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Metformin and pancreatic cancer survival: Real effect or immortal time bias?

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High heterogeneity has been reported among cohort studies investigating the association between metformin and pancreatic cancer survival. Immortal time bias may be one importance source of heterogeneity, as it is widely present in previous cohort studies and may severely impair the validity. Our study aimed to examine whether metformin therapy improves pancreatic cancer survival, and to assess the impact of immortal time bias on the effect estimation of metformin in cohort studies. PubMed, EMbase and SciVerse Scopus were searched. Pooled relative risks (RRs) were derived using a random-effects model. Pooled RR from the six studies without immortal time bias showed no association between metformin and mortality in pancreatic cancer patients (RR 0.93, 95% CI 0.82, 1.05; $p = 0.22$ and $I^2 = 75\%$). In contrast, pooled RR from the nine studies with immortal time bias showed a reduction of 24% in mortality associated with metformin (RR 0.76, 95% CI 0.69, 0.84; $p < 0.001$ and $I^2 = 1\%$). From a meta-regression model, existence of immortal time bias was associated with a reduction of 18% in the effect estimate of metformin on pancreatic cancer survival (ratio of RR 0.82, 95% CI 0.70, 0.96; $p = 0.02$). In conclusions, cumulative evidence from cohort studies does not support a beneficial effect of metformin on pancreatic cancer survival. The association between metformin and pancreatic cancer survival has been greatly exaggerated in previous cohort studies due to the wide existence of immortal time bias. More rigorous designs and statistical methods are needed to account for immortal time bias.

Metformin is a first-line drug recommended for the management of Type 2 diabetes. Recently, it has being studied as a cancer treatment. A field synopsis of cohort studies suggests that metformin might prolong survival for cancer patients.[1] Despite this encouraging finding, the study also highlighted a high heterogeneity between cohort studies.[1]

The heterogeneity may result, at least, in part from the time-varying nature of metformin use over time. For example, a cancer patient did not receive metformin prescription when entering the cohort, but may take metformin some time later, say 2 months. If this patient is classified as metformin exposed without taking the 2-month time window into account, the 2-month period will, by definition, be at essentially no risk of mortality. The logic is simple: this patient has to survive this 2-month time window to receive metformin. Thus, this patient is artificially protected in the time window. The mortality rate in the metformin-exposed group would be underestimated if this 2-month time window is incorporated into the denominator of rate formula, and the effect estimate of metformin on cancer survival may in turn be biased toward beneficial. This is a type of exposure misclassification, also called immortal time bias.[2]

Pancreatic cancer ranks the 12th most common cancer in the world, but its survival is one of the worst among all cancers.[3] Due to the aggressive nature of the disease, it progresses rapidly. The median survival is approximately 5–8 months, and the 5-year survival rate is only 3–7%. For cohort studies of a drug's effect on pancreatic cancer survival, immortal time bias is worth particular attention because it may impair the validity of the study severely. For example, a previous cohort study[4] examined the effect of metformin on pancreatic cancer survival. There was no effect on pancreatic cancer survival with metformin treatment immediately before cancer diagnosis (hazard ratio 1.26, 95% confidence interval (CI) 0.85–1.85), whereas a magnificent survival benefit to pancreatic cancer

Key words: metformin, pancreatic cancer, survival, immortal time bias, time-dependent bias, guarantee time bias, survivor treatment selection bias, heterogeneity

Abbreviations: CI: confidence interval; RR: relative risk

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What's new?

Metformin is a first-line drug in the management of type 2 diabetes. More recently, metformin has also been suggested to prolong survival for cancer patients. However, high heterogeneity has been reported among cohort studies investigating pancreatic cancer survival, possibly due to immortal time bias. Here, the authors found that the cumulative evidence from cohort studies does not support a beneficial effect of metformin on pancreatic cancer survival. The association between metformin and pancreatic cancer survival has been greatly exaggerated due to the wide existence of immortal time bias in cohort studies, calling for more rigorous designs and statistical methods.

survival was observed (hazard ratio 0.65, 95% CI 0.38–1.11) when using the criteria of metformin treatment ≤3 months after cancer diagnosis. This dramatic change is most probably the result of immortal time bias.

