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Prognostic significance of metformin treatment in endometrial cancer: a meta-analysis

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Received February 12, 2020, accepted March 20, 2020

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Pharmazie 75: 401-406 (2010) *doi: 10.1691/ph.2020.0346*

Background: Previous studies suggested that metformin treatment could affect the survival outcomes of endometrial cancer (EC). This meta-analysis aims to investigate the prognostic value of metformin use in patients with EC. *Methods:* Pubmed and Embase databases were searched from inception to November 2019. We analyzed the association between metformin intake and survival of EC. Summary hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using the random-effects model. The primary outcome was overall survival (OS) and the secondary outcome was progression-free survival (PFS). *Results:* A total of eight cohort studies enrolling 6911 participants were eligible for this meta-analysis. For patients with diabetes mellitus (DM), the pooled results showed metformin could significantly improve the OS (HR=0.57, 95% CI 0.42 to 0.78) and PFS (HR=0.61, 95% CI 0.46 to 0.80,). However, no significant difference in OS (HR= 0.79, 95% CI 0.58 to 1.08) and PFS (HR=1.05, 95% CI 0.93 to1.19) was found between the patients with diabetes who used metformin and the subjects without diabetes. *Conclusions:* This study showed, based on only a limited number of studies, that metformin use was significantly associated a favorable survival outcome with of EC in diabetes patients.

1. Introduction

Endometrial cancer (EC) is the third major gynecologic malignancy after breast and cervical tumors in the worldwide, moreover, its incidence is increasing at alarming rates (MacKintosh and Crosbie 2018; Tergas and Wright 2019). The 5-year survival rate for EC in phase iii-iv was only 17% (McDonald and Bender 2019). Although some patients diagnosed with EC were cured, most of them with local or advanced EC still suffer from disease recurrence-even death (Makker et al. 2017).

Studies have shown that the occurrence of EC is strongly associated with obesity and diabetes (Yang and Wang 2019). Diabetes mellitus (DM) is a well-known risk factor for EC (Van Arsdale et al. 2019). Metformin is a widely used oral antidiabetic agent for type 2 DM. More and more studies showed that metformin has antitumor effects (Markowska and Leracz-Jacczak 2018), including EC (Lee et al. 2018). Some studies have suggested that metformin could improve survival outcome of EC (Ezewuiro et al. 2016; Ko et al. 2013; Pierce et al. 2014), while others have not revealed beneficial effects (Al Hilli et al. 2015; Insin and Prueksaritanond, 2017; Lemanska et al. 2013; Nevadunsky et al. 2014; Seebacher et al. 2016). In order to clarify the controversial results, we carried out this systematic review to investigate the prognostic value of metformin use among EC patients.

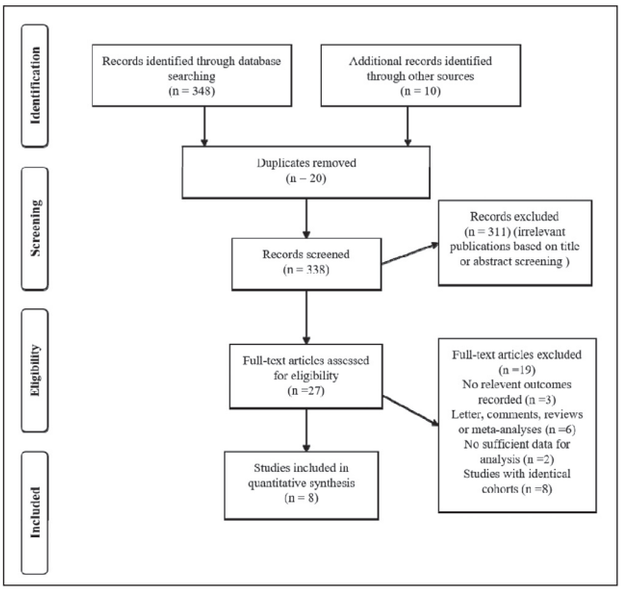

Fig 1: Flow diagram of study selection

2. Investigations and results

2.1. Description of the included studies

The database search yielded a total of 348 citations for eligibility. After removing the duplicates and irrelevant articles through screening the titles and abstracts, we identified 27 potentially relevant studies for further review. Finally, a total of 8 studies met our inclusion criteria for meta-analysis (Fig. 1). The baseline characteristics of included studies are presented in Table 1. In summary, the effect of metformin on the prognosis of EC was examined by eight studies including 6,911 patients. The median follow-up period ranged from 2.75 to 4.3 years. The studies were mainly conducted in the USA except three. Age, grade, disease stage were three conventional influential factors that were adjusted for several studies. Six studies involved EC patients with I-IV disease stages, and one with stage III-IV. Evaluation of methodological quality for cohort studies based on NOS criteria generated a score range of 7 to 9, and 6 of 8 studies had a score of 9 (S5 Table).

