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Review

Metformin and risk of cancer among patients with type 2 diabetes mellitus: A systematic review and meta-analysis

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ABSTRACT

Aim: We carried out this meta-analysis on all published studies to estimate the overall cancer risk of the use of metformin in T2DM patients.
Methods: We searched the PubMed, Embase and CNKI databases for all articles within a range of published years from 2007 to 2019 on the association between the use of metformin and cancer risk in T2DM patients. The odds ratio (OR) corresponding to the 95% confidence interval (95% CI) was used to assess the association using a random-effect meta-analysis.
Results: Finally, 67 studies met the inclusion criteria for this study, with 10,695,875 T2DM patients and 145,108 cancer cases. Overall, For T2DM patients of ever vs. never metformin users, there was statistical evidence of significantly decreased cancer risk was found to be associated with ever metformin users (OR = 0.70, 95% CI = 0.65–0.76). Considering T2DM may be a specific and independent risk factor for various forms of cancer, due to its particular metabolic characteristics of glucose intolerance and hyperinsulinemia, we performed a comparison to estimate the effects of metformin on cancer risk with other anti-diabetes medications (ADMs), our results found significantly decreased cancer risk to be associated with the use of metformin (OR = 0.80, 95% CI = 0.73–0.87).
Conclusion: Our meta-analysis indicated that metformin may be a independent protective factor for cancer risk in T2DM patients.

Contents

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1. Introduction

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It is emerging as one of the most prevalent human ailments next to cardiovascular diseases and is the sixth leading cause of death worldwide (WHO), and the prevalence of T2DM is rapidly increasing worldwide [1]. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels [2].

Cancer is a leading cause of death worldwide, particularly in less developed countries, in which about 82% of the world's population resides [3]. There is strong evidence to suggest that cancer incidence is increased in patients with DM [4]. The pathophysiological hypotheses to explain the link between diabetes or hyperglycaemia and cancer rely on biological, particularly hormonal, mechanisms involving insulin-resistance [5]. Indeed, in the genesis of type 2 diabetes, reduced insulin sensitivity plays a key role, inducing compensatory hyperinsulinaemia with an increased level of circulating Insulin-like Growth Factors (IGF), well-known to stimulate cell proliferation in many organs, including the liver, pancreas, colon, ovary, breast, the most frequent sites with an increased risk of cancer in type 2 diabetic patients [6].

Metformin is one of the most used oral glucose-lowering drugs for the treatment of T2DM [7]. The two main biguanides, metformin and phenformin were introduced for the first time in the late 1950s, but phenformin had to be withdrawn because of a strong association with lactic acidosis. So actually, although there are many different medications to treat T2DM, metformin is still a cornerstone in the T2DM therapy. In fact, a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes, recommend metformin as the first step in T2DM treatment, if there is not a contraindication [8]. Despite the length of its use, continuing research on metformin's mechanisms of action and particularly its potential role in cancer has restored its popularity [9]. Recently, the associations of risk relating to cancer with the use of metformin in T2DM patients have already been widely studied [10–76]. However, the results remained inconsistent.

Considering a single study might have been underpowered to detect the overall effects, a quantitative synthesis of the accumulated data from different studies was deemed important to provide evidence on the association between the use of metformin in T2DM patients and cancer risk. So, we carried out this meta-analysis on all published studies to estimate the overall cancer risk of the use of metformin in T2DM patients. Furthermore, T2DM may be considered as a specific and independent risk factor for various forms of cancer, due to its particular metabolic characteristics of glucose intolerance and hyperinsulinemia [77]. We performed a comparison to estimate the effects of metformin on cancer risk with other ADMs.

