The effect of metformin on mortality following cancer among patients with diabetes: a systematic review and meta-analysis

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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 10th, 2014 for studies with 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 hazard ratios (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% 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 (4 studies, HR 0.65 (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 methodological 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.
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 cancer patients, as compared to no diabetes (2). With nearly 20% of cancer patients concurrently having diabetes (3), this represents a large and growing population of cancer patients 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 2 diabetes is characterized by insulin resistance and compensatory hyperinsulinemia, which may also affect cancer outcomes. Elevated insulin levels have been shown to increase tumour 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 2 diabetes. It is the most commonly prescribed drug for type 2 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 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 breast cancer patients, 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 methodological quality of studies. Two recent meta-analyses have summarized the existing studies on metformin and cancer mortality (17, 18); however neither review focused on the methodological concerns of these observational studies, namely the risk of time-related and selection biases (19). Our objective was to systematically summarize the data regarding the association between metformin and all-cause mortality in patients with diabetes and cancer, whilst 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 10th, 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, glucagon-like-peptide-1 agonists) in grouped or separate categories. We included studies that compared, among diabetic patients, metformin exposed to non-exposed 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 hazard ratio [HR] or odds ratio [OR]) with an estimate of precision (95% CI).

Studies that included non-diabetic 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 1 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 (IL, DM) 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
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Studies. A third reviewer (WW) 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 (LL).

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 to 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, since stage is well known predictor of mortality. Second, we analyzed results from studies that adjusted for diabetes severity (HbA1c or diabetes duration) separately since this variable is associated with both choice of diabetes treatment and mortality. Third, to assess for methodological heterogeneity, we excluded studies that scored 6 points or less on the NOS. Finally, we reported separate estimates for cancer sites with at least 3 estimates available (prostate, colon, breast).

RESULTS

Our literature search yielded 1172 articles, of which 109 were duplicates (figure 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 non-diabetic 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 twenty-one studies for inclusion in our review and meta-analysis (figure 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). Though we did
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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 cancer patients. 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 while one study used administrative databases (21). Ascertainment of exposure and outcome was consistent among studies and were 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, tumour size, node status) as the most important covariates. Accounting for diabetes severity helps to minimize indication bias whereas stage information is a strong confounder for
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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 since 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 which 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, twelve reported a reduction in all-cause mortality with metformin exposure, seven found a non-significant association and one study showed an increase in mortality among cancer patients 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 8327 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; figure 2) compared to no metformin exposure. There was significant statistical heterogeneity in this estimate.
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(\(I^2=82\%\); \(p<0.00001\)). For cancer-specific mortality, metformin exposure was associated with a 26\% reduction in mortality (HR 0.74, 0.62-0.88; \(I^2=53\%\); figure 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\% 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), while Peeters reported a 45\% reduction for patients receiving 21-31 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 (0.88, 0.85-0.91) (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 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 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). Though two meta-analyses (17, 18) have previously concluded that metformin is associated with an improvement in survival,
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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 since 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 non-random allocation of the exposure of interest. This is particularly an issue with our included studies since they were conducted in prevalent diabetic cohorts where there is variation in diabetes severity and duration.

Given that metformin is first-line therapy for type 2 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 since metformin exposure prior to cancer diagnosis may reflect the effect of metformin on cancer phenotype, development and severity as opposed to any.
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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 reported a 45% reduction with 21-30 scripts for metformin (27, 28). More studies that use this
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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 multi-centre randomized trial among early stage breast cancer patients (19), will also be critical in determining the clinical utility of metformin on prognosis in cancer patients.

An association between metformin exposure and cancer outcomes has biologic plausibility. In pre-clinical studies, metformin has been shown to have anti-cancer effects through both direct and indirect mechanisms. Directly, metformin activates 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 tumour burden in vitro (51). Indirectly, metformin reduces insulin levels by improving insulin sensitivity; hyperinsulinemia is a tumour growth factor and reductions in endogenous insulin levels have been shown to reduce tumour 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 tumours of non-diabetic 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 anti-cancer activities (52). In addition, metformin reduced aberrant crypt formations in rectal pre-euplastic tumours in a trial involving non-diabetic 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 methodological limitations and thus may also have been subject to biases.
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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. Furthermore, we were rigorous in ensuring methodological 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 five 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 methodological limitations of individual studies may have introduced biases in these findings. There is pre-clinical, clinical and epidemiological evidence to support the anti-cancer properties of metformin. However, there is a need for more high-quality, methodologically strong studies including randomized controlled trials to further evaluate this question.
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Table 1: Summary characteristics of included studies.

