Int J Clin Exp Med 2016;9(9):17559-17568
www.ijcem.com /ISSN:1940-5901/IJCEM0031948

Original Article

The effects of metformin on ovarian cancer: an updated systematic review and meta-analysis

Lifeng Li[1,2*], Xiaolong Qi[1,2*], Mingxin Xu[3*], Xianfei Ding[2], Xueliang Zhou[2], Chaoqi Zhang[1,2], Zhirui Fan[2], Yongzhao Zhao[3], Hui Sheng[3], Yi Zhang[1,2,4,5]

[1]Biotherapy Center, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, China; [2]Department of Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, China; [3]Department of Endocrinology, Shanghai Tenth People's Hospital, Tongji University, Shanghai 200072, China; [4]School of Life Sciences, Zhengzhou University, Zhengzhou 450001, Henan, China; [5]Henan Key Laboratory of Tumor Immunology and Biotherapy, Zhengzhou 450052, Henan, China. [*]Equal contributors.

Received May 10, 2016; Accepted July 26, 2016; Epub September 15, 2016; Published September 30, 2016

Abstract: Objective: The potential therapeutic effects of metformin on several cancers have been reported. However, there is no consensus on whether metformin has anti-tumor impact on ovarian cancer. We performed this systematic review and meta-analysis to assess the effect of metformin on ovarian cancer. Methods: We conducted searches of PubMed, EMBASE and the Cochrane Central Register of Controlled Trials to identify studies evaluating risk or survival data of ovarian cancer in diabetic patients taking metformin versus those not. All articles were reviewed independently by two authors with a standardized approach, to extract study design, patient characteristics, metformin exposure, and clinical outcomes. The meta-analysis estimating ovarian cancer risk was done using a random-effect model. Results: Among 9 included studies, 4 studies determined the effect of metformin on survival in diabetic ovarian cancer patients, while the rest 5 studies assessed whether metformin could protect diabetes patients from ovarian cancer occurrence. The findings of studies reporting survival outcomes indicated that metformin may prolong overall, disease-specific, and progression-free survival in ovarian cancer patients. The results of studies reporting the effect of metformin on preventing ovarian cancer were meta-analyzed, which demonstrated that metformin significantly decreased incidence of ovarian cancer among diabetic patients with the pooled odds ratio of 0.54 (95% confidence interval: 0.32-0.93). Conclusions: Our findings showed that metformin can reduce ovarian cancer risk and may prolong ovarian patents' survival among diabetic patients.

Keywords: Ovarian cancer, metformin, diabetes, meta-analysis

Introduction

Despite low morbidity of ovarian cancer approximately 3% of all female cancers, it is the leading cause of cancer-related death in women [1]. This is probably due to the late diagnosis of ovarian cancer with extensive disease and limited efficacy of currently available therapies [2]. Increasing age, positive familial history and associated genetic predisposition are the major risk factors of ovarian cancer [3]. In addition, ovarian cancer occurs more frequently in patients with high fat diet, use of fertility drugs, and prolonged estrogen replacement therapy [4]. On the contrary, protective factors are bilateral tubal ligation, use of oral contraceptives, hysterectomy, multiparity, late menarche and early menopause [4].

Metformin, currently recommended as first-line therapy for patients with type 2 diabetes [5], is attracting increasing attention as a potential anti-cancer agent. Preclinical studies have demonstrated that metformin can inhibit the proliferation of cancer cell lines *in vitro* [6]. And, converging clinical data suggested that diabetics treated with metformin had a substantially lower risk of overall and certain cancer (liver cancer, lung cancer, etc.) and improved outcomes than those treated with other agents [5-8]. The biologically plausible mechanisms of anti-cancer impact of metformin exist, including direct effect on cancer cells and indirect influence on the host [9]. Metformin activates adenosine monophosphate-activated protein kinase (AMPK) and suppresses activity of mammalian target of rapamycin (mTOR) pathway,

