



The effect of metformin use on gastric cancer in patients with type 2 diabetes: A systematic review and meta-analysis of cohort studies

Ghobad Abangah¹, Diana Sarokhani², Zahra Abdan³, Moloud Fakhri⁴, Hassan Nourmohammadi⁵

¹School of Medicine, Shahid Mostafa Khomaeini Hospital, Ilam University of Medical sciences, Ilam, Iran

²Research Center for Environmental Determinants of Health, School of Public Health, Kermanshah University of Medical Sciences, Kermanshah, Iran

³Clinical Research Development Center, Imam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran

⁴Traditional and Complementary Medicine Research Center, Addiction Institute, Mazandaran University of Medical Sciences, Sari, Iran

⁵Department of Internal Medicine, Shahid Mostafa Khomeini Hospital, Ilam University of Medical Sciences, Ilam, Iran

*Correspondence to

Moloud Fakhri, Email: mmfir@yahoo.com, and m.fakhri@mazums.ac.ir, and Hassan Nourmohammadi, Email: Nourmohammadi-h@medilam.ac.ir

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Abstract

Introduction: Gastric cancer is one of the main causes of cancer-related deaths in the world. Various studies have so far been conducted to determine the risk of gastric cancer in relation to taking metformin. Therefore, this systematic review and meta-analysis study aims to evaluate the relationship between the administration of metformin in type II diabetes patients and their risk of developing gastric cancer.

Materials and Methods: All studies were cohorts. A comprehensive literature searches of the databases, including Cochrane, Web of Science, PubMed, Scopus, and Google Scholar web browser was conducted using standard keywords. Data analysis of this meta-analysis was conducted using STATA 14 software and $P < 0.05$ was considered as a significant level for tests.

Results: In a set of 17 cohort studies, including an overall number of 1383404 patients, it was concluded that metformin consumption had reduced the risk of gastric cancer in type II diabetes patients [OR: 0.80 (95% CI: 0.71-0.91)]. In these patients, the impact of metformin on overall survival rates was not statistically significant [OR: 0.71 (95% CI: 0.42-1.18)]. Data analysis revealed the effects of metformin on the risk of gastric cancer development, which involved a reduction [OR: 0.69 (95% CI: 0.44-1.07)] for those who had been taking metformin for less than five years, [OR: 1.04 (95% CI: 0.83-1.30)] for those who had been taking metformin for 5-10 years, and [OR: 0.71 (95% CI: 0.59-0.84)] for the patients who had a history of taking metformin for over 10 years.

Conclusion: Metformin administration in type II diabetes patients resulted in the reduction of the risk of gastric cancer, but did not affect the overall survival rates. Furthermore, it was observed that type II diabetes patients, who had been treated by metformin for more than 10 years, had a 29% lower risk for gastric cancer.

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Introduction

Gastric cancer is a lethal condition which was globally announced as the 5th most diagnosed form of cancer, and the 3rd cause of cancer-related deaths in 2018, with over 1 000 000 documented new cases and about 783 000 mortalities reported (1 in 12 deaths around the world) (1). Even if surgical procedures are performed, almost 10%-80% of these patients suffer relapse and die (2). Obesity and type II diabetes are related to many types of cancer, including gastric cancer (3). It is predicted that type II diabetes prevalence will increase from 2.8% in 2000 to 4.4% in 2030 (4).

Metformin is one of the most common first-line choices in treating type II diabetes (5). This drug mainly increases the tissues' sensitivity to insulin and consequently reduces

Key point

In a set of 17 cohort studies, including an overall number of 1383404 patients, it was concluded that metformin consumption had reduced the risk of gastric cancer in type II diabetes patients [OR: 0.80 (95% CI: 0.71-0.91)]. In these patients, the impact of metformin on overall survival rates was not statistically significant [OR: 0.71 (95% CI: 0.42-1.18)]. Data analysis revealed the effects of metformin on the risk of gastric cancer development, which involved a reduction [OR: 0.69 (95% CI: 0.44-1.07)] for those who had been taking metformin for less than five years, [OR: 1.04 (95% CI: 0.83-1.30)] for those who had been taking metformin for 5-10 years, and [OR: 0.71 (95% CI: 0.59-0.84)] for the patients who had a history of taking metformin for over 10 years.

insulin levels (6). Metformin can affect the cancerous cells of the stomach and inhibit their multiplication, both in vivo and in vitro (7). Furthermore, studies have shown a reduction in the occurrence of gastric cancer



in diabetic patients treated by metformin (8), as well as an anti-cancerous impact on gastric cancer cells in vitro and in vivo (9). Considering the contradictions in the results of previous studies, the current systematic review and meta-analysis study was designed to evaluate the effects of metformin consumption on the risk of gastric cancer in type II diabetes patients.

