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Association of metformin use and cancer incidence: a systematic review and meta-analysis

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Abstract

Background: Metformin is among the most widely used antidiabetics medications because of its minimal toxicity, favorable safety profile, availability, and low cost. In addition to its role in diabetes management, metformin may reduce cancer risk.

Methods: We conducted a comprehensive systematic review and meta-analysis to investigate the association between metformin use and cancer risk, with evaluation by specific cancer type when possible. Applicable studies were identified in PubMed/MEDLINE, Embase, Cochrane Library, Web of Science, and Scopus from inception through March 7, 2023, with metformin use categorized as "ever" or "yes" and a cancer diagnosis as the outcome. Article quality was evaluated using National Heart, Lung, and Blood Institute guidelines, and publication bias was evaluated using the Egger test, Begg test, and funnel plots. Pooled relative risk (RR) estimates were calculated using random-effects models, and sensitivity analysis was completed through leave-one-out cross-validation.

Results: We included 166 studies with cancer incidence information in the meta-analysis. Reduced risk for overall cancer was observed in case-control studies (RR = 0.55, 95% confidence interval [CI] = 0.30 to 0.80) and prospective cohort studies (RR = 0.65, 95% CI = 0.37 to 0.93). Metformin use was associated with reduced gastrointestinal (RR = 0.79, 95% CI = 0.73 to 0.85), urologic (RR = 0.88, 95% CI = 0.78 to 0.99), and hematologic (RR = 0.87, 95% CI = 0.75 to 0.99) cancer risk. Statistically significant publication bias was observed within the studies (Egger *P* < .001).

Conclusions: Metformin may be associated with a decreased risk of many cancer types, but high heterogeneity and risk of publication bias limit confidence in these results. Additional studies in populations without diabetes are needed to better understand the utility of metformin in cancer prevention.

In the United States, approximately 11.3% (37.3 million) of adults 18 years of age and older have been diagnosed with type 2 diabetes, with an additional 8.5 million adults predicted to have undiagnosed diabetes (1,2). Metformin, which received US Food and Drug Administration approval in 1994 (3), has become the first-line oral therapy for the treatment of type 2 diabetes largely because of its low toxicity, acceptable safety profile, low cost, widespread availability, and efficacy, making it the most commonly prescribed glucose-lowering medication worldwide (4). Although the increased risk of cancer in patients with type 2 diabetes may be attributed to overlapping comorbidities (5), metformin use may reduce cancer risk. *In vitro* and *in vivo* studies have reported antitumorigenic activity following metformin

treatment, including reduced epithelial cell proliferation as well as aberrant crypt foci and tumor volume in xenograft studies (6,7). Few randomized trials have evaluated the effect of metformin treatment on cancer risk, however, instead primarily focusing on mechanistic effects. For example, following a breast cancer diagnosis, women randomly assigned to metformin therapy showed decreased cellular Ki67 staining, indicating reduced proliferation (8). In contrast, a clinical trial of women without diabetes and with operable breast cancer found that metformin treatment did not influence Ki67 expression (9). In a cohort study of patients with breast cancer, however, women who had received metformin treatment had reduced HER2 expression, better clinical outcomes, and lower overall mortality than

women not receiving metformin (10). Despite these promising data, prospective studies evaluating the role of metformin in cancer prevention remain limited.

Several meta-analyses investigating metformin and cancer risk have been conducted to date, but these prior reviews have focused on specific cancer types or locations (eg, reproductive cancers, gastrointestinal cancers) or metformin therapy after cancer diagnosis (11,12). Many of these meta-analyses included a small number of studies and did not consider the rapidly growing number of studies conducted in the past decade. To broaden our understanding of the impact of metformin use on overall cancer risk, the objective of this systematic review and meta-analysis was to summarize the association between metformin use and cancer incidence from eligible randomized controlled trials, case-control studies, and cohort studies. These study designs provide the most comprehensive information about the relationship between metformin use and cancer risk. In addition to summarizing the association between metformin use and overall cancer risk, we evaluated the association by specific cancer type.

Methods
Registration and procedures
A systematic review of the literature was conducted according to the updated Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines and the AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) critical appraisal tool (13,14). The protocol for this systematic review was registered at the International Prospective Registrar of Systematic Reviews (PROSPERO) before the database search was started (PROSPERO 2022 CRD42022295986, available from https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022295986). One revision was made to the protocol after completion of data extraction, as noted on PROSPERO and described in the text that follows. Additionally, it was not appropriate to address the following question included in our protocol because the definition of "metformin use" was highly variable between studies: "What timeframe [sic] of metformin use is necessary to exert a cancer preventive effect?" The Population, Intervention, Comparator, Outcome, and Study design question is shown in Supplementary Table 1 (available online).

Search strategy
A preliminary search strategy and database selection was piloted before conducting the final search. An information specialist at the National Institutes of Health (NIH) library (G.B.) aided in the development of the search protocol. We searched PubMed/MEDLINE, Embase, Cochrane Library/Cochrane Central Register of Controlled Trials, Web of Science, and Scopus for all studies indexed from inception until January 28, 2022. Search was updated on March 7, 2023. The keywords used were tailored to the individual databases and can be found in Supplementary Table 2 (available online) (15). Throughout the meta-analysis, the term *article* refers to the entirety of the publication identified from the search process (Figure 1). More than 1 article could correspond to the same study if secondary or tertiary analyses were identified in our search, referenced in the original article, or provided by the researchers. A citation search of included articles was performed to identify additional relevant articles not captured in the search. As all data used in this meta-analysis are publicly available, this study was exempt from institutional review.

Eligibility criteria
The database results were imported into citation management software EndNote 20 (Clarivate Analytics, London, UK) and duplicates removed. The records were then imported into the online screening software Covidence (Melbourne, VIC, Australia), where further duplicates were identified and records were screened against the eligibility criteria. Studies were considered eligible for inclusion if the publication 1) was available in English; 2) was not an abstract, review, meta-analysis, case study, case report, or unpublished clinical trial; 3) had cancer incidence as an outcome; 4) included metformin or antidiabetes medications where metformin exposure could be isolated; 5) had a control population that included individuals without type 2 diabetes, individuals with type 2 diabetes but not cancer, individuals without cancer, or individuals with cancer who were not on metformin; 6) had a control group that received a placebo, no treatment, or was not on metformin (co-treatments were eligible); and 7) included effect estimates for extraction, the effect estimates could be calculated from the presented data, or data could be obtained from the study authors. To allow for a comprehensive assessment of cancer risk, the search was not limited by cancer type. As stated in the PROSPERO protocol, after completion of data extraction, we adjusted the comparison group for the review to "no metformin use" rather than "placebo" or "no treatment." This was done because few, if any, studies had a placebo or no-treatment group but rather classified participants as metformin nonusers. Therefore, by making this adjustment, we could complete a more comprehensive evaluation of the literature.

Study selection and extraction
The literature search was conducted by the NIH Library (G.B.). All retrieved article titles and abstracts were reviewed by 2 independent reviewers, and disagreements were resolved through discussions. Those articles that passed the title and article screening phase were retrieved for full-text review. Full-text articles were also reviewed by 2 independent reviewers, and disagreements were resolved through discussion. We used Covidence to generate a template for all reviewers to use for extraction. Two of the three reviewer pairs (H.A.L. and K.N.L.H., A.B.S. and L.E.O., M.B.W. and M.B.) extracted data that were later cross-checked by the lead investigator (H.A.L). Extracted data included study information (eg, authors, study location), population demographics, cancer types, study design, metformin treatment and dosage, and effect estimates with corresponding 95% confidence intervals (CIs). Effect estimates from multivariable models were extracted wherever possible, along with the variables included in the final published model. If adjusted model estimates were not available, crude or unadjusted estimates and 95% CIs were used. Extraction templates were compared between reviewers to verify study data. Any disagreements in the extraction were resolved by discussion. Study corresponding authors were contacted a maximum of 2 times to provide clarification or additional data not available in the published article. If the corresponding authors were nonresponsive and the requested data were required for meta-analysis calculation, the article was excluded from review. Our original search included cancer incidence and cancer-specific mortality outcomes, but for this analysis, because of the large volume of papers found in our search, we included only studies that evaluated cancer incidence.

