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Diabetes and gastric cancer: The potential links

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Abstract

This article reviews the epidemiological evidence linking diabetes and gastric cancer and discusses some of the potential mechanisms, confounders and biases in the evaluation of such an association. Findings from four meta-analyses published from 2011 to 2013 suggest a positive link, which may be more remarkable in females and in the Asian populations. Putative mechanisms may involve shared risk factors, hyperglycemia, *Helicobacter pylori* (*H. pylori*) infection, high salt intake, medications and comorbidities. Diabetes may increase the risk of gastric cancer through shared risk factors including obesity, insulin resistance, hyperinsulinemia and smoking. Hyperglycemia, even before the clinical diagnosis of diabetes, may predict gastric cancer in some epidemiological studies, which is supported by *in vitro*, and *in vivo* studies. Patients with diabetes may also have a higher risk of gastric cancer through the higher infection rate, lower eradication rate and higher reinfection rate of *H. pylori*. High salt intake can act synergistically with *H. pylori* infection in the induction of gastric cancer. Whether a higher risk of gastric cancer in patients with diabetes may be ascribed to a higher intake of salt due to the loss of taste sensation awaits further investigation. The use of medications such as insulin, metformin, sulfonylureas, aspirin, statins and antibiotics may also influence the risk of gastric cancer, but most of them have not been extensively studied. Comorbidities may affect the development of gastric cancer through the use of medications and changes in lifestyle, dietary intake, and the metabolism of drugs. Finally, a potential detection bias related to gastrointestinal symptoms more commonly seen in patients with diabetes and with multiple comorbidities should be pointed out. Taking into account the inconsistent findings and the potential confounders and detection bias in previous epidemiological studies, it is expected that there are still more to be explored for the clarification of the association between diabetes and gastric cancer.

Key words: Diabetes mellitus; Gastric cancer; Epidemiology; Meta-analysis; Literature review

Core tip: Epidemiological studies suggested a possible higher risk of gastric cancer in patients with diabetes. This article summarizes the findings in four meta-analyses and proposes some mechanisms explaining the association. Findings in the meta-analyses suggested that the association between diabetes and gastric cancer is more remarkable in females and in the Asian populations. Although the mechanisms for such a link remain to be explored, these may involve shared risk factors between diabetes and gastric cancer (such as obesity, insulin resistance, hyperinsulinemia and smoking), hyperglycemia, *Helicobacter pylori* infection, high salt intake, medications and comorbidities.

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INTRODUCTION

Diabetes mellitus may increase the risk of several cancers involving the breast[1,2], liver[3,4], pancreas[5-7], colorectum[8-10], endometrium[11,12], kidney[13], non-Hodgkin lymphoma[14,15] and urinary bladder[16-20]. The underlying mechanisms for a higher risk of cancer in patients with diabetes may be due to insulin resistance, poor glycemic control, oxidative stress and pro-inflammatory status[21,22]. In addition, the use of anti-diabetic drugs, diabetes duration and the severity of diabetes status accompanied by various comorbidities may play some roles[22-24].

Gastric cancer is more common in men and in people aged 50 years or older[25-27]. Obesity, smoking, salt intake and *Helicobacter pylori* (*H. pylori*) infection are important risk factors[28,29]. Gastric cancer is very common in developing countries in East Asia, East Europe and South America; while the incidence is low in North America and most parts of Africa[26]. The prognosis of gastric cancer is very poor, with a 5-year survival < 20% for advanced disease[27]. The incidence of gastric cancer has decreased in most parts of the world in recent years, probably due to the increasing use of refrigerators and less dependence on salt for food preservation, increasing availability of fresh fruits and vegetables, and the control of chronic infection with *H. pylori*. However, it remains as a major cancer affecting human health, and in 2008 it may account for 8% of the total cancer incidence and 10% of the total cancer death worldwide[26].

Recent observational studies suggested that diabetes or hyperglycemia may increase the risk of gastric cancer incidence or mortality[30-36]. In this article, we review the current evidence, and discuss the potential mechanisms, confounders and biases in the evaluation of such an association.

