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Systematic Review

A systematic review and meta-analysis on the effects of metformin on survival outcomes and risk in women with cervical cancer

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Summary

Objective: A systematic review and meta-analysis was conducted to quantitatively assess the effects of metformin on both the treatment and risk of cervical cancer in women. Materials and Methods: A search was conducted in a number of databases including CNKI, VIP, Wanfang Digital Journal Full-text Database, PubMed, Cochrane, and Web of Science. In accordance with inclusion and exclusion criteria screening in the literature, Newcastle-Ottawa scale and RevMan 5.3 software were employed to perform the meta-analysis. Results: A total of five studies taken from four articles involving 149,742 participants were finally included in meta-analysis,two random clinical trials (RCTs) and three retrospective cohort studies. Evaluation of metformin usage in two of the studies did not show significant association with five-year overall survival (OS) of patients receiving adjuvant whole-pelvic radiation therapy (WPRT) as a primary therapy compared to those . not using metformin (RR = 1.08, 95% CI 1.00-1.18, $p = 0.06$). In the three other studies metformin use was associated with a significant reduction in cervical cancer risk in diabetes mellitus patients (RR = 0.60, 95% CI 0.44-0.82, $p = 0.001$). Conclusion: Merformin use is associated with a reduction in cervical cancer risk in patients with diabetes mellitus, but is not associated with five-year OS of patients receiving WPRT. Further studies are required to confirm survival outcomes for use of metformin in cervical cancer.

Key words: Cervical cancer; Meta-analysis; Metformin; Outcomes; Systematic review.

Introduction

In resent years, the incidence of cancer and diabetes is increasing year by year in China, threatening patient's lives and causing a heavy economic burden. An epidemiological study has shown that patients with diabetes have a higher risk of developing tumors which also affects their prognosis [1]. Compared with the general population, the gynecologic malignancy tumor incidence rate is relatively high in female patients with type 2 diabetes mellitus (T2DM), which may be accounted for by obesity, hyperinsulinemia, insulin resistance and other metabolic abnormalities caused by the lack of insulin [2, 3]. Gynecologic cancers, common in adult women, mainly include vaginal tumors, uterine tumors, ovarian tumors, endometrial cancer and cervical cancer (add ref) Amongst these, cervical cancer is the predominant gynecological malignancy in China and patients tend to be diagnosed younger than elsewhere [4, 5]. Some reports have shown that metformin can inhibit protein synthesis in tumours through the LKB1-AMPK-mTOR pathway by reducing the downstream phosphorylation of p70S6Ks and 4E-BPs. This leads to the promotion of tumor apoptosis and autophagy by upregulating p53 expression and transcription of its downstream target genes Bax and p21 [6, 7]. Clinical research on the use and effect of metformin on gynecological malignancy has demonstrated ——— Need to provide some description of these studies [8, 9]. To better understand this issue, a systematic review and meta-analysis of metformin has been undertaken to estimate the association between use of this drug and the survival outcomes for patients with cervical cancer.

Materials and Methods

A search was performed in a number of databases including CNKI, VIP, Wanfang Digital Journal Full-text Database, PubMed, Cochrane, and Web of Science from their inception to March 15, 2018. The search terms were "metformin" or "dimethylbiguanidine" or "glucophage" and "cervical cancer" or "cervical neoplasms". There were no language restrictions in the literature search strategy.

The inclusion criteria were as follows: (a) randomized controlled clinical trials (RCTs), cohort studies or case-control studies, (b) association between metformin use, survival outcomes, and cervical cancer risk, (c) sufficient data for metformin use and outcomes of interest being available or being able to be extracted.

The exclusion criteria were: (a) no control group and (b) letters, reviews, editorials, conference papers, case re-

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Table 1. — *All the cohort studies included were considered to be of high-quality.*

Study	Region	Study design	Study population	Stage	Sample size	Reference group	Outcomes	NOS value
Home 2010 (ADOPT) [11]	UK	RCT	DM patients	NA	4351	rosiglitazone and glibenclamide	Incident of CC	-
Home 2010 (RECORD) [11]	UK	RCT	DM patients	NA	4447	sulfonylurea and rosiglitazone	Incident of CC	-
Han 2016 [12]	Canada	retrospective cohort study	CC patients with DM	NA	181	antidiabetics other than metformin	CC specific death, overall mortality	9
Li 2016 [13]	China	RCT	CC patients with DM	IIB∼IIIB	43	hypoglycemic agents other than metformin	PFS, OS	-
Tseng 2016 [14]	Taiwan	retrospective cohort study	DM patients	NA	139911	Other antidiabetic drugs other than metformin	Incident of CC	9
Takiuchi 2017 [15]	USA	retrospective cohort study	CC patients	I∼IV	785	nonmetformin	PFS 5-y(%), OS 5-y(%), WPRT-PFS 5-y(%), WPRT-OS 5-y(%), recurrent/progressed cases	7
Hanprasertpong 2017 [16]	Thailand	retrospective cohort study	CC patients with DM	IA2∼IVA	248	nonmetformin	WPRT-PFS 5-y(%), DFS	9

Abbreviations: CC, cervical cancer; DM, diabetes mellitus; PFS, progression-free survival; OS, overall survival; DFS, recurrence or disease-free survival; WPRT, whole pelvic radiotherapy; 5-y (%), 5-year rates; NOS, Newcastle-Ottawa scale;

ports, cell line studies, animal studies. If there were multiple publications based on the same study or population, the one which provided the most abundant information or contained the largest amount of data and number of cases was included.