<table>
<thead>
<tr>
<th>Source, year (country)</th>
<th>Cancer Site</th>
<th>Study period</th>
<th>Metformin users/total (%)</th>
<th>Definition of Metformin exposure</th>
<th>Follow-up time</th>
<th>Adjustment variables</th>
<th>Overall survival</th>
<th>Cancer survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayraktar, 2011 (USA) (26)</td>
<td>Breast</td>
<td>1995-2007</td>
<td>63/130 (48)</td>
<td>Ever/never at cancer diagnosis</td>
<td>5.2 yrs (median)</td>
<td>age, T score, lymph node status, nuclear grade, lymphovascular invasion, chemo</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Lega, 2013 (Canada) (27)</td>
<td>Breast</td>
<td>1997-2008</td>
<td>1094/2361</td>
<td>Time-varying cumulative</td>
<td>4.5 yrs</td>
<td>age, year of diagnosis, chemo, rad, surgery, other OHA, dm duration, ACG score</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Peeters, 2013 (Denmark) (28)</td>
<td>Breast</td>
<td>1996-2008</td>
<td>508/1058</td>
<td>Time-varying never/ever and time-varying cumulative</td>
<td>2971 person-years</td>
<td>age, Charlson score, years from 1997 to Bca dx, su, tzd, other dm drugs, hrt, statins</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>He, 2011 (USA) (25)</td>
<td>Breast</td>
<td>1998-2010</td>
<td>NR/54</td>
<td>Ever/never at cancer diagnosis</td>
<td>NR</td>
<td>age, race, BMI, grade, hormone receptor status, stage, insulin, tzd, su, met</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Cossor, 2013 (USA) (31)</td>
<td>Colon (women)</td>
<td>1993-2005</td>
<td>84/212 (39.6)</td>
<td>Ever/never at cancer diagnosis</td>
<td>NR</td>
<td>age, stage, propensity score (insulin, bmi, smoking, alcohol, diet, physical activity, stage, dm meds, asa, nsaids)</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Garrett, 2012 (USA) (29)</td>
<td>Colon</td>
<td>2004-2008</td>
<td>208/424 (49.1)</td>
<td>Ever/never at cancer diagnosis</td>
<td>NR</td>
<td>age, sex, race, BMI, asa, tumour/node/ stage</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Spillane, 2013 (Ireland) (32)</td>
<td>Colon</td>
<td>2001-2006</td>
<td>207/315 (66)</td>
<td>Ever/never year prior to cancer diagnosis</td>
<td>NR</td>
<td>age, stage, grade, year of dx, comorbidty, asa, other dm meds, SES, rad</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Lee, 2012 (Korea) (30)</td>
<td>Colon</td>
<td>2000-2008</td>
<td>258/595 (43.3)</td>
<td>Ever/never at cancer diagnosis</td>
<td>3.4 yrs (mean)</td>
<td>age, sex, stage, BMI, dm duration, smoking, HbA1c level, insulin, su, tzd</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Ko, 2013 (USA) (39)</td>
<td>Endometrial</td>
<td>2005-2010</td>
<td>200/363 (55.1)</td>
<td>Ever/never at cancer diagnosis</td>
<td>33 mo (median)</td>
<td>age, race, grade, histology, stage, adjuvant treatment</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Nevadunsky, 2014 (USA) (40)</td>
<td>Endometrial</td>
<td>1999-2009</td>
<td>114/250 (45.6)</td>
<td>Ever/never at cancer diagnosis</td>
<td>3.3 yrs (median)</td>