Study quality assessment and risk of bias
Study quality and risk of bias assessment was completed by 2 independent researchers for each extracted study, per guidelines
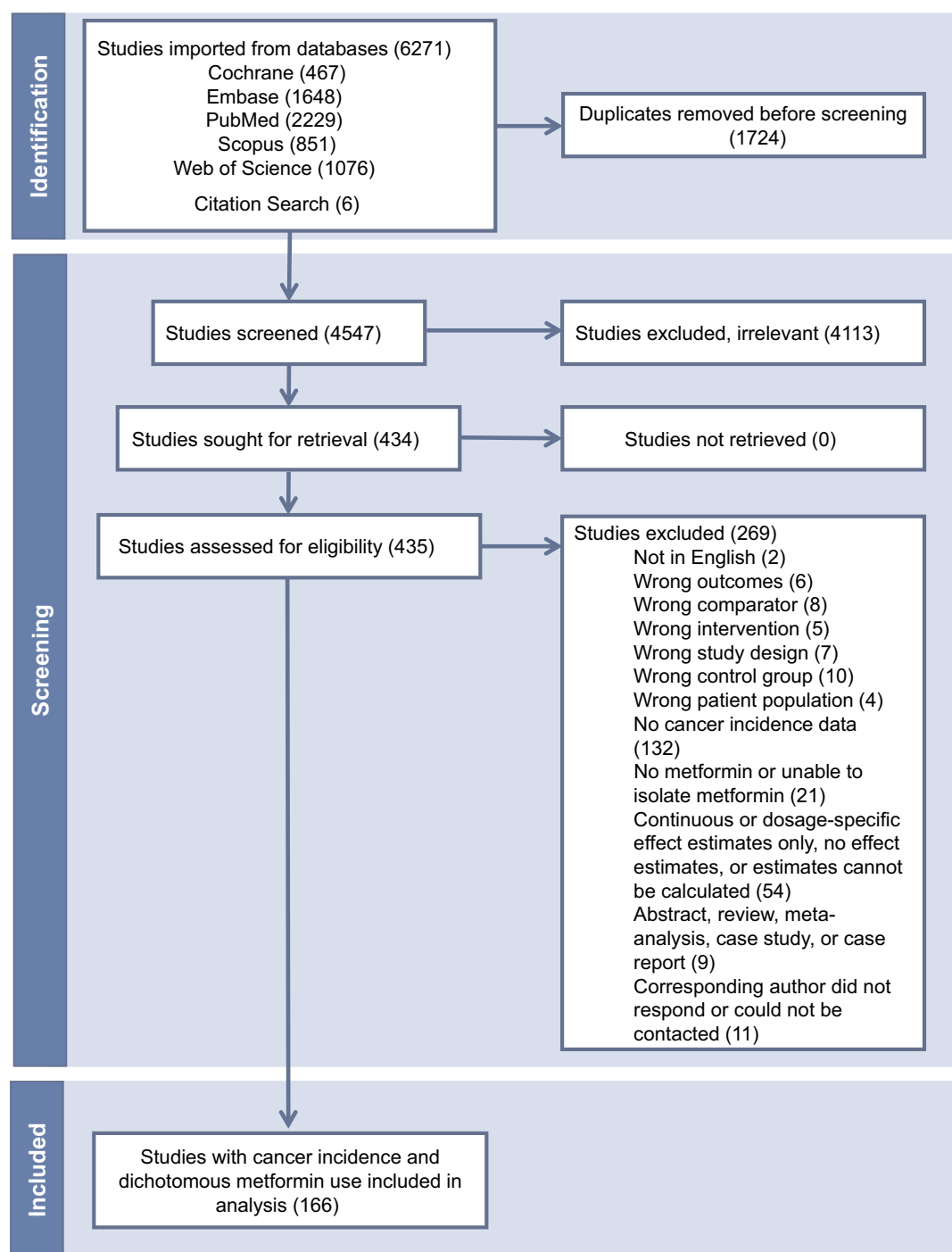
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┌─────────────────────────────────────────┐       ┌─────────────────────────────────┐
│ Studies imported from databases (6271)  │       │ Duplicates removed before       │
│        Cochrane (467)                   │──────▶│ screening (1724)                │
│        Embase (1648)                    │       │                                 │
│        PubMed (2229)                    │       └─────────────────────────────────┘
│        Scopus (851)                     │
│        Web of Science (1076)            │
│        Citation Search (6)              │
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Identification

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┌─────────────────────────────┐       ┌─────────────────────────────────┐
│ Studies screened (4547)     │──────▶│ Studies excluded, irrelevant    │
│                             │       │ (4113)                          │
└─────────────────────────────┘       └─────────────────────────────────┘

┌─────────────────────────────┐       ┌─────────────────────────────────┐
│ Studies sought for          │──────▶│ Studies not retrieved (0)       │
│ retrieval (434)             │       │                                 │
└─────────────────────────────┘       └─────────────────────────────────┘

┌─────────────────────────────┐       ┌─────────────────────────────────┐
│ Studies assessed for        │──────▶│ Studies excluded (269)          │
│ eligibility (435)           │       │    Not in English (2)           │
└─────────────────────────────┘       │    Wrong outcomes (6)           │
                                       │    Wrong comparator (8)         │
                                       │    Wrong intervention (5)       │
                                       │    Wrong study design (7)       │
                                       │    Wrong control group (10)     │
                                       │    Wrong patient population (4) │
                                       │    No cancer incidence data     │
                                       │    (132)                        │
                                       │    No metformin or unable to    │
                                       │    isolate metformin (21)       │
                                       │    Continuous or dosage-specific│
                                       │    effect estimates only, no    │
                                       │    effect estimates, or         │
                                       │    estimates cannot be          │
                                       │    calculated (54)              │
                                       │    Abstract, review, meta-      │
                                       │    analysis, case study, or case│
                                       │    report (9)                   │
                                       │    Corresponding author did not │
                                       │    respond or could not be      │
                                       │    contacted (11)               │
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Screening

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┌─────────────────────────────────────────┐
│ Studies with cancer incidence and       │
│ dichotomous metformin use included in   │
│ analysis (166)                          │
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Included

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analyses flow diagram for identification of relevant studies for inclusion.

established by the National Heart, Lung, and Blood Institute (Supplementary Table 3, available online) (16). Publication bias was assessed using the Egger test and Begg test, with the accompanying funnel plots. P less than .05 was indicative of publication bias.

Statistical analyses

Our main objective was to assess the association between metformin use (vs no metformin use [referent]) and overall risk of cancer incidence. To explore possible sources of heterogeneity, we conducted a subgroup analysis stratified by study design (randomized controlled trial, cohort, case control), individual cancer types, and organ system groups (digestive, gynecologic, hematologic, urologic). Digestive system cancers included estimates for colon, rectum, esophagus, gastric, liver, and pancreatic cancers. Gynecologic system cancers included cervical, endometrial, and ovarian cancers. Hematologic malignancies included leukemia, lymphoma, and multiple myeloma, and urologic system cancers included bladder and prostate cancers. Most of the studies used in this study were cohort studies (retrospective, prospective); therefore, relative risks (RRs) were considered the primary estimate for the analysis and presented as a pooled relative risk with 95% confidence interval. Only 1 estimate per study was included in the pooled estimates to limit overlapping

populations. To calculate a pooled effect estimate, we used adjusted effect sizes and 95% CIs when possible and calculated unadjusted estimates when necessary, as described earlier. Heterogeneity was assessed by using Higgins I^2, a measure of study variation (17). Pooled RR estimates were calculated using random-effects models and reported using restricted maximum likelihood and sensitivity analysis completed through leave-one-out cross-validation for the main study estimates. All statistical analyses were performed using Stata/SE, version 10.0 statistical software (StataCorp LP, College Station, TX).

