The Analysis Study of Effects of Metformin on Ovarian Cancer: A Comprehensive Systematic Review

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ABSTRACT

Background: Ovarian cancer is one of the 10 most common cancers in women, with an estimated 295,414 new cases and 184,799 deaths worldwide in 2018. Metformin also activates the adenosine monophosphate-activated protein kinase pathway via liver kinase B1, which is a key gate pathway related to inhibition of subsequent tumor growth biomarkers, insulin signaling cascade, and cell cycle regulatory pathways. The aim: The aim of this study to show about effects of metformin on ovarian cancer. 

Methods: By the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements.

Result: Eight publications were found to be directly related to our ongoing systematic examination after a rigorous three-level screening approach. Subsequently, a comprehensive analysis of the complete text was conducted, and additional scrutiny was given to these articles.

Conclusion: Long-term metformin use reduced all-cause mortality, but not cancer-specific survival (CSS) in ovarian cancer. Whether metformin itself reduces deaths because of ovarian cancer requires further investigation.

Keyword: Ovarian cancer, metformin, chemotherapy, therapy, effect.
INTRODUCTION

Ovarian cancer is the fifth leading cause of mortality in developed countries. In the United States, an estimated 22,240 women were diagnosed with ovarian cancer in 2018, and 14,070 deaths due to ovarian cancer occurred. Complete cytoreductive surgery followed by standard first-line platinum-taxane chemotherapy has been shown to improve the survival rate. However, the majority of patients experience relapse, and the 5-year survival rate is approximately 45%. Chemoresistance to platinum-based treatment remains a major challenge in the successful treatment of ovarian cancer, and the mechanisms underlying platinum resistance are multifactorial. Various cellular processes are observed in resistant cells, and activation of the PI3K/AKT pathway is believed to be a determinant of resistance in ovarian cancer. Thus, the development of an improved treatment to overcome acquired resistance in cancer cells or decrease the side effects of platinum-based treatment is needed to treat ovarian cancer.1–3

Metformin is a first line antidiabetic medication that lowers insulin levels. It displays anticancer effects since insulin has mitogenic and pro-survival effects with tumor cells often expressing high levels of the insulin receptor. Metformin exerts its direct, insulin-independent action through 5′ adenosine monophosphate-activated protein kinase (AMPK) activation, which decreases cancer cell mammalian target of rapamycin (mTOR) signaling and protein synthesis. The indirect insulin-dependent effects of metformin reduce fasting blood glucose and insulin levels. In addition, metformin is widely commercially available with minimal adverse effects. In the present investigation, the epithelial ovarian cancer cell line SKOV3 was selected to evaluate the effects of metformin on proliferation, apoptosis, invasion, migration and autophagy.4,5

A potential therapeutic role for metformin impacting tumor-
mediated CA-MSC reprogramming was recently implicated. Translational work done in conjunction with the clinical trial of metformin demonstrated significant changes in the DNA methylation of CA-MSCs. Analysis of CA-MSC DNA methylation from metformin-treated trial patients found that in 6 of 11 patients, CA-MSCs looked more like normal MSCs than CA-MSCs from control patients. The remaining five clustered with the control CA-MSCs. The patients whose CA-MSCs were not modified by metformin treatment had a poor outcome compared to patients whose CA-MSCs showed a normalization with therapy.6

Metformin may seem an unlikely candidate for repurposing as a cancer therapeutic. However, metformin alters metabolism and it is becoming increasingly clear that cancer cells have metabolic derangements that may make them uniquely vulnerable to drugs that target metabolism. Perhaps the most well characterized metabolic derangement in cancer cells is that of glucose utilization. Non-transformed cells, in the presence of oxygen, process glucose through glycolysis, the tricarboxylic acid (TCA) cycle, and the mitochondrial respiratory transport chain to produce 38 molecules of adenosine 5'-triphosphate (ATP) per molecule of glucose. In contrast, cancer cells preferentially generate energy only through glycolysis, even when oxygen is present, which inefficiently generates lactic acid and only 2 molecules of ATP per molecule of glucose. This reliance of cancer cells on glycolysis alone is referred to as “aerobic glycolysis” and was first described in the 1920s by German Nobel laureate Otto Warburg. In addition, cancer cells metabolize lipids in a unique fashion. Cancer cells are capable of de novo fatty acid synthesis, whereas non-transformed cells are dependent on fatty acids obtained from dietary intake.7,8