Table 1: Baseline characteristics of included studies investigating the survival outcomes of metformin use for EC patients

Authors (Ref.)	Study design	Country /Setting	No. of hospitals involved	Time period; Median F/U (years)	Source of date	Metformin user /non-user	Sample size	Disease stage	Survival end points	Adjusted variables
Ezewuiro et al.	Retrospective cohort	USA; hospital based	Multiple	1992-2013; 3.8	medical record; the cancer registries	31/27	349	III-IV	OS	study site, stage, age at chemotherapy
Al. Hilli et al.	Retrospective cohort	USA; hospital based	Single	1999-2008; 4.3	Medical records; tumor registry records	116/161	1303	I–IV	OS,PFS	multiple patient, disease, cancer treatment specific covariates
Nevadunsky et al.	Retrospective cohort	USA; hospital based	Single	1999-2009; 3.34	medical records; the national death registry	114/136	985	I–IV	OS,PFS	age, clinical stage, grade, chemotherapy treatment, radiation treatment and the presence of hyper-lipidemia
Ko EM et al.	Retrospective cohort	USA; population based	Multiple	2005-2010; 2.75	electronic medical records	200/163	1495	I–IV	OS,PFS	age, stage, grade, histology and adjuvant treatment.
Lemanska et al.	Retrospective cohort	Poland; population based	Single	2002-2010; NR	NR	30/38	107	NR	OS	NR
Pierce SR et al.	Retrospective cohort	USA; popula-tion-based	Multiple	1997-2012; NR	medical records	282/212	1995	I–IV	OS PFS	stage, grade, bodymass index, age, and treatment
Seebacher V et al.	Retrospective cohort	Australia; hospital-based	single	1995-2011; NR	medical records	46/41	465	I–IV	OS	age stage,grade,histol-ogy,BMI
Insin P et al.	Retrospective cohort	Thailand; hospital-based	single	2003-2013; 3.9	medical records	122/90	212	I–IV	OS PFS	NR

2.2. Metformin use and the survival of EC patients with DM (compared to metformin non-use)

Figure 2A shows the multivariate HRs (95% CI) including six studies for the OS comparing groups of metformin use and non-use in EC patients with DM and the summary HR is 0.57 (95% CI 0.42 to 0.78;P=0.05) with moderate inter-study heterogeneity (I^2 = 56%). Figure 2B shows the univariate HRs (95% CI) including five studies and the summary HR is 0.59 (95% CI 0.42 to 0.84;P=0.08) with moderate inter-study heterogeneity (I^2 = 52%). Besides, associations between metformin use and PFS in EC patients were also evaluated. Figure 2C shows the multivariate HRs (95% CI) including three studies for the PFS and the summary HR is 0.61(95% CI 0.46 to 0.80;P=0.58) with no significant inter-study heterogeneity (I^2 = 0%). Figure 2D shows the univariate HRs (95% CI) for the PFS including two studies and the summary HR is 1.09 (95% CI 0.31 to 3.71;P=0.01) with significant inter-study heterogeneity (I^2=84%).

The subgroup analyses for OS were summarized in Table 2 to further investigate potential sources of heterogeneity among certain major clinical characteristics of studies involved. The summary HRs for the majority of the subgroups remained stable for patients with some major study characteristics, including the number of hospitals, sample size, adjusted variables. A possible interaction was found in hospital number. Results of analyses limited to studies with some major variables adjusted (age, grade and disease stage) are shown in Table 2. For studies with these three variables adjusted, we noted a null prognostic association of metformin use. Nevertheless, further studies should be investigated to test the true survival outcome of metformin in EC patients due to the small amount of research involved in these subgroups.

Sensitivity analyses were conducted by omitting one study at a time and calculating the others and indicated no individual study affected the pooled HR significantly.