Materials and Methods

Study design

This meta-analysis study examines the association between metformin consumption and gastric cancer risk in patients with type 2 diabetes. The meta-analysis is carried out based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for systematic review and meta-analysis studies. The protocol of this meta-analysis was registered on the site of PROSPERO (ID: CRD42022339198, Date:11.06.2022).

Studies outcomes

Primary outcome: The association between metformin consumption and gastric cancer risk in patients with type 2 diabetes.

Search strategy

In this meta-analysis, international databases including Cochrane, Web of Science, PubMed, Scopus, and Google Scholar web browser, were searched without time or language restrictions. For papers published in languages other than Persian or English, the full article was translated to extract its data. The search strategy step was performed by standard keywords and, including “Metformin,” “Cancer,” “Neoplasm,” “Diabetes,” and “Stomach,” as well as (Updated until May 22, 2022). Keyword combinations using Boolean operators “AND” and “OR” were also included in the database search (See Table S1 of [Supplementary file 1](#) for details). Additionally, the list of references of all primary studies that remained at the end of the PRISMA flowchart and entered the meta-analysis was screened by manual search.

The inclusion and exclusion criteria

PICO components

The studied population: patients with type 2 diabetes, Intervention: Metformin consumption, Comparison: Those who do not metformin consumption, the studied outcomes: The risk of developing gastric cancer.

The inclusion criteria

This meta-analysis included cohort studies that explored the effect of metformin consumption on stomach cancer risk. The intervention group was metformin consumers, and the comparison or control group was the non-intervention status. The eligible studies must have evaluated the relationship between metformin consumption and stomach cancer.

The exclusion criteria

case-report or case series studies; lack of reporting of the required information for data analysis; unavailability of the full-text of articles; Studies that only qualitatively described the metformin effect on gastric cancer; studies that examined the effect of metformin consumption on other cancers; Low-quality studies evaluated using a quality assessment checklist based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement;

Qualitative assessment of studies

The two researchers independently assessed quality from different perspectives using the STROBE checklist (10). The STROBE checklist has 22 sections that cover different sections of a report. In this checklist, the sum of the scores is decisive, therefore a score of 1-15 indicates low quality, 16-30 indicates average quality and 31-44 indicates excellent quality. The cut-off point in this study was 15 points.

Data extraction

Two researchers extracted data from studies independently to minimize the biased reporting and error in data collecting. They entered the extracted data into a checklist containing the study title, researcher name, mean age, time of follow up, year of publication, country, sample size, control group, odds ratio (OR) between metformin consumption and stomach cancer risk and its upper and lower limits. A third researcher evaluated the data extracted by the two previous researchers to correct any existing discrepancies.

Statistical analysis

Odds ratio was applied to examine the relationship between metformin consumption and gastric cancer risk. The logarithm of OR was taken in each study to combine the studies' results. The heterogeneity of the studies was assessed using the I^2 index and Q-Cochrane test. The random-effects model was used in this work to combine the reviewed studies ($I^2=90.8\%$). Data analysis was executed using STATA 14 software. The significance level was considered $P<0.05$ for all tests. Meta-regression was employed to evaluate the relationship between “metformin consumption and gastric cancer risk in patients with type 2 diabetes” and “sample size” and “year of publication.”

Results

Initially, 421 articles were found in the search in the mentioned databases. After checking the studies' titles, 248 duplicate studies were excluded. The abstracts of 173 articles were explored, and 42 articles whose full texts were not available were excluded. The full texts of the 131 remaining papers were screened, and another 114 articles that met the other exclusion criteria were discarded. Eventually, 17 high-quality articles entered the meta-analysis process ([Figure 1](#)).

