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Evidence is being examined to determine if metformin could actually help prevent cancer in patients with type 2 diabetes.

Metformin is one of the common oral medications for the treatment of type 2 diabetes. The main actions of metformin are well-characterized: it decreases intestinal absorption of glucose, prevents glucose production in the liver and enhances the uptake of glucose throughout the body.[1] Patients with diabetes may effectively manage their blood glucose levels with proper use of metformin alone or in combination with other anti-diabetic agents. Individuals using metformin may see their hemoglobin A1C (HbA1C) lowered by as much as 1.5 to 2 percent.[2] This ultimately reduces the incidence of complications such as cardiovascular disease, end organ damage and dyslipidemia that patients could experience due to prolonged, elevated blood sugar.

One issue that has become particularly interesting to the health care community is the potential relationship between type 2 diabetes, metformin and cancer. Type 2 diabetes is often associated with an increased incidence of many cancers, including but not limited to colorectal, breast, liver and uterine cancer.[3] While we know that the risk of both diabetes and cancer may increase with factors such as age, inactivity and excessive alcohol intake, we are not entirely certain if or how type 2 diabetes and cancer are linked biologically.[3] So where does metformin play a role in all of this? Evidence is being examined to determine if metformin could actually help prevent cancer in patients with type 2 diabetes.

How could this common, inexpensive, and relatively old medication function as an anti-diabetic medication and aid in cancer prevention? The immediate answer is that the mechanisms behind metformin's anti-neoplastic effects are currently unknown and are being investigated.[2] In the past five years alone, upwards of 800 studies and meta-analyses have focused solely on examining the medication's impact on cancer. Simply put, malignancies are the result of dysregulated cell growth. However, cancer is a complex disease state with numerous potential origins and possible outcomes. This means that there are many ways metformin could potentially impact cancerous cell growth in the body, and it is possible that different types of cancer could be affected by various different mechanisms.[3]

In regard to cancer prevention, the majority of data we have pertaining to humans is derived from retrospective epidemiological data.[4] While this data suggests that metformin may prevent cancer in patients with type 2 diabetes, few randomized controlled trials have been published that validate this data. Researchers are also testing metformin's impact on tumor growth in cultures and in animal models.[4-6] Metformin has been shown to significantly reduce the number and growth rate of tumors in laboratory settings.[4-6] For example, in a study conducted by Chaudhary et al. that compared tumor size in mice receiving metformin versus placebo, it was observed that tumor volume was reduced by 60.8 percent in the metformin-treated group.[4] Although there is limited consensus on how this reduction occurs, one suggestion involves metformin's ability to activate and de-activate certain cellular proteins. Specifically, the activation of AMP-activated protein kinase (AMPK) and the deactivation of mTOR (mammalian target of rapamycin), which are both regulatory proteins, are thought to play a large role in anti-neoplastic activity.[4,5] These actions are believed to ultimately reduce the rate of cell replication, which is beneficial in the treatment of tumors.

It is important to keep in mind that this is only one of the simplified means by which metformin could potentially exert its anti-neoplastic effects. Many studies mention metformin's ability to stop DNA damage, which can also prevent malignancy.[4] Others include even more complex cellular signaling pathways and protein targets of interest.[4,5] Laboratory evidence also suggests that metformin can alter important calcium-dependent processes in cells, which may directly induce apoptosis (cell death).[4,5] As these preliminary laboratory trials have suggested, there are various mechanisms by which metformin could impact cancer prevention and treatment. However, we want to draw conclusions about the most pertinent question: How does this medication impact patients? Although not a comprehensive review, some recently published studies that shed light on this question are described below.

Breast Cancer

Breast cancer is one of the primary causes of female death in the United States, with about one in eight women developing invasive breast cancer over the course of her lifetime.[6] Numerous studies have indicated that concurrent diabetes amplifies the negative outcomes and mortality rates for patients with breast cancer. More recently, it has been found that a regimen of metformin can be beneficial to breast cancer patients as it improves clinical outcomes and reduces risk of mortality. In a study published in October 2012 in Breast Cancer Research and Treatment, the pathological, clinical and prognostic characteristics of breast cancer patients with diabetes were thoroughly investigated. Participants were divided into a nondiabetic group that did not use metformin and a diabetic group consisting of metformin-treated and nonmetformin-treated subgroups. This study found that the percentage of patients testing positive for HER2 (human epidermal growth factor receptor 2), a cancer cell-proliferating protein whose presence signifies a more aggressive form of breast cancer, was lower in the metformin-treated subgroup than the nonmetformin-using group.[7] Patients undergoing therapy with metformin had the highest five-year survival rate of 88 percent, while the nondiabetic patients and diabetic patients not using metformin had survival rates of 82 percent and 73 percent, respectively.[7] It is important to note that most patients with diabetes have a long and complicated medication history and that the possible influence of patients' combined medication regimens was not measured in the study.

