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Review Article

Diabetes mellitus and gastric carcinoma: Is there an association?

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Abstract

Diabetes mellitus (DM) has been associated with the risk of several gastrointestinal cancers including liver, pancreas, colon and rectum. However, the evidence is inconclusive for gastric adenocarcinoma (GC). In the current review, we summarize 20 population-based cohort studies that compared GC incidence and mortality between diabetic and non-diabetic population. We discuss the shared risk factors and provide qualitative and quantitative (meta-analytic) summary of the current evidence evaluating the association by high-risk subgroups. The overall risk-estimate based on all studies did not show an increased risk of GC in diabetics. However, 2 cohort studies conducted in East Asian countries, where *Helicobacter pylori* infection and GC rates are higher, showed a higher risk of GC in diabetics. Additionally, high plasma glucose levels in the presence of *Helicobacter pylori* infection increased the risk of GC by over four times, suggesting a multiplicative effect. Results from the meta-analysis show that, the risk of GC was also higher in populations with greater prevalence of type 1 DM (relative risk = 1.60), suggesting an insulin-independent carcinogenic process in this subgroup. The risk of mortality due to GC was higher in diabetics compared to non-diabetics (relative risk = 1.62). Although the overall risk estimates do not show an association between DM and GC, complex interactions between infectious, molecular, demographic and host factors may convey a higher risk in certain subgroups. Future studies should be sufficiently powered for detailed subgroup analysis to elucidate the causative and mechanistic association between DM and GC.

Keywords: Diabetes mellitus, gastric carcinoma, *Helicobacter pylori*, hyperglycemia, hyperinsulinemia

INTRODUCTION

The relationship between diabetes mellitus (DM) and cancer has evoked strong interest among clinical and scientific community for well over half a century.[1,2] Although early studies were inconclusive, the identification of common risk factors and an enormous increase in global prevalence of both these diseases[3] ensured that a causative and mechanistic association was further explored. Currently, based on several large-scale and prospective epidemiological studies, the consensus is that type 2 DM is a risk factor for cancers of liver, pancreas, colon, rectum, breast, bladder and endometrium. History of DM is considered to be a protective factor for prostate cancer. The evidence, however, is not as conclusive for other cancers.[4]

Gastric adenocarcinoma (GC) is a cancer with a high incidence rate and very poor survival, especially in developing

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countries.[5] The 5-year survival rate after GC is less than 20% for advanced stage (Stage III or greater) disease.[6] GC is the third most common cause of cancer deaths in males and fifth among females. As per Global statistics from 2008, almost 990,000 patients were diagnosed with an incident GC and 738,000 patients died due to GC.[7] This is an equivalent of 10% of all worldwide cancer deaths, 70% of which occurred in developing countries, especially in East Asia, East Europe and South America. In the United States, GC is more common in Hispanics and African Americans, than in Caucasians.[8] In addition to geographical and racial differences in risk, GC incidence has been shown to be greater in males and in people over 50 years of age.[9] However, recently, a more worrisome trend of increased incidence of GC in younger age group (25–39 years) has been observed, especially for non-cardia GC.[10,11] Obesity and smoking have also shown to be risk factors for gastric cardia cancers. However, the primary risk factor for GC is the long-term *Helicobacter pylori* (*H. pylori*) infection, associated with over 60% of all gastric carcinoma cases, primarily gastric lymphoma.[12,13]

Notably, most of these risk factors for GC have also been shown to be associated with an increased risk of DM.[14,15] Common pathways involving hyperinsulinemia and hyperglycemia, which are the proposed mechanisms for shared risk between DM and other cancers, may also be relevant for GC.[16,17] Though the presence of common factors makes a causative, mechanistic and prognostic association between these two conditions a possibility, the epidemiological evidence overall has been sparse and inconsistent. Therefore, the current consensus report does not support the theory that DM is a risk factor for GC.[4]

The complexity presented by these strong confounding risk factors necessitates the evaluation of the effect of DM separately for each of the risk groups, in order to understand the association. However, most studies evaluated the relationship between GC and DM either in populations in which GC prevalence is very low or as a small part of a broader report on risk of all cancers. So, the association in these high-risk subgroups has not been thoroughly explored. In this review, we discuss the shared risk factors for DM and GC and the complexity of their association, and provide qualitative and quantitative (meta-analytic) summary of the current evidence evaluating the association by risk groups, when possible.