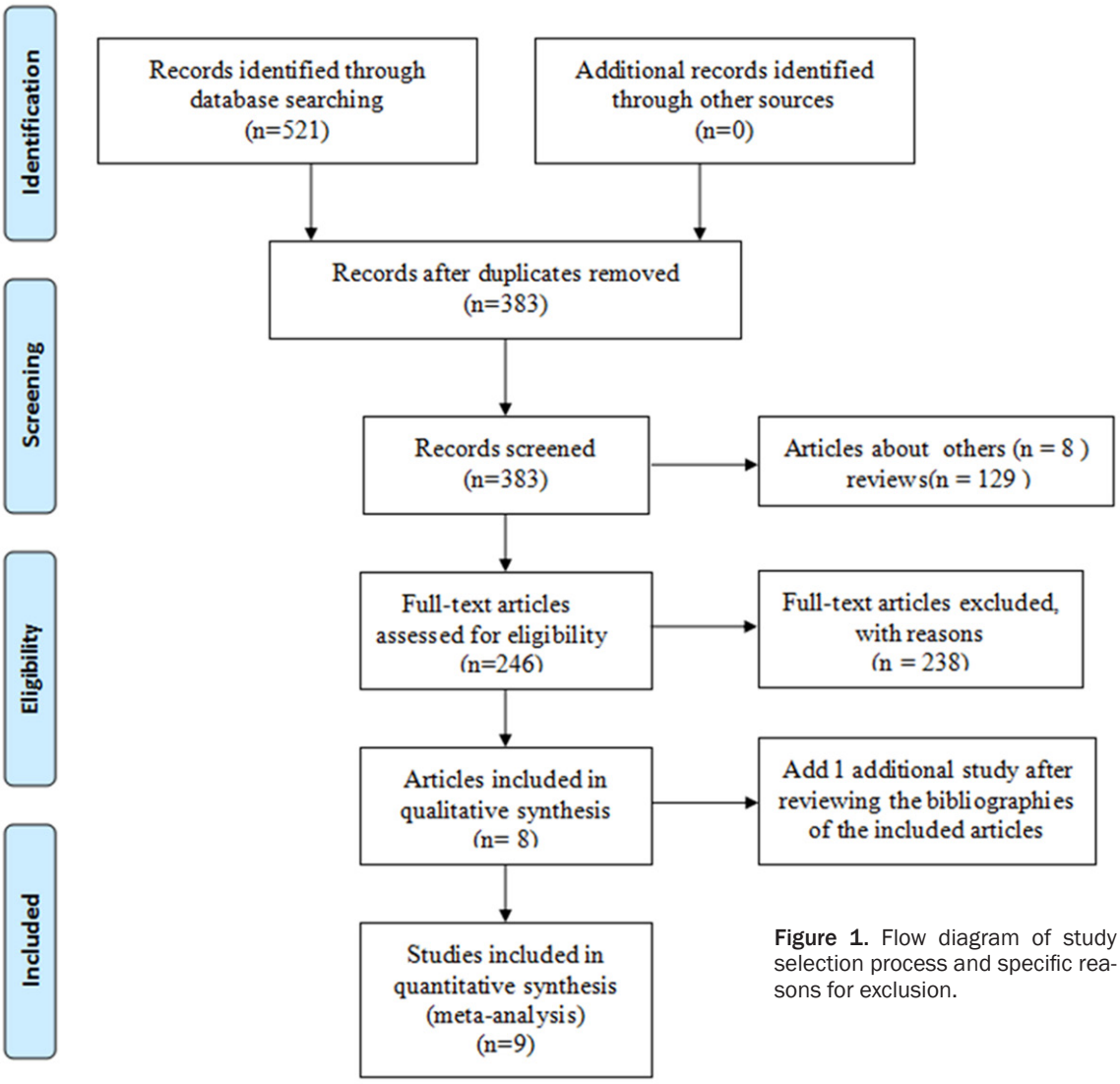

Figure 1. Flow diagram of study selection process and specific reasons for exclusion.

leading to a direct cytostatic effect on cancer cells. Study in vivo indicated that direct AMPK activator A-769662 had antineoplastic activity [10]. In addition, activation of AMPK by metformin requires its upstream regulator LKB1, a well-recognized tumor suppressor, which may contribute to its antitumor effect [11, 12]. Moreover, metformin executes indirect antineoplastic activity on insulin-sensitive cancers by inducing hepatic energy stress, which decreases gluconeogenesis and lower insulin and glucose levels in the host [13]. Albeit antineoplastic activity of metformin has been investigated in several cancers among patients with diabetes mellitus, question persists about the association between metformin and ovarian cancer. Therefore, we conducted this study to investigate whether metformin could improve prognosis (cancer risk and survival outcomes) in diabetic ovarian cancer patients.

Materials and methods

Search strategy

We conducted extensive searches of PubMed, EMBASE and the Cochrane Central Register of Controlled Trials until Jan. 14, 2016, using keywords including variations on “metformin” AND “ovarian cancer” AND “diabetes”. Studies investigating risk or survival data of ovarian cancer in diabetic patients taking metformin versus those not was eligible. The reference lists of identified studies were manually checked for additional relevant reports. We also checked ongoing clinical trials status

from the clinical trials register available at www.clinicaltrial.gov.

Selection criteria

Studies that satisfied the followed criteria were included: (I) Published in journals with full-text in English; (II) Comparing risk or survival data of ovarian cancer between metformin ever-users and metformin never-users; (III) Containing sufficient published data to estimate odds ratios (ORs) with a 95% confidence interval (CI). The exclusion criteria were as follows: (I) Publications that were not within the field of interest; (II) Inadequate information for data extraction; (III) Study design of review articles and case report.

