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

Shouji Shimoyama

Shouji Shimoyama, Gastrointestinal Unit, Settlement Clinic, Tokyo 120-0003, Japan
Author contributions: Shimoyama S solely contributed to this paper.
Correspondence to: Shouji Shimoyama, MD, Gastrointestinal Unit, Settlement Clinic, 4-20-7, Towa, Adachi-ku, Tokyo 120-0003, Japan. shimoyama@apost.plala.or.jp
Telephone: +81-3-36057747 Fax: +81-3-36050244
Received: May 14, 2013 Revised: June 27, 2013 Accepted: July 30, 2013 Published online: October 28, 2013

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 results 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.

© 2013 Baishideng. All rights reserved.

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/reverse 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.

Shimoyama S. Diabetes mellitus carries a risk of gastric cancer: A meta-analysis. World J Gastroenterol 2013; 19(40): 6902-6910 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i40/6902.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i40.6902

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[3] or inverse[11] 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[14,15]. 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 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[11,12] and Korean[13] 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)[14], or were based on different DM criteria such as treatment[15,16], fasting blood glucose[11,17], or self-report[18]. 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[11,14,16,21-23] studies were from East Asia, 6[17,24,25] 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).
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\(^{[19,28]}\). However, against the background of controversial findings\(^{[18-24]}\) in this matter in the literature, this study provided 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
| A | Study or subgroup | DM | nonDM | Risk ratio | Risk ratio |
|---|-----------------|-----|-------|------------|------------|
| | Events | Total | Events | Total | Weight | M-H, Random, 95%CI | M-H, Random, 95%CI |
| Atchison 2011 | 1063 | 594815 | 6452 | 3906763 | 9.7% | 1.08 [1.01, 1.15] |
| Chen 2012 | 47 | 19625 | 216 | 78500 | 8.4% | 1.08 [0.64, 1.19] |
| Chodick 2010 | 51 | 16721 | 256 | 83874 | 8.5% | 1.00 [0.74, 1.35] |
| Hsieh 2012 | 523 | 61777 | 2700 | 677378 | 9.6% | 2.12 [1.93, 2.33] |
| Ikeda 2009 | 36 | 528 | 47 | 1685 | 7.6% | 2.44 [1.60, 3.73] |
| Inoue 2006 | 107 | 4668 | 1232 | 93103 | 9.2% | 1.73 [1.42, 2.11] |
| Kuriki 2007 | 142 | 1725 | 1808 | 46034 | 9.4% | 2.10 [1.78, 2.47] |
| La Vecchia 1994 | 31 | 443 | 692 | 8114 | 8.2% | 0.82 [0.58, 1.16] |
| Lin 2011 | 100 | 41388 | 631 | 428060 | 9.1% | 1.64 [1.33, 2.02] |
| O’Mara 1985 | 10 | 140 | 312 | 4480 | 6.1% | 1.03 [0.56, 1.88] |
| Oggunleye 2009 | 16 | 9577 | 46 | 19154 | 6.4% | 0.70 [0.39, 1.23] |
| Rapp 2006 | 24 | 5028 | 183 | 129227 | 7.6% | 2.91 [1.90, 4.45] |
| Total (95%CI) | | 757235 | 5476372 | 100.0% | 1.41 [1.10, 1.81] |
| Total events | 2150 | 14575 |

Heterogeneity: Tau^2 = 0.16; I^2 = 218.75, df = 11 (P < 0.00001); I^2 = 95%
Test for overall effect: Z = 2.74 (P = 0.006)

| B | Study or subgroup | DM | nonDM | Risk ratio | Risk ratio |
|---|-----------------|-----|-------|------------|------------|
| | Events | Total | Events | Total | Weight | M-H, Random, 95%CI | M-H, Random, 95%CI |
| Inoue 2006 | 87 | 3097 | 890 | 43451 | 27.2% | 1.37 [1.10, 1.70] |
| Kuriki 2007 | 110 | 945 | 1208 | 13245 | 33.5% | 1.28 [1.06, 1.53] |
| La Vecchia 1994 | 17 | 177 | 426 | 3399 | 8.2% | 0.77 [0.48, 1.21] |
| Lin 2011 | 83 | 27833 | 595 | 253000 | 25.3% | 1.27 [1.01, 1.59] |
| O’Mara 1985 | 5 | 62 | 204 | 2138 | 2.6% | 0.85 [0.36, 1.98] |
| Rapp 2006 | 7 | 2467 | 102 | 57651 | 3.2% | 1.60 [0.75, 3.45] |
| Total (95%CI) | | 34581 | 372884 | 100.0% | 1.24 [1.08, 1.43] |
| Total events | 309 | 3425 |