METHODS

Literature search

A comprehensive literature search, on DM and GC, was performed using PubMed, SCOPUS and MEDLINE databases. The search included all possible combinations of relevant terms like diabetes mellitus, hyperglycemia, serum glucose, cancer, gastric cancer, stomach cancer, gastric adenocarcinoma, incidence and mortality. Additionally, all appropriate references that were cited in previously published articles and reviews were also manually identified. The search was limited to English language studies. Overall, 36 articles that discussed the association between GC and DM/high fasting plasma glucose (FPG) levels were identified and evaluated. The final meta-analysis and review is limited only to cohort studies that presented separate risk estimates for GC in diabetic patients or patients with high FPG. The final review is based on 20 cohort studies that evaluated GC in DM patients/subjects with high FPG, wherein 11 studies[18-28] evaluated GC incidence rates alone, 7 studies[29-35] evaluated mortality rates alone and 2 studies[36,37] evaluated both incidence and mortality rates for GC. In studies that used questionnaire data or medical record review, any clinical diagnosis of DM was used for confirmation of the disease. When studies provided FPG measurements, the highest strata were compared to the lowest strata. The relative risk (hazard ratios) or standardized incidence/mortality rates were recorded.

Meta-analysis

The meta-analysis was conducted to identify the overall pooled risk of incidence and mortality related to GC in diabetic patients. The risk estimates (with 95% confidence interval) were evaluated by using both fixed and random effects models. The heterogeneity between studies was explored using study-specific Q statistic. The significance level was maintained at $P = 0.05$. If significant heterogeneity was observed between studies, the random effects model was used to provide the final estimate. Stratified analysis was conducted, when possible, by gender, age group and geographical location. STATA V.11 software was utilized for the meta-analysis.

RESULTS

Risk of GC incidence in diabetic patients

Ten population-based cohort studies that evaluated the risk of GC in DM patients are summarized in Table 1.[18-25,36,37] Most of these studies utilized hospital or national health records to confirm the diagnosis of DM and GC. Three studies were from Eastern Asia, 4 from Europe and 2 from United States. Among the four European studies, only the study by Wideroff *et al*. showed a borderline 10–20% increase in risk of GC in diabetic patients.[19] In the other population-based cohort from UK, there was a non-significant increase in risk only in diabetic patients who were less than 30 years of age at diagnosis, probably mostly type 1 diabetics.[37] Similarly,

a Swedish study conducted in a predominantly type 1 diabetic population (less than 30 years of age at diagnosis) showed almost twice the risk of GC.[20] Among the three Asian studies, two studies showed a statistically significant increased risk of GC in diabetic patients,[21,36] while the other study showed a statistically significant decrease in risk.[22] Only one study, an American study conducted by Lin *et al.*, differentiated between gastric cardia and gastric non-cardia adenocarcinoma. This study showed a statistically significant increased in risk of gastric cardia cancers, but not for non-cardia cancers.[24]

Four other population-based cohort studies evaluated the role of hyperglycemia in the risk of GC [Table 2].[26-28,36] These studies utilized FPG levels and compared the risk of GC between patients in the lowest and highest strata of glucose levels. One Japanese study by Yamagata *et al*. showed a statistically significant three times increase in risk of GC in patients in the highest tertile of FPG level, compared to the lowest tertile.[28] In this study, the increased risk was significantly higher (four times) in patients who were in the highest FPG level and were positive for *H. pylori*. This increased risk was not noted in *H. pylori* negative patients.

On meta-analysis, based on random effects model, there was no significant increase of overall risk of GC in diabetic patients [relative risk (RR): 1.01 (0.90–1.11)]. No significant increase in risk was noted when stratified by geographical location [Figure 1]. Similarly, no significant increase in risk was noted when stratified by gender (data not shown). When the two studies that provided estimates for patients less than 30 years of age (predominantly type 1 diabetics) were evaluated,[20,37] a 60% increased risk of GC was observed. This risk increase was not statistically significant [RR: 1.60 (0.56–2.64)], probably due to the small number of GC cases (data not shown).

Risk of GC mortality in diabetic patients

Table 3 lists the nine cohort studies that evaluated the all-cause mortality in diabetic population compared to non-diabetics.[29-37] All three studies from Asia showed that risk of death due to GC was significantly higher in diabetics compared to non-diabetic population, especially in males.[33,35,36] One Taiwanese study showed a statistically