Results

The PRISMA flowchart is shown in Figure 1. The initial search was completed on January 28, 2022, and updated on March 7, 2023. Our search yielded 6271 results. After removing duplicates and irrelevant studies, 435 studies were assessed for eligibility. Studies were excluded from the final analysis for the following reasons: not published in English (2 studies); abstract, review, meta-analysis, case study, or case report (9 studies); incorrect outcomes (6 studies), comparator (8 studies), intervention (5 studies), study design (7 studies), control group (10 studies), or patient population (4 studies); no cancer incidence data (132 studies); no metformin or unable to isolate metformin for estimates (21 studies); continuous or dosage-specific effect estimates only, no effect estimates, or effect estimates cannot for calculated (54 studies); and corresponding author was nonresponsive or could not be contacted (11 studies). Excluded studies and individual reasons for exclusion are shown in Supplementary Table 4 (available online). This left 166 studies with cancer incidence data and reported dichotomous metformin use that fulfilled the inclusion criteria (Supplementary Table 5, available online). The included studies were retrospective cohort (85 studies), case control (55 studies), cross-sectional (2 studies), prospective cohort (21 studies), and a randomized control trial (1 study). Two studies included estimates for both retrospective cohort and nested case-control studies. The majority of the studies included in our analysis were considered to be good (71 studies) or fair (88 studies) quality, with few (7 studies) considered poor quality (Supplementary Table 6, available online). Five of the 7 poor-quality studies were cohort studies, while the remaining 2 were case-control studies. The most common weaknesses of these studies were insufficient follow-up, no sample size justification, and lack of appropriate model adjustment. The full list of the included studies, study characteristics, and quality scores is provided in Supplementary Table 6 (available online).

As shown in Figure 2, metformin use was associated with a statistically significant reduction in overall cancer incidence. Pooled RRs were similar between prospective studies (RR = 0.65, 95% CI = 0.37 to 0.93; I^2 = 98.0%) and case-control studies (RR = 0.55, 95% CI = 0.30 to 0.80; I^2 = 98.5%), while cross-sectional studies (RR = 0.96, 95% CI = 0.67 to 1.24; I^2 = 0.0%) and retrospective cohort studies (RR = 0.86, 95% CI = 0.70 to 1.03; I^2 = 99.9%) showed no difference in cancer risk with metformin use (Figure 2). Significant publication bias was observed within the studies (Egger $P < .001$) (see Supplementary Figure 1, available online, for Begg funnel plots of all estimates).

Next, we evaluated the relationship between metformin use and cancer incidence for individual cancer types. Among the included studies, most estimates were provided for breast (25 studies), colorectal (29 studies), liver (32 studies), and prostate (29 studies) cancers. Pooled RRs were similar between the included case-control studies (RR = 0.92, 95% CI = 0.83 to 1.00;

I^2 = 66.8%), retrospective cohort studies (RR = 0.99, 95% CI = 0.72 to 1.26; I^2 = 97.1%), and prospective cohort studies (RR = 0.93, 95% CI = 0.79 to 1.08; I^2 = 50.2%) for breast cancer (Figure 3; Supplementary Figure 1, available online). Leave-one-out analysis suggested that the estimate from 1 study (Andersson et al., 2012) may have been different from the other included studies, though overall heterogeneity did not improve following removal of the study (Supplementary Figure 2, available online). A statistically significant reduction in colorectal cancer incidence with metformin use was observed in case-control studies (RR = 0.71, 95% CI = 0.50 to 0.92; I^2 = 92.4%), prospective cohort studies (RR = 0.37, 95% CI = 0.29 to 0.45; I^2 = 0.0%), and retrospective cohort studies (RR = 0.85, 95% CI = 0.75 to 0.96; I^2 = 98.2%) but not nested case-control studies (RR = 0.92, 95% CI = 0.84 to 1.01; I^2 = 12.6%) (Figure 4; Supplementary Figure 1, available online).

Metformin use was associated with reduced liver cancer incidence for case-control studies (RR = 0.54, 95% CI = 0.29 to 0.79; I^2 = 98.4%), nested case-control studies (RR = 0.70, 95% CI = 0.63 to 0.78; I^2 = 0.0%), and retrospective cohort studies (RR = 0.73, 95% CI = 0.61 to 0.85; I^2 = 97.5%) (Figure 5; Supplementary Figure 1, available online). A statistically significant reduction in prostate cancer incidence with metformin use was observed in case-control studies (RR = 0.91, 95% CI = 0.88 to 0.94; I^2 = 0.0%) and prospective cohort studies (RR = 0.80, 95% CI = 0.61 to 0.99; I^2 = 82.1%) but not among nested case-control studies (RR = 1.02, 95% CI = 0.78 to 1.25; I^2 = 81.7%) or retrospective cohort studies (RR = 0.85, 95% CI = 0.71 to 1.00; I^2 = 98.1%) (Figure 6; Supplementary Figure 1, available online). Summary estimates for colorectal, liver, and prostate cancers were not substantially altered in the leave-one-out analysis (Supplementary Figure 2, available online). Of note, the studies and estimates for all or multiple, breast, colorectal, liver, and prostate cancers demonstrated significantly high heterogeneity.

Table 1 includes the summary relative risks for the remaining cancers included in our analysis. Because of the limited number of studies for each cancer type, we did not stratify by study design. Metformin use was associated with reduced risk of bladder cancer (RR = 0.70, 95% CI = 0.56 to 0.83; I^2 = 61.3%), cervical cancer (RR = 0.68, 95% CI = 0.49 to 0.87; I^2 = 50.3%), esophageal cancer (RR = 0.68, 95% CI = 0.50 to 0.86; I^2 = 88.5%), gastric cancer (RR = 0.76, 95% CI = 0.63 to 0.89; I^2 = 94.8%), head and neck or oral cancer (RR = 0.58, 95% CI = 0.45 to 0.72; I^2 = 65.8%), lung cancer (RR = 0.88; 95% CI = 0.76 to 0.99; I^2 = 90.9%), ovarian cancer (RR = 0.53, 95% CI = 0.21 to 0.85; I^2 = 73.3%), and thyroid cancer (RR = 0.74, 95% CI = 0.51 to 0.97; I^2 = 81.9%). Metformin use was not statistically significantly associated with an increased risk of any specific cancer type. Funnel plots are included for each cancer type in Supplementary Figure 1 (available online).

Finally, we investigated the association between metformin use and cancer by grouped organ system (Table 2). Evaluating the association with metformin by organ system allowed for the inclusion of additional papers and estimates. We included 13 estimates for gynecologic cancer (endometrial, ovarian, cervical), 110 for gastrointestinal cancers (esophagus, gastric, pancreatic, colorectal, liver), 41 for urologic cancers (kidney, bladder, prostate), and 8 for hematologic cancers. We found that metformin use was associated with reduced incidence for gastrointestinal cancers (RR = 0.79, 95% CI = 0.73 to 0.85; I^2 = 99.9%), urologic cancers (RR = 0.88, 95% CI = 0.78 to 0.99; I^2 = 98.3%), and hematologic cancers (RR = 0.87, 95% CI = 0.75 to 0.99; I^2 = 72.0%) but not for gynecologic cancers (RR = 1.03, 95% CI = 0.75 to 1.31; I^2 = 96.4%).