We hypothesize that presence of immortal time bias exaggerates the effect estimates of metformin on pancreatic cancer survival, and immortal time bias may, at least partly, explain the reported heterogeneity[1] between previous cohort studies. Accordingly, we carried out our study to examine whether metformin therapy improve survival in pancreatic cancer and evaluate the impact of immortal time bias on the effect estimation of metformin on pancreatic cancer survival.

Research Design and Methods

Study selection

Relevant studies were identified by searching the PubMed, EMbase and SciVerse Scopus databases for all published articles up to January 31, 2019. Keywords for searching included "metformin," "biguanides," "cancer" and "neoplasms." The search was further restricted to English-language articles and human subjects. Additional studies were retrieved through a hand search of references from original reports and review articles. Studies on this topic were considered eligible if they provided data on the relationship between metformin therapy and pancreatic cancer survival. The papers published more recently were given precedence if there were multiple publications from the same study.

Data extraction and statistical analyses

Two authors independently reviewed each retrieved article. Whether immortal time bias was present in the epidemiologic studies was examined by the first author. Relevant data were extracted through a structured table. Differences, if any, were reconciled through group discussion. The quality of each study was appraised in reference to the STROBE statement. Data extracted included the first author, publication year, region of study, cancer type, exposure and comparison treatment, effect estimate and covariate adjustment. When a study provided series of effect estimates, we selected the one that was free from immortal time bias. Relative risk (RR) was used as the common measure of association across studies in the present study. Forest plots were used to compare results across studies. Random-effects models were used to derive the pooled effect estimates.[5]

Forest plots were generated to visually examine and assess the estimate of RR and corresponding 95% CI across studies. To assess heterogeneity across studies, Cochran's Q statistic was calculated with a significance level of $p < 0.10$.[6] The I^2 statistic was also calculated. The values of I^2 less than 25%, 50% and 75% indicate low, medium and high heterogeneity, respectively.[7] Sources of heterogeneity were explored by fitting the covariate indicating the presence of immortal time bias (yes *vs.* no) in a random-effects model. Subgroup analyses were performed according to the status of immortal time bias. Evidence of publication bias was assessed by visually examining Begg's funnel plot and performing Begg's test and Egger's test for asymmetry. The Meta-analysis Of Observational Studies in Epidemiology guidelines for meta-analysis of observational studies were followed,[8] and PRISMA criteria were performed for the search methodology.[9]

All analyses were performed using Stata version 13.0 (StataCorp, College Station, TX). A two-tailed $p < 0.05$ was considered significant for statistical tests.

Results

A total of 16 eligible studies were retrieved.[4,10–23] Because two studies were both based on the surveillance, epidemiology and end results-medicare databases,[14,23] the more recent one was used.[14] Hence, a total of 15 retrospective cohort studies were included in the final analysis.[4,10–22] The process of paper selection is depicted in Figure 1. The information on author, publication year, region, cancer type and covariate adjustment is shown in Table 1.

The existence of immortal time bias in all retrieved studies was appraised. Four studies used an "initial treatment carried forward" approach to define metformin exposure,[4,10–12] that is, receiving metformin at the time of pancreatic diagnosis,[4,12] or very close to the date of pancreatic diagnosis, for example, within 30 days.[10,11] Another two studies used time-varying variable as metformin exposure.[13,14] Thus, these six studies were deemed to be not subject to immortal time bias.[4,10–14] The other nine studies did not account for the time-varying nature of metformin treatment and were deemed to be affected by immortal time bias.[12,15–22]

