Published in final edited form as:

Am J Med Sci. 2017 September ; 354(3): 246–251. doi:10.1016/j.amjms.2017.05.006.

Metformin has Positive Therapeutic Effects in Colon Cancer and Lung Cancer

DeAnna Henderson, MD^{1,*}, Danielle Frieson, MS^{1,*}, Jeffrey Zuber, MA³, and Solomon S. Solomon, MD^{1,2}

¹University of Tennessee Health Science Center-Endocrinology Division 920 Court Avenue, Memphis, TN 38163, United States of America

²Veterans Affairs Medical Center- Memphis Research Service (151) 1030 Jefferson Ave. Memphis, TN 38104, United States of America

³University of Tennessee Health Science Center-Department of Preventive Medicine 66 N. Pauline Street, Suite 633, Memphis, TN 38163, United States of America

Abstract

Purpose—Metformin, a diabetic drug, has anti-neoplastic activity as adjuvant therapy for breast cancer and prostate cancer. Metformin is thought to work via inhibition of mammalian target of rapamycin (mTOR) and activation of p53 and Liver Kinase B1 (LKB1) via 5' adenosine monophosphate-activated protein kinase (AMPK). We investigated survival, recurrences, and metastasis in type 2 diabetes mellitus (DM2) patients with Colorectal cancer (CC) or Lung cancer (LC) taking metformin using the electronic medical record (EMR) in Memphis Veterans Affairs Medical Center (MVAMC) (N=202, Colon; N=180, Lung).

Methods—Patients with CC or LC and DM2 on metformin were compared to controls taking any medication except metformin. Recurrences, metastases, secondary cancers, survival, and CEA levels were compared using T-tests and chi square tests. Inclusion criteria was based on metformin use, CC or LC diagnosis, and DM2.

Results—For CC, the metformin group noted fewer deaths (48% vs 76%, $p<0.001$), recurrences (4% vs 19%, $p=0.002$), metastases (23% vs 46%, $p=0.001$), better 5-year survival rates (57% vs 37%, $p=0.004$), overall survival years (5.7 vs 4.1, $p=0.007$), and greater CEA decrease (72% vs 47%, $p=0.015$). Metformin was associated with improved 5-year survival rates (29% vs 15%, $p=0.023$) and overall survival years (3.4 vs 1.8, $p<0.001$) in LC.

Conclusions—Our study shows metformin therapy is associated with significantly better prognosis in patients with CC and improved survival in LC. CC patients on metformin had fewer recurrences and metastases. Differences in metabolic pathways between CC and LC likely account for differences in effect of metformin.

Corresponding author: Solomon S. Solomon, MD ssolomon@uthsc.edu, 901-523-8990 ext 7614.

*These authors share co-first authorship

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

Colon Cancer; Lung Cancer; Metformin; Type 2 Diabetes Mellitus

Before the turn of the twentieth century, a diagnosis of Diabetes Mellitus (DM2) was synonymous with insidious death. Defronzo et al. described the Ominous Octet, noting that insulin resistance at the levels of skeletal muscle and liver only denotes a part of the diabetes story and that interactions at other end-organs also play a leading role (1). Recently, associations between DM2 and increased risk of cancer have been established, with cancer being recognized as a potential complication of DM2 (2). Jamal et al. noted a 3-fold increase in the risk of pancreatic cancer and a two-fold increase in the risk of extrahepatic biliary cancer in diabetic American veterans compared to non-diabetic veterans (3). A 1.3-fold increase in the risk of colon cancer in patients with DM2 vs patients without diabetes was recently noted by Peeters et al., corroborating the results of several prior studies, which also noted a modest increase in colorectal cancer risk in patients with DM2 (4). Several different studies investigated the relationship between hyperglycemia and cancer risk, however, it was noted that improvement in and optimization of glycemic control did not necessarily lead to a decrease in risk or prevalence of malignancy (2, 5-8). Evidence identifying the relationship between insulin resistance with hyperinsulinemia, and malignancy is rapidly evolving. The Cremona study from Italy was a population study evaluating the prevalence of diabetes mellitus as well as insulin resistance/hyperinsulinemia, and cancer mortality over a total of 15 years. At the 15 year mark, there were 180 cancer related deaths out of 2011 Caucasian patients. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and smoking were independently noted to be associated with cancer mortality. It was also noted that patients with insulin levels in the highest quintile had a 62% higher risk of cancer mortality and a 161% higher risk of gastrointestinal cancer mortality (9).

