Review Article

The Relationship between Metformin Consumption and Cancer Risk: An Updated Umbrella Review of Systematic Reviews and Meta-Analyses

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Abstract

Background: Considering that metformin is widely used in the treatment of diabetes, and its protective role against various malignancies, the strength and validity of the available evidence from related systematic reviews and meta-analysis were evaluated. **Methods:** Scopus, PubMed, Embase, Cochrane, Web of science databases, and Google Scholar and manual screening of retrieved references were systematically searched from their inception dates to 24 March 2020 by extracting the effect size (Odds ratios (OR) and relative risk (RR) in each study. To present the forest plot of effect of metformin on each cancer, Stata version 14.2 was used. **Results:** This study included 36 meta-analysis studies and 620 original research studies (26 randomized control trials studies and 594 observational studies (cohort, case–control)) covering 15 different cancers. Overall, metformin medication prevented different cancers, including ovarian cancer (OR = 0.76, 95% CI: 0.62,0.93), cervical cancer (OR = 0.60, 95% CI: 0.43, 0.83), endometrial cancer (OR = 1.05, 95% CI: 0.82,1.35), liver cancer (OR = 0.59, 95% CI: 0.47,0.74), pancreatic cancer (OR = 0.59, 95%CI 0.50,0.69), head and neck cancer (OR = 0.71, 95% CI: 0.61,0.83), stomach cancer (OR = 0.72, 95% CI: 0.26,1.99), colorectal cancer (OR = 0.73, 95% CI: 0.59,0.91), colorectal adenoma cancer (OR = 0.75, 95% CI: 0.65,0.86), colon cancer (OR = 0.79, 95% CI: 0.69,0.91), esophagus cancer (OR = 0.90, 95% CI: 0.83,0.98), lung cancer (OR = 0.92, CI95%:0.85,0.99), breast cancer (OR = 0.93, 95% CI: 0.84,1.02), prostate cancer (OR = 0.94, 95% CI: 0.85-1.04), and bladder cancer (OR = 0.94 95% CI: 0.64,1.38). **Conclusions:** Treatment with metformin can significantly decrease the chance of all cancers with larger preventive effect on hepatocellular carcinoma and smaller preventive effect on lung and breast cancers.

Keywords: *Diabetes mellitus, meta-analysis, metformin, neoplasms, review*

Introduction

Diabetes comprises a major component of the global burden of disease.[1] Diabetes mellitus is a risk factor for cardiovascular diseases, retinopathy, chronic kidney disease, and neuropathy and causes other adverse health effects. Findings from a number of population-based studies have also shown that diabetic patients face an increased risk of various types of malignant tumors.[2] Therefore, physicians are interested in prescribing antidiuretic drugs for diabetic patients to reduce the risk of cancer.

The role of insulin resistance has recently been proved as a risk factor for cancer in diabetes.[3] Metformin is a biguanide drug that is mainly used as first-line drug to treat type II diabetes for improving insulin resistance.[4] The effect of anti-diabetic drugs on reducing the risk of cancer has recently attracted researchers' attention. Some documents show metformin medication may reduce the incidence of cancer, progression, and even cancer-related mortality.[5]

Cancer is the second leading cause of death across both developing and developed countries, approximately 9.6 million death was recorded because of cancer worldwide in 2018.[6] The cancer-related burden is expected to rise worldwide because of aging of population.[7]

The major anti-cancer mechanism of metformin relates to its ability to activate Liver Kinase B/AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) that blocks the tumor growth because of decreased circulating insulin levels.[8] Recent studies show that metformin can reduce the risk of various cancers in diabetic population, such as

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thyroid cancer,[9] oral cancer,[10] gastric cancer,[11] bladder cancer,[12] prostate cancer,[13] breast cancer,[14] endometrial cancer,[15] ovarian cancer,[16] and cervical cancer.[17]

An initial meta-analysis of studies in diabetic patients showed that compared to other diabetes treatments, the metformin medication can reduce the risk of all metformin-related cancers up to 30%.[18] Systematic review and meta-analyses on the effects of the metformin medication on incidence of various cancers have been carried out. Furthermore, a published umbrella review of the systematic review and meta-analyses has been searched up to 2018. However, some systematic review and meta-analysis studies after this date are controversial,[19,20] and in some cases, studies have reviewed a new outcome, such as colorectal adenoma[21] and cervical cancers.[22] In addition, in case of finding more than one meta-analysis regarding a certain cancer, authors selected the meta-analysis that has the most number of the original article. It is possible that the meta-analysis study that we exclude has several basic studies that are not present in the largest existing meta-analysis, and we miss those studies. Therefore, for a more precise estimation, the umbrella review needs to be updated.

Methods

Protocol and registration

This is an updated umbrella review study investigating meta-analyses that have examined the relationship between metformin consumption to treat diabetes and the risk of developing cancers. Our report follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes protocol (www.prisma-statement.org).[23] The protocol for this study has been registered at PROSPERO (ID: 124229, Date: 02-02-2019).

Eligibility criteria

The following studies were excluded from this umbrella review: studies that examined (a) the effect of combination of metformin and another antidiabetic drug, (b) the effect of metformin on the mortality rate of cancer patients, (c) the effect of metformin on cancer recurrence among patients with history of cancer, and (d) the effect of metformin on the prognosis of cancer patients.

