

DIABETES MELLITUS A RISK FACTOR OF GASTRIC CANCER : SYSTEMATIC REVIEW

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ABSTRACT

Background: It is estimated that 500 million individuals globally would have diabetes mellitus (DM) by 2030. A deadly tumor that affects the digestive tract is called gastric cancer (GC). It ranks as the fourth leading cause of cancer death worldwide and the fifth most common kind of cancer. Every year, there are around 700,000 fatalities and one million new cases of GC globally.

Aims : This systematic review is to review the association of diabetes mellitus as a risk factor of gastric cancer.

Methods: This study demonstrated compliance with all requirements by means of a comparison with the standards established by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020. Thus, the specialists were able to guarantee that the research was as current as feasible. Publications released between 2014 and 2024 were considered for this search strategy. This was accomplished by utilizing a number of distinct online reference sites, including Pubmed, ScienceDirect, and SagePub. It was determined that reviews, previously published works, and partially completed works would not be included.

Result: In the PubMed database, the results of our search brought up 343 articles, whereas the results of our search on SAGEPUB brought up 2178 articles, our search on SCIENCE DIRECT brought up 23102 articles. The results of the search conducted for the last year of 2014 yielded a total 231 articles for PubMed, 1017 articles for SAGEPUB and 12260 articles for SCIENCE DIRECT. In the end, we compiled a total of 5 papers, 2 of which came from PubMed, 1 of which came from SAGEPUB and 2 of which came from SCIENCE DIRECT. We included five research that met the criteria.

Conclusion: In summary, there is no direct association of diabetes mellitus and gastric cancer, but diabetes mellitus can increase the risk factor of gastric cancer cases.

Keyword: Diabetes mellitus, gastric cancer

INTRODUCTION

Diabetes mellitus raises the risk of several malignancies, including non-Hodgkin lymphoma, bladder, kidney, colorectum, liver, pancreas, and breast. Diabetes patients may have oxidative stress, pro-inflammatory state, insulin resistance, and inadequate glycemic management as the underlying causes of their increased cancer risk. Furthermore, the length of diabetes, the severity of diabetes, and the usage of anti-diabetic medications, together with a number of comorbidities, may all be factors.¹

A increasing amount of research, mostly from case-control studies, cohort studies, and meta-analyses, indicates that diabetic mellitus (DM) may raise the risk of several different types of cancer. Prostate cancer exhibits a positive or inverse relationship with diabetes mellitus, but the risk rises twofold for cancers of the liver, pancreas, and endometrial and 1.2–1.5 times for malignancies of the colon and rectum, breast, bladder, and kidney. In actuality, DM is a disease with a global pandemic scope. From 171 million in 2000 to 366 million in 2011, the population of people with diabetes was expected to reach 552 million by 2030.²

Given the rising incidence of DM and the expected 200 million more cases over the next 20 years, it is clear that even a little rise in cancer risk will have an effect on public health. Therefore, a DM-cancer relationship may have a significant impact on global health levels in addition to the sharp rise in the incidence of DM and the effects of its comorbidities.²

Despite the heightening clinical awareness of the DM-cancer association, however, the risk of gastric cancer (GC) in DM patients has seemingly attracted little attention among diabetes researchers and healthcare providers, and this topic has been scarcely addressed in the English literature with contradictory findings. This dearth of data may be attributable to the fact that the disease *per se* has been paid little attention in the West, with fewer established regular screening programs for GC. Consequently, the risk of GC in DM patients is still overshadowed by the more common acute and chronic DM complications such as cardiovascular and renal diseases, which largely account for the 2-fold increase in mortality associated with DM.²

By 2030, 500 million people worldwide are predicted to develop diabetes mellitus (DM). Gastric cancer (GC) is a fatal tumor affecting the digestive system. It is the fifth most frequent kind of cancer and the fourth biggest cause of cancer-related deaths globally. Approximately one million new cases and 700,000 fatalities worldwide are reported from GC each year. However, despite a substantial amount of study on the relationship between diabetes mellitus and cancer, the link with GC varied between studies.^{3,4}