EPIDEMIOLOGICAL EVIDENCE FOR A LINK BETWEEN DIABETES AND GASTRIC CANCER

Whether diabetes may increase the risk of gastric cancer has become a focus of attention in recent years. On October 1, 2013, we used the keywords of "diabetes, gastric cancer, meta-analysis" to search the Pubmed, eight papers were available. After further scrutiny, four of them were excluded because they are not related to the topic under review. Finally, there are four meta-analyses[33-36] published within a 3-year period from 2011 to 2013. The main findings of these four meta-analyses are summarized in Table 1 and briefly described below.

In the first meta-analysis by Ge *et al*[33], which included 21 (4 case-control and 17 cohort) studies evaluating either incidence or mortality of gastric cancer, patients with diabetes did not show an overall higher risk of gastric cancer when sex was not analyzed separately. The summary relative risk (SRR) was 1.09, 95%CI: 0.98-1.22. However, when men and women were analyzed separately, diabetes was associated with a significantly increased risk of gastric cancer in women (SRR = 1.18, 95%CI: 1.01-1.39) but not in men (SRR = 1.04, 95%CI: 0.94-1.15)[33]. In other subgroup analyses including both sexes, studies with a follow-up duration < 10 years showed a null association, but those with a follow-up duration ⩾ 10 years showed a significant SRR (1.14, 95%CI: 1.01-1.29)[33].

The second meta-analysis by Marimuthu *et al*[34] included 20 population-based cohort studies evaluating gastric cancer incidence and mortality separately. The overall SRR for gastric cancer incidence was 1.01 (95%CI: 0.90-1.11). The null association was similarly observed in studies conducted in Europe, Asia and United States. It is interesting that the link with gastric cancer incidence was more remarkable, though not significant, in patients with type 1 diabetes (< 30 years of age at diagnosis), with SRR of 1.60 (95%CI: 0.56-2.64) derived from two studies[34]. When gastric cancer mortality was evaluated, patients with diabetes had a significantly higher risk in overall analysis (SRR = 1.62, 95%CI: 1.36-1.89) and in studies from Asian populations (SRR = 1.98, 95%CI: 1.57-2.39), but not in studies from Europe or the United States[34].

The third meta-analysis by Tian *et al*[35] included 25 (7 case-control and 18 cohort) studies involving incidence and mortality of gastric cancer. The overall analysis showed a significant link between diabetes and gastric cancer incidence and mortality with respective SRR of 1.11 (95%CI: 1.00-1.24) (P = 0.045) and 1.29 (95%CI: 1.04-1.59)[35]. Subgroup analyses from various numbers of studies with a mixture of incidence and mortality of gastric cancer showed a positive association in studies conducted in Asian countries, in cohort study design, in patients with type 2 diabetes and in studies adjusted for more confounders, with respective SRR of 1.19 (95%CI: 1.07-1.32), 1.14 (95%CI: 1.01-1.30), 1.16 (95%CI: 1.01-1.33) and 1.16 (95%CI: 1.03-1.30)[35].

The latest meta-analysis by Yoon *et al*[36] included 17 (6 case-control and 11 cohort) studies comparing gastric cancer incidence between patients with diabetes and control subjects. This meta-analysis excluded studies investigating only mortality but not incidence or studies reporting only standardized incidence ratios without control groups. The overall SRR was 1.19 (95%CI: 1.08-1.31), and was consistently significant in subgroup analyses conducted in cohort studies, in studies done in populations of either Western or Eastern countries, in females, and in studies with high quality[36]. The significantly higher risk was also demonstrated in analyses confined to studies controlling well-known risk factors such as smoking or *H. pylori* infection, with respective SRR of 1.17 (95%CI:

Table 1 Main findings in four meta-analyses on the association between diabetes and incidence or mortality of gastric cancer