Data abstraction

For each study, the following information was extracted: the first author's surname, year of publication, study design, purpose of study (prevention or treatment), outcome measures, and number of subjects assigned to metformin versus non-metformin and corresponding risk or survival data of ovarian cancer in both group. Information was extracted independently by two reviewers according to the inclusion criteria listed above from all eligible publications. Decisions were compared and a consensus was reached. Disagreements were resolved by discussion.

Statistical analysis

Due to the limited number of studies investigating survival data of ovarian cancer and inconsonant outcome measures used among those reports, we just tabulate the main results of them and conducted meta-analysis for studies appraising ovarian cancer risk. The pooled OR with the 95% CI assessing risk of ovarian cancer between metformin ever-users and metformin never-users was calculated using Mantel-Haenszel methods. Heterogeneity among the studies was evaluated using the χ^2-based Q statistic. Provided heterogeneity existed, sensitivity analysis was conducted to explore potential source of heterogeneity. All analyses used Stata version 12.0.

Results

Initially, a total of 521 articles were identified through searching electronic databases and gray literature, of which 8 articles met the inclusion criteria [14-21]. Among the 513 excluded articles, 138 articles were duplicates, 129 articles were reviews, 8 articles were letters or editorial and 238 articles were not within the field of interest. One additional study was added after reviewing the bibliographies of the included articles. In total, 9 studies were included in our final analysis (**Figure 1**).

Characteristics of included studies

Characteristics of all included studies are presented in **Table 1**. Among 9 studies, 4 studies determined the effect of metformin on survival in diabetic ovarian cancer patients [14-17], whereas the rest 5 studies evaluated whether metformin had preventive effect on ovarian cancer in diabetic patients [18-21]. The 9 included trials incorporated 5 retrospective cohort studies, 1 retrospective case-control study, 1 prospective cohort study, and 2 randomized controlled trials (RCTs) (ADOPT [A Diabetes Outcome Progression Trial and RECORD [Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes]).

Quality assessment

Quality assessment for eligible studies was evaluated by the NOS, which is recommended by the Cochrane Non-Randomized Studies Methods Working Group. In this scale, studies include three parts: selection, comparability and outcome. The quality of each study get eight stars at most, grading was as follows: <5 stars as low quality, and >6 stars as high quality. Quality assessment was performed by two investigators (Chaoqi Zhang, Xueliang Zhou), and any differences was resolved by Xianfei Ding. All papers scores are higher than 6 stars, so these papers are included.

Effects of metformin on clinical outcomes

We divided the included studies into two parts according to study aims: prevention [18-21] or treatment [14-17]. There were four studies evaluating treatment efficacy of metformin with varied outcome that measures meta-analysis of those studies that could not be conducted. Thereby, we summarized the main results of those studies instead of qualifying the data. Meta-analysis was performed among studies

Table 1. Baseline characteristics of included studies

Outcome measures	Overall DSS and 5-y DSS	5-y PFS and 5-y OS	Mortality, mean and median survival	Median PFS and median OS	Risk of OC	Risk of OC	Risk of OC	Risk of OC	Risk of OC
Exposure variable	Metformin	Metformin	Metformin	Metformin	Metformin	Metformin	Metformin	Metformin	Metformin
Population	Diabetic patients with OC	Diabetic patients with OC	Diabetic patients with OC	Diabetic patients with OC	Diabetic patients	Diabetic patients	Diabetic patients	Diabetic patients	Diabetic patients
Study design	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective case-control	Randomized clinical trial	Randomized clinical trial	Prospective cohort	Retrospective cohort
Purpose	Treatment	Treatment	Treatment	Treatment	Prevention	Prevention	Prevention	Prevention	Prevention
Study (year)	Kumar et al. (2012) [14]	Romero et al. (2012) [15]	Currie et al. (2012) [16]	Shah et al. (2014) [17]	Bodmer et al. (2011) [18]	Home et al. (2012): ADOPT [19]	Home et al. (2012): RECORD [19]	Soffer et al. (2015) [20]	Tseng et al. (2015) [21]

DSS = Disease-specific survival, OC = Ovarian cancer, OS = Overall survival, PFS = Progression-free survival.