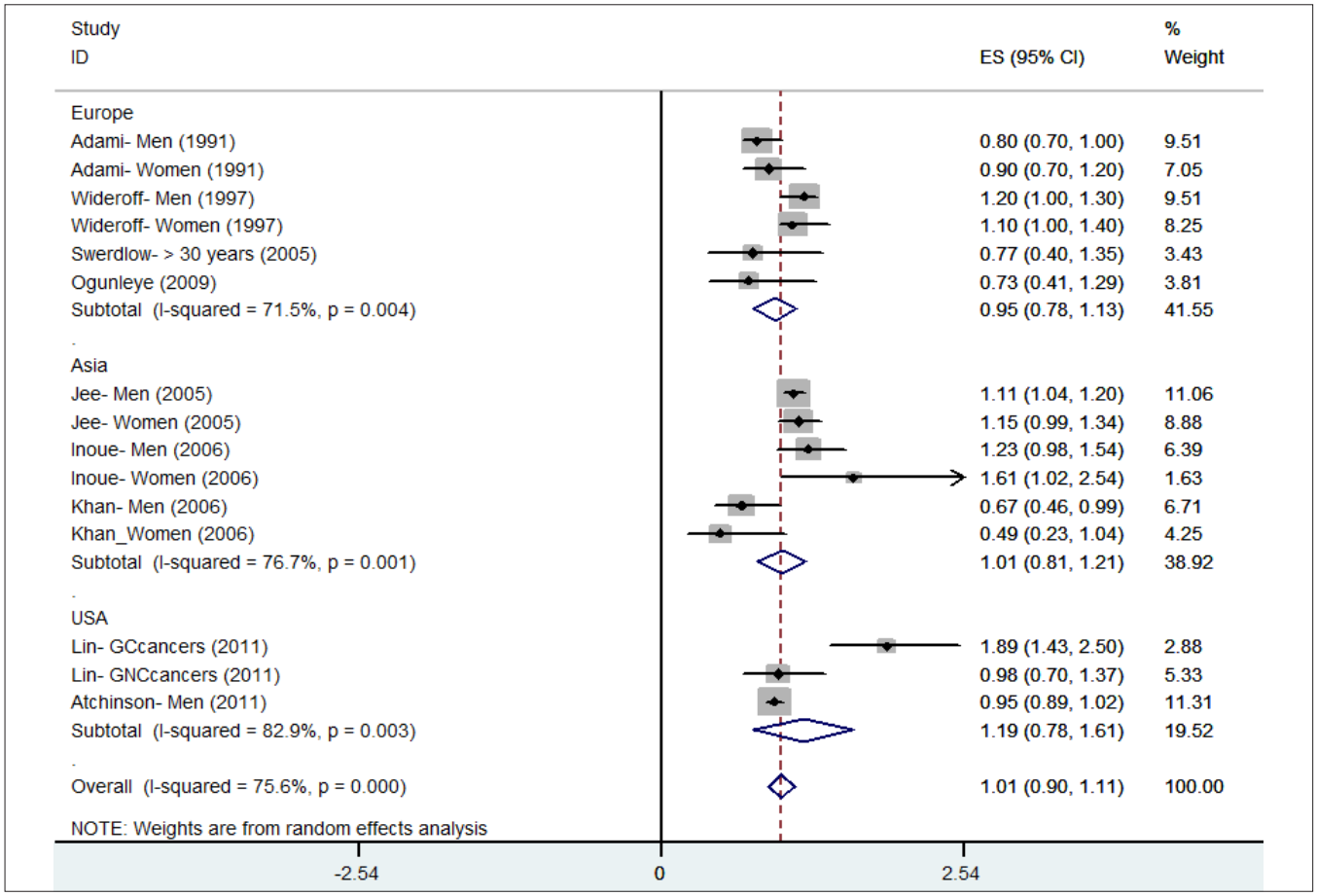

Figure 1: Meta-analysis of cohort studies evaluating the risk of gastric carcinoma incidence in diabetic patients, stratified by geographical region of the study