Ref.	Studies included	Summary RR (95%CI)		Notes and comments for specific studies	Limitations common to the meta-analysis studies
		Overall	Subgroup analysis		
Ge *et al*[33], 2011	4 case-control and 17 cohort	1.09 (0.98-1.22)	Women: 1.18 (1.01-1.39) Men: 1.04 (0.94-1.15) Duration of follow-up < 10 yr: 0.95 (0.72-1.26) Duration of follow-up ⩾ 10 yr: 1.14 (1.01-1.29)	Evaluating incidence and mortality together A mixture of incidence and mortality studies may not be appropriate Ethnicity differences not considered	Heterogeneity in terms of study design, population demographics, diabetes ascertainment, duration of follow-up, and confounders Type 1 and type 2 diabetes not distinguished in most studies
Marimuthu *et al*[34], 2011	20 population-based cohort	Incidence: 1.01 (0.90-1.11) Mortality: 1.62 (1.36-1.89)	Type 1 diabetes (incidence): 1.60 (0.56-2.64) Asians (mortality): 1.98 (1.57-2.39)	Evaluating incidence and mortality separately in overall analysis Considering type 1 diabetes and ethnicity differences in subgroup analyses	Cardia and non-cardia gastric cancer not discerned in most studies Confounding effects of *H. pylori*, smoking and diet are not considered in most studies
Tian *et al*[35], 2012	7 case-control and 18 cohort	Incidence: 1.11 (1.00-1.24) Mortality: 1.29 (1.04-1.59)	Asians: 1.19 (1.07-1.32) Cohort design: 1.14 (1.01-1.30) Type 2 diabetes: 1.16 (1.01-1.33) Studies adjusted for more confounders: 1.16 (1.03-1.30)	Evaluating incidence and mortality separately in overall analysis Subgroup analysis was conducted with a mixture of incidence and mortality	Numbers of studies in subgroup analyses varied and may be too small for some analyses Most studies included in meta-analyses were conducted in developed western countries and not primarily designed for evaluating the association between diabetes and gastric cancer Publication bias is possible
Yoon *et al*[36], 2013	6 case-control and 11 cohort	1.19 (1.08-1.31)	Cohort design: 1.20 (1.08-1.34) Case-control design: 1.12 (0.87-1.45) East Asian countries: 1.19 (1.02-1.38) Western countries: 1.18 (1.03-1.36) Men: 1.10 (0.97-1.24) Women: 1.24 (1.01-1.52) Studies adjusted for smoking: 1.17 (1.01-1.34) Studies adjusted for infection of *H. pylori*: 2.35 (1.24-4.46) Cardia cancer: 1.39 (0.72-2.69) Noncardia cancer: 1.19 (0.80-1.77)	Evaluating only incidence Strengths include considering subgroup analyses in studies with adjustment for smoking and *H. pylori* infection Subgroup analyses on cardia and noncardia cancer are available, but only 2 studies are included	

H. pylori: *Helicobacter pylori*.

1.01-1.34) and 2.35 (95%CI: 1.24-4.46). Another strength is the subgroup analysis for cardia and noncardia gastric cancer, with respective SRR of 1.39 (95%CI: 0.72-2.69) and 1.19 (95%CI: 0.80-1.77). But only two studies are available for these site-specific analyses.

SOME COMMENTS ON THE OBSERVATIONAL STUDIES

Because the findings are inconsistent from observational studies[30-36], a consensus report does not support diabetes as a risk factor for gastric cancer[22]. However, some common limitations in the above meta-analysis studies should be pointed out (Table 1).

First, heterogeneity exists in study design, diabetes diagnosis, cancer ascertainment, use of incidence, prevalence or mortality, consideration of confounders (*e.g.*, age, sex, obesity, smoking, salt intake and *H. pylori* infection), follow-up duration, and population demography.

Second, most studies did not differentiate type 1 and type 2 diabetes, and did not discern between different histopathology (adenocarcinoma, lymphoma or other types) or anatomical sites (cardia or noncardia) of gastric cancer. It is worth to point out that patients with diabetes may increase the risk of adenocarcinoma located specifically at the gastric cardia by 89% in one United States population-based study[37]. On the other hand, *H. pylori* infection-related gastric cancer may be primarily located at the noncardiac portion[38].