2. Methods

2.1. Publication search and inclusion criteria

We searched the PubMed, Embase and CNKI (China National Knowledge Infrastructure) databases for all articles within a range of published years from 2007 to 2019 on the association between the use of metformin and cancer risk (last search was update Nov. 23 2019) in T2DM patients. The following terms were used in this search: 'metformin' and 'cancer' and 'type 2 diabetes mellitus or T2DM'. In order to identify the relevant publications, the references cited in the research papers were also scanned. Combining searches resulted in 684 abstracts (Supplementary figure 1). An additional 13 studies were identified through review articles and meta-analysis, for a total of 693 studies were screened after duplicated records removed. After screening the titles and abstracts, 97 were retrieved for more detailed evaluation.

We evaluated the eligible studies if all the following conditions were met: (1) evaluation of the association of metformin usage and cancer risk; (2) including data for analysis between ever and never metformin usage patients or metformin usage compared with other anti-diabetes medications (ADMs); (3) inclusion of sufficient data or the data can be acquired from the manuscript or Supplementary materials to calculate ORs and 95% CIs; (4) the publication was a cohort study or case-control study; and (5) the study was published in English.

2.2. Data extraction

Two authors (Kui Zhang and Peng Bai) independently reviewed and extracted the data needed. Disagreements were resolved through discussion among the authors to achieve a consensus. The following information was recorded for each study: first author, year of publication, region, study type, follow-up period, cancer type, sex, number of cases, number of controls (all of the data are shown in Table 1).

2.3. Statistical analysis

The odds ratio (OR) corresponding to the 95% confidence interval (95% CI) was used to assess the association between metformin usage (ever vs. never and compared with other ADMs). To minimize the influence of recall and selection bias that occur in studies, we performed stratified analyses to assess the association in different study type. In addition to the above comparison, we also performed analyses stratified by different cancer type. The statistical heterogeneity among studies was assessed with the Q-test and I^2 statistics [78]. If there was no obvious heterogeneity, the fixed-effects model (the Mantel-Haenszel method) was used to estimate the summary OR [79]; otherwise, the random-effects model (the DerSimonian and Laird method) was used [80]. Finally, random effects models were used to calculate the overall RR estimates and 95% CIs. To explore sources of heterogeneity across studies, we did logistic meta-regression analyses. We examined the following study characteristics: publication year, region, study type, follow-up period, cancer type, number of cases, number of controls, morbidity of cases, and morbidity of controls. Publication bias was evaluated with funnel plot and Begg's rank correlation method [81]. The statistical analyses were performed by STATA 12.0 software (Stata Corp., College Station, TX).

3. Results

3.1. Characteristics of studies

Out of a total of 693 titles and abstracts were screened, 97 were retrieved for more detailed evaluation. Among the 30 excluded studies, 14 papers were reviews, 6 papers were not associated with the topic, and 10 papers lacked sufficient data (shown in Supplementary figure 1). Finally, 67 studies including 80 comparisons met the inclusion criteria for this study [10–76], with 10,695,875 T2DM patients and 145,108 cancer cases. Among them, 65 prospective cohort studies with 135,184 cancer cases and 10,132,888 T2DM patients were included. The details of including first author, year of publication, region, study type, follow-up period, cancer type, gender (male, female, or both), number of cases, and number of controls in the selected studies were listed in Table 1.

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Table 1
Characteristics of literatures included in the meta-analysis.

