Metformin and endometrial cancer risk: A Meta-analysis

Weimin Xie (xwm315423@163.com)
Southern Medical University
Dan Wen
Southern Medical University

Research article

Keywords: Metformin, Endometrial cancer, Cancer risk, Meta-analysis

Posted Date: December 19th, 2019

DOI: https://doi.org/10.21203/rs.2.19317/v1

Abstract

Objective: To assess the association between metformin and endometrial cancer risk by conducting a meta-analysis.

Methods: A comprehensive search of electronic databases, conference abstracts, and clinical trial registers was performed to identify available evidence. Studies that evaluated the association between metformin use and endometrial cancer risk were considered. We pooled relative risk (RR) estimates with 95% confidence intervals (CIs) by using either a fixed-effects or a random-effects model.

Results: Nine studies (1 randomized controlled trial, 5 cohort studies, and 3 case-control studies) involving more than 1.20 million participants and 7,762 cases of endometrial cancer met eligibility criteria. There was no evidence of an association between metformin use and endometrial cancer risk (RR, 0.96; 95% CI, 0.80 to 1.16). Similarly, the pooled data showed that metformin use was not significantly associated with endometrial cancer risk in patients with diabetes (RR, 0.93; 95% CI, 0.78 to 1.11). In subgroup analyses, the results were stable across different study designs and comparisons, and remained unchanged after adjusting for age and BMI or obesity.

Conclusions: The current meta-analysis suggests that metformin has no chemopreventive effect against endometrial cancer.

Introduction

Endometrial carcinoma is the most common gynaecologic cancer in developed countries, with 60,050 new cases in the United States alone in the year 2016 [1]. Several risk factors have been reported to be related to an increased risk of endometrial cancer, including reproductive factors, obesity, and diabetes mellitus [2 – 4].

Diabetes mellitus has been linked to associated with an increased risk of endometrial cancer via mechanisms involving insulin resistance and secondary hyperinsulinemia [5, 6]. In the condition of insulin resistance, the elevated insulin may have growth stimulation effects and directly and indirectly increase the risk of endometrial cancer [7, 8]. The direct mechanism includes activation of key signaling pathways, while in the indirect mechanism, insulin interacts with insulin-like growth factor-1 (IGF-1) and affects sex hormone levels, which in turn may promote cell growth [7 – 9]. Insulin resistance is associated with a spectrum of disease, such as abnormal glucose metabolism, type II diabetes mellitus, obesity, polycystic ovary syndrome (PCOS) [10, 11].

Metformin, an oral biguanide hypoglycaemic drug, is the the first line treatment of type II diabetes [12]. It is a well-tolerated and effective drug that normalizes hyperglycemia by reducing insulin resistance and lowering insulin levels [12, 13]. Metformin also has beneficial effects in women with PCOS, obesity, and metabolic syndrome [14 – 16].

A growing body of evidence suggests that metformin may have a chemopreventive role against cancer. Several meta-analyses have shown that metformin use may decrease the incidence of site-specific cancers, including colorectal, pancreatic, and liver cancer [17 – 19], while others have not shown this effect, including prostate and breast cancer [20 – 21]. Recently, several studies have investigated the relationship between metformin use and endometrial cancer risk, with inconsistent findings. Some studies have shown that that metformin use may be associated with a reduced risk of endometrial cancer, whereas others have found no protective effect. Therefore, we carried out a meta-analysis of existing evidence to determine the effect of metformin on endometrial cancer risk.

Materials And Methods

This meta-analysis was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22].

Search strategy

A systematic search was performed in the databases of PubMed, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) to find all relevant articles from inception to October 2019. Both subject headings and free text words were used in the search. The detailed search strategies are presented in Appendix A. We searched the following trial registers electronically for potentially relevant ongoing trials: ClinicalTrials.gov, ISRCTN registry, and World Health Organization International Clinical Trials Registry Platform (ICTRP). We also searched conferences reports in the following sources: Annual Meeting on Women's Cancer of the Society of Gynecologic Oncology, Biannual Meeting of the International Gynecologic Cancer Society, Biannual Meeting of the European Society of Gynecologic Oncology, and Annual Meeting of the American Society of Clinical Oncology. No language restrictions were applied in our search strategy. In addition, we screened the reference lists of the relevant papers for additional studies.

Eligibility criteria

After removing duplicate records, two reviewers screened the titles and abstracts independently. The potentially relevant studies were evaluated in detail to determine their eligibility. The inclusion criteria were as follows: (1) randomized controlled trials (RCTs) or non-randomized studies; (2) evaluated exposure to metformin and endometrial cancer risk; (3) reported risk ratio (RR) and a 95% confidence interval (CI) or provided data for their calculation. Articles were excluded if they were: (1) editorials, letters, reviews, and case reports; (2) studies without appropriate data for determining an estimate of RR and a 95% CI. In cases of multiple publications from the same population, only the most comprehensive studies were included.

Data extraction and quality assessment

The following information was collected from each study: publication data (ie, first author's name, year of publication, and study location), study design, study population, type of comparison, sample size, definition of metformin exposure, RRs and 95% CIs, and control for potential confounders by matching or adjustments. When multiple RR estimates were presented, the most adjusted estimate was extracted.

