

Diabetes mellitus carries a risk of gastric cancer: A meta-analysis

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Abstract

AIM: To investigate the association and quantify the relationship between diabetes mellitus (DM) and gastric cancer (GC) by an updated meta-analysis.

METHODS: The initial PubMed search identified 1233 publications. Studies not reporting GC or those not reporting actual number of GC were excluded. Twelve pertinent studies were retrieved from the PubMed database or from a manual search and considered for the meta-analysis. Pooled risk ratios and 95%CI were estimated by a random-effects model. Subgroup analysis was performed according to gender or geographical regions. Heterogeneity and publication bias were evaluated by I^2 and funnel plot analysis, respectively.

RESULTS: DM was significantly associated with GC with a RR of 1.41 ($P = 0.006$) (95%CI: 1.10-1.81). Subgroup analyses revealed that both sexes showed a significant association with GC, with a greater magnitude of risk in females (RR = 1.90; 95%CI: 1.27-2.85; $P = 0.002$) than in males (RR = 1.24; 95%CI: 1.08-1.43; $P = 0.002$). In addition, the link between DM and GC was significant in East Asian DM patients (RR = 1.77; 95%CI: 1.38-2.26; $P < 0.00001$) but not in Western DM patients (RR = 1.23; 95%CI: 0.90-1.68; $P = 0.2$). There was no evidence of publication bias, but the re-

sults indicated significant heterogeneity.

CONCLUSION: This updated meta-analysis has provided evidence of positive DM-GC associations. The limited information on potentially important clinical confounding factors in each study deserves further investigation.

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Key words: Gastric cancer; Diabetes mellitus; Meta-analysis; Hyperglycemia; Hyperinsulinemia

Core tip: Diabetes mellitus (DM) was significantly associated with gastric cancer (GC) with a risk ratio of 1.41. This positive DM-GC association was also observed in both sexes with a greater magnitude of risk in females than male, and in East Asian patients but not in Western patients. This study could provide one answer to current inconsistent knowledge across trials concerning a positive/inverse DM-GC association. Since DM patients are less likely to be screened for cancers, clinicians caring for DM patients should remain alert to detect GC especially in females, since there are fewer female than male GC patients in the general population.

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INTRODUCTION

A growing body of evidence, derived largely from case-control studies, cohort studies, and meta-analyses, suggests that diabetes mellitus (DM) is associated with an increased risk of a number of cancers. The risk increases 2-fold for cancers of the liver, pancreas, and endome-

trium, and 1.2-1.5-fold for cancers of the colon and rectum, breast, bladder, and kidney^[1], while prostate cancer shows a positive^[2] or inverse^[1] association with DM. In fact, DM is a disease of global epidemic proportions. The DM population has increased from 171 million in 2000 to 366 million in 2011, a figure projected to increase to 552 million by 2030^[3,4]. This increasing prevalence of DM with its anticipated 200 million more patients over the next two decades suggests that even a small increase in cancer risk will have an undeniable impact on the health of the general population. Therefore, in addition to the dramatic increase in the prevalence of DM and the consequences of its complications, a DM-cancer association may greatly affect worldwide health levels.

Despite the heightening clinical awareness of the DM-cancer association, however, the risk of gastric cancer (GC) in DM patients has seemingly attracted little attention among diabetes researchers and healthcare providers, and this topic has been scarcely addressed in the English literature with contradictory findings. This dearth of data may be attributable to the fact that the disease *per se* has been paid little attention in the West, with fewer established regular screening programs for GC. Consequently, the risk of GC in DM patients is still overshadowed by the more common acute and chronic DM complications such as cardiovascular and renal diseases, which largely account for the 2-fold increase in mortality associated with DM^[5]. Under these circumstances, the reported risks of GC in DM patients have been inconsistent, being high^[6,7], neutral^[8], or inverse^[9] with an odds ratio or incidence RR of 1.14 (95%CI: 1.03-1.31) to 2.07 (95%CI: 1.40-3.08), 1.2 (95%CI: 0.74-1.70) to 1.6 (95%CI: 0.79-2.32), and 0.67 (95%CI: 0.46-0.99), respectively. Mixed results were also observed while evaluating the association between fasting glucose and GC risk; the Japanese Hisayama study^[10] showed a positive association, but European^[11] and Korean^[12] studies did not. Furthermore, the studies investigating DM-GC associations comprised heterogeneous participants without distinguishing between type 1 DM (T1DM) and type 2 DM (T2DM)^[13], or were based on different DM criteria such as treatment^[14,15], fasting blood glucose^[11], or self-report^[16,17]. Even three recent meta-analyses have provided mixed results with neutral^[18], marginal^[19], and positive^[20] DM-GC associations. This article aims to update the DM-GC association by including several of the most recent articles as well as others investigating the actual number of GC patients in DM and non DM cohorts.

