JNCI Cancer Spectrum (2017) 1(1): pkx007

doi: 10.1093/jncics/pkx007
First published online November 28, 2017
Meta-Analysis

META-ANALYSIS

The Effect of Metformin on Mortality Among Diabetic Cancer Patients: A Systematic Review and Meta-analysis

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Abstract

Background: Most data suggest that cancer patients with diabetes have worse outcomes, which may be reversed with metformin. Metformin might modulate the clinical outcomes of diabetic cancer patients. We performed a systematic review and meta-analysis based on published studies over the past five years to summarize the effects of metformin on diabetic cancer patients.
Methods: We systematically searched for studies that were published over the past five years. Then, we evaluated these studies for inclusion and extracted the relevant data. The summary risk estimates for the association between metformin treatment and all-cause mortality (ACM) and cancer-specific mortality (CSM) were analyzed using random or fixed-effects models. Stratified analyses by cancer site and country were also conducted.
Results: Based on the 42 studies included in our analysis (37 015 diabetic cancer patients), we found a significant benefit associated with metformin treatment on survival corresponding to 27% and 26% reductions in ACM (hazard ratio [HR] = 0.73, 95% confidence interval [CI] = 0.68 to 0.79, $P < .001$) and CSM (HR = 0.74, 95% CI = 0.64 to 0.86, $P < .001$), respectively. The ACM rates for colorectal cancer, endometrial cancer, breast cancer, prostate cancer, and ovarian cancer showed significant benefits associated with metformin treatment in our stratified analyses by cancer site. Stratified analyses by cancer site also showed a significant reduction in CSM for breast cancer. This association between metformin treatment and reduced CSM for diabetic breast cancer patients was also observed in our country subgroup analyses.
Conclusions: We found an association between metformin exposure and reduced ACM and CSM in diabetic patients with cancer. Our findings suggest that metformin treatment could be an effective treatment option for diabetic cancer patients.

Diabetes mellitus is the most common form of metabolic disease and is due to either a deficiency in pancreatic insulin production or resistance of insulin-responsive cells to the insulin produced (1). Clinically, diabetic patients develop cancer relatively frequently (2). Moreover, approximately 20% of patients with cancer have concurrent diabetes, which could be due to the biological links between these two diseases (3). Previous experimental studies have suggested that increased neoplastic proliferation rates and an increased risk of tumor progression or metastases in cancer patients occur with concurrent diabetes mellitus, which could be due to the effects of hyperinsulinemia, hyperglycemia, and inflammatory cytokines (2,4–6).

Metformin is a glucose-lowering agent that improves insulin sensitivity and lowers circulating insulin in patients with type II diabetes mellitus (7). It is the most commonly prescribed oral antidiabetic drug and is recommended as firstline therapy

Received: July 24, 2017; **Revised:** September 16, 2017; **Accepted:** September 26, 2017

because it is relatively inexpensive, safe, effective, and well tolerated (8). Over the past several years, some studies have investigated the associations between metformin treatment and cancer. Basic biochemical studies have provided a better understanding of the mechanisms of the antitumor activity of metformin and the potential for metformin to modulate molecular pathways involved in cancer cell signaling and metabolism. The anticancer effects of metformin include decreased insulin/insulin-like growth factor-1 (IGF-1) signaling, inhibition of the mammalian target of rapamycin (mTOR), inhibition of mitochondrial complex I in the electron transport chain, activation of AMP-activated kinase (AMPK), and reduction of endogenous production of reactive oxygen species (ROS) and associated DNA damage (9–11). Metformin has also been associated with the risk of cancer incidence and mortality in recent studies. Although the results of these studies have been inconsistent in the context of different cancers, these findings have led to increasing interest in the potential role of metformin as an anticancer agent.

Several published studies have reported that metformin treatment could widely improve the survival of cancer patients with diabetes; however, the results from these studies have been inconsistent. Since 2014, a growing number of studies have evaluated the effect of metformin on the mortality of patients with diabetes in types of cancers that had not been reported previously, including endometrial cancer (12,13), lung cancer (14–17), bladder cancer (18), renal cell cancer (19), and laryngeal squamous cell carcinoma (20). Therefore, we conducted the present systematic review and meta-analysis to evaluate these studies. The first objective of our analysis was to determine whether the results of recently published studies could change the outcomes of the previous meta-analyses. Furthermore, we sought to summarize the association between metformin treatment, all-cause mortality (ACM), and cancer-specific mortality (CSM) in patients with concurrent cancer and diabetes as well as to summarize these associations according to cancer site and country.

Methods

Study Selection and Data Extraction

The following computerized bibliographic databases were used to search for relevant articles: PubMed, EMBASE, and the ISI Web of Science (Science Citation Index Expanded). We used the following search terms: “cancer,” “neoplasm,” “diabetes mellitus or diabetes,” “metformin,” “mortality,” “survival,” and “prognosis.” A manual search was performed for references cited in the selected articles and in the selected reviews. Articles for which the abstract or full text was not available in English were excluded after review. The search included studies up to January 2017.

We included both observational studies and clinical trials of patients with concurrent cancer at any site and diabetes that evaluated the effect of metformin treatment on mortality. All included studies defined glucose-lowering drug exposure (metformin or nonmetformin: insulin, sulfonylureas, thiazolidinedione, and other medications) in subgroups and further compared metformin-treated patients with non-metformin-treated patients (either patients on other glucose-lowering drugs and/or diabetic patients not on pharmacological treatment regimens). The criteria for excluding studies in the present analyses were 1) studies that did not provide an adjusted hazard ratio with an estimated 95% confidence interval, 2) studies that included nondiabetic patients in the nonmetformin group, 3) studies that included patients with type I diabetes mellitus, 4) diabetes was diagnosed after enrollment in the analysis, or 5) the patients did not have cancer at the baseline reading. Two investigators independently extracted the following data from each of the included studies: first author, region of study, publication year, study period, study design, cancer site, length of follow-up, glucose-lowering drug treatment (metformin or nonmetformin exposed), adjustment covariates, and adjusted estimates. A third investigator reviewed the extracted data. Group discussion was used to resolve any discrepancies in the course of article selection and data extraction.