Two reviewers assessed the quality of included studies independently. The risk of bias in RCTs was evaluated according to the Cochrane Collaboration's tool [23]. The methodological quality of non-randomized studies was assessed according to the Newcastle–Ottawa scale [24]. Studies with a score of 7 or higher were considered as high quality studies.

Statistical analysis

Heterogeneity among study results was explored using the Chi-square (χ^2, or Chi^2) and I^2 test. If substantial heterogeneity (p value < 0.10 or I^2 > 50%) was found, a random-effects model was used to calculate the pooled effect with appropriate cautious interpretation; otherwise, a fixed-effects model was applied. Heterogeneity was explored in subgroup analyses by study design, reference therapy, and adjustment for age and BMI or obesity. Sensitivity analysis was performed to assess the stability of the results. The analyses were performed using Stata version 12.0 software (Stata Corporation, College Station, TX).

Results

Description of studies

A total of 744 records were screened of which 13 articles were assessed for eligibility. Of these, 4 studies were excluded for the following reasons: 1 used overlapping data [25], and 3 did not have available data [(26 – 28]. No additional studies were identified from reference lists. Finally, 9 studies fulfilled the eligibility criteria and were included in the meta-analysis [29 – 37]. The flow diagram for study selection is showed in Fig. 1.

The characteristics of the included 9 studies (1 RCT, 5 cohort studies, and 3 case–control studies) are described in Table 1. The studies were published between 2010 and 2017. Of these, 1 study was carried out in Europe and Australasia [29], 3 in USA [30,32,35], 2 in UK [31,33], 1 in Taiwan [34], 1 in Italy [36], and 1 in Canada [37]. These 9 studies included more than 1.20 million participants. The number of endometrial patients was 14 in the RCT, ranged from 71 to 2885 in cohort studies, and from 376 to 2,554 in case–control studies. All non-randomized studies [30 – 37] were controlled for potential confounders by matching or adjustments. Of the included 9 studies, 7 evaluated the association between metformin use and endometrial cancer risk in diabetic patients [29, 30, 32 – 34, 36, 37], while 2 in both diabetic and non-diabetic patients [31,35].

The risk of bias in the included RCT is shown in Fig. 2. The study [29] was considered at low risk of selection bias, attrition bias, and other bias, but unclear risk of detection bias, high risk of performance bias and reporting bias. The NOS scores calculated for non-randomized studies are shown in Table 1. Five studies were considered as high-quality studies (scores of 7 or higher) [30, 32 – 35].

Metformin use and endometrial cancer risk

In meta-analysis of all studies involving 7,762 cases of endometrial cancer, no evidence for an association between metformin use and endometrial cancer risk was observed (RR, 0.96; 95% CI, 0.80 to 1.16). The results showed significant heterogeneity among the studies (p = 0.000; I^2 = 75.5%) (Fig. 3).

After stratifying the data into subgroups based on study design, we found that metformin had no effect on endometrial cancer risk in RCT (RR = 0.98; 95% CI, 0.35 to 2.77), cohort studies (RR = 0.92; 95% CI, 0.71 to 1.20), or case–control studies (RR = 1.01; 95% CI, 0.85 to 1.20). Analyses stratified by comparisons showed no significant differences between patients receiving metformin vs metformin non-users (RR = 0.86; 95% CI, 0.71 to 1.04), or patients receiving other hypoglycemic agents (RR = 1.16; 95% CI, 0.96 to 1.39). When we limited the meta-analysis to studies that adjusted for potential confounders, the pooled data also showed no significant association between metformin use

and endometrial cancer risk in the studies that adjusted for age (RR, 0.95; 95% CI, 0.73 to 1.23), or BMI or obesity (RR, 1.02; 95% CI, 0.90 to 1.17).

Metformin use and endometrial cancer risk in diabetic patients

Nine studies [29–37] investigated the association between metformin use and endometrial cancer risk in diabetic patients, involving 920,478 participants. There was significant heterogeneity among the studies ($p = 0.001$; $I^2 = 68.7\%$). The pooled data using the random effects model showed no evidence for an association between metformin use and endometrial cancer risk in diabetic patients (RR, 0.93; 95% CI, 0.78 to 1.11) (Fig. 4).

In subgroup meta-analyses, we found that metformin had no effect on endometrial cancer risk in RCT (RR = 0.98; 95% CI, 0.35 to 2.77), cohort studies (RR = 0.86; 95% CI, 0.69 to 1.07), or case–control studies (RR = 1.03; 95% CI, 0.86 to 1.23). Analyses stratified by comparisons showed no significant differences between diabetic patients receiving metformin vs metformin non-users (RR, 0.86; 95% CI, 0.71 to 1.05), or patients receiving other hypoglycemic agents (RR, 1.04; 95% CI, 0.84 to 1.30). When we limited the meta-analysis to studies that adjusted for potential confounders, the pooled data also showed no significant association between metformin use and endometrial cancer risk in the studies that adjusted for age (RR, 0.89; 95% CI, 0.71 to 1.12), or BMI or obesity (RR, 0.96; 95% CI, 0.83 to 1.12).

Sensitivity analysis

In sensitivity analysis, each study was excluded sequentially and the influence was accessed by recalculating the pooled RR. The analysis confirmed the stability of our findings because the results did not change substantially after sequentially excluding each study.