MATERIALS AND METHODS

All publications concerning the DM-GC association were retrieved from the English literature. A computerized literature search between the years 1950 and January 2013 was conducted in PubMed using Boolean operators, with ("cancer" or "carcinoma") and "diabetes" as keywords. Additional studies that were considered pertinent were sought by a manual search through reference lists

in the retrieved publications. The reference retrieval was additionally complemented by a manual search of references from previous meta-analyses^[18-20]. When more than one analysis of the same cohort was published, the most recent was selected. Articles which apparently reported cancers other than GC in their title/abstract were excluded. Afterwards, following a thorough review of the selected articles, 12 studies reporting comparisons on actual numbers of GC patients between DM and non DM subjects were finally judged to qualify^[11,15-17,21-28]. The reference lists of the identified meta-analyses were searched to identify original research reports on this topic. Reports from Japan^[16,21,22] and Taiwan^[15,23] were defined as East Asian studies, and those from the United States^[17,24,25] and Europe^[11,26,27] defined as Western studies.

Statistical analysis

Each GC incidence in each publication was treated as a dichotomous variable. Data from all relevant studies were combined to estimate the pooled RR with a 95%CI using the random effects model^[29] provided by the Cochrane Library software Review Manager 5. An RR less than or greater than 1.0 meant respectively a negative or positive DM-GC association. Heterogeneity was quantified using the I^2 measure, in which $I^2 < 30\%$ indicated mild heterogeneity, 30%-70% moderate heterogeneity, and $> 70\%$ severe heterogeneity^[30]. Publication bias was evaluated by funnel plot analysis using Comprehensive Meta Analysis version 2 software. $P < 0.05$ was considered significant.

RESULTS

The initial PubMed search identified 1233 publications. After the title and abstract review, studies reporting cancers other than GC in DM patients were excluded, and 152 articles deemed potentially relevant were retrieved for further evaluation. Excluding studies not reporting the actual number of GC patients in DM and nonDM cohorts, 12 publications were ultimately selected (Figure 1), yielding a total of 16725 GC patients: 2150 DM and 14575 non-DM. T1DM and T2DM were not differentiated in these publications except for two in which only T2DM patients were investigated. Five^[15,16,21-23] studies were from East Asia, 6^[11,17,24-27] were from the West, and one^[28] was from Israel. Each publication provided mixed results concerning the DM-GC association with adjustment of confounders (Table 1).

The pooled results showed a significant increase in GC risk in the DM cohort (RR = 1.41; 95%CI: 1.10-1.81; $P = 0.006$) with significant statistical heterogeneity ($I^2 = 95\%$; $P < 0.00001$) (Figure 2A). The subgroup analyses stratified by gender or geographical regions revealed positive GC associations in both sexes, with a larger magnitude of correlation in females (RR = 1.90; 95%CI: 1.27-2.85; $P = 0.002$) than in males (RR = 1.24; 95%CI: 1.08-1.43; $P = 0.002$) (Figure 2B and C). East Asian subjects showed a 77% increased risk of GC (RR = 1.77; 95%CI: 1.38-2.26; $P < 0.00001$) but Western subjects did not (RR = 1.23; 95%CI: 0.90-1.68; $P = 0.2$) (Figure 2D

