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Review: The Emerging Role of Metformin as Aromatase Inhibitor in Breast Cancer

Amrilmaen Badawi^{1*}

¹Monash Biomedicine Discovery Institute, Monash University, Melbourne, Australia

Corresponding author (*): amrilbadawi@gmail.com, abad0005@student.monash.edu

ABSTRACT

The prevalence of breast cancer is still very high among women, in particular post-menopausal women. There are many factors contributed to the diseases, including diabetes. Recently, it has been emerged that metformin, an antidiabetic agent, is capable of reducing the risk of developing breast cancer among post-menopausal women, and act as aromatase inhibitors (AIs) which inhibits the production of estrogen. In this review, we focus in discussing the possible work mechanism of metformin as AIs and what is in the pipeline on clinical trials.

Keywords: Metformin; Aromatase Inhibitor; Breast Cancer

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Email :

medicaljournal@umi.ac.id

Phone :

+6282293330302

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INTRODUCTION

Breast cancer (BC), one of the most common types of cancer in women, is primarily characterized by uncontrolled growth of breast epithelial cell. The global health burden of BC is very high among older women, particularly in post-menopausal women.¹ There are around two million women globally affected by this disease every year, and WHO estimated that more than 600.000 women died from breast cancer in 2018.² Also, a meta-analysis from 126 studies in 2017 found out that the survival rate of a breast cancer patient is worsening within three years post-diagnosis.³

To date, there are numerous factors involved in the development of breast cancer in women, including age, genetics, environment, and lifestyle.¹ Diabetes is also correlated to breast cancer incidence and was observed by Marble et al. for the first time in the early 1930s.⁴ Also, several epidemiological studies observed that metformin, an antidiabetic drug, could significantly reduce the incidence and mortality rate of the breast cancer patient with type II diabetes.⁵⁻⁷ Furthermore, one of pre-clinical study in mice demonstrated that metformin can inhibit the development of breast cancer cells through the inhibition of stromal aromatase, which result-in blockade of estrogen production.⁸ That finding opened a possibility to use metformin, an antidiabetic agent, as an adjuvant treatment for the breast cancer patient. Henceforth, In this article, we aim on discussing the role of metformin against tumorigenesis, especially as aromatase inhibitors for breast cancer.

ESTROGEN, AROMATASE INHIBITOR, AND BREAST CANCER

Estrogen is a hormone which promotes the growth and survival not only the normal cells but also the carcinoma cells, by binding to its receptor on the cell, estrogen receptor (ER).⁹ Interestingly, Fabian et al. found out that around 70% of breast cancers cells express a high number of ER on the cell surface.¹⁰ Consequently, long-exposure of estrogen during the lifetime has been identified as one of the main risks of breast cancer progression in women.¹¹ There are three main ways (**Figure 1**) to disrupt the estrogen-dependent development of breast cancer cells. The first method is to prevent the binding of estrogen to its receptor with selective modulators such as tamoxifen. Secondly, eliminate the receptor expression in cells with ER down-regulator, causing less ER available for estrogen binding. Lastly, the most effective way is by reducing estrogen production via ovarian ablation in premenopausal women or using aromatase inhibitors (AIs) in menopausal women.¹⁰