We studied prostate cancer with apparent comparable improvement in cancer outcomes (10). Other recent literature also contains a few studies, most supporting improved outcomes with metformin use in a number of different cancers, including Non-small cell lung cancer (NSCLC) (11) and colorectal cancer (CC) (12). Both these studies address associated improved survival of cancer patients taking metformin and propose that metformin should be used as adjuvant therapy. In this paper, we observed for survival rates in addition to recurrence rates and metastatic disease in the patients.

There are many biochemical mechanisms that could link DM2 and malignancy. Data from in vitro and in vivo studies suggests interactions between hyperinsulinemia, insulin receptors, IGF-1/2 receptors in endocrine, autocrine, and paracrine functions as possible etiologies. The IR, IGF-1R, and IGF-2R are tyrosine kinase receptors with significant homology. Binding through any of these receptors would lead to activation of MAPK, PI3K, and Janus kinase signaling (13). Signaling through PI3/Akt and Ras/MAPK pathways upregulates the mammalian target of rapamycin (mTOR) activity, ultimately leading to increased cell proliferation, protein synthesis, and reduction of apoptosis. Aberrant mTOR signaling is thought to be present in up to 80% of human malignancies (14). 5' adenosine monophosphate-activated protein kinase (AMPK) is a serine/threonine kinase that senses

and regulates mTOR activity, and as such, is also integral to cell metabolism, cell growth, and autophagy. Tumor cells are known to have established mechanisms to dampen AMPK signaling, leading to uninhibited cell proliferation (15).

Interestingly, inactivation of a gene for tumor suppressor and serine/threonine kinase, Liver Kinase B1 (LKB1), which is found upstream of AMPK and is required for its activation, was found to be responsible for genetic susceptibility to Peutz-Jeghers syndrome. LKB1 is also noted to be the second most commonly mutated tumor suppressor in sporadic human lung cancer and is present in at least 15-30% of non-small cell lung cancers (16). LKB1 phosphorylates AMPK leading to an increase in the AMP/ATP ratio, thus regulating cell polarity, cell growth and cell autophagy through inhibition of mTOR (15, 16).

Metformin, a first line anti-hyperglycemic medication, is thought to have both direct and indirect anti-tumor effects. In a review article, Duque et al. notes that metformin downregulates oxidative stress and alters the ATP/AMP ratio leading to indirect activation of AMPK. Metformin may also stimulate the tumor suppressor LKB1, which would cause direct activation of AMPK and inhibition of mTOR(17). This theory has been tested in patients with and without diabetes, revealing varying results.

The well-established inhibitory effect of metformin on complex 1 of the electron transport chain, which is required for tumorigenicity, is a major contributor to metformin's overall anticancer effect. Inhibition of complex 1 causes energetic stress within the cells and increases the AMP:ATP ratio and the increase in AMP directly causes hepatic AMPK activation, leading to a decrease in gluconeogenesis (18).

Our group conducted a retrospective analysis of Veteran patients with DM2 and prostate cancer who were treated for their DM2 with regimens including and not including metformin. We found that patients with DM2 and prostate cancer had significant improved survival, decline in secondary cancers and metastasis. PSA levels were also reduced in the patients treated with metformin (10).

Non-small cell lung cancer consists of 85% of all lung cancer and still has 5-year survival rates of 15-18%. Colon cancer survival rates have been improving over the last 60 years, and screening has led to a decrease in the incidence of colorectal cancer. However, colon cancer still ranks as the third highest cause of cancer death in both men and women. As the Memphis Veteran Affairs Medical Center (MVAMC) has high rates of colon cancer and lung cancer, we chose to investigate the association of metformin in patients diagnosed with NSCLC or colon cancer with DM2, on metformin therapy or without metformin therapy. In this study, we hypothesized that metformin therapy would be associated with improved overall survival, reduced metastasis and reduced recurrences in patients with DM2 and either CC or NSCLC.

The primary endpoint for both studies was overall survival. Secondary endpoints included recurrences, metastases, and secondary malignancies.

