known gastric cancer risk factors such as smoking (RR = 1.17; 95%CI: 1.01-1.34) and *H. pylori* infection (RR = 2.35; 95%CI: 1.24-4.46).

CONCLUSION: Pre-existing diabetes mellitus may increase the risk of gastric cancer by approximately 19%. This effect seems to be unrelated to geographical region.

INTRODUCTION

Diabetes mellitus is currently an epidemic. Approximately 171 million individuals worldwide had diabetes mellitus in 2000, and it is estimated that 366 million people will have diabetes by 2030, which corresponds to nearly 4.5% of the global population[1]. The estimated prevalence of diabetes among adults in the United States currently ranges from 5.9% to 12.4% (median 8.3%)[2], and some cancers, such as colorectal, endometrial, breast, liver, and pancreatic cancer, are reportedly more prevalent in diabetes patients[3-7]. Diabetes mellitus has also been associated with an increased risk of long-term and all-cause mortality in cancer patients[8].

Although the incidence and associated mortality of gastric cancer is decreasing, it remains the fourth most common cancer and the second leading cause of cancer-related mortality worldwide[9]. Despite the success in gastric cancer control, the persistence of the public health burden of gastric cancer indicates the need to expand efforts to identify and address the individual and social determinants of the disease. The public health significance of a potential causal link between diabetes mellitus and gastric cancer highlights the need for a systematic assessment of the association between these 2 diseases.

Therefore, several systematic reviews have recently been performed to examine the above mentioned associations. One review suggested that diabetic individuals have an increased risk of gastric cancer[10]. However, this review had some limitations as it included studies without control groups[11-14] and excluded appropriate studies[15,16]. Two other reviews showing inconclusive results[17,18] did not include any recent studies[19,20], and did not differentiate between "incidence" and "mortality" in terms of describing the risk[17]. Such methodological weaknesses of the previous meta-analysis made it difficult to understand the association between preexisting diabetes mellitus and the risk of gastric cancer.

In the present study, we aimed to clarify the association between diabetes and gastric cancer through an extensive search of the literature, which we reviewed using strict criteria.

MATERIALS AND METHODS

Methods

The procedures performed in this meta-analysis are in accordance with recent guidelines for the reporting of meta-analysis (PRISMA guidelines).

Data sources and searches

We conducted a systematic search of electronic databases and the bibliographies of all eligible studies to identify all relevant studies. We initiated the search on February 7, 2012 without any limitations with respect to publication date or language. The electronic databases searched included MedLine (PubMed), EMBASE, and the Cochrane Library. The search strategy included terms for diabetes (glucose, diabetes, or hyperglycemia), gastric cancer (stomach cancer, gastric cancer, stomach malignant neoplasm, or gastric malignant neoplasm), and risk (incidence, prevalence, or risk). We also searched the references of included articles.

Study selection

Case-control studies, cohort studies, and randomized controlled trials comparing the risk of gastric cancer between diabetic patients and control subjects were eligible for inclusion. We included studies evaluating self-reported diabetes, registered diabetes, and high HbA1c and blood glucose levels. To be included in our meta-analysis, articles had to contain both of the following: (1) a risk estimate (hazard ratio, relative risk, or odds ratio relating preexisting diabetes to subsequent occurrences of gastric cancer); and (2) an estimate of precision (standard error or 95%CI). We also included articles that failed to report precision directly, but from which we could reconstruct a precision estimate using the data described[21,22]. We excluded studies reporting only standardized incidence ratios without control groups. We also excluded studies that investigated only mortality without incidence and studies in which the classification of the subjects' diabetes status (diabetic or non-diabetic) was not possible due to insufficient ranges in blood glucose levels. Studies were excluded if either the abstract[23] or the full text[24] was unavailable after author contact was made.

Data extraction and quality assessment

The titles, abstracts, and full articles were reviewed independently by two authors (Yoon JM and Son KY). Yoon JM performed a full abstraction of the data, and Son KY verified the accuracy. Disagreements were resolved by discussion, consensus, and arbitration by a third author (Park SM). Abstracted data included type of study, study population characteristics, criteria for diabetes mellitus or hyperglycemia, duration of follow-up, incidence of cancer, adjustment variables, and study quality. Quality was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) for case-control or cohort studies.