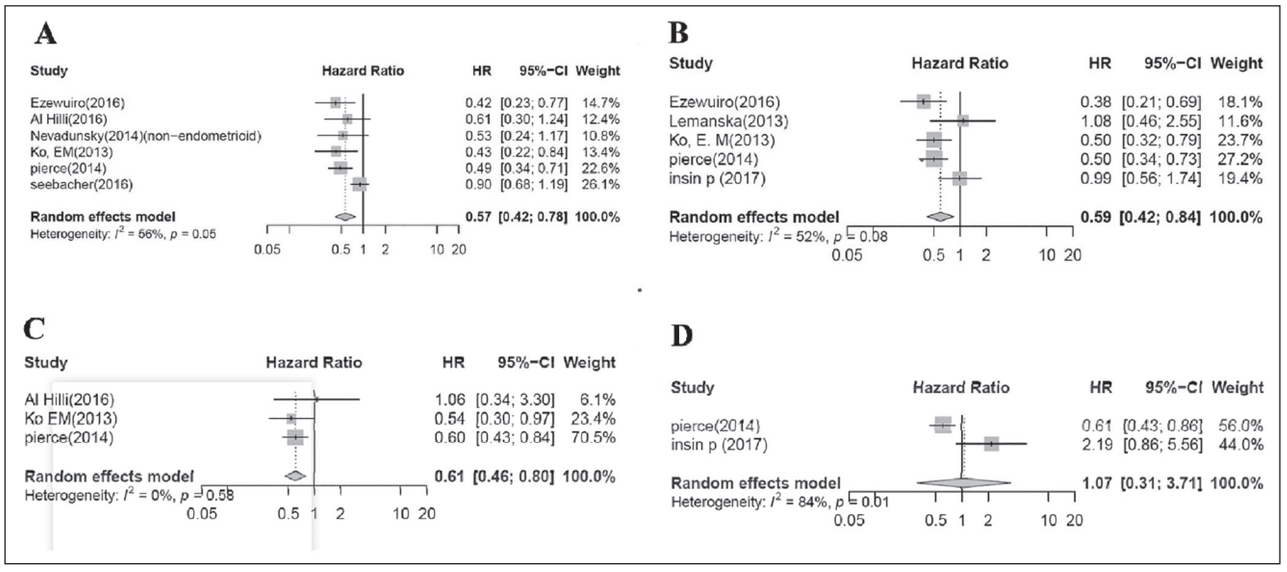

Fig. 2: Forest plot of the association between metformin use and the survival of EC within DM patients.(A) the multivariate HRs (95% CI) for the OS; (B) the univariate HRs (95% CI) for the OS; (C)the multivariate HRs (95% CI) for the PFS; (D)the unitivariate HRs (95% CI) for the PFS.

Table 2: Subgroup analyses of the associations between metformin use and overall survival

Comparison variables	Overall survival			
	No. of studies	I^2 statistics; %	HR (95% CI)	$P_{interation}$
Total	5	20.3	0.79 (0.58 – 1.08)	NA
Hospital number				0.7097
Single	3	14.2	0.75(0.50 – 1.41)	
Multiple	2	61.8	0.88(0.45 –1.71)	
Sample size				0.039
≥1000	2	0	1.14 (0.72;1.78)	
<1000	3	0	0.63 (0.45; 0.88)	
Main variable adjusted*				0.963
Yes	3	44.2	0.80(0.46 – 1.4)	
No	2	30.3	0.79(0.51 –1.23)	

2.3. Survival differences between the patients with diabetes who used metformin and the subjects without diabetes

As is shown in Fig. 3A**,** the multivariate HRs (95% CI) for the OS comparing the patients with diabetes who used metformin and the subjects without diabetes were analysed and the summary HR was 0.79(95% CI 0.58 to 1.08; P=0.29) with low inter-study heterogeneity (I^2 = 20%). Figure 3B shows the univariate HRs (95% CI) including three studies and the summary HR is 0.60 (95% CI 0.93 to 1.19; P=0.47) with low inter-study heterogeneity (I^2 = 0%). Figure 3C shows the multivariate HRs (95% CI) for the PFS and the summary HR is 1.05(95% CI 0.93 to1.19; P=0.85) with no significant inter-study heterogeneity (I^2 = 0%).