Statistical Analysis

We used adjusted Cox proportional hazard ratios for the quantitative analysis, and we calculated the combined hazard ratios for ACM and CSM in patients with cancer and diabetes treated with or not treated with metformin. Subgroup analyses according to specific cancer sites and country were performed when at least two studies were available and clinical evaluation permitted a meta-analysis. Heterogeneity across studies was estimated by the χ^2 test and the I^2 statistic, and correct effect models were chosen accordingly. Statistically significant heterogeneity was defined as an I^2 greater than 50% or a χ^2 P value of less than .1 (www.nature.com/nrc/journal/v3/n7/glossary/nrc1125_glossary.html) (21). If significant heterogeneity was observed, the summary estimation was based on a random-effects model according to the DerSimonian and Laird method (22). If significant heterogeneity was not observed, we reported the summary estimation results on the basis of a fixed-effects model. Potential publication bias was assessed using Egger tests. All statistical analyses were conducted using STATA software version 14.0 (StataCorp, College Station, TX). A two-sided P value of less than .05 was considered significant for all analyses except for the heterogeneity tests.

Results

Meta-analysis Database

Figure 1 shows the flow chart for study selection. Initially, 3079 articles were retrieved from the computerized bibliographic databases, of which 2014 were duplicates. After title screening, 175 studies were recommended for abstract review. Studies that did not report the mortality information and studies that were reviews, commentaries, or meta-analyses were excluded from our analysis. Of the abstracts reviewed, 70 studies were eligible for further full-text review. We further excluded studies that 1) were reviews or meta-analyses, 2) were experimental studies, 3) did not provide the abstract in English, 4) did not provide sufficient statistical details in the abstract, or 5) did not report mortality information. After full-text review, we finally included 42 studies in total, which consisted of 26 studies that reported the ACM (12–17,20,23–41), one study that reported the CSM (42), and 15 studies that presented both measures (18,19,43–55). Two studies included all cancer sites (35,39), nine studies reported on breast cancer (23,30,40,42–44,47,52,55), seven studies reported on colorectal cancer (25,27,34,45,50,51,53), five studies reported on lung cancer (14–17,41) and prostate cancer (37,46,48,49,54), four studies reported on pancreatic cancer (24,28,31,33), three studies reported on liver cancer (26,29,38),

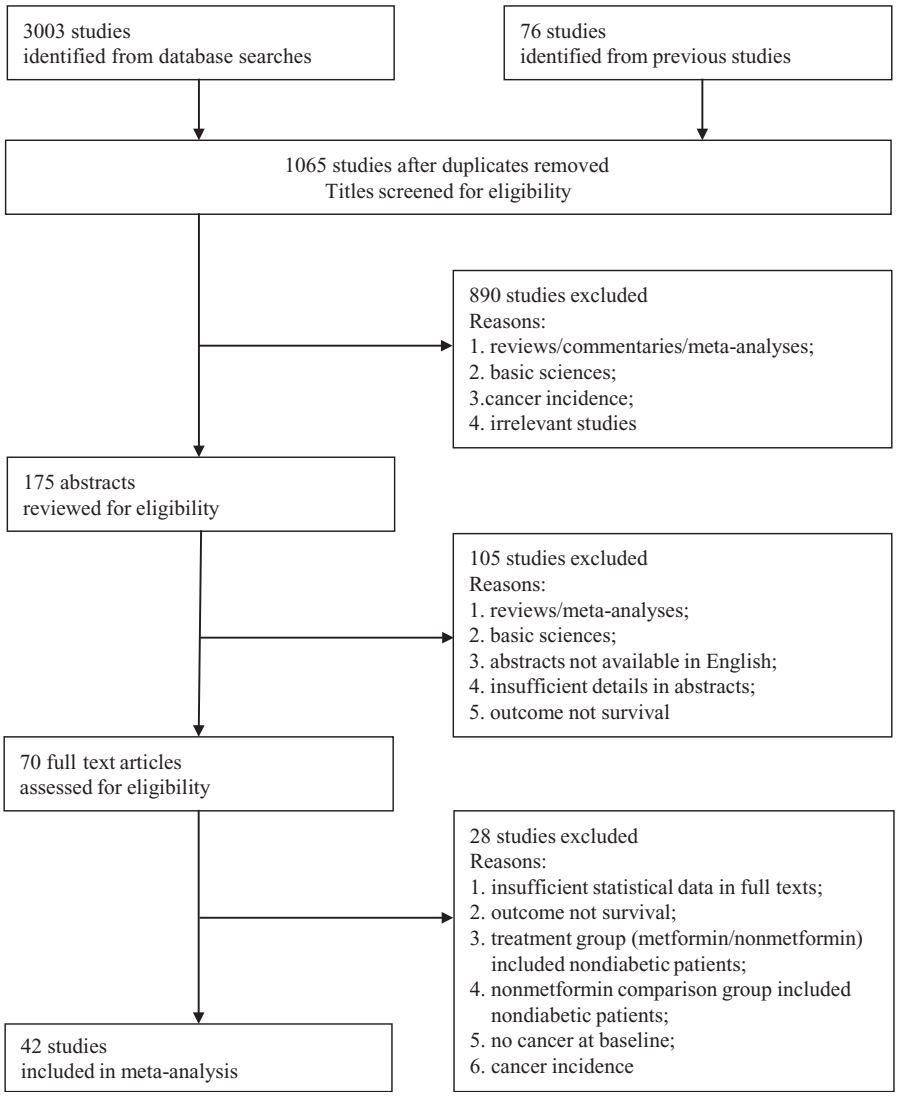

Figure 1. Flow diagram showing inclusion and exclusion criteria for the studies.

two studies reported on ovarian cancer (32,36) and endometrial cancer (12,13), and one study each reported on bladder (18), kidney (19), and laryngeal cancers (20). Among the 42 studies, which consisted of 37 015 cases, 18 977 cases received metformin alone or in combination with other glucose-lowering regimens, and the remaining 18 038 cases received nonmetformin therapy, such as insulin, sulfonylurea, thiazolidinedione, or other medications. The detailed characteristics of the included studies are shown in Table 1.