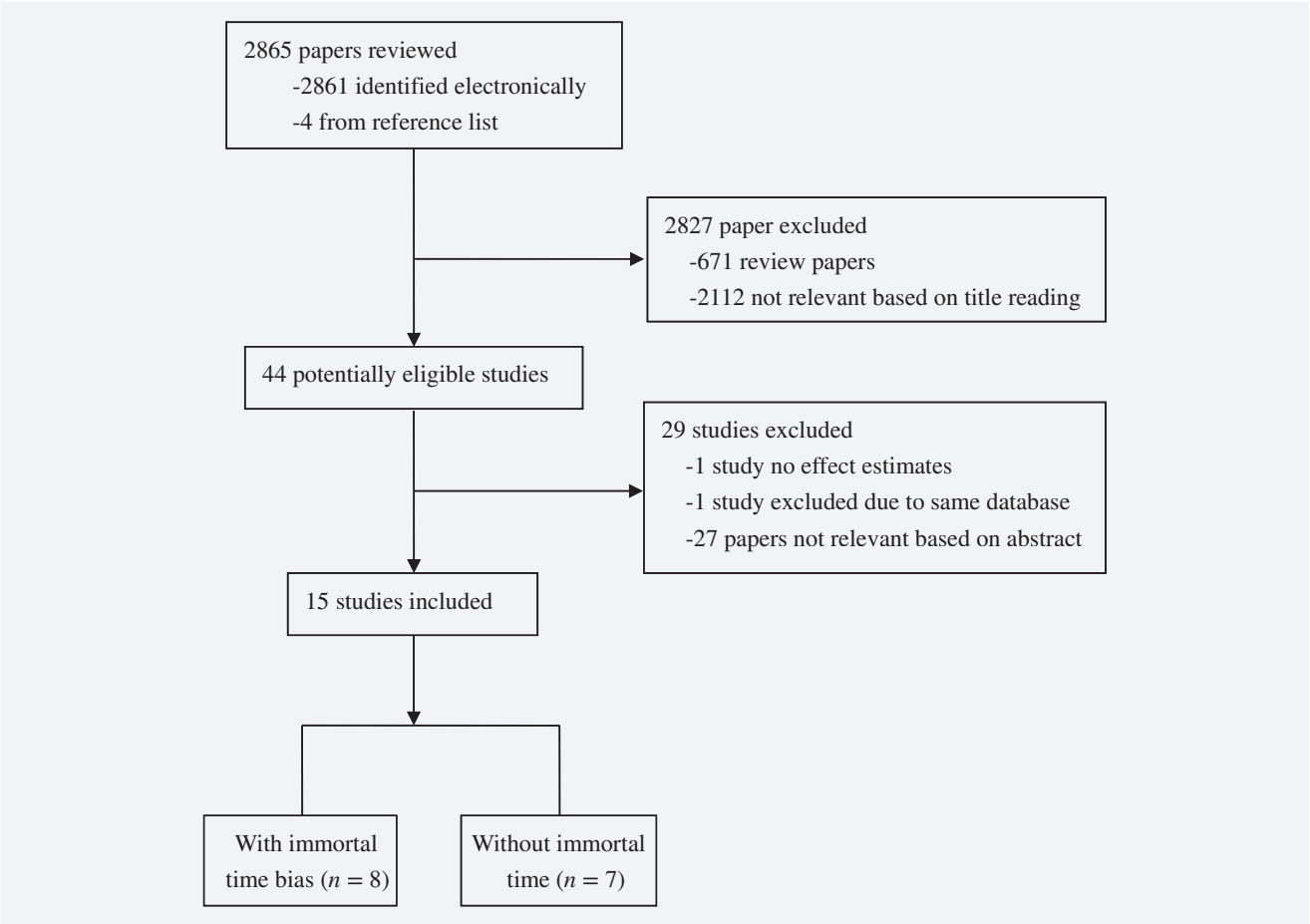

Figure 1. Flow chart of the study selection process.

Pooled effect estimate from the 15 studies,[4,10–22] regardless of the presence of immortal time bias, showed significant inverse association between metformin therapy and mortality after the diagnosis of pancreatic cancer (RR 0.85, 95% CI 0.77, 0.94; $p = 0.002$; Fig. 2*a*). There was evidence of high heterogeneity ($I^2 = 68\%$). There was no evidence of publication bias from Begg's funnel plot examination (Fig. 3*a*) or from the Begg's test ($p = 0.84$) or Egger's test ($p = 0.25$).

Pooled effect estimate from the six cohort studies without immortal time bias[12,15–22] showed no association between metformin and mortality in pancreatic cancer patients (RR 0.93, 95% CI 0.82, 1.05; $p = 0.22$; Fig. 2*b*). There was evidence of high heterogeneity ($I^2 = 75\%$). There was no evidence of publication bias from Begg's funnel plot examination (Fig. 3*b*) or from the Begg's test ($p = 0.71$) or Egger's test ($p = 0.81$). In contrast, pooled effect estimate from the nine studies[12,15–22] subject to immortal time bias showed metformin was associated with lower mortality risk in pancreatic cancer patients (RR 0.76, 95% CI 0.69, 0.84; $p < 0.001$; Fig. 2*c*). There was no evidence of heterogeneity ($I^2 = 1\%$). There was no evidence of publication bias from Begg's funnel plot examination (Fig. 3*c*) or from the Begg's test ($p = 0.75$) or Egger's test ($p = 0.71$).