Statistical analysis

To avoid overlapping patient populations, we compared data sources and geographic locations. If a patient population was found to overlap, we included the article with the most comprehensive population or the most adjusted risk estimate associated with preexisting diabetes. If an article reported estimates separately by sex[15,19,25-29] or by different cohorts[16], we regarded the study as 2 independent studies. If an article did not report the risk ratio and confidence interval, we estimated the risk using Fisher's exact test without adjustment[20-22], and the estimates were rounded off to the nearest hundredth. In case-control studies, odds ratios were regarded as relative risks because of the low prevalence of gastric cancer[9,30,31].

For the meta-analysis, we calculated pooled estimates for all the studies. For the subgroup analyses, we separated studies by study type, region, sex, and method to determine the confounding factors and reliability. We also
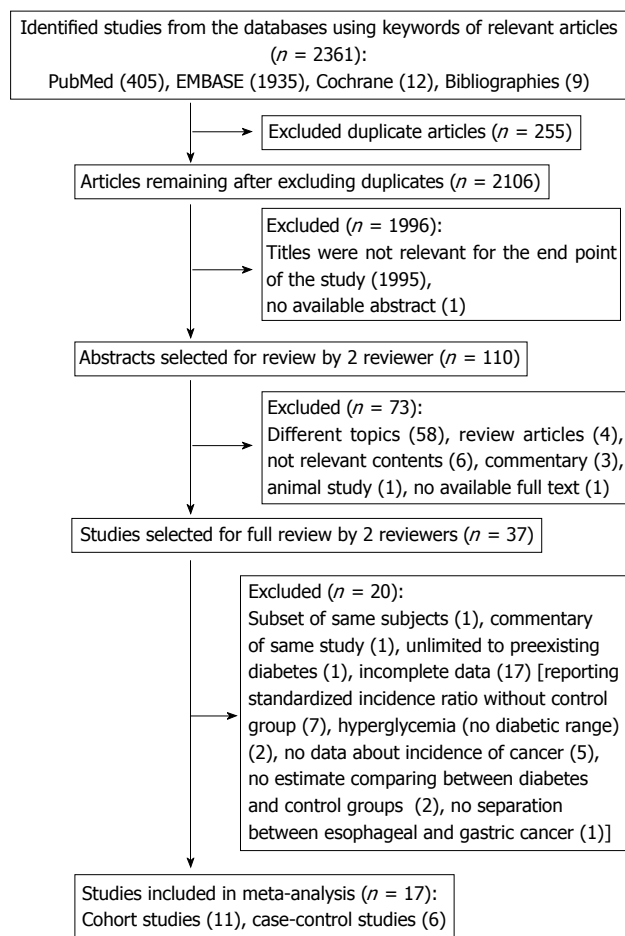
Identified studies from the databases using keywords of relevant articles
(*n* = 2361):
PubMed (405), EMBASE (1935), Cochrane (12), Bibliographies (9)

→ Excluded duplicate articles (*n* = 255)

Articles remaining after excluding duplicates (*n* = 2106)

→ Excluded (*n* = 1996):
Titles were not relevant for the end point
of the study (1995),
no available abstract (1)

Abstracts selected for review by 2 reviewer (*n* = 110)

→ Excluded (*n* = 73):
Different topics (58), review articles (4),
not relevant contents (6), commentary (3),
animal study (1), no available full text (1)

Studies selected for full review by 2 reviewers (*n* = 37)

→ Excluded (*n* = 20):
Subset of same subjects (1), commentary
of same study (1), unlimited to preexisting
diabetes (1), incomplete data (17) [reporting
standardized incidence ratio without control
group (7), hyperglycemia (no diabetic range)
(2), no data about incidence of cancer (5),
no estimate comparing between diabetes
and control groups (2), no separation
between esophageal and gastric cancer (1)]

Studies included in meta-analysis (*n* = 17):
Cohort studies (11), case-control studies (6)

Figure 1 Flow diagram of studies identified and selected.

conducted subgroup analyses to examine the effects of smoking, *Helicobacter pylori* (*H. pylori*) infection, and cancer site, which are major factors influencing the risk of gastric cancer[32-34]. We calculated all the pooled estimates using the DerSimonian-Laird method for random effects. We also reported I^2 values for heterogeneity assessment. Publication bias was evaluated using Begg's test. All analyses were conducted using Stata software(version12.1, StataCorp, United States).

RESULTS

The systematic literature search identified 2361 relevant references (Figure 1). After screening the titles, we excluded 255 duplicated and 1996 non-relevant studies. By reviewing the abstracts, we further excluded 73 articles. The full texts of the 37 remaining articles were retrieved for formal review. After independent review, 20 studies were excluded; 2 studies[35,36] used the same populations as another trial[37], and 1 did not limit the exposure group to individuals with preexisting diabetes[38].