All-Cause Mortality

Forty-one studies were available for inclusion in the ACM analyses based on metformin treatment in diabetic patients with cancer, of which 23 studies reported a reduction in ACM (13–17,20,25,28,32–35,37–40,43,47,48,51,53–55), 16 studies found no correlation (12,18,19,23,24,27,29–31,36,44–46,49,50,52), and two studies reported an increase in ACM (26,41). Our meta-analysis demonstrated that diabetic cancer patients who were treated with metformin displayed a significantly reduced risk of ACM compared with those who did not receive metformin (random-effects model, pooled hazard ratio [HR] = 0.73, 95% confidence interval [CI] = 0.68 to 0.79, $P < .001$). We observed statistically significant heterogeneity in our analysis ($I^2 = 78.1\%$, $P < .001$). The details of our analysis are summarized in Figure 2. The results of an Egger test suggested the possible presence of publication bias ($P = .006$).

In addition, we performed subgroup analyses for the cancer sites, for which we had at least two studies available.

Colorectal Cancer

Data on colorectal cancer were available from seven studies (25,27,34,45,50,51,53). Four studies found a significant reduction in ACM in metformin-treated patients (25,34,51,53), whereas the other three studies found no reduction in ACM (27,45,50). Subgroup analyses demonstrated that metformin treatment was associated with a 22% reduction in ACM relative to nonmetformin treatment, and this difference reached statistical significance (random-effects model, pooled HR = 0.78, 95% CI = 0.67 to 0.90, $P = .001$) (Figure 2). We also observed evidence of heterogeneity in this cohort ($I^2 = 56.7\%$, $P = .031$).

Table 1. Summary characteristics of included studies*

Study (country)	Year (study period)	Study design	Cancer site	Follow-up time	Treatment comparison, No.	Adjustment variables	ACM	CSM
Fransgaard et al. (Denmark)	2016 (2003–2012)	Retrospective case–control study	Colorectal cancer	No reported	Met: 1962 Insulin: 388	Age, sex, ASA score, BMI, blood transfusions, smoking, alcohol consumption, elective or emergency surgery, cancer site, T stage, lymph node status, distant metastasis	Y	N
Choi et al. (Korea)	2016 (2003–2010)	Retrospective case–control study	Pancreatic cancer	10.2 mo (median)	Met: 56 Other meds: 127	None reported	Y	N
Chaiteerakij et al. (USA)	2016 (2000–2011)	Retrospective cohort study	Pancreatic cancer	9.26 mo (median)	Met: 366 Other meds: 614	Age, sex, BMI, pancreatic cancer diagnosis year group, stage	Y	N
Hilli et al. (USA)	2016 (1999–2008)	Retrospective case–control study	Endometrial cancer	4.3 y (median)	Met: 116 Other meds: 161	Age, BMI, pulmonary dysfunction, prior cardiac, vascular disease, smoking, ASA score, endometrioid histology, FIGO grade/stage, residual disease, tumor diameter, LVS/cervical stromal/myometrial invasion, adnexal/serosal involvement, positive peritoneal cytology, operative complexity, extent of LND, adjuvant therapy	Y	N
Menamin et al. (UK)	2016 (1998–2009)	Retrospective cohort study	Colorectal cancer	4 y (mean)	Met: 675 Other meds: 522	Age, sex, year of diagnosis, deprivation, cancer site, stage, surgery, radiotherapy, chemotherapy, comorbidities, other antidiabetic meds, other meds usage	Y	Y
Gardini et al. (Italy)	2015 (2008–2014)	Retrospective case–control study	Hepatocellular carcinoma	No reported	Met: 31 Insulin: 11	Age, sex, smoking habits, etiology	Y	N
Lin et al. (USA)	2015 (2007–2009)	Retrospective cohort study	Lung cancer (non–small cell lung cancer)	No reported	Met: 458 Other meds: 292	Age, sex, marital status, race/ethnicity, income, diabetes severity index score, comorbidity score, diabetes medications, histology, cancer site, chemotherapy, PS	Y	N
Chen et al. (China)	2015 (2006–2014)	Retrospective cohort study	Lung cancer (non–small cell lung cancer)	No reported	Met: 44 Other meds: 46	Age, sex, smoking, stage, ECOG PS, BMI, Histological diagnosis, diabetes duration, type of EGFR mutation, EGFR-TKI	Y	N
Kong et al. (China)	2015 (2001–2011)	Retrospective cohort study	Lung cancer (combined small cell lung cancer)	68 mo (median)	Met: 120 Other meds: 139	Age, sex, neuronal specific enolase, lactate dehydrogenase, smoking, performance status, stage	Y	N
Xu et al. (China)	2015 (2000–2010)	Retrospective cohort study	Lung cancer (small cell lung cancer)	65 mo (median)	Met: 36 Other meds: 43	Age, sex, NSE, LDH, smoking, stage, performance status	Y	N
Zanders et al. (Netherlands)	2015 (1998–2011)	Retrospective cohort study	Colorectal cancer	3.4 y (mean)	Met: 666 Other meds: 377	Age, sex, year of diagnosis, cancer site, stage, treatment, sulfonylurea derivatives, insulin, other diabetes meds, statins, aspirin usage	Y	N
Vissers et al. (UK)	2015 (1998–2009)	Retrospective cohort study	Breast cancer	4.4 y (mean)	Met: 1125 Other meds: 638	Age, year of diagnosis, diabetes duration, treatment, hormone replacement therapy, comorbidity, sulphonylurea derivatives/insulin/other glucose-lowering drugs	Y	Y
			Bladder cancer	50 mo (median)	Met: 39		Y	Y

(continued)

Table 1. (continued)