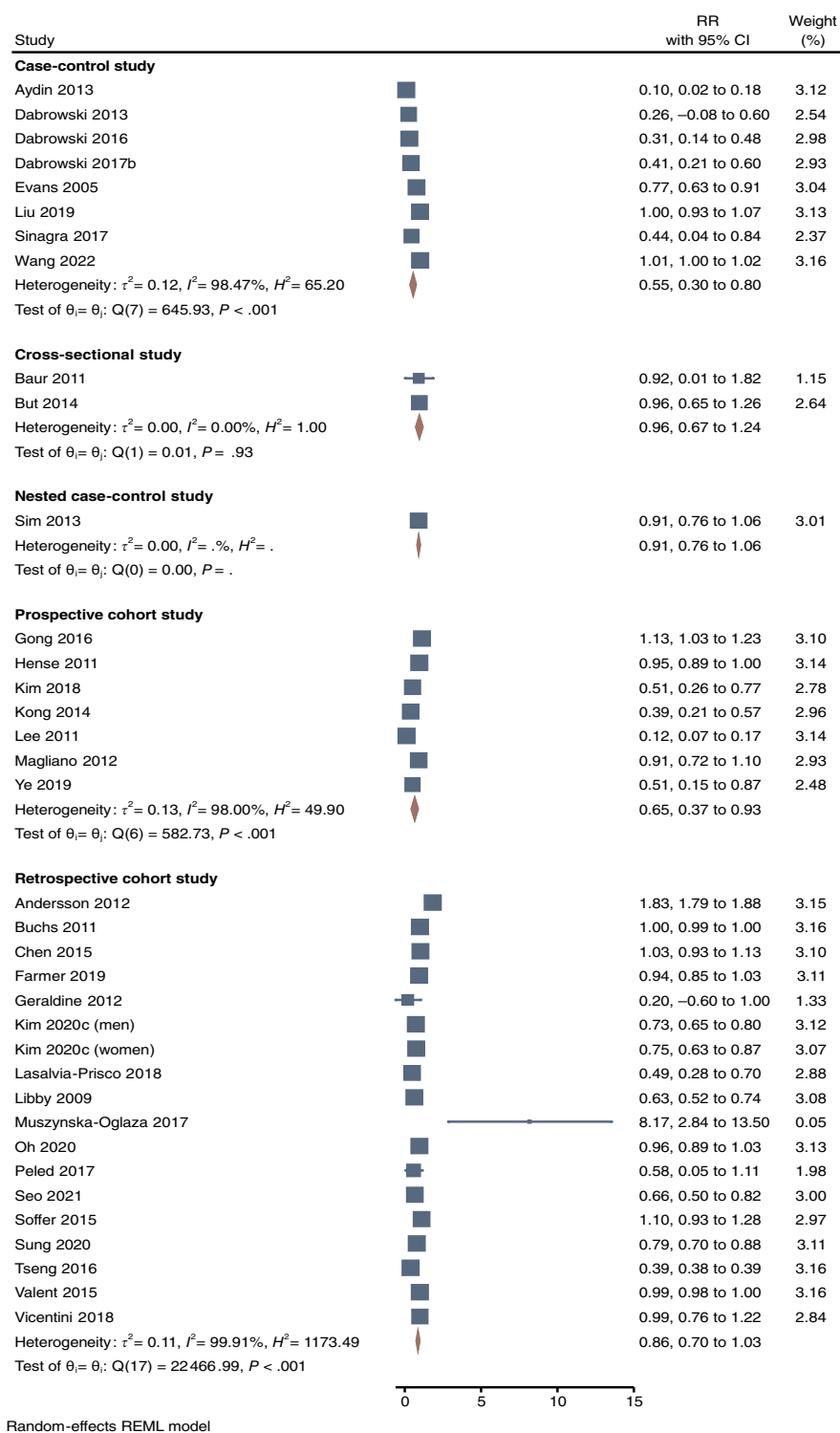| Study		RR with 95% CI	Weight (%)
Case-control study			
Aydin 2013		0.10, 0.02 to 0.18	3.12
Dabrowski 2013		0.26, −0.08 to 0.60	2.54
Dabrowski 2016		0.31, 0.14 to 0.48	2.98
Dabrowski 2017b		0.41, 0.21 to 0.60	2.93
Evans 2005		0.77, 0.63 to 0.91	3.04
Liu 2019		1.00, 0.93 to 1.07	3.13
Sinagra 2017		0.44, 0.04 to 0.84	2.37
Wang 2022		1.01, 1.00 to 1.02	3.16
Heterogeneity: $\tau^2 = 0.12$, $I^2 = 98.47\%$, $H^2 = 65.20$		0.55, 0.30 to 0.80	
Test of $\theta_i = \theta_j$: Q(7) = 645.93, $P < .001$			
Cross-sectional study			
Baur 2011		0.92, 0.01 to 1.82	1.15
But 2014		0.96, 0.65 to 1.26	2.64
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$		0.96, 0.67 to 1.24	
Test of $\theta_i = \theta_j$: Q(1) = 0.01, $P = .93$			
Nested case-control study			
Sim 2013		0.91, 0.76 to 1.06	3.01
Heterogeneity: $\tau^2 = 0.00$, $I^2 = .\%$, $H^2 = .$		0.91, 0.76 to 1.06	
Test of $\theta_i = \theta_j$: Q(0) = 0.00, $P = .$			
Prospective cohort study			
Gong 2016		1.13, 1.03 to 1.23	3.10
Hense 2011		0.95, 0.89 to 1.00	3.14
Kim 2018		0.51, 0.26 to 0.77	2.78
Kong 2014		0.39, 0.21 to 0.57	2.96
Lee 2011		0.12, 0.07 to 0.17	3.14
Magliano 2012		0.91, 0.72 to 1.10	2.93
Ye 2019		0.51, 0.15 to 0.87	2.48
Heterogeneity: $\tau^2 = 0.13$, $I^2 = 98.00\%$, $H^2 = 49.90$		0.65, 0.37 to 0.93	
Test of $\theta_i = \theta_j$: Q(6) = 582.73, $P < .001$			
Retrospective cohort study			
Andersson 2012		1.83, 1.79 to 1.88	3.15
Buchs 2011		1.00, 0.99 to 1.00	3.16
Chen 2015		1.03, 0.93 to 1.13	3.10
Farmer 2019		0.94, 0.85 to 1.03	3.11
Geraldine 2012		0.20, −0.60 to 1.00	1.33
Kim 2020c (men)		0.73, 0.65 to 0.80	3.12
Kim 2020c (women)		0.75, 0.63 to 0.87	3.07
Lasalvia-Prisco 2018		0.49, 0.28 to 0.70	2.88
Libby 2009		0.63, 0.52 to 0.74	3.08
Muszynska-Oglaza 2017		8.17, 2.84 to 13.50	0.05
Oh 2020		0.96, 0.89 to 1.03	3.13
Peled 2017		0.58, 0.05 to 1.11	1.98
Seo 2021		0.66, 0.50 to 0.82	3.00
Soffer 2015		1.10, 0.93 to 1.28	2.97
Sung 2020		0.79, 0.70 to 0.88	3.11
Tseng 2016		0.39, 0.38 to 0.39	3.16
Valent 2015		0.99, 0.98 to 1.00	3.16
Vicentini 2018		0.99, 0.76 to 1.22	2.84
Heterogeneity: $\tau^2 = 0.11$, $I^2 = 99.91\%$, $H^2 = 1173.49$		0.86, 0.70 to 1.03	
Test of $\theta_i = \theta_j$: Q(17) = 22 466.99, $P < .001$			

Random-effects REML model

Figure 2. Estimated summary relative risk for overall cancer risk with metformin use in a random-effects model. This summary includes article estimates for all malignancies, multiple cancers, or several cancers. CI = confidence interval; REML = residual maximum likelihood; RR = relative risk.