**METHODS**

**Protocol**

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author
of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

**Criteria for Eligibility**

For the purpose of this literature review, we compare and contrast effects of metformin on ovarian cancer. It is possible to accomplish this by researching of effects of metformin on ovarian cancer. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about effects of metformin on ovarian cancer. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the time period that this systematic review deems to be relevant.

Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

**Search Strategy**

We used "effects of metformin on ovarian cancer." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed, SagePub, and Sciencedirect databases.

**Data retrieval**

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in
English and cannot have been seen anywhere else.

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

**Quality Assessment and Data Synthesis**

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. In order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.
Table 1. Search Strategy

<table>
<thead>
<tr>
<th>Database</th>
<th>Search Strategy</th>
<th>Hits</th>
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<tbody>
<tr>
<td>Pubmed</td>
<td>(&quot;Ovarian&quot;[MeSH Subheading] OR &quot;Ovarian cancer&quot;[All Fields] OR &quot;Metformin&quot; [All Fields]) AND (&quot;Effects&quot;[All Fields] OR &quot;Impact&quot;[All Fields]) AND (&quot;Management&quot;[All Fields] OR (&quot;Outcome&quot;[All Fields]))</td>
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<tr>
<td>Science Direct</td>
<td>(&quot;Ovarian&quot;[MeSH Subheading] OR &quot;Ovarian cancer&quot;[All Fields] OR &quot;Metformin&quot; [All Fields]) AND (&quot;Effects&quot;[All Fields] OR &quot;Impact&quot;[All Fields]) AND (&quot;Management&quot;[All Fields] OR (&quot;Outcome&quot;[All Fields]))</td>
<td>14</td>
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<tr>
<td>Sagepub</td>
<td>(&quot;Ovarian&quot;[MeSH Subheading] OR &quot;Ovarian cancer&quot;[All Fields] OR &quot;Metformin&quot; [All Fields]) AND (&quot;Effects&quot;[All Fields] OR &quot;Impact&quot;[All Fields]) AND (&quot;Management&quot;[All Fields] OR (&quot;Outcome&quot;[All Fields]))</td>
<td>5547</td>
</tr>
</tbody>
</table>
Figure 1. Article search flowchart
### Table 2. Critical appraisal of Study

<table>
<thead>
<tr>
<th>Parameters</th>
<th>(Park, JY et al., 2021)</th>
<th>(Urpilainen, E et al., 2018)</th>
<th>(Bar, D et al., 2016)</th>
<th>(Wang, SB et al., 2017)</th>
<th>(Shah, MM et al., 2014)</th>
<th>(Broekman, KE et al., 2020)</th>
<th>(Micha, JP et al., 2023)</th>
<th>(Brown, JR et al., 2020)</th>
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<tbody>
<tr>
<td><strong>1. Bias related to temporal precedence</strong></td>
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<td>Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<td><strong>2. Bias related to selection and allocation</strong></td>
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<td>Was there a control group?</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<td><strong>3. Bias related to confounding factors</strong></td>
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<tr>
<td>Were participants included in any comparisons similar?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td><strong>4. Bias related to administration of intervention/exposure</strong></td>
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<tr>
<td>Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<td><strong>5. Bias related to assessment, detection, and measurement of the outcome</strong></td>
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<tr>
<td>Were there multiple measurements of the outcome, both pre and post the intervention/exposure?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Were the outcomes of participants included in any comparisons measured in the same way?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<tr>
<td>Were outcomes measured in a reliable way?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td><strong>6. Bias related to participant retention</strong></td>
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<td>Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td><strong>7. Statistical conclusion validity</strong></td>
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<td>Was appropriate statistical analysis used?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</table>
RESULT

Using reputable resources like Science Direct, PubMed, and SagePub, our research team first gathered 49284 publications. A thorough three-level screening strategy was used to identify only eight papers as directly relevant to our ongoing systematic evaluation. Next, a thorough study of the entire text and further examination of these articles were selected. Table 1 compiles the literature that was analyzed for this analysis in order to make it easier to view.