From a meta-regression model, existence of immortal time bias was associated with a reduction of 18% in RR estimate of metformin on pancreatic cancer survival (ratio of RR 0.82, 95% CI 0.70, 0.96; $p = 0.02$, Fig. 4), suggesting that the presence of immortal time bias led to an overestimation of metformin's effect on pancreatic cancer survival.

Discussion

The present study examined the effect of metformin therapy on pancreatic cancer survival in studies with and without immortal time bias, respectively. The cumulative evidence from cohort studies up to today does not support a beneficial effect on pancreatic cancer survival with metformin therapy. The present study also highlights the importance of avoiding immortal time bias in future cohort studies on pancreatic cancer survival.

Cumulative evidence from cohort studies does not support a beneficial effect of metformin on pancreatic cancer survival. In the present study, the pooled RR from the six cohort

Table 1. Characteristics of 15 cohort studies included in the final analysis

Author, year	Region	Cancer type	Txt in exposure	Txt in comparison	Covariate adjustment
Currie (2012)[4]	UK	Pancreatic cancer	Metformin immediately before diagnosis	No metformin prescription immediately before diagnosis	Age, sex, smoking, Townsend index of deprivation, Charlson comorbidity index, number of primary care contacts and year of diagnosis
Sadeghi (2012)[12]	US	PAC	Metformin at diagnosis	No metformin at diagnosis	Tumor size, tumor site, stage, CA-19-9 and performance status
Nakai (2013)[18]	Japan	Locally advanced/metastatic pancreatic cancer	Metformin use identified from medical records	No metformin use	None
Hwang (2013)[10]	UK	Advance PAC	Metformin prescription between 6 months prior and 1 month after diagnosis	No metformin around cancer diagnosis	Age, sex, diabetes duration, diabetic complications, pancreatitis, Charlson index, BMI, GFR, smoking, insulin, sulfonylurea, TZD and HbA1c
Cheon (2014)[22]	South Korea	Advanced pancreatic cancer	Ever use of metformin	Never use of metformin	Age, HbA1c, CA19-9, T stage, parenchymal atrophy, lymph node involvement, TNM, smoking, alcohol, BMI and chemotherapy
Lee (2016)[11]	South Korea	Pancreatic cancer	Receive metformin at diagnosis and maintain for at least 1 month	Not receive metformin at diagnosis or maintain for less than 1 month	Tumor size, tail involved, CA19-9, stage and ECOG
Kozak (2016)[17]	US	PDAC after surgical resection	Metformin use at the time of initial consultation or upon discharge with exclusion of those receiving metformin after this period	No metformin use at the time of initial consultation or upon discharge	N stage, margin status, age, statin, adjuvant radiation and adjuvant gemcitabine
Choi (2016)[15]	South Korea	Advance PA	Metformin users	Non-metformin users	Performance status, cancer extent and weight loss during first-line therapy
Ambe (2016)[16]	US	PAC after resection	Metformin users	Non-metformin users	None
Chaiteerakij (2016)[13]	US	PDAC	Time-varying variable for metformin use	Time-varying variable for non-metformin use	Age, sex, BMI, stage of disease and year of diagnosis
Cerullo (2016)[21]	US	PC after resection	Ever use of metformin	Never use of metformin	Age, sex, region, lymph node involvement, diabetes diagnosis at surgery, Charlson comorbidity index and treatment regimen
Kozak (2016)[17]	US	Resectable PC	Continuous use before or after resection	Never use of metformin	N stage, margin status, age, statin, radiation and gemcitabine
Frouws (2017)[19]	The Netherlands	PC	Using metformin before and after diagnosis	Never use of metformin	Age, number of comorbidities, stage, year of diagnosis and therapy (surgery, radiotherapy and chemotherapy)
E (2017)[14]	US	PDAC	Metformin use before diagnosis	Never use of metformin	Stage, grade, tumor size, treatment: resection, radiation, chemotherapy, propensity scores and imbalanced variables after propensity scores adjustment
Jang (2017)[20]	South Korea	Localized resectable PC	Metformin for >90 days from 6 months before diagnosis till last follow-up	Never use of metformin	Age, sex and Charlson comorbidity index

Abbreviations: PAC, pancreatic adenocarcinoma; PDAC, pancreatic ductal adenocarcinoma; PA, pancreatic cancer, BMI, body mass index; ECOG, eastern cooperative oncology group; NA, not available; TZD, thiazolidinedione.

