

## The Effect of Metformin on Mortality Following Cancer among Patients with Diabetes

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### Abstract

Diabetes may be a risk factor for cancer and is associated with worse cancer outcomes. Metformin may reduce cancer risk; however, its effect on mortality following cancer remains less clear. EMBASE and Medline were searched through February 10, 2014, for studies reporting an adjusted risk estimate for the effect of metformin therapy on mortality following cancer among diabetic patients. Random-effects models were used to obtain summary HR for the association between metformin and all-cause and cancer-specific mortality. Twenty-one observational studies were meta-analyzed in the primary analysis. Metformin was associated with a reduction in all-cause mortality [HR, 0.73; 95% confidence intervals (CI), 0.64–0.83] and cancer-specific mortality (HR, 0.74; 95% CI, 0.62–0.88). Subgroup analyses by cancer site showed a significant reduction in mortality for colon cancer (four studies, HR, 0.65; 95% CI, 0.56–0.76) but not for breast and prostate cancers. Observational studies indicate that metformin exposure at cancer diagnosis may be associated with a reduction in mortality. However, these findings need to be interpreted with caution as methodologic limitations of individual studies may have introduced biases in these findings. Our results emphasize the need for well-designed studies to further understand the relationship between metformin and survival following cancer. *Cancer Epidemiol Biomarkers Prev*; 23(10); 1974–84. ©2014 AACR.

### Introduction

Diabetes has been associated with a higher risk of certain cancers and worse cancer outcomes (1). Pre-existing diabetes may increase the risk of mortality by as much as 40% in patients with cancer, as compared with no diabetes (2). With nearly 20% of patients with cancer concurrently having diabetes (3), this represents a large and growing population of patients with cancer who are at risk of worse outcomes.

The increased risk of death following cancer among patients with diabetes has been attributed to lower cancer screening rates, more advanced stage at diagnosis, and less aggressive cancer treatments being offered (4, 5). Furthermore, type II diabetes is characterized by insulin resistance and compensatory

hyperinsulinemia, which may also affect cancer outcomes. Elevated insulin levels have been shown to increase tumor proliferation rates and, in some settings, increase the risk of cancer progression and metastases (6–8).

Metformin is a glucose-lowering agent that improves insulin sensitivity and lowers circulating insulin in patients with type II diabetes. It is the most commonly prescribed drug for type II diabetes and is recommended as first-line therapy (9). There is mounting epidemiologic evidence that metformin is associated with a reduction in cancer incidence (10, 11). Metformin is hypothesized to reduce cellular growth and proliferation both indirectly, by lowering insulin levels, and directly via the AMPK/mTOR pathways (12, 13). These findings have led to interest in the potential role of metformin as an adjunct to standard therapy for patients with cancer. Metformin exposure has been associated with improved surrogate prognostic markers in patients with breast cancer, such as pathologic complete response following chemotherapy (14) and decreased cellular proliferation following surgery (15, 16). Several observational studies have also examined the association between metformin and cancer mortality. However, interpretation of those findings has been difficult due to variations in the definitions of metformin exposure, the populations studied, and methodologic quality of studies. Two recent meta-analyses have summarized the existing studies on metformin and cancer

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doi: 10.1158/1055-9965.EPI-14-0327

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mortality (17, 18); however, neither review focused on the methodologic concerns of these observational studies, namely, the risk of time-related and selection biases (19). Our objective was to systematically summarize the data about the association between metformin and all-cause mortality in patients with diabetes and cancer, while carefully identifying studies that attempted to minimize important biases. Our secondary objective was to summarize the association between metformin and cancer-related mortality, as well as to summarize the association by cancer site.

## Materials and Methods

We used a search strategy developed in consultation with an information specialist and searched EMBASE and MEDLINE databases from their inception to identify pertinent articles published as of February 10, 2014. Our search strategy included terms for diabetes, cancer, metformin, mortality, and prognosis. We did not use any date or language restrictions. Once we retrieved articles of interest, we also manually reviewed bibliographies and identified further eligible studies.

We included all studies of diabetic patients with cancer at any site that evaluated the effect of metformin therapy on mortality. We searched for both observational studies and randomized controlled trials. Given that diabetes is associated with higher cancer mortality (2), we limited our review to studies that were conducted within a population who had diabetes to separate drug effects from the effects of diabetes.