Table 3. The literature included in this study

<table>
<thead>
<tr>
<th>Author</th>
<th>Origin</th>
<th>Method</th>
<th>Sample</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park, JY et al., 2021&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Korea</td>
<td>A national sample cohort of the Korean National Health Insurance Service Data was analyzed. Cox proportional hazards regression was used to analyzing hazard ratios (HRs) and 95% confidence intervals (CIs) after adjusting for underlying diseases and medications as confounding factors for overall survival (OS) and cancer-specific survival (CSS).</td>
<td>866</td>
<td>A total of 866 eligible patients were included from among 1,025,340 cohort participants. Among them, 101 (11.7%) were metformin users. No difference in OS was observed between non-users and users. No difference in OS was observed according to age and Charlson Comorbidity Index. Long-term metformin use (≥720 days) was associated with better OS (adjusted HR=0.244; 95% CI=0.090–0.664; p=0.006). A multivariate Cox proportional hazards model showed that long-term metformin use was an independent favorable prognostic factor for OS (HR=0.193; 95% CI=0.070–0.528; p=0.001) but not for CSS (HR=0.599; 95% CI=0.178–2.017; p=0.408).</td>
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<tr>
<td>Urpilainen, E et al., 2018&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Finland</td>
<td>Study cohort consisted of women with T2D diagnosed with ovarian cancer in Finland 1998–2011. They were identified from a nationwide diabetes database</td>
<td>421</td>
<td>During the accrual period 421 newly diagnosed ovarian cancers were identified in the FinDM database. No evidence was found for any differences in mortality from ovarian cancer or other causes between different antidiabetic</td>
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</table>
(FinDM), being linked to several national registers. Pre-diagnostic use of statins was observed to be associated with decreased mortality from ovarian cancer compared with no such use (HR 0.72, 95% CI 0.56–0.93).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Reference Description</th>
<th>Number</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td>Bar, D et al., 2016</td>
<td>Israel</td>
<td>Files of ovarian cancer patients treated between 2000 and 2012 were retrospectively reviewed. Data regarding disease characteristics, presence of diabetes mellitus and hypertension, recurrence and death were extracted. The use of drugs was assessed using the Clalit Health Services (CHS) pharmacy records.</td>
<td>143</td>
<td>143 patients treated by debulking surgery and platinum based chemotherapy were included. Median age was 62.5, 22 (15.4%) had diabetes mellitus, 61 (42.7%) had chronic hypertension. Statins were used by 43 (30%) patients, 31 (21.7%) used aspirin, 25 (17.5%) used beta blockers and 12 (8.4%) used metformin. In multivariate analysis diabetes mellitus was associated with a shorter recurrence free survival (RFS) and the use of aspirin and metformin was associated with a prolonged RFS in this cohort. Overall survival (OS) was longer in patients using aspirin and shorter in patients with hypertension.</td>
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<tr>
<td>Wang, SB et al., 2017</td>
<td>China</td>
<td>we retrospectively examined the effects of metformin on ovarian cancer patients with diabetes at our institution.</td>
<td>568</td>
<td>Patients with type 1 diabetes, incomplete records (including medication records) and any other cancer before their ovarian cancer diagnosis, as well as those diagnosed with diabetes more than 6 months after their ovarian cancer diagnosis, were excluded. Out of 568 patients, 48 (8.5%) patients with type 2 diabetes continuously used metformin, 34 (5.9%) patients with type 2 diabetes did not take metformin, 22 (3.9%) patients with type 2 diabetes discontinued metformin, and</td>
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464 (81.7%) ovarian cancer patients were nondiabetic controls. Longer progression-free survival (PFS) and overall survival (OS) were observed in ovarian cancer patients with diabetes who were taking metformin than in diabetic patients not taking metformin, diabetic patients who discontinued metformin, and nondiabetic ovarian cancer patients ($P=.001$). After adjusting for possible confounders, metformin use was associated with a lower risk for disease relapse [hazard ratio (HR)=$0.34$; 95% confidence interval (CI): $0.27$–$0.67$; $P<.01$] and disease-related death (HR=$0.29$; 95% CI: $0.13$–$0.58$, $P=.03$) among ovarian cancer patients with diabetes.