Study (country)	Year (study period)	Study design	Cancer site	Follow-up time	Treatment comparison, No.	Adjustment variables	ACM	CSM
Nayan et al. (Canada)	2015 (1997–2013)	Retrospective cohort study			Other meds: 46	Age, sex, Charlson comorbidity index, extravesical disease (T3/4 or N+), neoadjuvant/adjuvant chemotherapy, surgical margin status, other oral hypoglycemics or insulin usage		
Kim et al. (Korea)	2015 (1997–2007)	Retrospective case–control study	Breast cancer	100.3 mo (median)	Met: 202 Other meds: 184	Age, BMI, tumor size, lymph node metastasis, ER/PR/HER2 status, chemotherapy and hormone therapy	Y	Y
Xu et al. (USA)	2015 (1995–2010)	Retrospective cohort study	All sites	No reported	Met: 2218/3029 Insulin: 377/1462 Other meds: 903/1629	Age, sex, race, BMI, tobacco use, insulin use, cancer type, and Charlson index	Y	N
Psutka et al. (USA)	2015 (1994–2008)	Retrospective cohort study	Renal cell cancer	8.1 y (median)	Met: 83 Other meds: 200	Age, sex, smoking, chronic kidney disease stage, ECOG PS, Charlson score, obesity, histology, T status, N status, grade, coagulative tumor necrosis, sarcomatoid differentiation	Y	Y
EI-Benhawy et al. (Egypt)	2014 (2008)	Retrospective case–control study	Breast cancer	46 mo (median)	Met: 25 Other meds: 14	Age, stage, lymph node metastasis, grade, ER/PR status	N	Y
Bhat et al. (USA)	2014 (2005–2011)	Retrospective case–control study	Hepatocellular carcinoma	No reported	Met: 56 Other meds: 207	Age, sex, etiology of chronic liver disease, Barcelona-Clinic Liver Cancer stage	Y	N
Ko et al. (USA)	2014 (2005–2010)	Retrospective cohort study	Endometrial cancer	33 mo (median)	Met: 200 Other meds: 163	Age, race, BMI, grade, histology, stage, and adjuvant treatment	Y	N
Xiao et al. (China)	2014 (2002–2006)	Retrospective cohort study	Breast cancer	70 mo (median)	Met: 275 Other meds: 405	Age, BMI, cardiovascular/cerebrovascular complications, amenorrhea, pathologic stage, lymph node, vessel carcinoma embolus, chemotherapy/endocrine regime	Y	N
Sandulache et al. (USA)	2014 (2000–2012)	Retrospective cohort study	Laryngeal squamous cell carcinoma	No reported	Met: 21 Other meds: 22	Age, stage, tumor subsite, race, smoking and drinking	Y	N
Oppong et al. (USA)	2014 (2000–2005)	Retrospective cohort study	Breast cancer	87 mo (median)	Met: 76 Other meds: 65	Age, stage, menopausal status, BMI, lymph node positivity, ER status, grade, lymphovascular invasion, years since diabetes diagnosis	Y	N
Bensimon et al. (UK)	2014 (1998–2009)	Retrospective case–control study	Prostate cancer	3.7 y (mean)	Met: 272 Other meds: 108	Alcohol use, smoking, obesity, HbA1c, sulfonylureas/thiazolidinediones/insulin/other antidiabetic meds usage, Charlson comorbidity index, PSA, Gleason score, prostatectomy, radiotherapy, chemotherapy, and androgen deprivation therapy	Y	Y
Kaushik et al. (USA)	2014 (1997–2010)	Retrospective case–control study	Prostate cancer	5.1 y (median)	Met: 323 Other meds: 562	Age, BMI, Gleason score, stage, soft tissue margin, preoperative PSA, statins usage and treatment	Y	Y
Hwang et al. (UK)	2013 (2003–2010)	Retrospective cohort study	Pancreatic cancer	118 305 patient-days	Met: 247 Other meds: 269	Age, sex, duration of diabetes, diabetic complications, history of pancreatitis, Charlson index, BMI, GFR,	Y	N

(continued)

Table 1. (continued)

Study (country)	Year (study period)	Study design	Cancer site	Follow-up time	Treatment comparison, No.	Adjustment variables	ACM	CSM
						smoking, insulin/sulfonylurea/thiazolidinedione usage, and HbA1c		
Spillance et al. (Ireland)	2013 (2001–2006)	Retrospective cohort study	Colorectal cancer	No reported	Met: 207 Other meds: 108	Age, tumor stage, tumor grade, year of diagnosis, comorbidity score, aspirin use, exposure to other antidiabetic meds, socioeconomic status, and radiation therapy	Y	Y
Margel et al. (Canada)	2013 (1997–2008)	Retrospective cohort study	Prostate cancer	4.64 y (median)	Met: 1619 Other meds: 2218	Age, tumor grade, tumor volume, treatment, androgen-deprivation therapy, socioeconomic status, Johns Hopkins Adjusted Clinical Groups Case-Mix System weighted sum of adjusted diagnostic groups, year of cohort entry, COX-2 inhibitors/statins/antidiabetic drug usage	Y	Y
Lega et al. (Canada)	2013 (1997–2008)	Retrospective cohort study	Breast cancer	4.5 y 3.7 y (mean)	Met: 1094 Other meds: 1267	Age, sulfonylurea/insulin/thiazolidinediones use, duration of diabetes, comorbidity score, treatments, and exposure to glucose-lowering drugs before breast cancer diagnosis	Y	Y
Peeters et al. (Denmark)	2013 (1996–2008)	Retrospective case–control study	Breast cancer	2971 person-years	Met: 508 Other meds: 550	Age, Charlson score, year of diagnosis, sulfonylureas/thiazolidinediones other antidiabetic meds usage, hormone replacement therapy, statin usage	Y	Y
Kumar et al. (USA)	2013 (1995–2010)	Retrospective case–control study	Ovarian cancer	No reported	Met: 72 Other meds: 103	Age, year of diagnosis, BMI, disease stage, histology, chemotherapy, and grade	Y	N
Cossor et al. (USA)	2013 (1993–2005)	Retrospective cohort study and clinical trials	Colorectal cancer	4.1 y (median)	Met: 84 Other meds: 128	Propensity score model: age, race, BMI, smoking status, alcohol use, dietary history, physical activity level, stage, insulin use, total number of diabetic meds, aspirin/NSAID use	Y	Y
Spratt et al. (USA)	2013 (1992–2008)	Retrospective cohort study	Prostate cancer	8.7 y (median)	Met: 157 Other meds: 162	Age, PSA, T stage, Gleason score, diabetic status, and androgen-deprivation therapy use	Y	Y
Garrett et al. (USA)	2012 (2004–2008)	Retrospective cohort study	Colorectal cancer	No reported	Met: 208 Other meds: 216	Age, sex, race, BMI, aspirin usage, and tumor/node/metastatic staging	Y	N
Sadeghi et al. (USA)	2012 (2000–2009)	Retrospective cohort study	Pancreatic cancer	11.4 mo (median)	Met: 117 Other meds: 185	Tumor size, tumor site, stage, CA19-9, performance status	Y	N
Lee et al. (Korea)	2012 (2000–2008)	Retrospective cohort study	Colorectal cancer	41 mo (median)	Met: 258 Other meds: 337	Age, sex, stage, BMI, diabetes duration, smoking status, HbA1c level, use of aspirin, use of insulin/sulfonylurea/thiazolidinediones	Y	Y
He et al. (USA)	2012 (1998–2010)	Retrospective cohort study	Breast cancer	47.6 mo (median)	Met: 88 Other meds: 66	Age, BMI, stage, ER/PR status, insulin/insulin secretagogue/thiazolidinedione usage	Y	Y
Bayraktar et al. (USA)	2012 (1995–2007)	Retrospective cohort study	Breast cancer	62 mo (median)	Met: 63 Other meds: 67	Age, T stage, N stage, nuclear grade, lymphovascular invasion, chemotherapy	Y	N
Romero et al. (USA)	2012 (1992–2010)	Retrospective cohort study	Ovarian cancer	63 mo (median)	Met: 16 Other meds: 28	Age, BMI, creatinine, residual implant, histological type, grade, stage	Y	N