Methods

The MVAMC Institutional Review Board approved this study design. The Tumor Registry at MVAMC provided a separate cohort of patients with CC and a separate cohort of patients with NSCLC, each diagnosis identified by ICD-9 codes between 1998-2012. A retrospective chart review was conducted using the electronic medical record. Inclusion criteria included patients that were diagnosed with DM2 prior to a diagnosis of either CC or NSCLC. Patients were included in the metformin (MF) group if they had a history of DM2 and had been treated with metformin for two years or greater. Patients treated with any other hypoglycemic agent except metformin were included in the non-metformin (NMF) group.

For the first arm of the project, a total of 202 CC patients were extracted from the cohort. The metformin group contained 104 patients and the non-metformin group contained 98 patients. Patients were matched for age and race. The patients were observed for CEA levels, recurrences, metastases, secondary malignancies, and survival.

The second arm of the study included 180 patients with NSCLC, 93 patients in the MF and 87 patients in the NMF. Patients were matched for age, race, and smoking status and were observed for recurrences, metastases, secondary malignancies, and survival (Figure 1).

Data for both arms of the study was analyzed using independent samples t-tests and chi-squared tests. ANCOVA and logistic regression was performed to test for significant results while controlling for potential confounders. Cohen's *d* and Cramer's *V* effect sizes were also calculated.

Colon Results

Most baseline characteristics were matched (see Table 1). However, a significant difference was noted regarding BMI, hemoglobin A1c, creatinine, and age at diagnosis. MF patients with DM2 and CC were found to have a higher mean BMI than NMF patients (29.8 vs 26.0, $p<0.001$) as well as a higher hemoglobin A1c than NMF patients (7.4 vs 6.7, $p=0.002$). Patients in the NMF group were found to have a higher creatinine at baseline (2.3 vs 1.5, $p=0.010$) and were older when diagnosed with cancer (67.4 vs 64.9 years, $p=0.049$) than the MF group.

As shown in Table 2, outcomes were significant for more MF patients living (51.9% vs 24.5%, $p<0.001$) than NMF patients, more patients having a CEA decrease (72.1% vs 46.7%, $p=0.015$), improved 5-year survival (56.3% vs 33.7%, $p=0.001$), improved overall survival (5.7 vs 4.1 years, $p=0.007$), decreased metastasis in the MF vs NMF group (23.1% vs 45.9%, $p=0.001$), decreased recurrences (4.3% vs 18.8%, $p=0.003$). None of these outcomes changed when controlling for any of the significant baseline differences.

NSCLC Results

Significant differences in the baseline characteristics (Table 3) in this cohort included higher hemoglobin A1c in the MF vs NMF (7.6 vs 7.1, $p=0.043$) and more Caucasians/fewer African Americans (65.6% vs 50.6%, 32.3% vs 49.4%, $p=0.024$). NMF patients compared

to MF patients had higher creatinine (1.1 vs 1.4, $p=0.029$) and were older at time of cancer diagnosis (69.4 vs 66.6 years, $p=0.035$).

Outcomes in Tables 3 and 4 show that overall survival and 5-year survival was significantly greater in the MF vs NMF (3.4 vs 1.8 years, $p<0.001$), (29.0% vs 14.9%, $p=0.023$). The MF group also experienced a longer period of progression-free remission than the NMF (2.3 vs 1.1 years, $p=0.008$). Controlling for age at diagnosis resulted in 5-year survival becoming non-significant ($p=0.061$). No other baseline differences significantly affected outcome findings.

Discussion

Overall, the results of both the CC and the NSCLC studies suggests that treatment modalities that include treatment with metformin therapy are associated with improvement in overall survival in CC and NSCLC patient with DM2. In CC patients, secondary parameters showed significant improvement in the MF vs NMF. Except in one instance, findings were unchanged when controlling for significant baseline differences.

Though patients were matched, it was noted that patients with CC in the MF were significantly more overweight, though both the MF and NMF groups had BMI levels greater than 25. There was no significant difference in BMI in the NSCLC cohort. Calle et al. found in a prospective study that mortality from colon cancer increased as the BMI increased above the normal range weight range (18.5-24.9). Patients with BMIs in the range of 25-29.9 were found to have a 1.2 mean relative risk of death secondary to colon cancer. This same study found that an elevated BMI was protective in male patients with lung cancer (19). Interestingly, metformin has also been hypothesized as having a role against cancer cachexia. It is theorized that metformin may activate hypothalamic AMPK pathway which could alter neuropeptide signaling in the hypothalamus and protect against cancer cachexia (17). Our study was not designed to investigate this topic and further prospective trials would be needed; however, this could be a possible explanation for the elevated BMI in our CC MF group.