Discussion

With the high incidence of endometrial cancer and extremely poor prognosis associated with advanced-stage disease, it is important to identify potential chemopreventive agents. The present comprehensive meta-analysis included all available clinical studies, involving more than 1.20 million participants with 7762 cases of endometrial cancer. In this meta-analysis, metformin use was not associated with a substantially decreased or increased risk of endometrial cancer. Similarly, for women with diabetes mellitus, metformin use did not affect endometrial cancer risk.

A climbing amount of laboratory studies have shown that metformin has direct and indirect anti-tumorigenic effects. Metformin may exert direct anti-tumor effects mainly by activating LKB1 dependent AMP-activated protein kinase (AMPK) [38,39]. AMPK activation leads to the regulation of multiple downstream signaling pathways, including down-regulation of PI3K/Akt/mTOR pathway and the block of lipid biosynthesis through inhibition of the acetyl co-carboxylase [ACC] [40 – 42]. In addition, metformin may indirectly affect tumor growth by reducing insulin resistance, lowering insulin and IGF-1 levels [12,43]. Recent laboratory studies have shown that metformin has several anti-tumorigenic effects in endometrial cancer cell lines, such as inhibits cell proliferation, induces apoptosis, attenuates invasion and metastasis, and reverses progestin resistance [44 – 47].

Apart from the results from laboratory studies, the present meta-analysis did not support the metformin have clinical chemopreventive potential against endometrial cancer. Luo et al. [32] contributed the difference to that metformin may not be a effective chemopreventive agent against endometrial cancer, but has a therapeutic role. Our findings are consistent with a meta-analysis of RCTs suggesting a neutral effect of metformin on the overall incidence of cancer [48]. A recently published meta-analysis found that metformin use was associated with a decreased risk of endometrial cancer among patients with diabetes (RR = 0.87, 95% CI, 0.80 to 0.95) [49]. However, there were only 5 studies included in this meta-analysis.

Compared with the existing study [49], our meta-analysis has several advantages. We carried out a comprehensive search, including electronic databases, conference abstracts and clinical trial registers for available published and unpublished evidence with no language restrictions. Hence, the likelihood of important publication bias was small. As a result, we identified a much larger number of studies and patients, which may provide more precise results. Since metformin can have benefits and be prescribed for multiple indications in women, we evaluated the association between metformin use and endometrial cancer risk in both diabetic and non-diabetic patients, and assessed the association exclusively in diabetic patients. In addition, besides study design, we performed additional subgroup analyses by comparisons and adjustments for age and BMI or obesity. As obesity is an established risk factor for endometrial cancer [50], it is important to adjust for the confounding effect of BMI when evaluating the association between metformin use and endometrial cancer risk. In subgroup analyses, our results were stable across different study designs and comparisons, and remained unchanged after adjusting for age and BMI or obesity.

Nevertheless, several limitations of the present meta-analysis should be acknowledged. First, most of the included studies were non-randomized studies. Meta-analysis of RCTs allows for a more objective evaluation of the evidence because they are more likely to provide unbiased findings than other study designs. However, non-randomized studies should be included in the meta-analysis when the available RCTs are limited. Second, there was significant heterogeneity among the studies, which might partly due to the diversity of study design, definition of drug exposure, and control for potential confounders. To minimize the biases in this meta-analysis, we extracted the most adjusted estimates to pool the effects, performed subgroup analyses and sensitivity analysis. Third, the limited data made it impractical to evaluate dose, duration effects of metformin.

In conclusion, this comprehensive meta-analysis does not support a chemopreventive effect of metformin against endometrial cancer at the population level. However, the results should be interpreted with caution given the limited data and possibility of residual confounding. Therefore, further randomized chemoprevention trials are needed to validate our findings.

Declarations

Author details

[1] Department of Obstetrics and Gynecology, Affiliated Nanhua hospital of university of south china Hengyang, Hunan Province 421000 , China

[2] Department of Gastrointestinal Surgery, The First affiliated hospital of university of south chinaHengyang, Hunan Province 421000 , China

[3] Department of Gynecology, Affiliated Hengyang Hospital, Southern Medical University (Hengyang Central Hospital), Hengyang, Hunan Province 421000 , China

Authors' contributions

WX and DW conceived and designed the study. ST and RT did the literature search and identified eligible studies. ST, RT and DW coded articles and decided on their inclusion. ST, RT did statistical analyses and interpreted results. All drafts of the reports, including the final version, were written by DW and revised by WX. All authors read and approved the final paper.