However, other studies have shown that there is no clinical significance in regard to metformin's effect on long-term breast cancer outcomes. A study cohort published March 2012 in Cancer investigated the link between metformin use and survival rates in patients with triple receptor-negative breast cancer (TNBC) while receiving concurrent chemotherapy. Following a 62-month trial period, there was no significant difference in the five-year distant metastasis-free survival (p=0.23), recurrence-free survival (p=0.38), or overall survival (p=0.58) between the nondiabetic group, the metformin-treated diabetic group and the nonmetformin -treated diabetic group.[8] There was still a trend toward a decreased risk of developing metastasis in diabetic patients taking metformin compared to the other two groups.[8] However, these findings are not solid evidence to make a clinical decision. Additional testing with prospective studies is needed to draw a definite conclusion regarding metformin's benefits in cancer treatment. Currently, a large, phase 3, randomized clinical trial is underway to test metformin's relation to breast cancer in greater than 200 oncology centers (National Clinical Trial identifier NCT01101438).

Ovarian Cancer

Though ovarian cancer accounts for only 3 percent of cancers in women, it is among the most deadly considering the fact that 75 percent of patients have advanced stage disease at the time of diagnosis.[9] The ratio of case incidence to fatality is extremely high, as evidenced by the Ovarian Cancer National Alliance's projected statistics from 2012: 15,500 deaths occurred per 22,280 total diagnoses.[10] Desiring to address this major health issue, researchers from the Mayo Clinic College of Medicine utilized the idea of drug repositioning to investigate the potential of metformin to improve the prognosis in patients with ovarian cancer. In this retrospective case-control study the 72 ovarian cancer patients who received metformin had a 73 percent five-year disease-specific survival rate (p=0.0002), whereas the 143 patients not receiving metformin therapy had only a 44 percent rate of five-year survival.[9] In a similar retrospective cohort study published in Obstetrics and Gynecology in January 2012, researchers found that the five-year survival rate without disease progression was 51 percent for diabetic patients treated with metformin, 23 percent for patients without diabetes, and only 8 percent for diabetics who were not subjected to metformin therapy.[11] When compared to nonmetformin-treated diabetic patients, diabetic patients who used metformin also had a significantly decreased hazard for disease recurrence (HR (hazard ratio) 0.38, 95 percent CI (confidence interval) 0.16–0.90).[11] The results from both studies suggest that metformin intake independently predicts increased survival in ovarian cancer patients, although further large-scale clinical trials will be necessary to prove direct causation.

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Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer among men in the United States afflicting about one in every six men.[12] Most research implicates diabetes as a risk factor for cancer, yet diabetes seems to have a protective factor regarding prostate cancer.[13] The data concerning metformin is conflicting and the majority of studies published are observational in nature. In a meta-analysis conducted by Zhang et al. it was found that there was a decreased mortality relative risk in metformin users versus nonusers associated with pancreatic, breast, colorectal and liver cancer. However, these researchers found no association (increased or decreased risk) regarding metformin therapy and prostate cancer.[14] A nested case-control study conducted by Azoulay et al. published in February 2011 found that metformin did not decrease risks of prostate cancer (RR (relative risk) 1.23 95 percent CI 0.99-1.52).[15]

However, several studies have found a decreased incidence of prostate cancer with use of metformin. Wright et al. published a case-control trial in November 2009, which found that there was a 44 percent decrease in the relative risk of prostate cancer in type 2 diabetics that were treated with metformin (OR (odds ratio) 0.56 CI 0.32-1).[16] A nested case-control study's results from Hitron et al. published in August 2012 suggested that metformin had a decreased incidence of prostate cancer compared to insulin and sulfonylureas, although the results were not statistically significant.[17] Another study from Sahra et al. published in March 2012 concluded that in vitro, metformin had a dose dependent inhibition of prostate cell lines and in vivo mice had decreased tumor growth while treated with metformin, although this was not tested in humans.[12] The most promising data regarding metformin and prostate cancer was a retrospective cohort conducted by Spratt et al. published in April 2013 that looked at metformin in the treatment of castration resistant prostate cancer. This study found that there was a significant improvement in biological markers compared to nonmetformin diabetics.[18] Due to the conflicting evidence of metformin and prostate cancer prevention in observational studies, randomized clinical trials are necessary to determine if metformin is effective in preventing and treating prostate cancer or if there really is no benefit of metformin in this cancer population.