Glycemic control was less well achieved in the MF vs NMF in both CC and NSCLC. This baseline characteristic is important. It suggests that glycemic control is not the etiology of the improved survival and secondary outcomes associated with metformin therapy in our study and that both direct and indirect anti-tumor effects of metformin are involved.

Our study is subject to selection bias, as is evident in the lower creatinine levels in the MF vs NMF group in both the CC and NSCLC. Recently, the FDA revised the recommendation for metformin therapy in patients with renal disease from being based on creatinine to eGFR. However, previously the FDA recommended cessation of metformin therapy with a creatinine of 1.4mg/dl in women and 1.5mg/dl in men.

While metformin therapy is associated with a significant improvement in primary outcomes in both CC and NSCLC, this improvement in secondary parameters was not noted in patients with DM2 and NSCLC. Reasons for the differences in secondary outcomes cannot be inferred from our study. However, we speculate that differences in the mechanism of

development of these two different categories of cancer may affect response to metformin therapy. It has been noted that NSCLC in mouse models with mutations in LKB1 and KRAS, but not LKB1 and p53 mutations, have prolonged survival thought to be secondary to a selective response to phenformin, an earlier biguanide analog of the current most commonly used anti-hyperglycemic biguanide medication metformin. It is possible that the presence of multiple mutations in various forms of NSCLC led to the development of tumor cells that are no longer responsive to metformin.

Limitations of our study includes selection bias, length time bias, differences in the therapies amongst the two treatment groups, as well as limitations in generalizability due to a predominantly male, Veteran population.

A number of investigators have studied colorectal cancer and metformin, most demonstrating an improvement in many outcome parameters such as metformin being associated with reduced incidence of cancer-related deaths (20) as we have. Some investigators have also shown less positive outcomes that do not demonstrate a significant difference in the outcome of colorectal cancer patients who use metformin versus those who do not (21).

In conclusion, our study notes that metformin therapy is associated with marked improvements in primary and secondary outcomes in CC or NSCLC and DM2. Prospective trials are needed to confirm and fully establish the therapeutic benefit of metformin therapy in CC and NSCLC.

Acknowledgments

There are no conflicts of interest. Supported by NIH/NIDDK Grant DK 007405-30/31

References

1. DeFronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009; 58(4):773–95. [PubMed: 19336687]
2. Buysschaert M, Sadikot S. Diabetes and cancer: a 2013 synopsis. *Diabetes Metab Syndr*. 2013; 7(4): 247–50. [PubMed: 24290094]
3. Jamal MM, Yoon EJ, Vega KJ, et al. Diabetes mellitus as a risk factor for gastrointestinal cancer among American veterans. *World J Gastroentero*. 2009; 15(42):5274–8.
4. Peeters PJ, Bazelier MT, Leufkens HG, et al. The risk of colorectal cancer in patients with type 2 diabetes: associations with treatment stage and obesity. *Diabetes Care*. 2015; 38(3):495–502. [PubMed: 25552419]
5. Jee SH, Ohrr H, Sull JW, et al. Fasting serum glucose level and cancer risk in Korean men and women. *JAMA*. 2005; 293(2):194–202. [PubMed: 15644546]
6. Rapp K, Schroeder J, Klenk J, et al. Fasting blood glucose and cancer risk in a cohort of more than 140,000 adults in Austria. *Diabetologia*. 2006; 49(5):945–52. [PubMed: 16557372]
7. Stocks T, Rapp K, Bjorge T, et al. Blood glucose and risk of incident and fatal cancer in the metabolic syndrome and cancer project (me-can): analysis of six prospective cohorts. *PLoS Med*. 2009; 6(12):e1000201. [PubMed: 20027213]
8. Johnson JA, Bowker SL. Intensive glycaemic control and cancer risk in type 2 diabetes: a meta-analysis of major trials. *Diabetologia*. 2011; 54(1):25–31. [PubMed: 20959956]