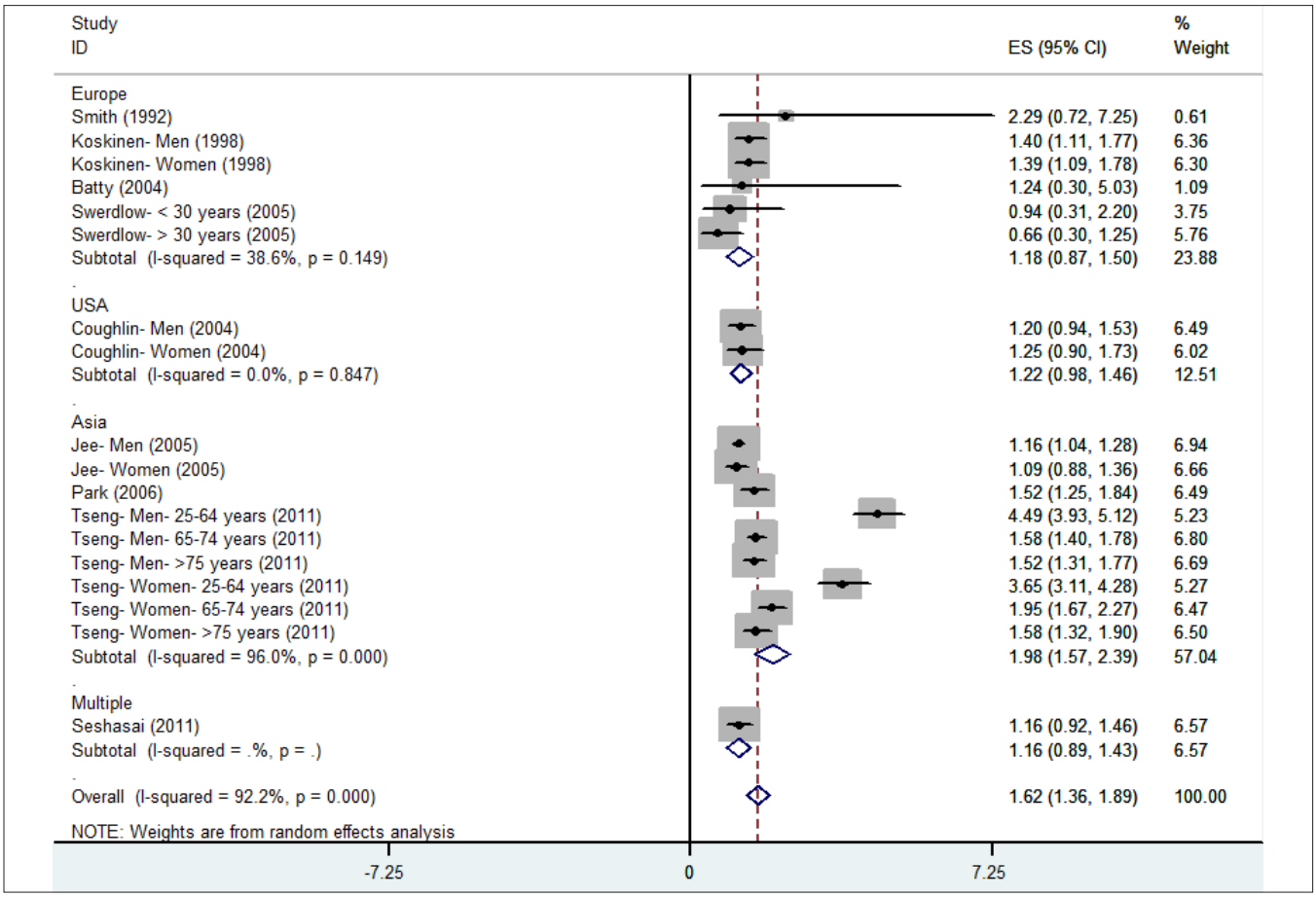

Figure 2: Meta-analysis of cohort studies evaluating the risk of mortality due to gastric carcinoma in diabetic patients, stratified by geographical region of the study

significant 3–4 times greater risk in diabetics compared to non-diabetics in younger age groups.[35] Among the five studies done in western countries, one Finnish study showed a statistically significant 40% risk of GC deaths,[30] while four other studies showed a statistically insignificant increase in risk.[29,31,34,37] On meta-analysis of these eight cohort studies [Figure 2], the risk of GC deaths was higher in diabetics compared to non-diabetics [RR: 1.62 (1.36–1.89)]. Asian studies showed a statistically significant increased risk of GC deaths in diabetic patients [RR: 1.98 (1.57–2.39)]. The studies from western countries showed a statistically insignificant increase in risk of GC in diabetic patients. The risk of GC deaths in diabetics was increased both in men [RR: 1.75 (1.35–2.16)] and in women [RR: 1.78 (1.26–2.30)], when compared to non-diabetics.

DISCUSSION

Mechanism of shared risk

Both cancer and DM are very common diseases that have heterogeneous developmental pathways. Increasing incidence trends of both these diseases may at least partly be due to the shared risk factors and mechanistic pathways.[4,16] Shared risk factors include both non-modifiable (age, gender and race) and modifiable risk factors (obesity, diet and smoking). Hyperglycemia, insulin resistance, hyperinsulinemia and chronic inflammation are considered to be some of the shared mechanistic processes between these two diseases.[4,16,17,38] Among these factors, hyperinsulinemia is considered to be the primary mechanism of shared risk of DM and cancer. Insulin has been shown to possess both metabolic and mitogenic capabilities. Hyperinsulinemia, either through insulin resistance or through insulin-like growth factor I (IGF-I) system, may result in up-regulation of the mitogenic and anti-apoptotic effect, thus mediating the cancer initiation and progression.[16] Hyperglycemia, on the other hand, has been shown to aid carcinogenesis indirectly by increasing insulin production and also by providing glucose for energy metabolism of cancer cells. However, direct role of hyperglycemia in cancer initiation has not been confirmed.[4] Similarly, obesity has also been shown to indirectly increase the risk of cancers due to increased hyperglycemia, insulin resistance and inflammation.[4] Some preliminary evidence also shows that insulin use may increase the risk of certain