(continued)

Table 1. (continued)

Study (country)	Year (study period)	Study design	Cancer site	Follow-up time	Treatment comparison, No.	Adjustment variables	ACM	CSM
Currie et al. (UK)	2012 (1990–2009)	Retrospective cohort study	All sites	1.6 y (median)	Met: 1428 Sulfonylurea: 1519 Insulin: 654	Age, sex, smoking status, Charlson comorbidity index, and year of cancer diagnosis	Y	N
Mazzone et al. (USA)	2012 (1978–2010)	Retrospective case–control study	Lung cancer	No reported	Met: 184 Other meds: 323	Age, stage	Y	N
Chen et al. (Taiwan)	2011 (2003–2009)	Retrospective cohort study	Hepatocellular carcinoma	32.2 mo (mean)	Met: 21 Other meds: 32	Age, gender, BMI, HbA1c, positive anti-HCV antibody test, and tumor size	Y	N
He et al. (USA)	2011 (1999–2008)	Retrospective cohort study	Prostate cancer	No reported	Met: 132 Other meds: 101	Age, race, Gleason grade, stage, PSA, BMI, use of insulin/insulin secretagogues/thiazolidinediones	Y	N

*ACM = all-cause mortality; ASA = American Society of Anesthesiologists; BMI = body mass index; CSM = cancer-specific mortality; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor; ER = estrogen receptor; FIGO = International Federation of Gynecoloyg and Obstetrics; GFR = glomerular filtration rates; HCV = hepatitis C virus; LDH = lactate dehydrogenase; LND = lyphadenectomy; LVS = lymphovascular space; Met = Metformin; Meds = medications; NSAID = nonsteroidal anti-inflammatory drug; NSE = neuronal specific enolase; PR = progesterone receptor; PSA = prostate-specific antigen.

Endometrial Cancer

Two studies on endometrial cancer provided data on ACM (12,13). One study reported that the ACM of metformin-treated patients was significantly lower than that of non-metformin-treated patients (13), whereas the other study did not find a significant association (12). The pooled hazard ratio was 0.50 (95% CI = 0.32 to 0.78 by fixed-effects model, $P = .002$) (Figure 2). We observed no evidence of heterogeneity in these studies ($I^2 = 0\%$, $P = .456$).

Breast Cancer

Data on breast cancer were available from eight studies (23,30,40,43,44,47,52,55). Four studies reported that the ACM of metformin-treated patients was significantly lower than that of non-metformin-treated patients (40,43,47,55), whereas the other four studies did not find a significant association (23,30,44,52). Our analysis found that metformin treatment yielded a significantly reduced ACM compared with that of non-metformin treatment (random-effects model, pooled HR = 0.63, 95% CI = 0.49 to 0.80, $P < .001$; heterogeneity, $I^2 = 80.2\%$, $P < .001$) (Figure 2). In the Xiao et al. study, patients with all three breast cancer subtypes (luminal A/B/C) who were treated with metformin showed a significant reduction in ACM (40).

Prostate Cancer

ACM data for diabetic prostate cancer patients were reported in five studies (37,46,48,49,54). Three studies found that the ACM rate of metformin-treated patients was significantly lower than that of non-metformin-treated patients (37,48,54), whereas the other two studies did not find a significant association (46,49). Our analysis revealed that the ACM rate was significantly decreased in patients treated with metformin (pooled HR = 0.72, 95% CI = 0.56 to 0.93, $P = .011$) (Figure 2). This analysis was based on a random-effects model because we observed evidence of heterogeneity among the included studies ($I^2 = 56.5\%$, $P = .056$).

Ovarian Cancer

Two studies on ovarian cancer in diabetic patients provided ACM results (32,36). One study showed that the ACM rate of metformin-treated patients was significantly lower than that of non-metformin-treated patients (32), whereas the other study did not find a significant association (36). The pooled hazard ratio was 0.39 (95% CI = 0.22 to 0.67 by fixed-effects model, $P = .001$) (Figure 2). We observed no evidence of heterogeneity among the data ($I^2 = 0\%$, $P = .806$).

All Cancer Sites

Data on all cancer types were available from two studies, both of which showed a reduction in ACM rate in metformin-treated patients (35,39). Metformin treatment resulted in a benefit, with a pooled hazard ratio of 0.70 (95% CI = 0.65 to 0.75, $P < .001$, by fixed-effects model; heterogeneity, $I^2 = 34.5\%$, $P = .178$) (Figure 2). In the study by Xu et al., among patients from the Vanderbilt electronic health records system, metformin treatment was associated with a significant decrease in ACM rate relative to other oral hypoglycemic medications and insulin (39). The benefit of metformin was similar in patients included in a study based on the Mayo Clinic health records system (39). In a study where the data were stratified according to the category of glucose-lowering medications used, Currie et al. compared different therapies in diabetic cancer patients and found that those who received metformin therapy demonstrated a significantly decreased ACM rate relative to insulin or sulfonylurea treatment (35).