**Shah, MM et al., 2014**

A retrospective cohort study of EOC patients diagnosed between 2004 and 2009 at a single institution was performed. Demographic, pathologic and DM diagnosis data were abstracted.

62 (17%) of 367 patients had a diagnosis of DM. No differences in age, histology, debulking status, or administration of intraperitoneal chemotherapy between ND and DM patients were present, although there were more stage I and IV patients in the ND group ($p=0.04$). BMI was significantly different between the two groups (ND vs. DM, 27.5 vs. 30.7 kg/m², $p<0.001$). While there were no differences in survival based on BMI, diabetic patients had a poorer PFS (10.3 vs. 16.3 months, $p=0.024$) and OS (26.1 vs. 42.2 months, $p=0.005$) compared to ND patients. Metformin use among diabetic
<table>
<thead>
<tr>
<th>Broker, KE et al., 2020&lt;sup&gt;14&lt;/sup&gt;</th>
<th>Netherlands</th>
<th>In this single-center trial the RP2D of metformin in combination with carboplatin area under the concentration-time curve (AUC) 6 and paclitaxel 175 mg/m² every 3 weeks (q3w) in patients with advanced epithelial ovarian cancer was determined using a 3+3 escalation rule at three fixed dose levels: 500 mg three times daily (tds), 850 mg tds and 1000 mg tds.</th>
<th>15</th>
<th>Fifteen patients with epithelial ovarian cancer and an indication for neo-adjuvant (n = 5) or palliative (n = 10) treatment were included. No DLTs were observed. Three patients discontinued study treatment during cycle 1 for other reasons than DLT. Six patients were treated at the RP2D of metformin 1000 mg tds. The most frequent low-grade toxicities were anemia, hypomagnesemia and diarrhea. Grade 3 adverse events (AEs) occurred in ten patients, most common were leucopenia (n = 4), thrombocytopenia (n = 3) and increased GGT (n = 3). There were no grade 4 AEs. Metformin increased the platinum (Pt) AUC (Δ22%, p = 0.013) and decreased the Pt clearance (Δ-28%, p = 0.013). Metformin plasma levels were all within the therapeutic range for diabetic patients (0.1–4 mg/L).</th>
</tr>
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<tbody>
<tr>
<td>Micha, JP et al., 2023&lt;sup&gt;15&lt;/sup&gt;</td>
<td>USA</td>
<td>Eligible subjects underwent surgery and 6 cycles of neoadjuvant or adjuvant dose-dense intravenous paclitaxel (80 mg/m²), carboplatin (area under the curve 5 or 6 on Day 1), and oral metformin (850 mg daily).</td>
<td>30</td>
<td>Thirty subjects received a median of 6 cycles (range, 5–6) of primary induction chemotherapy and were eligible for response evaluation; twenty-three patients exhibited a complete response, while 3 study patients obtained a PR (an overall response rate of 86.7%). Grade 3–4 hematological toxicity included neutropenia (43.3%), thrombocytopenia (10%) and anemia (36.7%). There was no incidence of grade 3–4</td>
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</table>
neuropathy although 15 patients (50%) developed grade ≤2 neurotoxicity. Additionally, we observed grade ≤2 diarrhea in 20 (66.7%) subjects. The median progression-free survival was 21 months (range, 3–52) and overall median survival was 35 months (range, 15–61). The subjects also received an aggregate 103 cycles (median, 12; range, 6–12) of maintenance chemotherapy.