Discussion

In this meta-analysis, we found that metformin use was associated with reduced risk of overall cancer incidence as well as of several individual cancer types, despite high statistical heterogeneity likely due to methodological differences across studies. We found protective associations of metformin use with cancer incidence for liver and colorectal cancers. Additional significant associations were observed for prostate, bladder, cervical, esophageal, gastric, head and neck or oral, lung, ovarian, and thyroid cancers. The results of this meta-analysis suggest that metformin use may have pleiotropic effects against cancer, given the different etiologies. Interestingly, many of the cancers where we observed this protective relationship are associated with type 2 diabetes, which could suggest either direct cancer preventive
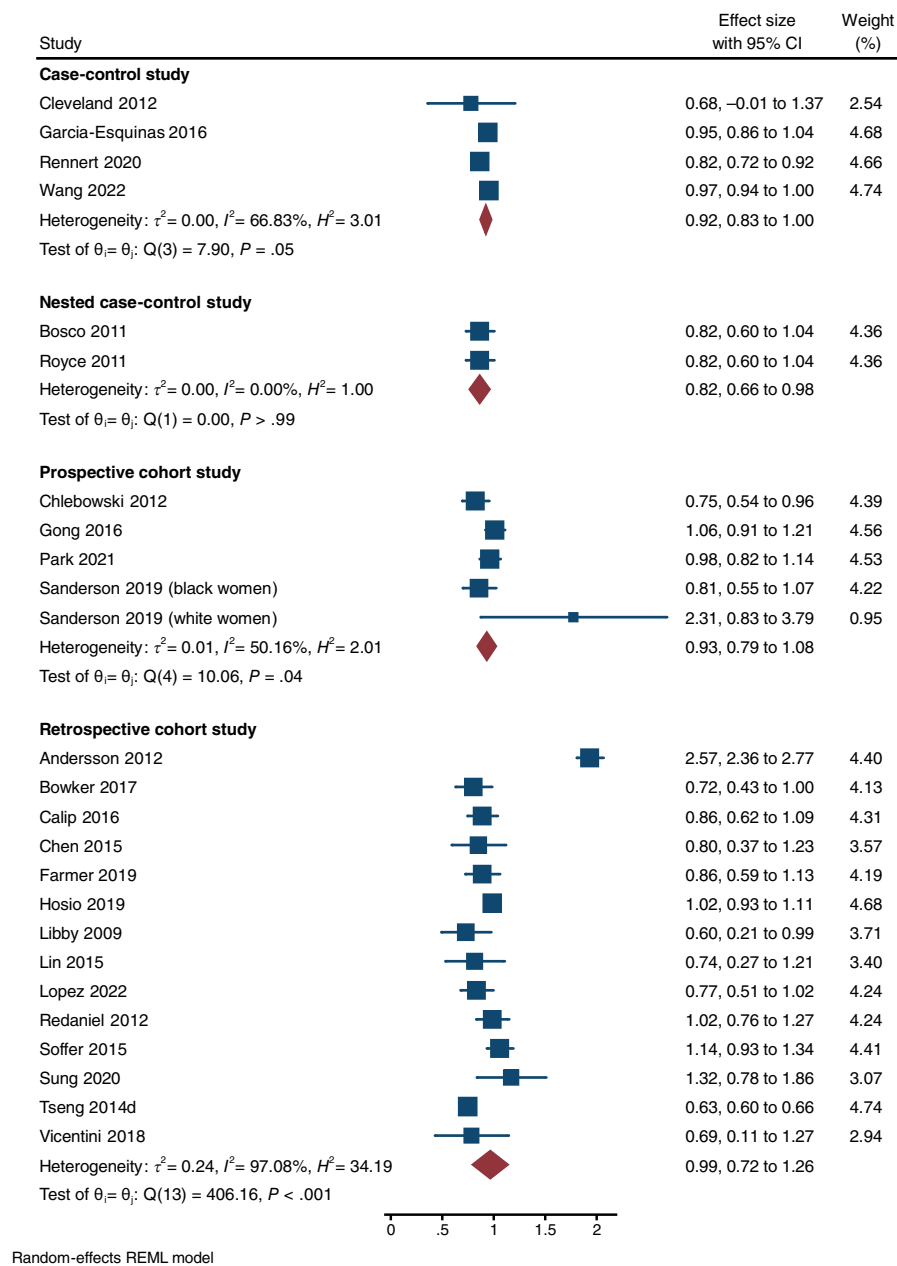
Study	Effect size with 95% CI	Weight (%)
Case-control study		
Cleveland 2012	0.68, –0.01 to 1.37	2.54
Garcia-Esquinas 2016	0.95, 0.86 to 1.04	4.68
Rennert 2020	0.82, 0.72 to 0.92	4.66
Wang 2022	0.97, 0.94 to 1.00	4.74
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 66.83\%$, $H^2 = 3.01$	0.92, 0.83 to 1.00	
Test of $\theta_i = \theta_j$: Q(3) = 7.90, P = .05		
Nested case-control study		
Bosco 2011	0.82, 0.60 to 1.04	4.36
Royce 2011	0.82, 0.60 to 1.04	4.36
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$	0.82, 0.66 to 0.98	
Test of $\theta_i = \theta_j$: Q(1) = 0.00, P > .99		
Prospective cohort study		
Chlebowski 2012	0.75, 0.54 to 0.96	4.39
Gong 2016	1.06, 0.91 to 1.21	4.56
Park 2021	0.98, 0.82 to 1.14	4.53
Sanderson 2019 (black women)	0.81, 0.55 to 1.07	4.22
Sanderson 2019 (white women)	2.31, 0.83 to 3.79	0.95
Heterogeneity: $\tau^2 = 0.01$, $I^2 = 50.16\%$, $H^2 = 2.01$	0.93, 0.79 to 1.08	
Test of $\theta_i = \theta_j$: Q(4) = 10.06, P = .04		
Retrospective cohort study		
Andersson 2012	2.57, 2.36 to 2.77	4.40
Bowker 2017	0.72, 0.43 to 1.00	4.13
Calip 2016	0.86, 0.62 to 1.09	4.31
Chen 2015	0.80, 0.37 to 1.23	3.57
Farmer 2019	0.86, 0.59 to 1.13	4.19
Hosio 2019	1.02, 0.93 to 1.11	4.68
Libby 2009	0.60, 0.21 to 0.99	3.71
Lin 2015	0.74, 0.27 to 1.21	3.40
Lopez 2022	0.77, 0.51 to 1.02	4.24
Redaniel 2012	1.02, 0.76 to 1.27	4.24
Soffer 2015	1.14, 0.93 to 1.34	4.41
Sung 2020	1.32, 0.78 to 1.86	3.07
Tseng 2014d	0.63, 0.60 to 0.66	4.74
Vicentini 2018	0.69, 0.11 to 1.27	2.94
Heterogeneity: $\tau^2 = 0.24$, $I^2 = 97.08\%$, $H^2 = 34.19$	0.99, 0.72 to 1.26	
Test of $\theta_i = \theta_j$: Q(13) = 406.16, P < .001		

Random-effects REML model

Figure 3. Estimated summary relative risk for breast cancer with metformin use in a random-effects model. CI = confidence interval; REML = residual maximum likelihood; RR = relative risk.

benefit or indirect benefit through type 2 diabetes control (18,19). Because the primary indication of metformin prescription is a type 2 diabetes diagnosis, both the control populations and the experimental populations in this study were typically composed of individuals with diabetes. Having type 2 diabetes can increase the risk of cancer, particularly pancreatic, liver, breast, colon, and prostate cancers. Thus, although we have gained insight about metformin use and cancer prevention, further studies are needed to clarify the relationship between metformin and cancer risk in nondiabetic populations.