Colorectal Cancer

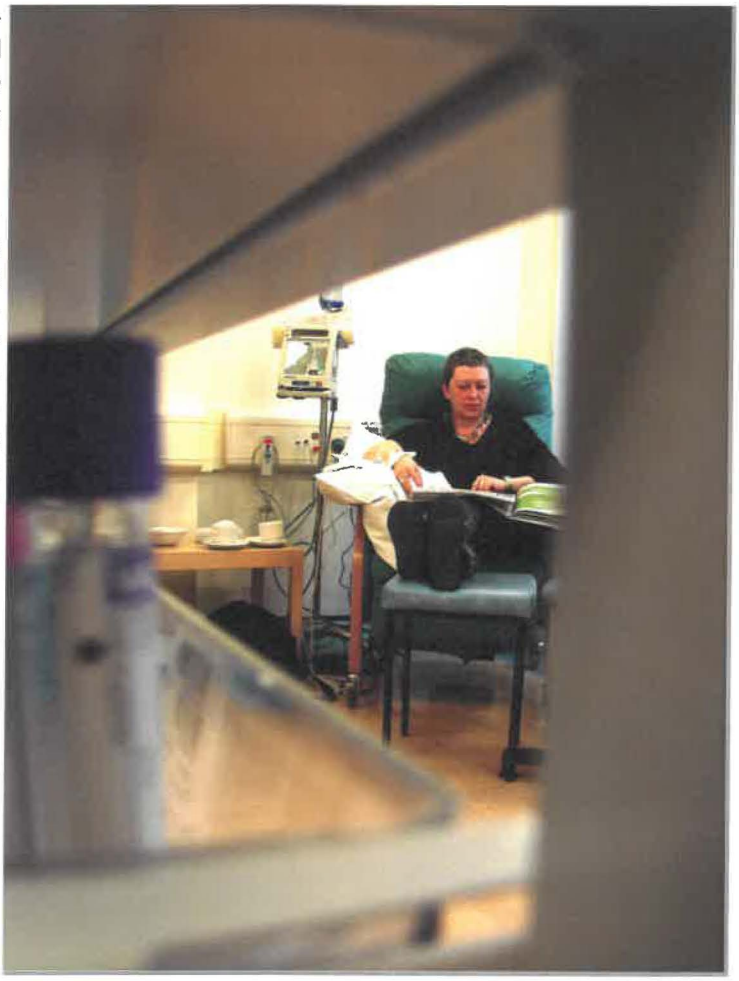
Colorectal cancer is the fourth most common cancer worldwide.[19] Many observational studies have been conducted evaluating the

relationship between metformin, diabetes and colorectal cancer. A study conducted by Suh et al. (2011) looked at the association of type 2 diabetes and aggressiveness or colorectal cancer polyps found that patients with diabetes had an increased number of colorectal polyps.[20] Although there is evidence pointing toward metformin's effectiveness in regard to colorectal cancer prevention and treatment, the literature remains controversial. In a meta-analysis published by Zhang et al. in October of 2011, it was found that metformin was associated with a decrease in colorectal cancer neoplasms (RR 0.63 95 percent CI 0.5-0.79, p=0.001), as well as a significant lower risk of colorectal cancer (RR 0.63, 95 percent CI 0.47-0.84, p=0.002).[21] Another study conducted by Lee et al. (2012) found that patients with diabetes diagnosed with colorectal cancer and treated with metformin had a decrease in overall mortality (HR 0.66 95 percent CI 0.476-0.923, p=0.015) as well as a decrease in colorectal specific mortality (HR 0.66, 95 percent CI 0.45-0.975, p=0.037).[22] A study published by Hosono et al. in September 2010, randomizing nondiabetic patients into a metformin treatment group versus a placebo, found that after one month the metformin group had a significant decrease in mean number of rectal aberrant crypt foci at one month (p=0.007); the change in the placebo group at one month was not statistically significant.[23]

There have also been studies published showing no association or increased association between metformin and colorectal cancer. A nested case-control analysis by Bodmer et al. published in February 2012 looked at electronic medical records and identified patients diagnosed with colorectal cancer as well as a previous diagnosis of diabetes. It was found that extensive use of metformin, defined as ≥50 prescriptions filled, was associated with an increased risk of colorectal cancer (OR 1.43, 95 percent CI 1.08-1.9) compared to nonmetformin users.[24] A retrospective cohort by Lewis et al. published in July 2007 found that patients who filled prescriptions for metformin were more likely to undergo lower endoscopies (HR 1.17 95 percent CI 1.07-1.26). Thus, discussing the association between a higher rate of lower endoscopies and diabetes treatments, which may skew results regarding metformin's preventative effects, is important.[25] Additional studies need to be conducted to evaluate metformin's true effects on colorectal cancer.