Third, because most studies were conducted in the developed western countries where gastric cancer is less common, and these studies were mainly designed to evaluate the risk of all or multiple cancer sites and not specifically of gastric cancer, they might not have suf-

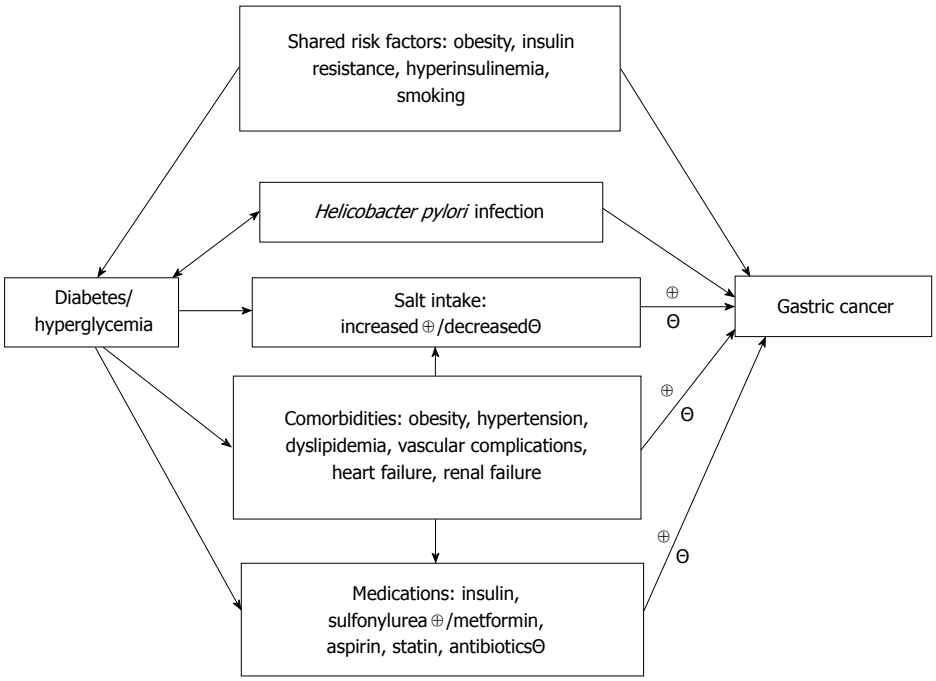

Figure 1 Putative mechanisms linking diabetes and gastric cancer ("⊕" denotes a positive effect and "Θ" denotes a negative effect). A direct effect of hyperglycemia and a synergistic effect between salt intake and *Helicobacter pylori* infection are both possible but not shown in the dendrogram. Comorbidities may affect the development of gastric cancer, either positively or negatively, through the use of medications and changes in lifestyle, salt intake, dietary components, and the metabolism of drugs. A summary of the explanations on the links can be seen in Table 2.

ficient power for investigating the association between diabetes and gastric cancer. If the effect of diabetes on gastric cancer is smaller than its effect on the other types of cancer, then a much larger sample size will be required.

Fourth, dietary factors may also modify the development of gastric cancer induced by carcinogens[27], but most of these factors have not been considered in previous studies.

As described in the above meta-analyses, there are signals indicating a positive link between diabetes and gastric cancer, especially in females[33,36] and in Asian populations[34,35]. Estrogen has been shown to interact with insulin/insulin-like growth factor 1 (IGF-1) in the development of breast cancer[39], and gastrointestinal tissues may express estrogen receptor[40,41]. Therefore, estrogen may play a role in the differential effect between men and women on the link between diabetes and gastric cancer. The stronger link found in studies conducted in the Asian populations may either indicate a higher *H. pylori* infection rate in the patients with diabetes in these populations, or it may suggest an effect of different ethnic/genetic backgrounds, dietary habits, lifestyle, or disease prevalence.