Reference	Year	Region	Study type	Follow up time (year)	Cancer type	Sex	No. of cases	No. of subjects
Bradley MC [14]	2018	USA	Cohort study	15.5	Colorectal cancer	Both	812	47,351
Lai SW [37]	2012	Taiwan	Cohort study	9	Lung cancer	Both	129	19,624
Haring A [28]	2017	Finland	Cohort study	15	Prostate cancer	Male	767	78,615
Arima R [10]	2017	Finland	Cohort study	16	Endometrial cancer	Female	590	92,366
Hagberg KW [26]	2014	USA	Case control study		Liver cancer	Both	305	1151
Li D [41]	2009	USA	Case control study		Pancreatic cancer	both	255	106
Kowall B [33]	2015	Germany	Cohort study	4.8	Any cancer	Both	1446	22,556
Ye JH [74]	2019	China	Cohort study	5	Any cancer	Both	94	2353
Hosio M [29]	2019	Finland	Cohort study	16	Breast cancer	Female	2300	141,194
Chen YC [20]	2015	Taiwan	Cohort study	2.5	Any cancer	Both	549	7272
Chen HH [19]	2015	Taiwan	Cohort study	5	Liver cancer	Both	340	1360
Calip GS [15]	2016	USA	Cohort study	6.7	Breast cancer	Female	301	10,050
Tseng CH [56]	2012	Taiwan	Cohort study	3	Colorectal cancer	Both	678	87,991
Chlebowski RT [21]	2012	USA	Cohort study	11.8	Breast cancer	Female	444	3401
Chang YT [17]	2018	Taiwan	Cohort study	7.17	Colorectal cancer	Both	914	47,597
Vicentini M [72]	2018	Italy	Cohort study	3	Any cancer	Both	531	11,520
Yen YC [75]	2015	Taiwan	Cohort study	17	Head and neck cancer	Both	485	66,600
Kim G [30]	2017	Korea	Case control study		Liver cancer	Both	229	1145
Lin HC [43]	2014	Taiwan	Cohort study	6	Any cancer	Both	5221	32,877
Simo R [51]	2013	Spain	Case control study		Any cancer	Both	609	1829
Mamtani R [44]	2014	U.K	Cohort study	10	Bladder cancer	Both	262	87,600
Goossens ME [25]	2015	U.K	Cohort study	5	Bladder cancer	Both	693	165,398
Qiu H [47]	2013	U.K	Cohort study	14	Any cancer	Both	2554	56,844
Kim YI [32]	2014	Korea	Cohort study	7	Gastric cancer	Both	318	39,989
Yang X [73]	2011	Hong Kong	Cohort study	5.51	Any cancer	Both	129	2529
Lai SW [36]	2012	Taiwan	Cohort study	9	Liver cancer	Both	224	19,349
Ruiter R [48]	2012	Netherlands	Cohort study	11	Any cancer	Both	2036	85,289
Soffer D [54]	2015	USA	Cohort study	12	Breast cancer	Female	852	66,778
Soffer D [54]	2015	USA	Cohort study	12	Endometrial cancer	Female	852	66,778
Soffer D [54]	2015	USA	Cohort study	12	Ovarian cancer	Female	852	66,778
Monami M [45]	2011	Italy	Case control study		Any cancer	Both	112	370
Tseng CH [60]	2015	Taiwan	Cohort study	11	Endometrial cancer	Female	2885	478,921
Tseng CH [66]	2017	Taiwan	Cohort study	13	Esophageal cancer	Both	381	304,229
Tseng CH [67]	2017	Taiwan	Cohort study	13	Lung cancer	Both	2576	295,573
Tseng CH [68]	2018	Taiwan	Cohort study	5.5	Head and neck cancer	Both	98	30,972
Tseng CH [69]	2018	Taiwan	Cohort study	5.3	Liver cancer	Both	3261	195,817
Azoulay L [11]	2011	U.K	Case control study		Prostate cancer	Male	739	7359