In this study, to achieve targeted studies, eligible meta-analyzes based on cancer site were separated. If there was only one meta-analysis study for a particular cancer site, then the same study was chosen as the most comprehensive study. Whenever more than one meta-analysis study examined the relationship between metformin consumption and the risk of a particular cancer, a meta-analysis that was more up-to-date and comprehensive than other meta-analysis studies was chosen. In this case, three conditions were considered for selecting the most comprehensive and up-to-date meta-analysis. In the first step, the timeframe of meta-analysis studies to find out which meta-analysis study is more up-to-date and has covered more years was compared. Second, the number of included studies of each meta-analysis was compared. In the third step, the quality of meta-analysis studies were examined using the AMSTAR checklist If a meta-analysis was found to meet all three conditions (more comprehensive timeframe, number of more basic studies, and higher quality level), that meta-analysis was chosen. But whenever more than one eligible meta-analysis study was selected for each cancer site, the remaining studies were re-analyzed by integrating each of those meta-analyzes and eliminating overlapping (duplicate) cases and a new meta-analysis was carried out in these cases,

Search strategy

Different databases were systematically searched: Scopus, PubMed, Embase, Cochrane, Web of Science and Google Scholar from inception by 24 March 2020. Limited the search to humans and no language or time restrictions were applied. Supplementary Table S1 in the appendix shows the search strategy. The References list of the eligible reviews were also reviewed.

Main keywords or corresponding MeSH terms were as follows: cancer, carcinoma, neoplasia, tumor, neoplasm, Meta-analysis, Meta-analyses, Systematic review, Metformin, Diabetes Mellitus, and Malignancy. A manual search was also done for references cited in the selected articles, in selected reviews, or books.

Methodological quality assessment

Using the online version of assessing the Methodological Quality of Systematic Reviews (AMSTAR) (https://amstar.ca) the systematic reviews and meta-analyses graded into three levels of quality: "high," "moderate," and "low." AMSTAR is an 11-item assessment tool that has been validated and is being increasingly used by health care policy makers, health technology assessment agencies, and some authors and journal editors.[24]

Data extraction

Two investigators carried out data extraction independently and then, the extracted data were compared and discrepancies were resolved with discussion. A third investigator arbitrated on any remaining differences. For each eligible article, the first author, year of publication, study design, cancer site, number of studies (by study design), and OR/RR with its confidence interval were extracted [Table 1].

Statistical analysis

To evaluate the effect of metformin on the risk of cancer, the odds ratio (OR) and Relative Risk (RR) were used. To present the forest plot for the effect of metformin for each cancer, Stata version 14.2 (Stata Corp, College Station, Texas) was used.

Results

Description of meta-analyses

Using the search strategy outlined in the Materials and Methods Section, a total number of 814 articles were found in the reviewed databases. According to inclusion and exclusion criteria, 36 meta-analysis articles remained eligible that included a total of 620 articles (26 randomized control trial – RCT studies and 594 observational studies (cohort, case–control)) [Figure 1]. The largest sample size belonged to a meta-analysis by Lang Wu *et al*,[43] (sample size = 7,600,000, number of study = 265) and the smallest meta-analysis carried out by Hui Zhang *et al*.[40] (sample size = 16,549, number of study = 7) [Table 1].

In all studies, taking metformin prevents the development of cancers (RR <1, OR <1) with the exception of four studies [Table 1].[20,30,51,53] Thakkar *et al*.[30] reviewed clinical trials (RCT) investigating the association between metformin consumption and cancers and concluded that metformin consumption increased the risk of cancer (RR >1); however, the result was not statistically significant. On the other hand, the same article had reported the protective effect of metformin consumption in cohort, case–control studies (RR <1), indicating that metformin consumption prevented the risk of cancer. Christopher B. Chen *et al*.[20] investigated the relationship between prostate cancer and metformin consumption in 26 included studies with no statistically and clinically important effect. Overall, in this study, out of all the reviewed articles, only 12 articles[20,29,30,37,42,45,46,48,51-53,56] indicated that metformin consumption had no statistically significant effect on cancer risk (with 77.6 of heterogeneity), but the effect of metformin consumption on cancer prevention was significant in other meta-analyses [Table 1].

In this umbrella review study, some studies focused on one specific type of cancer.[33,42,45] Others have investigated the association between metformin consumption and the risk of several different cancers that were reported by type of cancer.[26,29] To eliminate overlap between studies, the remaining 36 meta-analyses were separated by site of cancer. Of all reported meta-analyses on different sites of cancers, the most comprehensive and updated meta-analysis were retained. Finally, there were 15 different site of cancer [Table 2 and Figure 2].

Diabetic patients who received metformin medication had a lower risk for liver cancer, pancreatic cancer, cervical cancer, head and neck cancer, colorectal cancer, colorectal adenoma cancer, colon cancer, ovarian cancer, esophageal cancer, and lung cancer. Furthermore, a protective role also (but not significant) between metformin medication and incidence of prostate cancer, bladder cancer, gastric cancer, and breast cancer was observed. The largest protective effect of metformin was related to liver and pancreatic cancers and the least to lung cancer. However, metformin was a risk factor for incidence of endometrial cancer. Some of the meta-analyses evaluated all cancer incidence. They also revealed a protective role of the metformin [Table 2].