Limitations and Biases to Consider

It is important to remember that a majority of the studies discussed above are cohort and case-control studies, which are two examples of analytic observational study designs. This type of observational study design involves rigorous data collection and analysis that can be used to examine associations between an exposure and the outcome of interest. Observational studies can provide good data and show associations between the exposure and outcome of interest, but it is important to remember that researchers cannot control for all residual or unknown confounding variables. The only way to remove these residual confounding variables is with the use of proper randomization.[27] Observational studies also may be subject to biases and limitations. These biases and limitations need to be addressed when reviewing these studies.



An article by Suissa and Azoulay (2012) addressed some common issues with many of the observational studies attempting to show a relationship between metformin and decreased risk of cancer. They concluded that time-related biases were frequent in many of these observational studies and potentially exaggerated some of the results that may have shown a protective relationship between metformin and cancer. These time-related biases include immortal time bias, time-window bias and time-lag bias.[28] The potential for these types of biases must be taken into consideration when interpreting the results of observational studies.

Immortal time bias, which is a common type of bias in cohort studies, is also called "survival bias." Immortal time bias results when the time dependency of prescription drug use in a large cohort is not adequately controlled. For example, this type of bias was seen in a study by Lee et al. (2011) that showed a statistically significant association between metformin use and decreased risk of cancer.[29] The study found associations between metformin exposure and decreased risk of colorectal cancer, liver cancer and pancreatic cancer. The bias resulted from their definition of exposure to metformin which was receipt of at least two prescriptions of metformin during the seven-year study period. The researchers attributed the time

between the two metformin prescriptions as "exposed" time. Suissa and Azoulay explain how this causes immortal time bias—patients must have been alive ("immortal") to receive the second metformin prescription and be included in the study.[28] In addition, patients who had extended periods of time between filling their first and second prescription resulted in significant amounts of "unexposed" time recorded as "metformin-exposed" time. This misclassification of data could exaggerate the results and show a statistically significant association which may not be present.

Other biases include time-window bias and time-lag bias. Time-window bias can be seen in case-control and nested case-control studies and occurs when the length of the treatment or follow-up time window(s) are not equal between the cases and the controls. Time-lag bias can be seen in cohort studies and occurs when researchers compare different treatment options that are given at varying stages or progressions of the disease.[28]

This is not an exhaustive list of the potential biases in observational studies, but rather these are the most commonly seen biases in many of the observational studies that look at metformin's role in cancer prevention. For example, Suissa and Azoulay found 13 cohort studies that looked at metformin and the risk of cancer that had immortal time bias, nine case-controls and nested case-control studies that had time-window bias, and two cohort studies that included time-lag bias. The problem is that these biases can greatly skew the results, suggesting an association that is not actually present.[28] It is important to look at these studies closely for these and other potential types of bias.

Future Directions

As of April 2013, there are 60 studies listed on http://www.ClinicalTrials.gov examining the effects of metformin and cancer; these trials are at all stages from recruiting patients to completed trials. These trials vary widely and include studies on metformin's influence on cancer biomarkers; metformin as adjuvant therapy in children with relapsing solid tumors; and metformin as chemoprevention of cancers. The studies include early stage cancers as well as relapsing cancers, such as solid tumors, breast, prostate, endometrial, lymphoma, leukemia, colorectal, thyroid, lung, brain, and skin cancers.[26] The majority of these new studies are randomized blinded controlled trials that will add to the current epidemiological evidence concerning use of metformin in treatment and prevention of many cancers and should provide more definitive data for clinical use of metformin in oncology practice.

Conclusion

Many studies have been published that suggest that metformin may play a role in preventing and possibly treating cancer; however, results have been mixed. Many in vivo and in vitro studies have provided mechanistic evidence that support the hypothesis that metformin may be protective against cancer. Results from observational studies and meta-analysis show there may be an association with the use of metformin and a decreased incidence of many different types of cancer. So, the main question to answer is: What role does metformin currently play in the prevention of cancer? Although some data suggests there could be a benefit, there is currently not enough evidence to recommend using metformin to prevent cancer. Randomized, controlled trials will need to show a benefit before recommendations can be made.

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