Heterogeneity: Tau^2 = 0.01; I^2 = 6.33, df = 5 (P = 0.28); I^2 = 21%
Test for overall effect: Z = 3.05 (P = 0.002)

| C | Study or subgroup | DM | nonDM | Risk ratio | Risk ratio |
|---|-----------------|-----|-------|------------|------------|
| | Events | Total | Events | Total | Weight | M-H, Random, 95%CI | M-H, Random, 95%CI |
| Inoue 2006 | 20 | 1571 | 342 | 49652 | 18.1% | 1.85 [1.18, 2.89] |
| Kuriki 2007 | 32 | 780 | 600 | 32789 | 19.9% | 2.24 [1.58, 3.18] |
| La Vecchia 1994 | 14 | 266 | 266 | 4715 | 16.8% | 0.93 [0.55, 1.57] |
| Lin 2011 | 17 | 13505 | 136 | 175060 | 17.1% | 1.62 [0.98, 2.68] |
| O’Mara 1985 | 5 | 78 | 98 | 2342 | 11.2% | 1.53 [0.64, 3.66] |
| Rapp 2006 | 17 | 3361 | 81 | 71576 | 16.8% | 4.47 [2.65, 7.53] |
| Total (95%CI) | | 19561 | 336134 | 100.0% | 1.90 [1.27, 2.85] |
| Total events | 105 | 1523 |

Heterogeneity: Tau^2 = 0.18; I^2 = 19.35, df = 5 (P = 0.002); I^2 = 74%
Test for overall effect: Z = 3.12 (P = 0.002)

| D | Study or subgroup | DM | nonDM | Risk ratio | Risk ratio |
|---|-----------------|-----|-------|------------|------------|
| | Events | Total | Events | Total | Weight | M-H, Random, 95%CI | M-H, Random, 95%CI |
| Chen 2012 | 47 | 19625 | 216 | 78500 | 17.7% | 0.87 [0.64, 1.19] |
| Hsieh 2012 | 523 | 61777 | 2700 | 677378 | 24.0% | 2.12 [1.93, 2.33] |
| Ikeda 2009 | 36 | 528 | 47 | 1685 | 14.3% | 2.44 [1.60, 3.73] |
| Inoue 2006 | 107 | 4668 | 1232 | 93103 | 21.5% | 1.73 [1.42, 2.11] |
| Kuriki 2007 | 142 | 1725 | 1808 | 46034 | 22.4% | 2.10 [1.78, 2.47] |
| Total (95%CI) | | 88323 | 896700 | 100.0% | 1.77 [1.38, 2.26] |
| Total events | 855 | 6003 |

Heterogeneity: Tau^2 = 0.06; I^2 = 31.82, df = 4 (P < 0.00001); I^2 = 87%
Test for overall effect: Z = 4.53 (P < 0.00001)
activate numerous cell signaling pathways related to cell growth and apoptosis\(^3\) that could eventually promote carcinogenesis and cell invasion\(^4\). Indeed, in vitro analyses have revealed the AGE/RAGE interaction positively correlating with the invasion and metastasis of gastric\(^5\), pancreatic\(^6\), and biliary\(^7\) cancers. However, considering that epidemiological studies failed to find any increased risk of pancreatic, breast, colorectal, kidney, liver, or bladder cancers in T1DM patients\(^8,9\), which in turn are associated with cases of T2DM, and that the association