Seventeen studies reported only limited data (uncertain diabetes diagnosis[39,40], usage of a standardized incidence ratio[11,13,14,41-44], lack of an acceptable control group[45,46], reporting of only mortality data[47-51], and uncertain gastric cancer diagnosis[52]). Table 1 provides the details of

the 17 studies that met our predefined inclusion and exclusion criteria. In total, 11 cohort[15,16,19,22,26-28,37,53-55] and 6 case-control[20,21,25,29,56,57] studies were used. We were unable to find any suitable randomized control trials.

Description of studies
The 17 articles included in our analysis were heterogeneous in many respects. Geographically, 6 studies were conducted in East Asia, 1 in West Asia, 5 in North America, and 5 in Europe. According to the cohort studies, the prevalence of diabetes varied from 3.0% to 13.2%. Four studies used measurement criteria to define diabetes mellitus, and 2 studies differentiated between gastric cardia and non-cardia cancer. The reporting of age and follow-up time varied widely. In 13 studies, a time interval of more than 1 year between the diagnoses of diabetes and cancer was required in order to minimize reverse causality, although 2 studies showed only the estimates without time intervals[16,54]. Quality varied from 4 to 9 stars according to the NOS, but 3 studies were downgraded because we used recalculated estimates without adjusting for pooled analysis[20-22]. After downgrading, the mean NOS score was 7.3. We therefore conducted subgroup analysis according to methodological quality (with "high-quality" defined as a score of $\geqslant 8$).

Fifteen studies included both sexes and 10 reported data separated by sex. In one of the latter, fewer than 5 female patients were diagnosed with both diabetes mellitus and subsequent gastric cancer[15]; the estimate was therefore not reported. In total, we found 28 independent groups separated by sex and cohort, and we yielded 27 eligible estimates. Only 2 studies described the specific risk ratios of cardia and non-cardia gastric cancers[20,22].

Overall
As shown in Figure 2, diabetes mellitus was associated with a significantly increased risk of gastric cancer in all included studies using random effects model analysis [relative risk (RR) = 1.19; 95%CI: 1.08-1.31; I^2 = 70.7%; 95%CI: 56.8%-80.2%].

Subgroup meta-analysis
We examined methodological differences when determining the quality of the studies. According to Figure 2, subgroup meta-analysis by study design revealed significant associations in cohort studies (RR = 1.20; 95%CI: 1.08-1.34), while the results of case-control studies were not statistically significant. Positive associations were observed in more reliable subgroup studies using the registration record or laboratory measurements as diabetes criteria and studies that were highly graded by NOS. A subgroup meta-analysis of studies designed to minimize reverse causality, including the shortest cancer-free interval, indicated that diabetes seemed to increase subsequent gastric cancer (Table 2).

Regional and gender-based differences are presented in Table 2. East Asian (RR = 1.19; 95%CI: 1.02-1.38) and Western studies (RR = 1.18; 95%CI: 1.03-1.36) showed

Table 1 Characteristics of 15 studies included in the meta-analysis of the gastric cancer risk of preexisting diabetes