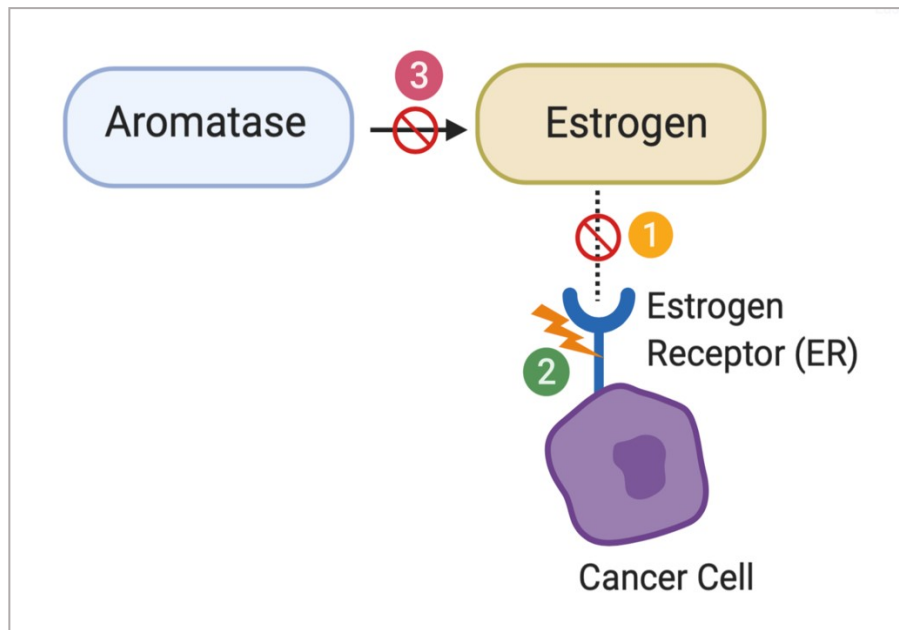


Figure 1. Main strategies to interfere the binding of estrogen and ER. Direct inhibition of estrogen and ER (1), elimination of ER (2), or interfere the production of estrogen (3). Reproduced from Fabian et al. (2005).¹⁰

Aromatase inhibitors are one of class drugs that is capable of disrupt estrogen conversion by suppressing the activities of aromatase enzyme.¹⁰ AIs play a role as adjuvant treatment for breast cancer, and it has been proved to prevent the recurrence of the disease.¹³ Of three AIs generations available for clinical use, the third-generation is far more superior compared to the first and second line AIs, due to the fact that it has minimal adverse effects. In premenopausal women, estrogen is synthesized and produced in ovaries, while in post-menopausal women, the production of estrogen is predominantly in peripheral body tissue.¹² Henceforth, AIs are more effective for reducing circulating estrogen in post-menopausal than pre-menopausal women.

DIABETES AND RISK OF BREAST CANCER

Obesity and diabetes, especially type II diabetes (T2D), are known to be linked with an increased risk of many cancer incidences,⁴ including breast cancer.¹⁴ A meta-analysis study reported that there was a significantly higher risk of breast cancer incidence among diabetic women (SRR = 1.13, 95% CI = 1.04, 1.24) compared to the non-diabetic women.¹⁵ Another study also observed that the risk of breast cancer incidence even higher in postmenopausal women with type II diabetes than pre-menopausal women.¹⁶ Overall, these studies implicated that there is a high correlation between diabetes, post-menopausal state, and breast cancer incidence in women.

Moreover, multiple factors are contributed to a high risk of breast cancer in diabetes patients, particularly in T2D, including hyperinsulinemia, hyperglycaemia, and elevated insulin-like growth factor (IGF).¹⁷ These factors can interfere the binding of insulin and insulin receptors (IR) that mainly act to regulate the metabolism of glucose through phatidylinositol-3-kinase (PI3K)/Akt signalling pathway. It also exerts an indirect positive effect on RAS/MAPK/ERK signalling pathway which plays

an essential role in the cells growth, including cancerous cells.^{18,19} Additionally, breast cancer tissue also expresses more IR compared to healthy women breast tissue, hence why the cancerous epithelial cells can grow exponentially.²⁰

Surprisingly, Evans et al. (2005) found out that there is a decline in the risk of breast cancer among women with T2D who take metformin on a long-term basis.⁵ Supporting these findings, a meta-analysis from a hundred researches around the world demonstrated that metformin might have a protective effect on breast cancer especially for postmenopausal women with T2D.⁶ In contrast, short-term administration of metformin did not reduce the risk of developing breast cancer in diabetic women.⁵ Also, metformin did not show any significant advantage for any breast cancer patients who had recent-onset diabetes.²¹ Overall, these studies opened new possibilities for metformin to reduce and prevent the incidence, even for treating breast cancer in postmenopausal women with type II diabetes.

METFORMIN SAFETY

Biguanide, such as metformin, is widely used as first line oral drugs to regulate hyperinsulinemia and lower blood glucose in type II diabetic patients. It has been approved for clinical purpose since 1958 in United Kingdom and since 1995 in the United States.²² The mechanisms of metformin actions to regulate hyperglycaemia in T2D patients include lowering small intestinal glucose absorption, improving cellular glucose transport and uptake, decrease plasma insulin level, and increased insulin sensitivity.²³ Metformin also reduce hepatic gluconeogenesis via activation of AMP-activated protein kinase or AMPK, which have an essential role in energy regulation in diabetes and other metabolic diseases.²⁴ Subsequently, activation of AMPK by metformin might exerts an anti-tumour, anti-aging, cardiovascular, and neuroprotective effect in human.²⁵

