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The association between metformin therapy and risk of gynecological cancer in patients: Two meta-analyses

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ABSTRACT

Background: Recently, metformin, first-line drug for type 2 diabetes, has been reported to treat some gynecological tumors. However, these epidemiological studies have never been formally summarized. Considering a single study may lack the power to provide reliable conclusion, we performed two meta-analyses with different indicators to assess metformin's role in reducing the risk of gynecological cancers.
Materials and methods: A systematic literature search was carried out in PubMed, Medline (Ovid), Embase database (last search was performed on August 15, 2018). The relative risk (RR) along with a random-effects model were performed on Revman 5.3 and STATA 15.1 for risks analyzing.
Results: A total of 1,710,080 patients in 7 studies were included in first meta-analysis. The results suggested metformin may reduce the risk of gynecological cancers (RR=0.49, 95%CI=0.29−0.82, and p=0.006). In the subgroup analyses: significantly decreased risks were found among Asians (RR=0.27, 95% CI=0.17−0.41, and p<0.00001), ovarian cancer (RR=0.18, 95%CI=0.12−0.28, and p<0.00001), and cervical cancer (RR=0.60, 95%CI=0.43−0.83, and p=0.002), but not in Caucasians (RR=0.81, 95%CI=0.50−1.32, and p=0.40) or in endometrial cancer (RR=0.71, 95%CI=0.29−1.74, and p=0.45). Meanwhile, another total of 8,335,332 cumulative follow-up years, person years, were conducted in 8 studies. The results indicated no statistical significance in general (RR=0.59, 95%CI=0.32−1.10, p=0.10), and no difference in Caucasians (RR=1.15, 95%CI=0.88−1.48, and p=0.30), endometrial cancer (RR=0.89, 95%CI=0.27−2.95, and p=0.84) or ovarian cancer (RR=0.37, 95%CI=0.09−1.49, and p=0.16) when performing subgroup analyses. However, in the subgroup analyses, results in Asians (RR=0.26, 95%CI=0.17−0.40, and p<0.00001) and cervical cancer (RR=0.56, 95%CI=0.40−0.78, and p=0.0005) had an apparent significance.
Conclusions: The results suggested the metformin can be used as a potential anticarcinogenic drug for gynecological cancers' prevention, especially for Asians and cervical cancer. The question remains, still, whether metformin is beneficial for ovarian cancer. Also, we don't know whether it is worth to give metformin to non-diabetes to prevent gynecological cancer.

Introduction

Worldwide, gynecological cancer continues to represent a significant public health issue for women and comprise as a large proportion of female cancer. Furthermore, gynecological cancer appears to be associated with obesity and type 2 diabetes [1].So it is crucial to prevent diabetic population from gynecological cancer and develop novel treatment strategies to target this population.

Metformin is an oral biguanide drug, typically used for diabetes treatment. Although metformin's antidiabetic effect is commonly prescribed, it is currently under investigation for its effect on gynecological tumors. Metformin may be effective for the prevention of gynecological tumors. Previous studies have provided evidence that diabetic patients receiving metformin have lower cancer incidence [2]. Also, preclinical studies have

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shown that metformin can inhibit the proliferation of ovarian cancer cell lines [3]. The anticarcinogenic effect of metformin is considered to involve several mechanisms. Since some studies have shown that the increased cancer risk may be related to the high insulin and glucose levels induced by type 2 diabetes [4], metformin may exert antitumor effects by reducing both insulin and glucose levels. Additionally, metformin negatively affects protein synthesis in cancer cells and reduces cell growth via the activation of liver kinase B1(LKB1)/ Adenosine monophosphate-activated protein kinase(AMPK) pathway and the inhibition of mammalian target of rapamycin (mTOR) [5].

Although evidence from epidemiological studies reveal that metformin can reduce the risk of gynecological cancer among women, these data have never been formally summarized. Therefore, we systematically review available evidence on the existing evidence to explore the effects of metformin in reducing the risk of gynecological cancer among women.

Materials and methods

Selection of studies

Relevant studies investigating the association between metformin and the risk of gynecological cancers were searched using Pubmed, Medline(Ovid), and Embase database. The search terms were used as follows: “metformin” and “ovarian cancer”; “metformin” and “endometrial cancer”; “metformin” and “cervical cancer”. References from the retrieved articles and previous meta analysis were further screened for earlier original studies.

The search results were limited to English languages. Studies included in our meta-analysis met the following inclusion criteria: [1] studies should assess the relationship between metformin and the risk of gynecological cancers [2]; the design had to be a cohort analysis or case-control design published in a journal, which can provide us the required data [3]; sufficient data (The distributions of Patients who develop a gynecological cancer in metformin users and non-metformin users for each study) to estimate an relative risk (RR) with its 95% confidence interval (CI); (4)diagnosis should be classified by imaging examination or pathological diagnosis.

The exclusion criteria were as follows: [1] no controls [2]; studies did not provide sufficient data to extract the information we needed [3]; abstracts, reviews, repeat studies and meta-analysis. For studies with overlapping data, studies with the largest size of samples or recently published were included.

Data extraction

Data were manually extracted from each report and reached a consensus on all items by Wen Q and Zhou *J* independently. A third author, Wen JR, would assess these articles. The following items were extracted from each study: first author’s name, year of publication, purpose of studies, number of patients, total number of person years, tumor group, ethnicity, case age, population, exposure variable and average follow-up period.