Competing interests

The authors declare that they have no competing interests.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66:7-30.
2. Purdie DM, Green AC. Epidemiology of endometrial cancer. Best Pract Res Clin Obstet Gynaecol. 2001;15:341-54.
3. Dossus L, Allen N, Kaaks R, Bakken K, Lund E, Tjonneland A, Olsen A, Overvad K, Clavel-Chapelon F, Fournier A, Chabbert-Buffet N, Boeing H, Schütze M, et al. Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2010;127:442-51.
4. Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia. 2007;50:1365-74.
5. Parazzini F, La Vecchia C, Negri E, Riboldi GL, Surace M, Benzi G, Maina A, Chiaffarino F. Diabetes and endometrial cancer: an Italian case-control study. Int J Cancer. 1999;81:539-42.
6. Lucenteforte E, Bosetti C, Talamini R, Montella M, Zucchetto A, Pelucchi C, Franceschi S, Negri E, Levi F, La Vecchia C. Diabetes and endometrial cancer: effect modification by body weight, physical activity and hypertension. Br J Cancer. 2007;97:995-8.
7. Straus DS. Growth-stimulatory actions of insulin in vitro and in vivo. Endocr Rev. 1984;5:356-69.
8. Mu N, Zhu Y, Wang Y, Zhang H, Xue F. Insulin resistance: a significant risk factor of endometrial cancer. Gynecol Oncol. 2012;125:751-7.
9. Weiderpass E, Brismar K, Bellocco R, Vainio H, Kaaks R. Serum levels of insulin-like growth factor-I, IGF-binding protein 1 and 3, and insulin and endometrial cancer risk. Br J Cancer. 2003;89:1697-704.
10. Mitsuhashi A, Uehara T, Hanawa S, Shozu M. Prospective evaluation of abnormal glucose metabolism and insulin resistance in patients with atypical endometrial hyperplasia and endometrial cancer. Support Care Cancer. 2017;25:1495-1501.
11. Shao R, Li X, Billig H. Promising clinical practices of metformin in women with PCOS and early-stage endometrial cancer. BBA Clin. 2014;2:7-9.

12. Stine JE, Bae-Jump V. Metformin and gynecologic cancers. Obstet Gynecol Surv. 2014;69:477-89.
13. Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. Clin Sci (Lond). 2012;122:253-70.
14. Palomba S, Falbo A, Zullo F, Orio F Jr. Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: a comprehensive review. Endocr Rev. 2009;30:1-50.
15. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393-403.
16. Ratner RE, Christophi CA, Metzger BE, Dabelea D, Bennett PH, Pi-Sunyer X, Fowler S, Kahn SE; Diabetes Prevention Program Research Group. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J Clin Endocrinol Metab. 2008;93:4774-9.
17. Wang Z, Lai ST, Xie L, Zhao JD, Ma NY, Zhu J, Ren ZG, Jiang GL. Metformin is associated with reduced risk of pancreatic cancer in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2014;106:19-26.
18. Liu F, Yan L, Wang Z, Lu Y, Chu Y, Li X, Liu Y, Rui D, Nie S, Xiang H. Metformin therapy and risk of colorectal adenomas and colorectal cancer in type 2 diabetes mellitus patients: A systematic review and meta-analysis. Oncotarget. 2017;8:16017-26.
19. Zhang ZJ, Zheng ZJ, Shi R, Su Q, Jiang Q, Kip KE. Metformin for liver cancer prevention in patients with type 2 diabetes: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2012;97:2347-53.
20. Wu GF, Zhang XL, Luo ZG, Yan JJ, Pan SH, Ying XR, Pan JG, Zhang GF. Metformin therapy and prostate cancer risk: a meta-analysis of observational studies. Int J Clin Exp Med. 2015;8:13089-98.
21. Yang T, Yang Y, Liu S. Association between Metformin Therapy and Breast Cancer Incidence and Mortality: Evidence from a Meta-Analysis. J Breast Cancer. 2015;18:264-70.
22. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8:336-41.
23. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
24. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp Accessed 9 May 2017.
25. Luo J, Margolis K, Kuller L, Chlebowski R, Wactawski-Wende J, Beresford S, Chen C, Garcia L, Regier M. Association between diabetes, diabetes treatment and endometrial cancer. Diabetes. 2013;62 SUPPL. 1: A395.
26. Fortuny J, Sima C, Bayuga S, Wilcox H, Pulick K, Faulkner S, Zauber AG, Olson SH. Risk of endometrial cancer in relation to medical conditions and medication use. Cancer Epidemiol Biomarkers Prev. 2009;18:1448-56.
27. Soffer D, Shi J, Chung J, Lentz S, Haque R. Does metformin use among women with type II diabetes reduce the risk of gynecologic cancers? Int J Gynecol Cancer. 2012; 22 SUPPL. 3:E162.
28. Soffer D, Shi J, Chung J, Schottinger JE, Wallner LP, Chlebowski RT, Lentz SE, Haque R. Metformin and breast and gynecological cancer risk among women with diabetes. BMJ Open Diabetes Res Care. 2015;3(1):e000049.
29. Home PD, Kahn SE, Jones NP, Noronha D, Beck-Nielsen H, Viberti G; ADOPT Study Group; RECORD Steering Committee. Experience of malignancies with oral glucose-lowering drugs in the randomised controlled ADOPT (A Diabetes Outcome Progression Trial) and RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) clinical trials. Diabetologia. 2010;53:1838-45.
30. Ferrara A, Lewis JD, Quesenberry CP Jr, Peng T, Strom BL, Van Den Eeden SK, Ehrlich SF, Habel LA. Cohort study of pioglitazone and cancer incidence in patients with diabetes. Diabetes Care. 2011;34:923-9.
31. Becker C, Jick SS, Meier CR, Bodmer M. Metformin and the risk of endometrial cancer: a case-control analysis. Gynecol Oncol. 2013;129(3):565-9.
32. Luo J, Beresford S, Chen C, Chlebowski R, Garcia L, Kuller L, Regier M, Wactawski-Wende J, Margolis KL. Association between diabetes, diabetes treatment and risk of developing endometrial cancer. Br J Cancer. 2014;111:1432-9.
33. Tsilidis KK, Capothanassi D, Allen NE, Rizos EC, Lopez DS, van Veldhoven K, Sacerdote C, Ashby D, Vineis P, Tzoulaki I, Ioannidis JP. Metformin does not affect cancer risk: a cohort study in the U.K. Clinical Practice Research Datalink analyzed like an intention-to-treat trial. Diabetes Care. 2014;37:2522-32.
34. Tseng CH. Metformin and endometrial cancer risk in Chinese women with type 2 diabetes mellitus in Taiwan. Gynecol Oncol. 2015;138:147-53.