<td>age, stage, grade, histology, chemo, rad, hyperlipidemia</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Sandulache, 2013 (USA) (43)</td>
<td>Laryngeal</td>
<td>2000-2012</td>
<td>21/43 (48.8)</td>
<td>During treatment</td>
<td>NR</td>
<td>age, stage</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Chen, 2011 (Taiwan) (42)</td>
<td>Liver</td>
<td>2003-2009</td>
<td>21/53 (39.6)</td>
<td>Ever/never at cancer diagnosis</td>
<td>2.7 yrs (mean)</td>
<td>age, gender, BMI, HbA1c, anti-HCV, tumor size stage, age</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Mazzone, 2012 (USA) (44)</td>
<td>Lung</td>
<td>1978-2010</td>
<td>184/522</td>
<td>Never/ever at cancer diagnosis</td>
<td>NR</td>
<td>stage, age</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Hwang, 2013 (UK) (38)</td>
<td>Pancreas</td>
<td>2003-2010</td>
<td>247/516 (49.2)</td>
<td>6 month prior to/1 month after cancer diagnosis</td>
<td>99 days</td>
<td>age, sex, duration of dm, dm complications, hx pancreatitis, charls, bmi, gfr, smoking, ins, su, tzd, hba1c</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Sadeghi, 2012 (USA) (37)</td>
<td>Pancreas</td>
<td>2000-2009</td>
<td>107/302 (35.4)</td>
<td>Ever/never at cancer diagnosis</td>
<td>11.4 mo (median)</td>
<td>Y</td>
<td>N</td>
<td></td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Disease</th>
<th>Time Frame</th>
<th>Cases/Control (N)</th>
<th>Exposure/Non-Exposure</th>
<th>Follow-up</th>
<th>Covariates</th>
</tr>
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<tbody>
<tr>
<td>He, 2012</td>
<td>USA</td>
<td>Prostate</td>
<td>1999-2008</td>
<td>41/233 (17.6)</td>
<td>Ever/never at cancer diagnosis</td>
<td>NR</td>
<td>black race, gleason, stage, obesity, insulin, su, tzd, met, age at dx, PSA</td>
<td></td>
</tr>
<tr>
<td>Kaushik, 2012</td>
<td>USA</td>
<td>Prostate</td>
<td>1997-2010</td>
<td>323/885 (36.5)</td>
<td>Never/ever 3 months prior to cancer diagnosis</td>
<td>5.1 yrs (median)</td>
<td>age, BMI, gleason, stage, margin, PSA, statin</td>
<td></td>
</tr>
<tr>
<td>Margel, 2013</td>
<td>Canada</td>
<td>Prostate</td>
<td>1997-2008</td>
<td>1619/3837 (42)</td>
<td>Time-varying cumulative between ca diagnosis and end of follow-up</td>
<td>4.6 yrs (median)</td>
<td>age, grade, tumour volume, comorbidity score, SES, rural, year of cohort entry</td>
<td></td>
</tr>
<tr>
<td>Spratt, 2013</td>
<td>USA</td>
<td>Prostate</td>
<td>1992-2008</td>
<td>157/319 (49.2)</td>
<td>Ever/never at diagnosis or RT</td>
<td>8.7 yrs (median)</td>
<td>age, gleason, stage, PSA, neoadjuvant ADT</td>
<td></td>
</tr>
<tr>
<td>Romero, 2012</td>
<td>USA</td>
<td>Ovary</td>
<td>1992-2010</td>
<td>28/44 (63.6)</td>
<td>Ever/never at cancer diagnosis</td>
<td>5.3 yrs (mean)</td>
<td>age, BMI, creatinine, stage, grade, residual implants larger than 1cm after debulking surgery and histologic subtype</td>
<td></td>
</tr>
<tr>
<td>Currie, 2012</td>
<td>UK</td>
<td>All sites</td>
<td>1990-2009</td>
<td>2843/8392 (33.8)</td>
<td>Never/ever within 3 months of cancer diagnosis</td>
<td>NR</td>
<td>age, sex, smoking, year of cancer diagnosis, Charlson</td>
<td></td>
</tr>
</tbody>
</table>