At the data extraction stage, two of the authors performed the tasks independently. Information about the first author, publication year, region, study design, study population, stage of the study, sample size, drug usage, and cervical cancer-related outcomes were all collected. The cohort studies were evaluated by two authors using the Newcastle-Ottawa scale (NOS) [10]. The NOS star system awards a maximum of nine stars with respect to the selection, comparability and outcome. In this review, the authors considered studies awarded seven or more stars as high-quality studies.

Statistical tests were performed using Review Manager (RevMan 5.3, Cochrane Center). Heterogeneity analyses among studies was performed using the Chi-square test and I^2 statistic. The fixed-effects model was chosen when $p > 0.05$ or $I^2 < 50\%$ and the random-effects model was applied for $p < 0.05$ or $I^2 > 50\%$. Relative risk (RR) and 95% confidence interval (95% CI) was chosen as the analysis statistic.

Results

The flow diagram of the study selection process is shown in Figure 1. In the database search, 107 related publications were identified, 28 of which were discarded after removing duplicates. Seventy-nine articles were screened by title or abstract and consequently eight articles were retrieved for full-text assessment for eligibility. Two records were excluded for not meeting the eligibility criteria. And finally five studiies from four articles were included in the meta-analysis.

The main characteristics of the studies included are summarized in Table 1. A total of five studies from four articles involving 149,742 participants were finally included in the meta-analysis, two studies were RCTs and three were retrospective cohort studies, published between 2010, and 2017. Of these, two studies were conducted in the UK [11], one in Taiwan [14], one in USA [15] one in Thailand [16], and the sample size ranged from 248 to 139,911 all of which are outlined in.

Two studies involving 1,033 participants investigated the association between metformin use and five-year overall survival (OS). As shown in Figure 2, there was no substantial heterogeneity between the two studies ($p = 0.27$, $I^2 = 0\%$) and accordingly the fixed-effects model was used. The results showed that the use of metformin was not significantly associated with five-year OS for patients who received WPRT as the primary therapy compared to those not using metformin (RR = 1.08, 95%CI 1.00-1.18, $p = 0.06$) despite the appearance of an increased tendency.

Three studies involving 148,709 participants investigated the association between metformin use and cervical cancer risk in diabetes mellitus patients. As shown in Figure 3, there was no obvious study heterogeneity across the three studies ($p = 0.99$, $I^2 = 0\%$) and again the fixed-effects model was used. Metformin use was associated with a significant reduction in cervical cancer risk in diabetes mellitus patients (RR = 0.60, 95%CI 0.44-0.82, $p = 0.001$) compared to patients not taking metformin.

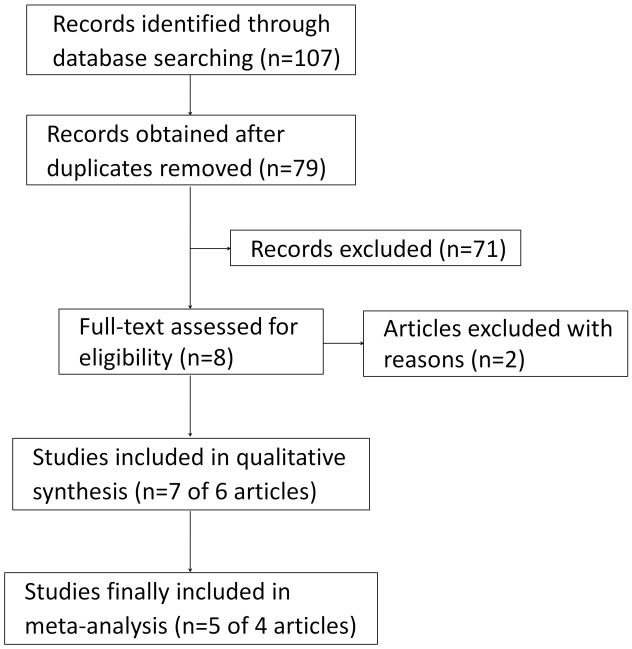

Figure 1. — Flow diagram of study selection process.

Discussion

Metformin, is the first-line and most widely used oral drug treatment for type 2 diabetes because of its broad spectrum of pleiotropic effects and good tolerability by patients,.iThe major functions of metformin are to inhibit gluconeogenesis and glucose release, improve insulin sensitivity, and increase glucose uptake and utilization (Add Ref). Recent research shows that metformin also has an anticancer effect, functioning primarily through activation of AMP-activated protein kinase (AMPK) and regulating the activity of the AMPK/mTOR signaling pathway [17, 18]. In addition, metformin can be anti-proliferative by reducing tumor vasculature through reduction in VEGF levels; increasing progesterone receptor, which increases the response to hormonal therapy; activating the AKT signaling pathway, inhibiting the IGF1R signaling pathway and reducing MRP2 expression [19-21].