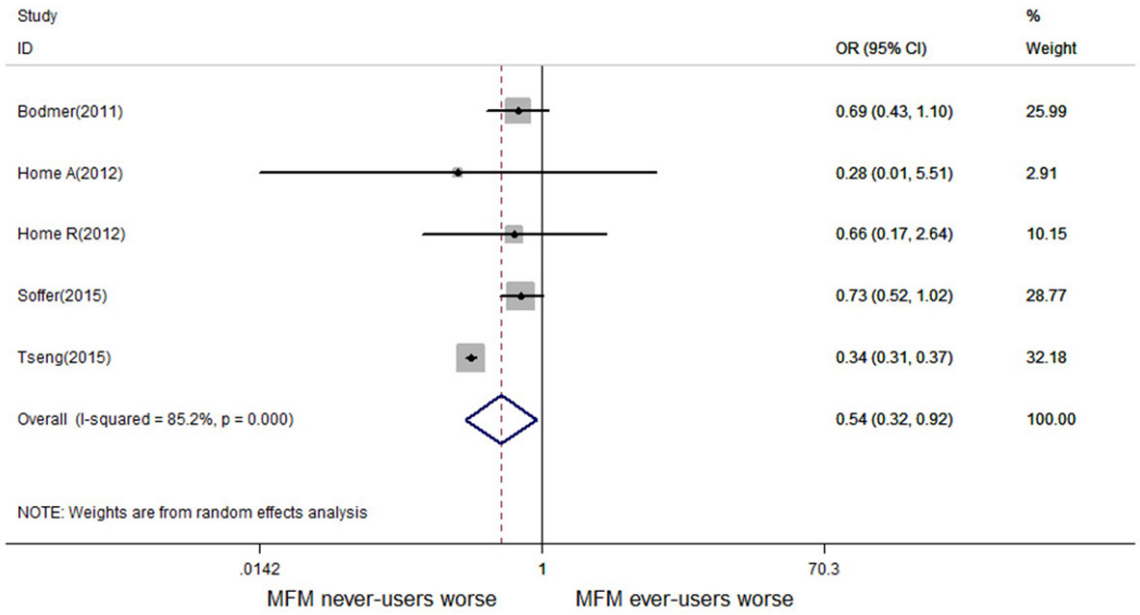

Figure 2. Forest plots on the association of metformin with ovarian cancer prevention.

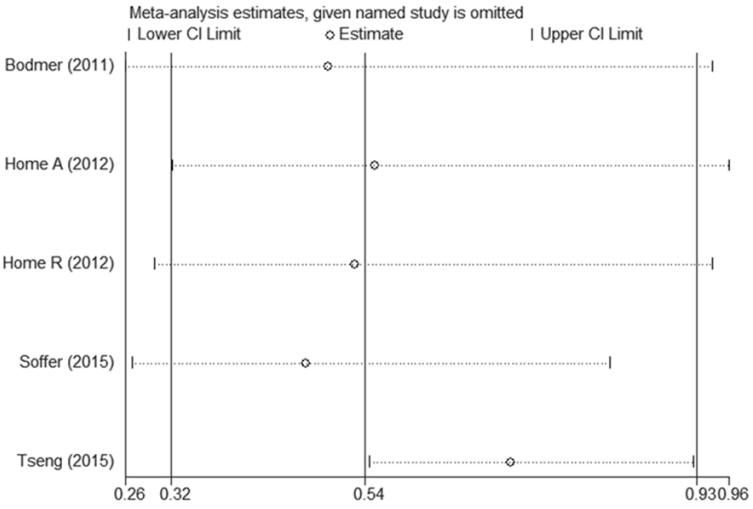

Figure 3. Sensitivity analysis of studies conducted for sources of heterogeneity.

assessing preventive effect of metformin on ovarian cancer with ovarian cancer incidence as the primary outcome.

Effects of metformin on survival outcome

Four studies evaluated the therapeutic effect of metformin on ovarian cancer [14-17]. The study by Kumar et al. [14] incorporated a preliminary analysis and a definitive analysis. The difference between the two analyses was that case cohort of the former analysis included ovarian cancer patients while the later only enrolled patients with epithelial ovarian cancer. Despite the discrepancy, both analyses showed better survival outcome in ovarian patients treated with metformin than those nondiabetic controls (5-year disease specific survival for cases versus controls: 73% vs. 44%, P = 0.002 for preliminary analysis; 67% vs. 47%, P = 0.006 for definitive analysis). Additionally, the multivariate analysis indicated that metformin exposure was an independent predictor of ovarian cancer survival in both preliminary and definitive analysis.

Need to mention that, the authors primarily chose nondiabetic patients as controls to minimize the bias given to the negative effect of diabetes on ovarian survival and the major proportion of nondiabetic ovarian cancer patients. Still, there was a comparison between epithelial ovarian cancer cohort and diabetic controls, which ascertained metformin's advantage on

prolonging cancer survival (5-year disease specific survival for cases versus controls: 67% vs. 40%, P = 0.003). Romero et al. [15] also reported significantly improved progression-free survival and overall survival at 5 years in diabetic patients treated with metformin when compared to nondiabetic patients and diabetic patients who didn't use metformin. In addition, the study suggested that metformin could protect diabetic ovarian cancer patients from diseases occurrence, compared with diabetic patients without metformin intake (the adjusted HR = 0.38, 95% CI: 0.16-0.90). Moreover, in the study by Currie et al. [16], reduced mortality was found in patients treated with metformin monotherapy at the time of diagnosis for ovarian/endometrial cancer (0.48 [0.28-0.81]) and patients treated with monotherapy for 90 days after a cancer diagnosis (0.42 [0.23-0.77]). Nevertheless, the retrospective cohort study by Shah et al. [17], including 367 ovarian cancer patients, suggested that metformin exposure didn't seem to affect median progression-free survival (use vs. non-use, 10.1 vs. 10.3 months, P = 0.7) or median overall survival (use vs. non-use, 23.9 vs. 26.1 months, P = 0.6) among diabetic patients, which was in disagreement with studies by Kumar et al. and Romero et al. [14, 15].