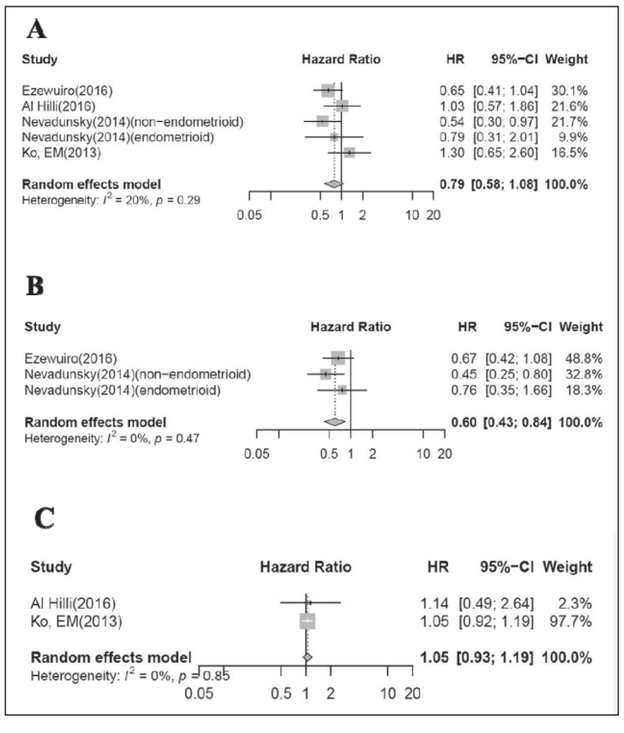

Fig. 3: Forest plot of the association between metformin use and the survival of EC comparing the patients with diabetes who used metformin and the subjects without diabetes. (A) Multivariate HRs (95% CI) for the OS; (B) Univariate HRs (95% CI) for the OS; (C) Multivariate HRs (95% CI) for the PFS.

Funnel plots were generated to assess the possibility of publication bias. As shown in Fig. 4, no evident asymmetry was detected, which was also supported by Egger's test (P=0.136) or Begg's test (P=0.707) (**Fig. 4A**), and the Egger's test (P=0.462) or Begg's test (P=0.501) (**Fig. 4B**), indicating that there was no obvious publication bias in our study.

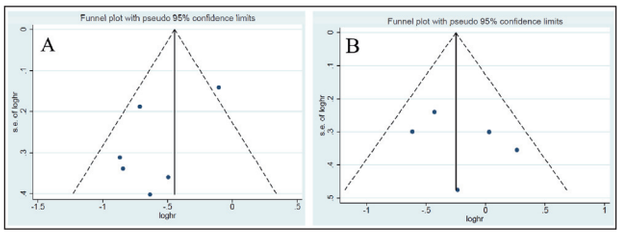

Fig. 4: Funnel plot for the publication bias on the association of metformin use with the survival of EC. A: Test between metformin use and non-use in patients with DM. B: Test between metformin use and the survival of EC comparing the patients with diabetes who used metformin and the subjects without diabetes.

3. Discussion

This meta-analysis examined the prognostic value of metformin use on the survival of EC patients and included 8 studies with a total of 6911 patients. We compared not only between group of metformin use and metformin non-use in EC patients with DM but also between the patients with diabetes who used metformin and the subjects without diabetes. To our best knowledge, this is the first time to compare the survival difference between the patients with diabetes who used metformin and the subjects without diabetes. Besides, we included a recent study to further examine the effect of metformin on the prognosis of endometrial cancer in patients with diabetes. We analyzed the multivariate and univariate HR separately. The pooled data indicated that the use of metformin could substantially improve the prognosis of EC patients with DM in terms of OS and PFS.

Metformin is the most widely used antihyperglycemic drug. In the past decade, many studies reported that metformin would improve the survival of patients with several types of cancers (Markowicz-Piasecka et al. 2018; Safe et al. 2018), including EC (Soliman et al. 2020). Metformin has anticancer properties with various mechanisms (Feng et al. 2018; Xue et al. 2019), including insulin-dependent or independent manners. Previous research *in vitro* suggested that metformin inhibited EC cell proliferation and reduced invasion and metastasis.

Our meta-analysis has several important strengths. First, to the best of our knowledge, this is the first meta-analysis providing the survival difference between the patients with diabetes who used metformin and the subjects without diabetes. Second, we performed a systematic and comprehensive search strategy to identify all relevant studies or trials in the two databases without language or publication date limitations. Third, we conducted several subgroup analyses based on some important variables, including sample size and main variable adjusted. The findings showed consistency across subgroups.

However, limitations of our systematic review should not be ignored. Firstly, EC patients with DM may take more than one anti-diabetic medication (ADM. We did not analyze whether other ADMs influence the survival of EC patients with DM. Secondly, the studies included did not provide dose or duration-response analysis for metformin, so it is difficult for us to conduct this kind of analysis. Therefore, we need to further focus on this aspect. Thirdly, although we identified and adjusted major variables including age, grade and disease stage, some other confounders (such as study site, body mass index or chemotherapy) could modify our exploration of associations between metformin and EC survival. Moreover, although significant publication bias for the metformin group in studies involved was not found, we could not

fully exclude the possible influence of unpublished articles on the summary results, which might have led to reporting bias.
In conclusion, this meta-analysis showed that metformin use is associated with OS and PFS in EC patients with DM, however, due to a small number of studies, further large-scale studies should be investigated to determine this associations between metformin intake and EC patients.