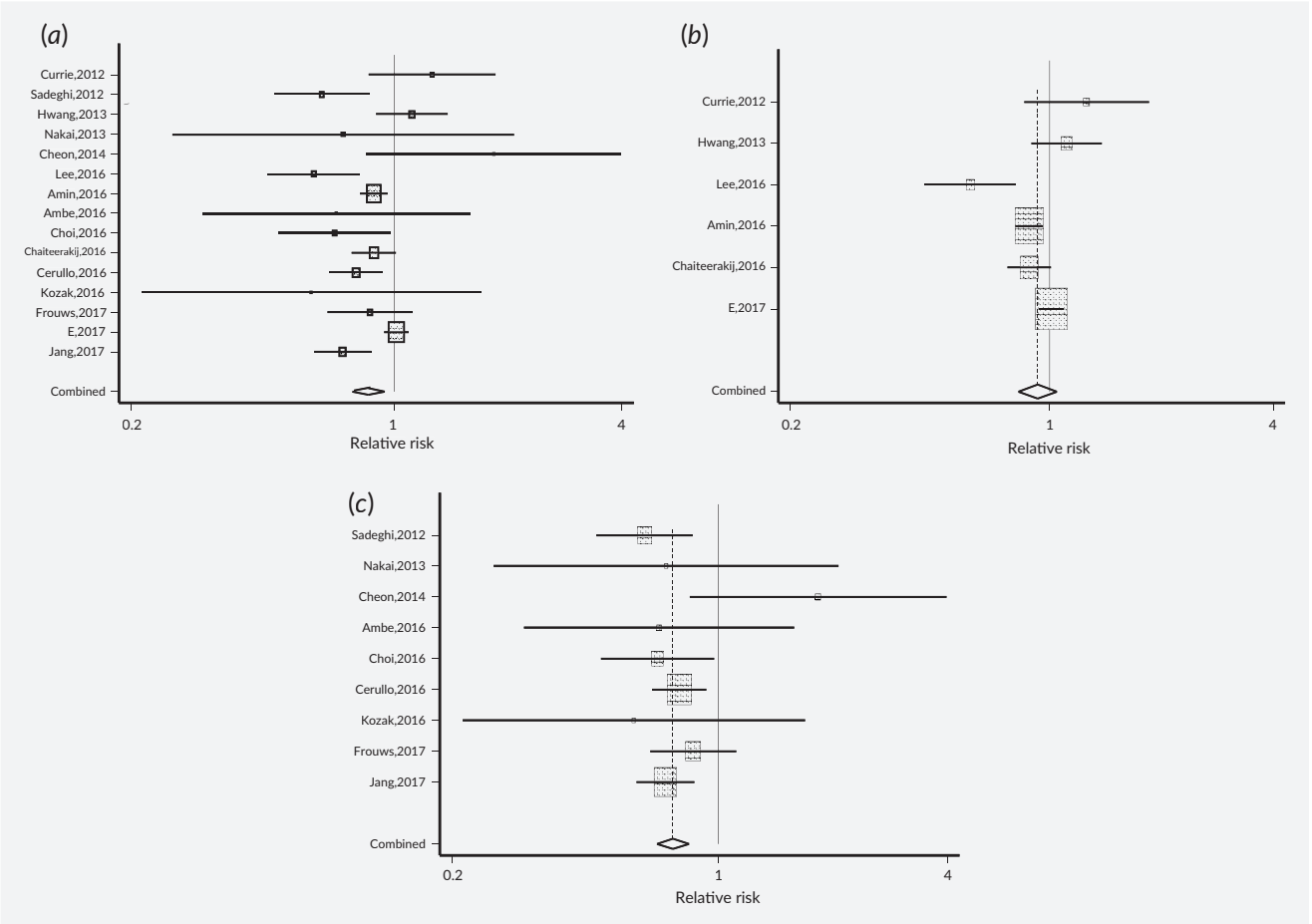

Figure 2. Pooled relative risk and 95% confidence interval (CI) from (*a*) 15 cohort studies with or without immortal time bias, (*b*) six cohort studies without immortal time bias and (*c*) nine cohort studies with immortal time bias. Squares indicate relative risk in each study. Square size is proportional to the weight of the corresponding trial in the meta-analysis; the length of the horizontal lines represents the 95% CI. The unshaded diamond indicates the pooled relative risk and 95% CI.