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, thiazolidenedione; yrs, years.
The effect of metformin on mortality following cancer among patients with diabetes: a systematic review and meta-analysis
Lega et al. 2014

Table 2: Summary pooled HR (95% CI) for sensitivity & subgroup analyses

<table>
<thead>
<tr>
<th></th>
<th>No. of studies</th>
<th>HR, Random, 95% CI</th>
<th>( I^2 ) statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity analyses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies that adjust for cancer stage</td>
<td>14</td>
<td>0.66 (0.52-0.83)</td>
<td>73%</td>
</tr>
<tr>
<td>Studies that adjust for DM severity</td>
<td>4</td>
<td>0.87 (0.68-1.12)</td>
<td>75%</td>
</tr>
<tr>
<td>Studies with higher quality score (&gt;6) on NOS</td>
<td>13</td>
<td>0.77 (0.68-0.87)</td>
<td>82%</td>
</tr>
<tr>
<td><strong>Subgroup analyses (by cancer site)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>4</td>
<td>0.65 (0.56-0.76)</td>
<td>0%</td>
</tr>
<tr>
<td>Breast</td>
<td>4</td>
<td>0.81 (0.64-1.04)</td>
<td>63%</td>
</tr>
<tr>
<td>Prostate</td>
<td>4</td>
<td>0.73 (0.51-1.06)</td>
<td>75%</td>
</tr>
</tbody>
</table>
The effect of metformin on mortality following cancer among patients with diabetes: a systematic review and meta-analysis
Lega et al. 2014

**Figure Legends:**

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

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

**Figure 3:** Secondary outcome - Forest plot and summary HR (95% CI) for association between metformin exposure and cancer-specific mortality.
1172 articles retrieved
  EMBASE (n=1067)
  Medline (n=105)

1063 abstracts reviewed

109 duplicates

78 commentaries/reviews
  130 conference abstracts
    85 basic sciences
    163 cancer incidence
    548 not cancer/metformin

51 full texts reviewed

12 unpublished/abstracts
  3 non-dm as comparator
    1 no metformin
    5 outcome not survival
    3 no cancer at baseline
    4 basic sciences
    2 same author/population

21 studies included in review
Figure 2

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayraktar, 2011</td>
<td>-0.1988</td>
<td>0.316</td>
<td>2.9%</td>
<td>0.82 [0.44, 1.52]</td>
<td></td>
</tr>
<tr>
<td>Chen, 2011</td>
<td>-1.469675</td>
<td>0.6214</td>
<td>1.0%</td>
<td>0.23 [0.07, 0.78]</td>
<td></td>
</tr>
<tr>
<td>Cossor 2013</td>
<td>-0.17435338</td>
<td>0.2520804</td>
<td>3.8%</td>
<td>0.84 [0.51, 1.38]</td>
<td></td>
</tr>
<tr>
<td>Currie, 2012</td>
<td>-0.34249</td>
<td>0.0609418</td>
<td>8.2%</td>
<td>0.71 [0.63, 0.80]</td>
<td></td>
</tr>
<tr>
<td>Garrett, 2012</td>
<td>-0.51</td>
<td>0.1198988</td>
<td>6.8%</td>
<td>0.60 [0.47, 0.76]</td>
<td></td>
</tr>
<tr>
<td>He (Breast)</td>
<td>-0.6539</td>
<td>0.316965</td>
<td>2.9%</td>
<td>0.52 [0.28, 0.97]</td>
<td></td>
</tr>
<tr>
<td>He (Prostate)</td>
<td>-0.59783</td>
<td>0.28012582</td>
<td>3.4%</td>
<td>0.55 [0.32, 0.95]</td>
<td></td>
</tr>
<tr>
<td>Hwang 2013</td>
<td>0.10436</td>
<td>0.11189</td>
<td>7.0%</td>
<td>1.11 [0.89, 1.38]</td>
<td></td>
</tr>
<tr>
<td>Kaushik 2013</td>
<td>0.1484</td>
<td>0.23859368</td>
<td>4.1%</td>
<td>1.16 [0.73, 1.85]</td>
<td></td>
</tr>
<tr>
<td>Ko 2013</td>
<td>-0.832909</td>
<td>0.2973856</td>
<td>3.1%</td>
<td>0.43 [0.24, 0.78]</td>
<td></td>
</tr>
<tr>
<td>Kumar 2013</td>
<td>-0.798507</td>
<td>0.29610818</td>
<td>3.1%</td>
<td>0.45 [0.25, 0.80]</td>
<td></td>
</tr>
<tr>
<td>Lee, 2012</td>
<td>-0.4155</td>
<td>0.1659662</td>
<td>5.6%</td>
<td>0.66 [0.48, 0.91]</td>
<td></td>
</tr>
<tr>
<td>Lega 2013</td>
<td>-0.0304592</td>
<td>0.0263225</td>
<td>8.7%</td>
<td>0.97 [0.92, 1.02]</td>
<td></td>
</tr>
<tr>
<td>Margel 2013</td>
<td>-0.27443684</td>
<td>0.04036326</td>
<td>8.5%</td>
<td>0.76 [0.70, 0.82]</td>
<td></td>
</tr>
<tr>
<td>Mazzone 2013</td>
<td>0.3852624</td>
<td>0.13749911</td>
<td>6.3%</td>
<td>1.47 [1.12, 1.92]</td>
<td></td>
</tr>
<tr>
<td>Peeters 2013</td>
<td>-0.301105</td>
<td>0.128547</td>
<td>6.6%</td>
<td>0.74 [0.58, 0.95]</td>
<td></td>
</tr>
<tr>
<td>Romero, 2012</td>
<td>-0.84397</td>
<td>0.511871</td>
<td>1.4%</td>
<td>0.43 [0.16, 1.17]</td>
<td></td>
</tr>
<tr>
<td>Sadeghi, 2012</td>
<td>-0.446</td>
<td>0.1487618</td>
<td>6.1%</td>
<td>0.64 [0.48, 0.86]</td>
<td></td>
</tr>
<tr>
<td>Sandulache 2013</td>
<td>-1.098612</td>
<td>0.53291097</td>
<td>1.3%</td>
<td>0.33 [0.12, 0.95]</td>
<td></td>
</tr>
<tr>
<td>Spillane 2013</td>
<td>-0.37106</td>
<td>0.1742068</td>
<td>5.4%</td>
<td>0.69 [0.49, 0.97]</td>
<td></td>
</tr>
<tr>
<td>Spratt 2013</td>
<td>-0.82098055</td>
<td>0.25021154</td>
<td>3.8%</td>
<td>0.44 [0.27, 0.72]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.73 [0.64, 0.83]