Metformin is a widely used and prescribed drug to treat type 2 diabetes. In the context of diabetes, metformin decreases fasting and postprandial glucose through a reduction in gluconeogenesis and glucose production (20,21). Though the exact mechanism remains unclear, metformin suppresses gluconeogenesis while enhancing insulin secretion, likely through activation of adenosine monophosphate–activated protein kinase (22). Other proposed mechanisms may involve glucagon-induced inhibition of cyclic adenosine monophosphate, suppression of mitochondrial adenosine triphosphate production, inhibition of mammalian target of rapamycin complex 1 synthesis, reduced gluconeogenesis through mitochondrial glycerophosphate dehydrogenase, and inhibition of cell growth through the suppression of mitochondrial respiration (20,23,24). As a result of these pleiotropic effects, metformin is now prescribed for additional morbidities, including polycystic ovary syndrome, weight management, obesity, diabetic neuropathy, and gestational diabetes (20,25). In a similar vein to type 2 diabetes, inhibition of gluconeogenesis may create unfavorable conditions for cancer cell survival (26). Previous research has shown that glucose deprivation of lung cancer cells can inhibit cellular proliferation and promote apoptosis; thus, targeting glucose metabolism may be a
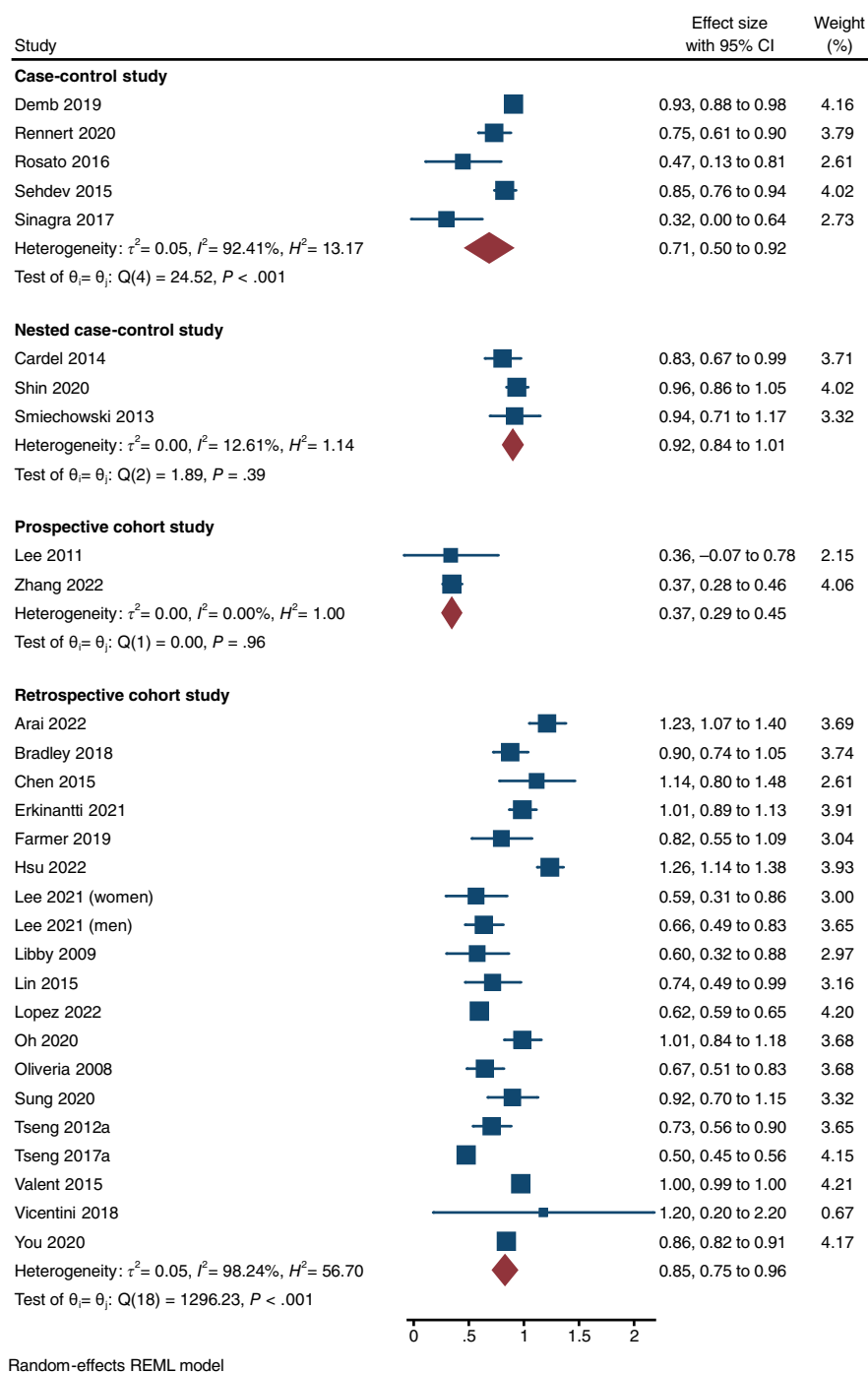
Figure 4. Estimated summary relative risk for colorectal cancer with metformin use in a random-effects model. CI = confidence interval; REML = residual maximum likelihood; RR = relative risk.

worthwhile strategy for cancer prevention (27,28). Metformin use has been primarily studied among people with type 2 diabetes, and evidence is emerging about its preventive utility among people without diabetes (29), though no current studies demonstrate cancer prevention efficacy.