PUTATIVE MECHANISMS EXPLAINING THE LINK BETWEEN DIABETES AND GASTRIC CANCER

The putative mechanisms linking diabetes and gastric cancer are shown in Figure 1. Table 2 summarizes the explanations for such links and discusses some limitations for each possible link. These potential links will be discussed below under the subtitles of: (1) shared risk factors; (2) hyperglycemia; (3) *H. pylori* infection; (4) salt intake; (5) medications; and (6) comorbidities.

SHARED RISK FACTORS

Diabetes and gastric cancer may share common risk factors such as obesity, insulin resistance, hyperinsulinemia and smoking.

Obesity is associated with inflammation, oxidative stress, insulin resistance and hyperinsulinemia. All of these may contribute to a higher risk of gastric cancer[42]. Because some patients with diabetes may be obese[43-46], it is possible that this shared risk factor may partly explain the higher risk of gastric cancer in patients with diabetes.

Insulin has both metabolic and mitogenic properties[47,48]. Hyperinsulinemia, especially in the presence of insulin resistance, may promote cancer cell growth either through the mitogenic pathways triggered by insulin receptor or IGF-1 receptor, or *via* increased bioavailability of free IGF-1 by inhibiting the expression of IGF binding proteins[47-49]. These effects have also been well demonstrated in gastric cancer cell lines and in *in vivo* studies[50-54].

Smoking is another common risk factor for diabetes[55] and gastric cancer[27]. Therefore, smoking may also confound the association between diabetes and gastric cancer. However, because the higher risk of gastric can-

Table 2 Explanations on the putative mechanisms linking diabetes and gastric cancer and the limitations of current studies

Factors	Explanations/limitations
Shared risk factors	Explanations: Diabetes and gastric cancer may share common risk factors such as obesity, insulin resistance, hyperinsulinemia and smoking Limitations: These shared risk factors are known to cause cancer. Therefore, if these shared risk factors are in play, they may also increase the risk of other types of cancer, like colorectal cancer and lung cancer. As demonstrated in some studies, the link between diabetes and gastric cancer may be independent of smoking. Evidence for such an effect in humans needs to be fortified by further studies
Hyperglycemia	Explanations: Hyperglycemia is associated with pro-inflammatory status, oxidative stress, impaired immune function and increased insulin secretion. All of these may contribute to the development of gastric cancer. Epidemiological studies conducted in Japan support hyperglycemia as a risk factor for gastric cancer, and an interaction between hyperglycemia and *H. pylori* infection. Such a link may also be supported by findings from *in vitro* studies Limitations: Confirmation of such a link in other ethnicities is necessary
H. pylori infection	Explanations: Diabetes and *H. pylori* infection may be mutually causative. Patients with diabetes may have a higher infection rate, a lower eradication rate, and/or a higher reinfection rate of *H. pylori*. On the other hand, the inflammatory process induced by *H. pylori* infection may also increase the risk of diabetes Limitations: Findings in epidemiological studies are controversial with regards to the higher infection rate of *H. pylori* in patients with diabetes. Detection bias can not be excluded because patients with diabetes may suffer from more gastrointestinal symptoms leading to the diagnosis of *H. pylori* infection and gastric cancer
Salt intake	Explanations: A synergistic effect between *H. pylori* infection and salt intake on gastric cancer is supported by recent human studies and by *in vivo* and *in vitro* studies. Patients with diabetes may consume more salt because of loss of sensitivity to taste Limitations: Patients with diabetes may also be advised to take less salt especially in those with hypertension, kidney disease or congestive heart failure. Epidemiological studies evaluating the link between salt intake and gastric cancer in patients with diabetes are lacking
Medications	Explanations: Insulin and sulfonylureas may increase the risk of cancer. On the other hand, metformin, aspirin and statin may potentially reduce the risk of gastric cancer. Patients who repeatedly use antibiotics may have a lower risk of infection with *H. pylori* Limitations: Research of well quality on the use of medications and gastric cancer risk is lacking
Comorbidities	Explanations: Patients with diabetes may have multiple comorbidities including obesity, hypertension, dyslipidemia, vascular complications and heart failure. All of these may affect the development of gastric cancer, either positively or negatively, through the use of medications and changes in lifestyle, salt intake, dietary components, and the metabolism of drugs Limitations: A detection bias on *H. pylori* infection or gastric cancer is possible in patients with multiple comorbidities. Studies clarifying such links are still lacking