4. Experimental

4.1. Literature search and study selection

Based on the PRISMA statement, a comprehensive literature search in PUBMED and EMBASE databases up to November 2019 was conducted for all relevant studies with no language restrictions. The detailed search strategies are provided in Tables S1-S4. Manual searching was also performed on the reference lists of relevant research papers, reviews and meta-analysis for other possible publications.
Published studies were included if they met the following criteria: (1) reported survival outcomes in EC patients comparing metformin users and non-users; the survival endpoints were overall survival (OS), and/or progression-free survival (PFS); (2) provided prognostic date with a summary statistic of hazard ratios (HRs) with 95% confidence intervals (CIs) or reported date for calculation as described by Parmar et al. In our meta-analysis, randomized controlled trials or observational studies were eligible. When multiple studies for the same cohort were found, the most detailed or recent study was selected for analysis. Two investigators performed the study selection independently (HG and DZ).

4.2. Data extraction

Two reviewers performed the data extraction independently (YC and HG). Any disagreement was resolved by a consensus discussion with a third investigator (DZ). The following information was extracted: first author name, publication year, research country, study design, study setting, number of hospitals involved, time period of study, source of date, total number of patients (exposed vs. not exposed), sample size, disease stage, median follow-up duration, survival outcomes and adjusted HR or unadjusted HR, and 95% confidence intervals (CIs). We assessed the methodological quality of each study using the Newcastle-Ottawa Quality Assessment Scale. Three domains including cohort selection of the participants, comparability of the participants, and outcomes were evaluated with a score range of 0 to 9 and nine represents the highest quality.

4.3. Statistical analysis

All data analyses were carried out using STATA statistical software (version 12.0, StataCorp LP, College Station, TX) and R statistical software (version 3.6.1). To assess the association between metformin use and survival of EC, summary HRs and associated 95% CIs (metformin use vs no-use; metformin use vs non-diabetes) were calculated with random-effects model. We tested the between-study heterogeneity by the Cochrane Q statistic (with a $P < 0.10$ considering statistically significant) and the I2 statistic (with an I2 >50% indicating substantial heterogeneity). OS in patients treated with metformin was evaluated for primary meta-analysis. Other outcomes such as PFS were also assessed. We assessed the risk of publication bias by visually inspecting a funnel plot as well as by Egger's or Begg's regression model. All statistical analyses were two-sided and a P value less than 0.05 was indicated statistically significant.

Conflicts of interests: None declared.

References

Al Hilli MM, Bakkum-Gamez JN, Mariani A, Cliby WA, Mc Gree ME, Weaver AL, Dowdy SC, Podratz KC (2015) The impact of diabetes and metformin on clinical outcomes is negligible in risk-adjusted endometrial cancer cohorts. Gynecol Oncol 137: 156–157.

Ezewuiro O, Grushko TA, Kocherginsky M, Habis M, Hurteau JA, Mills KA, Hunn J, Olopade OI, Fleming GF, Romero IL (2016) Association of metformin use with outcomes in advanced endometrial cancer treated with chemotherapy. PLoS One 11: e0147145.

Feng X, Tan A, Long P, Wang T, Yang J (2018) Efficacy and mechanism of different doses of metformin on early endometrial cancer patients with fertility requirements. Anti-Tumor Pharmacy 8: 208–210.

Insin P, Prueksaritanond N (2017) Therapeutic use of metformin in diabetes and survival outcomes in endometrial cancer patients with diabetes. J Obstet Gynaecol Res 43 (Suppl. 1): 195.

Ko EM, Walter P, Clark LH, Jackson A L, Franasiak J, Havrilesky LJ, Secord AA, Moore DT, Gehrig PA, Bae-Jump VL (2013) The impact of diabetes and obesity on endometrial cancer outcomes. J Clin Oncol 31 (Suppl. 1): 15.

Lee TY, Martinez-Outschoorn UE, Schilder RJ, Kim CH, Richard S D, Rosenblum NG, Johnson JM (2018) Metformin as a therapeutic target in endometrial cancers. Frontiers Oncol 8: 341.

Lemanska A, Zaborowski M, Magnowska M, Spaczynski M, Nowak-Markwitz E(2013) Metformin does not improve survival in endometrial cancer. Int J Gynecol Cancer 23 (Suppl. 1): 335.

MacKintosh ML, Crosbie EJ (2018) Prevention strategies in endometrial carcinoma. Curr Oncol Rep 20: 101.

Makker V, Green AK, Wenham RM, Mutch D, Davidson B, Miller DS (2017) New therapies for advanced, recurrent, and metastatic endometrial cancers. Gynecol Oncol Res Pract 4: 19.

Markowicz-Piasecka M, Huttunen KM, Mikiciuk-Olasik E, Mateusiak Ł, Sikora J (2018) Metformin-from anti-diabetic drug to anti-cancer drug. Acta Polon Pharm Drug Res 75: 3–18.