All included studies evaluated patients with cancer with at least a subset of diabetic patients exposed to glucose-lowering therapies. The primary exposure of all included studies was metformin and the primary outcome was all-cause mortality in cancer population. All included studies clearly defined glucose-lowering drug exposure (metformin, insulin, sulfonylureas, thiazolidinediones, acarbose, dipeptidyl-peptidase IV inhibitors, and glucagon-like-peptide-1 agonists) in grouped or separate categories. We included studies that compared, among diabetic patients, metformin exposed with nonexposed patients. Thus, comparator groups were either patients on other glucose-lowering drugs and/or patients with diabetes not on pharmacologic treatment (i.e., diet controlled). To be included, study had to report an adjusted risk estimate (either HR or OR) with an estimate of precision (95% confidence intervals; CI).

Studies that included nondiabetic patients in the non-metformin comparator group, studies where the results specifically for diabetic patients could not be ascertained, studies of patients who had type I diabetes, or in whom diabetes was diagnosed after cohort entry, and studies of children (<18 years of age) were excluded. Furthermore, studies where patients were diagnosed with cancer subsequent to study entry were also excluded. When more than one publication of a study population existed, we

included either the largest study or the most recent publication. We did not include case reports, case series, commentaries, reviews, letters, abstracts, or unpublished data in our review.

Two reviewers (I.C. Lega and D. Margel) independently assessed the eligibility of studies to be included. Data from included studies were abstracted independently by each reviewer into a data abstraction form. Both reviewers assessed the risk of bias among included studies. A third reviewer (Wei Wu, Women's College Research Institute, Women's College Hospital) performed the data abstraction and risk of bias assessment on results from an updated search. As we only retrieved observational studies through our search, we used the Newcastle-Ottawa Scale (NOS) for assessing the risk of bias in observational studies (20). The NOS scale was developed for cohort studies and uses a star system to evaluate three domains: selection of study groups, comparability of groups, and ascertainment of either exposure or outcome (according to study design). In cases where authors had not reported on a criterion, we contacted the authors to obtain the missing information. Discrepancies were resolved by consensus and involvement of a third reviewer (L.L. Lipscombe).

We performed a meta-analysis using Review Manager 5.1 software and combined HRs that reported on risk of mortality, both overall and cancer-specific, for individuals with diabetes ever or never exposed to metformin. Studies that did not report an adjusted HR were excluded from the review and analysis. If an article reported estimates for both site-specific and overall cancer, we used the overall cancer estimate for the primary meta-analysis and the site-specific estimate for site-specific meta-analyses. For one study, we combined risk estimates from analyses that compared metformin monotherapy with insulin monotherapy and sulphonylurea monotherapy separately to obtain the HR to be included in the meta-analysis (21). Heterogeneity was assessed using the Q test and the  $I^2$  statistic. Publication bias was assessed using a funnel plot. As we anticipated clinical heterogeneity, we used a random-effects model (DerSimonian and Laird) that accounts for variability both within and between studies. Subgroup analyses on specific cancer sites were performed for cancer sites when at least three estimates were available and clinical evaluation permitted meta-analysis (colorectal, breast, and prostate).

To test the robustness of our findings, we performed the following four sensitivity analyses. First, we excluded studies that did not adjust for cancer stage at diagnosis because stage is well-known predictor of mortality. Second, we analyzed results from studies that adjusted for diabetes severity (HbA1c or diabetes duration) separately because this variable is associated with both choice of diabetes treatment and mortality. Third, to assess for methodologic heterogeneity, we excluded studies that scored 6 points or less on the NOS. Finally, we reported separate estimates for cancer

sites with at least three estimates available (prostate, colon, and breast).

## Results

Our literature search yielded 1,172 articles, of which 109 were duplicates (Fig. 1). Most studies were excluded because metformin was not the primary exposure or because overall mortality was not the primary outcome. Other articles were excluded for being commentaries, case reports, or reviews. From the initial abstracts reviewed, 51 studies were deemed eligible for inclusion and were reviewed in detail. We excluded studies that only reported on cancer-specific mortality or studies that included nondiabetic patients in the "no metformin" comparison group. Among them, we identified 24 initially for inclusion, but after further review, three of these studies were excluded because the study population did not have cancer at baseline (22–24). In these studies, the effect of metformin on cancer incidence cannot be separated from its effect on cancer mortality. Our final sample included 21 studies for inclusion in our review and meta-analysis (Fig. 1).

All studies included in our review were observational studies that evaluated the effect of metformin on mortality in diabetic patients with cancer (Table 1). Although we did not limit our search to observational studies, we were unable to identify any randomized controlled clinical trials that met our eligibility criteria. Sample sizes of diabetic patients ranged from 54 to 10,309 and percentage of metformin users ranged from 17.6% to 67.6%. One

study included all cancer sites (21), four on breast (25–28), colon (29–32), and prostate cancers each (33–36), two each on pancreatic (37, 38) and endometrial cancers (39, 40), and one study each on ovarian (41), liver (42), laryngeal (43), and lung cancers (44).