Statistical analysis

To summarize the information, the patients are divided into metformin users and non-metformin users. The strength of association between the metformin and the risk of gynecological cancers was assessed by relative risk (RR), and 95%CI was calculated. According to the heterogeneity, the pooled RR was calculated by random-effects model. Heterogeneity was tested by a chisquare-based Q-test and I^2 statistics expressed as a percentage between 0 and 100%. A $p < 0.10$ for the Q test was considered statistically significant. Values of $p > 0.1$ in this test indicated a lack

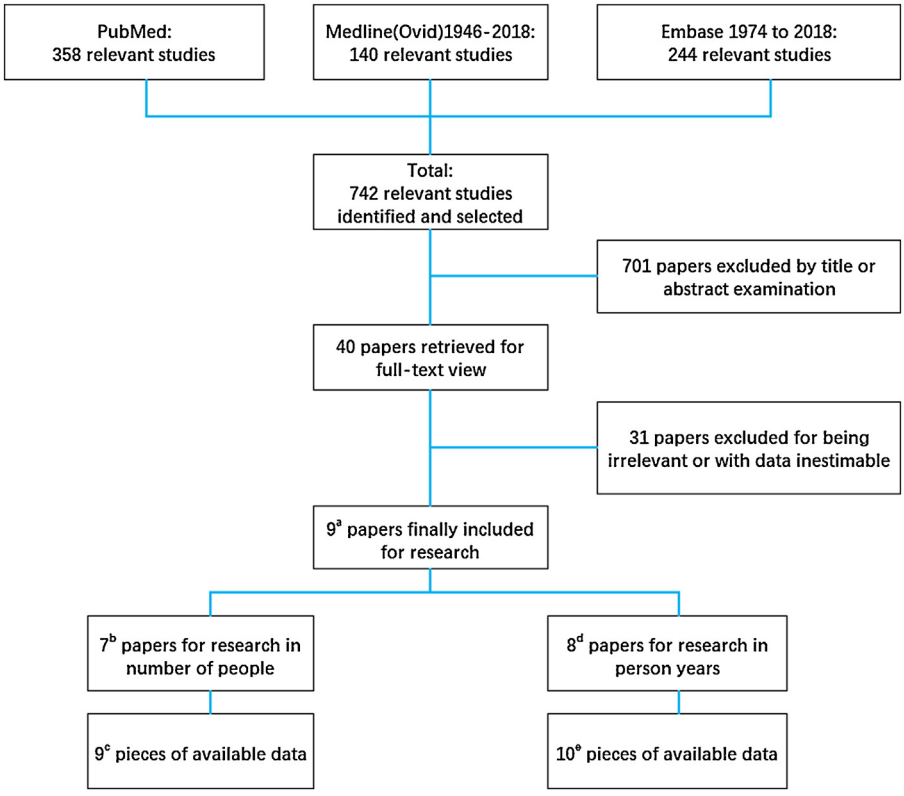

Fig. 1. Flow chart of the study selection process.
a,b,c,d,e We extracted the required data from 9 studies, respectively, based on the number of people and person years, of which 2 studies each provided two sets of valid data.

of heterogeneity among studies, and RR was pooled according to the random-effect model. Z test was taken to analyze the statistical significance of RR, and $p < 0.05$ was considered as statistically significant. Sensitivity analysis was also performed by sequence excluding individual study to test the stability of the meta analyses. The possible publication bias was examined visually in a Begg's funnel plot and the degree of asymmetry was tested by Egger's test [6,7]. Statistical analysis was performed using ReviewManager (version 5.3; Oxford, England) and STATA 15.1 softwares (Stata Corporation, College Station, Texas).

Results

Study inclusion and characteristics

As shown in Fig. 1, the initial search identified 742 results from the selected electronic databases. After reading the titles and abstracts, 40 potential articles were included for full-text view. After reading full texts, 31 studies were excluded for being irrelevant to the metformin and gynecological cancer risk among women or being unable to provide the required data. Therefore, 9 full-text articles which met our inclusion criteria were identified, of which 7 were for population meta-analysis and of which 8 were for person-year research. The former meta-analysis includes 1,710,080 patients in number and 8,335,332 person years for the later one. The characteristics of each study were listed in Table 1. The distributions of patients in number who develop a gynecological cancer in metformin users and non-metformin users for each study are shown in Table 2. And the distributions of person years are displayed in Table 3. As for population, there were 4 papers finally included for the association between the effects of metformin on endometrial cancer prevention [8–11], 3 papers on ovarian cancer prevention [10,12,13], and 2 papers on cervical cancer prevention [12,14]. Besides, as for person years, 4 papers on endometrial cancer prevention [9,9,10,11,15], 4 papers on ovarian cancer prevention [10,12,13,16], and 2 papers on cervical cancer prevention were adapted ultimately [12,14]. All the included reports, 9 eligible sets of data for population and 10 sets for person years, were written in English.

Quantitative data synthesis

Studies for number of persons: As shown in Fig. 2, the heterogeneity of (metformin user vs non-metformin user) for all 9 studies was assessed. The I-square, which is the index of the test of heterogeneity, was 98%. Also, the value of χ^2 was 373.62 with 8 ° of freedom and $p < 0.00001$ in a random-effects model, suggesting a distinct heterogeneity. Thus, we decided to proceed with further analysis by subgroups. Overall, we found that metformin was associated with the risk of gynecological cancers (RR=0.49, 95% CI=0.29−0.82, $p = 0.006$) (Fig. 2), and the test for overall effect Z value was 2.73 for (metformin user vs non-metformin users) model.