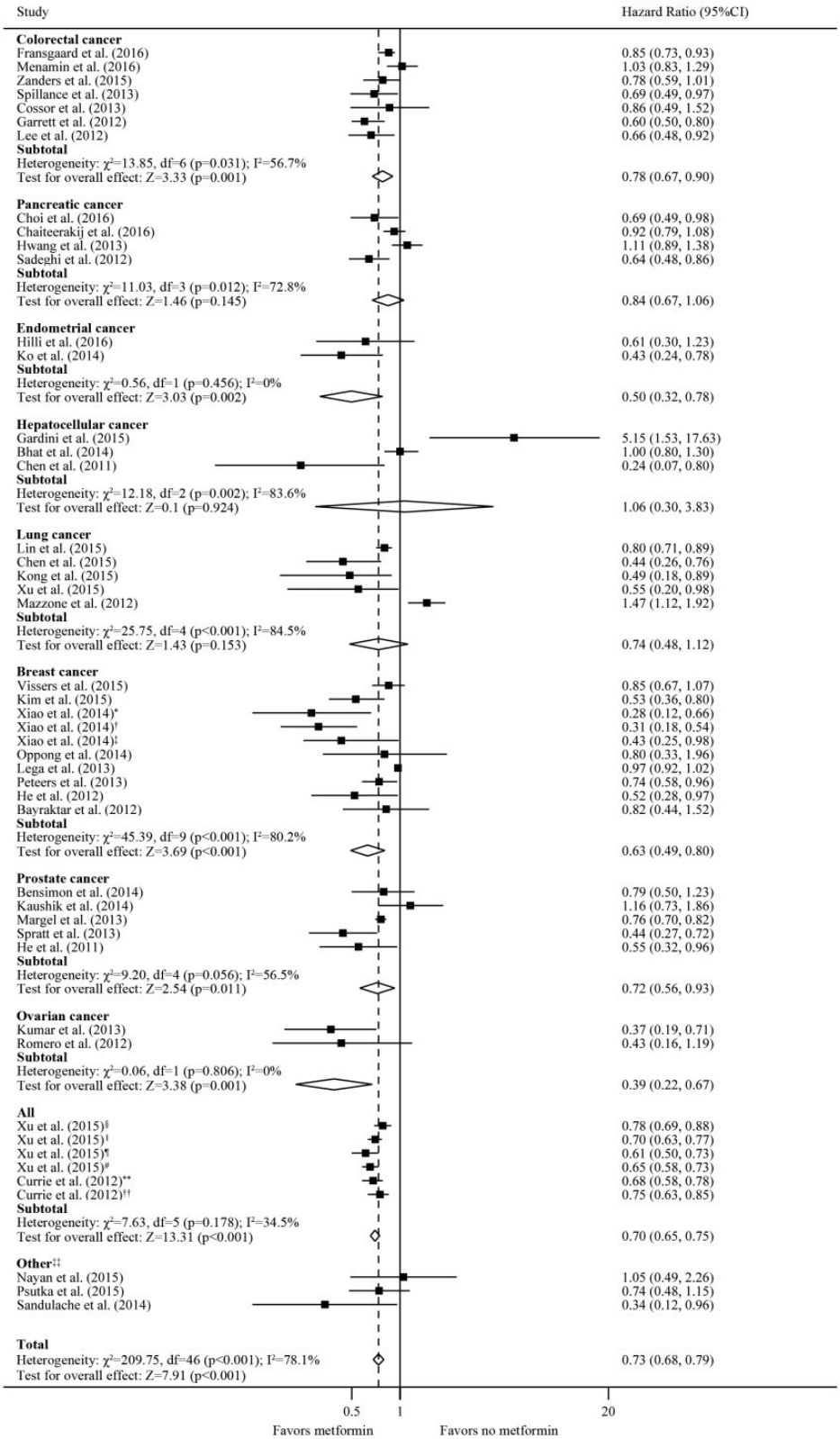

Figure 2. All-cause mortality for metformin treatment compared with nonmetformin treatment among patients with cancer and diabetes. *Breast cancer subtype luminal A. †Breast cancer subtype luminal B. ‡Breast cancer subtype luminal C. §Results from Vanderbilt electronic health records system: metformin vs other medications. ‖Results from Mayo Clinic electronic health records system: metformin vs other medications. ¶Results from Vanderbilt electronic health records system: metformin vs insulin. #Results from Mayo Clinic electronic health records system: metformin vs insulin. **Comparison between metformin and sulfonylurea. ††Comparison between metformin and insulin. ‡‡Includes bladder cancer, kidney cancer, and laryngeal cancer. CI = confidence interval; HR = hazard ratio.