According to the included 4 studies, 3 of them suggested that metformin was likely to be effective for treating ovarian cancer while 1 indicated no therapeutic effect of metformin on ovarian cancer. This inconsistency might be caused by confounders such as disease stage, chemotherapy regimens, and body mass index among studies due to the retrospective nature of those studies. But this cannot deny the highly potential trend that metformin therapy is associated with a better prognosis in ovarian cancer patients using metformin versus those not.

Effects of metformin on ovarian cancer prevention

Metformin's role in the prevention of ovarian cancer was evaluated in 5 trials by meta-analysis [18-21]. Pooling the data of those studies showed that metformin could significantly decrease ovarian cancer incidence when compared with metformin never-users (OR = 0.54, 95% CI: 0.32-0.93) (**Figure 2**). However, considerable heterogeneity among these trials exists, with I^2 statistic of 85.7% (**Figure 2**). To overcome this problem, we did a sensitivity analysis to explore potential sources of significant heterogeneity. As indicated by sensitivity analysis, the study by Tseng et al. [21] generated statistically heterogeneous outcomes (**Figure 3**). The study, thus, was excluded. The pooled OR of the rest studies was 0.71 (95% CI: 0.55-0.92; I^2 statistic = 0.0%) supporting a beneficial role of metformin in preventing ovarian cancer in diabetic population (**Figure 4**). Begg's test was performed to evaluate the publication bias (**Figure 5**). No evidence of publication bias for the association between metformin with ovarian cancer prevention was found.

Discussion

Our findings show that metformin significantly decreases the risk of ovarian cancer and tends to prolong survival in diabetic ovarian cancer patients when compared to those not taking metformin. In 2012, Noto et al. published a meta-analysis investigating the association between metformin intake and risk and mortality of any-site cancers, involving 21,195 and 210,892 patients respectively [22]. The study reported a significantly decreased risk of overall cancer risk (RR = 0.67, 95% CI: 0.53-0.85) and mortality (RR = 0.66, 95% CI: 0.49-0.88) in diabetic patients treated with metformin. Furthermore, the study demonstrated that metformin can also lower incidences of site-specific cancers (0.68 (0.53-0.88) for colorectal cancer, 0.20 (0.07-0.59) for hepatocellular cancer, 0.67 (0.45-0.99) for lung cancer [22]. The results were then supported by another meta-analysis [23]. However, they failed to show clues to the association between metformin and ovarian cancer. In 2013, Franciosi et al. conducted a systematic review to assess whether metformin therapy could affect cancer risk in patients with type 2 diabetes [24]. The study, involving 12 RCTs (21,595 patients) and 41 observational studies (1,029,389 patients), showed a potential role of metformin therapy in reducing risk of cancer and cancer-related mortality as evident from data in observational studies, but not in RCTs. The study determined the association between metformin use and ovarian cancer as well. Unlike our results, they found no significantly decreased risk of ovarian cancer in patients taking metformin. The incon-