Markowska A, Leracz-Jacczak A (2018) Metformin in cancer treatment. Curr Gynecol Oncol 16: 46–49.

McDonald ME, Bender DP (2019) Endometrial cancer: obesity, genetics, and targeted agents. Obstet Gynecol Clin North Am 46: 89–105.

Nevadunsky NS, Van Arsdale A, Strickler HD, Moadel A, Kaur G, Frimer M, Conroy E, Goldberg GL, Einstein MH (2014) Metformin use and endometrial cancer survival. Gynecol Oncol 132: 236–240.

Pierce SR, Doll KM, Davidson B, Lee C, Ko EM, Snavely AC, Gehrig PA, Secord AA, Havrilesky LJ, Bae-Jump VL (2014) Endometrial cancer outcomes in diabetic women treated with metformin, statins, and aspirin. Gynecol Oncol 133 (Suppl. 1): 43.

Safe S, Nair V, Karki K (2018) Metformin-induced anticancer activities: Recent insights. Biol Chem 399: 321–335.

Seebacher V, Bergmeister B, Grimm C, Koelbl H, Reinthaller A, Polterauer S (2016) The prognostic role of metformin in patients with endometrial cancer: a retrospective study. Eur J Obstet Gynecol Reprod Biol 203: 291–296.

Soliman PT, Westin SN, Iglesias DA, Fellman BM, Ying Y, Zhang Q, Yates MS, Broaddus RR, Slomovitz BM, Lu KH, Coleman RL (2020) Everolimus, letrozole, and metformin in women with advanced or recurrent endometrioid endometrial cancer: A multi-center, single arm, phase II study. Clin Cancer Res 26: 581–587.

Tergas AI, Wright JD (2019) Cancer prevention strategies for women. Obstet Gynecol 134: 30–43.

Van Arsdale A, Miller DT, Kuo DY, Isani S, Sanchez L, Nevadunsky NS (2019) Association of obesity with survival in patients with endometrial cancer. Gynecol Oncol 154: 156–162.

Xue J, Li L, Li N, Li F, Qin X, Li T, Liu M (2019) Metformin suppresses cancer cell growth in endometrial carcinoma by inhibiting PD-L1. Eur J Pharmacol 859: 172541.

Yang X, Wang JL (2019) The role of metabolic syndrome in endometrial cancer: a review. Frontiers Oncol 9: 744.

Supplementary Material

Table S1: Search strategy for Pubmed (Publication date to 2019/11/05)

1.	"Endometrial Neoplasms "[Mesh]
2. 3.	**endometrial** [Title/Abstract] OR **endometrium** [Title/Abstract] (Cancer OR tumor OR tumour OR carcinoma OR neoplas* OR malignan*)[Title/Abstract]
4.	2AND3
5.	1 OR 4
6.	"Metformin"[Mesh]
7.	metformin[Title/Abstract]OR Dimethylbiguanidine[Title/Abstract]OR Dimethylguanylguanidine[Title/Abstract]OR Glucophage[Title/Abstract]
8.	9 OR 10
9.	"Mortality"[Mesh]
10.	"Survival"[Mesh]
11.	"Prognosis"[Mesh]
12.	((((((prognos*[Title/Abstract]) OR survival[Title/Abstract]) OR recurren*[Title/Abstract]) OR mortality[Title/Abstract]) OR predict*[Title/Abstract]) OR outcome*[Title/Abstract]) OR death[Title/Abstract]
13.	9 OR 10 OR 11 OR 12
14.	5 AND 8 AND 13

Table S2: Search strategy for Embase (Publication date to 2019/11/05)

1.	' **endometrium tumor** '/exp
2.	(**endometrial** OR **endometrium**):ab,ti
3.	(Cancer OR tumor OR tumour OR carcinoma OR neoplas* OR malignan*):ab,ti
4.	2 AND 3
5.	1 OR 4
6.	'metformin'/exp
7.	(metformin OR dimethylbiguanidine OR dimethylguanylguanidine OR glucophage):ab,ti
8.	6 OR 7
9.	'mortality'/exp
10.	'survival'/exp
11.	'cancer prognosis'/exp
12.	(prognos* OR survival OR recurren* OR mortality OR predict* OR outcome* OR death):ab,ti
13.	9 OR 10 OR 11 OR12
14.	5 AND 8AND13