Metformin is relatively cheap and safe for diabetes treatment. According to the United States Food and Drug Administration (FDA), there are several metformin-containing medicines approved for commercial use, including Glucophage and Glucovance.²⁶ These drug are not associated with any hypoglycaemia events due to its pharmacokinetics, unless it is used with combination of other oral antidiabetic class or insulin injection.²⁷ Yet, the use of metformin in the patient with severe renal impairment might be restricted, because there have been several incidences of lactic acidosis reported in patients treated with metformin (around 1.5% cases per 1000 patients per year). Other than that, minor side effects such as nausea, diarrhea, and gastritis might also occur during metformin administration.^{26,27} Earlier study has demonstrated that metformin used for diabetes patient is safe and well-tolerated for long term basis, at least for ten years.²⁸ Metformin is also relatively safe not only for young adults but also for older people. Unfortunately, there is no data about the safety profile of this drug in very old people (more than 80 years old).²⁹

METFORMIN ACTION IN BREAST CANCER

The underlying mechanism of metformin action in cancer remains debatable. According to Rice et al. (2015), metformin might have dual effect in breast cancer. It could inhibit the cell growth directly, but also reduce oestradiol or estrogen production that have indirect impact to cell proliferation.³⁰

Firstly, as previously mentioned, metformin could lower gluconeogenesis in the liver by activation of AMPK via Liver Kinase B1 (LKB1) dependent mechanism. LKB1 is a tumour suppressor gene in epithelial tissues, and loss of its function is associated with a significant increase in lifetime risk of numerous epithelial cancer, including breast cancer.³¹ Zakikhani et al. (2006) observed that metformin could act as a growth inhibitor for epithelial cells, particularly for MCF-7 cells in breast cancer. They also demonstrated that AMPK activation by metformin is a hurdle for the antiproliferative effect of the drug by using small interfering RNA (siRNA).³² These finding suggested that metformin have a direct action as an activator of the LKB1/AMP kinase signalling pathway to suppress breast cancer cells. In addition, another study was demonstrated that metformin also could inhibit protein translation initiation and be able to reduce 30 to 40% protein synthesis in MCF-7 breast cancer. It caused a dose-dependent decrease in cap-dependent translation. The effect on translation was associated with mammalian target of rapamycin (mTOR) inhibition, which is mediated by AMPK, consequently lowering phosphorylation of S6 kinase and eIF4E-binding protein.³³ This observation implicated that activation of AMPK lead to mTOR inhibition and result in the inhibition of breast cancer cells growth.

Secondly, another suggested role of metformin in breast cancer is as an **aromatase inhibitor**. Estrogen inhibition also might play indirect role for reducing breast cancer growth. In rodent model of postmenopausal breast cancer, Giles et al. (2018) found out that metformin is capable of lowering the expression of local stromal aromatase (**Figure 2**), leading to reduction of estrogen production and estrogen receptor activation in the cells. Besides, they also showed that metformin could reduce the expression of CD68+ macrophages, an aromatase-positive macrophage which is responsible for aromatase production.³⁴ Similar to these findings, a study using human endometrial cell as sample also showed that metformin attenuate aromatase activity. It was worked by decrease cAMP-induced mRNA expression for aromatase in endometriotic stromal cells (ESCs).³⁵ In summary, these observations suggest that metformin might be highly effective to inhibit the growth of cells via aromatase signalling pathway related to estrogen production.