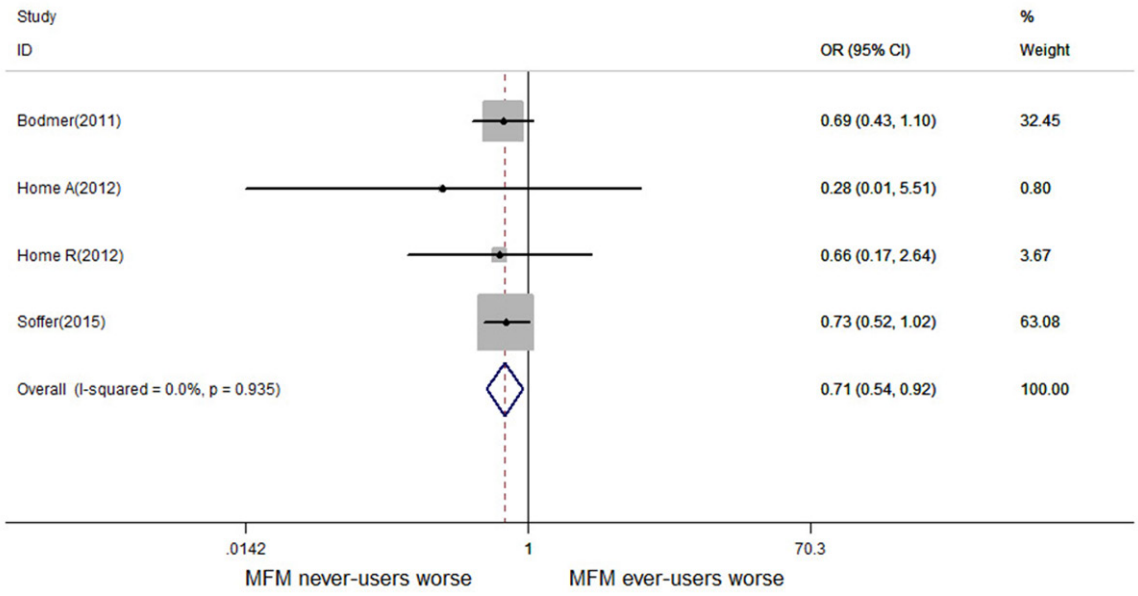

Figure 4. Meta-analysis of studies conducted for ovarian cancer prevention.

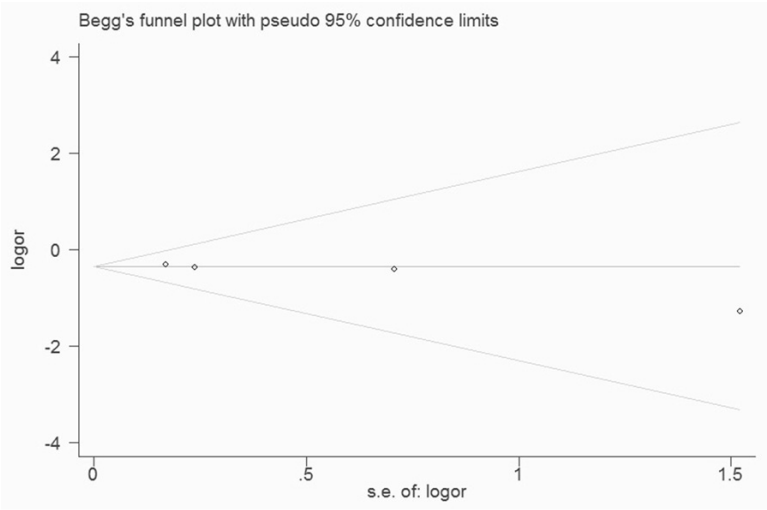

Figure 5. Begg's funnel plots for publication bias test of the association between metformin with ovarian cancer prevention.

sistency between the study by Franciosi et al. and ours, we thought, was because the limited trails included in Franciosi et al.'s study. They only included 3 trials, being less convincible. Collectively, the existing evidence opens a new avenue for diabetic patients against cancers.

Metformin is currently the first-line drug of choice for type 2 diabetes. Tantalizing clues to metformin as an anticancer drug are emerging. It shows anticancer effect in various cancer cell types including the breast [3], glioma cells [25], stomach [26], colon [27], prostate [28] and ovarian [14-16], indicating its broad range of therapeutic targets. The mechanisms of anti-ovarian cancer effect of metformin have been studied. It has been reported that metformin treatment significantly inhibited proliferation of diverse chemo-responsive and -resistant ovarian cancer cell lines (A2780, CP70, C200, OV202, OVCAR3, SKVO3, PE01 and PE04) in both AMPK-dependent and AMPK-dispensable manners [29]. In addition, metformin can affect factors promoting ovarian cancer. For example, high levels of luteinizing hormone, which induce angiogenesis, facilitate the development of ovarian cancer. But this effect can be inhibited by metformin through blocking the mTOR signaling pathway [30]. Omental adipocytes promote development of ovarian cancer by secreting adipokines, cytokines and growth factors, and playing as fuel depots, which can also be altered by metformin [31]. Moreover, metformin has an impact on ovarian cancer stem cells growth [32]. But the detailed mechanisms need to be further elucidated.

"The most fruitful basis for the discovery of a new drug is to start with an old drug". New use of approved drugs can reduce both the cost and the time expended introducing a new drug [33]. Thus, the antineoplastic effect of widely used antidiabetic drug metformin is very encouraging. Preclinical findings suggested that metformin increased chemotherapy sensitivity in ovarian cancer of mouse models. Mice treated with paclitaxel plus metformin had a 60% reduction in tumor weight compared with mice treated with either paclitaxel or metformin alone ($P<0.02$) [34]. Unfortunately, there is no clinical evidence to support this hypothesis so far or large clinical trials that the synergistic effects of metformin with chemo therapy for ovarian cancer are warranted.