Table 1: Summary of 10 population -based cohort studies that evaluated the risk of gastric carcinoma incidence in diabetic patients

Author, year	Country	Population	Follow-up duration	Diabetes diagnosis	Stomach cancer diagnosis	Incidence/ diabetic patients	Incidence/ non-diabetic subjects	Risk estimate	Adjusting variables
Adami, 1991	Sweden	51,008 diabetics	>1–20 years	National health registry	National cancer registry	Men: 82/23,146 Women: 77/27,862	-	Standardized estimates: Men: 0.8 (0.7–1.0) Women: 0.9 (0.7–1.2)	-
Wideroff, 1997	Denmark	109,581 diabetics	>4–17 years	National hospital registry	National cancer registry	Men: 188/54,571 Women: 131/55,010	-	Standardized estimates: Men: 1.2 (1.0–1.3), Women: 1.1 (1.0–1.4)	-
Zendehdel, 2003	Sweden	29,187 type 1 diabetics (<30 years of age)	>14 years	National hospital in-patient registry	National cancer and death registry	10/29,187	-	Standardized estimate: 2.3 (1.1–4.1)	-
Swerdlow, 2005	UK	29,701 insulin-treated diabetics under 50 years of age at diagnosis	10–35 years	National health registry	Cancer registry	<30 years of age: 7/23,834; 30–49 years of age: 12/5066		Standardized estimates: <30 years of age: 1.20 (0.48–2.47); 30–49 years of age: 0.77 (0.40–1.35)	-
Jee, 2005	Korea	1,298,385 participants	7–10 years	Diabetes medication use and/or fasting blood measurement (>126 mg/dl)	National cancer registry and hospitalization records	Standardized incidence rate per 100,000 population: Men: 140.3 Women: 54.2	-	Men: 1.11 (1.04–1.20) Women: 1.15 (0.99–1.34)	Age, age squared, smoking, alcohol
Inoue, 2006	Japan	133,084 participants aged 40–69 years	10–14 years	Self-administered questionnaire	Hospital record, cancer registry and death certificates	Men: 87/3097 Women: 20/1571	Men: 890/4345, Women: 342/49,652	Men: 1.23 (0.98–1.54), Women: 1.61 (1.02–2.54)	Age at baseline, study area, cerebrovascular disease, ischemic heart disease, smoking, ethanol intake, body mass index, leisure-time physical activity, green vegetable intake and coffee intake
Khan, 2006	Japan	56,881 participants aged 40–79 years	7–10 years	Self-administered questionnaire	Follow-up survey, cancer registry and death certificates	Men: 496 patients Women: 265 patients	-	Standardized estimates: Men: 0.67 (0.46–0.99) Women: 0.49 (0.23–1.04)	Age, BMI, smoking, and alcohol intake
Ogunleye, 2009	UK	9577 diabetics and 19,154 non-diabetic comparators	>1–11 years	Clinical information system	National cancer registry	661/9577	1364/19,154	0.73 (0.41–1.29)	Deprivation decile
Lin, 2011	USA	469,448 participants aged 50–71 years	10 years	Self-administered questionnaire	Cancer registry	61 GCA, 291 GNCA in 41,388 diabetics	39 GCA, 340 GNCA in 428,060 non-diabetics	GCA: 1.89 (1.43–2.50), GNCA: 0.98 (0.70–1.37)	Age, sex, calories, alcohol consumption, smoking, fruit consumption, vegetable consumption, ethnicity, education, and physical activity
Atchison, 2011	USA	594,815 diabetic men and 3,906,763 non-diabetic men as comparators	>1–27 years	Veteran's hospital discharge records	Hospital discharge records and Social security administration mortality files	1063/594,815	6452/3,906,763	All men: 0.95 (0.89–1.02)	Age, time, latency, race, number of visits, diagnoses of alcohol–related conditions, obesity and COPD

Table 2: Summary of four population-based cohort studies that evaluated the risk of gastric carcinoma incidence by different strata of fasting plasma glucose levels