Men and those 50 years of age and older are more likely to get stomach cancer. Important risk factors include salt consumption, smoking, obesity, and *Helicobacter pylori* (*H. pylori*) infection. While the prevalence is low in North America and the majority of Africa, stomach cancer is more prevalent in developing nations in East Asia, East Europe, and South America. For advanced illness, the 5-year survival rate is less than 20%, indicating an extremely bad prognosis for stomach cancer. In most parts of the world, the incidence of gastric cancer has declined recently. This is most likely because more people are using refrigerators and relying less on salt to preserve food, as well as because fresh produce is more readily available and *H. pylori* infections are being managed. Nonetheless, it continues to be a significant malignancy that affects human health; in 2008, it may have contributed 10% of all cancer deaths and 8% of all cancer incidence globally.¹

Elevated blood glucose levels are a hallmark of diabetes patients. Because type 1 diabetes is defined by insulin shortage, a mechanism involving hyperglycemia that is independent of the insulin impact may be implied by the same discovery of an elevated risk of gastric cancer in individuals with type 2 diabetes and type 1 diabetes. Human research from Japan supports this, demonstrating a link between hyperglycemia prior to a diabetes diagnosis and an increased risk of stomach cancer. Moreover, it has been shown that there is a significant risk increase when hyperglycemia and *H. pylori* infection combine. It is necessary to confirm this association between hyperglycemia and other ethnic groups.⁴

By raising reactive oxygen species, which damage DNA, or by upregulating the production of vascular endothelial growth factor, which is linked to tumor vascularity and metastasis, hyperglycemia may also contribute to the development of cancer. Moreover, hyperglycemia may compromise immunological function, increasing the risk of *H. pylori* infection and postponing the healing of stomach ulcers caused by the infection. Additionally, insulin production may be triggered by hyperglycemia, resulting in hyperinsulinemia. This is particularly true when insulin resistance is present, as insulin signaling may raise the risk of cancer. Hyperglycemia offers a more conducive environment for tumor cells to thrive because cancer cells are less effective at utilizing glucose for energy expenditure and may use more glucose than normal cells (the Warburg effect).¹

METHODS

Protocol

The author of this study ensured that it complied with the standards by adhering to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. This is done to guarantee the accuracy of the results that are derived from the investigation.

Criteria for Eligibility

In order to complete this literature evaluation, we looked at published research that discusses the association of diabetes mellitus as a risk factor of gastric cancer. This is done to enhance the patient's therapy management and to offer an explanation. This paper's primary goal is to demonstrate the applicability of the issues that have been noted overall.

To be eligible to participate in the study, researchers had to meet the following requirements: 1) English must be used to write the paper. The manuscript must fulfill both of these conditions in order to be considered for publication. 2) A few of the examined studies were released after 2013 but prior to the time frame considered relevant by this systematic review. Editorials, submissions without a DOI, already published review articles, and entries that are nearly exact replicas of journal papers that have already been published are a few examples of research that are prohibited.

Search Strategy

We used "diabetes mellitus" and "gastric cancer" as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SAGEPUB databases by inputting the words: ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields]) AND ("stomach neoplasms"[MeSH Terms] OR ("stomach"[All Fields] AND "neoplasms"[All Fields]) OR "stomach neoplasms"[All Fields]) OR ("gastric"[All Fields] AND "cancer"[All Fields]) OR "gastric cancer"[All Fields]) AND ("risk factors"[MeSH Terms] OR ("risk"[All Fields] AND "factors"[All Fields]) OR "risk factors"[All Fields] OR ("risk"[All Fields] AND "factor"[All Fields]) OR "risk factor"[All Fields]) used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else