All studies reported an adjusted HR for the effect of metformin therapy on overall mortality in patients with cancer. All studies used a Cox proportional hazards regression model to calculate adjusted estimates. Seven studies examined the effect of metformin on cancer-specific mortality as a secondary outcome (27, 30–32, 35, 36). Most studies defined metformin exposure as a fixed never/ever exposure around the time of cancer diagnosis (i.e., at study baseline), whereas two studies defined metformin exposure at baseline based on current and/or future metformin exposure (25, 33). Three studies used a time-varying definition for metformin exposure but used different units of time (27, 28, 35).

Risk of bias varied across studies. Most studies used hospital-based cohorts, whereas one study used administrative databases (21). Ascertainment of exposure and outcome was consistent among studies and was obtained from chart reviews or data linkage to death registries or medical records. Studies varied most in terms of covariates included for adjustment. We identified diabetes-related variables (HbA1c or diabetes duration) as markers of diabetes severity and the presence of a cancer stage variable (stage, tumor size, node status) as the most important covariates. Accounting for diabetes severity helps to minimize indication bias whereas stage

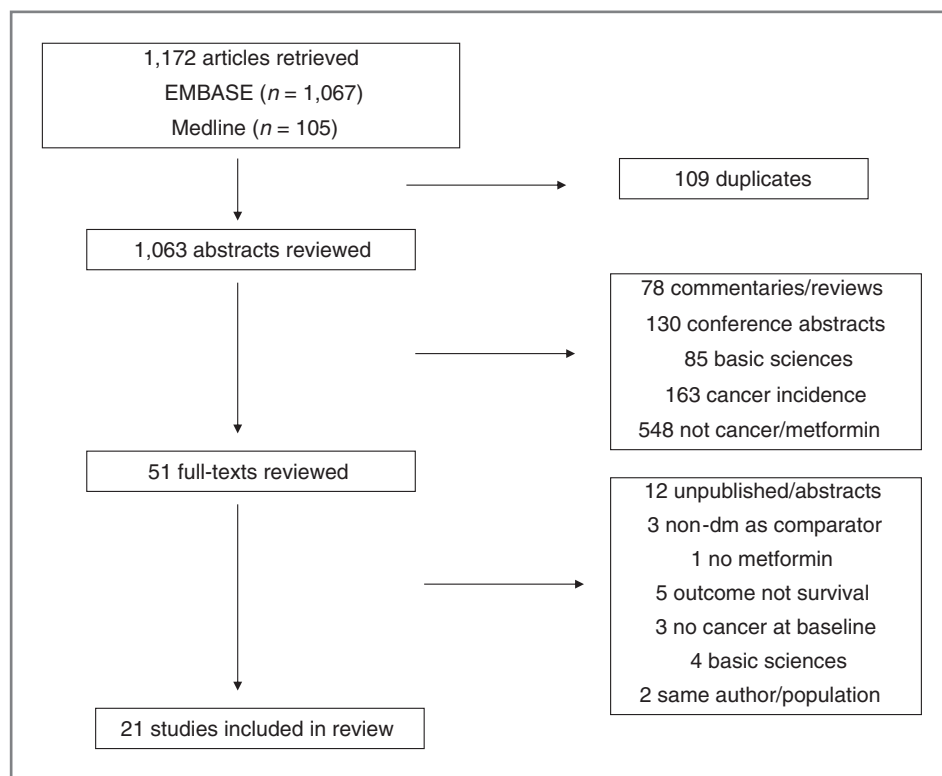


Figure 1. Flow chart on literature search for studies on the association between metformin use and survival following cancer.