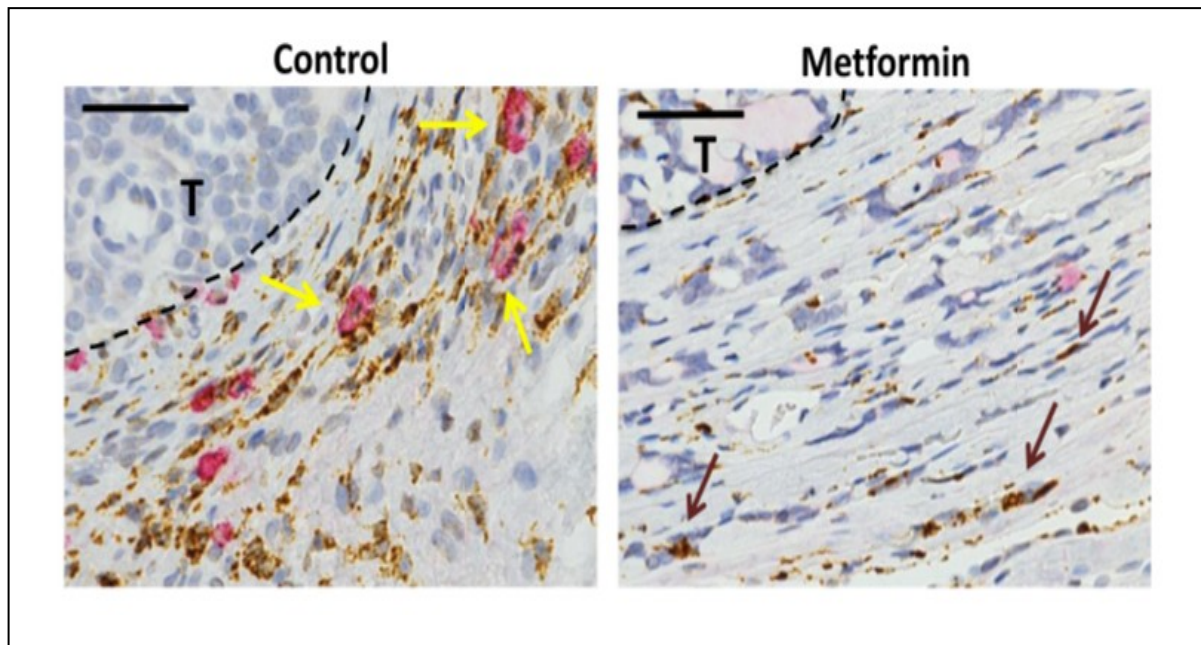


Figure 2. Higher expression of local stromal aromatase (yellow line) was observed in untreated breast cancer mice compared to metformin group (brown line). Adapted from Giles et al. (2018).³⁴

Brown et al. (2009) introduced cAMP response element binding (CREB) protein, a compound that highly expressed in postmenopausal women with breast cancer. They observed that Inhibition of LKB1/AMPK signalling pathway in breast cancer, particularly in diabetic women, will cause dephosphorylation of CREB regulated transcription co-activator 2 (CRCT2), which will result in activation of aromatase promoter named PII, and increase the production of estrogen in peripheral body tissue.³⁶ Thus, higher activity of AMPK will give a negative effect for cancer cells. Moreover, recent observational study with human cells tissue has shown that metformin could decrease aromatase promoter PII activity via cytoplasmic retention of CRCT2. The inhibition of PII was a consequence of increase AMPK phosphorylation by higher LKB1 expression. So, CREB could not be activated, and cause the inhibition of aromatase stimulation.³⁷

All of the observation above might provide a better information about the dual use of metformin in breast cancer for future study. The direct and indirect mechanism of metformin to inhibit breast cancer growth are summarized in **Figure 3**.