studies[12,15–22] not subject to immortal time bias was 0.93 (95% CI 0.82, 1.05; $p = 0.22$). These findings concur with data from clinical trials: three Phase II clinical trials did not found significant improvement in pancreatic cancer survival with adjuvant metformin therapy.[24–26] Although the pooled RR from the other nine cohort studies showed a reduction of 24% in pancreatic cancer mortality with metformin (RR 0.76, 95% CI 0.69, 0.84; $p < 0.001$), these nine studies[12,15–22] compared metformin versus non-metformin and were subject to immortal time bias. Theoretically, the presence of immortal time bias in these nine cohort studies leads to smaller values for effect estimates, favoring a beneficial effect of metformin. Although we do not have sufficient data to quantify the magnitude of the immortal time bias in these nine cohort studies, the observed 24% reduction would for sure be offset to some extent by correcting the bias.

Besides immortal time bias, other limitations inherent in observational studies may affect the validity of the effect estimation, as were described extensively elsewhere.[1] In addition, it is also possible that the aggressive nature and rapid progress of pancreatic cancer may make the potential effect of metformin untestable due to insufficient statistical power. Thus, the findings of null effect on pancreatic cancer survival based on cohort studies need confirmation from ongoing randomized clinical trials among pancreatic cancer patients, although current data from randomized clinical trials do not support an efficacy of metformin on the survival for other cancers, for example, breast cancer.[27] However, it is worthwhile to note that the findings of a null effect in terms of cancer treatment in the present study does not argue against its potential role in chemoprevention of cancer, as epidemiologic research has shown that metformin may reduce the risks of a variety of cancers, for example, lung cancer,[28] colorectal cancer,[29] liver cancer,[30] though not for prostate cancer.[31]

The present study highlighted the importance of controlling immortal time bias in cohort studies of metformin and pancreatic cancer survival. Results from meta-regression showed that the pooled RR from studies subject to immortal