Author, year	Country	Population	Follow-up duration	Gastric cancer diagnosis	Comparison group	Risk estimate	Adjusting variables
Jee, 2005	Korea	1,298,385 participants	7–10 years	National cancer registry and hospitalization records	<90 mg/dl	FGL 126–139 mg/dl: Men: 1.08 (0.94–1.24) Women: 0.99 (0.87–1.12) FGL ≥ 140 mg/dl: Men: 1.00 (0.91–1.10) Women: 1.01 (0.88–1.19)	Age, age squared, smoking, alcohol
Rapp, 2006	Austria	140,813 participants	8 years	Cancer registry	4.2–5.2 mmol/l	FGL: Men (≥7 mmol/l): 0.84 (0.38–1.87) Women (≥6 mmol/l): 1.16 (0.66–2.05)	Stratified by age and adjusted for smoking status, occupational group, BMI
Stattin, 2007	Sweden	64,597 participants	10 years	National and regional cancer registry	Lowest quartile (value not provided)	FGL highest quartile: 1.46 (0.75–2.94)	Age, calendar year, and smoking
Yamagata, 2005	Japan	2466 subjects	9 years	Annual mass screening and health records	<5.3 mmol/l	FGL > 5.8 mmol/l: 3.10 (1.50–6.4) FGL > 5.8 mmol/l and *H. pylori* negative*: 1.5 (0.5–5.2) FGL > 5.8 mmol/l and *H. pylori* positive*: 4.2 (1.6–11.1)	Age, sex, BMI, serum cholesterol, *H. pylori* seropositivity, smoking habits, alcohol intake, history of peptic ulcer disease, and dietary factors

*Age and gender only, BMI – body mass index, FGL – fasting glucose level.

cancers by binding to IGF-1 receptors, but this hypothesis is still being debated.[39-43]

Most of these shared factors and mechanisms are not site specific and would be common to many cancer sites. If the association between DM and cancer is only because of these common factors, the increased risk should be consistent across most anatomical sites. The current evidence, however, suggests that there is risk association only for certain anatomical sites. Therefore, in order to explain the difference in rates between different organs, it is very important to further explore the interaction effect of other site-specific risk factors. However, most studies on DM and cancer have been designed to evaluate the risk of all/multiple cancer sites, and so have been powered to provide significant risk estimates only for the more common cancers. Since most of these studies had been conducted in the developed western countries, where GC is relatively less common, they were not powered to evaluate the risk of GC in detail. Consensus based just on these studies is bound to be inconclusive. Therefore, the role of GC-specific risk factors needs to be further explored, especially in high-risk population.

Diabetes and gastric carcinoma incidence

The role of Helicobacter pylori

It is interesting to note that the risk of GC in diabetic patients seems slightly higher in studies conducted in Asian countries, where the prevalence of GC is high. While ethnicity could itself be an independent risk factor, *H. pylori* has been shown to be the most important risk factor for GC, especially in Eastern Asian population.[44] *H. pylori* may increase the risk of GC either directly through mutagenic or protein modulatory effect on the epithelium or indirectly by induction of inflammatory process in the epithelium.[45-47] However, not all individuals infected with *H. pylori* develop GC, suggesting the requirement of other cofactors to aid *H. pylori* mediated carcinogenic process. A higher prevalence and lower eradication rate of *H. pylori* in diabetic patients was reported by some studies, suggesting the possibility of interaction between *H. pylori* and hyperglycemia.[48] *H. pylori*, through

Table 3: Summary of nine population-based cohort studies that evaluated the risk of gastric carcinoma mortality in diabetic patients

Author, year	Country	Population	Follow-up duration	Diabetes diagnosis	Mortality diagnosis	GC mortality/ diabetic patients	GC mortality/ non-diabetes subjects	Mortality risk estimate	Adjusting variables
Smith, 1992	UK	18,274 men	18–20 years	Self-reported and blood measurement (>200 mg/100 ml)	National health registry	3/224		2.29 (0.72–7.25)	Age
Koskinen, 1998	Finland	1,142,857 men and 1,307,692 women	5 years	Medication history from national drug register	Cause of death registers and census records	Men: 79/24,000 Women: 73/34,000		Age standardized rates: Men: 1.40 (1.11–1.77) Women: 1.39 (1.09–1.78)	Univariate
Batty, 2004	UK	18,403 men aged 40–64 years	25 years	Self-reported and blood measurement	Information from national registry	2/188	149/16,843	1.24 (0.30–5.03)	Age, employment grade, smoking status, physical activity, systolic blood pressure, blood pressure-lowering medication, marital status, disease at study entry, unexplained weight loss, BMI, triceps skinfold thickness, height-adjusted FEV 1, plasma cholesterol
Coughlin, 2004	USA	467,922 men and 588,321 women, aged 30 years or older	16 years	Self-reported	Personal inquiries and also National Death Index information	Men: 69/26,617 Women: 40/26,186	Men: 1057/441,305 Women: 559/562,135	Men: 1.20 (0.94–1.53) Women: 1.25 (0.90–1.73)	For both genders: age, race, years of education, body mass index, smoking history, consumption of alcohol, total red meat, citrus fruits, juices and vegetables, physical activity Females: use of replacement estrogens
Jee, 2005	Korea	846,907 men and 482,618 women	7–10 years	Self-reported and blood measurement	Medical records/Death certificates	Standardized death rate per 100,000 population: Men: 63.1 Women: 24.1		Men: 1.16 (1.04–1.28) Women: 1.09 (0.88–1.36)	Age, age squared, smoking and alcohol use
Swerdlow, 2005	UK	29,701 insulin-treated diabetic patients	10–35 years	Insulin-treated diabetes history from health registry	Data from cancer registries	Age: <30 years: 5/23,834 30–49 years: 9/5066		Standardized mortality rates: <30 years: 0.94 (0.31–2.20) 30–49 years: 0.66 (0.30–1.25)	-