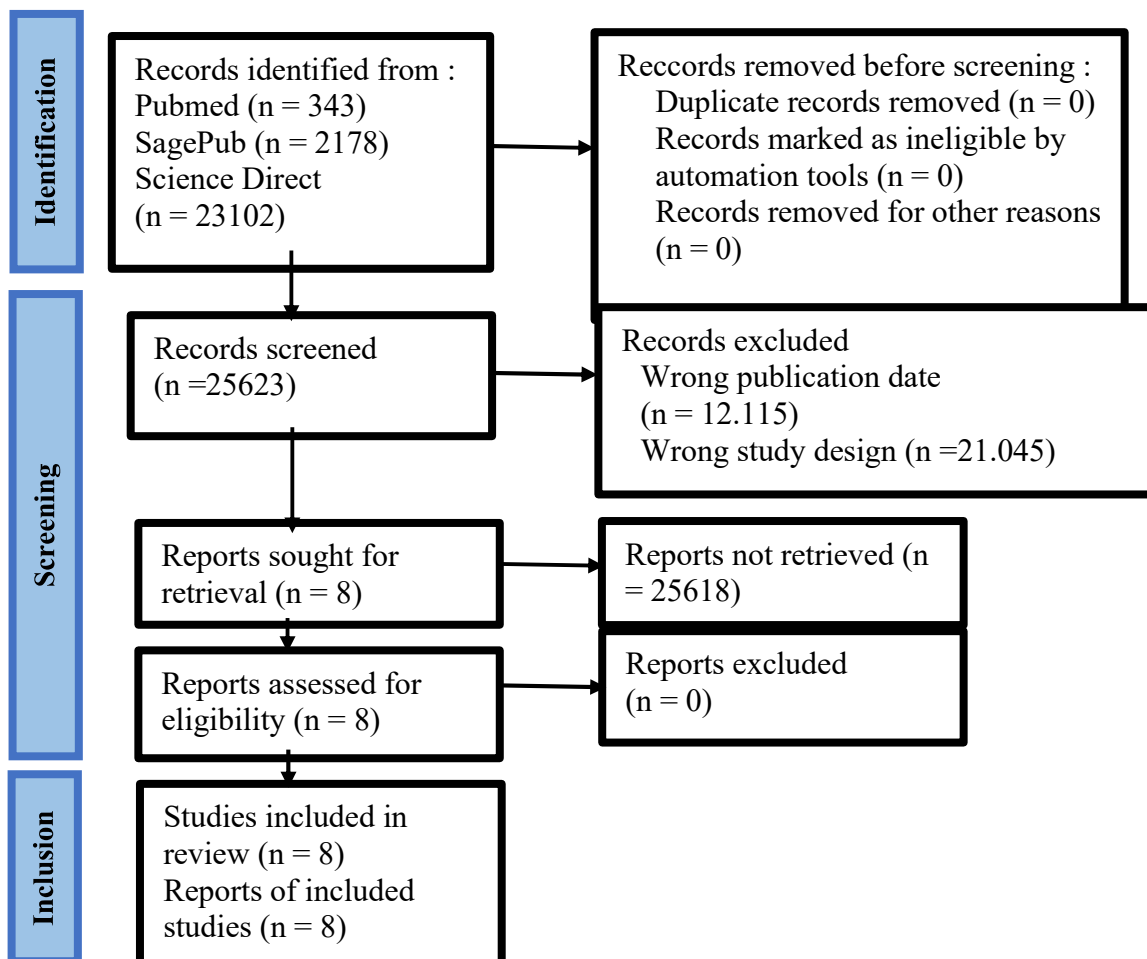


Figure 1. Prisma Flow Diagram

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. In order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 343 articles, whereas the results of our search on SAGEPUB brought up 2178 articles, our search on SCIENCE DIRECT brought up 23102 articles. The results of the search conducted for the last year of 2014 yielded a total 231 articles for PubMed, 1017 articles for SAGEPUB and 12260 articles for SCIENCE DIRECT. In the end, we compiled a total of 5 papers, 2 of which came from PubMed, 1 of which came from SAGEPUB and 2 of which came from SCIENCE DIRECT. We included five research that met the criteria.

Sekikawa, et al⁵ (2014) showed that 26 patients out of the 1449 patients whose stomach cancer was not discovered at the initial examination had a new detection of early gastric cancer during the follow-up period (range 36–108 months; mean 70.0 months).

