

The Use of Metformin in Breast Cancer Treatment in Non-Diabetic Women

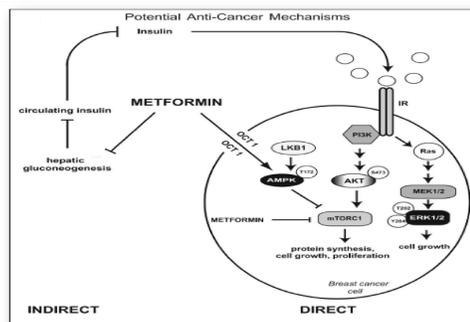
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ABSTRACT

Metformin is the most commonly prescribed drug for diabetes mellitus type 2.³ Studies have shown that diabetic patients taking metformin have a decreased risk of developing breast cancer, in addition to a better prognosis in those diagnosed with breast cancer.³ However, they have not reached a conclusion about the benefit of metformin in non-diabetic patients with breast cancer. This review article describes the numerous proposed anti-tumor mechanisms and metabolic benefits of metformin. If its effectiveness is proven as an adjuvant treatment, breast cancer patients could reach remission with less harmful radiation and chemotherapy.



INTRODUCTION

Metformin is an oral biguanide medication that works by decreasing hepatic gluconeogenesis, decreasing glucose absorption in the GI tract, and increasing peripheral insulin sensitivity.³ **Metformin has been used for decades, is inexpensive, and has a favorable safety profile.** The proposed anti-tumor effects of Metformin are studied using tumor-marker levels, metabolic profiles, and tumor growth pathways.⁶ The suggested mechanism is that metformin **increases AMPK** which inhibits gluconeogenesis in epithelial cells, therefore starving the breast cancer cells.^{3,6} In addition, it is being shown to **down regulate the HER2 pathway** of oncogenic signaling.¹¹ It also **reduces Ki67**, a cell stain measured to represent tumor proliferation.³ In addition, many studies showed the **multiple metabolic benefits** of metformin which indirectly improve prognosis.

SIGNIFICANCE

One in seven American women will be diagnosed with breast cancer in their lifetime. It is the second leading cause of death of American women.¹ There are numerous modifiable and non-modifiable risk factors for developing breast cancer.¹ These include age over 50, family history, BRCA1/BRCA2 genetic mutations, obesity and increased exposure to estrogen.² **Obesity is not only a risk factor for developing breast cancer, but also worsens prognosis in patients diagnosed with breast cancer.**⁸ Increased insulin levels and insulin resistance might explain the correlation between breast cancer and obesity, and worse prognosis.⁹ These risk factors serve as metformin's window of opportunity for potential benefit in non-diabetic breast cancer patients.

SUMMARY OF FINDINGS

Author (year)	Total patients (n)	Study type	Methods	results
Decensi (2015)	142	RCT	Analyzed the effect of presurgical metformin 1700mg vs. placebo in non-diabetic women with breast cancer	Significantly lower tumor proliferation in metformin vs. placebo group
Bonanni (2012)	200	RCT	Studied the effects of Metformin 850mg BID vs. placebo in pre-surgical window	Statistically significant reduction in tumor proliferation in patients with increased BMI only
Niraula (2012)	39	RCT	Analyzed the effects of starting metformin 500mg TID vs placebo in newly diagnosed BC on metabolic profile and tumor cells	Metformin group showed significant decreases in Ki67
Pimetnal (2019)	40	RCT	Multi-national analysis of metformin 850mg BID vs. placebo on the progression free survival of BC in women taking chemotherapy	The addition of metformin did not show any significant benefit to survival



CONCLUSIONS

Much more research is needed to conclude metformin's benefit in the treatment of breast cancer. It appears as though metformin might benefit certain subtypes of non-diabetic breast cancer more than others, as well as in women with higher BMI.¹³ It is important that there be more studies which control for these differences to prove its effectiveness. It is not recommended to discontinue further studies. There have been very few serious adverse events associated with these trials.¹⁶ **With continued research and the utilization of widely used, tolerable and safe medications such as metformin, the future of breast cancer is bright.**

CURRENT TREATMENT

The primary treatment of breast cancer is done by surgical resection.¹ **Lumpectomy vs. mastectomy** with sentinel node biopsy is determined based on the extent of the cancerous cells.¹ Adjuvant therapies include radiation, chemotherapy, aromatase inhibitors, monoclonal antibodies, and selective estrogen receptor modulators (SERMs).¹ While these have all proven effectiveness, they are not benign.¹⁰ It is unknown if these toxic drugs are providing more harm than good to the breast cancer patients.¹⁰ **Common side effects of the various treatments include: fatigue, hair-loss, nausea, radiation burns and anemia.** These side effects are often severe, and greatly alter the patients quality of life. There is an essential need for a safer adjuvant therapy for breast cancer.

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