Becker C [12]	2014	U.K	Case control study		Head and neck cancer	Both	2874	17,244
Chen CB [18]	2017	U.K	Cohort study	9	Prostate cancer	Male	3557	80,001
Becker C [13]	2017	USA	Case control study		Renal cancer	Both	3506	21,038
Tsai MJ [55]	2014	Taiwan	Cohort study	11	Lung cancer	Both	673	47,356
Tsilidis KK [70]	2014	U.K	Cohort study	5.1	Any cancer	Both	3805	69,748
Sehdev A [50]	2015	USA	Case control study		Colorectal cancer	Both	2682	5364
Tseng CH [57]	2014	Taiwan	Cohort study	7	Breast cancer	Female	11,734	476,282
Tseng CH [62]	2016	Taiwan	Cohort study	7	Head and neck cancer	Both	1392	304,461
Tseng CH [63]	2016	Taiwan	Cohort study	7	Gastric cancer	Both	848	304,188
Tseng CH [61]	2015	Taiwan	Cohort study	7	Ovarian cancer	Female	3201	640,193
Kuo YJ [35]	2019	Taiwan	Cohort study	5	Prostate cancer	Male	166	5812
Kim HJ [31]	2018	Korea	Cohort study	5.8	Any cancer	Both	164	1918
Tseng CH [58]	2014	Taiwan	Cohort study	4	Head and neck cancer	Both	2297	1,414,723
Tseng CH [59]	2014	Taiwan	Cohort study	8	Prostate cancer	Male	12,418	545,815
Tseng CH [64]	2016	Taiwan	Cohort study	7	Cervical cancer	Female	476	139,911
Murff HJ [46]	2018	USA	Cohort study	7	Bladder cancer	Both	219	137,863
Murff HJ [46]	2018	USA	Cohort study	7	Breast cancer	Female	22	137,863
Murff HJ [46]	2018	USA	Cohort study	7	Colorectal cancer	Both	307	137,863
Murff HJ [46]	2018	USA	Cohort study	7	Esophageal cancer	Both	77	137,863
Murff HJ [46]	2018	USA	Cohort study	7	Gastric cancer	Both	59	137,863
Murff HJ [46]	2018	USA	Cohort study	7	Liver cancer	Both	126	137,863
Murff HJ [46]	2018	USA	Cohort study	7	Lung cancer	Both	652	137,863
Murff HJ [46]	2018	USA	Cohort study	7	Pancreatic cancer	Both	96	137,863
Murff HJ [46]	2018	USA	Cohort study	7	Prostate cancer	Male	884	137,863
Murff HJ [46]	2018	USA	Cohort study	7	Renal cancer	Both	133	137,863
Sakoda LC [49]	2015	USA	Cohort study	15.5	Lung cancer	Both	747	47,351
Zheng J [76]	2019	Sweden	Cohort study	5.8	Gastric cancer	both	892	544,130
Franchi M [24]	2017	Italy	Case control study		Endometrial cancer	Female	376	7485
Libby G [42]	2009	U.K	Cohort study	12	Any cancer	Both	771	8170
Kowall B [34]	2015	Germany and U.K	Cohort study	4.8	Any cancer	Both	4779	80,263
Haggstrom C [27]	2017	Sweden	Cohort study	5	Prostate cancer	Male	656	25,238
Cho YY [22]	2018	Korea	Cohort study	7.2	Head and neck cancer	Both	827	256,906
Dabrowski M [23]	2016	Poland	Case control study		Any cancer	Both	203	203
Chaiteerakij R [16]	2013	USA	Case control study		Liver cancer	Both	48	139
Lehman DM [40]	2012	USA	Cohort study	5	Prostate cancer	Male	360	5042
Lee DY [38]	2018	Korea	Cohort study	4.9	Pancreatic cancer	Both	2915	966,453
Urpilainen E [71]	2018	Finland	Cohort study	5.4	Ovarian cancer	Female	303	137,643
Urpilainen E [71]	2018	Finland	Case control study		Ovarian cancer	Female	303	6060