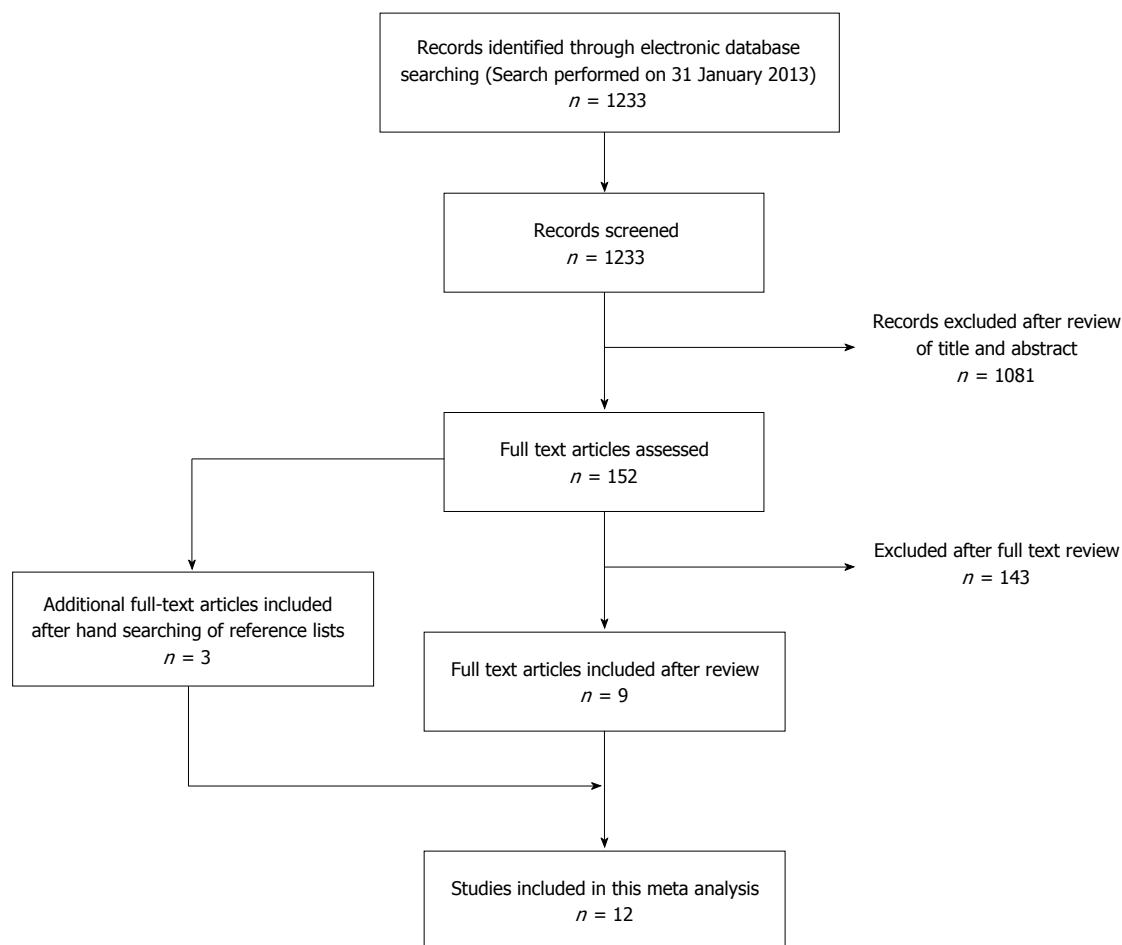


Figure 1 Flow chart of the publication selection process.

and E). The visual inspection of the funnel plots seemed basically symmetric, and Egger's test did not indicate statistically significant asymmetry for all included studies (intercept = 0.70, one-tailed $P = 0.37$), indicating no evidence of publication bias (Figure 3).