Discussion

This umbrella review showed that diabetic patients who received metformin treatment had a lower risk of cancer compared to diabetic patients who did not use metformin, with a non-significant effect on endometrial cancer. Metformin as an AMPK inhibitor exerts its anticancer

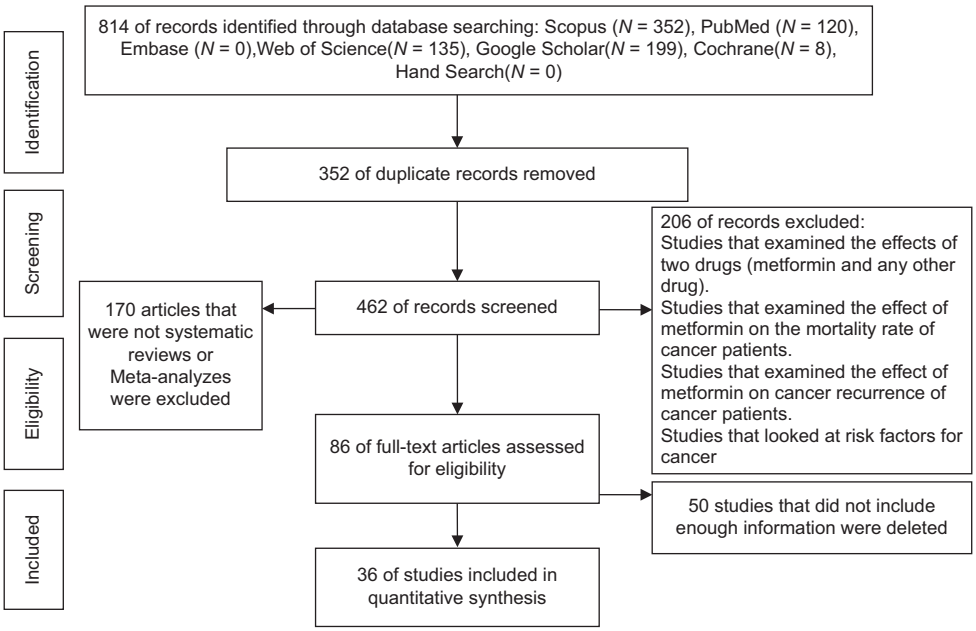

Figure 1: Diagram of selection of studies for inclusion in umbrella review

Table 1: Summary of retrieved meta-analyses

Reference	Name of Author	Year of study	Country	Number of Study	Sample size	Type of control group	Type of cancer	OR/ RR	LOW OR/RR	UP OR/ RR	*P*	I^2 (%)
[18]	Andrea Decensi	1966-2009	UK, Italy, Scotland, Netherlands, USA, and Canada	11 (case-control (8), cohort (3))	35662	Nonmetformin users SUs Exogenous insulin other hypoglycaemic drugs users insulin-based treatment	Breast, Colon	0.69	0.61	0.79	----	64
[25]	Zhi-Jiang Zhang	1966-2011	Korea, China, and UK	5 (case-control (2), cohort (3))	108161	Non metformin users sulfonylurea use NSAID/aspirin use insulin, aspirin other drug use other oral anti-hyperglycemic	Colorectal	0.63	0.5	0.79	<0.001	18
[26]	Hiroshi Noto	Until 2011	----	10 (case-control (2), cohort (6), RCT (2))	210892	Non metformin users	Hepatocellular, Lung, Colorectal, Prostate, Breast, Pancreatic, Gastric, Bladder	0.67	0.53	0.85	<0.001	93
[27]	Zhi-Jiang Zhang	1966-2012	Italy, France, Netherlands, USA, and China	5 (case-control (2), cohort (3))	105495	Non metformin users SUs Insulin	Liver	0.38	0.24	0.59	<0.001	78
[28]	Nananda F Col	1966-2009	Scotland, UK, Denmark, Netherlands, and USA	7 (case-control (3), cohort (4))	418541	Other drug used for diabetes therapy SUs insulin thiazolidinediones	Breast	0.83	0.71	0.97	----	51

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Table 1: Contd...