This study suggested that diabetic or ovarian cancer patients could benefit from metformin. However, some limitations need to be acknowledged. First, the number of trials included in the study is limited. There are currently a number of ongoing registered trials (www.clinicaltrial.gov.) testing metformin as a treatment strategy for women with ovarian cancers (NCT02122185, NCT01579812, NCT02050009), and the results of these trials would be crucial to determine clinical use of metformin in ovarian cancer. Second, only two of included studies were RCTs. The rest were retrospective or prospective study, which were unpredictably prone to bias and confounding inherent to their design. Considerable heterogeneous outcome was observed when pooling all 5 studies. To find the possible source of heterogeneity, we did a sensitivity analysis which identified the study by Tseng et al. [21]. The possible reasons are hard to tell because of its retrospective nature. Third, different doses of metformin might have different impact on ovarian cancer risk and survival. Nevertheless, this issue is not being elucidated due to the scarce data and needs to be further investigated.

In conclusion, the present study suggests that metformin exposure is associated with reduced risk of ovarian cancer and has a tendency to improve survival in female patients with diabetes. Well-designed randomized clinical trials are needed to further confirm the findings.

Acknowledgements

This work was supported by grants from National Natural Science Foundation of China (Grant No.812111102, 81171986 and 8127-1815), Research Grant from the Ministry of Public Health (No.201501004), the Basic and Advanced Technology Research Foundation from Science and Technology Department of Henan Province (Grant No.112300410153, Grant No.122300410155), Funds for Creative Research Team of Henan Province, Creative Research Team of Higher Education of Henan Province.

Disclosure of conflict of interest

None.

Authors' contribution

Study concepts and design: Yi Zhang, Lifeng Li; Literature search and data extraction: Lifeng Li, Xiaolong Qi, Zhirui Fan, Chaoqi Zhang, Xueliang Zhou; Statistical analysis: Xiaolong Qi, Mingxin Xu, Hui Sheng, Yongzhao Zhao, Xianfei Ding; Manuscript preparation and revision: Lifeng Li, Xiaolong Qi, Mingxin Xu, Yi Zhang. All authors have participated sufficiently in the study and approved the final version.

Address correspondence to: Dr. Yi Zhang, Biotherapy Center, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, China; Department of Oncology, The First Affiliated Hospital of Zhengzhou University, Jianshe East Road, Zhengzhou 450052, Henan, China. Tel: +86 371-66295320; Fax: +86 371-66295320; E-mail: yizhang@zzu.edu.cn

References

[1] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014; 64: 9-29.
[2] Cannistra SA. Cancer of the ovary. N Engl J Med 1993; 329: 1550-1559.
[3] Brown KA, Hunger NI, Docanto M, Simpson ER. Metformin inhibits aromatase expression in human breast adipose stromal cells via stimulation of AMP-activated protein kinase. Breast Cancer Res Treat 2010; 123: 591-596.
[4] Roett MA, Evans P. Ovarian cancer: an overview. Am Fam Physician 2009; 80: 609-616.
[5] Standards of medical care in diabetes--2014. Diabetes Care 2014; 37 Suppl 1: S14-80.
[6] Gotlieb WH, Saumet J, Beauchamp MC, Gu J, Lau S, Pollak MN, Bruchim I. In vitro metformin anti-neoplastic activity in epithelial ovarian cancer. Gynecol Oncol 2008; 110: 246-250.
[7] Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced