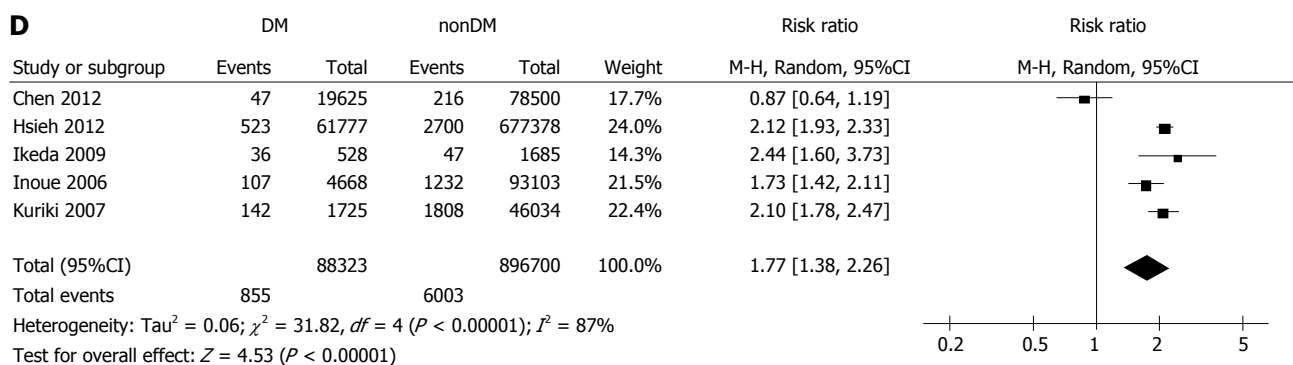
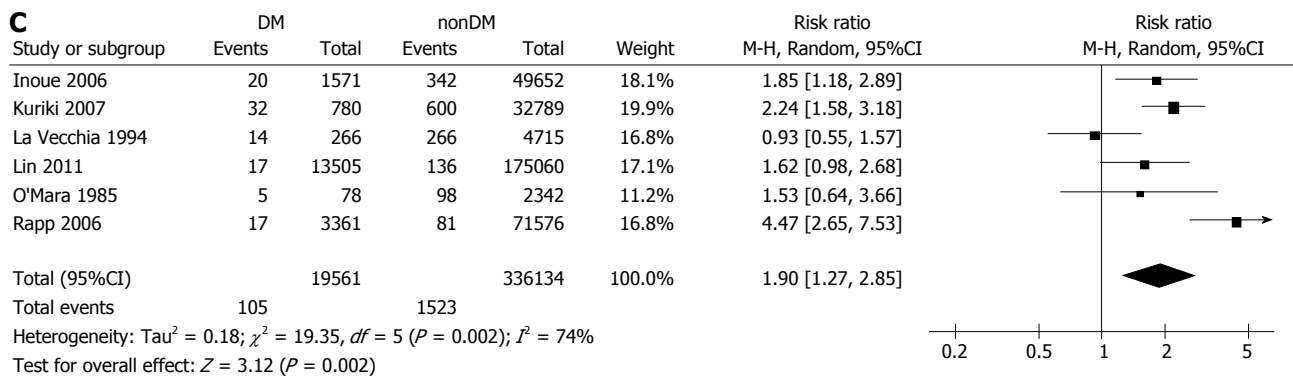
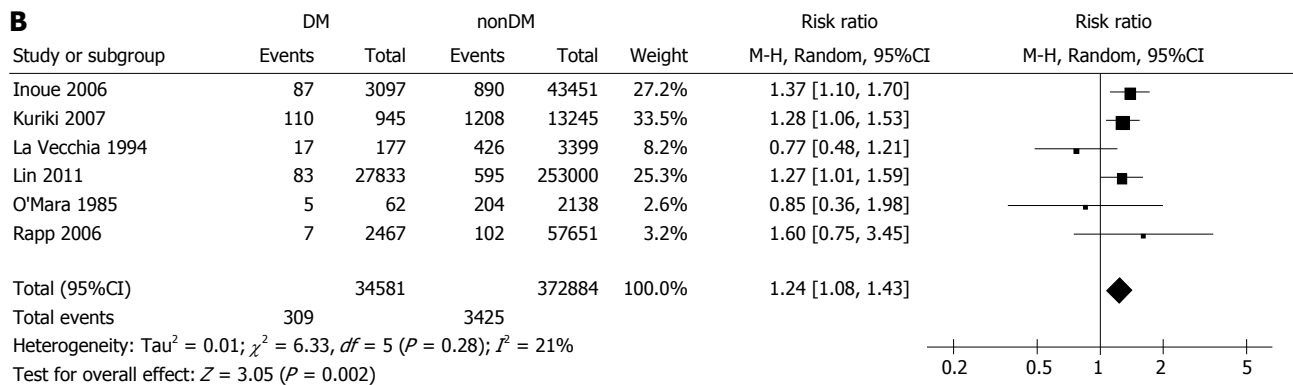
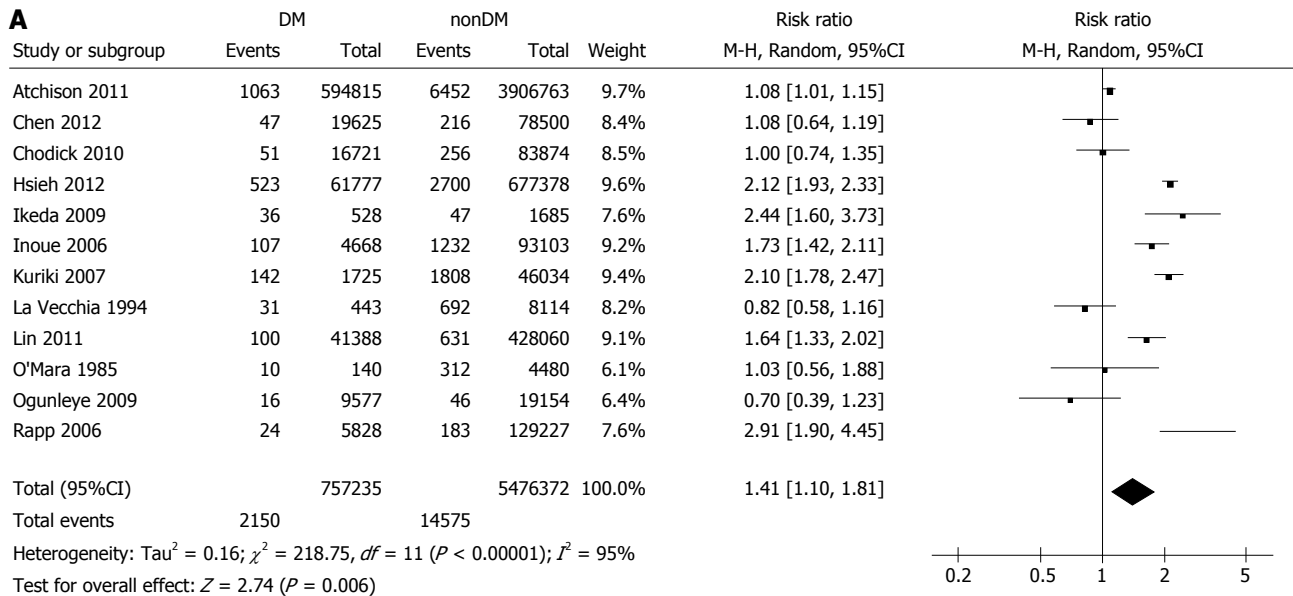
DISCUSSION