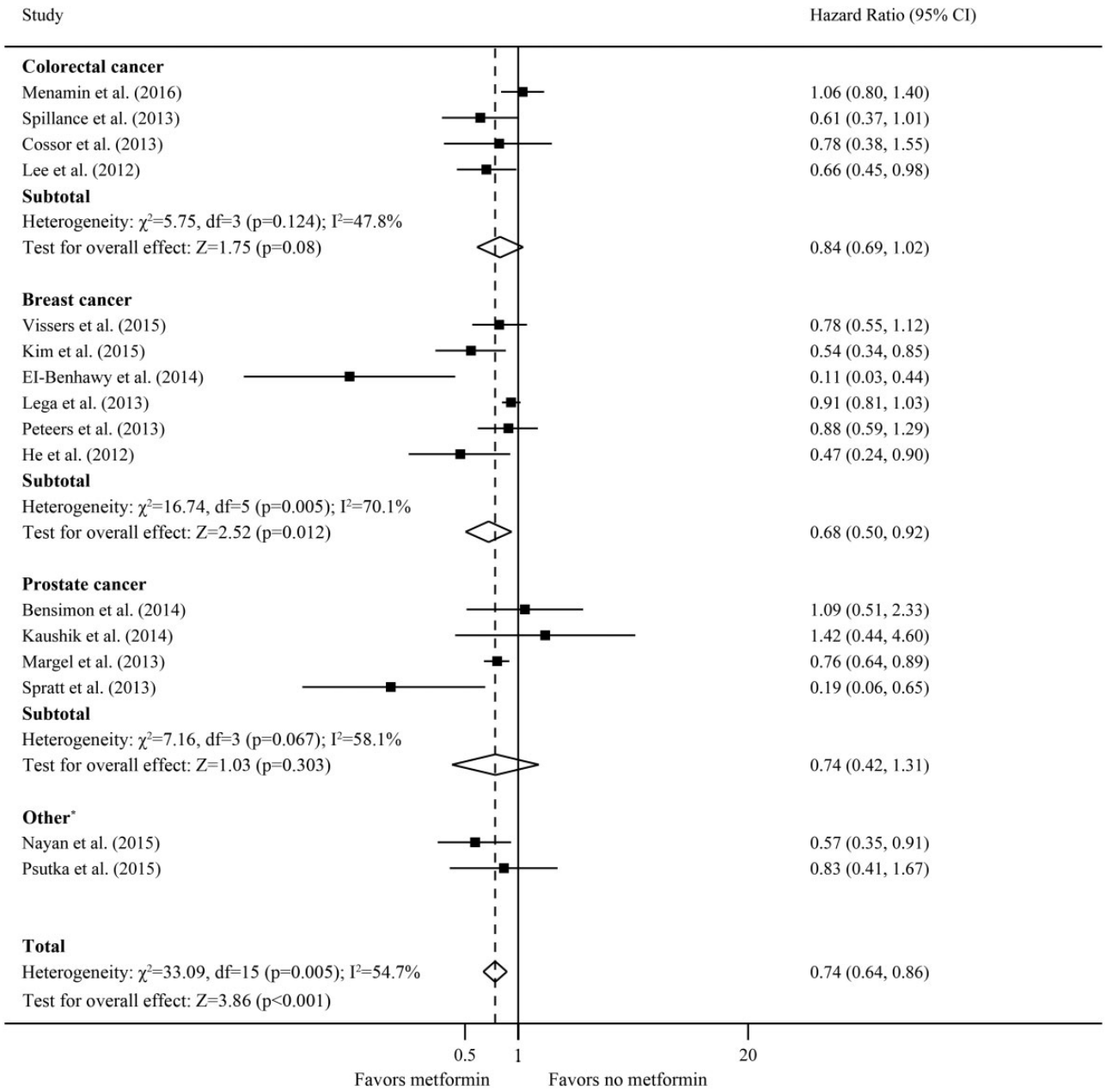

Figure 3. Cancer-specific mortality for metformin-treated patients compared with non-metformin-treated patients among patients with cancer and diabetes. *Includes bladder cancer and kidney cancer. CI = confidence interval; HR = hazard ratio.

Our results did not identify a significant correlation between metformin treatment and a reduction in ACM rate in diabetic patients with pancreatic cancer, hepatocellular cancer, or lung cancer.

In the subgroup analyses by country, a significant reduction in ACM rate was observed in metformin-treated patients in Asian countries (fixed-effects model, pooled HR = 0.50, 95% CI = 0.41 to 0.62, $P < .001$) and Western countries (random-effects model, pooled HR = 0.78, 95% CI = 0.72 to 0.84, $P < .001$).

Cancer-Specific Mortality

Of the 16 studies that reported CSM data only, seven studies reported a reduction in CSM rate in metformin-treated patients (18,42,43,48,53–55), and nine studies found no association between metformin treatment and CSM rate in diabetic cancer patients (19,44–47,49–52). Our meta-analysis revealed that diabetic cancer patients who were treated with metformin demonstrated a significantly reduced risk of CSM compared with those who did not receive metformin (random-effects model, pooled HR = 0.74, 95% CI = 0.64 to 0.86, $P < .001$). We observed statistically significant heterogeneity in this analysis ($I^2 = 54.7\%$, $P = .005$). The details of this analysis are summarized in Figure 3. Publication bias was not observed based on an Egger test ($P = .586$).

In the CSM subgroup analysis by cancer site, metformin treatment was significantly associated with a reduction in CSM rate for diabetic patients with breast cancer (random-effects

model, pooled HR = 0.68, 95% CI = 0.50 to 0.92, P = .012; heterogeneity, I^2 = 70.1%, P = .005) (Figure 3). A reduction in CSM rate for metformin-treated patients was also observed in our country subgroup analyses for Asian countries (fixed-effects model, pooled HR = 0.61, 95% CI = 0.45 to 0.82, P = .001) and Western countries (random-effects model, pooled HR = 0.77, 95% CI = 0.65 to 0.90, P = .002).

Discussion

Since 2010, investigations on metformin use and cancer mortality have expanded considerably. A series of previous research studies and meta-analyses have suggested that metformin might modulate the clinical outcomes of diabetic cancer patients, whereby patients treated with metformin demonstrated significantly lower ACM and/or CSM rates than those who used other antidiabetic medications. Recently, the results of some studies seemed to contradict these reports, and conflicting data were reported based on differences in cancer type. Menamin et al. found no evidence of an association between metformin usage and mortality in a cohort of 1197 patients with diabetes and colorectal cancer (45). The findings of Chaiteerakij et al. showed no difference in mortality between metformin exposure and nonmetformin exposure in diabetic patients with pancreatic cancer (24). Additionally, in studies on bladder cancer (18) and renal cell cancer (19), the results seemed to indicate no effect of metformin usage. In the present study, we included research studies on all cancer types in patients with diabetes that have been reported so far to provide further up-to-date evidence on the effect of metformin on ACM and CSM rates.

Based on data from 42 studies, we showed 27% and 26% reductions in ACM and CSM rates in patients with cancer and diabetes who used metformin. In the stratified analyses by cancer site, we demonstrated that metformin exposure yielded a significantly lower ACM than other antidiabetic medications in colorectal cancer, endometrial cancer, breast cancer, prostate cancer, and ovarian cancer. Metformin usage was also associated with a significant reduction in CSM for breast cancer. In our subgroup analyses by country (Asian or Western countries), decreases in ACM and CSM rates were found for Asian and Western patients treated with metformin. However, stratified analysis by country represents a rough evaluation of ethnicity because, while most patients in the studies from Western countries were white, some Asian or African ethnicity could have been included in the analytic population. Unfortunately, we were unable to perform further analyses by ethnicity because these details were unavailable.