Table S3: Selection procedure of included and excluded studies

	Suppl. Ref. list no.
Studies included in the meta-analysis (n =8)	[1, 2, 3, 4, 5, 6, 7, 8]
Studies excluded from meta-analysis, and reasons are listed below (n = 19)	
Reason for exclusion	
Publication with cases included in a selected study (n =8)	[9, 10, 11, 12, 13, 14, 15, 16]
No prognostic outcomes recorded (n =3)	[17, 18, 19]
Letters, comments, reviews or meta-analyses (n =6)	[20, 21, 22, 23, 24, 25]
No sufficient data for analysis (n =2)	[26, 27]

Table S4: List of excluded studies using overlapping populations in the included studies

Included studies (First author, publication year, country/ region) [Reference]	**Excluded studies**
Al Hilli et al. (2016) USA [4]	Al Hilli et al. (2015) USA [14]
Nevadunsky et al. (2014) USA [5]	Nevadunsky et al. (2013) USA [12] Nevadunsky et al. (2013) USA [11]
Ko et al. (2013) USA [7]	Ko et al. (2013) USA [10] Ko et al. (2012) USA [9] Ko et al. (2014) USA [13]
Lemanska et al. (2013) Poland [6]	Lemańska et al. (2015) Poland [15]
Insin P et al. (2017) Thailand [1]	Insin P et al. (2018) Thailand [16]

Table S5: Methodological quality of included studies based on the Newcastle–Ottawa Scale for cohort studies

Observational studies[a]					
Study	**Design**	**Selection**	**Comparability**	**Outcome/ exposure**	**Overall quality (max 9)**
Ezewuiro et al. (2016)	Cohort	****	**	***	9
Al Hilli et al. (2016)	Cohort	****	**	***	9
Nevadunsky et al. (2014)	Cohort	****	**	***	9
Ko et al. (2014)	Cohort	****	**	***	9
Lemanska et al. (2013)	Cohort	****		***	7
Pierce et al. (2014)	Cohort	****	**	***	8
Seebacher (2016)	Cohort	****	**	***	9
Insin (2017)	Cohort	****	**	***	9

A Study quality assessment of observational studies performed using the Newcastle–Ottawa scale (each asterisk represents if individual criterion within the subsection were fulfilled).

Supplementary reference list

[1] Insin P, Prueksaritanond N (2017) Therapeutic use of metformin in diabetes and survival outcomes in endometrial cancer patients with diabetes. J Obstet Gynaecol Res 43 (Suool. 1): 195.

[2] Seebacher V, Bergmeister B, Grimm C, Koelbl H, Reinthaller A, Polterauer S (2016) The prognostic role of metformin in patients with endometrial cancer: a retrospective study. Eur J Obstet Gynecol Reprod Biol 203: 291–296.

[3] Ezewuiro O, Grushko TA, Kocherginsky M, Habis M, Hurteau JA, Mills KA, Hunn J, Olopade OI, Fleming GF, Romero IL (2016) Association of metformin use with outcomes in advanced endometrial cancer treated with chemotherapy. PLoS One 11: e0147145.

[4] Al Hilli MM, Bakkum-Gamez JN, Mariani A, Cliby WA, Mc Gree ME, Weaver AL, Dowdy SC, Podratz KC (2016) The effect of diabetes and metformin on clinical outcomes is negligible in risk-adjusted endometrial cancer cohorts. Gynecol Oncol 140: 270–276.

[5] Nevadunsky NS, Van Arsdale A, Strickler HD, Moadel A, Kaur G, Frimer M, Conroy E, Goldberg GL, Einstein MH (2014) Metformin use and endometrial cancer survival, Gynecologic Oncology 132: 236–240.

[6] Lemanska A, Zaborowski M, Magnowska M, Spaczynski M, Nowak-Markwitz E (2013) Metformin does not improve survival in endometrial cancer, Int J Gynecol Cancer 23 (Suppl. 1): 335.

[7] Ko EM, Walter P, Clark LH, Jackson AL, Franasiak J, Havrilesky LJ, Secord AA, Moore DT, Gehrig PA, Bae-Jump VL (2013) The impact of diabetes and obesity on endometrial cancer outcomes. J Clin Oncol 31 Suppl. 1: 15.

[8] Pierce SR, Doll KM, Davidson B, Lee C, Ko EM, Snavely AC, Gehrig PA, Secord AA, Havrilesky LJ, Bae-Jump VL (2012) Endometrial cancer outcomes in diabetic women treated with metformin, statins, and aspirin, Gynecol Oncol 133 (Suppl. 1): 43.

[9] Ko EM, Franasiak J, Clark LH, Gehrig PA, Victoria LBJ (2012) Impact of metformin use on risk of recurrence in high-grade endometrial cancers. J Clin Oncol 30 (Suppl. 1): 5009.