**Table 1.** Summary characteristics of included studies

Source (country)	Cancer site	Study period	Metformin users/total (%)	Definition of metformin exposure	Follow-up time	Adjustment variables	Overall survival	Cancer survival
Bayraktar et al. (USA) (26)	Breast	1995–2007	63/130 (48)	Ever/never at cancer diagnosis	5.2 y (median)	Age, T score, lymph node status, nuclear grade, lymphovascular invasion, chemo	Y	N
Lega et al. (Canada) (27)	Breast	1997–2008	1,094/2,361	Time-varying cumulative	4.5 y	Age, year of diagnosis, chemo, rad, surgery, other OHA, dm duration, ACG score	Y	Y
Peeters et al. (Denmark) (28)	Breast	1996–2008	508/1,058	Time-varying never/ever and time-varying cumulative	2,971 person-years	Age, Charlson score, years from 1997 to Bca dx, su, tzd, other dm drugs, hrt, statins	Y	Y
He et al. (USA) (25)	Breast	1998–2010	NR/54	Ever/never at cancer diagnosis	NR	Age, race, BMI, grade, hormone receptor status, stage, insulin, tzd, su, met	Y	Y
Cossor et al. (USA) (31)	Colon (women)	1993–2005	84/212 (39.6)	Ever/never at cancer diagnosis	NR	Age, stage, propensity score (insulin, bmi, smoking, alcohol, diet, physical activity, stage, dm meds, asa, nsaiids)	Y	Y
Garrett et al. (29)	Colon	2004–2008	208/424 (49.1)	Ever/never at cancer diagnosis	NR	Age, sex, race, BMI, asa, tumor/node/stage	Y	N
Spillane et al. (Ireland) (32)	Colon	2001–2006	207/315 (66)	Ever/never year before cancer diagnosis	NR	Age, stage, grade, year of dx, comorbidity, asa, other dm meds, SES, rad	Y	Y
Lee et al. (Korea) (30)	Colon	2000–2008	258/595 (43.3)	Ever/never at cancer diagnosis	3.4 y (mean)	Age, sex, stage, BMI, dm duration, smoking, HbA1c level, asa, insulin, su, tzd	Y	Y

*(Continued on the following page)*

**Table 1.** Summary characteristics of included studies (Cont'd)

Source (country)	Cancer site	Study period	Metformin users/total (%)	Definition of metformin exposure	Follow-up time	Adjustment variables	Overall survival	Cancer survival
Ko et al. (USA) (39)	Endometrial	2005–2010	200/363 (55.1)	Ever/never at cancer diagnosis	33 mo (median)	Age, race, grade, histology, stage, adjuvant treatment	Y	N
Nevadunsky et al. (USA) (40)	Endometrial	1999–2009	114/250 (45.6)	Ever/never at cancer diagnosis	3.3 y (median)	Age, stage, grade, histology, chemo, rad, hyperlipidemia	Y	N
Sandulache et al. (USA) (43)	Laryngeal	2000–2012	21/43 (48.8)	During treatment	NR	Age, stage	Y	N
Chen et al. (Taiwan) (42)	Liver	2003–2009	21/53 (39.6)	Ever/never at cancer diagnosis	2.7 y (mean)	Age, gender, BMI, HbA1c, anti-HCV, tumor size	Y	N
Mazzone et al. (USA) (44)	Lung	1978–2010	184/522	Never/ever at cancer diagnosis	NR	Stage, age	Y	N
Hwang et al. (UK) (38)	Pancreas	2003–2010	247/516 (49.2)	6 month before/1 month after cancer diagnosis	99 d	Age, sex, duration of dm, dm complications, hx pancreatitis, Charlson, bmi, gfr, smoking, ins, su, tzd, hba1c	Y	N
Sadeghi et al. (USA) (37)	Pancreas	2000–2009	107/302 (35.4)	Ever/never at cancer diagnosis	11.4 mo (median)	NR	Y	N
He et al. (USA) (33)	Prostate	1999–2008	41/233 (17.6)	Ever/never at cancer diagnosis	NR	Black race, Gleason, stage, obesity, insulin, su, tzd, met, age at dx, PSA	Y	N
Kaushik et al. (USA) (34)	Prostate	1997–2010	323/885 (36.5)	Never/ever 3 months before cancer diagnosis	5.1 y (median)	Age, BMI, Gleason, stage, margin, PSA, statin	Y	N
Margel et al. (Canada) (35)	Prostate	1997–2008	1,619/3,837 (42)	Time-varying cumulative between ca diagnosis and end of follow-up	4.6 y (median)	Age, grade, tumor volume, comorbidity score, SES, rural, year of cohort entry	Y	Y
Spratt et al. (USA) (36)	Prostate	1992–2008	157/319 (49.2)	Ever/never at diagnosis or RT	8.7 y (median)	Age, Gleason, stage, PSA, neoadjuvant ADT	Y	Y

*(Continued on the following page)*

Table 1. Summary characteristics of included studies (Cont'd)

Source (country)	Cancer site	Study period	Metformin users/total (%)	Definition of metformin exposure	Follow-up time	Adjustment variables	Overall survival	Cancer survival
Romero et al. (USA) (41)	Ovary	1992–2010	28/44 (63.6)	Ever/never at cancer diagnosis	5.3 y (mean)	Age, BMI, creatinine, stage, grade, residual implants larger than 1 cm after debulking surgery and histologic subtype	Y	Y
Currie et al. (UK) (21)	All sites	1990–2009	2,843/8,392 (33.8)	Never/ever within 3 months of cancer diagnosis	NR	Age, sex, smoking, year of cancer diagnosis, Charlson	Y	N