Takeuchi, et al⁶ (2014) showed that It is important to recognize that gastric cancer (GC) patients with DM/obesity may have other primary cancers (OPC). They have to have thorough OPC screening both before and after their gastrectomy.

Zheng, et al⁷ (2018) showed that there is no correlation between the risk of gastric adenocarcinoma and prediabetes or diabetes when adjusted for several possible factors and long and thorough follow-up.

Table 1. The literature include in this study

Author	Origin	Method	Sample	Result
Sekikawa et al, 2014 ⁵	Japan	Cohort study	1463 patients	Twenty six patients (1.8%) out of the 1449 patients whose stomach cancer was not discovered at the initial examination had a new detection of early gastric cancer during the follow-up period (range 36–108 months; mean 70.0 months). Of the 148 patients with DM, 9 (6.1%) had gastric cancer, while 17 (1.3%) of the 1301 patients without DM had it (P < 0.0001). Multivariate studies revealed an independent relationship between the onset of early gastric cancer and open-type gastric atrophy and diabetes mellitus (P < 0.0001 and P = 0.020, respectively). Of the 274 patients with open-type atrophic gastritis without diabetes mellitus (DM), gastric

				cancer was found in 14 (5.1%) of them, while in 8 (16.0%) of the 50 patients with both DM and open-type atrophic gastritis (P = 0.0042).
Takeuchi et al, 2014⁶	Japan	Cohort study	435 patients	Colorectal cancer was the most common OPC (22.8%). OPC was often seen in DM patients (p = 0.0022), and DM was found to be an independent risk factor (odds ratio, 2.215; 95% confidence range, 1.2007–4.0850; p = 0.011) for OPC incidence. Obesity was an independent risk factor for the incidence of synchronous OPC (odds ratio, 2.354; 95% confidence range, 1.1246–4.9279; p = 0.023), and synchronous OPC was commonly found in individuals with obesity (p = 0.025). Patients with diabetes mellitus (DM) were more likely to have metachronous OPC (p = 0.0071), and DM was found to be an independent risk factor for OPC incidence (odds ratio, 2.680; 95% confidence range, 1.0291–6.9780; p = 0.044).
Zheng et al, 2019⁷	Swedish	Cohort study	111.198 patients	The incidence of gastric adenocarcinoma was not higher in individuals with diabetes (HR 0.77, 95% CI 0.46–1.29), prediabetes (HR 1.07, 95% CI 0.79–1.44), or any combination of these exposures (HR 0.96, 95% CI 0.73–1.27) when compared to normoglycaemic subjects. In stratified analyses or in studies that separated gastric adenocarcinoma into cardia and non-cardia, no relationships were found between prediabetes or diabetes and the risk of gastric adenocarcinoma.
Dabo et al, 2022⁸	USA	Cohort study	5592 patients	The overall correlation between diabetes and stomach cancer was not found by the authors (pooled OR = 1.01, 95% CI, 0.94–1.07). However, those with type 2 diabetes had a much increased chance of developing cardiac gastric cancer (OR = 1.16, 95% CI, 1.02–1.33). Diabetes did not correlate with the risk of stomach cancer in the strata of age, sex, BMI, smoking status,

				fruit and vegetable intake, alcohol use, gastric cancer histologic type, or source of controls.
Yang et al, 2019⁹	USA	Cohort study	195,312 patients	At baseline, the prevalence of DM was 3.0% (n = 5774). In a follow-up period of 865,511 person-years, 198 patients experienced stomach cancer. When comparing individuals with and without diabetes mellitus at baseline, the fully adjusted hazard ratio (HR) for incident gastric cancer was 1.76 [95% confidence interval (CI) 1.04–2.97; P = 0.033]. The completely adjusted HR, when DM was included as a time-varying covariate, was 1.66 (95% CI 1.04–2.68; P = 0.036). The presence of intestinal metaplasia had no effect on the link between DM and incidence gastric cancer (P for interaction = 0.61).