Reference	Name of Author	Year of study	Country	Number of Study	Sample size	Type of control group	Type of cancer	OR/ RR	LOW OR/RR	UP OR/ RR	*P*	I^2 (%)
[29]	Monica Franciosi	1966-2012	----	41 Observational	1029389	Non metformin users SUs Thiazolidinediones insulin other drug use	Liver, colorectal, Pancreas, stomach, Oesophagus, Breast, Prostate, Lung, Ovarian	0.73	0.61	0.88	0.001	97
[29]	Monica Franciosi	1966-2012	----	RCT (12)	1029389		Liver, colorectal, Pancreas, stomach, Oesophagus, Breast, Prostate, Lung, Ovarian	0.98	0.81	1.19	0.832	0
[30]	Bindiya Thakkar	Until 2012	USA, Canada, Europe, Australia, China, Japan, Taiwan, Germany, Italy, Netherlands, UK, and Denmark	RCT (2)	415014	Non metformin users	Overall	1.01	0.81	1.26	----	10
[30]	Bindiya Thakkar	Until 2012	USA, Canada, Europe, Australia, China, Japan, Taiwan, Germany, Italy, Netherlands, UK, and Denmark	Cohort (9)	415014		Overall	0.7	0.67	0.73	----	97
[30]	Bindiya Thakkar	Until 2012	USA, Canada, Europe, Australia, China, Japan, Taiwan, Germany, Italy, Netherlands, UK, and Denmark	Case-control (13)	415014		Overall	0.90	0.84	0.98	----	83.20
[31]	Zhi-Jiang Zhang	2009-2013	USA, UK, Netherlands, and China	6 (case-control (2), cohort (4))	566435	Non metformin users	Lung and Respiratory	0.85	0.75	0.96	0.01	56
[32]	Zhihang Nie	Until to 2014	USA, UK, Netherlands, Scotland, Denmark, and Taiwan	11 (case-control (3), cohort (8))	321306	non metformin users SUs Insulin	Colorectal	0.75	0.66	0.86	----	74.70
[33]	Lifeng Li	Until Jan 2016	----	5 Observational	----	N on metformin users	Ovarian	0.54	0.32	0.93	----	85.20
[34]	T. Rokkas	Until 2015	USA, UK, Denmark, Netherlands, Taiwan, and Korea	17 (RCT (1), Observational studies (16 (Cohort (13), Case-control (3)))	709980	Non metformin users	Colon	0.75	0.65	0.87	<0.001	86

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Table 1: Contd...

Reference	Name of Author	Year of study	Country	Number of Study	Sample size	Type of control group	Type of cancer	OR/ RR	LOW OR/RR	UP OR/ RR	*P*	I^2 (%)
[35]	Shujuan Ma	Until July 2016	USA, Canada, Europe, China, Japan, Italy, Netherlands, UK, Spain, France, and Turkey	19 (RCT (2), Cohort (10), Case-control (7))	550882	Non metformin users	Liver	0.52	0.4	0.68	----	83.70
[36]	Ping Wong	Until to 2011	UK, Italy, Greece, USA, Canada, Taiwan, and Japan	49 (case-control (17), cohort (32))	----	Non metformin users SUs Insulin	Hepatocellular	0.31	0.19	0.49	----	----
[37]	Siddharth Singh	Until to June 2012	UK, Netherlands, USA, Taiwan, and Australia	11 (case-control (3), cohort (6), RCT (2))	730664	SUs Thiazolidinediones Insulin	Pancreatic	0.76	0.57	1.03	0.073	86
[38]	Siddharth Singh	Until to Sep 2012	UK, Scotland, Netherlands, USA, and Taiwan	15 Observational	840787	SUs Thiazolidinediones Insulin	Colorectal	0.89	0.81	0.99	<0.010	62
[39]	Siddharth Singh	Until to Aug 2012	USA, Europe, Japan, Italy, Netherlands, UK, France, and Australia	10 (case-control (3), cohort (5), RCT (2))	334307	SUs Thiazolidinediones Insulin	Hepatocellular	0.5	0.34	0.73	----	----
[40]	Hui Zhang	1966-2011	Italy, France, USA, China, Japan, and Taiwan	7 (case-control (4), cohort (3))	16549	Non metformin users	Hepatocellular	0.24	0.13	0.46	<0.001	66.80
[41]	Zheng Wang	1995-2013	UK, Netherlands, USA, Taiwan, and China	11 Observational	766195	Non metformin users SUs Insulin	Pancreatic	0.63	0.46	0.86	0.003	86
[42]	Shu-ping Nie	Until to Aug 2013	UK, Netherlands, USA, Taiwan, and China	15 (case-control (4), cohort (11))	----	Non metformin users SUs Thiazolidinediones Insulin	Lung	0.99	0.87	1.12	<0.001	80.40
[43]	Lang Wu	----	----	Case-control (39)	7600000	Non metformin users SUs Thiazolidinediones Insulin alpha glucosidase	Overall	0.86	0.83	0.90	<0.001	88.60

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Table 1: Contd...

Reference	Name of Author	Year of study	Country	Number of Study	Sample size	Type of control group	Type of cancer	OR/ RR	LOW OR/RR	UP OR/ RR	*P*	I^2 (%)
[44]	Contanza Saka Herran	2012-2017	USA, Brazil, UK, Italy, Switzerland, Taiwan, and Korea	13 Observational	----	Non metformin users anti-inflammatory drugs NSAID/aspirin use	Head and Neck Cancer	0.71	0.61	0.84	<0.001	55
[45]	Bahareh Ghiasi	Until to 2018	---	11 Observational	----	Non metformin users	Prostate	0.89	0.67	1.17	<0.001	99.6
[46]	Grace H. Tang	Inception to Nov 2016	---	12 Observational	----	Non metformin users	Breast	0.93	0.85	1.03	0.16	35
[20]	Christopher B. Chen	Inception to Aug 2015	Asia Western	26 (case-control (9), cohort (17))	1572307	Non metformin users	Prostate	1.01	0.86	1.18	---	97
[47]	Long Yao	Until September 20, 2017	UK, Netherlands, USA, Taiwan, China, Canada, France, and Germany	13 (case-control (3), cohort (10))	----	Non metformin users SUs Insulin	Lung	0.89	0.83	0.96	0.002	66
[48]	Zhaohan Feng	Through July 2018 (these studies were published between 2011 and 2017)	UK, Netherlands, USA, Taiwan, Canada, France, Germany, Sweden, switzerlands, and Denmark	18 (case-control (3), cohort (15))	----	Non metformin users Other antidiabetic agents NSAID/aspirin use antihypertensive, antithrombotic agents	Prostate	0.97	0.80	1.16	<0.001	98.1
[49]	MohammadMoradi-Joo	Up to June 2015	UK-Denmark-Spain-Germany-France-USA- Switzerland-Taiwan- Netherlands	11(case-control (1), cohort (9), RCT (1))	----	SU, metformin group	Breast	0.63	0.56	0.70	<0.001	94
[50]	Feifei Liu	Aug 31, 2016	China - UK- Netherlands-Danish- USA- Germany	17 (16 observational and 1 randomized controlled trial study)	---	Non Metformin group	Colorectal	0.73	0.62	0.86	<0.0002	
[22]	Wen, Q	Last search was performed on August 15, 2018	Asian and Caucasian	7 (ovarian (4), cervical (2), endometrial (6))	1710080	Non metformin users	Gynecological (ovarian, cervical, endometrial	0.49	0.29	0.82	0.006	98