Abbreviations: ACG, adjusted clinical groups; ASA, aspirin; ADT, androgen deprivation therapy; Bca, breast cancer; BMI, body mass index; chemo, chemotherapy; DM, diabetes mellitus; dx, diagnosis; gfr, glomerular filtration rate; HRT, hormone replacement therapy; mo, months; NR, not reported; OHA, oral hypoglycemic agents; PSA, prostate-specific antigen; rad, radiation; su, sulphonylurea; tzd, thiazolidenidione.

information is a strong confounder for mortality. Four studies adjusted for HbA1c or diabetes duration (27, 30, 38, 42) and fourteen adjusted for cancer stage in multivariable analyses.

Overall scores ranged from five to eight out of a total possible eight points. Four studies scored five points (36, 37, 42, 43). Most studies lost one point on representativeness of exposed cohort because the population was taken from referral centers that do not represent the general population. The second most common reason for losing points was because of lack of adjustment for variables related to diabetes severity.

Our funnel plot indicated that there may be a publication bias of small studies that might have results indicative of increased mortality. This is statistical possibility; however, we searched literature extensively and contacted experts and were unable to find any missing articles. This needs to be kept in mind in the interpretation of results.

Among the included studies, 12 reported a reduction in all-cause mortality with metformin exposure, seven found a nonsignificant association, and one study showed an increase in mortality among patients with cancer who were on metformin. Among studies that reported a protective association between metformin exposure and mortality, HRs varied from 0.23 to 0.97. Seven studies reported on the association between metformin exposure and cancer-specific mortality; three for colon, two each for prostate and breast cancers.

For the primary outcome of all-cause mortality, data were available for 20,908 diabetic patients, of which 8,327 were exposed to metformin (Table 1). Among patients with diabetes, metformin exposure was associated with a 27% reduction in all-cause mortality (pooled adjusted HR = 0.73; 95% CI, 0.64–0.83; Fig. 2) compared with no metformin exposure. There was significant statistical heterogeneity in this estimate ( $I^2 = 82\%$ ;  $P < 0.00001$ ). For cancer-specific mortality, metformin exposure was associated with a 26% reduction in mortality (HR = 0.74; 0.62–0.88;  $I^2 = 53\%$ ; Fig. 3).

We conducted several sensitivity analyses to address heterogeneity and the fact that adjustment for confounding factors differed among included studies. In the first sensitivity analysis, we only included studies that adjusted for cancer stage at presentation (11 studies; pooled HR = 0.66; 95% CI, 0.52–0.83;  $I^2 = 73\%$ ; Table 2).

Four studies adjusted for diabetes severity (HbA1c or diabetes duration) included colon (30), hepatic (42), pancreatic (38), and breast cancer (27). The pooled HR for these studies did not show a significant reduction in mortality with metformin exposure (HR = 0.87; 95% CI, 0.68–1.12;  $I^2 = 75\%$ ).

The three studies that used time-dependent modeling of the metformin exposure could not be combined for analyses given the different units of time used. In breast cancer, our group reported no significant association in mortality (HR = 0.97; 0.92–1.02) per additional cumulative year of metformin exposure (27), whereas Peeters reported a 45% reduction for patients receiving 21–31