---

**Table 1** Summary of included studies

| Ref. | Country | Study population | Diagnosis of DM | RR of GC (95%CI) | Confounders or Adjusted factors |
|------|---------|------------------|-----------------|------------------|--------------------------------|
| Atchison et al\(^{10}\) | 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 et al\(^{11}\) | Taiwan | National Health Insurance database | Antidiabetic drug | 0.90 (0.65-1.23) | Age, gastric polyph, partial gastrectomy, gastric ulcer, pneumoniaosis |
| Chodick et al\(^{12}\) | Israel | Healthcare service registry | Antidiabetic drug | Men 1.44 (0.98-2.11) | Women 0.99 (0.55-1.80) |
| Hsieh et al\(^{13}\) | Taiwan | National Health Insurance database | Ambulatory or inpatient care | 0.92 (0.84-1.01) | Age, region, use of healthcare service, BMI, cardiovascular disease, age, sex |
| Ikeda et al\(^{14}\) | Japan | Hisayama, population-based | Oral glucose tolerance test, fasting plasma glucose | 2.13 (1.30-3.47) | 2.69 (1.24-5.85) |
| Inoue et al\(^{15}\) | Japan | Public Health Center-based prospective study | Questionnaire | Men 1.23 (0.98-1.54) | Women 1.61 (1.02-2.54) |
| Kuriki et al\(^{16}\) | Japan | Hospital-based epidemiologic research program | Questionnaire | Men 1.16 (0.93-1.44) | Women 1.70 (1.16-2.48) |
| La Vecchia et al\(^{17}\) | Italy | Case-control study | Questionnaire | Questionnaire | 0.6 (0.4-0.9) | Cardia 1.89 (1.43-2.50) | Noncardia 0.98 (0.70-1.37) |
| Ge et al\(^{18}\) | United States | National Institutes of Health American Association of Retired Persons diet and health study | Questionnaire | Questionnaire | Age, sex, calories, alcohol, smoking, fruit intake, vegetable intake, ethnicity, education, physical activity |
| O’Mara et al\(^{19}\) | United States | Case-control study | Questionnaire | Men 0.7 (ND) | Women 1.2 (ND) |
| Ogunleye et al\(^{20}\) | United Kingdom | Health Informatics Center Registry | Questionnaire | 0.73 (0.41-1.29) | Deprivation decile |
| Rapp et al\(^{21}\) | Austria | Vorarlberg Health Monitoring and Promotion Programme | Fasting blood glucose | Men 0.84 (0.38-1.87) | Women 1.16 (0.66-2.05) |

1Hemoglobin A1c, 6.0%-6.9%; 2Hemoglobin A1c, ≥ 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.
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)-1 by enhancing hepatic IGF-1 synthesis and is also capable of increasing the bioavailability of IGF-1 by reducing hepatic production of the IGF-binding proteins[39,40]. Enhanced insulin and IGF-1 signals through insulin and IGF-1 receptors, respectively, promote cell proliferation and growth via multiple cellular signaling cascades[39-41]. Indeed, the overexpression of IGFs and the IGF-1 receptor was observed in GC tissues[42,43], and increased expression of the IGF-1 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[47,48]. Accordingly, one recent meta-analysis has revealed that overweight and obesity correlated with GC[49], findings which are consistent with other types of cancer[47,48,49]. Regarding H. pylori infection, DM patients showed a higher frequency than non DM subjects both in the West[50] and in the East[51], and H. pylori infection was in turn correlated with insulin resistance[52], 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[53].

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[54], leading to increased bioavailability of estrogen in both sexes and increased levels of bioavailable testosterone in women but not in men[55]. 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[56]. These results can be explained partly by the geographical difference in GC risk[57], 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[58]. 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 appears to be confounded by the possible presence of shared cancer-promoting or -preventing factors such as an unhealthy diet (e.g., high salt intake[59] or heavy alcohol drinking[59]), sedentary lifestyle with lack of physical activity, duration of the DM state, and the consumption of vegetables, fruit[60], and green tea[61]. 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[62], 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[63,64], which may be attributable to the patient preference to focus on the treatment of DM.
rather than prevention of cancer\(^6\) 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 glycated 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.