Study	Study type	Country	DM criteria	Age (yr)	Follow up (yr)	Least interval¹ (yr)	Sex	DM prevalence	RR or OR (95%CI)	Adjustment variables/matched variable of selection	NOS
Atchison et al[53]	CS	United States (veterans)	Registration	18-100	27	1	Male	13.2%	0.95 (0.89-1.02)	Age, time, latency, race, number of visits, diagnoses of alcohol-related conditions, obesity and COPD	8
Carstensen et al[19]	CS	Denmark	Registration	No limit	15	Not mentioned	Male / Female		1.28 (1.15-1.43) / 1.34 (1.14-1.58)	Age, calendar time, date of birth	8
Jiang et al[20]	CC	United States	Self reported	30-74		1	Both		1.51 (1.10-2.07)²	Age, sex, race, education, birth place, smoking and BMI	7 (5)⁵
Lin et al[22]	CS	United States	Self reported	50-71	10	2	Male / Female	9.9% / 7.2%	1.52 (1.21-1.92)² / 1.62 (0.98-2.68)²	Age, calories, alcohol consumption, smoking, fruit consumption, vegetable consumption, ethnicity, education, and physical activity	8 (6)⁵
Wotton et al[16] ORLS1 / ORLS2	CS	England	Registration	≥ 30	35 / 9	0	Both	5.5% / 4.0%	1.11 (0.89-1.37) / 2.05 (1.30-3.10)	Sex, age in 5-year bands, time and district of residence	8
Chodick et al[54]	CS	Israel	Registration	≥ 21	8	0	Male / Female		1.44 (0.98-2.11) / 0.99 (0.55-1.80)	Age, region, SES level, use of healthcare, BMI, and history of CVD/ matched for age, sex	8
Ikeda et al[37]	CS	Japan	HbA1c (5.0%-5.9% vs 7.0%)	≥ 40	14	Not mentioned	Both	3.9%	2.69 (1.24-5.85)	Age, sex, H. pylori, history of peptic ulcer, BMI, TC, alcohol intake, smoking, dietary factor⁴	8
Ogunleye et al[55]	CS	Scotland	Registration (only type 2 DM)	No limit	11	1	Both		0.77 (0.36-1.66)	Deprivation deciles of Carstairs/matched for age, sex and doctor practice	8
Kuriki et al[29]	CC	Japan	Self reported	40-80		Not mentioned	Male / Female		1.16 (0.93-1.44) / 1.70 (1.16-2.48)	Age, BMI, drinking, smoking, exercise, bowel movement, FHx of cancer and DM, dietary restriction, vegetable intake, greasy food, snack	6
Inoue et al[27]	CS	Japan	Self reported	40-69	13	5	Male / Female	6.7% / 3.0%	1.09 (0.79-1.5) / 1.92 (1.06-3.47)	Age, study area, history of CVD and IHD, smoking, BMI, physical activity, alcohol, vegetable, coffee	9
Jun et al[57]	NCC	Korea	FBS (< 99 mg/dL vs ≥ 126 mg/dL)	≥ 35	Case 2.4/ control 6.5 h	2	Both		1.77 (0.57-5.45)	H. pylori, smoking, drinking, and education level/matched on age, sex, year and area of enrollment, and follow-up duration	9
Khan et al[28]	CS	Japan	Self reported	40-79	19	2	Male / Female	7.5% / 4.6%	0.72 (0.40-1.09) / 0.26 (0.08-0.82)	Age, BMI, smoking, drinking	8
Rapp et al[15]	CS	Austria	FBS (4.2-5.2 mmol/ L vs 7.0 mmol/L)	> 19	14	1	Male / Female	3.9% / 3.0%	0.84 (0.38-1.87) / -³	Age, smoking, occupation, BMI	8
Rousseau et al[56]	CC	Canada	Self reported	35-70		2	Male		1.0 (0.5-1.8)	Age, income, education, ethnicity, proxy status, BMI, smoking, beta-carotene, alcohol	7
Jee et al[26]	CS	South Korea	FBS (< 90 mg/dL vs ≥ 126 mg/dL or DM medication)	30-95	10	1	Male / Female	5.1% / 4.5%	1.11 (1.04-1.2) / 1.15 (0.99-1.34)	Age, age squared, smoking, alcohol	8
La Vecchia et al[25]	CC	Italy	Self reported	≤ 75		Not mentioned	Male / Female		0.6 (0.4-1.0) / 0.7 (0.4-1.2)	Age	6
O'Mara et al[21]	CC	USA (only white)	Self reported	30-89		1	Male / Female		0.91 (0.28-2.27)² / 1.57 (0.48-3.94)	Age	4 (3)⁵

¹Interval between diabetes mellitus (DM) and gastric cancer to be selected as population; ²Calculated from table without adjustment by Fisher's exact test; ³No estimate was reported due to less than 5 cases in DM patients; ⁴Energy, fat, salt, vitamin, dietary fibers; ⁵The first numbers are Newcastle-Ottawa Quality Assessment Scale (NOS) of original studies. The second numbers in brackets are downgraded NOS because we calculated new estimates without adjustment. Subgroup analysis were done according to the second numbers. CS: Cohort study; CC: Case-control study; NCC: Nested case-control study; BMI: Body mass index; FBS: Fasting blood glucose; FHx: Family history; TC: Total cholesterol; CVD: Cardiovascular disease; IHD: Ischemic heart disease; ORLS: Oxford Record Linkage Study; H. pylori: Helicobacter pylori; COPD: Chronic obstructive pulmonary disease.

similar increased risks. In the sexual subgroup, only women exhibited statistical significance (RR = 1.24; 95%CI: 1.01-1.52). Pooled estimates adjusted for well-known gastric cancer risk factors (cigarette smoking and H. pylori infection) were also significant. The pooled estimate adjusted for ciga-