This updated meta-analysis, with GC as the disease in focus in articles published up to January 2013, has elucidated a positive DM-GC association, the findings being consistent with one previous meta-analysis^[20]. A subgroup analysis has provided the first evidence of a significantly increased risk of GC in both sexes, with a more prominent association in females than in males. Furthermore, the DM-GC association was positive for East Asians but not for Western subjects.

This meta-analysis focused on GC incidence rather than GC mortality, because GC mortality could be mainly influenced by the treatment modalities for GC such as extent of surgery and chemotherapy regimens, which differ markedly between countries. These are the reasons for the relatively fewer number of papers included in this meta-analysis compared with the previous ones^[19,20]. However, against the background of controversial findings^[18-20] in this matter in the literature, this study pro-

vided data supporting a positive DM-GC association.

There is a consensus that T2DM is associated with a spectrum of cancers. Although the exact underlying mechanisms linking DM and cancers remain unknown, several possible mechanisms have been debated and proposed: (1) the association between DM and cancer is direct through hyperglycemia; (2) diabetes is preceded by hyperinsulinemia and insulin resistance that alter cancer risk; and (3) the DM-cancer association is due to common risk factors such as obesity. Each of these represents a hallmark metabolic abnormality identified in T2DM and can potentially underlie the association between DM and GC. First, Swedish T1DM patients had more than twice the relative risk of GC than the general population^[31,32], suggesting that the associations between GC and hyperglycemia are biologically plausible since T1DM is an autoimmune disease manifesting as hyperglycemia due to pancreatic beta-cell destruction and insulin deficiency. Several mechanisms have been proposed that could explain the relationship between hyperglycemia and cancer. Hyperglycemia causes oxidative stress which promotes the formation of advanced glycation products (AGEs) and the expression of their receptor (RAGE); the AGE/RAGE interaction in turn stimulates oxidative stress. Furthermore, the crosstalk between the AGE/RAGE system and oxidative stress has been known to