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Table 1 (*Continued*)

Reference	Year	Region	Study type	Follow up time (year)	Cancer type	Sex	No. of cases	No. of subjects
Smiechowski B [52]	2013	U.K	Case control study		Colorectal cancer	Both	607	5837
Smiechowski BB [53]	2013	U.K	Case control study		Lung cancer	Both	808	7764
Lee MS [39]	2011	Taiwan	Cohort study	3.52	Any cancer	Both	339	15,717
Tseng CH [65]	2016	Taiwan	Cohort study	4	Any cancer	Both	40,242	234,007
Tseng CH [65]	2016	Taiwan	Cohort study	4	Renal cancer	Both	1741	247,252

Table 2
Associations between metformin usage and risk of cancer.

	Metformin(ever users vs. never users)				Compare with other ADMs			
	N^a	Case/control	OR (95%CI)	P^b	N^a	Case/control	OR (95%CI)	P^b
Overall	80	145,108/10,695,875	**0.70 (0.65–0.76)**	<0.001	53	56,815/5,254,835	**0.80 (0.73–0.87)**	<0.001
Cohort study	65	135,184/10,132,888	**0.69 (0.63–0.75)**	<0.001	42	45,336/5,192,832	**0.78 (0.71–0.87)**	<0.001
Case control study	15	9924/562,987	**0.81 (0.70–0.93)**	<0.001	11	11,479/62,003	**0.88 (0.79–0.99)**	0.001
Bladder cancer	4	4979/460,609	**0.76 (0.63–0.91)**	0.070	4	4979/460,609	**0.76 (0.63–0.91)**	0.070
Breast cancer	11	27,575/1,090,558	0.78 (0.52–1.17)	<0.001	8	14,539/594,586	0.91 (0.77–1.09)	<0.001
Colorectal Cancer	12	18,261/602,710	**0.73 (0.60–0.87)**	<0.001	6	13,898/425,878	**0.73 (0.57–0.93)**	<0.001
Esophageal cancer	5	6638/612,846	**0.72 (0.53–0.96)**	0.050	3	5918/292,900	0.75 (0.55–1.03)	0.143
Gastric cancer	7	8297/1,196,924	0.72 (0.43–1.22)	<0.001	4	6748/597,088	**0.53 (0.42–0.65)**	0.165
Liver cancer	11	11,244/539,098	**0.61 (0.49–0.75)**	<0.001	6	6725/314,545	**0.62 (0.44–0.89)**	<0.001
Head and neck cancer	6	7973/2,090,906	**0.55 (0.38–0.79)**	<0.001				
Lung cancer	11	17,507/810,521	**0.69 (0.60–0.80)**	<0.001	6	14,183/688,360	**0.63 (0.56–0.73)**	0.006
Endometrial cancer	5	8508/715,298	1.11 (0.65–1.88)	<0.001	6	7327/369,933	1.15 (0.92–1.44)	0.001
Ovarian cancer	4	4659/850,674	0.78 (0.53–1.15)	<0.001	3	3807/783,896	1.20 (0.76–1.89)	<0.001
Pancreatic cancer	7	9977/1,286,696	**0.62 (0.45–0.84)**	<0.001	5	9132/1,259,467	**0.57 (0.35–0.93)**	<0.001
Prostate cancer	12	30,698/1,132,565	**0.74 (0.63–0.86)**	<0.001	7	13,716/482,058	**0.76 (0.59–0.97)**	<0.001
Renal cancer	3	5380/406,153	0.71 (0.34–1.45)	<0.001				

Boldfaced values indicate a significant difference at the 5% level.
[a] Number of comparisons.
[b] P value of Q-test for heterogeneity test.