Studies for person years: As shown in Fig. 3, the heterogeneity of (metformin user vs non-metformin user) for all 10 studies was assessed. The I-square was 99% and the value of χ^2 was 717.62 with 9 ° of freedom and $p < 0.00001$ in a random-effects model, which suggested a distinct heterogeneity. However, we found that metformin had no association with the risk of gynecological cancers (RR=0.59, 95%CI=0.32−1.10, $p = 0.10$) (Fig. 3), and the test for overall effect Z value was 1.67 for (metformin user vs non-metformin users) model. Next, we decided to perform further analysis by subgroups of ethnicity and tumor group.

Subgroup analyses for number of persons: Subgroup analyses by ethnicity and tumor group were performed. For ethnicity, the analysis was stratified into two subgroups: Asians, and Caucasians (Fig. 4). Although there were no obvious statistical relationship between metformin and Caucasians (RR = 0.81, 95%CI = 0.50–1.32, and $p = 0.40$), significantly decreased risks were found among Asians (RR=0.27, 95%CI=0.17−0.41, and $p < 0.00001$). The results suggested that metformin may reduce the risk of gynecological cancers in Asians rather than in Caucasians. Additionally, in the subgroup analysis by tumor group, the analysis was stratified into three subgroups: endometrial cancer, ovarian cancer and cervical

Table 1
The characteristics of studies involved.

Study[a]	Year	Purpose of Studies	Total number	Person Years	Tumour Group	Ethnicity	Case Age	Population	Exposure Variable	Average Follow-up Period	Note
Tseng CH(1)	2015	Prevention	478921	1772594	endometrial cancer	Asian	56	Diabetic patients	Metformin	–	T2DM[b]
Tseng CH(2)	2015	Prevention	479475	1775476	ovarian cancer	Asian	56	Diabetic patients	Metformin	–	T2DM
Tseng CH(3)	2016	Prevention	139911	641413	cervical cancer	Asian	58	Diabetic patients	Metformin	–	T2DM
Diana Soffer (1)	2015	Prevention	29876	28571	ovarian cancer	Caucasian	56	Diabetic patients	Metformin	6.5 years	T2DM
Diana Soffer (2)	2015	Prevention	29876	28571	endometrial cancer	Caucasian	56	Diabetic patients	Metformin	6.5 years	T2DM
Emily M.Ko	2015	Prevention	541128	–	endometrial cancer	Caucasian	54	Diabetic patients	Metformin	1.2 year	T2DM
Home PD(1)	2010	Prevention	4351	4906	cervical cancer	Caucasian	60	Diabetic patients	Metformin	–	T2DM
Home PD(2)	2010	Prevention	4351	4906	ovarian cancer	Caucasian	60	Diabetic patients	Metformin	–	T2DM
J Luo	2014	Prevention	2191	4996	endometrial cancer	Caucasian	64	Diabetic patients	Metformin	11 years	T2DM
Reetta Arima	2017	Prevention	92366	321349	endometrial cancer	Caucasian	40	Diabetic patients	Metformin	5.5 years	T2DM
E Urpilainen	2018	Prevention	137643	486197	ovarian cancer	Caucasian	40	Diabetic patients	Metformin	5.4 years	T2DM

type 2 diabetes mellitus (T2DM)

a. Tseng CH(1), Tseng CH(2) and Tseng CH(3) are three different papers by one author. As for Diana Soffer(1) and Diana Soffer(2), as well as Home PD(1) and Home PD(2), they are both two sets of data from the corresponding articles.
b. T2DM is an abbreviation for type 2 diabetes mellitus.

Table 2
The distributions of patients in number.

Study	Tumour Group	Ethnicity	Metformin users			Non-Metformin users		
			n	N	N-n*	n	N	N-n
Tseng CH(1)	endometrial cancer	Asian	728	285916	285188	2157	193005	190848
Tseng CH(2)	ovarian cancer	Asian	601	286106	285505	2600	193369	190769
Tseng CH(3)	cervical cancer	Asian	438	132971	132533	38	6940	6902
Diana Soffer(1)	ovarian cancer	Caucasian	5	4887	4882	79	24989	24910
Diana Soffer(2)	endometrial cancer	Caucasian	36	4887	4851	130	24989	24859
Emily M.Ko	endometrial cancer	Caucasian	574	456838	456264	155	84290	84135
Home PD(1)	cervical cancer	Caucasian	1	1454	1453	4	2897	2893
Home PD(2)	ovarian cancer	Caucasian	0	1454	1454	3	2897	2894
J Luo	endometrial cancer	Caucasian	12	529	517	30	1662	1632

* **N-n** is a formula used for calculation in Stata 15.1. **N** means the total number of metformin users or non-metformin users, and **n** is to represent the number of patients suffering from gynecological cancers among those metformin users or non-metformin users.

Table 3
The distributions of person years.