35. Ko EM, Stürmer T, Hong JL, Castillo WC, Bae-Jump V, Funk MJ. Metformin and the risk of endometrial cancer: a population-based cohort study. Gynecol Oncol. 2015;136:341-7.
36. Franchi M, Asciutto R, Nicotra F, Merlino L, La Vecchia C, Corrao G, Bosetti C. Metformin, other antidiabetic drugs, and endometrial cancer risk: a nested case-control study within Italian healthcare utilization databases. Eur J Cancer Prev. 2017;26:225-231.
37. Kwon JS, Albert AY, Gill S, Hutcheon JA. Diabetic Pharmacotherapy and Endometrial Cancer Risk Within a Publicly Funded Health Care System. J Obstet Gynaecol Can. 2017;39:42-8.
38. Del Barco S, Vazquez-Martin A, Cufí S, Oliveras-Ferraros C, Bosch-Barrera J, Joven J, Martin-Castillo B, Menendez JA. Metformin: multi-faceted protection against cancer. Oncotarget. 2011;2:896-917.
39. Brown KA, Samarajeewa NU, Simpson ER. Endocrine-related cancers and the role of AMPK. Mol Cell Endocrinol. 2013;366:170-9.
40. Wullschleger S, Loewith R, Hall MN. TOR signaling in growth and metabolism. Cell. 2006;124:471-84.
41. El-Mir MY, Nogueira V, Fontaine E, Avéret N, Rigoulet M, Leverve X. Dimethylbiguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex I. J Biol Chem. 2000;275:223-8.
42. Hardie DG. AMPK: a key regulator of energy balance in the single cell and the whole organism. Int J Obes (Lond). 2008;32 Suppl 4:S7-12.
43. Gadducci A, Biglia N, Tana R, Cosio S, Gallo M. Metformin use and gynecological cancers: A novel treatment option emerging from drug repositioning. Crit Rev Oncol Hematol. 2016;105:73-83.
44. Sarfstein R, Friedman Y, Attias-Geva Z, Fishman A, Bruchim I, Werner H. Metformin downregulates the insulin/IGF-I signaling pathway and inhibits different uterine serous carcinoma (USC) cells proliferation and migration in p53-dependent or -independent manners. PLoS One. 2013;8:e61537.
45. Cantrell LA, Zhou C, Mendivil A, Malloy KM, Gehrig PA, Bae-Jump VL. Metformin is a potent inhibitor of endometrial cancer cell proliferation–implications for a novel treatment strategy. Gynecol Oncol. 2010;116:92-8.
46. Mitsuhashi A, Kiyokawa T, Sato Y, Shozu M. Effects of metformin on endometrial cancer cell growth in vivo: a preoperative prospective trial. Cancer. 2014;120:2986-95.
47. Zhang Z, Dong L, Sui L, Yang Y, Liu X, Yu Y, Zhu Y, Feng Y. Metformin reverses progestin resistance in endometrial cancer cells by downregulating GloI expression. Int J Gynecol Cancer. 2011;21:213-21.
48. Stevens RJ, Ali R, Bankhead CR, Bethel MA, Cairns BJ, Camisasca RP, Crowe FL, Farmer AJ, Harrison S, Hirst JA, Home P, Kahn SE, McLellan JH, et al. Cancer outcomes and all-cause mortality in adults allocated to metformin: systematic review and collaborative meta-analysis of randomised clinical trials. Diabetologia. 2012;55(10):2593-603.
49. Tang YL, Zhu LY, Li Y, Yu J, Wang J, Zeng XX, Hu KX, Liu JY, Xu JX. Metformin Use Is Associated with Reduced Incidence and Improved Survival of Endometrial Cancer: A Meta-Analysis. Biomed Res Int. 2017;2017:5905384.
50. Zhang Y, Liu H, Yang S, Zhang J, Qian L, Chen X. Overweight, obesity and endometrial cancer risk: results from a systematic review and meta-analysis. Int J Biol Markers. 2014;29:e21-9.