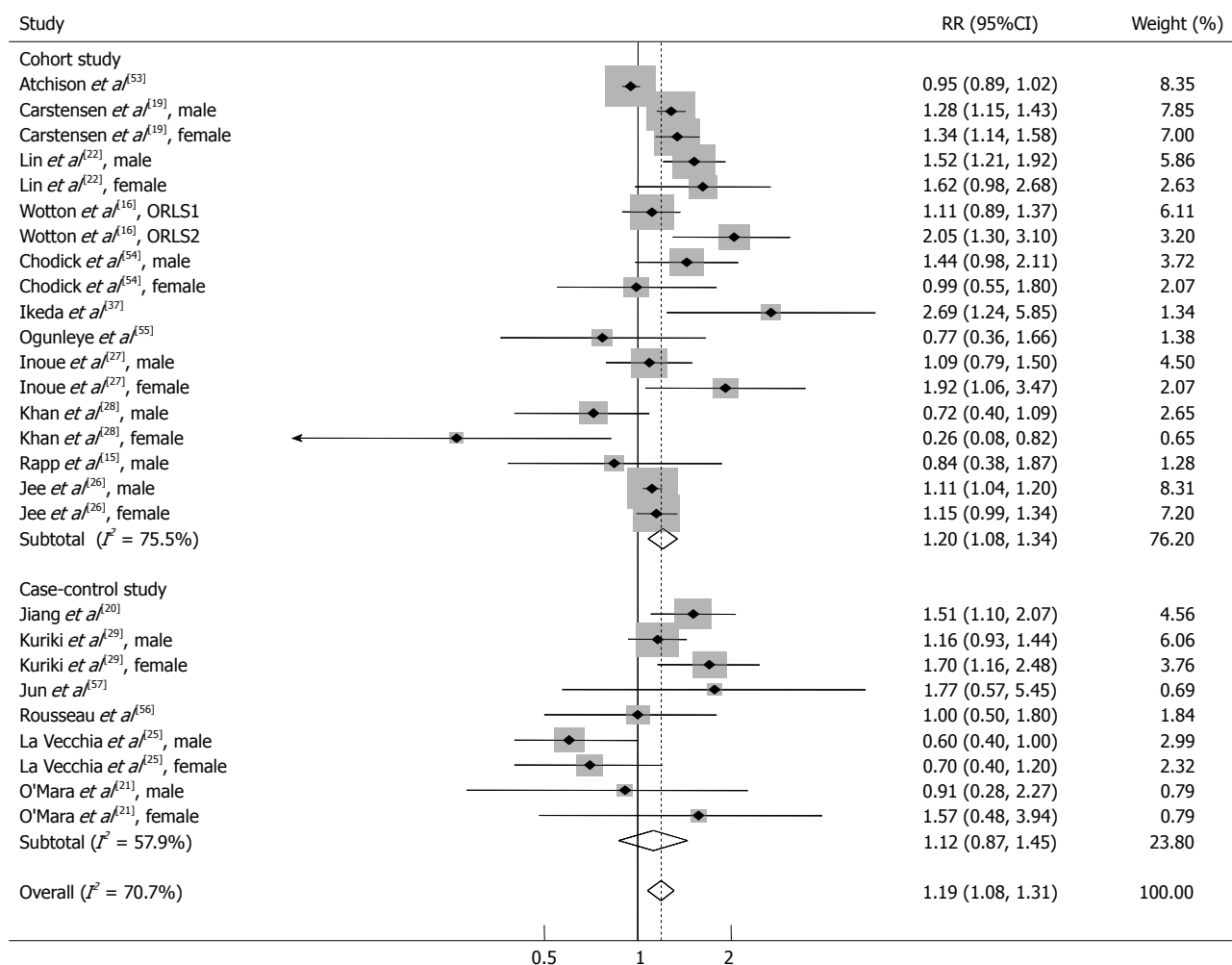| Study		RR (95%CI)	Weight (%)
Cohort study			
Atchison *et al*[53]		0.95 (0.89, 1.02)	8.35
Carstensen *et al*[19], male		1.28 (1.15, 1.43)	7.85
Carstensen *et al*[19], female		1.34 (1.14, 1.58)	7.00
Lin *et al*[22], male		1.52 (1.21, 1.92)	5.86
Lin *et al*[22], female		1.62 (0.98, 2.68)	2.63
Wotton *et al*[16], ORLS1		1.11 (0.89, 1.37)	6.11
Wotton *et al*[16], ORLS2		2.05 (1.30, 3.10)	3.20
Chodick *et al*[54], male		1.44 (0.98, 2.11)	3.72
Chodick *et al*[54], female		0.99 (0.55, 1.80)	2.07
Ikeda *et al*[37]		2.69 (1.24, 5.85)	1.34
Ogunleye *et al*[55]		0.77 (0.36, 1.66)	1.38
Inoue *et al*[27], male		1.09 (0.79, 1.50)	4.50
Inoue *et al*[27], female		1.92 (1.06, 3.47)	2.07
Khan *et al*[28], male		0.72 (0.40, 1.09)	2.65
Khan *et al*[28], female		0.26 (0.08, 0.82)	0.65
Rapp *et al*[15], male		0.84 (0.38, 1.87)	1.28
Jee *et al*[26], male		1.11 (1.04, 1.20)	8.31
Jee *et al*[26], female		1.15 (0.99, 1.34)	7.20
Subtotal (I^2 = 75.5%)		1.20 (1.08, 1.34)	76.20
Case-control study			
Jiang *et al*[20]		1.51 (1.10, 2.07)	4.56
Kuriki *et al*[29], male		1.16 (0.93, 1.44)	6.06
Kuriki *et al*[29], female		1.70 (1.16, 2.48)	3.76
Jun *et al*[57]		1.77 (0.57, 5.45)	0.69
Rousseau *et al*[56]		1.00 (0.50, 1.80)	1.84
La Vecchia *et al*[25], male		0.60 (0.40, 1.00)	2.99
La Vecchia *et al*[25], female		0.70 (0.40, 1.20)	2.32
O'Mara *et al*[21], male		0.91 (0.28, 2.27)	0.79
O'Mara *et al*[21], female		1.57 (0.48, 3.94)	0.79
Subtotal (I^2 = 57.9%)		1.12 (0.87, 1.45)	23.80
Overall (I^2 = 70.7%)		1.19 (1.08, 1.31)	100.00