Study	Tumour Group	Ethnicity	Metformin users			Non-Metformin users		
			n	PY	PY-n*	n	PY	PY-n
Tseng CH(1)	endometrial cancer	Asian	728	1772594	1771866	2157	1213341	1211184
Tseng CH(2)	ovarian cancer	Asian	601	1775476	1774875	2600	1216104	1213504
Tseng CH(3)	cervical cancer	Asian	438	641413	640975	38	31308	31270
Diana Soffer(1)	ovarian cancer	Caucasian	5	28571	28566	79	162820	162741
Diana Soffer(2)	endometrial cancer	Caucasian	36	28571	28535	130	162820	162690
Home PD(1)	cervical cancer	Caucasian	1	4906	4905	4	9198	9194
Home PD(2)	ovarian cancer	Caucasian	0	4906	4906	3	9198	9195
J Luo	endometrial cancer	Caucasian	12	4996	4984	30	16891	16861
Reetta Arima	endometrial cancer	Caucasian	411	321349	320938	179	182588	182409
E Urpilainen	ovarian cancer	Caucasian	200	486197	485997	103	262085	261982

* **PY-n** is a formula used for calculation in Stata 15.1. **PY** is the abbreviation of Person Years, and **n** is to represent the number of patients suffering from gynecological cancers among those metformin users or non-metformin users.

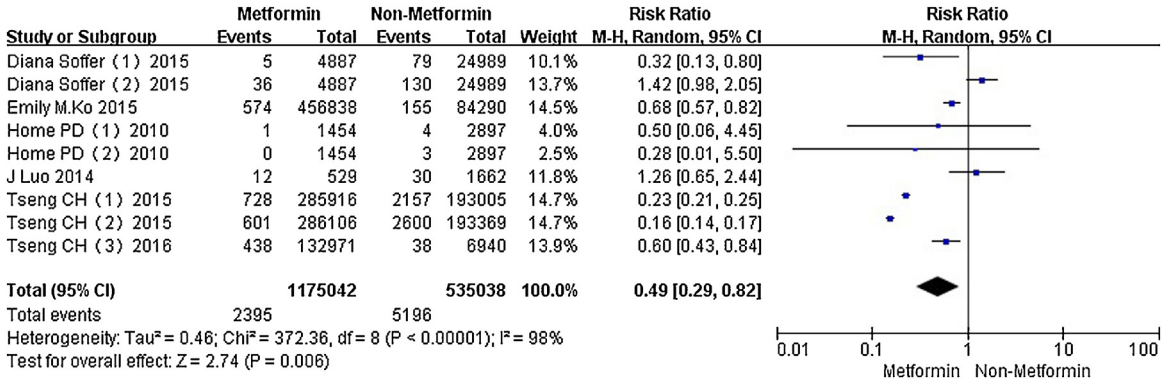

Fig. 2. The results and heterogeneity for number of persons.

cancer (Fig. 5). Significantly decreased risk was identified among ovarian cancer (RR = 0.18, 95%CI = 0.12−0.28, and $p < 0.00001$) and cervical cancer (RR=0.60, 95%CI=0.43−0.83, and $p = 0.002$), but not in endometrial cancer (RR=0.71, 95%CI=0.29−1.74, and $p = 0.45$).

Subgroup analyses for person years: Subgroup of ethnicity, no statistical significance were found among Caucasians (RR = 1.15, 95%CI = 0.88–1.48, and $p = 0.30$), but among Asians (RR=0.26, 95% CI=0.17−0.40, and $p < 0.00001$) (Fig. 6). The results also suggested that metformin can reduce the risk of gynecological cancers in Asians but do nothing with that in Caucasians. In the tumor group (Fig. 7), by contrast, the analysis found a significant decrease in the risk among cervical cancer (RR = 0.56, 95%CI = 0.40−0.78, and $p = 0.0005$), but not in endometrial cancer (RR=0.89, 95% CI=0.27−2.95, and $p = 0.84$) as well as ovarian cancer (RR=0.37, 95%CI=0.09−1.49, and $p = 0.16$).

Sensitivity analysis

The one-way sensitivity analyses were performed to assess the stability of the results, namely, a single study in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled RR. After sequentially excluding each case-control study for number of persons, the corresponding pooled RRs were not materially altered in general (seven nineths of these cases, p values were <0.05), except for group Tseng CH(1) ($p = 0.16$)and group Tseng CH(2) ($p = 0.12$). As for person years, the corresponding pooled RRs were slightly altered (eight out of ten of these cases, p values were >0.05), while groups excluding Diana Soffer [2] ($p = 0.04$) or group Reetta Arima ($p = 0.02$) differed from the overall p-value. The above two sensitivity analysis results confirmed that our meta-analyses were statistically reliable to some extent. But it

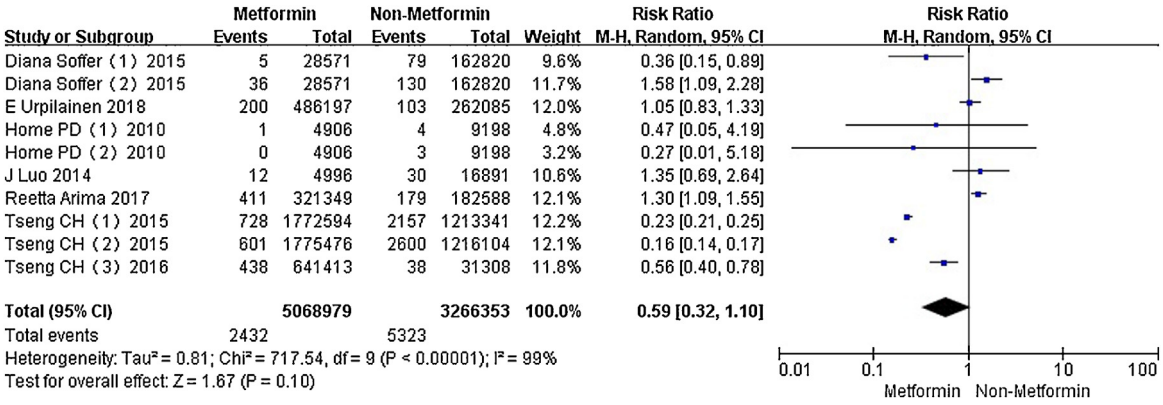

Fig. 3. The results and heterogeneity for person years.