Tables

Table 1 Characteristics of included studies

Study	Study Location	Study Design	Population	Comparison groups	No. of paticipants	No. of EC patients	RR	95% CI	Control for Potential Confounders [a]	NOS value
Home et al., 2010	Europe and Australasia	RCT	Diabetics	Metformin vs. rosiglitazone	2225	14	0.98	0.35 to 2.79	Randomization	–
Ferrara et al., 2011	USA	Cohort	Diabetics	Metformin users vs. non-users	117,603	552	0.9	0.8 to1.2	1–10	7
Becker et al., 2013	UK	C–C	Diabetics and non-diabetics	Metformin users vs. non-users	17,878	2,554	0.92 0.79	0.65 to 1.31 0.54 to 1.17	1, 6, 11–15	6
Luo et al., 2014	USA	Cohort	Diabetics	Metformin users vs. non-users	4,247	71	0.97	0.60 to 1.58	11	8
Tsilidis et al., 2014	UK	Cohort	Type 2 diabetics	Metformin vs. sulfonylurea	30,277	89	1.38	0.74 to 2.57	1, 6, 8, 11, 16–20	9
Tseng et al., 2015	Taiwan	Cohort	Type 2 diabetics	Metformin users vs. non-users	478,921	2,885	0.675	0.614 to 0.742	1, 21–33	7
Ko et al., 2015	USA	Cohort	Diabetics and non-diabetics	Metformin vs. sulfonylurea	541,128	729	1.09	0.88 to1.35	1, 12, 28, 34–40	8
Franchi et al., 2015	Italy	C–C	Diabetics	Metformin users vs. non-users	7,861	376	1.07	0.82 to 1.41	1–3, 11, 17–19, 34, 41–44	6
Kwon et al., 2017	Canada	C–C	Diabetics	Metformin only vs. other diabetes medications	4,896	492	1.5	0.9 to 2.4	1, 20	6

EC, endometrial cancer; RR, relative risk; CI, confidence interval; NOS, Newcastle–Ottawa scale; USA, United States of America; United Kingdom; C–C, case–control; NA, not available

[a] Potential Confounders: 1, age; 2, ever use of other diabetes medications; 3, year of cohort entry; 4, race/ethnicity; 5, income; 6, smoking; 7, baseline HbA1c; 8, diabetes duration; 9, creatinine; 10, congestive heart failure; 11, BMI; 12, diabetes mellitus; 13, calendar time; 14, general practice; 15, number of years of active history prior to the index date; 16, alcohol consumption status; 17, use of aspirin or non-steroidal anti-inflammatory drugs; 18, use of statins; 19, use of exogenous hormones; 20, year of the first antidiabetes prescription; 21, hypertension; 22, chronic obstructive pulmonary disease; 23, stroke; 24, nephropathy; 25, ischemic heart disease; 26, peripheral arterial disease; 27, eye disease; 28, obesity; 29, dyslipidemia; 30, urinary tract disease; 31, other cancers; 32, other drugs; 33, propensity score; 34, Charlson index; 35, polycystic ovarian syndrome; 36, endometrial hyperplasia; 37, infertility; 38, combination oral contraceptive; 39, ultrasound; 40, inverse probability of treatment weights (IPTW) derived from the propensity score; 41, duration of follow-up; 42, cardio/cerebrovascular diseases; 43, antihypertensive drugs; 44, antidepressants

Table 2 Subgroup analysis

Subgroups	No. of studies	RR (95% CI)	Heterogeneity	
			I^2 (%)	*p* value
Study design				
RCT	1	0.98 (0.35 to 2.77)	–	–
Cohort studies	5	0.92 (0.71 to 1.20)	83.4	0.000
Case–control studies	3	1.01 (0.85 to 1.20)	33.3	0.213
Comparison				
Metformin non-users	5	0.86 (0.71 to 1.04)	70.4	0.005
Other hypoglycemic agents	4	1.16 (0.96 to 1.39)	0.0	0.619
Adjustment for confounders				
Adjustment for age	5	0.95 (0.73 to 1.23)	86.1	0.000
Adjustment for BMI or obesity	5	1.02 (0.90 to 1.17)	0.0	0.631
Risk in diabetic patients				
Study design				
RCT	1	0.98 (0.35 to 2.77)	–	–
Cohort studies	5	0.86 (0.69 to 1.07)	71.5	0.007
Case–control studies	3	1.03 (0.86 to 1.23)	17.5	0.304
Comparison				
Metformin non-users	5	0.86 (0.71 to 1.05)	70.4	0.005
Other hypoglycemic agents	4	1.04 (0.84 to 1.30)	28.8	0.239
Adjustment for confounders				
Adjustment for age	5	0.89 (0.71 to 1.12)	79.6	0.001
Adjustment for BMI or obesity	5	0.96 (0.83 to 1.12)	0.0	0.759

Abbreviations: ; RR, odds ratio.