9. Perseghin G, Calori G, Lattuada G, et al. Insulin resistance/hyperinsulinemia and cancer mortality: the Cremona study at the 15th year of follow-up. *Acta Diabetol.* 2012; 49(6):421–8. [PubMed: 22215126]
10. Chong RW, Vasudevan V, Solomon S, et al. Metformin Has a Positive Therapeutic Effect on Prostate Cancer in Patients With Type 2 Diabetes Mellitus. *The American journal of the medical sciences.* 2016; 351(4):416–9. [PubMed: 27079349]
11. Lin JJ, Gallagher EJ, Sigel K, et al. Survival of patients with stage IV lung cancer with diabetes treated with metformin. *Am J Respir Crit Care Med.* 2015; 191(4):448–54. [PubMed: 25522257]
12. Coyle C, Cafferty FH, Vale C, et al. Metformin as an adjuvant treatment for cancer; a systematic review and meta-analysis. *Ann Oncol.* 2016; 27(12):2184–2195. [PubMed: 27681864]
13. Gallagher EJ, LeRoith D. Minireview: IGF, Insulin, and Cancer. *Endocrinology.* 2011; 152(7):2546–51. [PubMed: 21540285]
14. Cargnello M, Tcherkezian J, Roux PP. The expanding role of mTOR in cancer cell growth and proliferation. *Mutagenesis.* 2015; 30(2):169–76. [PubMed: 25688110]
15. Han D, Li SJ, Zhu YT, et al. LKB1/AMPK/mTOR signaling pathway in non-small-cell lung cancer. *Asian Pac J Cancer Prev.* 2013; 14(7):4033–9. [PubMed: 23991948]
16. Shackelford DB, Abt E, Gerken L, et al. LKB1 inactivation dictates therapeutic response of non-small cell lung cancer to the metabolism drug phenformin. *Cancer Cell.* 2013; 23(2):143–58. [PubMed: 23352126]
17. Duque JE, Cruz N, Samudio I, et al. Antitumor mechanisms of metformin: Signaling, metabolism, immunity and beyond. *Universitas Scientiarum.* 2010; 15(2):122–9.
18. Luengo A, Sullivan LB, Vander Heiden MG. Understanding the complexity of metformin action: limiting mitochondrial respiration to improve cancer therapy. *BMC Biology.* 2014; 12:82. [PubMed: 25347702]
19. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults. *New England Journal of Medicine.* 2003; 348(17):1625–38. [PubMed: 12711737]
20. Garrett CR, Hassabo HM, Bhadamkar NA, et al. Survival advantage observed with the use of metformin in patients with type II diabetes and colorectal cancer. *Br J Cancer.* 2012; 106(8):1374–8. [PubMed: 22421948]
21. Singh PS, Shi Q, Foster N, et al. The relationship between metformin use and recurrence and survival in patients with resected stage III colon cancer receiving adjuvant chemotherapy: results from north central cancer treatment group N0147 (Alliance). *The Oncologist.* 2016; 21(12):1509–21. [PubMed: 27881709]

Figure 1.

Flow chart of study design.

The two study arms of the project (Colorectal Cancer and Non-small Cell Lung Cancer) were both divided into two groups; one group was taking metformin and the other group not taking metformin.

Table 1
Baseline characteristics of colon cancer patients taking metformin (n = 104) versus those not taking metformin (n = 98)

Variable	Metformin M $\pm$ SD or %	Non-Metformin M $\pm$ SD or %	Cohen's <i>d</i>	Cramer's <i>V</i>	<i>p</i> -value
Age, years	70.5 $\pm$ 8.8	71.6 $\pm$ 9.7	0.11	---	0.433
Sex, male	99.0	99.0	---	<0.01	>0.999
Race			---	0.06	0.677
African American	43.3	48.0			
Caucasian	54.8	51.0			
Other/Unknown	1.9	1.0			
BMI	29.8 $\pm$ 6.9	26.0 $\pm$ 5.3	0.61	---	<0.001
Hemoglobin A1c, %	7.4 $\pm$ 1.6	6.7 $\pm$ 1.4	0.46	---	0.002
Creatinine, mg/dL	1.5 $\pm$ 1.5	2.3 $\pm$ 2.3	0.40	---	0.010
Cancer treatment					
Surgery	94.2	89.8	---	0.08	0.243
Chemotherapy	44.2	48.0	---	0.04	0.595
Radiation (XRT)	14.4	18.4	---	0.05	0.449
Age at diagnosis, years	64.9 $\pm$ 8.8	67.4 $\pm$ 9.8	0.28	---	0.049
Age at death, years	70.0 $\pm$ 9.3	71.7 $\pm$ 10.2	0.18	---	0.341
Years with colon cancer ^a	1.5 $\pm$ 0.8	2.3 $\pm$ 1.6	0.62	---	0.004
Years in remission ^b	6.8 $\pm$ 3.8	6.0 $\pm$ 4.8	0.20	---	0.299