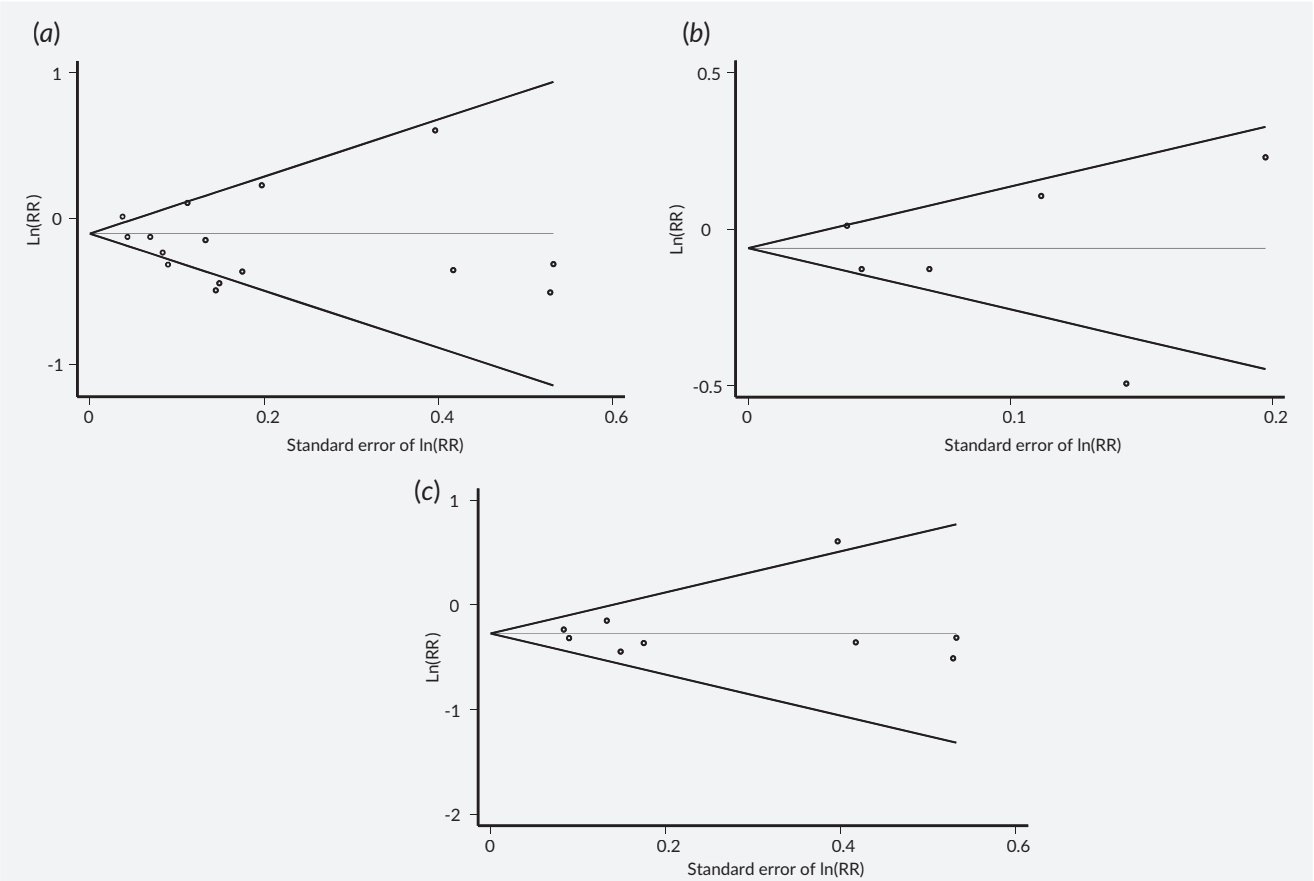

Figure 3. Begg's funnel plot with pseudo 95% confidence limits for (*a*) 15 cohort studies with or without immortal time bias, (*b*) six cohort studies without immortal time bias and (*c*) nine cohort studies with immortal time bias.

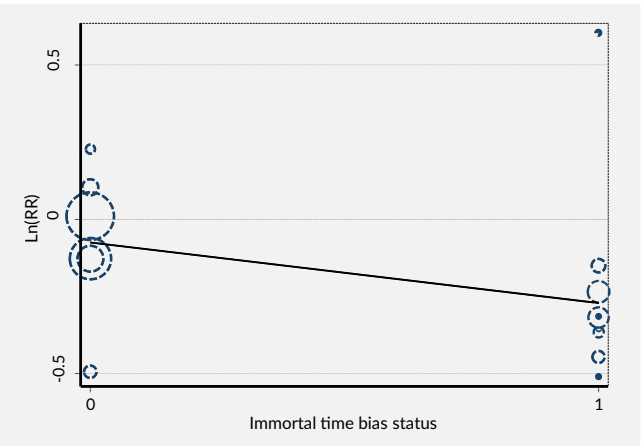

Figure 4. Relation between the effect size of metformin on pancreatic cancer survival and the presence of immortal time bias in the 15 cohort studies. The relation is modeled by meta regression with 0 indicating absence of immortal time bias and 1 indicating presence of immortal time bias in each of the 15 cohort studies. The solid line represents the regression line. Circles indicate ln(RR) in each study. The sizes of circles are proportional to the precision of the RRs (inverse of variance). [Color figure can be viewed at wileyonlinelibrary.com]

time bias was 18% lower than that from studies not subject to immortal time bias, and the difference was statistically significant (p = 0.02). As immortal time bias, in most cases, results in exaggerated effect estimate favoring the exposure at interest, the exciting findings of an outstanding effect estimate may spawn keen interest and hasty but unnecessary investment, which of course has a negative impact on drug development. To avoid futile quest based on exaggerated effect estimation, it is important and necessary for researchers and journals to discern and evaluate immortal time bias. The impact of immortal time bias should be evaluated for each individual study, as its impact is study-specific. Sensitivity analysis is highly recommended to evaluate the impact of immortal time bias.[32]

In conclusion, cumulative evidence from cohort studies does not support a beneficial effect of metformin on pancreatic cancer survival. The association between metformin and pancreatic cancer survival has been greatly exaggerated in previous cohort studies due to the wide existence of immortal time bias. More rigorous designs and statistical methods are needed to account for immortal time bias.

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