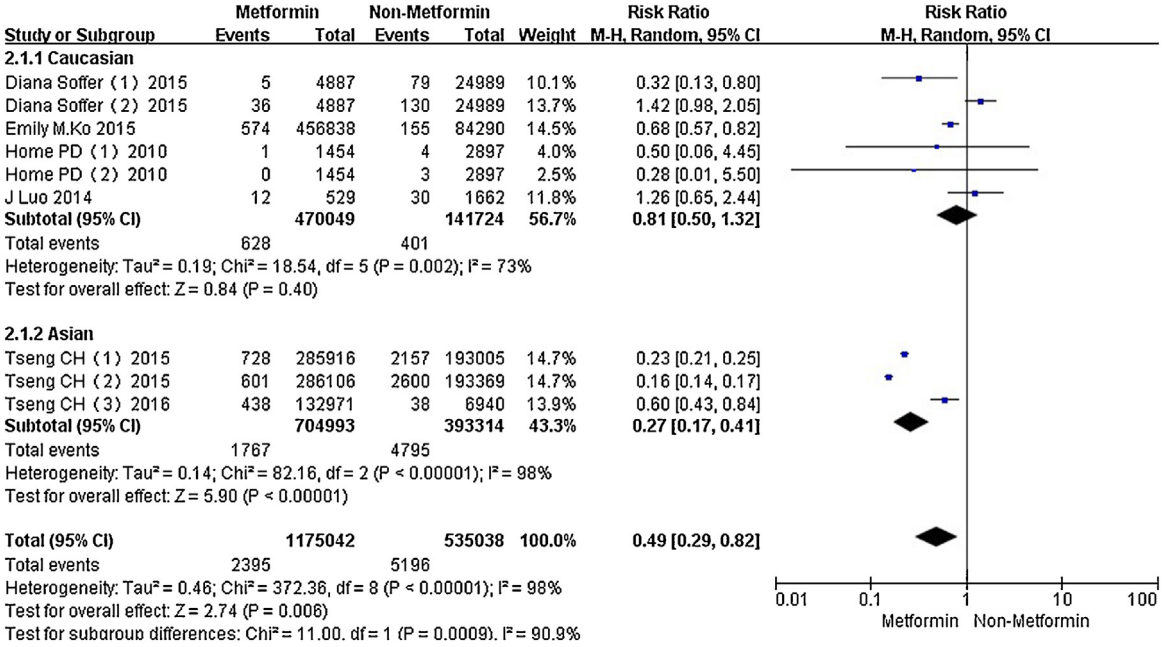

Fig. 4. Subgroup analyses by ethnicity for number of persons.

should be noted that there may be some differences among these literatures, which may come from variant research methods.

Publication bias

Begg's funnel plot and Egger's test for population and for person years were separately performed to access the publication bias of literatures. As shown in Figs. 8 and 9, the shapes of the funnel plots both appeared to be asymmetrical in the (metformin users vs non-metformin users). However, the population's results of Egger's test revealed the absence of publication bias ($p = 0.120$ for metformin users vs non-metformin users), and for person years, the results of Egger's test revealed the absence of publication bias ($p = 0.118$ for metformin users vs non-metformin users). The reasons of different statistical significance between this two test methods might derived from small sizes of this study or the amount of included studies.

Discussion

Metformin exhibits a number of attributes through both indirect and direct effects on tumor growth that make it appealing for repurposing as an anticarcinogenic drug. For gynecological cancers, metformin has been shown to have anticarcinogenic activity both in vivo and in vitro. Experimental investigations revealed that metformin inhibits the adherence, invasion and migration of human ovarian cancer cell lines in vitro as well as reduces hepatic, intestinal and lung metastases in a nude mouse model [17]. Other investigations revealed that metformin also induces apoptosis and inhibition of uterine papillary serous carcinoma cell lines [18] as well as decreased tumor growth in xenograft mouse models of endometrial cancer [19]. On the other hand, an increasing number of clinical studies of metformin have demonstrated efficacy and safety in endometrial and ovarian cancer [20]. Also, although there have not been enough clinical studies to examine the effect of metformin in cervical cancer so far, the efficacy of metformin on human cervical cancer cell lines in vitro has been observed [21]. Based on these findings, we performed the two meta-analyses to specifically assess the association between metformin and the risk of gynecological cancers.