Figures

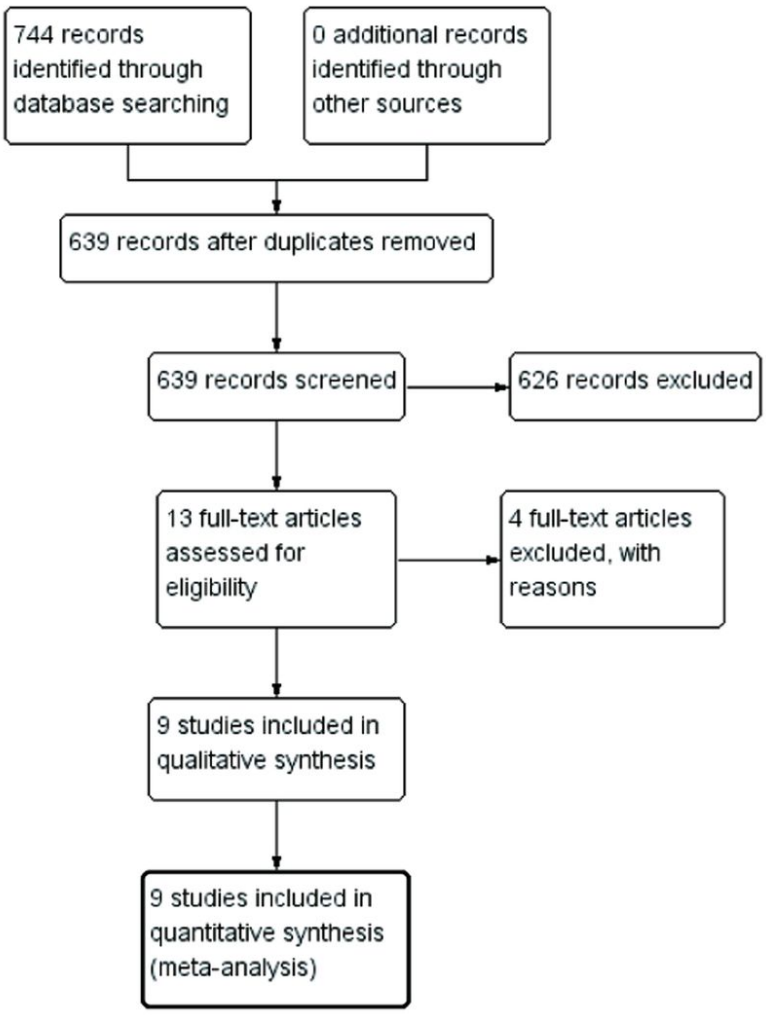

Figure 1

Study flow diagram.

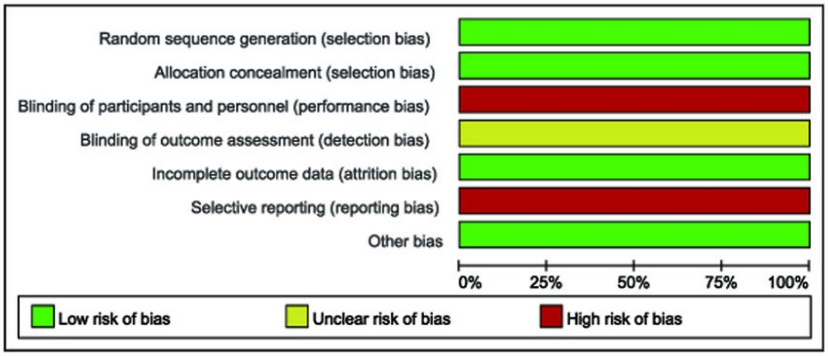

Figure 2

Risk of bias graph: review authors' judgements about each risk of bias item. The study was considered at low risk of selection bias, attrition bias, and other bias, unclear risk of detection bias, and high risk of performance bias and reporting bias.