H. pylori: *Helicobacter pylori*.

cer associated with diabetes remains significant after adjustment for multiple risk factors including smoking[35,36], the link between diabetes and gastric cancer can also be independent of smoking.

It should also be pointed out that if shared risk factors are in play, their effects may not be site-specific and the risk of other types of cancer like colorectal cancer and lung cancer may also be increased. Furthermore, evidence for such a link through shared risk factors is not sufficient in humans and needs to be fortified by further studies.

HYPERGLYCEMIA

Patients with diabetes are characterized by an increased serum level of glucose. Similar observation of an increased risk of gastric cancer in patients with type 1 diabetes[34,56,57] and type 2 diabetes[35,36] may imply a mechanism involving hypgerglycemia, which is independent of insulin effect because type 1 diabetes is characterized by insulin deficiency. This is supported by human studies conducted in Japan showing an association between hyperglycemia even before the diagnosis of diabetes with a higher risk of gastric cancer[31,58]. Furthermore an interaction between hyperglycemia and *H. pylori* infection was reported to markedly increase the risk[31,58]. However, such a link with hyperglycemia needs to be confirmed in other ethnicities.

It is worth mentioning that a higher risk of gastric cancer in patients with type 1 diabetes may not completely exclude a mechanism involving insulin resistance or hyperinsulinemia because of the following facts: (1) recent studies strongly support the presence of insulin resistance in patients with type 1 diabetes[59]; (2) insulin injected subcutaneously bypasses the first-pass clearance by the liver; and (3) therapeutic insulin dose can not always be adjusted exactly to the physiological demands and hyperinsulinemia should be the usual phenomenon if glycemic control is aimed close to the normal range.

Some *in vitro* and *in vivo* studies may support a link between hyperglycemia and gastric cancer. An *in vitro* study indicated that glucose *per se* may affect the development of cancer *via* β-catenin acetylation with increased Wnt signaling[60], which is also a characteristic of gastric cancer[61]. Patients with diabetes may have an increased expression of pro-inflammatory cytokines such as interleukin-1, interleukin-6 and tumor necrosis factor-α[62]. It is also shown that these factors may upregulate and activate the Wnt/β-catenin pathway[63]. An animal study supported that gastric cancer induced by *N*-methyl-*N*-nitrosourea is enhanced in diabetic (*db*/*db*) mice through the effects of hyperglycemia and/or hyperinsulinemia[64].

Hyperglycemia may also promote carcinogenesis *via* increasing reactive oxygen species resulting in DNA damage[65] or increasing the expression of vascular endothelial growth factor, which is correlated with tumor vascularity and metastasis[66]. Furthermore, hyperglycemia may impair immune function rendering susceptibility to *H. pylori* infection and delaying wound healing in gastric ulcer following *H. pylori* infection. Hyperglycemia may also trigger insulin secretion, leading to hyperinsulinemia, especially in the presence of insulin resistance, which may increase the risk of cancer through insulin signaling. Because cancer cells are less efficient in using glucose for energy expenditure and they may consume more glucose than normal cells (the Warburg effect)[67], hyperglycemia provides a more suitable condition for tumor cells to grow.

H. PYLORI INFECTION

H. pylori infection is well known as a risk factor for gastric ulcer and cancer[27,68,69], possibly through DNA damage induced by reactive oxygen species in the infected gastric epithelial cells[70]. A research conducted in Taiwan suggested that early *H. pylori* eradication decreases the risk of gastric cancer in patients with peptic ulcer disease[71]. However, the role of diabetes on the relation between *H. pylori* infection and gastric cancer is still under investigation.