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Table 1: Contd...

Reference	Name of Author	Year of study	Country	Number of Study	Sample size	Type of control group	Type of cancer		OR/ RR	LOW OR/RR	UP OR/ RR	*P*	I^2 (%)
[21]	Deng, M	Jan 13, 2019	Asian and non-Asian	50 (Case-control (14), cohort (34), RCT (2))	238540	Non metformin users or users of other antidiabetic agents	Colorectal adenoma, colorectal	Colorectal adenoma colorectal	0.75 0.73	0.65 0.58	0.86 0.90	0.308 <0.001	13.6 90.4
[51]	Tain, J	Through Oct 2017	USA, China, Europe, and England	6(Case-control (4), cohort (2))	510344	SUs, insulin	Endometrial		1.29	1.16	1.44	<0.001	8
[52]	Mekuria, AN	Until Dec 2018	UK, Taiwan, Netherlands, Germany, and USA	8	520106	SUs	Overall		0.76	0.54	1.07	<0.001	98.12
[53]	Chu, D	Between 1980 and July 2016	USA, UK, China, Finland, Poland, Italy, and Australia	7 (2 case-control, 4 retrospective studies, one prospective study)	---	Non-metformin users	Endometrial		1.05	0.82	1.35	0.70	90.9
[54]	Hu, H	Until September 2016	UK, Taiwan, Netherlands, and USA	9(Case-control (2), cohort (7))	534699	Other antidiabetic drugs (SUs, thiazolidinediones, or insulin)	Pancreatic		0.61	0.55	0.67	<0.001	31
[55]	Shi, J	Up to August 2018	USA, UK, Germany, Finland, China, Canada, and Israel	6 (Observational (5), RCT (1))	---	Non-metformin users or other hypoglycemic drug users	Ovarian		0.76	0.62	0.93	0.008	32.2
[56]	Chai, S	Inception to 23 June 2017	Network meta-analysis	84 RCT	101595	Incretin-based drugs with placebo or other antidiabetic drugs	Overall		0.32	0.07	1.38	---	---