Metformin is a practical chemoprevention agent because it is available, inexpensive, and safe; has few side effects; and can be used long term. Randomized controlled trials using metformin as a cancer prevention intervention in a population without diabetes, with cancer as an outcome, are necessary to fully understand the utility of this drug (30). For example, the Diabetes Prevention Program Outcomes Study, which randomly assigned individuals at high risk of type 2 diabetes to life-style intervention, metformin, or placebo, found no difference in cancer-associated mortality between interventions over a median of 21 years of follow-up, suggesting that metformin use may not influence cancer survival, though incidence data were not reported (31). Recently, an analysis of the ASPirin in Reducing Events in the Elderly trial showed a reduction in cancer risk but not mortality among individuals with type 2 diabetes taking metformin (32). Interestingly, those randomly assigned to the aspirin arm and taking metformin showed increased risk of cancer mortality. Though the
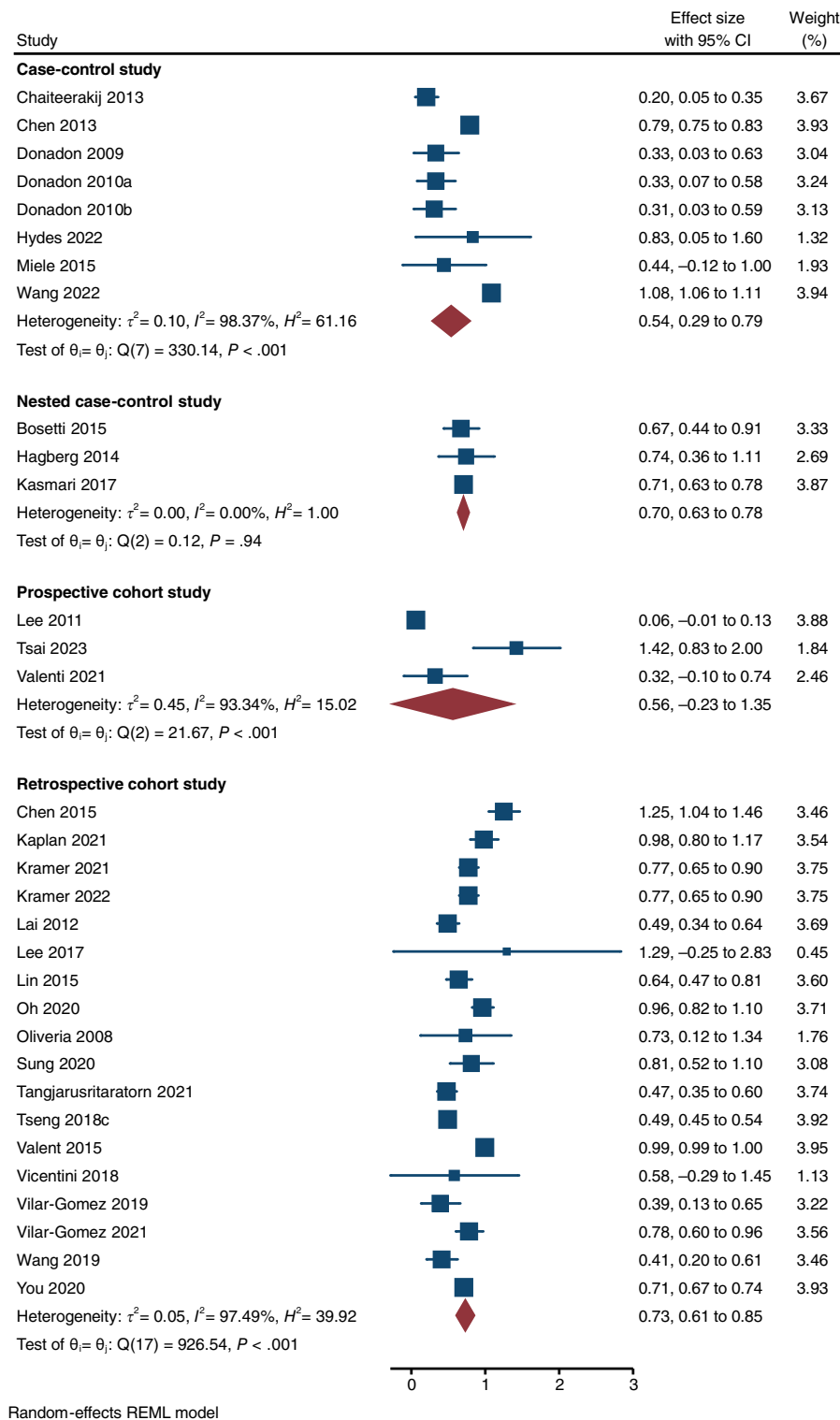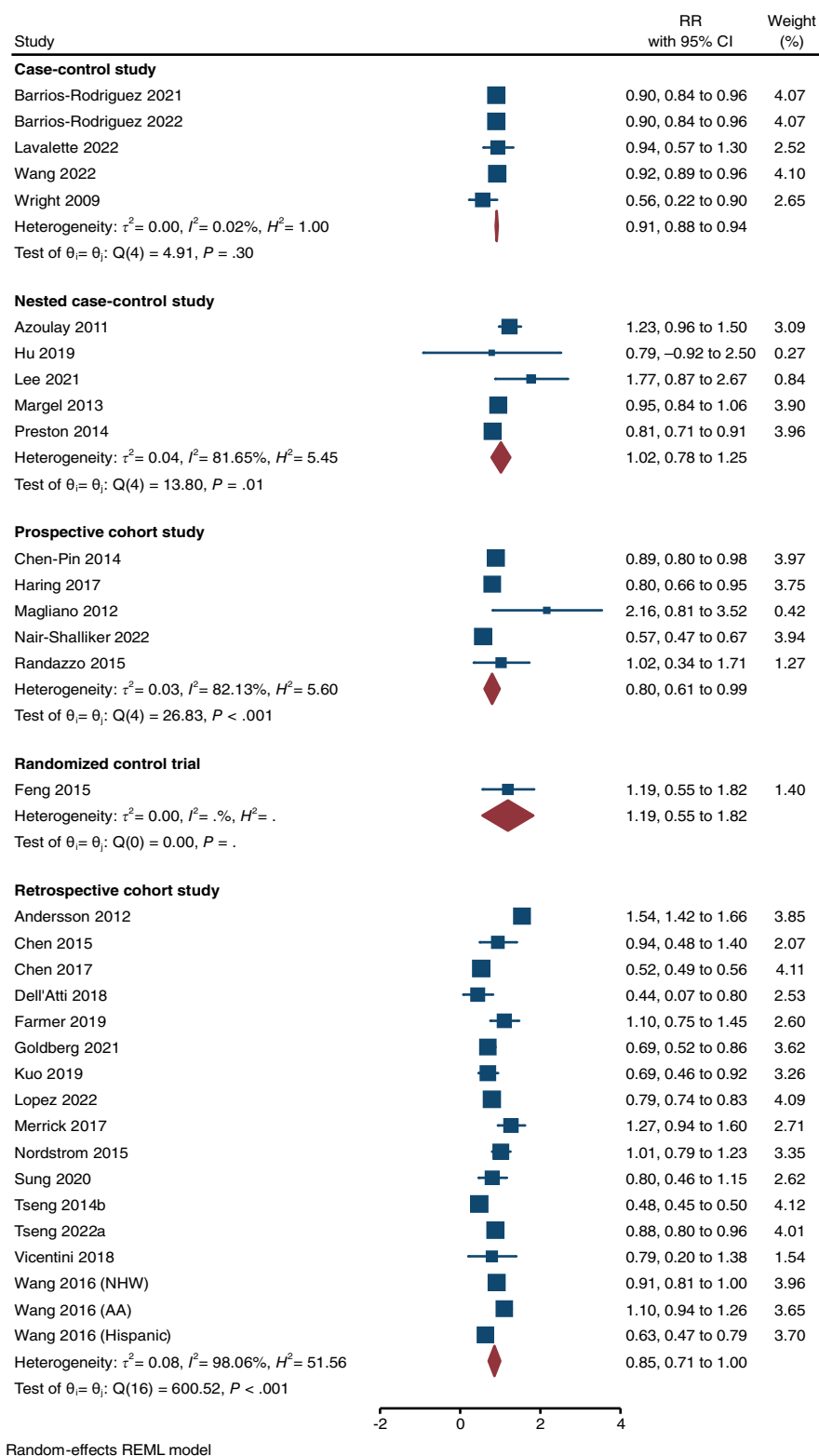
Study	Effect size with 95% CI	Weight (%)
Case-control study		
Chaiteerakij 2013	0.20, 0.05 to 0.35	3.67
Chen 2013	0.79, 0.75 to 0.83	3.93
Donadon 2009	0.33, 0.03 to 0.63	3.04
Donadon 2010a	0.33, 0.07 to 0.58	3.24
Donadon 2010b	0.31, 0.03 to 0.59	3.13
Hydes 2022	0.83, 0.05 to 1.60	1.32
Miele 2015	0.44, −0.12 to 1.00	1.93
Wang 2022	1.08, 1.06 to 1.11	3.94
Heterogeneity: $\tau^2 = 0.10$, $I^2 = 98.37\%$, $H^2 = 61.16$	0.54, 0.29 to 0.79	
Test of $\theta_i = \theta_j$: Q(7) = 330.14, $P < .001$		
Nested case-control study		
Bosetti 2015	0.67, 0.44 to 0.91	3.33
Hagberg 2014	0.74, 0.36 to 1.11	2.69
Kasmari 2017	0.71, 0.63 to 0.78	3.87
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$	0.70, 0.63 to 0.78	
Test of $\theta_i = \theta_j$: Q(2) = 0.12, $P = .94$		
Prospective cohort study		
Lee 2011	0.06, −0.01 to 0.13	3.88
Tsai 2023	1.42, 0.83 to 2.00	1.84
Valenti 2021	0.32, −0.10 to 0.74	2.46
Heterogeneity: $\tau^2 = 0.45$, $I^2 = 93.34\%$, $H^2 = 15.02$	0.56, −0.23 to 1.35	
Test of $\theta_i = \theta_j$: Q(2) = 21.67, $P < .001$		
Retrospective cohort study		
Chen 2015	1.25, 1.04 to 1.46	3.46
Kaplan 2021	0.98, 0.80 to 1.17	3.54
Kramer 2021	0.77, 0.65 to 0.90	3.75
Kramer 2022	0.77, 0.65 to 0.90	3.75
Lai 2012	0.49, 0.34 to 0.64	3.69
Lee 2017	1.29, −0.25 to 2.83	0.45
Lin 2015	0.64, 0.47 to 0.81	3.60
Oh 2020	0.96, 0.82 to 1.10	3.71
Oliveria 2008	0.73, 0.12 to 1.34	1.76
Sung 2020	0.81, 0.52 to 1.10	3.08
Tangjarusritaratorn 2021	0.47, 0.35 to 0.60	3.74
Tseng 2018c	0.49, 0.45 to 0.54	3.92
Valent 2015	0.99, 0.99 to 1.00	3.95
Vicentini 2018	0.58, −0.29 to 1.45	1.13
Vilar-Gomez 2019	0.39, 0.13 to 0.65	3.22
Vilar-Gomez 2021	0.78, 0.60 to 0.96	3.56
Wang 2019	0.41, 0.20 to 0.61	3.46
You 2020	0.71, 0.67 to 0.74	3.93
Heterogeneity: $\tau^2 = 0.05$, $I^2 = 97.49\%$, $H^2 = 39.92$	0.73, 0.61 to 0.85	
Test of $\theta_i = \theta_j$: Q(17) = 926.54, $P < .001$		

