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# Metformin improves pancreatic cancer and lymphoma outcomes in DM2 patients

Type 2 diabetics are at increased risk of cancer in part because of increased insulin in the blood from insulin resistance. Insulin and its related growth factor IGF-1 can stimulate cell growth through the Ras-Raf-MEK-ERK or the PI3K-AKT-mTOR pathways. Metformin is one of the most commonly used drugs to treat Type 2 diabetes. It primarily works to decrease liver glucose production and increase peripheral insulin uptake from the blood. This is accomplished by inhibiting Complex I of the mitochondrial electron transport chain which indirectly activates an enzyme called AMP-kinase. Through AMP-kinase, metformin inhibits mTOR, a protein synthesis regulator, which is the proposed mechanism for many of metformin's anti-cancer actions. Independent of AMP-kinase, metformin's anti-cancer effects include suppressing new blood vessel formation and promoting cell death. Also, metformin is thought to independently boost the immune system and reduce inflammation.

Recent studies from our group have shown that metformin is associated with improved outcomes for cancer patients with Type 2 diabetes suffering from prostate, colon, gastroesophageal, lung, and thyroid cancers. Other groups have shown positive outcomes in lymphoma and pancreatic cancer in metformin-treated Type 2 diabetics.

We examined the medical charts of 304 pancreatic cancer patients and 360 lymphoma patients at the Memphis VA Medical Center from 1988-2018. These numbers were reduced to include only pancreatic cancer and lymphoma patients with diabetes to 46 and 38 total patients, respectively. For each cancer, one group contained patients taking metformin and the other group consisted of patients taking other agents, but not metformin, to treat their diabetes. Baseline characteristics were very similar between groups. Parameters such as cancer spread, remission, recurrence and survival were compared between the two groups. Statistical tests called unpaired t-tests, Chi-squared tests and analysis of covariance were used. P-values $\leq 0.05$ were significant and values between 0.05 and 0.10 trended toward significance.

In the lymphoma study, there was significant increase in survival after cancer diagnosis in the metformin group (5.89 years) compared to the non-metformin group (1.29 years) ($p<0.001$). There was no statistical difference in cancer recurrence or the number of new cancers between the two groups. The increase in survival with metformin in lymphoma remained significant even after controlling for differences in baseline kidney function and age at diagnosis. In the pancreatic cancer study, there was also a significant increase in survival in the metformin group (0.68 years) compared to the non-metformin group (0.22 years) ($p=0.016$). There was no statistical difference between the groups for metastases. The increased survival in pancreatic cancer associated with metformin remained significant after controlling for baseline kidney function and it trended toward significance after controlling for age at diagnosis.

Findings from the pancreatic cancer and lymphoma studies suggest Type 2 diabetics taking metformin are associated with increased overall survival compared to Type 2 diabetics not taking metformin. One potential mechanism supporting this association in pancreatic cancer is that a common pancreatic cancer gene forces the cells to rely more upon mitochondrial energy and metformin disrupts this process. Limitations of the study include our small sample sizes, almost exclusively male population and using one medical center. In the

future, we anticipate metformin or a similar or modified drug may be used as an additional anti-cancer drug, even independent of diabetic status.

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## Publication

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