3.2. Quantitative synthesis

For T2DM patients of ever vs. never metformin users, there was statistical evidence of significantly decreased cancer risk was found to be associated with ever metformin users (OR = 0.70, 95% CI = 0.65–0.76) in the overall comparison. In stratified analysis by study type, significantly decreased cancer risk was found in the cohort studies (OR = 0.69, 95% CI = 0.63–0.75) and in the case control studies (OR = 0.81, 95% CI = 0.70–0.93) (shown in Table 2 and Supplementary figure 2). As shown in Table 2, in terms of subgroup analyses by cancer type, the use of metformin was significantly with decreased bladder cancer, colorectal cancer, esophageal cancer, liver cancer, head and neck cancer, lung cancer, pancreatic cancer and prostate cancer risk (OR = 0.76, 95% CI = 0.63–0.91 for bladder cancer, OR = 0.73, 95% CI = 0.60–0.87 for colorectal cancer, OR = 0.72, 95% CI = 0.53–0.96 for esophageal cancer, OR = 0.61, 95% CI = 0.49–0.75 for liver cancer, OR = 0.55, 95% CI = 0.38–0.79 for head and neck cancer, OR = 0.69, 95% CI = 0.60–0.80 for lung cancer, OR = 0.62, 95% CI = 0.45–0.84 for pancreatic cancer, and OR = 0.74, 95% CI = 0.63–0.86 for prostate cancer).

For comparison with other ADMs, there was statistical evidence of significantly decreased cancer risk was found to be associated with the use of metformin (OR = 0.80, 95% CI = 0.73–0.87) in the overall comparison. In stratified analysis by study type, significantly decreased cancer risk was found in the cohort studies (OR = 0.78, 95% CI = 0.71–0.87) and in the case control studies (OR = 0.88, 95% CI = 0.79–0.99) (shown in Table 2 and Supplementary figure 3). As shown in Table 2, in terms of subgroup analyses by cancer type, the use of metformin was significantly with decreased bladder cancer, colorectal cancer, gastric cancer, liver cancer, lung cancer, pancreatic cancer and prostate cancer risk (OR = 0.76, 95% CI = 0.63–0.91 for bladder cancer, OR = 0.73, 95% CI = 0.57–0.93 for colorectal cancer, OR = 0.53, 95% CI = 0.42–0.65 for gastric cancer, OR = 0.62, 95% CI = 0.44–0.89 for liver cancer, OR = 0.63, 95% CI = 0.56–0.73 for lung cancer, OR = 0.57, 95% CI = 0.35–0.93 for pancreatic cancer, and OR = 0.76, 95% CI = 0.59–0.97 for prostate cancer).

3.3. Evaluation of heterogeneity

There was heterogeneity among studies in overall comparisons ($P_{heterogeneity} < 0.001$, $I^2 = 96.9\%$, $Tau^2 = 0.1026$). To explore sources of heterogeneity across studies, we perform stratified analysis by study type, there were high levels of heterogeneity between studies ($I^2 = 97.2\%$ for cohort studies, and $I^2 = 83.5\%$ for case control studies). Furthermore, stratified analysis was performed by cancer type, the heterogeneity was inconsistent ($I^2 = 91.5\%$ for colorectal cancer, $I^2 = 80.2\%$ for liver cancer, $I^2 = 80.4\%$ for pancreatic cancer, $I^2 = 98.8\%$ for breast cancer, $I^2 = 57.4\%$ for bladder cancer, $I^2 = 82.5\%$ for lung cancer, $I^2 = 57.9\%$ for esophageal cancer, $I^2 = 95.5\%$ for gastric cancer, $I^2 = 97.6\%$ for endometrial cancer, $I^2 = 96.6\%$ for head and neck cancer, $I^2 = 92.8\%$ for ovarian cancer, $I^2 = 93.8\%$ for prostate cancer, and $I^2 = 98.4\%$ for renal cancer). Finally, logistic meta-regression analyses revealed that morbidity of cases and morbidity of controls may substantially influence the initial heterogeneity.

3.4. Sensitivity analysis

The influence of a single study on the overall meta-analysis estimate was investigated by omitting one study at a time, and the omission of any study made no significant difference, indicating that our results were statistically reliable.

3.5. Publication bias

The Begg's test was performed to evaluate the publication bias of selected displays a funnel plot that examined the use of metformin and cancer risk included in the meta-analysis. No evidence of publication bias in our study was observed ($P = 0.584$).