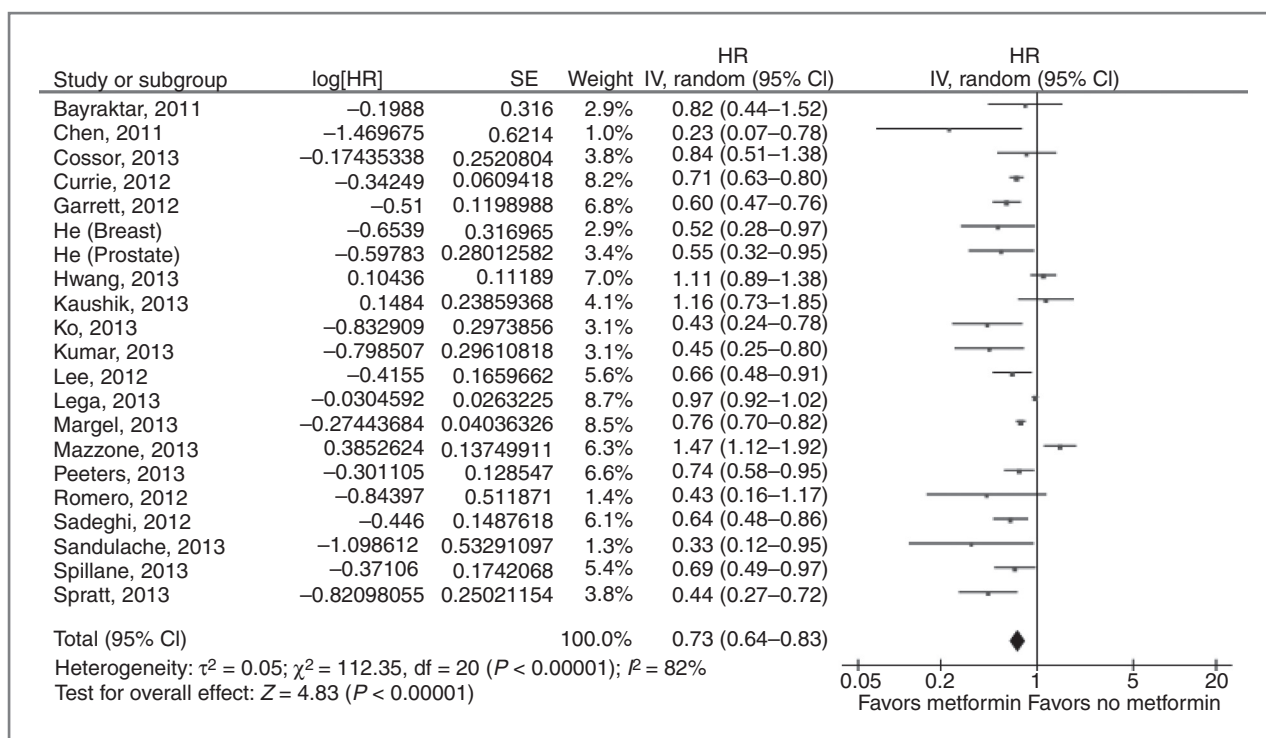


Figure 2. Forest plot and summary HR (95% CI) for association between metformin exposure and all-cause mortality among patients with diabetes and cancer.

scripts for metformin exposure (HR 0.55, 0.31–0.96), though this association was not robust across varying durations of metformin exposure (28). In prostate cancer, each additional 6 months of metformin use was associated with a 24% decrease in prostate cancer specific-mortality (HR 0.76, 0.64–0.89). The association with all-cause mortality was also significant but declined over time from an HR of 0.76 in the first 6 months to 0.93 between 24 and 30 months (0–6 months HR 0.76, 0.70–0.82; 24–30 months HR 0.93, 0.91–0.96; ref. 35).

Finally, we performed subgroup analyses for cancer sites where we had more than two studies available:

breast, colon, and prostate. Metformin exposure was associated with a significant reduction in mortality for colon cancer (HR 0.65, 0.56–0.76;  $I^2 = 0\%$ ) but not in prostate (HR 0.73, 0.51–1.06;  $I^2 = 75\%$ ) or breast cancer (HR 0.81, 0.64–1.04;  $I^2 = 63\%$ ).

### Discussion

In this systematic review of 21 observational studies, we found that metformin exposure at the time of cancer diagnosis may be associated with a reduction in all-cause mortality in patients with diabetes; however, this

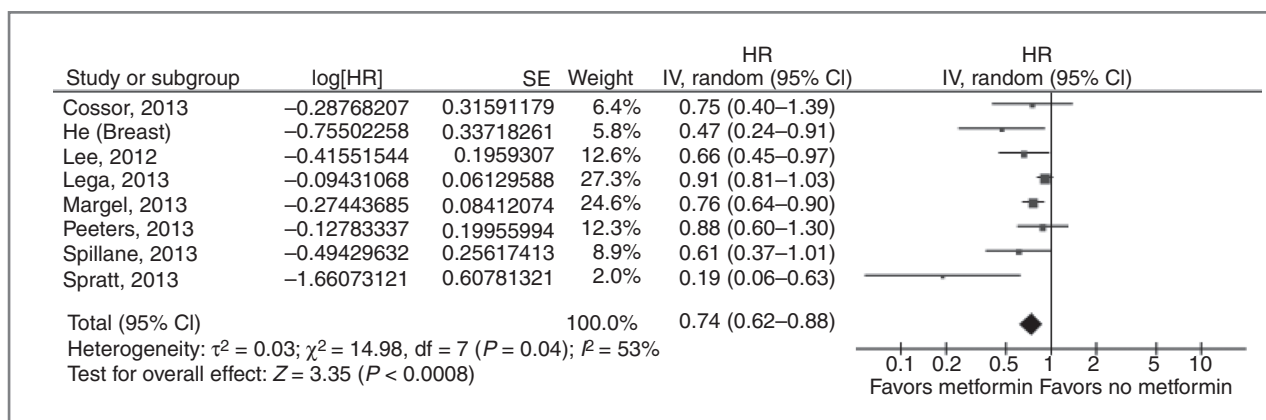


Figure 3. Secondary outcome. Forest plot and summary HR (95% CI) for association between metformin exposure and cancer-specific mortality.