risk of cancer in diabetic patients. BMJ 2005; 330: 1304-1305.
[8] Gandini S, Puntoni M, Heckman-Stoddard BM, Dunn BK, Ford L, DeCensi A, Szabo E. Metformin and cancer risk and mortality: a systematic review and meta-analysis taking into account biases and confounders. Cancer Prev Res (Phila) 2014; 7: 867-885.
[9] Pollak MN. Investigating metformin for cancer prevention and treatment: the end of the beginning. Cancer Discov 2012; 2: 778-790.
[10] Huang X, Wullschleger S, Shpiro N, McGuire VA, Sakamoto K, Woods YL, McBurnie W, Fleming S, Alessi DR. Important role of the LKB1-AMPK pathway in suppressing tumorigenesis in PTEN-deficient mice. Biochem J 2008; 412: 211-221.
[11] Hawley SA, Boudeau J, Reid JL, Mustard KJ, Udd L, Makela TP, Alessi DR, Hardie DG. Complexes between the LKB1 tumor suppressor, STRAD alpha/beta and MO25 alpha/beta are upstream kinases in the AMP-activated protein kinase cascade. J Biol 2003; 2: 28.
[12] Lizcano JM, Goransson O, Toth R, Deak M, Morrice NA, Boudeau J, Hawley SA, Udd L, Makela TP, Hardie DG, Alessi DR. LKB1 is a master kinase that activates 13 kinases of the AMPK subfamily, including MARK/PAR-1. EMBO J 2004; 23: 833-843.
[13] Pollak M. The insulin and insulin-like growth factor receptor family in neoplasia: an update. Nat Rev Cancer 2012; 12: 159-169.
[14] Kumar S, Meuter A, Thapa P, Langstraat C, Giri S, Chien J, Rattan R, Cliby W, Shridhar V. Metformin intake is associated with better survival in ovarian cancer: a case-control study. Cancer 2013; 119: 555-562.
[15] Romero IL, McCormick A, McEwen KA, Park S, Karrison T, Yamada SD, Pannain S, Lengyel E. Relationship of type II diabetes and metformin use to ovarian cancer progression, survival, and chemosensitivity. Obstet Gynecol 2012; 119: 61-67.
[16] Currie CJ, Poole CD, Jenkins-Jones S, Gale EA, Johnson JA, Morgan CL. Mortality after incident cancer in people with and without type 2 diabetes: impact of metformin on survival. Diabetes Care 2012; 35: 299-304.
[17] Shah MM, Erickson BK, Matin T, McGwin G Jr, Martin JY, Daily LB, Pasko D, Haygood CW, Fauci JM, Leath CA 3rd. Diabetes mellitus and ovarian cancer: more complex than just increasing risk. Gynecol Oncol 2014; 135: 273-277.
[18] Bodmer M, Becker C, Meier C, Jick SS, Meier CR. Use of metformin and the risk of ovarian cancer: a case-control analysis. Gynecol Oncol 2011; 123: 200-204.
[19] Home PD, Kahn SE, Jones NP, Noronha D, Beck-Nielsen H, Viberti G. 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: 1838-1845.
[20] 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: e000049.
[21] Tseng CH. Metformin reduces ovarian cancer risk in Taiwanese women with type 2 diabetes mellitus. Diabetes Metab Res Rev 2015; 31: 619-26.
[22] Noto H, Goto A, Tsujimoto T, Noda M. Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis. PLoS One 2012; 7: e33411.
[23] Thakkar B, Aronis KN, Vamvini MT, Shields K, Mantzoros CS. Metformin and sulfonylureas in relation to cancer risk in type II diabetes patients: a meta-analysis using primary data of published studies. Metabolism 2013; 62: 922-934.
[24] Franciosi M, Lucisano G, Lapice E, Strippoli GF, Pellegrini F, Nicolucci A. Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review. PLoS One 2013; 8: e71583.
[25] Isakovic A, Harhaji L, Stevanovic D, Markovic Z, Sumarac-Dumanovic M, Starcevic V, Micic D, Trajkovic V. Dual antiglioma action of metformin: cell cycle arrest and mitochondria-dependent apoptosis. Cell Mol Life Sci 2007; 64: 1290-1302.
[26] Kato K, Gong J, Iwama H, Kitanaka A, Tani J, Miyoshi H, Nomura K, Mimura S, Kobayashi M, Aritomo Y, Kobara H, Mori H, Himoto T, Okano K, Suzuki Y, Murao K, Masaki T. The antidiabetic drug metformin inhibits gastric cancer cell proliferation in vitro and in vivo. Mol Cancer Ther 2012; 11: 549-560.
[27] Zhou XZ, Xue YM, Zhu B, Sha JP. [Effects of metformin on proliferation of human colon carcinoma cell line SW-480]. Nan Fang Yi Ke Da Xue Xue Bao 2010; 30: 1935-1938, 1942.
[28] Ben Sahra I, Laurent K, Loubat A, Giorgetti-Peraldi S, Colosetti P, Auberger P, Tanti JF, Le Marchand-Brustel Y, Bost F. The antidiabetic drug metformin exerts an antitumoral effect in vitro and in vivo through a decrease of cyclin D1 level. Oncogene 2008; 27: 3576-3586.
[29] Rattan R, Giri S, Hartmann LC, Shridhar V. Metformin attenuates ovarian cancer cell growth in an AMP-kinase dispensable manner. J Cell Mol Med 2011; 15: 166-178.
[30] Liao H, Zhou Q, Gu Y, Duan T, Feng Y. Luteinizing hormone facilitates angiogenesis in ovarian

epithelial tumor cells and metformin inhibits the effect through the mTOR signaling pathway. Oncol Rep 2012; 27: 1873-1878.
[31] Tebbe C, Chhina J, Dar SA, Sarigiannis K, Giri S, Munkarah AR, Rattan R. Metformin limits the adipocyte tumor-promoting effect on ovarian cancer. Oncotarget 2014; 5: 4746-4764.
[32] Shank JJ, Yang K, Ghannam J, Cabrera L, Johnston CJ, Reynolds RK, Buckanovich RJ. Metformin targets ovarian cancer stem cells in vitro and in vivo. Gynecol Oncol 2012; 127: 390-397.
[33] Chong CR, Sullivan DJ Jr. New uses for old drugs. Nature 2007; 448: 645-646.
[34] Lengyel E, Litchfield LM, Mitra AK, Nieman KM, Mukherjee A, Zhang Y, Johnson A, Bradaric M, Lee W, Romero IL. Metformin inhibits ovarian cancer growth and increases sensitivity to paclitaxel in mouse models. Am J Obstet Gynecol 2015; 212: 479, e1-479, e10.