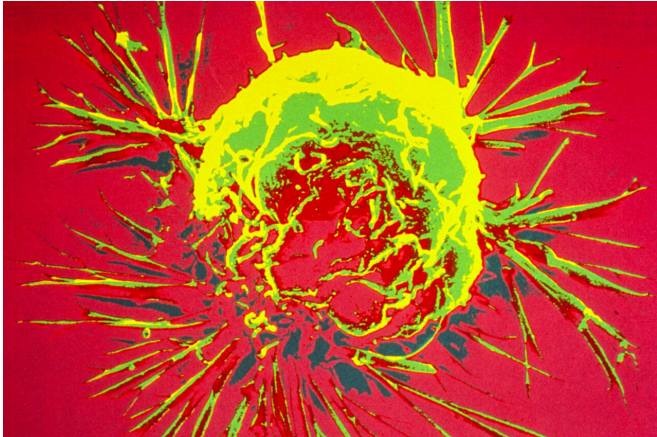


Metformin may affect risk of breast cancer in women with type 2 diabetes

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A breast cancer cell, photographed by a scanning electron microscope. Credit: Bruce Wetzell and Harry Schaefer, National Cancer Institute, National Institutes of Health

A study of 44,541 women has found that there appears to be no association between type 2 diabetes and developing breast cancer overall. This may be because most women in the study with type 2 diabetes were taking metformin, a medication widely used to treat type 2 diabetes, whose actions may help to reduce the risk of developing oestrogen positive (ER-positive) breast cancer.

ER-positive [breast cancer](#) (cancer that has receptors on cell surfaces for the hormone oestrogen) accounts for about 80% of breast cancer diagnosed in the USA. Associations uncovered in the study suggested that the link between type 2 diabetes and breast cancer varied by breast cancer subtype and was affected by the use of metformin to treat diabetes. The study is published in *Annals of Oncology* today.

Over the period of the study, which had an average of more than eight years of follow-up, the

researchers found that type 2 diabetes was associated with a 40% increased risk of triple negative breast cancer (TNBC, breast cancer that lacks receptors for the hormones oestrogen and progesterone and the HER2 protein) when compared with women who did not have diabetes. In contrast, there was a small (8%) decrease in risk for ER-positive breast cancer. These results were not statistically significant.

When the researchers considered women according to the type of treatment they received, type 2 diabetes treated with metformin was associated with a 14% decreased risk of developing ER-positive breast cancer but a 25% increased risk of developing ER-negative breast cancer (breast cancer that lacks receptors for the hormone oestrogen) when compared to non-diabetic women. These results were also not statistically significant. However, there was a statistically significant 74% increased risk of developing TNBC among those treated with metformin.

Professor Dale Sandler, chief of the Epidemiology Branch at the US National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (USA), who led the research, said: "We also found that having type 2 diabetes for 15 years or more seemed to be associated with a 39% reduced risk of ER-positive breast cancer, and we think this is most likely to be because of long-term use of metformin. We found that, compared to non-diabetic women, the risk of developing ER-positive breast cancer was reduced by 38% among women with type 2 diabetes who had used metformin for ten years or more.

"Taken together, these findings suggest that having type 2 diabetes may increase the risk of developing breast cancer, but that taking metformin may protect against developing ER-positive breast cancer, the most common type of breast cancer. Metformin did not appear to protect against ER-

negative or triple negative breast cancer. We can't say for sure if the increased risk of triple negative breast cancer is because metformin doesn't protect women against the [negative effects](#) of having type 2 diabetes or because metformin use can cause triple negative breast cancer. Since there are no mechanistic data supporting a causal effect of metformin, the former interpretation seems more likely."

The researchers also found that among women who developed type 2 diabetes after joining the study, those who were treated with medications other than metformin had twice the risk of developing any type of breast cancer compared to non-diabetic women, and 2.6 times the risk of developing ER-positive breast cancer. However, the numbers in this group were small, only 13 women developed any type of breast cancer, and so this result needs to be treated with caution.

Previous studies have reported an increase risk of breast cancer in women with type 2 diabetes, but there has been conflicting evidence from more recent studies and on the association between metformin and breast cancer. The current study analysed data from the Sister Study, which enrolled women from the USA and Puerto Rico between 2003 and 2009 using follow-up data through to the end of 2017 (although women continue to be followed after that date). At enrolment, the women were 35-74 years old, had no previous diagnosis of breast cancer, but were sisters or half-sisters of women diagnosed with breast cancer. The women completed annual health updates and follow-up questionnaires every three years.

The first author of the study, Dr. Yong-Moon Mark Park, a postdoctoral fellow at the NIEHS, NIH, when the study was conducted (now an assistant professor at the University of Arkansas for Medical Sciences, USA), said: "Our study is the first to try to disentangle the effects of type 2 diabetes and the effects of metformin use. Having information about subtypes of breast cancer that may have different causes helped us to reach our conclusions. However, it's important to note that some of our findings, especially for triple negative breast cancer, were based on a small number of cases and those results need replication. Further studies

are needed to discover whether the apparent increased risk of triple negative breast cancer is caused by metformin or is due to the absence of protection from metformin."

Possible mechanisms by which metformin may reduce breast cancer risk include that it improves [insulin sensitivity](#), and corrects high insulin levels by reducing the amount of insulin and insulin-like growth factor circulating in the body, which may activate cell signals involved in cancer; it may slow breast cancer growth by activating an enzyme called adenosine monophosphate activated protein kinase (AMPK), which inhibits a pathway involved in the proliferation of cancer cells; and it may reduce the risk of ER-positive breast cancer by inhibiting oestrogen receptors that plays a role in the development and progression of breast cancer.

Strengths of the study include its prospective design, a large group of women and high rates of follow-up (90%). Limitations include the fact that the researchers were unable to account for glucose control and progression or improvement of type 2 diabetes, which could affect the risk of [breast cancer](#); it was difficult to disentangle the effects of diabetes from the effects of medication as so many women were prescribed metformin and used it for many years; there was no information on metformin dose, which could reflect severity of diabetes or duration, but also might play a role in the degree of protection it provided.

In an accompanying editorial, Dr. Ana Lohmann from the University of Western Ontario, and Dr. Pamela Goodwin from the University of Toronto, Canada, write: "Despite the inclusion of 44,541 subjects, there were only 277 BCs [breast cancers] diagnosed in [women](#) with T2D [type 2 [diabetes](#)], including 25 TNBC; 177 and 20, respectively of these received metformin. The significant association of T2D with risk of TNBC in the subgroup treated with [metformin](#) (n=20) may have reflected chance and/or uncontrolled bias and confounding."

They conclude: "The report by Park adds to the growing evidence linking T2D and its treatment to BC risk but definitive conclusions regarding these associations are not yet possible. Clearly, this is an

important area and additional research is needed to untangle the web of inter-related associations of T2D, its treatment and BC risk . . . Over time, consistency of associations across studies should be sought and the biologic plausibility of any associations that are identified established."

More information: Y.-M.M. Park et al, A prospective study of type 2 diabetes, metformin use, and risk of breast cancer, *Annals of Oncology* (2021). [DOI: 10.1016/j.annonc.2020.12.008](https://doi.org/10.1016/j.annonc.2020.12.008)

A.E. Lohmann et al. Diabetes, metformin and breast cancer: a tangled web, *Annals of Oncology* (2021). [DOI: 10.1016/j.annonc.2020.12.014](https://doi.org/10.1016/j.annonc.2020.12.014)

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