| Brown, JR et al., 2020\(^\text{16}\) | USA | Thirty-eight patients with stage IIC \((n = 1)\)/III \((n = 25)\)/IV \((n = 12)\) EOC were treated with either (a) neoadjuvant metformin, debulking surgery, and adjuvant chemotherapy plus metformin or (b) neoadjuvant chemotherapy and metformin, interval debulking surgery, and adjuvant chemotherapy plus metformin. | 38 | Metformin was well tolerated. Median progression-free survival was 18.0 months (95% CI 14.0–21.6) with relapse-free survival at 18 months of 59.3% (95% CI 38.6–70.5). Median overall survival was 57.9 months (95% CI 28.0–not estimable). Tumors treated with metformin had a 2.4-fold decrease in ALDH\(^+\)CD133\(^+\) CSCs and increased sensitivity to cisplatin ex vivo. Furthermore, metformin altered the methylation signature in CA-MSCs, which prevented CA-MSC–driven chemoresistance in vitro. |
DISCUSSION

Metformin is one of the most widely prescribed oral anti-diabetic medications. It is the first line therapy for type 2 diabetes mellitus. It has an anti-hyperglycemic effect which is mediated by inhibiting gluconeogenesis, decreasing glucose absorption from the small intestine, increasing glucose uptake in cells, and decreasing plasma free fatty acid concentration. Metformin also increases insulin induced translocation of glucose transporters to the cellular plasma membrane, thus reducing insulin resistance. Use of metformin has been found to be generally safe, with mild gastrointestinal symptoms being the most common adverse effects. There is substantial preclinical evidence suggesting that metformin has anticancer properties. In-vitro and in-vivo analysis of metformin has exhibited anti-proliferative activity by inhibiting intracellular pathways. It has also been observed that metformin activates the T cell mediated immune response against cancer cells.17–19

Cancer is the second leading cause of death worldwide, with ovarian cancer (OC) being the fifth leading cause of cancer-related death, affecting about seven per 100,000 women annually. According to data from 2015-2017, about 1% of women will be diagnosed with OC at some point during their lifetime. In 2018, the financial burden of cancer care in the United States was about $150.8 billion. These numbers are expected to increase, with the rising cost of cancer medications being one of the factors.20–22

Surgical resection is preferable for women with early stage OC; while for most cases of advanced cancer, tumor debulking followed by adjunctive therapy could be performed. However, the recurrence of the cancer remains high despite of these treatments. Therefore, effective treatments are urgently needed to improve the survival and quality of life in women with OC. Metformin is a conventional oral antidiabetic agent which has been suggested to confer anticancer efficacy. Previous studies have confirmed that metformin use is associated with reduced risk of cancer.
in diabetic patients, including the incidence of OC. However, studies evaluating the influence of metformin on mortality in women with OC showed inconsistent results. Some studies suggested that metformin use was associated with reduced mortality in women with OC, while others did not.  

Becker et al. reported that metformin use and other antidiabetic drugs were not associated with an altered risk of endometrial cancer. Regarding association between metformin use and prognosis of gynecological cancer, Deng et al. found that both overall survival (OS) and progression-free survival (PFS) of T2DM patients who took metformin were significantly prolonged compared with those of T2DM patients who did not take metformin in endometrial cancer. Hanprasertpong et al. demonstrated that metformin use was associated with improved disease-free survival (DFS) in patients with cervical cancer with T2DM. However, Seebacher et al. found that metformin was not associated with prolonged recurrence-free survival (RFS) or cancer-specific survival (CSS) of endometrial cancer. Garcia et al. reported that no statistically significant association was observed between metformin use and OS of 360 ovarian cancer patients. Takiuchi et al. reported that metformin use was not associated with survival of women with cervical cancer. Meta-analyses comparing the incidence of gynecologic cancer in diabetics using metformin with those using insulin or other anti-diabetic agents have shown somewhat variable results.  

CONCLUSION

In conclusion, long-term metformin use reduced all-cause mortality, but not cancer-specific survival (CSS) in ovarian cancer. Whether metformin itself reduces deaths because of ovarian cancer requires further investigation.

REFERENCES


25. He XK, Su TT, Si JM, Sun LM. Metformin is associated with slightly reduced risk of