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4. Discussion

As a major risk factor for type 2 diabetes, the inflammatory and endocrine effects of obesity have been proposed as central mechanisms explaining associations between diabetes and cancer. Metformin is one of the most used oral glucose-lowering drugs for the treatment of T2DM [7]. The glucose-lowering action is largely due to the improvement in hepatic insulin resistance leading to a reduction in hepatic glucose output, mainly as result of reduction in gluconeogenesis [82]. Metformin also increases glucose uptake in muscle, without extra lactate production, and raises insulin binding to insulin receptors (IR), while increasing the phosphorylation and tyrosine kinase activity of the IR [9]. In human hepatic cells, metformin increases insulin receptor activation independently of insulin, acting predominantly through insulin receptor substrate 2 [83]. Previous meta analysis indicated that metformin therapy can decrease the risk of gastric cancer [84], breast cancer [85], lung cancer [86,87], liver cancer [88], pancreatic cancer [89], and colorectal cancer in T2DM patients [90,91]. Considering the metformin of glucose-lowering effect, we performed a comparison of ever vs. never metformin users in T2DM patients, our results indicated that there was statistical evidence of significantly decreased cancer risk was found to be associated with ever metformin users in the overall comparison. In stratified analysis by study type, significantly decreased cancer risk was found in the cohort studies and in the case control studies. In terms of subgroup analyses by cancer type, the use of metformin was significantly with decreased bladder cancer, colorectal cancer, esophageal cancer, liver cancer, head and neck cancer, lung cancer, pancreatic cancer and prostate cancer risk.

Considering that T2DM may be a specific and independent risk factor for various forms of cancer, due to its particular metabolic characteristics of glucose intolerance and hyperinsulinemia. All ADMs may have the glucose-lowering effects, and previous meta-analysis does not support a protective or harmful association between ADMs use and risk of cancer [92,93] in patients with DM. We performed a comparison to estimate the effects of metformin on cancer risk with other ADMs, our results indicated that there was statistical evidence of significantly decreased cancer risk was found to be associated with the use of metformin in the overall comparison. In stratified analysis by study type, significantly decreased cancer risk was found in the cohort studies and in the case control studies. In terms of subgroup analyses by cancer type, the use of metformin was significantly with decreased bladder cancer, colorectal cancer, gastric cancer, liver cancer, lung cancer, pancreatic cancer and prostate cancer risk.

Metformin's mechanism of action is complex. The basic mechanism of metformin action involves AMP-activated serine/threonine kinase (AMPK), AMPK activation by metformin is mediated by liver kinase B1 (LKB1), which is a suppressor protein [94].

The major downstream target of AMPK is the mammalian target of rapamycin (mTOR), a kinase whose activity is very important in cellular growth processes and is inhibited by AMPK, leading to reduction of protein synthesis [95]. The inhibiting effect of AMPK on mTOR results in blocking of the PI3K/PKB/Akt pathway, thus down-regulating the synthesis of many proteins which were responsible for mitotic promotion, which lead to the inhibition of cell division and/or promotion of apoptosis [96]. AMPK also promotes cellular autophagy through the phosphorylation of cyclin-dependent kinase inhibitor protein, p27 [97]. Furthermore, the mechanism of metformin action involves down-regulation of circulating insulin and activation of the immune system [98]. These may be the potential mechanisms, and further efforts should be made to confirm these findings.

A few limitations of our study should be considered. Although we did not observe significant publication bias, publication bias is possible in any meta-analysis. Moreover, original data were acquired to calculate ORs and 95% CIs that may omit some valuable studies and ignore potential adjusted risk factors. Finally, due to the lack of sufficient data, the dose and duration related effect of metformin cannot be analyzed.

In conclusion, our meta-analysis indicated that metformin may be a independent protective factor for cancer risk in T2DM patients. Moreover, further studies estimating the functional effect and side effects may eventually provide a better, comprehensive understanding.

Conflicts of interests

No conflicts of interests to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.pcd.2020.06.001.

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