0.5   1   2

Figure 2 Meta-analysis and pooled relative risk of gastric cancer comparing non-cancer population with and without preexisting diabetes mellitus by random effect model. ORLS: Oxford Record Linkage Study.

rette smoking status was similar to the overall results (RR = 1.17; 95%CI: 1.01-1.34). The pooled estimate adjusted for *H. pylori* infection was greater than the overall estimate (RR = 2.35; 95%CI: 1.24-4.46). Nevertheless, subgroup analyses on either cardia or noncardia cancer did not produce significant results.

Publication bias
Begg's test indicated no publication bias in our analysis (Figure 3).

DISCUSSION
Summary of results
We found a significant association between preexisting diabetes and gastric cancer incidence. In diabetic patients, we found that the risk of subsequent gastric cancer incidence was increased by approximately 19%, and this effect was significant in women. The subgroups of cohort, Western and Eastern studies, showed similar results. These results persisted in studies using self-reported criteria and those adjusted for known risk factors such as cigarette smoking and *H. pylori* infection.

Explanations
We observed some discrepancy between our analysis and previous meta-analysis. Three previous meta-analysis have explored the association between diabetes and gastric cancer incidence. One of these, a meta-analysis of cohort studies[18], produced a misleading result due to the exclusion of appropriate cohort studies[16,19,54] and the inclusion of a study using a glucose level that was not clearly defined and an unrepresentative range of diabetes mellitus[40]. The study also presented an incomprehensible method for summarizing 2 estimates of cardia and noncardia cancer from the same control group. A different study[17] used the term "risk" without a distinction between incidence and mortality. This methodological weakness made the result heterogeneous and biologically implausible. Another meta-analysis[10] also excluded several recent studies[15,16,19,20] and included studies reporting a standardized incidence ratio without quality assessment.

To supplement the previous insufficient meta-analyses, we restricted inclusion in our analysis to studies reporting a risk ratio compared to a control group, and we assessed the quality of these studies using various criteria. As a result, we found that diabetes and the risk of gastric
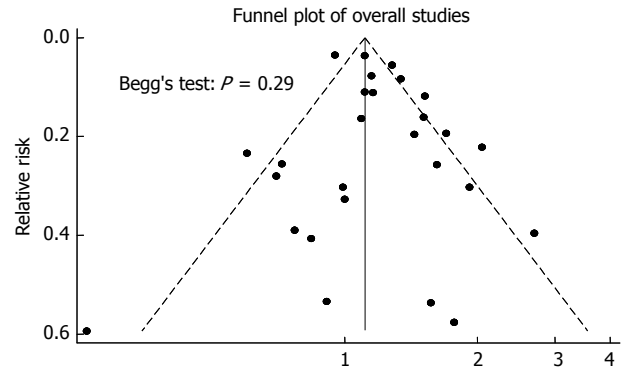
Table 2 Preexisting diabetes and risk of gastric cancer by subgroup meta-analysis using random effect model