Table 3 (contd...)

gastrin secretion, can increase the glucose-stimulated insulin release, thereby resulting in hyperinsulinemia.[49] It has also been shown to independently promote insulin resistance and related oxidative stress,[50,51] thereby also possibly facilitating the hyperinsulinemia-mediated carcinogenic process in the gastric mucosa. The strongest epidemiological proof yet of the possible multiplicative effect of hyperglycemia and *H. pylori* infection was presented by the Japanese cohort study summarized in Table 2.[28] This study evaluated the FPG levels and GC risk stratified by *H. pylori* status. This study showed that higher FPG levels were associated with a significant risk of GC, only in patients who were *H. pylori*

Table 3 (contd...)

Table 3: Summary of nine population-based cohort studies that evaluated the risk of gastric carcinoma mortality in diabetic patients

Author, year	Country	Population	Follow-up duration	Diabetes diagnosis	Mortality diagnosis	GC mortality/ diabetic patients	GC mortality/ non-diabetes subjects	Mortality risk estimate	Adjusting variables
Park, 2006	Korea	14,578 Men	9 years	Serum fasting glucose levels of ≥126 mg/dl	National statistical office records	150 Deaths	1349 Deaths	1.52 (1.25–1.84)	Age, alcohol, BMI, fasting serum glucose, cholesterol, physical activity, food preference, blood pressure, and other comorbidities (heart disease, liver disease, and cerebrovascular disease)
Seshasai, 2011	Multiple	820,900 participants from 97 studies	-	Self-reported/ medication use/ fasting glucose level	Medical records/Death certificates	40,116 deaths	674,945 deaths	1.16 (0.92–1.46)	Stratified on the basis of study, sex, and trial group, and adjusted for baseline age, smoking, and body mass index
Tseng, 2011	Taiwan	113,347 men with diabetes and 131,573 women with diabetes	8–10 years	Self-reported and blood measurement	Death certificate data	Men: 627 deaths Women: 422 deaths		Age-specific mortality Age 25–64 years: Men: 4.49 (3.93–5.12) Women: 3.65 (3.11–4.28) Age 65–74 years: Men: 1.58 (1.40–1.78) Women: 1.95 (1.67–2.27) Age >75 years: Men: 1.52 (1.31–1.77) Women: 1.58 (1.32–1.90)	-

BMI – body mass index, FEV1 – forced expiratory volume in 1 second.

seropositive. The GC risk was increased not only in the high-FPG group in which DM was prevalent, but also in modest-FPG group, in which DM was not as common. This study suggests an important effect-modifying role for hyperglycemia in *H. pylori* related carcinogenesis.

The relevance of anatomical subsite

A population-based cohort study, conducted in the United States, evaluated the GC risk stratified by anatomical subsites as adenocarcinoma of gastric cardia (GCA) and non-cardia (GNCA).[24] The results showed a statistically significant 89% increased risk of GCA in diabetics, but no increase in risk of GNCA. One of the possible mechanisms for this increased risk could be obesity-mediated hyperinsulinemia.[52,53] However, this study also showed that the risk remained significantly higher even after adjusting for body mass index (BMI) or when stratified by BMI categories. This result suggests a different carcinogenic mechanism, independent of obesity, for diabetes-related GCA. Recent studies have shown that *H. pylori* infection may be associated with higher risk of GCA also.[54] However, the cohort study did not evaluate the role of *H. pylori* in GCA, and this relationship needs to be further explored.