SUs=Sulfonylureas, RCT=randomized control trials

Table 2: The effect of metformin on the risk of cancers by type of cancer

Type of cancer	Authors name	Number of study	Year of study	RR/ OR	lower RR/OR	upper RR/OR	Study selection	AMSTAR score
Hepatocellular/ Liver	Siddharth Singh	10	Update to Aug 2012	0.50	0.34	0.73	Removed	---
	Hui Zhang	7	1966-2011	0.24	0.13	0.46	Removed	---
	Ping Wong	49	Update to 2011	0.31	0.19	0.49	Selected	Moderate
	Hiroshi Noto	4	Until 2011	0.20	0.07	0.59	Removed	
	Shujuan Ma	19	Until July 2016	0.52	0.40	0.68	Selected	Moderate
	Zhi-Jiang Zhang	5	1966-2012	0.38	0.24	0.59	Removed	---
	Monica Franciosi	8	1966-2012	0.34	0.19	0.60	Removed	---
	New meta-analysis (Ping Wong, Shujuan Ma)	67	Up to 2017	0.59	0.46	0.72	Selected	---
Ovarian	Shi, J	6	Up to August 2018	0.76	0.62	0.93	Selected	High
	Wen, Q	4	Last search was performed on August 15, 2018	0.18	0.12	0.28	Removed	---
	Lifeng Li	5	Until Jan 2016	0.54	0.32	0.93	Selected	---
Pancreatic	Hu, H	9	Until September 2016	0.61	0.55	0.67	Selected	Moderate
	Zheng Wang	11	1995-2013	0.63	0.46	0.86	Selected	Moderate
	Siddharth Singh	11	Update to June 2012	0.76	0.57	1.03	Removed	---
	Monica Franciosi	9	1966-2012	0.56	0.36	0.86	Removed	---
	Hiroshi Noto	6	Until 2011	0.48	0.20	1.17	Removed	---
	New meta-analysis (Zheng Wang, Hu, H)	13	Up to 2016	0.59	0.50	0.69	Selected	---
Head and Neck	Contanza Saka Herran	13	2012-2017	0.71	0.61	0.84	Selected	Moderate
Colorectal adenoma	Deng, M	13	Jan 13, 2019	0.75	0.65	0.86	Selected	Moderate
	Feifei Liu	5	Aug 31, 2016	0.80	0.71	0.90	Removed	---
Colorectal	Deng, M	14	Jan 13, 2019	0.73	0.58	0.90	Selected	Moderate
	Feifei Liu	12	Aug 31, 2016	0.80	0.72	0.89	Removed	---
	Zhihang Nie	11	Update to 2014	0.75	0.66	0.86	Removed	---
	Hiroshi Noto	6	Until 2011	0.68	0.53	0.88	Removed	---
	Monica Franciosi	12	1966-2012	0.83	0.74	0.92	Removed	---
	Zhi-Jiang Zhang	5	1966-2011	0.63	0.47	0.84	Removed	---
	Siddharth Singh	15	Update to Sep 2012	0.89	0.81	0.99	Removed	---
Colon	T. Rokkas	17	Until 2015	0.79	0.69	0.91	Selected	High
	Andrea Decensi	11	1966-2009	0.64	0.38	1.08	Removed	---
Stomach/ Gastric	Monica Franciosi	2	1966-2012	0.83	0.76	0.91	Removed	---
	Hiroshi Noto	3	Until 2011	0.72	0.26	1.98	Selected	High
Prostate	Zhaohan Feng	18	These studies were done between 2011 and 2017	0.97	0.80	1.16	Selected	Moderate
	Bahareh Ghiasi	11	2009-2017	0.89	0.67	1.17	Removed	---
	Christopher B. Chen	26	Inception to Aug 2015	1.01	0.86	1.18	Selected	High
	Hiroshi Noto	7	Until 2011	0.89	0.66	1.19	Removed	---
	New meta-analysis of (Christopher B. Chen, Zhaohan Feng)	30	Up to 2018	0.94	0.85	1.04	Selected	---
Lung	Long Yao	13	Until September 20, 2017	0.89	0.83	0.96	Selected	Moderate
	Shu-ping Nie	15	Update to Aug 2013	0.99	0.87	1.12	Selected	Moderate
	Zhi-Jiang Zhang	6	2009-2013	0.71	0.55	0.95	Removed	---
	Hiroshi Noto	3	Until 2011	0.67	0.45	0.99	Removed	---
	Monica Franciosi	4	1966-2012	0.83	0.64	1.06	Removed	---
	New meta-analysis of (Long Yao, Shu-ping Nie)	20	Up to 2018	0.92	0.85	0.99	Selected	---

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Table 2: Contd...

Type of cancer	Authors name	Number of study	Year of study	RR/ OR	lower RR/OR	upper RR/OR	Study selection	AMSTAR score
Breast	Grace H. Tang	12	Inception to Nov 2016	0.93	0.85	1.03	Selected	High
	MohammadMoradi-Joo	11	Up to June 2015	0.63	0.56	0.70	Removed	---
	Hiroshi Noto	7	Until 2011	0.98	0.80	1.20	Removed	---
	Andrea Decensi	11	1966-2009	0.70	0.28	1.77	Removed	---
	Nananda F Col	7	1966-2009	0.83	0.71	0.97	Removed	---
	Monica Franciosi.ob	9	1966-2012	0.97	0.88	1.08	Removed	---
Esophagus	Monica Franciosi	2	1966-2012	0.90	0.83	0.98	Selected	Moderate
Bladder	Hiroshi Noto	3	Until 2011	0.94	0.64	1.38	Selected	High
Cervical	Wen, Q	2	Last search was performed on August 15, 2018	0.60	0.43	0.83	Selected	High
Endometrial	Wen, Q	6	Last search was performed on August 15, 2018	0.71	0.29	1.74	Removed	---
	Tain, J	6	Through Oct 2017	1.29	1.16	1.44	Removed	---
	Chu, D	7	Between 1980 and July 2016	1.05	0.82	1.35	Selected	High
All Cancer	Bindiya Thakkar	RCT (2)	Until 2012	1.01	0.81	1.26	Removed	---
		Cohort (9)		0.7	0.67	0.73	Removed	---
		Case-control (13)		0.90	0.84	0.98	Removed	---
	Lang Wu	39	---	0.86	0.83	0.9	Removed	---
	Mekuria, AN	8	Until Dec 2018	0.76	0.54	1.07	Removed	---
	Chai, S	84	Inception to 23 June 2017	0.32	0.07	1.38	Removed	---

RCT=randomized control trial

effect by activating mTOR pathway. Metformin inhibits cancer cell mitosis by inducing activation of the activated protein kinase-adenosine monophosphate and consequently reducing growth factor signaling. Inhibition of GTPase and microRNA222 suppression induced by metformin administration leads to increased levels of p27 and p57 molecules and consequently disrupts cell cycle in tumor cells. Other possible mechanisms underlying the metformin potential anti-neoplasm effect could be the following: antagonizing effect on obesity or via the reduction of inflammation,[57] p-53 activation,[58] down regulation of cyclin D1,[59] and killing of cancer stem cells.[60]

Metformin consumption plays a protective role on cancer incidence, although it was not statistically significant in some meta-analyzes.[18,26] Previous studies have shown that metformin at lower doses can block HER2 activity. In addition, metformin can prevent drug resistance to targeted HER2 chemotherapy with drugs such as trastuzumab and lapatinib. Therefore, treatment with both metformin and HER2 may have a synergistic effect. These results confirmed that the risk of invasive breast cancer in metformin-treated diabetics is lower than in recipients of other antidiabetic drugs. There was also a significant effect of metformin treatment on reducing risk of both ovarian and cervical cancer, supported by high quality meta-analyses according to AMSTAR 2.