Note: *p*-values from independent samples t-tests or chi-squared tests, as appropriate.^a n = 34, 45 for metformin and non-metformin groups respectively^b n = 72, 45 for metformin and non-metformin groups respectively

Outcome comparisons of colon cancer patients taking metformin (n = 104) versus those not taking metformin (n = 98)

Table 2

Variable	Metformin M $\pm$ SD or %	Non-Metformin M $\pm$ SD or %	Cohen's <i>d</i>	Cramer's <i>V</i>	<i>p</i> -value
Had CEA decrease ^a	72.1	46.7	---	0.26	0.015
Still living	51.9	24.5	---	0.28	<0.001
Overall survival, years ^b	5.7 $\pm$ 4.1	4.1 $\pm$ 4.0	0.39	---	0.007
5-year survival ^c	56.7	36.7	---	0.20	0.004
Cancer outcomes					
Recurrence	4.3	18.8	---	0.23	0.002
Metastasis	23.1	45.9	---	0.24	0.001
Secondary cancer	31.7	32.7	---	0.01	0.888

Note: *p*-values from independent samples *t*-tests or chi-squared tests, as appropriate.

^a *n* = 43, 45 for metformin and non-metformin groups respectively

^b Years survived after cancer diagnosis

^c Patients who survived at least 5 years after cancer diagnosis

Table 3
Baseline characteristics of lung cancer patients taking metformin (n = 93) versus those not taking metformin (n = 87)

Variable	Metformin M ± SD or %	Non-Metformin M ± SD or %	Cohen's d	Cramer's V	p-value
Age, years	70.0 ± 8.9	71.2 ± 9.3	0.13	---	0.370
Sex, male	97.8	97.7	---	0.01	>0.999
Race			---	0.20	0.024
African American	32.3	49.4			
Caucasian	65.6	50.6			
Other/Unknown	2.2	---			
Current smoker	54.3	54.0	---	<0.01	0.965
BMI	26.6 ± 5.8	25.7 ± 5.2	0.15	---	0.317
Hemoglobin A1c, %	7.6 ± 1.8	7.1 ± 1.6	0.31	---	0.043
Creatinine, mg/dL	1.1 ± 0.7	1.4 ± 1.1	0.33	---	0.029
Cancer treatment					
Surgery	48.4	40.2	---	0.08	0.271
Chemotherapy	47.3	42.5	---	0.05	0.519
Radiation (XRT)	40.9	47.1	---	0.06	0.397
Age at diagnosis, years	66.6 ± 8.7	69.4 ± 9.5	0.32	---	0.035
Age at death, years	69.4 ± 8.8	71.3 ± 9.7	0.20	---	0.228
Years with lung cancer	1.5 ± 1.6	1.2 ± 1.1	0.19	---	0.215
Years in remission	2.3 ± 4.1	1.1 ± 2.0	0.39	---	0.008

Note: *p*-values from independent samples *t*-tests or chi-squared tests, as appropriate.

Table 4
Outcome comparisons of lung cancer patients taking metformin (n = 93) versus those not taking metformin (n = 87)

Variable	Metformin M $\pm$ SD or %	Non-Metformin M $\pm$ SD or %	Cohen's <i>d</i>	Cramer's <i>V</i>	<i>p</i> -value
Still living	24.7	16.1	---	0.11	0.152
Overall survival, years ^a	3.4 $\pm$ 3.9	1.8 $\pm$ 2.0	0.52	---	<0.001
5-year survival ^b	29.0	14.9	---	0.17	0.023
Cancer outcomes					
Recurrence	20.4	20.7	---	<0.01	0.966
Metastasis	54.8	50.8	---	0.07	0.325
Secondary cancer	30.1	33.3	---	0.04	0.642

Note: *p*-values from independent samples *t*-tests or chi-squared tests, as appropriate.

^aYears survived after cancer diagnosis

^bPatients who survived at least 5 years after cancer diagnosis