Previous meta-analyses were conducted to assess the association between metformin and risk of cancer and cancer mortality in patients with diabetes (Add Ref). They proposed that metformin therapy may be associated with a reduction in the risk of cancer, reduced cancer-related mortality and decreased colorectal cancer risk in type 2 diabetes patients. On examining the recurrence rate of type I endometrial cancer patients, they reported that the incidence in the metformin group was significantly lower than in the non-metformin group [22-24]. Notwithstanding these reports, the effects of metformin use on survival outcomes and cervical cancer risk in women remained uncertain. Therefore a systematic review and meta-analysis of the existing studies was conducted in order to better understand this issue.

In the present study, we identified only one article that reported cervical cancer specific death and overall mortality of metformin users and metformin non-users. This cohort study was restricted to women with diabetes age $\geq$ 66 years, and the results showed that metformin treatment after diagnosis appears to be associated with a decrease in cervical cancer specific death and overall mortality in older women with diabetes [12]. Li et al. assessed the effects of metformin on efficacy of chemoradiotherapy in T2DM patients with advanced cervical cancer. Compared to the control group (using oral antidiabetic medicine other than metformin), the objective response rate was slightly higher in the metformin treatment group, the PFS, OS, and adverse reactions were not significantly different between the two groups [13]. Since the outcomes of the above two studies were not reported in the literature, they were not included in the final meta-analysis. Nevertheless, there are several limitations in the present study. Firstly, statistical analyses with stratification were not performed on cervical cancer stage, according to metformin dose, or patients' age. Secodly, the number of studies included was relatively small and data were limited, resulting in a lack of consistent outcomes among the studies included such as those involving progression-free survival (PFS),overall survival (OS), disease-free survival (DFS), and recurrent cases.

In conclusion, metformin treatment caused a reduction in cervical cancer risk in diabetes mellitus patients but had no significant association with five-year OS of patients receiving WPRT. Considering the limited studies and the data included, the results of this meta-analysis should be carefully interpreted and further studies are required to confirm the conclusions of this study. Other effects of metformin use and survival outcomes in cervical cancer should be further assessed.

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Conflict of Interest

The authors declare no conflict of interest.

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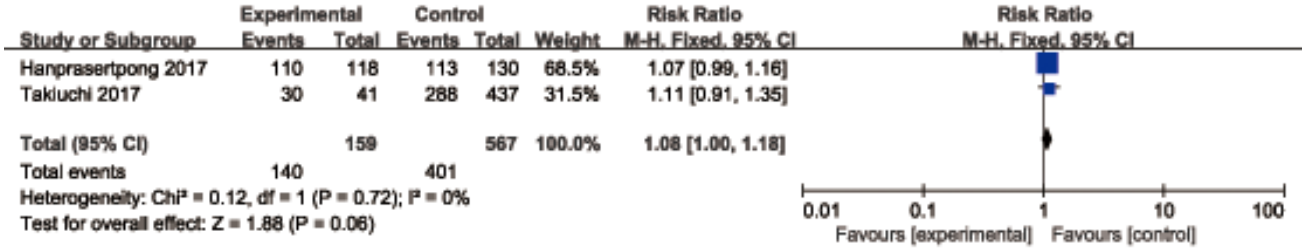

Figure 2. — Forest plot of metformin use on OS in cervical cancer patients receiving WPRT as primary therapy.

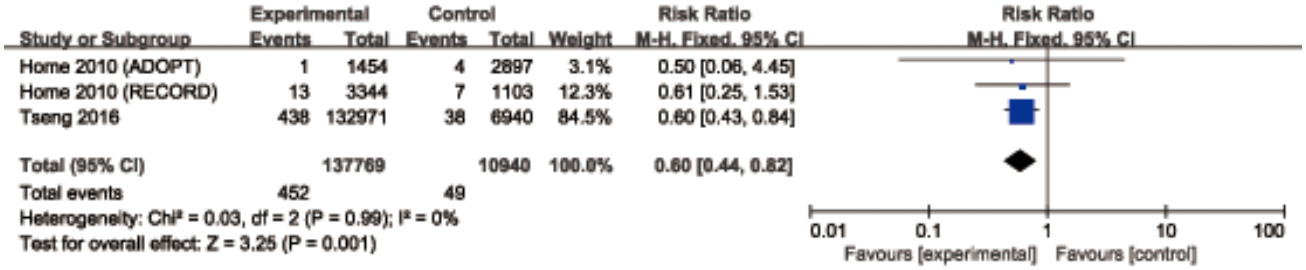

Figure 3. — Forest plot of metformin use on cervical cancer risk in diabetes mellitus patients.

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