So far, two meta-analyses have been conducted to investigate the relationship between metformin consumption and colon cancer risk, both of them showed a protective effect on colon cancer, which was statistically significant in study by Rokkas *et al*.[34] [RR: 0.79 (95% CI: 0.69–0.91)]. Such protective effect of metformin consumption was not statistically significant in the study by Decensi *et al*.[18] Clinical and laboratory studies have shown that metformin inhibits cell growth in colorectal cancer. Results of a meta-analysis reviewing five studies (total sample size = 108,161 diabetic patients) showed that metformin significantly reduces the risk of colorectal cancer. This study reported that metformin reduced the relative risk of colorectal cancer by 39%. The same meta-analysis examined the effects of insulin and thiazolidinediones, both of them were shown to be unable to reduce the mortality rate of colorectal cancer.[25]

The results of six studies that examined the relationship between metformin and colorectal cancer showed that metformin consumption reduced the risk of colorectal cancer and this relationship was statistically significant [Table 2]. Metformin consumption had no effect on the risk of colorectal cancer in the meta-analysis performed on RCT studies by Franciosi *et al*.[29] [RR: 1.02 (95% CI: 0.41-2.50]. In contrast, analysis performed on observational studies had a preventive effect.

All five meta-analyses on the association between metformin consumption and prostate cancer showed no statistically significant association. However, three studies by Noto *et al*.,[26] Ghiasi *et al*.,[45] and Feng *et al*.[48] indicated its

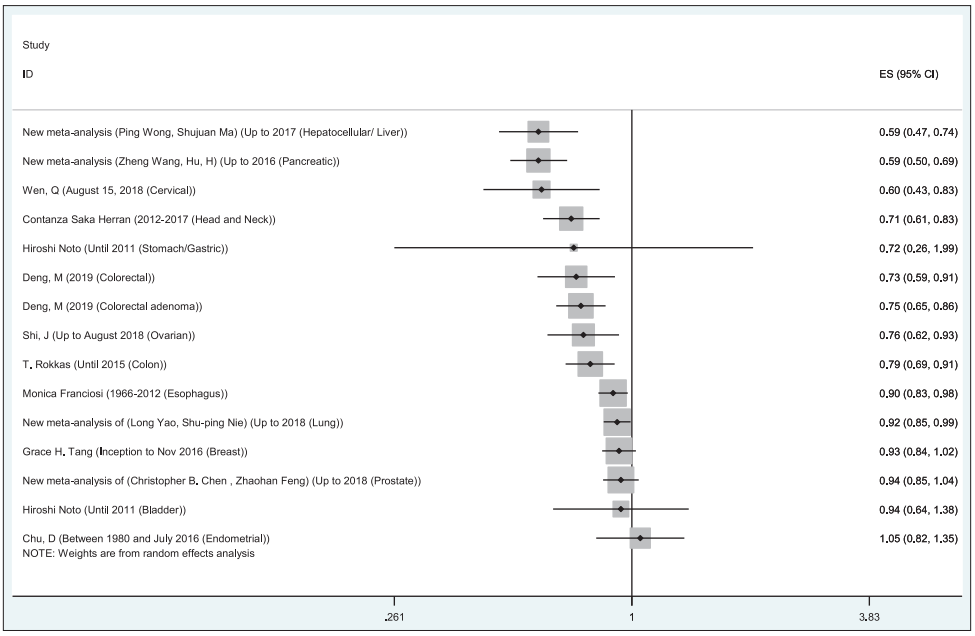

Figure 2: Relationship between metformin use and the risk of cancer worldwide. The midpoint of each segment estimates the odds ratio and length of the segment, showing the 95% confidence interval in each study

protective role. Low sex hormone-binding globulin levels may facilitate conversion of testosterone to estradiol, which in turn may increase the risk of hormone-dependent breast cancer. The duration of metformin treatment in diabetic patients was associated with a decrease in mortality from prostate cancer.[61]

Nie *et al*.[42] reported that metformin consumption had no effect on the risk of lung cancer (OR= 0.99 (95% CI: 0.87–1.12)). However, Zhang *et al*. showed metformin consumption reduced significantly the relative risk of lung cancer (RR= 0.71 (95% CI: 0.55–0.95)).[31] Noto *et al*.[26] also found that metformin consumption significantly reduced the risk of lung cancer (RR = 0.67, 95% CI: 0.45–0.99).