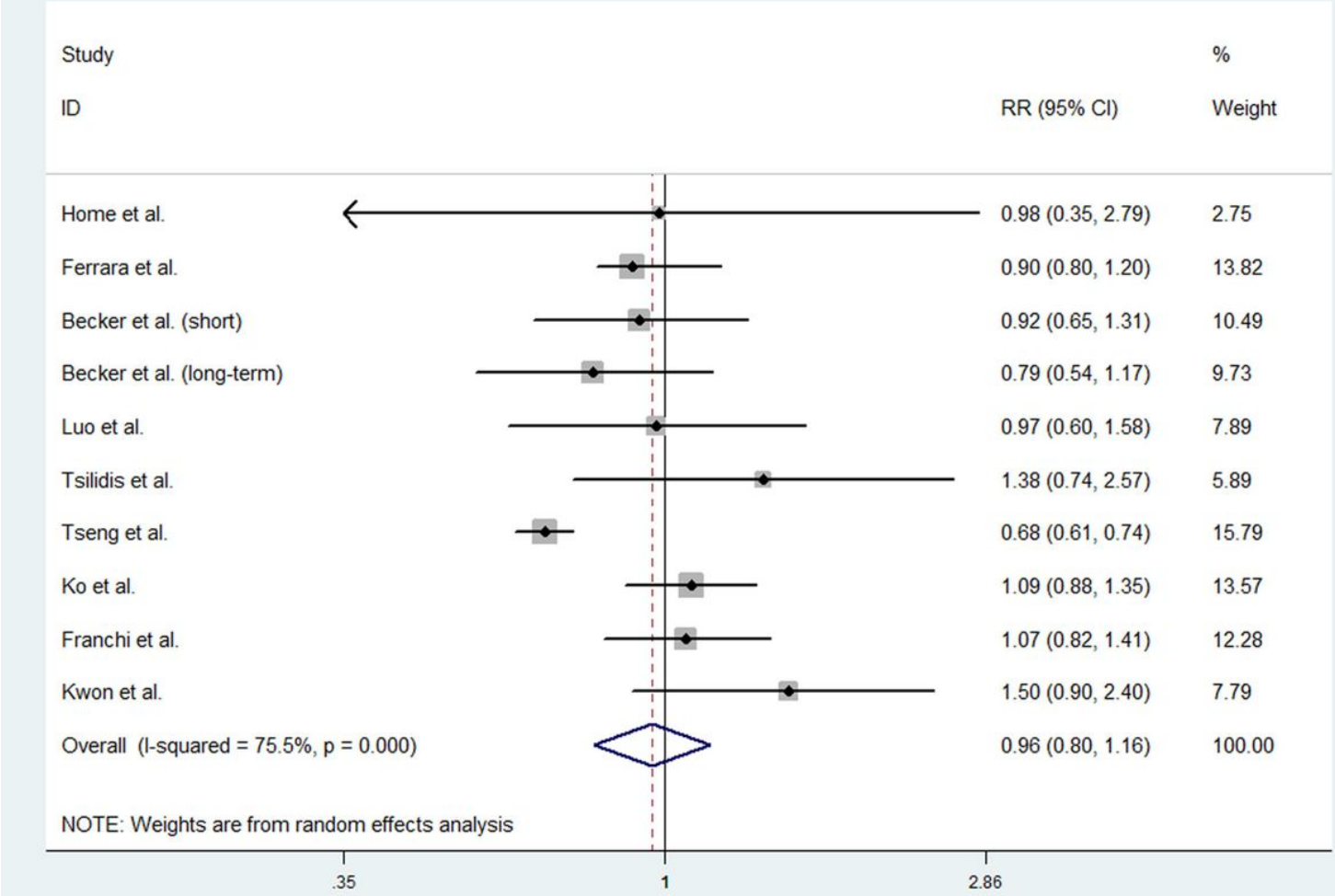

Figure 3

Forest plot of metformin use and endometrial cancer risk. Pooled effect estimate was from a random-effects model; RR, relative risk; CI, confidence interval.

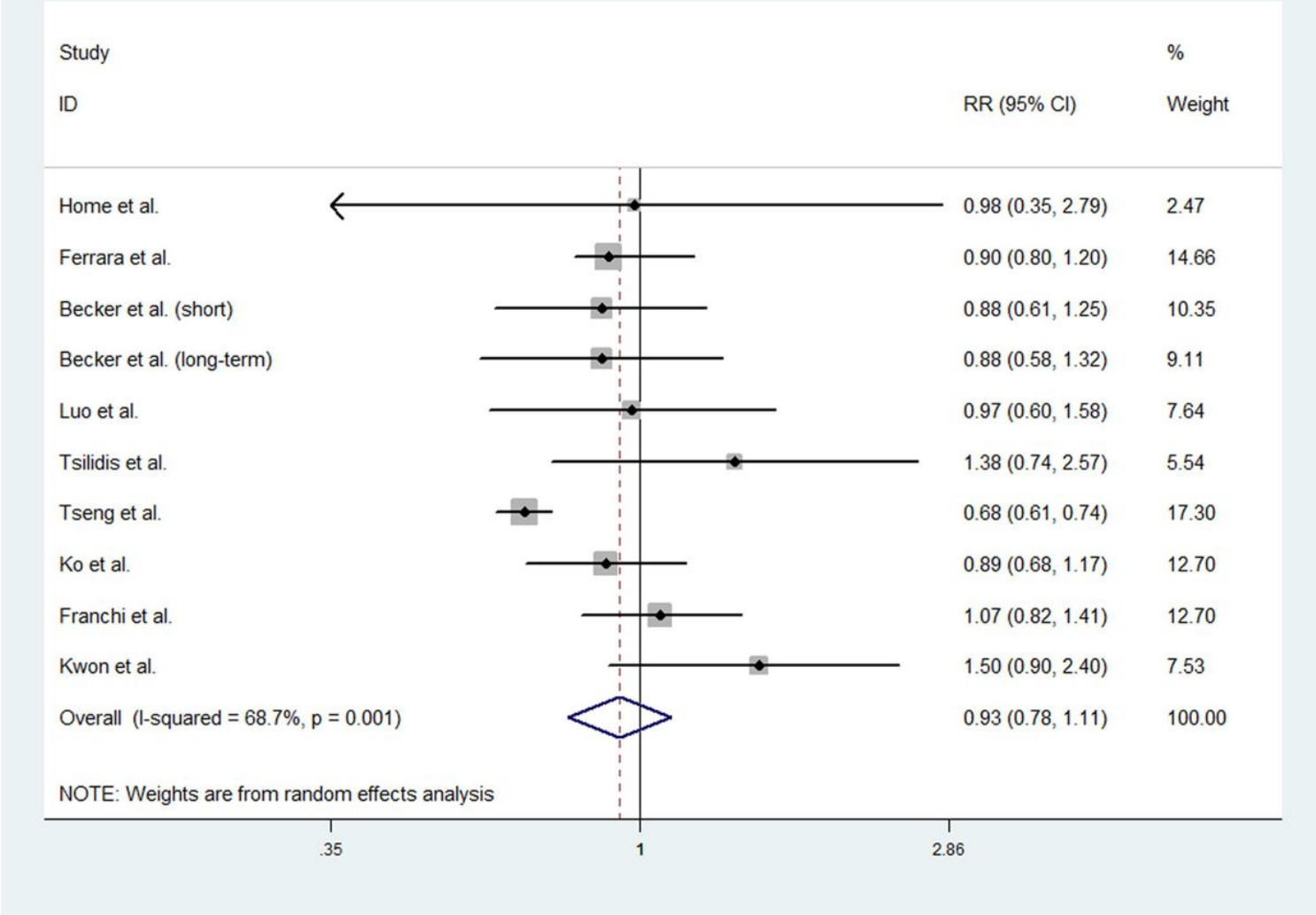

Figure 4

Forest plot of metformin use and endometrial cancer risk in patients with diabetes. Pooled effect estimate was from a random-effects model; RR, relative risk; CI, confidence interval.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AppendixA.doc