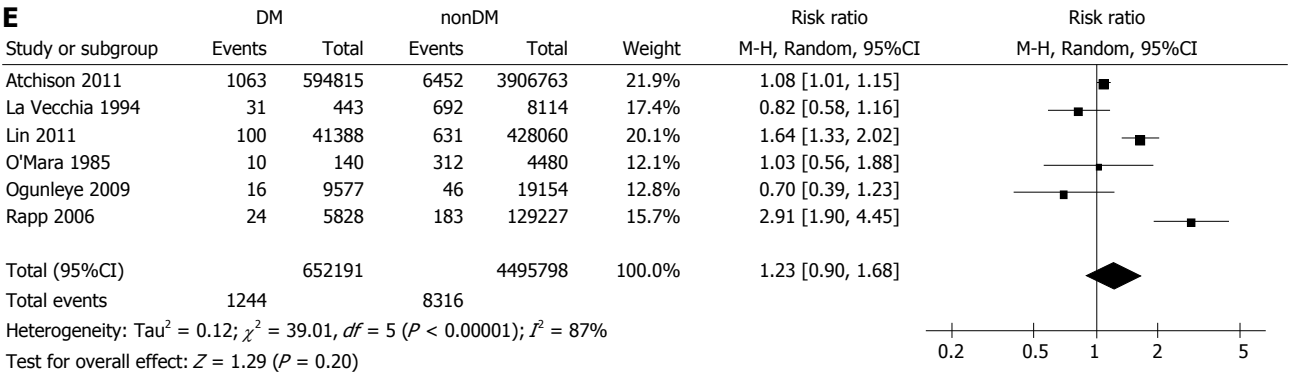


Figure 2 Forest plot representation-random-effects model. A: All included publications. Stratified by sex; B: Male; C: Female, and stratified by geographical area; D: East Asia; E: The West. The individual block squares denote the RR for each study of gastric cancer risk among diabetes mellitus (DM) patients, with an area proportional to the amount of statistical information in each study. The horizontal line denotes a 95%CI, ending with an arrowhead when CI extends beyond the scale. The pooled estimate and its 95%CI are represented by a diamond. Squares or diamonds plotted in the right half indicate increased gastric cancer risk. The risk is considered significant only if the horizontal line or diamond does not overlap the solid vertical line.

Table 1 Summary of included studies					
Ref.	Country	Study population	Diagnosis of DM	RR of GC (95%CI)	Confounders or Adjusted factors
Atchison <i>et al</i> ^[24]	United States	Veteran men	Hospital disease record	0.95 (0.89-1.02)	Age, time, latency, race, number of visits, alcohol, obesity, chronic obstructive pulmonary diseases
Chen <i>et al</i> ^[15]	Taiwan	National Health Insurance database	Antidiabetic drug	0.90 (0.65-1.23)	Age, gastric polyp, partial gastrectomy, gastric ulcer, pneumoconiosis
Chodick <i>et al</i> ^[28]	Israel	Healthcare service registry	Antidiabetic drug	Men 1.44 (0.98-2.11) Women 0.99 (0.55-1.80)	Age, region, use of healthcare service, BMI, cardiovascular disease
Hsieh <i>et al</i> ^[23]	Taiwan	National Health Insurance database	Ambulatory or inpatient care	0.92 (0.84-1.01)	age, sex
Ikeda <i>et al</i> ^[21]	Japan	Hisayama, population-based	Oral glucose tolerance test, fasting plasma glucose	2.13 (1.30-3.47) ¹ 2.69 (1.24-5.85) ²	Age, sex, <i>Helicobacter pylori</i> peptic ulcer, BMI, total cholesterol, alcohol, smoking, dietary factors
Inoue <i>et al</i> ^[16]	Japan	Public Health Center-based prospective study	Questionnaire	Men 1.23 (0.98-1.54) Women 1.61 (1.02-2.54)	Age, study area, cerebrovascular disease, ischemic heart disease, smoking, alcohol, BMI, physical activity, green vegetable intake, coffee intake
Kuriki <i>et al</i> ^[22]	Japan	Hospital-based epidemiologic research program	Questionnaire	Men 1.16 (0.93-1.44) Women 1.70 (1.16-2.48)	Age, BMI, drinking and smoking, physical activity, bowel movement, family history of cancer or diabetes, dietary restriction, raw vegetable intake, greasy food intake
La Vecchia <i>et al</i> ^[26]	Italy	Case-control study	Questionnaire	0.6 (0.4-0.9)	age, sex
Ge <i>et al</i> ^[19]	United States	National Institutes of Health American Association of Retired Persons diet and health study	Questionnaire	Cardia 1.89 (1.43-2.50) Noncardia 0.98 (0.70-1.37)	Age, sex, calories, alcohol, smoking, fruit intake, vegetable intake, ethnicity, education, physical activity
O'Mara <i>et al</i> ^[25]	United States	Case-control study	Questionnaire	Men 0.7 (ND) Women 1.2 (ND)	Age
Ogunleye <i>et al</i> ^[27]	United Kingdom	Health Informatics Center	Registry	0.73 (0.41-1.29)	Deprivation decile
Rapp <i>et al</i> ^[11]	Austria	Vorarlberg Health Monitoring and Promotion Programme	Fasting blood glucose	Men 0.84 (0.38-1.87) ³ Women 1.16 (0.66-2.05) ⁴	Age, smoking, occupational group, BMI