Studies have shown the protective role of metformin consumption against pancreatic cancer, although the effect was not statistically significant in some studies.[26,29,37,41] Metformin probably reduces inflammation and fibrosis, which is the most common cause of pancreatic cancer. Findings of cellular and animal models as well as in tumor specimens suggest that this positive effect may be observed in obese or overweight patients more frequently.[62]

In fact, metformin can reduce desmoplasia, an accumulation of dense connective tissue, and tumor-associated immune cells, and a key feature of pancreatic cancer. This function is accomplished by inhibiting the activity of pancreatic stellate cell (PaSCs). PaSCs produce extracellular matrix and reprogram immune cells to reduce inflammation. These effects are only visible in tumors found in obese and overweight people, as these tumors seem to be more fibrous in nature.

Review of previous studies showed that four meta-analyses were performed on the association between metformin consumption and the risk of hepatocellular cancer. All studies revealed that metformin consumption had a preventive effect on hepatocellular cancer and this relationship was statistically significant (Siddharth Singh,[38] RR = 0.50 (95% CI: 0.34–0.73), Hiroshi Noto[26] (RR = 0.20 (95% CI: 0.07–0.59), Ping Wang[36] (RR = 0.31 (95% CI: 0.19–0.49), and Hui Zhang[40] (RR = 0.24 (95% CI: 0.13–0.46).

Metformin not only inhibited proliferation and colony formation ability via (AMPK) in hepatocellular carcinoma cell[63] but also as an anti-hyperglycemic agent, it inhibited hepatic gluconeogenesis,[64] decreased serum concentrations of insulin and insulin growth factor,[65] improved the HbA1c levels, and reduced inflammatory response.[66] This process reduces the aggressive behavior of cancer cells. All previous relevant studies have shown that metformin consumption can prevent hepatocellular cancer.

Only three associations (between metformin and colon, ovarian, and cervical cancer) were supported by both high quality and statistically significant relationship. Patients who received metformin treatment have odds of 0.21, 0.24, and 0.40 to develop colon, ovarian, and cervical cancer, respectively.

Some of the reviews showed nonsignificant protective effect with a moderate to high quality. The possible reasons for the statistically insignificant results can be different, including the inadequate sample size and the study designs of included meta-analyses.

This study is an update of previous meta-analyses and umbrella reviews covering most common cancer sites.

Because most included studies did not report the relative risk of cancers on consumption of metformin by study type (cohort, clinical trial, case–control, etc.), this report failed to perform analyses stratified by study type. In addition, some meta-analysis studies were based on medical or insurance data that are not specifically designed to evaluate the impact of metformin therapy on cancer. There were incomplete details on dose, duration, changes occurring in treatment over time, and potential confounders.

In fact, considerable heterogeneity among included studies in terms of population of the studies, diversity of the disease duration, type of cancer, and study design did not allow to pool the data for estimating an effect size. Unadjusted measures and some possible confounding factors in the original studies may have rendered the results of this study less valid. Overestimation of the effect of metformin may have occurred. In some studies, the characteristics of comparison group has been defined as "Non-metformin consumer," which in turn may have received other glucose lowering drugs with synergistic effect with other medications, affecting the likelihood of cancer. The most commonly used drugs are insulin and sulfonylurea, which are associated with hyperinsulinemia which is associated with an increased risk of cancer. Therefore, hyperinsulinemia in comparison groups might overestimate the effect of metformin. On the other hand, the synergistic effect of metformin with some common medications in diabetic patients may have led to an overestimation of the effect of metformin on cancer.[67] Confounding by treatment indication such as using metformin medication in younger age with a lower risk of cancer also might overestimate the effect of metformin.

Conclusions

Metformin therapy in diabetic patients may be a reasonable prescription for the prevention of cancers if it has not been clinically contraindicated. Such effect was higher in hepatocellular carcinoma and lower in lung and breast cancers; however, it had no significant effect on some cancers, including prostate cancer, bladder cancer, endometrial cancer, gastric cancer, and breast cancer.

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Conflicts of interest

There are no conflicts of interest.

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Table S1: Search strategy in some databases

Databases	Search strategy
Search strategy in Scopus	(TITLE-ABS-KEY (cancer* OR neoplasia OR tumor* OR malignan*) AND TITLE-ABS-KEY (metformin) AND TITLE-ABS-KEY (diabetes AND mellitus) AND TITLE-ABS-KEY (meta-analysis OR eta-analyses))
Search strategy in PubMed	((((((neoplasms[MeSH Terms]) OR (cancer[Title/Abstract])) OR (malignan*[Title/Abstract])) OR (tumor*[Title/Abstract])) OR (neoplasm[Title/Abstract])) AND ((meta-analysis[Title/Abstract]) OR (Meta-Analysis[Publication Type]))) AND ((metformin[Title/Abstract]) OR (metformin[MeSH Terms]))
Search strategy in Web of Science	TOPIC: (metformin) AND TOPIC: (cancer OR neoplasm OR neoplasia OR tumor) AND TOPIC: (meta-analysis OR meta-analyses) AND TOPIC: (diabetes mellitus)
Search strategy in Cochrane	("Cancer"):ti, ab, kw AND ("metformin"):ti, ab, kw AND ("diabetes mellitus"):ti, ab, kw AND ("meta analysis"):ti, ab, kw"
Search strategy in Embase	'malignant neoplasm':ab, ti AND metformin: ab, ti AND 'meta analysis':ab, ti AND 'diabetes mellitus':ab, ti