	Studies (n)	RR (95%CI)	I^2 % (95%CI)
Overall	27	1.19 (1.08-1.31)	70.7 (56.8-80.2)
Countries			
East Asian countries[1]	10	1.19 (1.02-1.38)	60.1 (20.0-80.1)
Western countries[2]	17	1.18 (1.03-1.36)	75.6 (61.0-84.8)
Study type			
Cohort study	18	1.20 (1.08-1.34)	75.5 (61.2-84.5)
Case control study	9	1.12 (0.87-1.45)	57.9 (11.8-79.9)
Sex			
Male	12	1.10 (0.97-1.24)	74.9 (55.7-85.8)
Female	9	1.24 (1.01-1.52)	58.9 (14.1-80.3)
DM criteria			
Registration	8	1.21 (1.02-1.44)	83.0 (67.8-91.0)
Measured[3]	5	1.15 (1.01-1.32)	35.5 (0.0-75.8)
Self report	14	1.13 (0.93-1.39)	65.2 (38.6-80.3)
Interval[4]			
One and more years	15	1.15 (1.02-1.31)	67.5 (44.3-81.0)
Quality (NOS)			
High quality (8 and more)	17	1.17 (1.05-1.31)	73.4 (57.0-83.6)
Low quality (7 and less)	10	1.20 (0.97-1.49)	61.2 (22.6-80.5)
Adjustment for risk factor			
Smoking[5]	12	1.17 (1.01-1.34)	52.6 (8.7-75.4)
H. pylori[5]	2	2.35 (1.24-4.46)	0.0 (UC)
Cancer site			
Cardia cancer	2	1.39 (0.72-2.69)	82.3 (UC)
Noncardia cancer	2	1.19 (0.80-1.77)	59.6 (UC)

[1]Japan, South Korea; [2]United States, Canada, Europe and Israel; [3]Using fasting blood glucose or HbA1c as criteria; [4]The least cancer-free time of subject according to study design; [5]The subgroup of studies designed to include the risk factor as adjustment variables. RR: Relative risk; UC: Unable to calculate due to low degree of freedom; NOS: Newcastle-Ottawa Quality Assessment Scale; *H. pylori*: *Helicobacter pylori*.

Figure 3 Funnel plots for publication bias.

IGF-IR inhibits tumor development[60,61].

Vascular endothelial growth factor (VEGF), the levels of which are increased in the blood of diabetic patients[62], is another cytokine that is related to the oncogenic properties of diabetes. VEGF is correlated with tumor vascularity and the frequency of hepatic metastasis, and it induces the proliferation and dilation of lymphatics culminating in node metastasis[63-65]. Moreover, the IGF/IGF-IR axis has also been shown to interact with the VEGF/VEGFR system in various tumors including gastrointestinal malignancies[66,67].

DNA damage in diabetic patients is another potential mechanism of oncogenesis. The increased production of reactive oxygen species could result in greater oxidative damage to DNA[68]. Furthermore, in an experimental study, high blood glucose levels were shown to directly induce DNA damage[69].

While we found that the association between diabetes and gastric cancer persisted irrespective of *H. pylori* infection, it nevertheless seems probable that diabetes and *H. pylori* infection, which is a known risk factor for gastric cancer, work synergistically to increase the risk of gastric cancer. Indeed, a previous cohort study in Japan demonstrated that a high HbA1c level and a concomitant *H. pylori* infection increased the gastric cancer risk synergistically[37]. It is possible that reactive oxygen-dependent DNA damage enhances the modifying effect of *H. pylori* on epithelial cell proliferation.

To confirm this synergistic effect, we also performed subgroup analyses by cancer site. Although noncardia gastric cancers were known to be strongly associated with *H. pylori* infection[70,71], we failed to show a similar relationship between diabetes mellitus and specific sites of gastric cancer. As further studies dealing with site-specific data are performed, a reassessment will be required.