¹Hemoglobin A1c, 6.0%-6.9%; ²Hemoglobin A1c, $\geq 7.0\%$; ³Fasting blood glucose, ≥ 7 mmol/L; ⁴Fasting blood glucose, 6.1-6.9 mmol/L. GC: Gastric cancer; ND: Not described; BMI: Body mass index; DM: Diabetes mellitus.

activate numerous cell signaling pathways related to cell growth and apoptosis^[33] that could eventually promote carcinogenesis and cell invasion^[34]. Indeed, *in vitro* analyses have revealed the AGE/RAGE interaction positively correlating with the invasion and metastasis of gastric^[35],

pancreatic^[36], and biliary^[37] cancers. However, considering that epidemiological studies failed to find any increased risk of pancreatic, breast, colorectal, kidney, liver, or bladder cancers in T1DM patients^[31,32], which in turn are associated with cases of T2DM, and that the association

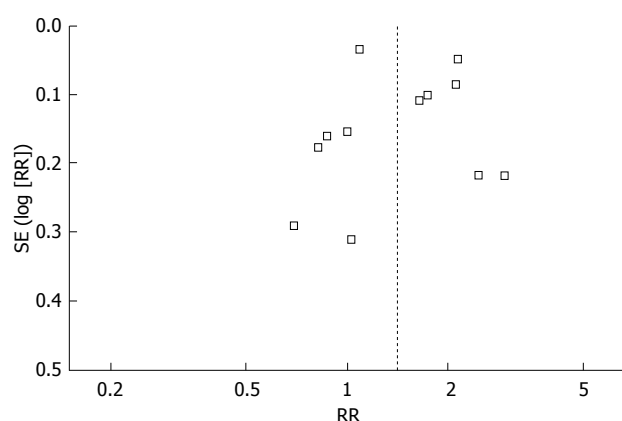


Figure 3 Funnel plot analysis of all the included publications.

between T1DM and a greater risk of developing cancer is equivocal^[38], factors other than glucose may play an important role. Besides hyperglycemia, a second hallmark of T2DM is hyperinsulinemia, resulting from insulin resistance in peripheral tissues for many years both before and after diagnosis; in fact, hyperinsulinemia may be the main culprit for cancer development. Insulin is capable of activating insulin-like growth factor (IGF)- I by enhancing hepatic IGF- I synthesis and is also capable of increasing the bioavailability of IGF- I by reducing hepatic production of the IGF-binding proteins^[39,40]. Enhanced insulin and IGF- I signals through insulin and IGF- I receptors, respectively, promote cell proliferation and growth via multiple cellular signaling cascades^[39-41]. Indeed, the overexpression of IGFs and the IGF- I receptor was observed in GC tissues^[42,43], and increased expression of the IGF- I receptor was correlated with cancer aggressiveness^[44] or poor survival^[45], suggesting a functional insulin-IGF axis in GC.

Third, the etiology of GC is multifactorial and may be associated with several confounding factors such as increased body mass index and *Helicobacter pylori* (*H. pylori*) infection. Visceral fat *per se* contributes to cancer risk^[46], and possible underlying molecular mechanisms linking with obesity that foster cancer development have been demonstrated^[39,46,47]. Accordingly, one recent meta-analysis has revealed that overweight and obesity correlated with GC^[48], findings which are consistent with other types of cancer^[39,46,47]. Regarding *H. pylori* infection, DM patients showed a higher frequency than non DM subjects both in the West^[49] and in the East^[50], and *H. pylori* infection was in turn correlated with insulin resistance^[51], suggesting that DM is liable to cause *H. pylori* infection and *vice versa*. Accordingly, GC risk was dramatically increased when DM and *H. pylori* infection coexisted^[21].