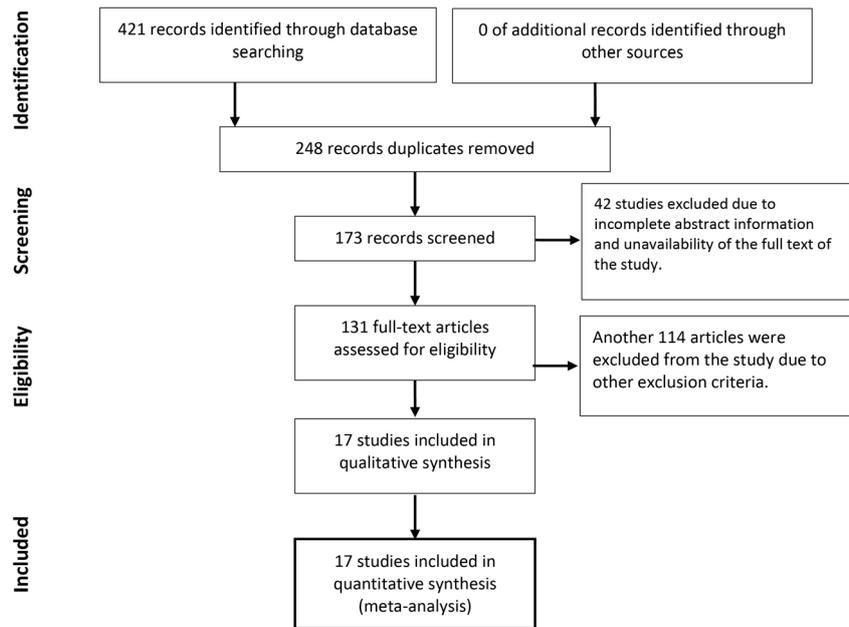


Figure 1. The process of entering the studies into the systematic review and meta-analysis.

The specifications of the reviewed articles are given in Table 1.

In this meta-analysis, 17 cohort studies with a sample size of 1383404 patients were investigated. The articles were published between 2014-2021 and the patients were within the age range of 20-94 years old. Figure 2 shows that taking metformin reduces the risk of gastric cancer in type II diabetes patients [OR: 0.80 (95% CI: 0.71-0.91)].

Analysis of the subgroups revealed that the effects of metformin on the overall survival rates of type II diabetes patients was not statistically significant [OR: 0.71 (95% CI: 0.42-1.18)]. The effects of metformin on the risk of gastric cancer development indicated a reduction [OR: 0.69 (95% CI: 0.44-1.07)] for those who had been taking metformin for less than five years, [OR: 1.04 (95% CI: 0.83-1.30)] for those who had been taking metformin for 5-10 years, and [OR: 0.71 (95% CI: 0.59-0.84)] for the patients who had a history of taking metformin for over 10 years. As it appears, the risk of gastric cancer was significantly lower in type II diabetes patients who were being treated by metformin for more than 10 years (Table 2).

In Figure 3, meta-regression indicates no statistically significant connection between “the effects of metformin consumption on the risk of gastric cancer” and “study publication year” ($P = 0.820$).

Figure 4 shows that there is no statistically significant connection between “the effects of metformin consumption on the risk of gastric cancer” and “study sample size” ($P = 0.820$).

Discussion

In this meta-analysis, 17 studies and an overall number of 138 304 patients were investigated, and the results showed

that the risk of gastric cancer in type II diabetes patients who had been treated by metformin was 20 percent lower compared to those who had not received metformin; in fact, taking metformin has a kind of protective effect against gastric cancer [OR: 0.80 (95% CI: 0.71-0.91)]. Moreover, this risk was measured to be 29 percent lower in patients who had taken metformin for over 10 years, compared to those who had not. But it did not reduce the overall survival rate among the patients [OR: 0.71 (95% CI: 0.42-1.18)].

In a meta-analysis comprised of 11 cohort studies which was conducted by Shuai et al, metformin consumption had resulted in the considerable amount of 21% decrease in the occurrence of gastric cancer in type II diabetes patients (Hazard ratio [HR] 0.790; 95% CI 0.624-1.001). In a combined analysis of three studies, metformin consumption was shown to increase the overall survival rates (HR 0.817; 95% CI 0.600–1.113) and the specific cancer-related survival rates (HR 0.824; 95% CI 0.614–1.106) among type II diabetes patients (27); these results do not correspond with the results of the current study.