Notably, in the subgroup analyses of lung cancer, the study conducted by Mazzone et al. concluded that diabetic cancer patients who received metformin could have a much higher ACM rate (41). In contrast, the other four studies in the data pool identified evidence of a positive effect of metformin treatment on ACM rate (14–17). Several possibilities could explain discrepancies such as this. First, differences in control variables could bias the results between the studies. For example, in the multivariable analyses in the study by Mazzone et al. (41), the risk estimates were corrected for only age and stage, whereas the risk estimates in the other four studies by Lin et al. (16), Chen et al. (14), Kong et al. (15), and Xu et al. (17) were adjusted for the type of epidermal growth factor receptor (EGFR) mutation, level of neuronal specific enolase and lactate dehydrogenase, performance status, and chemotherapy. Second, Chen et al. (14) and Lin et al. (16) included only non–small cell lung cancer (NSCLC) cases, and Xu et al. (17) included only small cell lung cancer (SCLC) cases, whereas Mazzone et al. included patients with NSCLC, SCLC, and other histological subtypes (41). In breast cancer, the salutary effect of metformin had been observed in five studies. Kim et al. (43) found a survival benefit for human epidermal growth factor receptor 2 (HER2)–positive and hormone receptor–positive patients with metformin exposure, and He et al. (55) noted that metformin users were associated with better clinical outcomes than nonusers in diabetic patients with HER2-positive breast cancer. In ALTTO Phase III Randomized Trial, Sonnenblick et al. reported that metformin may improve the worse prognosis in diabetic patients with primary HER2-positive and hormone receptor-positive breast cancer (56). In the Xiao and colleagues study (40), patients with luminal A/B/C subtypes who were treated with metformin showed a significant reduction in mortality, whereas the other two studies included all types of breast cancer (42,47). Thus, the unknown and potential interactions between metformin, different histological cancer subtypes, and genetic biomarkers could influence the clinical outcomes of these populations; these possibilities merit additional research.

Glucose-lowering treatments are modified depending on glucose levels and side effects, which means the details of metformin usage (duration and dosage) do not accurately represent ongoing exposure status during the follow-up. The inclusion of time-dependent cumulative variables and dose-response variables for metformin exposure are important to further evaluate whether metformin exposure influences the clinical outcomes of patients with cancer and diabetes (57). In prostate cancer, Margel et al. demonstrated that the cumulative duration of metformin treatment was associated with a significant improvement in ACM and CSM rates, and that every additional six months of metformin results in a 24% decrease in CSM and a significant decrease in ACM (48). In colorectal cancer, cumulative metformin exposure did not correlate with ACM (27). In breast cancer, Lega et al. found no significant association between the cumulative duration of metformin use and ACM and CSM (52), whereas Vissers et al. and Peeters et al. both reported a cancer-specific survival benefit for patients who had cumulative metformin exposure (44,47). When we focused on the relationship between dose response and mortality, Menamin et al. demonstrated no evidence of a significant association between colorectal cancer–specific mortality and metformin use by increasing the number of prescriptions (45). To date, few studies have used the above-mentioned methods for modeling metformin treatment, and we think that further investigations are required to address this issue.

Cancer and diabetes are being diagnosed within the same individuals with increasing frequency (2). Researchers have revealed that the relationship between cancer and metformin treatment is complex, and factors that affect one or more parts of the network could be associated with cancer mortality. In laboratory studies, metformin has been shown to inhibit cell proliferation, reduce colony formation, and cause partial cell cycle interruption in several cancer cell lines (58–60). These research studies suggest that metformin-induced activation of AMPK pathways may inhibit downstream cellular growth and proliferation in tumor cells, at least through inhibiting protein synthesis to some extent (10,58). Metformin regulates insulin levels by ameliorating insulin sensitivity (1). Additional in vivo studies have found that metformin exerts less antitumor activity in mice receiving a control diet than it does in mice receiving a high-energy diet (61). This finding suggests that the reduction in endogenous insulin levels by metformin may contribute to

its antitumor activity (9). Other in vitro studies have reported similar findings that metformin may kill cancer cells, reduce cancer burden, and enhance the effectiveness of breast cancer treatment (62–64). In an observational study by Jiralerspong et al., the authors reported a higher pathologically complete response for patients who had metformin treatment compared with those who had nonmetformin treatment in early-stage breast cancer patients receiving neo-adjuvant therapy (65). On the basis of the growing evidence of the anticancer mechanisms of metformin in preclinical studies, along with the results of retrospective analyses focused on the associations between metformin and mortality, metformin has been considered a potential adjunctive cancer therapy (66). Moreover, at least 20 randomized controlled trials (RCTs) have been initiated to further evaluate the efficacy of metformin in cancer treatments (67). We think that the results of those RCTs are needed before making general recommendations or launching large-scale clinical efforts.

Several limitations are associated with our meta-analysis. First, the designs of the included retrospective studies differed, and the adjusted estimates we used were not adjusted by the same variables. All of these factors could have caused heterogeneity among the studies. Although we applied a random-effects model that takes potential heterogeneity into consideration, careful interpretation of the heterogeneity is necessary. Second, publication bias suggested by Egger's tests could be the result of small study effects rather than true publication bias, especially in the presence of significant heterogeneity among studies (68). Third, as we know, time-related biases could affect the results observed with a drug. These biases are known to exaggerate downward the effect of a drug, thus making a drug seem to be protective when in fact it may have no effect (69). In the present data pool, many studies have not considered time-related biases. Thus, careful interpretation is necessary. Although our findings should be interpreted cautiously, our results nevertheless raise a critical point regarding the debate on whether anticancer and metformin treatment is superior for diabetic cancer patients. Additionally, grouping patients according to metformin treatment or nonmetformin treatment could be an oversimplified comparison. Most patients with cancer and diabetes received one or more glucose-lowering medications and other medications with dosage changes during the follow-up period. It is extremely difficult to evaluate the effect of intricate interactions among various medications on clinical outcomes. In general, our meta-analysis was based on abstracted data and not on individual patient data (IPD). An IPD-based meta-analysis would provide a more robust estimation of the relationship between metformin usage and mortality (70). Therefore, one needs to carefully interpret our results, especially for the positive associations in the stratified analyses.

In conclusion, our results provide an overview of recent evidence on the effects of metformin treatment in diabetic cancer patients, which demonstrate an association between metformin exposure and reduced ACM and CSM rates in diabetic cancer patients. However, due to some limitations, our results should be interpreted cautiously. Further prospective, high-quality studies on the effect of metformin treatment in diabetic cancer patients will be needed to confirm our findings.

Notes

Author contributions: conception and design: XC, YPW, XW; collection and assembly of data: XC, YPW, JW, KYL, XW; data analysis and interpretation: XC, YPW, JW, KYL, XW; manuscript writing: XC, YPW, JW, KYL, XW; final approval of manuscript: XC, YPW, JW, KYL, XW.

The authors have no conflicts of interest to declare.

Our manuscript has been edited for proper English language, grammar, punctuation, spelling, and overall style at American Journal Experts (Certificate Verification Key: 85BE-7FBA-F338-1830-4FFA).

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