One novel finding in this study is a positive DM-GC association in both sexes with a more prominent association in females than in males, which contrasts with the male preponderance of GC in the general population. Such a seemingly inverse sex distribution of GC in DM subjects may be attributable to the decreased sex hormone-binding globulin under increased IGF-

I and hyperinsulinemia^[52], leading to increased bioavailability of estrogen in both sexes and increased levels of bioavailable testosterone in women but not in men^[53]. These mechanisms are plausible explanations for an increased risk of hormone-dependent cancers such as breast cancer in female DM patients. Therefore, it can be speculated that the alterations of sex hormones may influence the magnitude of GC risk by gender in DM patients. On the other hand, the present study revealed the increased risk of GC in populations in East Asia but not in the West, findings which are consistent with one previous study^[20]. These results can be explained partly by the geographical difference in GC risk^[54], and partly by the more established screening program in East Asian countries than in the Western countries. This speculation is supported by similar findings of a greater gastric cardia cancer risk in East Asia than in the West among the *H. pylori*-infected patients^[55]. Interestingly, a similar geographic difference was also observed in the DM-prostate cancer association^[1,2].

There are several limitations to this meta-analysis. First, besides obesity and *H. pylori* infection, GC development appear to be confounded by the possible presence of shared cancer-promoting or -preventing factors such as an unhealthy diet (*e.g.*, high salt intake^[56] or heavy alcohol drinking^[57]), sedentary lifestyle with lack of physical activity, duration of the DM state, and the consumption of vegetables, fruit^[58], and green tea^[59]. In addition, some diabetes treatments may increase or decrease cancer risk. These confounding factors make it difficult to accurately assess GC risk in DM patients. Therefore, investigation into the actual GC risk in DM patients requires adjustment based on these confounding factors. This is reflected by the significant heterogeneity, which has been also observed in the previous three meta-analyses; thus, further analyses are warranted. A second limitation is that most studies included in this study reported a DM and GC risk without distinction between T1DM and T2DM. Since T1DM is less prevalent than T2DM^[38], most patients in this meta-analysis can be regarded as T2DM. However, the DM-GC association should be further elucidated with distinction between the two types since they differ considerably in their metabolic characteristics.

The diversity of DM conditions and cancer biology, as well as the complexity of the potentially contributory mechanisms, preclude a definitive description of the association between DM and cancer risk at present. Although the precise biological mechanisms that might link DM to cancer remain a matter of debate, the recent surge in attempts to explore the relationship between the two diseases has motivated considerable investigation among the clinical and research communities. This meta-analysis suggests that newer, comprehensive approaches must be developed for the treatment of DM patients as a whole rather than as a single disease. However, it is also true that DM patients are less likely to be screened for several types of cancers^[60-62], which may be attributable to the patient preference to focus on the treatment of DM

rather than prevention of cancer^[62], when DM consumes his/her attention. Clinicians caring for patients with DM should remain alert to GC and minimize the number of missed opportunities for its treatment.

COMMENTS

Background

Besides cardiovascular complications, evidence has accumulated that diabetes mellitus (DM) patients are highly predisposed to many types of cancer. Among the cancer subtypes investigated, however, knowledge on the link between gastric cancer (GC) and DM has been insufficient and inconsistent even in previous meta-analyses.

Research frontiers

Several meta-analyses have been published to investigate the association between DM and GC, however, the results have been inconsistent and varied, from inverse to positive DM-GC associations, indicating that the link between the two diseases has been unclear.

Innovations and breakthroughs

DM exhibited significantly increased GC risk by 41% overall, and by 90% in females, 24% in males, and 77% in East Asians in subgroup analyses. These findings provide evidence in the current debate concerning the DM-GC association. Furthermore, a larger GC risk in female DM patients than in males was found to be marked.

Applications

Evidence of a positive DM-GC association, together with the positive link between DM and many other types of cancer, suggest a need for development of newer, comprehensive approaches for the treatment of DM patients as a whole rather than as a single disease. Clinicians caring for DM patients should remain alert to GC and minimize the number of missed opportunities for its treatment.

Terminology

Advanced glycation end products (AGEs) are proteins or lipids that become glyated after exposure to sugars. AGEs contribute to a variety of microvascular and macrovascular complications by engaging the receptor for advanced glycation end products.

Peer review

This meta-analysis provides useful information to clinical and research field for establishing comprehensive management to DM patients.

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