The relation between *H. pylori* infection and diabetes can be mutually causative. The increased risk of gastric cancer in patients with diabetes may be explained by either one of the following conditions related to *H. pylori* infection[72-76]: (1) higher infection rate; (2) lower eradication rate; or (3) higher reinfection rate. Patients with diabetes may be more susceptible to *H. pylori* infection because of impaired immune function associated with hyperglycemia[77]. However, whether patients with diabetes may really have a higher rate of *H. pylori* infection is controversial in epidemiological studies. Although studies from Qatar[78] and Egypt[79] suggested an increased infection rate in the patients with diabetes, this could not be similarly observed in studies conducted in Turkey[80] and Japan[81]. Because diabetes or poor glycemic control may be associated with an increased prevalence of gastrointestinal symptoms[82,83], it is not known whether the higher rate of *H. pylori* infection in some of the studies may be due to detection bias related to the symptoms[84]. Furthermore, it should be pointed out that an evaluation of the prevalence rate of *H. pylori* infection may not necessarily indicate an increased risk in terms of incidence. Patients with diabetes may have a lower eradication rate[72,76,85-88] and a higher reinfection rate after *H. pylori* infection[73,75,76]. Therefore, even in the condition that the incidence of *H. pylori* infection may not be increased in patients with diabetes, the prevalence rate may be significantly higher.

On the other hand, *H. pylori* infection can lead to diabetes because the active chronic inflammation may affect the normal secretion and function of insulin leading to glucose dysregulation[89-91]. For example, in a human study measuring the HOMA-IR (homeostasis model assessment of insulin resistance) levels in patients with and without *H. pylori* infection, insulin resistance is well demonstrated in those having *H. pylori* infection[89]. *H. pylori* infection may also affect the secretion of gastrointestinal hormones, such that basal and stimulated levels of serum gastrin are elevated but somatostatin level is decreased[92,93]. Gastrin increases food- or glucose-stimulated insulin secretion; but somatostatin inhibits the release of insulin. As a result, hyperinsulinemia may be seen following *H. pylori* infection. Whether *H. pylori* infection may directly affect insulin secretion from pancreas is not known. If the inflammatory process and oxidative stress induced by *H. pylori* infection[91] could also be demonstrated in the pancreas, it is expected that insulin secretion may be impaired. Insulin resistance, as induced by *H. pylori* infection, may also accelerate β-cell loss and leads finally to the clinical onset of diabetes[94]. Therefore, insulin deficiency as well as insulin resistance might be seen in chronic *H. pylori* infection.

SALT INTAKE

High salt intake has long been recognized as an important risk factor for gastric cancer[95-101], which can be independent of *H. pylori* infection[101]. However, some recent human studies showed a synergistic effect between salt intake and *H. pylori* infection[96,100]. Evidence from an *in vivo* study using Mongolian gerbils confirmed that high salt intake may exacerbate the risk of gastric cancer induced by *H. pylori* infection[102], which could probably be due to the upregulation of CagA synthesis in the bacteria in response to increased concentration of salt. The CagA protein is a bacterial oncoprotein related to the *H. pylori*-induced gastric cancer[102].

Whether high salt intake could be responsible for the increased risk of gastric cancer in patients with diabetes remains to be answered. It has been speculated that people with easy access to sugary, salty and fatty foods, which are calorie-rich but micronutrient-poor, may cause diseases such as obesity and diabetes[103]. On the other hand, patients with diabetes may consume more salt than people without diabetes because of the loss of sensitivity to taste, especially in those with a late stage of the disease complicated with neuropathy[104,105]. However, it is also possible that patients with diabetes may be advised to consume less salt than people without diabetes by their physicians, especially when the patients also suffer from hypertension, renal disease or congestive heart failure.