Dabo, et al⁸ (2022) showed that there was no overall correlation found between diabetes and stomach cancer in our extensive pooled study of individual-level data from 14 worldwide case-control studies. But according to the subgroup study, diabetes may increase the risk of stomach cancer in the cardia. To fully comprehend the underlying process causing the difference in the risk of gastric cancer associated with diabetes and that associated with noncardia, more study is necessary.

Yang, et al⁹ (2020) showed that a higher risk of stomach cancer was independently linked to diabetes mellitus. During follow-up, the elevated risk was consistent in participants with newly established DM and was independent of intestinal metaplasia and mucosal atrophy. DM patients might need more frequent endoscopic follow-ups in order to test for stomach cancer.

DISCUSSION

It is estimated that 500 million individuals globally would have diabetes mellitus (DM) by 2030. A deadly tumor that affects the digestive tract is called gastric cancer (GC). It ranks as the fourth leading cause of cancer death worldwide and the fifth most common kind of cancer. Every year, there are around 700,000 fatalities and one million new cases of GC globally. Nevertheless, the correlation with GC differed in different investigations, despite a large body of research on the connection between diabetes mellitus and cancer.

The significance of diabetes mellitus (DM) in gastric carcinogenesis still remains unclear. Sekikawa, et al investigated 1463 patients at the first endoscopic examination and was significantly associated with the severity of gastric atrophy and the presence of DM. Multivariate studies revealed an independent relationship between the onset of early gastric cancer and open-type gastric atrophy and diabetes mellitus (P < 0.0001 and P = 0.020, respectively). Of the 274 patients with open-type atrophic gastritis without diabetes mellitus (DM), gastric cancer was found in 14 (5.1%) of them, while in 8 (16.0%) of the 50 patients with both DM and open-type atrophic gastritis (P = 0.0042).⁵

Patients with gastric cancer (GC) have been documented to have other primary malignancies (OPC). Recent research by Takeuchi et al. has linked the development of cancer in several organs to obesity and diabetes mellitus. It is important to recognize that OPC may occur in GC individuals who also have diabetes mellitus or obesity. They have to have thorough OPC screening both before and after their gastrectomy.⁶

Zheng, et al in their study in 111,198 participants that followed up from November 1985 to April 2017 showed the results of their study Participants with prediabetes, diabetes, or any combination of these exposures did not have an elevated risk of gastric adenocarcinoma as compared to normoglycaemic individuals. In stratified analyses or in studies that separated gastric adenocarcinoma into cardia and non-cardia, no relationships were found between prediabetes or diabetes and the risk of gastric adenocarcinoma.⁷

Dabo, et al did study In 5592 gastric cancer cases from Europe, Asia, North America, and South America. Dabo, et al showed Diabetes and stomach cancer did not appear to be generally associated. However, those with type 2 diabetes had a much increased chance of developing cardiac gastric cancer. Diabetes did not correlate with the risk of stomach cancer in the strata of age, sex, BMI, smoking status, fruit and vegetable intake, alcohol use, gastric cancer histologic type, or source of controls.⁸

Yang, et al also evaluated the association of DM and gastric cancer in 5774 patients with follow up. A higher risk of stomach cancer was independently linked to diabetes mellitus. During follow-up, the elevated risk was consistent in participants with newly established DM and was independent of intestinal metaplasia and mucosal atrophy. DM patients might need more frequent endoscopic follow-ups in order to test for stomach cancer.⁹

Shared risk factors, hyperglycemia, H. pylori infection, excessive salt consumption, medicines, and comorbidities are examples of potential processes. It should be acknowledged that the estimated relative risk is moderate, the epidemiological findings are inconsistent, and the majority of research have intrinsic limitations pertaining to study design, sample size, confounders, and biases. Therefore, more thorough mechanistic research is needed to elucidate the potential connections between diabetes and stomach cancer in people, and well-designed epidemiological studies are needed to corroborate the correlation.

CONCLUSION

In summary, there is no direct association of diabetes mellitus and gastric cancer, but diabetes mellitus can increase the risk factor of gastric cancer cases.

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