Random-effects REML model

Figure 5. Estimated summary relative risk for liver cancer with metformin use in a random-effects model. CI = confidence interval; REML = residual maximum likelihood; RR = relative risk.

literature compiled for this study suggests reduced cancer risk with metformin use, it is important to note that many of the studies included were case-control studies, with only 1 clinical trial. Furthermore, with the significant heterogeneity in the data, the results of this study should be interpreted with caution. Gandini and colleagues (33) presented a similar conclusion in their meta-analysis of metformin and cancer risk and mortality.

The authors observed a 31% reduced risk of overall cancer incidence with metformin use, though the effect was muted when adjusted for body mass index and time-related biases. The role of metformin in cancer prevention must be further tested in controlled studies not only to confirm its effects but to determine how dose and utility influence those effects and who might benefit the most.

Figure 6. Estimated summary relative risk for prostate cancer with metformin use in a random effects model. CI = confidence interval; REML = residual maximum likelihood; RR = relative risk.

Limitations

Although this meta-analysis has provided insight into the relationship between metformin and cancer incidence, there are several limitations to consider. The definition of "metformin use" varied between studies; metformin use was either self-reported or acquired from prescription information or medical records (eg, ≥2 prescriptions over the course of a designated time would qualify as "use"). Duration of or cumulative use or dose were sometimes stated or included in the analyses of individual studies but overall was difficult to collect and accurately assess.

Table 1. Estimated summary relative risks and corresponding 95% confidence intervals for the association between metformin use and other cancers in a random-effects model[a]

Cancer type	Estimates included, No.	Summary relative risk (95% confidence interval)	Heterogeneity I^2, H^2	Bias test: Egger, Begg
Bile duct or biliary tract	4	0.82 (0.54 to 1.11)	93.3%, 14.91	<0.001, 0.73
Bladder	5	0.70 (0.56 to 0.83)	61.3%, 2.59	0.01, 0.22
Bone	3	0.90 (0.74 to 1.06)	30.2%, 1.43	0.57, 1.00
Cervical	3	0.68 (0.49 to 0.87)	50.3%, 2.01	0.61, 1.00
Endometrial	6	1.12 (0.89 to 1.35)	72.9%, 3.69	<0.001, 0.71
Esophageal	12	0.68 (0.50 to 0.86)	88.5%, 8.71	<0.001, 0.13
Gastric	15	0.76 (0.63 to 0.89)	94.8%, 28.73	<0.001, 0.14
Head and neck or oral	8	0.58 (0.45 to 0.72)	65.8%, 2.92	0.35, 0.90
Kidney	3	0.66 (0.12 to 1.19)	92.6%, 13.55	<0.001, 1.00
Lung	19	0.88 (0.76 to 0.99)	90.9%, 11.00	0.01, 0.15
Ovarian	2	0.53 (0.21 to 0.85)	73.3%, 3.75	NC
Pancreatic	15	1.13 (0.86 to 1.40)	95.6%, 22.92	0.04, 0.06
Skin	5	0.86 (0.63 to 1.09)	78.4%, 4.62	0.14, 0.81
Thyroid	6	0.74 (0.51 to 0.97)	81.9%, 5.53	0.02, 1.00

[a]   Estimates of publication bias are indicated in this table by the Begg test and in Supplementary Figure 1 (available online) (funnel plot). NC = not calculated.

Table 2. Estimated summary relative risk and corresponding 95% confidence interval for the association between metformin use and cancer risk by organ system in a random-effects model[a]

Organ system	Estimates included, No.	Summary relative risk (95% confidence interval)	Heterogeneity I^2, H^2	Bias test: Egger, Begg
Gastrointestinal	110	0.79 (0.73 to 0.85)	99.9%, 2624.94	0.04, <0.001
Gynecologic	13	1.03 (0.75 to 1.31)	96.4% 27.75	0.23, 0.20
Hematologic	8	0.87 (0.75 to 0.99)	72.0%, 3.57	0.59, 0.71
Urologic	41	0.88 (0.78 to 0.99)	98.3%, 58.48	<0.001

[a]   Measures of study heterogeneity and bias are included.

Of those stated, doses were often categorized, and cutoff values for metformin categories varied between studies. A subgroup analysis by length of metformin use, limited to studies with a clear definition of metformin use of at least 90 days, did not resolve issues with heterogeneity. Additionally, patient adherence to the dosage schedule can be difficult to determine, and given that individuals with type 2 diabetes are likely to have other comorbidities, interactions with other medications may interfere or enhance downstream pathways affected by metformin. Ideally, a metabolic measure (ie, biomarker) would provide the best assessment for metformin dosing and relationship with cancer risk. Only 1 randomized controlled trial identified in our search met inclusion criteria; thus, cause and effect cannot be determined from the observational nature of the included studies.

We had a large number of studies for analyses of common cancers, but heterogeneity remained high, indicated by most I^2 values above 75% (34). This finding likely represents methodological differences or variation in population characteristics of the combined studies, which means that there is variation in the effects estimated but not necessarily that the true effect varies (34). We attempted to identify the sources of heterogeneity through subgroup analysis. A likely cause of heterogeneity is differential comparison groups between studies. When we restricted our analysis to those studies using "no diabetes" or "no antidiabetic medication" as comparison or reference groups, heterogeneity was reduced (Supplementary Table 7, available online). Therefore, being cognizant of the differences in comparison and reference groups is necessary when interpreting study results. Further, the significant confidence intervals suggest that the signal is persistent, regardless of this level of variance or

heterogeneity. Further, the leave-one-out analyses did not indicate that inclusion or exclusion of certain point estimates meaningfully affected the results. For less common cancers that included a smaller number of studies, caution is warranted because the risk of publication bias is higher.

The results of this meta-analysis suggest that metformin use, compared with no metformin use, is associated with a decreased risk of overall cancer as well as several cancer subtypes, largely for populations that have type 2 diabetes, though these results should be interpreted with caution due to high heterogeneity in study design and risk for publication bias. Future cancer prevention trials for nondiabetic populations would further elucidate the preventative potential of metformin.

Data availability

All data used in this study are publicly available.

Author contributions

Lauren O'Connor, PhD, MPH (Data curation; Formal analysis; Validation; Writing—original draft; Writing—review & editing), Maeve Bailey-Whyte, PhD, MPH (Data curation; Writing—original draft; Writing—review & editing), Manami Bhattacharya, PhD, MPH (Data curation; Writing—original draft; Writing—review & editing), Gisela Butera, MLIS, MA (Methodology; Software; Validation), Kaitlyn Hardell, PhD, MPH (Data curation; Writing—original draft; Writing—review & editing), Andrew Seidenberg, PhD, MPH (Data curation; Writing—original draft; Writing—review & editing), Philip Castle, PhD, MPH (Conceptualization; Writing—review & editing), Holli A. Loomans-Kropp, PhD, MPH

Conflicts of interest

P.C., who is a *JNCI* associate editor and co-author on this paper, was not involved in the editorial review or decision to publish the manuscript. The authors declare no conflicts of interest. The content presented here is the sole responsibility of the authors and does not reflect the official views of the NIH.

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