Metformin – A Possible Way to Reduce Risk and Improve Oncological Outcome of Cervical Cancer

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ABSTRACT

Cervical cancer is one of the major cancer types, the leading causes of cancer-related deaths in women worldwide, with a significant socioeconomic burden. Metformin, an inexpensive, traditional oral anti-hyperglycemic drug, is one of the most widely used antidiabetic drug for type 2 diabetes mellitus. In recent years, there has been an increasing interest in the use of metformin to reduce cancer risk and improve oncological outcomes of various cancer types, including cervical cancer. The precise mechanism of the antitumor effect of metformin is still unclear. Herein I review the scientific evidence from preclinical and clinical studies on the antitumor effect of metformin on cancer risk and oncological outcomes of cervical cancer.

Keywords: cervical cancer, diabetes mellitus, metformin

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Among various gynecologic malignancies, one of the most common is cervical cancer, with a significant socioeconomic burden and the leading cause of cancer-related deaths in women worldwide\(^{(1)}\). The prevalence of cervical cancer varies considerably worldwide, with most cases in developing countries\(^{(1-2)}\). The treatment of cervical cancer varies with the stage of the disease and performance status. The prognosis of cervical cancer depends upon several factors including stage, histological type, parametrical involvement and tumor size as well as lymph node involvement\(^{(2-3)}\). Overall, 5-year disease-free survival rate are 86-88.5% for stages IA2 and IB1, 50-70% for stages IB2 and IIB, 30-50% for stage III, and 5-15% for stage IV\(^{(3-4,6)}\).

Recent epidemiological and clinical studies have suggested that type 2 diabetes mellitus (DM) is associated with an increased risk and mortality of many types of cancer, including cervical cancer\(^{(3,7-9)}\). In a population-based cohort study of 1,298,385 Koreans, Jee et al., found that the risk of developing cervical cancer was 2.2-fold higher in women with DM, and these patients also had a poorer oncological outcome with a 2.5-fold higher death rate\(^{(7)}\). Similarly, a large study based on the nationwide Taiwan Cancer Registry database by Kuo et al., found that type 2 DM may increase the risk of cancer recurrence and death for patients with cervical cancer stage I-IIA, even after curative treatment\(^{(8)}\). In addition, a recent observational
study from Thailand by Jiamset and Hanprasertpong reported that early stage cervical cancer patients who underwent radical hysterectomy with type 2 DM had poorer recurrence-free survival (RFS) after 5 years and overall survival (OS) than those without type 2 DM\(^3\).

Several possible mechanisms have been proposed to explain the association of type 2 DM and increased cancer risk and cancer-related mortality, including deregulation of insulin and insulin-like growth factor signaling, hyperglycemia, inflammation and obesity\(^3,9\). Oral antidiabetic drugs such as metformin and sulfonylurea may influence cancer risk and mortality in type 2 DM patients\(^2-9,12\).

**Metformin**

Metformin (biguanide) is an old, oral antidiabetic drug commonly prescribed for type 2 DM that reduces both glucose and insulin levels\(^2-3,10-12\). It has a favorable toxicity profile and is relatively inexpensive\(^10-12\). Previous studies have demonstrated that metformin is associated with both lower risk and improved survival in various types of cancer such as liver, breast, lung, endometrial and ovarian cancer in patients with type 2 DM\(^2,10-13\). To date, there have been few clinical studies that have investigated the association between metformin use and cervical cancer risk and oncological outcomes of type 2 DM patients with cervical cancer\(^2-3,11,14\).

The precise mechanism of the antitumor effect of metformin is still unclear. However, various preclinical studies indicate that the mechanism underlying the action of metformin could involve the activation of adenosine monophosphate activated protein kinase (AMPK), which inhibits the mammalian target of rapamycin (mTOR) pathway and reduces cervical cancer cell growth\(^2,12-17\). Metformin can inhibit the growth of cervical cancer cells by induction of both apoptosis and autophagy. It also activates the liver kinase B1 (LKB1)/AMPK signaling pathway, which suppresses the mTOR pathway\(^16\). These insights give hope that metformin may be a promising drug for the cervical cancer prevention and treatment.

**Metformin and risk of cervical cancer**

To our knowledge, only one population-based cohort study of 139,911 female patients with type 2 DM (n = 132,971, “ever used metformin”; n = 6,940, “never used metformin”) from Taiwan examined the association between metformin use and cervical cancer risk\(^11\). This study found the respective numbers of incidences of cervical cancer in ever users and never users were 438 and 38 respectively, with respective incidences of 68.3 and 121.4 per 100,000 person-years. The overall hazard ratio (HR) suggested a significantly lower risk in metformin users\(^11\). These findings suggest that metformin might be associated with a significant reduction in the risk of cervical cancer, especially when it has been used for more than 2 years.

**Metformin and oncological outcomes of cervical cancer**

Only two published studies have addressed the impact of metformin use and oncological outcomes of cervical cancer\(^3,14\). In 2015, a retrospective study of 181 DM patients with cervical cancer from Canada by Han et al., demonstrated that the cumulative dose of metformin use after cervical cancer diagnosis among older women (age ≥ 66 years) with DM was independently associated with a significant decrease in both cancer-specific and overall mortality\(^14\). Another retrospective study from Thailand by Jiamset and Hanprasertpong reported that there was no evidence that metformin use affected RFS or OS. However, this study mainly focused on investigating the impact of type 2 DM on oncological outcomes of early stage cervical cancer after radical hysterectomy and with only 42 type 2 DM patients, so we could not detect an effect of metformin use. In addition, Hanprasertpong et al., recently evaluated the impact of metformin use on oncological outcomes in 248 cervical cancer patients with type 2 DM who received primary treatment between 2004 and 2015 at Songklanagarind Hospital, and found that metformin use was associated with improved DFS, but not OS in cervical cancer in type 2 DM patients\(^2\).

**Conclusion**

Although this review discusses the potential positive effects of metformin in diminishing the risk and
improving the oncological outcomes of cervical cancer patients with type 2 DM, most of the available evidence is derived from a small number of epidemiological and observational studies. Therefore, more well-designed prospective clinical trials are required to confirm the effect of metformin on prevention and treatment of cervical cancer patients with or without type 2 DM. Further studies are also needed which focus on dose and duration of intake of metformin to gain a better understanding of the antitumor effects of this drug.

References