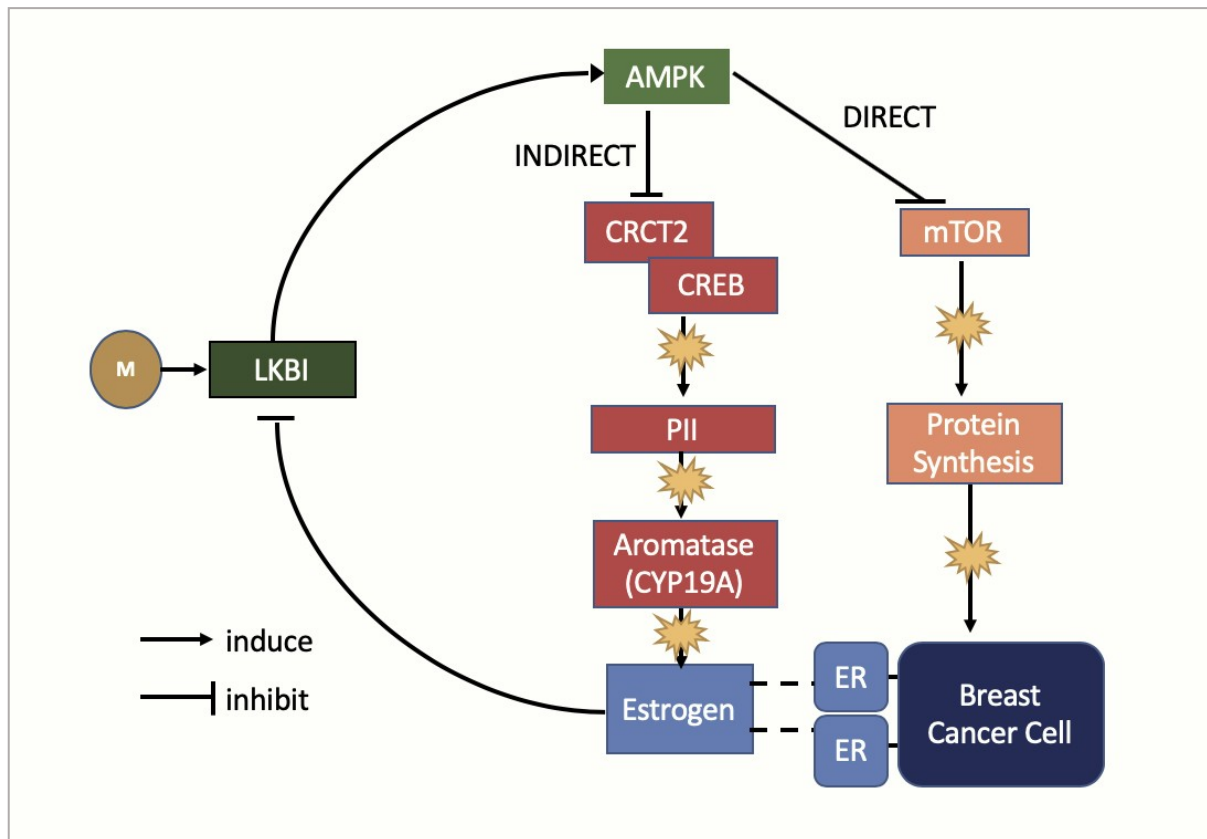


Figure 3. Proposed metformin mechanism of action on AMPK with direct inhibition of cancer cells via mTOR and indirect inhibition via CREB/PII/aromatase signalling pathway.^{32,33,37}

CLINICAL TRIAL OF METFORMIN AS AROMATASE INHIBITOR

Epidemiological studies heavily suggested that metformin is not only beneficial to prevent breast cancer but also clinically useful for preoperative and adjuvant therapy for the disease. Thus, many clinical studies are addressed to understand tumour biomarker involved in metformin and breast cancer cells interaction, whether it is a direct or indirect effect.

Moreover, animal studies suggested that there are in vitro inhibition of aromatase in breast cancer cells by using metformin. In contrast with these findings, a study in human showed that there is no such trend was found for aromatase expression in tumour cells from a diabetic patient treated with metformin. They analysed the aromatase expression by collected tumour sample from breast cancer patient aged 48-77 years treated with metformin or another antidiabetic agent, followed by staining the cells with monoclonal aromatase antibody-677. Unfortunately, metformin did not provide lower aromatase expression in the patients compared to other treatment groups.³⁸ But, that study was conducted in a small population which might interfere with the result. This finding might also implicate that using metformin alone as an aromatase inhibitor will not provide a promising result.

Combination therapy with aromatase inhibitors (AIs) drug line is also one of the main attractive options for breast cancer patient treatment. Recently, Zhao et al. (2017) conducted a clinical trial in post-menopausal women by using metformin with a combination of either exemestane 25 mg/d or

letrozole 2.5mg/d compared to these drugs alone. Again, this study also failed to show better improvement in small population patients with combination therapy compared to control group. In contrast, previous research about the combination of metformin with letrozole 2.5 mg/d to inhibit aromatase in Polycystic Ovarian Syndrome (PCOS) women were showing a positive effect of metformin as aromatase inhibitors.⁴⁰ Several clinical trials are still on the run to answer the hypothesis from pre-clinical studies, for example, a clinical trial (NCT03192293) investigating the effect of combining metformin with fulvestrant (chemotherapy regimen). Hence, there is still an open window to make further observation, especially by combining metformin with other cancer agent in bigger population.

CONCLUSION AND IMPLEMENTATION

In conclusion, based on pre-clinical evidence, metformin appears to be beneficial as an adjuvant treatment to eradicate cancer, especially breast cancer. It has a dual effect in breast cancer including a direct impact by inhibiting mTOR signalling pathway and protein translation, or indirect impact by inhibiting CREB, aromatase activator for estrogen production.

Considering metformin mechanism of action including pharmacokinetics, safety, and side effect has been explored, with extensive clinical use in type II diabetes patients around the world, the opportunity to study metformin for breast cancer treatment in the clinical trial setting is very captivating. Unfortunately, there are a lot of gaps to understand the benefit of metformin in treating cancer on human model diseases, especially breast cancer. Assessment for a cumulative duration of therapy and the cumulative dosage is necessary to answer the hesitance. The majority of the clinical trials aim to observe the treatment effect, while others evaluate metformin for prevention purpose. The result will be useful to define metformin future for breast cancer therapy option.

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