We have noticed that patients in various studies were followed up for different periods, and an increasing awareness, the importance of person years, has been gradually recognized by

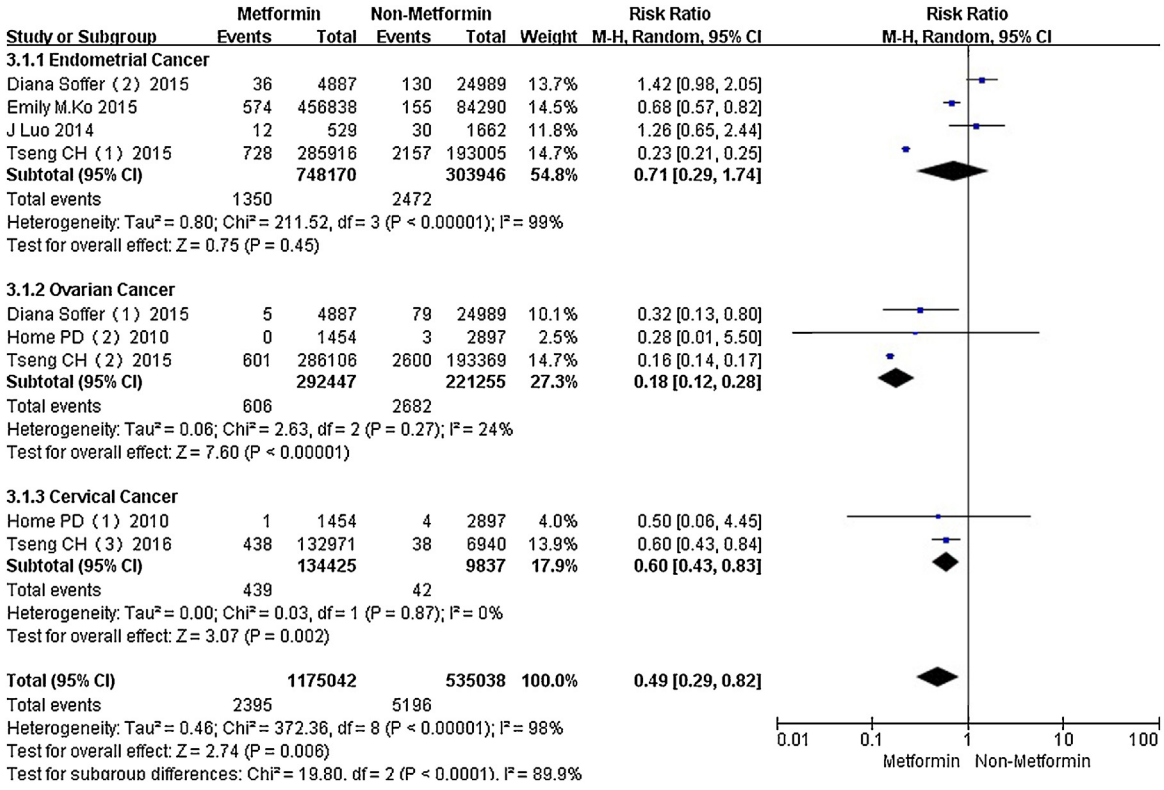

Fig. 5. Subgroup analyses by tumor group for number of persons.

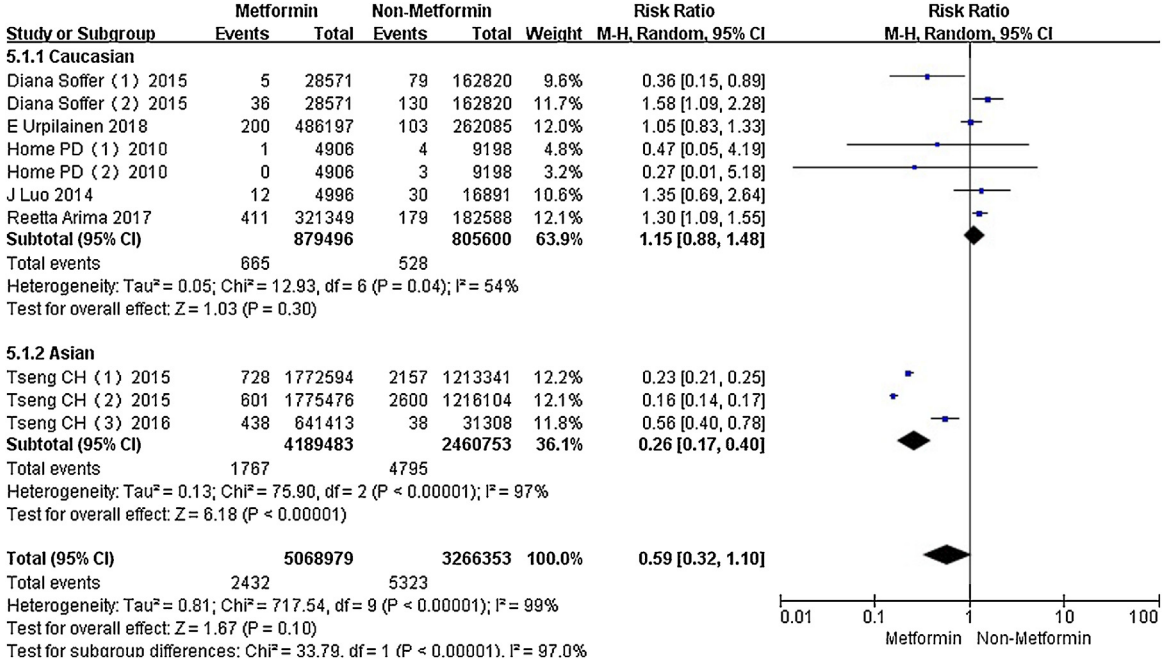

Fig. 6. Subgroup analyses by tumor group for person years.