**Table 2.** Summary pooled HR (95% CI) for sensitivity and subgroup analyses

	Number of studies	HR, random (95% CI)	I <sup>2</sup> statistic
Sensitivity analyses			
Studies that adjust for cancer stage	14	0.66 (0.52–0.83)	73%
Studies that adjust for DM severity	4	0.87 (0.68–1.12)	75%
Studies with higher quality score (>6) on NOS	13	0.77 (0.68–0.87)	82%
Subgroup analyses (by cancer site)			
Colorectal	4	0.65 (0.56–0.76)	0%
Breast	4	0.81 (0.64–1.04)	63%
Prostate	4	0.73 (0.51–1.06)	75%

association was not robust across all sensitivity analyses. Among individual cancers, statistical significance was observed for colon cancer only, and not in breast and prostate cancers. This association remained significant when including only studies that adjusted for cancer stage; however, not when limiting to studies that accounted for diabetes severity, suggesting possibility of healthy user bias. Similarly, an association was not identified among studies that defined metformin as a time-dependent exposure, although the number of studies reporting such results was small. Several methodological limitations may account for variability and heterogeneity among studies, including different cancer sites, non-standard definition of metformin exposure and variable adjustment for different confounding factors.

To our knowledge, this is the first systematic review and meta-analysis on metformin exposure at the time of diagnosis of cancer and mortality that carefully evaluated the risk of biases among included studies and accounted for them in sensitivity analyses. Our findings support the concern that the beneficial effects of metformin exposure may have been exaggerated due to indication and time-related biases that were not adequately accounted for in previous studies (45). Although two meta-analyses (17, 18) have previously concluded that metformin is associated with an improvement in survival, both reviews included studies of low methodological quality and made little attempt to account for this in their secondary analyses.

We chose to evaluate studies that adjusted for stage or diabetes severity separately because both are potential confounders in the relationship between diabetes and mortality. We showed that stage did not appear to have an effect on the risk estimate; however, pooled HR of studies that adjusted for markers of diabetes severity (HbA1c or diabetes duration) failed to find a significant association between metformin and mortality following cancer. This finding highlights the potential introduction of healthy user or indication bias in these observational studies and underscores the importance of accounting for this bias when there is nonrandom allocation of the exposure of interest. This is particularly an issue with our included studies because they were conducted in preva-

lent diabetic cohorts where there is variation in diabetes severity and duration. Given that metformin is first-line therapy for type II diabetes and is thus used in patients with earlier diabetes (9), metformin users may be healthier and may have an overall lower risk of mortality than patients in other comparator groups (46). By controlling for diabetes severity, the risk of indication bias was reduced in these studies, which may in part explain the attenuation of statistical significance.

All but three of the included studies defined metformin therapy as a never/ever exposure at, or around, time of cancer diagnosis and failed to take into account metformin exposure during follow up period (27, 28, 35). Classifying drug exposure at baseline, when most treatments vary over time, fails to account for effects of drug exposure during follow-up as well as cumulative exposure over time. One must bear this in mind when interpreting these results because metformin exposure before cancer diagnosis may reflect the effect of metformin on cancer phenotype, development and severity as opposed to any effect on prognosis after cancer develops. Moreover, two of the studies classified metformin ever/never use based on drug exposure *during* the follow up period and thus introduced an 'immortal time' bias (25, 33). The time between study baseline and start of metformin exposure is considered immortal since subjects must remain alive until start of exposure; considering this time as exposed may falsely exaggerate the benefit of metformin and leads to 'immortal-time' bias (47). This bias makes interpretation of findings from these two studies difficult (45, 48).