Li et al conducted a systematic review study to analyze the effects of metformin consumption on gastric cancer. In their study, 422 articles were initially assessed, five of which were according to the required criteria to enter the systematic review, with an overall number of 1804479 patients. The results indicated that long-term consumption of metformin was associated with a lower risk of gastric cancer, compared to not taking metformin or taking other blood sugar reducing agents (28). In a meta-analysis study conducted by Zhou et al, comprised of 7 cohort studies with 591077 patients in total, it was determined that treatment by metformin reduces the occurrence rate of gastric cancer

Table 1. Specifications of articles which entered into the meta-analysis process

Name of author, Year of publication	Country	Sample size	Mean age (year)	Control group	Follow Up (year)	OR	Low (OR)	Up (OR)
Lee CK, 2016 (7)	Korea	326	59	Non-metformin	6.2	-	-	-
Baglia ML, 2019 (11)	China	130	40-74	Non-metformin	3.4	-	-	-
Valent F, 2015 (12)	Italy	138524	20-94	Non-metformin	NR	0.99	0.986	0.994
Kim YI, 2014 (13)	Korea	32987	52-67	NIAD	4.5	0.73	0.53	1.01
Tsilidis KK, 2014 (14)	UK	69748	35-90	Sulfonylurea derivatives	5.1	0.96	0.6	1.56
Tseng CH, 2016 (15)	China	304188	25-74	Non-metformin	≥180 days	0.448	0.359	0.558
Cheung KS, 2019 (16)	China	7266	55-73	Non-metformin	7.1	0.47	0.23	0.96
Murff HJ, 2018 (17)	USA	84434	57.6-74.7	Sulfonylurea derivatives	NR	0.74	0.44	1.23
Zheng J, 2019 (18)	Sweden	544130	62.1	Non-metformin	5.8	1.08	0.98	1.26
de Jong RG, 2017 (19)	Netherlands	57114	63.5	NIAD	4.9	1.06	0.63	1.8
Dulskas A, 2019 (20)	Lithuania	251	NR	Non-metformin	NR	-	-	-
Cho MH, 2021 (21)	Korea	113198	40-79	Non-metformin	9	1.25	1.01	1.55
Seo HS, 2019 (22)	Korea	242	62.9	Non-metformin	4.25	0.446	0.302	0.657
Chung WS, 2020 (23)	Taiwan	651	63.37	Non-metformin	NR	-	-	-
Chen X, 2020 (24)	China	71	NR	Non-metformin	5	-	-	-
You JH, 2020 (25)	Korea	5331	NR	Non-metformin	NR	0.841	0.797	0.887
Kim J, 2020 (26)	Korea	15603	55.2	Non-metformin	12.7	0.71	0.579	0.87
Kim J, 2020 (26)	Korea	9210	60.1	Non-metformin	12.7	0.7	0.499	0.981

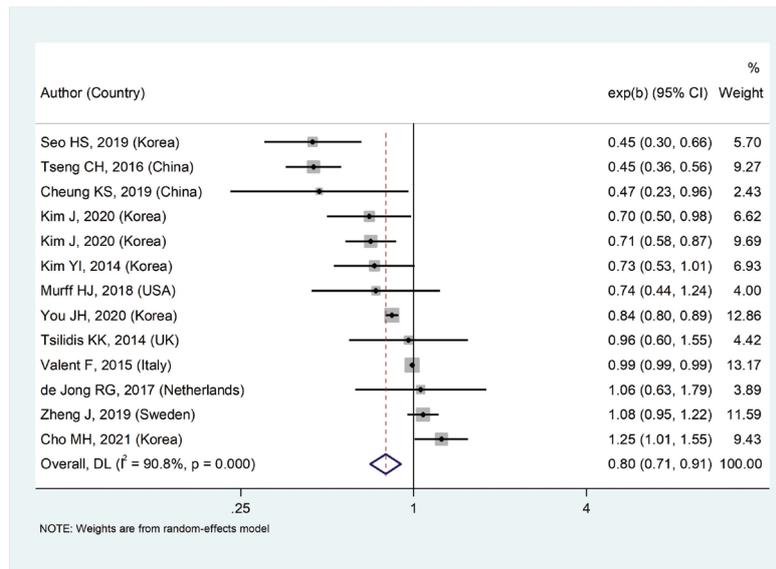


Figure 2. The plot of the relationship between metformin use and the risk of gastric cancer in patients with type 2 diabetes, by country and year of publication

in type II diabetes patient, in comparison with other types of drugs [HR=0.763, 95% CI: 0.642~0.905] (29). The results concluded from the current study support those of Li and Zhou’s studies.