Risk associated with type 1 diabetes mellitus

Most of the available evidence suggests that the relationship between DM and cancer is mainly because of the mechanisms related to or a result of hyperinsulinemia. Hyperglycemia

plays a role is this process mainly by increasing the insulin secretion. However, results from one large Swedish cohort study suggest an alternate insulin-independent mechanism for hyperglycemia-related gastric carcinogenesis.[20] This study included 30,000 patients with type 1 DM, a condition in which hyperglycemia is associated with a deficiency of endogenous insulin. While there was no increase in risk associated with other cancers like liver, pancreas and colon, the risk of GC was over two times greater. Another European study that separately evaluated patients less than 30 years of age at diagnosis (predominantly type 1 diabetics) also showed an increase in risk of GC, although statistically insignificant.[37] Pernicious anemia and *H. pylori* are proposed as the potential co-factors associated with this increased risk in type 1 diabetics.[55,56] *H. pylori* infection has been shown to be more prevalent and more recurrent in type 1 diabetics.[48] These results suggest a need to explore insulin-independent pathways by which *H. pylori* and hyperglycemia may influence the risk of GC.

The effect of insulin and insulin analogs

Insulin use, especially long-acting insulin glargine, has been shown to increase the risk of certain hyperinsulinemia-related cancers such as colon and pancreas.[39-41] Insulin glargine has been shown to have a very high affinity to IGF-1 receptor and also can act as a mitogenic agent, thereby promoting carcinogenesis.[42] However, several questions still remain about the other factors that may influence this relationship like duration of insulin use, insulin dosage, glucose control in these patients and other patient-related factors.[42] It is important to confirm this relationship because insulin is required for a big percentage of type 2 diabetics and all of the type 1 diabetics. Long-term insulin use can in fact be proposed as the explanation for the increased risk of GC in type 1 diabetics. This relationship has not been studied yet. On the other hand, if long-term insulin analog use is the reason for increased risk of GC in type 1 diabetics, similar increase in risk would have to be noted for other hyperinsulinemia-related cancer sites like liver and pancreas. However, studies have not noted any such association, possibly suggesting an alternative mechanism.

Diabetes and gastric carcinoma related mortality

Several studies also evaluated the risk of cancer-related mortality in diabetics compared to non-diabetics [Table 3]. The risk of mortality due to GC was higher in diabetics compared to non-diabetic population, especially in Asian population. Several mechanisms can be proposed to explain the increased risk of mortality due to GC in diabetics compared to non-diabetics. It is possible that DM, characterized by hyperinsulinemia and hyperglycemia, may promote cancer cell proliferation and metastasis, thereby resulting in poor overall survival after diagnosis. However, the more common treatment-related causes should first be ruled out. DM is one of the most common and important medical comorbidities which may affect the peri-operative outcomes during any surgical procedure. The most important DM related peri-operative complications would include: diffuse end organ damage due to longstanding DM, especially related to cardiac events, stroke, worsening of the pre-existing renal dysfunction, diabetic vasculopathy and small vessel disease leading to poor tissue healing, impaired neutrophil function predisposing to increased rate of wound infection and delayed gastric emptying/diabetic gastroparesis. So, it is expected that the post-operative mortality risk after any major gastric cancer resection is higher in diabetics than in non-diabetics. The above-mentioned factors that increase mortality risk also have the most severe impact on the recovery from immediate post-operative period. It is also possible that the pattern and frequency of recurrence of GC in diabetics is different from that in non-diabetics. Further research is needed to elucidate the different mechanisms contributing to the greater risk of GC mortality in diabetics. Irrespective of the mechanism causing this increased risk, this result suggests the importance of diabetic control and continuous monitoring in patients with newly diagnosed GC and the need for multi-disciplinary approach in treatment.

CONCLUSION

Although the overall risk estimates for DM and GC are not significant, a complex interaction between demographic, infectious and molecular factors cannot be ruled out, especially in certain high-risk populations. The risk of GC is higher in communities where *H. pylori* prevalence is high. *H. pylori* seems to be an integral component in the mechanism of increased risk in diabetic patients. Current epidemiological evidence suggests that hyperglycemia may be an effect-modifying factor that promotes the carcinogenic effect of *H. pylori* in gastric mucosa. There is also preliminary evidence to suggest that type 1 DM may be a risk factor for the development of GC, suggesting an insulin-independent mechanism of risk for these subtypes. Given the recent increasing trend in GC incidence in young adults in western countries, further evaluation of this complex inter-relationship is pertinent. Future studies, that are sufficiently powered and designed to evaluate these subgroups, are needed to further understand the mechanism and magnitude of risk of DM on GC.

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