Clinically, we know that glucose-lowering therapies are modified depending on glycemic control or side effects, and thus metformin at baseline does not necessarily represent ongoing exposure during the follow up period. To address the clinical question of whether metformin exposure influences cancerous cells and improves cancer prognosis once the cancer has been diagnosed, one needs to take into account metformin exposure between cancer diagnosis and end of follow up. One way to account for variations in metformin exposure over time is to use time-dependent modeling of drug exposure (45, 49). Three studies evaluated metformin as a time-dependent exposure and their risk estimates reflect cumulative, time-



dependent exposure to metformin and compared, and in some cases may have also minimized, healthy user bias by comparing different durations of exposure among metformin users (27, 35). Despite modeling metformin exposure in similar ways, results from these studies were inconsistent. In prostate cancer, cumulative metformin was associated with a modest decrease in overall mortality with the greatest reduction seen with less than 6 months of exposure and not with longer durations. In breast cancer, we identified no association between mortality and each additional year of cumulative metformin exposure, whereas Peeters and colleagues reported a 45% reduction with 21 to 30 scripts for metformin (27, 28). More studies that use this methodology for modeling metformin exposure are needed to clarify this association. Furthermore, given the inherent limitations of observational studies, results from clinical trials such as NCIC MA.32, the largest multicenter randomized trial among early-stage breast cancer patients (19), will also be critical in determining the clinical utility of metformin on prognosis in patients with cancer.

An association between metformin exposure and cancer outcomes has biologic plausibility. In preclinical studies, metformin has been shown to have anticancer effects through both direct and indirect mechanisms. Directly, metformin activates the AMPK–mTOR pathways and inhibits downstream cellular growth and proliferation in cancer cells (12, 50). Through this pathway, metformin has been shown to inhibit the growth of cancer cells and even reduce tumor burden *in vitro* (51). Indirectly, metformin reduces insulin levels by improving insulin sensitivity; hyperinsulinemia is a tumor growth factor and reductions in endogenous insulin levels have been shown to reduce tumor burden and growth (13). Furthermore, these *in vitro* effects have translated into positive results in *in vivo* studies. In two window-of-opportunity trials, metformin significantly reduced biomarkers of cellular proliferation in breast cancer tumors of nondiabetic patients (15, 16); however, in a third such study, metformin only reduced breast cancer proliferation among patients with obesity and insulin resistance, suggesting a host-specific effect for its anticancer activities (52). In addition, metformin reduced aberrant crypt formations in rectal pre-euplastic tumors in a trial involving nondiabetic patients (53). In epidemiologic studies, metformin therapy has been associated with a decreased risk of cancer in diabetic patients (10, 11). However, many of those studies had methodologic limitations and thus may also have been subject to biases.

Strengths of this study are that it is the first systematic review and meta-analysis to carefully evaluate studies according to their ability to minimize bias. We formulated a broad search strategy and included all relevant articles.

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Furthermore, we were rigorous in ensuring methodologic comparability in how we determined our sensitivity and subgroup analyses. It is noteworthy that studies included in this review have been published within the last 5 years, which minimized variability that might have arisen due to time-sensitive differences in cancer or diabetes treatments.

However, we must acknowledge limitations of this review. First, studies included were clinically heterogeneous in terms of populations, cancer sites, and diabetes variables. However, differences were not unexpected and were not significant enough to preclude meta-analyses. Second, studies were also limited in terms of variables they adjusted for in the multivariable analyses; this was addressed by conducting sensitivity analyses on studies that took important confounders into account. Third, in our primary meta-analysis, we included all cancer sites, though it is likely that metformin has differential effects on different cancer sites. Finally, all studies included in this review were observational studies inherent with selection, measurement, and attrition biases.

Our meta-analysis of observational studies indicates that metformin exposure may be associated with a reduction in all-cause mortality among cancer patients with diabetes. Caution must be taken when interpreting these results, as methodologic limitations of individual studies may have introduced biases in these findings. There is preclinical, clinical, and epidemiologic evidence to support the anticancer properties of metformin. However, there is a need for more high-quality, methodologically strong studies, including randomized controlled trials, to further evaluate this question.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Acknowledgments

The authors thank Elizabeth Ulyrek, Chief Librarian, Hospital for Sick Children, for her help in conducting the search and Wei Wu, Analyst, Women's College Research Institute, Women's College Hospital, for assistance with the search and data abstraction.

## Grant Support

This work was supported by a fellowship from the Canadian Breast Cancer Research Foundation (to I.C. Lega), an Applied Research Chair Award from the Canadian Institute of Health Research (to P.S. Shah), a Canadian Diabetes Association/Canadian Institutes of Health Research Clinician Scientist Award, and a CIHR New Investigator Award (L.L. Lipscombe).

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Received March 31, 2014; revised June 6, 2014; accepted July 3, 2014; published OnlineFirst July 16, 2014.

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