more and more researchers. Therefore, we not only pay attention to studies of the number of persons, but also attach equal importance to the studies of person years. Considering the background of patients may affect the results of meta-analysis, subgroup analyses were performed by ethnicity and tumor group. With regard to the subregion for population, we concluded that significantly decreased risks were found among Asians (RR = 0.27, 95%CI = 0.17 −0.41, and $p < 0.00001$), ovarian cancer (RR=0.18, 95% CI=0.12−0.28, and $p < 0.00001$), and cervical cancer (RR=0.60, 95%CI=0.43−0.83, and $p = 0.002$), but not in Caucasians (RR=0.81, 95%CI=0.50−1.32, and p=0.40) or in endometrial cancer (RR=0.71, 95%CI=0.29−1.74, and $p = 0.45$). As for person years, the results showed that risks decreased among Asians (RR=0.26, 95% CI=0.17−0.40, and $p < 0.00001$) and cervical cancer (RR=0.56, 95%CI=0.40−0.78, and $p = 0.0005$). However, there is no statistical significance to support the prevention effects for ovarian cancer

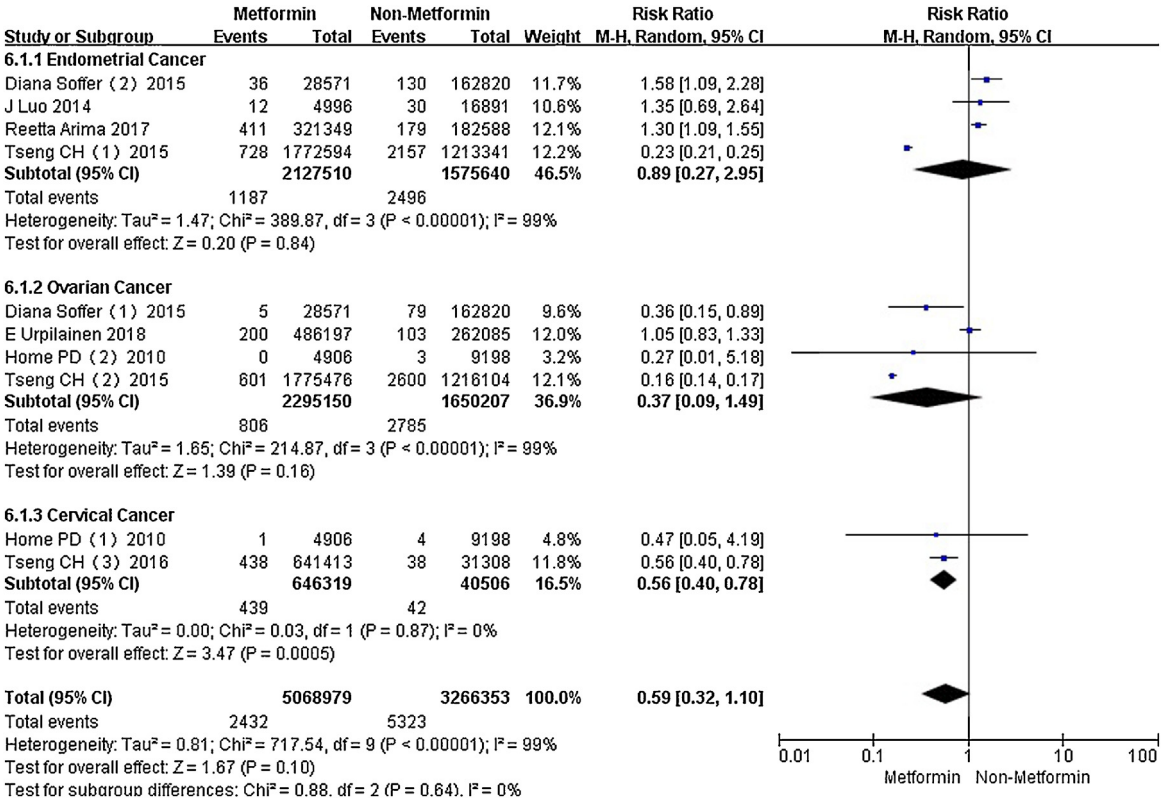

Fig. 7. Subgroup analyses by tumor group for person years.

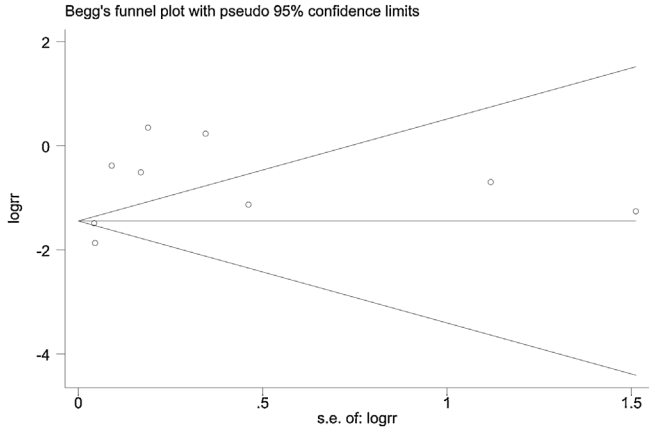

Fig. 8. Begg's funnel plot for number of persons.

contrasted with that mentioned above. However, these results should be explained with great caution because more than half of the studies were about Caucasian people, so the analyses on Asians might be insufficient.