[10] Ko EM, Paige W, Clark L, Jackson A, Franasiak J, Havrilesky L, Alvarez-Secord A, Gehrig P, Bae-Jump V (2013) Metformin reduces recurrence and improves survival in endometrial cancers. Gynecol Oncol 130: e83.

[11] Nevadunsky N, VanArsdale A, Kaur G, Frimer M, Conroy E, Einstein M, Goldberg G (2013) Use of metformin is associated with improved endometrial cancer survival. Gynecol Oncol 130: e74-e75.

[12] Nevadunsky NS, Van Arsdale A, Strickler HD, Moadel A, Kaur G, Frimer M, Conroy E, Goldberg GL, Einstein MH (2014) Metformin use and endometrial cancer survival, Gynecol Oncol 132: 236–240.

[13] Ko EM, Sturmer T, Hong JL, Camelo W, Bae-Jump VL, Funk MJ (2014) Metformin and the risk of endometrial cancer: A population-based cohort study, Gynecol Oncol 133: 32.

[14] Al Hilli M, Bakkum-Gamez JN, Mariani A, Shridhar V, Cliby BA, McGree M, Weaver AL, Dowdy SC, Podratz KC (2015) The impact of diabetes and metformin on clinical outcomes is negligible in risk-adjusted endometrial cancer cohorts, Gynecol Oncol 137: 156–157.

[15] Lemańska A, Zaborowski M, Spaczyński M, Nowak-Markwitz E (2015) Do endometrial cancer patients benefit from metformin intake? Ginekol Polska 86: 419–423.

[16] Insin P, Prueksaritanond N (2018) Therapeutic use of metformin in diabetes and survival outcomes in endometrial cancer patients with diabetes. Asian Pac J Cancer Prev 19: 1295–1302.
[17] Arima R, Läärä E, Arffman M, Ilanne-Parikka P, Sund R, Hinkula M, Puistola U (2016) Endometrial cancer survival in patients with type 2 diabetes: Questioning the beneficial effect of metformin use. Int J Gynecol Cancer 26: 52.
[18] Arima R, Hautakoski A, Marttila M, Arffman M, Sund R, Ilanne-Parikka P, Kangaskokko J, Hinkula M, Puistola U, Läärä E (2017) Cause-specific mortality in endometrioid endometrial cancer patients with type 2 diabetes using metformin or other types of antidiabetic medication. Gynecol Oncol 147: 678–683.
[19] Arima R, Marttila M, Hautakoski A, Arffman M, Sund R, Ilanne-Parikka P, Kangaskokko J, Urpilainen E, Laara E, Hinkula M, Puistola U (2018) Antidiabetic medication, statins and the risk and prognosis of non-endometrioid endometrial cancer in women with type 2 diabetes. Anticancer Res 38: 4169–4178.
[20] Guo J, Xu K, An M, Zhao Y (2017) Metformin and endometrial cancer survival: A quantitative synthesis of observational studies. Oncotarget 8: 66169–66177.
[21] Meireles CG, Pereira SA, Valadares LP, Rêgo DF, Simeoni LA, Guerra ENS, Lofrano-Porto A (2017) Effects of metformin on endometrial cancer: Systematic review and meta-analysis. Gynecol Oncol 147: 167–180.
[22] Tang YL, Zhu LY, Li Y, Yu J, Wang J, Zeng XX, Hu KX, Liu JY, Xu JX (2017) Metformin use is associated with reduced incidence and improved survival of endometrial cancer: a meta-analysis. BioMed Res Int 2017: 5905384.
[23] Chu D, Wu J, Wang K, Zhao M, Wang C, Li L, Guo R (2018) Effect of metformin use on the risk and prognosis of endometrial cancer: a systematic review and meta-analysis, BMC Cancer 18: 438.
[24] Clement N (2018) Metformin for endometrial hyperplasia (review). Int J Gynecol Obstet 143: 916.
[25] Zhang Q, Schmandt RE, Medepalli M, Nebgen D, Soletsky B, Milbourne A, Levy E, Fellman B, Urbauer D, Yuan Y, Broaddus RR, Basen-Engquist K, Lu K, Chu D, Wu J, Wang K, Zhao M, Wang C, Li L, Guo R (2018) Effect of metformin use on the risk and prognosis of endometrial cancer: a systematic review and meta-analysis. Cancer Prev Res (Phila) 18: 438.
[26] Hahn LA, Villella JA, Chalas E, Chan KC, Jimenez EA (2014) Metformin use is associated with improved survival in women with endometrial cancer. Gynecol Oncol 133: 159.
[27] Freeman S (2015) ASTRO: Metformin use during RT associated with better outcomes. Oncol Rep 11: 3-4.