MEDICATIONS

Exogenous insulin use has also been shown to increase the risk of several cancer types[106,107]. Whether this could also be applied to gastric cancer has not been extensively

studied. In studies conducted in Taiwan, patients with diabetes who used insulin had a significantly higher risk of *H. pylori* eradication, but none of the other anti-diabetic drugs including sulfonylurea, metformin, acarbose, pioglitazone or rosiglitazone was associated with *H. pylori* eradication[84]. However, insulin use was not associated with an increased risk of gastric cancer[108]. It has been explained that the use of insulin might indicate poor glycemic control with more severe disease conditions in the *H. pylori* eradication study[84], suggesting a deteriorating metabolic control following *H. pylori* infection.

Insulin glargine, a long-acting insulin analog, may increase the risk of certain cancers involving colon, pancreas and breast[107,109,110]. This has always been ascribed to the very high affinity of insulin glargine to the IGF-1 receptor in *in vitro* studies[111]. However, this may not be the case when insulin glargine is injected subcutaneously because it is converted at the injection site to less mitogenic metabolites[112]. It remains unknown whether clinical use of exogenous human insulin or insulin analogs may affect the risk of gastric cancer.

Metformin may protect against a number of cancers[10,107,113], but sulfonylureas may be associated with an increased risk[106,114]. Whether these medications may affect the risk of gastric cancer in humans has rarely been studied. An inhibitory effect of metformin on gastric cancer cell proliferation can be demonstrated in *in vitro* and *in vivo* studies[115]. Similarly, an early *in vitro* study suggested that glibenclamide (a sulfonylurea) may exert antitumor activity in a human gastric cancer cell line[116]. However, a preliminary human study conducted in Taiwan showed a slightly higher but not significant risk ratio while comparing users of sulfonylureas only to users of metformin only in patients with type 2 diabetes (age-sex-adjusted OR = 1.855, 95%CI: 0.779-4.419)[106]. Thiazolidinediones may also demonstrate some antitumor effects on gastric cancer cells in *in vitro* and *in vivo* studies[117,118]. However, whether this can be translated into a preventive effect on gastric cancer growth in humans remains unknown.

From meta-analyses, use of statins is associated with a significantly 32% lower risk of gastric cancer[119], and aspirin may significantly reduce the risk with a SRR of 0.71 (95%CI: 0.60-0.82)[120]. Although without evidence, patients who repeatedly use antibiotics may happen to have a reduced risk of *H. pylori* infection. The confounding effects of these commonly used medications have rarely been controlled in previous studies investigating the association between diabetes and gastric cancer. Some studies suggested a sex difference in the use of insulin (more common in women)[121] and statins (more common in men)[122] in patients with type 2 diabetes. Whether this may contribute to a sex difference in the association between diabetes and gastric cancer awaits further investigation.

COMORBIDITIES

Obesity, hypertension and dyslipidemia are common comorbidities observed in patients with diabetes[43-46,123]. All of these may be associated with insulin resistance. Patients with ischemic heart disease, other vascular complications, congestive heart failure or chronic kidney disease/end-stage renal disease may have changed their lifestyle, daily activity, salt intake and dietary components or may have taken some other medications, supplements or alternative treatment. Hepatic or renal insufficiency may also affect the metabolism of medications. The confounding effects of comorbidities in the association between diabetes and gastric cancer have rarely been addressed in previous studies.

A detection bias related to multiple comorbidities is also possible. Patients with more comorbidities may have a higher probability of receiving laboratory examinations leading to the diagnosis of gastric cancer. This detection bias should be seriously taken into account in future studies.

CONCLUSION

Epidemiological evidence signals a higher risk of gastric cancer in patients with diabetes, which is more remarkable in females and in the Asian populations. Potential mechanisms may include shared risk factors, hyperglycemia, *H. pylori* infection, high salt intake, medications and comorbidities. It should be recognized that epidemiological findings are inconsistent, the estimated relative risk is moderate, and most studies have inherent limitations related to study design, sample size, confounders and biases. Therefore, more well-designed epidemiological studies are required to confirm the association between diabetes and gastric cancer in humans, and in-depth mechanistic studies are necessary to explain the possible links.

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