Heterogeneity is one of the potential problems when elucidating the results of the present meta-analysis. Although we minimized the likelihood by performing a careful search for published studies, using the explicit criteria for study inclusion, performing data extraction and data analysis strictly, the significant heterogeneity between studies still existed. After subgroup analyses by subregion, the heterogeneity for both studies were partly removed in Caucasian group, suggesting that differences of genetic background existed among different ethnicity, which might account for the heterogeneity of the two meta-analyses to some extent. In addition, we attempted to determine if the heterogeneity might also be explained by other variables such as tumor group, and we found that the heterogeneity within two analyses were strikingly removed in cervical cancer groups of both studies, and was effectively wiped off in ovarian cancer of number of persons. Also, our results indicated stability of results in the two meta-analyses by sequentially excluding individual studies to a certain extent. But it should be noted that there may be some differences among these literatures, which may come from variant research methods. So more homogeneous data are needed to testify our conclusion persuasively.

The major strength of our meta-analyses are represented by several advantages. First, we update the recent data for the metformin and the risk of gynecological cancers and include large number of patients. More importantly, we have considered the effect of the follow-up years simultaneously, so we carried out another study for person years. Then, this is the first time to study the metformin and the risk of gynecological cancers. Finally, the methodological issues for meta-analysis, such as heterogeneity, publication bias, and stability of results were all thoroughly investigated. Notably, our findings are particularly important for the prevention of diabetic population from gynecological cancer. Because in our findings, all included patients are type 2 diabetic population and metformin significantly reduce the risk of gynecological cancers in diabetic population ($p = 0.006$), especially for Asians, and even as time goes on, metformin still play an positive role in the prevention of cervical cancer.

Several limitations of this meta-analysis should be addressed when explaining our results. Firstly, in our meta-analysis, as only certain published studies written in English were included, which indicates that some potential published studies in other languages or unpublished studies could be missed. Secondly, a more precise estimation was not specifically designed to assess the effect of metformin therapy on gynecological cancer because of the insufficient data. Details on dose, duration and variation for

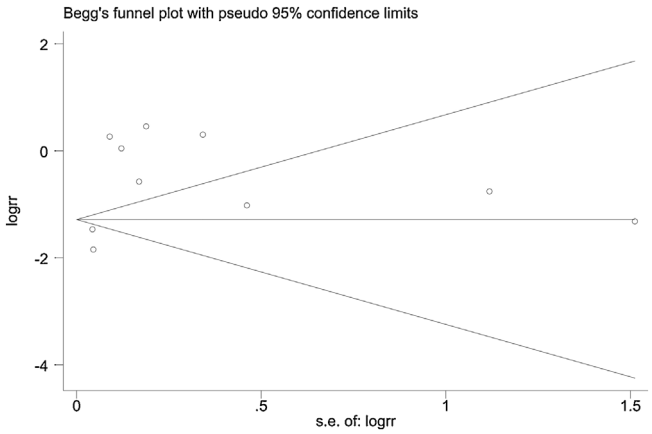

Fig. 9. Begg's funnel plot for person years.

treatments as well as full information on risk factors such as body mass index, lifestyle, drinking and smoking status were incomplete. In fact, these details are meaningful. Bodmer found that the ovarian cancer risk decreased with increasing duration of metformin user, but not associated with increased levels of HbA1c or the smoking status [22]. The adjusted odds ratio for 1–9 and 10–29 prescriptions of metformin user versus no prior use was 0.97 (0.50–1.90) and 0.61 (0.28–1.32), respectively. This observation is consistent with another study from Tseng, in which the reduced risk was associated with the increasing cumulative duration and increasing cumulative dose of metformin [13]. For endometrial cancer, the protective effect of metformin was also found with a dose-response relationship [11]. Similarly for cervical cancer, the hazard ratios for <23.0 months, 23.0–47.9 months and >47.9 months of cumulative duration were 1.272 (0.904-1.790), 0.523 (0.366−0.747) and 0.109 (0.070−0.172), respectively [14]. This observation suggested that metformin may significantly reduce the risk of cervical cancer especially when the cumulative duration is more than 2 years. For BMI, Luo found that the associations between diabetes, diabetes treatment, diabetes duration and the risk of endometrial cancer became non-significant after adjusting for BMI, suggesting there is a relationship between BMI and endometrial cancer risk [9]. Thirdly, in some studies, the "non-metformin users" group included the patients treated with insulin and sulphonylureas. While both insulin and sulphonylureas can cause hyperinsulinemia and probably with an increased risk of cancer, the effect of metformin therapy could be overestimated between the "metformin users" group and "non-metformin users" group. And the last, in the subgroup analyses, the studies of Asians and cervical cancer were relatively small, not having enough statistical power to explore the real association.

Metformin is widely accepted as a first-line drug for the treatment of type 2 diabetes mellitus [23]. All patients in the literature used for meta-analysis were diagnosed as T2DM, we may wonder naturally whether people without diabetes can take metformin as a strategy for prevention of gynecological tumors. If the research is carried out in the population suffering high-risk factors of gynecologic tumors or those with family history, we can observe whether metformin is beneficial to prevent the occurrence of gynecologic tumors. However, the safety and efficacy of metformin in non-diabetic population need further evaluation.

Conclusions

When we comprehensively synthesize the two meta-analyses, we can safely draw such a conclusion that the metformin can be used as a potential anticarcinogenic drug for the prevention of gynecological cancers, especially for Asians and cervical cancer. But for Caucasians and endometrial cancer, our meta-analysis could not reveal an association between metformin and the risk of endometrial cancer. Still, the question remains whether metformin is beneficial to preventing ovarian cancer. Also, we don't know whether it is worth to give metformin to non-diabetes to prevent gynecological cancer. Regarding some limitations for this study, therefore the results should be explained with great caution, and more large-scale studies with different environmental backgrounds are urgently needed.

Conflict of interest statement

None.

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