**REFERENCES**

1. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer 2009; 16: 1103-1123 [PMID: 19620249 DOI: 10.1677/ERC-09-00087]
2. Tseng CH. Diabetes and risk of prostate cancer: a study using the National Health Insurance. Diabetes Care 2011; 34: 616-621 [PMID: 21273499 DOI: 10.2337/dci10-1640]
3. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047-1053 [PMID: 15111519]
4. IDF diabetes atlas. Available from: URL: http://www.idf.org/diabetesatlas/5e/diabetes
5. Seshasai SR, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, Whincup PH, Mukamal KJ, Gilliam RF, Holme I, Njølstad I, Fletcher A, Nilsson P, Lewington S, Collins R, Gudnason V, Thompson SG, Sattar N, Selvin E, Hu FB, Danesh J. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011; 364: 829-841 [PMID: 21366474 DOI: 10.1056/NEJMoa1008862]
6. Gong Y, Yang YS, Zhang XM, Su M, Wang J, Han JD, Gou MZ. ABO blood type, diabetes and risk of gastrointestinal cancer in northern China. World J Gastroenterol 2012; 18: 563-569 [PMID: 22363124 DOI: 10.3748/wjg.v18.i6.563]
7. Tseng CH. Diabetes, insulin use, and gastric cancer: a population-based analysis of the Taiwanese. J Clin Gastroenterol 2013; 47: e60-e64 [PMID: 23269314]
8. Zhang PH, Chen ZW, Lv D, Xu YY, Gu WL, Zhang XF, Le YL, Zhu HH, Zhu YM. Increased risk of cancer in patients with type 2 diabetes mellitus: a retrospective cohort study in China. BMC Public Health 2012; 12: 567 [PMID: 22839452 DOI: 10.1186/1471-2458-12-567]
9. Khan M, Mori M, Fujiy Y, Shibata A, Sakauchi F, Washio M, Tamakoshi A. Site-specific cancer risk due to diabetes mellitus history: evidence from the Japan Collaborative Cohort (JACC) Study. Asian Pac J Cancer Prev 2006; 7: 253-259 [PMID: 16839219]
10. Yamagata H, Kiyohara Y, Nakamura S, Kudo M, Tanizaki Y, Matsumoto T, Tanaka K, Kato I, Shirota T, Iida M. Impact of fasting plasma glucose levels on gastric cancer incidence in a general Japanese population: the Hisayama study. Diabetes Care 2005; 28: 789-794 [PMID: 15793174]
11. Rapp K, Schroeder J, Klenk J, Ulmer H, Conc H, Diem G, Oberaigner W, Weiland SK. Fasting blood glucose and cancer risk in a cohort of more than 140,000 adults in Austria. Diabetologia 2006; 49: 945-952 [PMID: 16557372]
12. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005; 293: 194-202 [PMID: 15644687]
13. Lo SF, Chang SN, Mou CH, Niinomi S, Liay FY, Dee SW, Chen PC, Sung FC. Modest increase in risk of specific types of cancer types in type 2 diabetes mellitus patients. Int J Cancer 2013; 132: 182-188 [PMID: 22510866 DOI: 10.1002/ijc.27597]
14. Swerdlow AJ, Laing SP, Qiao Z, Slater SD, Burden AC, Booth JL, Waugh NR, Morris AD, Galting W, Gale EA, Patterson SC, Keen H. Cancer incidence and mortality in patients with insulin-treated diabetes: a UK cohort study. Br J Cancer 2005; 92: 2070-2075 [PMID: 15886701]
15. Chen YL, Cheng KC, Lai SW, Tsai JJ, Lin CC, Sung FC, Lin CC, Chen PC. Diabetes and risk of subsequent gastric cancer: a population-based cohort study in Taiwan. Gastric Cancer 2013; 16: 389-396 [PMID: 23053824]
16. Inoue M, Iwasaki M, Otani T, Sasaki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. Arch Intern Med 2006; 166: 1871-1877 [PMID: 17009444]
17. Szelip HM, Hoeger P, Feldman GM. Comparison between acetate and bicarbonate dialysis for the treatment of lithium intoxication. Am J Nephrol 1992; 12: 116-120 [PMID: 1415356 DOI: 10.1158/1055-9965.EPI-10-1244]
18. Marimuthu SP, Vijayaragavan P, Moysich KB, Jayaprakash V. Diabetes mellitus and gastric carcinoma: Is there an association? J Carcinog 2011; 10: 30 [PMID: 22190872 DOI: 10.4103/1477-3163.90481]
19. Ge Z, Ben Q, Qian J, Yang Y, Li Y. Diabetes mellitus and risk of gastric cancer: a systematic review and meta-analysis of observational studies. Eur J Gastroenterol Hepatol 2011; 23: 1127-1135 [PMID: 21934509 DOI: 10.1097/MEG.0b013e32834b8d73]
20. Tian T, Zhang LQ, Ma XH, Zhou JN, Shen J. Diabetes mellitus and gastric cancer: Is there an association? Cancer Prev Res (Phila) 2012; 5: 466-470 [PMID: 22512880 DOI: 10.1158/1940-6207.PCR-11-0773]
21. Kuriki K, Hirose K, Tajima K. Diabetes and cancer risk for all and specific sites among Japanese men and women. Eur J Cancer Prev 2007; 16: 83-89 [PMID: 17220079]
22. Atchison EA, Gridley G, Carreon JD, Leitzmann MF, Mc-
Shimoyama S. Diabetes mellitus and gastric cancer

ence and trends of receipt of cancer screenings among US women with diagnosed diabetes. J Gen Intern Med 2009; 24: 270-275 [PMID: 19089511 DOI: 10.1007/s11606-008-0858-8]

61 Lipscombe LL, Hux JE, Booth GL. Reduced screening mammography among women with diabetes. Arch Intern Med 2005; 165: 2090-2095 [PMID: 16216998]

62 Fontana SA, Baumann LC, Helberg C, Love RR. The delivery of preventive services in primary care practices according to chronic disease status. Am J Public Health 1997; 87: 1190-1196 [PMID: 9240111]

P- Reviewer Hajifathalian K S- Editor Zhai HH
L- Editor Cant MR E- Editor Ma S