In a population-based meta-analysis study conducted by Seo et al, which aimed to investigate the effects of administering aspirin, metformin and statins on gastric cancer development in South Korea, no specific connection was found between metformin consumption and gastric cancer development [HR= 0.85; 95% CI: 0.59-1.23] (30). The results from the current meta-analysis study contradict those of the Seo et al study. Limited number of investigated studies is one of the issues surrounding this concept. Therefore, considering the contradictory results of previous meta-analysis studies, it is suggested that more cohort studies be conducted on this matter.

Conclusion

Since the results clearly show that, the type II diabetes patients who were treated by metformin had a 20 percent lower risk of gastric cancer compared to those who were not, it is recommended that metformin be the first choice of therapy in type II diabetes patients. It is also

recommended that future studies consider the impact of the dose of metformin on the risk of gastric cancer. Moreover, further evaluations should also be performed to determine the possibly specific gender-related effects of metformin, which would ultimately resolve the limitations of the current study.

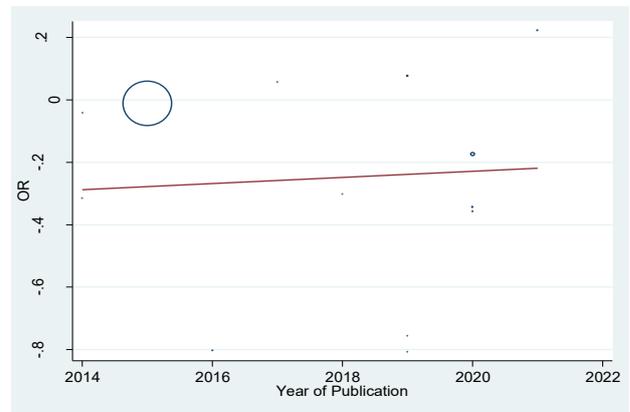


Figure 3. Meta-regression of the relationship between “the effect of metformin consumption on gastric cancer risk in patients with type 2 diabetes” and “year of publication.”

Table 2. The effect of metformin on gastric cancer risk in patients with type 2 diabetes in the studied subgroups

Subgroups	OR	LOW-OR	UP-OR	P value	I ² (%)
Total	0.80	0.71	0.91	<0.001	90.8
Overall survival	0.71	0.42	1.18	0.219	33.8
Total by follow-up (y)					
<5	0.69	0.44	1.07	0.025	73
5-10	1.04	0.83	1.30	0.066	58.3
>10	0.71	0.59	0.84	0.944	0

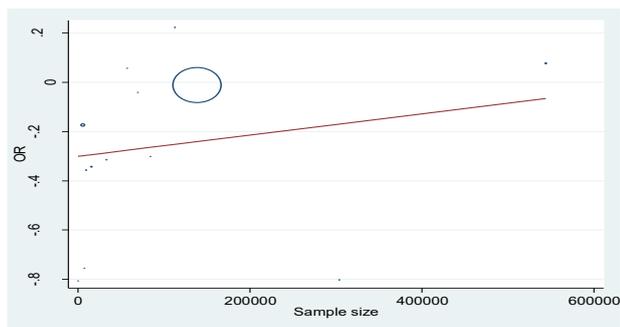


Figure 4. Meta-regression of the relationship between “the effect of metformin consumption on gastric cancer risk in patients with type 2 diabetes” and “sample size”

Limitations of the study

The limited number of studies to investigate; uneven distribution of studies in different countries; the impracticality of distinguishing the studies in separate age groups (patients were within a wide age range); and the fact that the consumed doses of metformin were not evaluated in the studies, which made it impossible to perform a dose-related analysis in the subgroups.

Authors' contribution

Conceptualization: HN, DS, ZA, GHA and MF. Methodology: DS. Formal Analysis: HN and MF. Resources: ZA. Writing—Original Draft Preparation: All authors. Writing—Review and Editing: All authors. Funding Acquisition: ZA.

Conflicts of interest

The authors declare that they have no conflict of interest regarding the contents of this article.

Ethical issues

This systematic review and meta-analysis was conducted in accord with the World Medical Association Declaration of Helsinki. Besides, ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

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Supplementary files

Supplementary file 1 contains Table S1.

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