Potential confounders
A positive association between diabetes and gastric cancer incidence was observed among women but not among men. These results must be interpreted carefully as there were only a few studies differentiating men and women. Sex hormones could represent one possible reason for this difference. In breast cancer, it is well established that

cancer were positively associated with each other. This positive association may be reliable based on consistent results from well-designed studies including cohort studies, studies of high quality based on assessment with the NOS, studies examining the time interval between onset of diabetes and subsequent gastric cancer, and studies using objective diabetic criteria (diabetes registry or laboratory measurements) that were adjusted based on important factors (smoking or *H. pylori* infection). Although a time interval of 1 year between diabetes and gastric cancer may be insufficient evidence of a causal relationship, we were able to minimize the reverse causality.

Regarding biological plausibility, the results of this study are consistent with previous studies in which preexisting diabetes was associated with an increased risk of a variety of cancers. The oncogenic properties of diabetes have been well documented. The increased insulin concentration in early diabetes can stimulate cell proliferation through activation of the insulin receptor or insulin-like growth factor-I receptor (IGF-IR) and the inhibition of IGF binding proteins, which may result in increased free and bioavailable IGF-I[58]. Additionally, a high level of serum IGF-I has been demonstrated to increase the risk for development of several carcinomas including gastrointestinal carcinomas[59]. Exogenous IGFs stimulate the proliferation of gastric cancer cells, while the blocking of

estrogen and IGF-1 interactively affect cell proliferation[72]. Gastrointestinal tissues, whether normal or cancerous, contain estrogen receptor β, and estrogen can bind to them[73,74]. Through an undefined mechanism, estrogen levels in diabetic women could influence or stimulate the proliferation of gastric cancer cells.

This gender-based difference could also be due to disparate methods of diabetes intervention. Metformin[46,75], aspirin[76,77], and statins[78] are known to protect against a number of cancers, while insulin is reported to increase the risk of several cancers[75]. Although gender differences in this matter were not explored in many previous studies, clues were obtained from the following studies: One study suggested that gender differences in adherence to diabetes management were minimal[79]. However, an Italian study reported that diabetic women were more likely to use insulin than men[80]. According to an American study, men use statins more frequently in type 2 diabetes mellitus[81]. These factors, however small, might contribute to the above-mentioned gender differences.

Limitations

Our study has several limitations. First, the studies we examined were highly heterogeneous. In particular, diabetes mellitus was defined by various methods and cut-off values. Diabetic prevalence and subject age also differed. Second, dietary food factors such as salt, nitrite[82-84], and fresh vegetable[85] intake could not be considered in the analysis despite being potential confounders. Finally, the selected studies contained no details regarding diabetes interventions that were sufficient to adjust for the effects of diabetes treatments.

In conclusion, despite the limitations, our meta-analysis suggests that preexisting diabetes mellitus may increase the risk of gastric cancer. Further prospective studies assessing confounders such as diabetes interventions are needed to specifically test the effects of diabetes mellitus on gastric cancer risk.

COMMENTS

Background

The burden of diabetes mellitus is increasing globally. Gastric cancer is the fourth most common cancer and the second leading cause of cancer-related mortality worldwide. Although the association between diabetes mellitus and a variety of cancers is well established, the association between diabetes mellitus and gastric cancer is currently unclear.

Research frontiers

Over the past 3 decades, many studies have been performed to understand the associations between preexisting diabetes mellitus and subsequent gastric cancer incidence. Moreover, several systematic reviews were recently performed to investigate these associations. However, these reviews were methodologically insufficient and thus could not achieve a comprehensive conclusion.

Innovations and breakthroughs

Based on this meta-analysis, preexisting diabetes mellitus may increase the risk of gastric cancer by approximately 19%. Similar associations were indicated in subgroup analyses of East Asian, Western, cohort, and high-quality studies. These findings were not presented clearly in previous systematic reviews.

Applications

Diabetes mellitus appears to be either directly or indirectly associated with the risk of gastric cancer. An exploration of the mechanism for this association may help them to reduce the gastric cancer risk.

Terminology

Insulin-like growth factors (IGFs) are proteins similar to insulin. IGF is a part of the cellular communication system. Recently, IGFs were proposed to play a role in aging. Vascular endothelial growth factor (VEGF) is a protein related to angiogenesis. In diabetes mellitus, the level of VEGF in the blood is high.

Peer review

This is a well-performed meta-analysis of currently available studies on the potential role of diabetes mellitus in the development of gastric cancer. The authors found that pre-existing diabetes mellitus may increase the risk of gastric cancer by approximately 19%. This finding was found to be unrelated to geographical region. This is a good meta-analysis and the authors have included many relevant issues missed by other research groups.

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