Heterogeneity: Tau² = 0.05; Chi² = 112.35, df = 20 (P < 0.00001); I² = 82%
Test for overall effect: Z = 4.83 (P < 0.00001)
Figure 3

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cossor 2013</td>
<td>-0.28768207</td>
<td>0.31591179</td>
<td>6.4%</td>
<td>0.75 [0.40, 1.39]</td>
<td></td>
</tr>
<tr>
<td>He (Breast)</td>
<td>-0.75502258</td>
<td>0.33718261</td>
<td>5.8%</td>
<td>0.47 [0.24, 0.91]</td>
<td></td>
</tr>
<tr>
<td>Lee, 2012</td>
<td>-0.41551544</td>
<td>0.1959307</td>
<td>12.6%</td>
<td>0.66 [0.45, 0.97]</td>
<td></td>
</tr>
<tr>
<td>Lega 2013</td>
<td>-0.09431068</td>
<td>0.06129588</td>
<td>27.3%</td>
<td>0.91 [0.81, 1.03]</td>
<td></td>
</tr>
<tr>
<td>Margel 2013</td>
<td>-0.27443685</td>
<td>0.08412074</td>
<td>24.6%</td>
<td>0.76 [0.64, 0.90]</td>
<td></td>
</tr>
<tr>
<td>Peeters 2013</td>
<td>-0.12783337</td>
<td>0.19955994</td>
<td>12.3%</td>
<td>0.88 [0.60, 1.30]</td>
<td></td>
</tr>
<tr>
<td>Spillane 2013</td>
<td>-0.49429632</td>
<td>0.25617413</td>
<td>8.9%</td>
<td>0.61 [0.37, 1.01]</td>
<td></td>
</tr>
<tr>
<td>Spratt 2013</td>
<td>-1.66073121</td>
<td>0.60781321</td>
<td>2.0%</td>
<td>0.19 [0.06, 0.63]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.74 [0.62, 0.88]

Heterogeneity: Tau² = 0.03; Chi² = 14.98, df = 7 (P = 0.04); I² = 53%
Test for overall effect: Z = 3.35 (P = 0.0008)
The effect of metformin on mortality following cancer among patients with diabetes

Iliana C Lega, Prakesh S. Shah, David Margel, et al.

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