Full Length Research Article

NEOPLASTIC DISORDERS AT PATIENTS WITH DIABETES MELLITUS TYPE 2: PREVALENCE AND CORRELATION WITH THE ANTIHYPERGLICEMIC THERAPY

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ABSTRACT

Background and aims: Recent estimations show us an important increase of the neoplastic disorders, especially in developed countries, cancer being the second cause of mortality after cardiovascular diseases. Diabetes mellitus type 2 is associated with an increased risk of neoplastic diseases (especially colorectal cancer, breast cancer, pancreatic cancer). The factors involved in the increase of this risk at patient with diabetes mellitus type 2 are hyperglycemia, hyperinsulinemia and high levels of the hormone insulin-like growth factor 1 (IGF-1). The main purpose of this study was to assess the prevalence of neoplastic diseases at patients with diabetes mellitus type 2, and to investigate the the effect of the antihyperglicemic therapy on different types of neoplasm.
Material and method: The study included 3094 patients with diabetes mellitus type 2, treated at the Center of Diabetes Timişoara, between 2013-2015. Data was collected related to a series of clinic and biologic parameters, to the presence and history of neoplastic diseases, as well as to the antidiabetic therapy that was used.
Results: The prevalence of neoplastic diseases in the group included in the study was of 3,5%, 109 patients having a form of cancer. Neoplasm prevalence was higher at patients that had taken insulin treatment, whereas the subgroup treated with sulfonylurea derivatives had a neoplasm prevalence twice as high as compared to the group that had undergone metformin monotherapy.
Conclusion: The prevalence of neoplastic disorders was 1,5 higher at patients with diabetes mellitus type 2 as compared to the general population of Timiş county, the conclusion being the existence of some correlations between neoplastic disorder and age, weight status and the duration of the evolution of diabetes mellitus.

INTRODUCTION

Diabetes mellitus (DM) and different types of neoplasm are chronic diseases, potentially fatal and extremely complex. All over the world, cancer is the second cause of death, whereas mortality due to DM ranks 7th. DM prevalence in the world is continuously increasing, from 171 million people with DM in 2000 at 382 million in 2013 and shall reach to 590 million in the following 25 years. The most recent estimation of IDF (International Diabetes Federation) indicates a DM worldwide prevalence of 8,3% among adults.

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It seems that patients suffering from DM have a higher risk of developing different types of neoplasm as compared to general population (Xu *et al*., 2014 and Garg, 2014). A questions rises naturally – whether the link between DM and cancer is caused by some common risk factors, unmodifiable (age, gender, race, ethnic group), or by modifiable factors (obesity, exercise, diet, alcohol consumption, smoking), or if perhaps DM and its characteristic metabolic modifications (hyperglycemia, hyperinsulinemia, resistance to insulin) increase the risk of different types of cancer (Noto *et al*., 2013 and Leroith *et al*., 2008). Since insulin is produced by the β pancreatic cell and afterwards transported through the portal vein to the liver, then both liver and pancreas are exposed to high levels of endogenous insulin. On the other hand, hepatic steatosis, non-alcoholic steatohepatises and cirrhosis can also increase susceptibility for hepatic cancer at people with DM type 2.

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There is also a strong association between different disorders of the glucidic metabolism and pancreatic neoplasm (Giovannucci *et al*., 2010 and Hense, 2011). Carcinogenesis is a complex process. Normally, cells undergo a series of modifications during the process of malignant transformation. DM can influence this process of neoplazic transformation through a series of mechanisms: hyperinsulinemia (either endogenous due to insulinresistance, or exogenous through the exogenous administration of insulin of sulfonylurea products), hyperglycemia and chronic inflammation (Vigneri, 2009). Besides the direct effects of insulin on the cancerous cells it is possible that hyperinsulinemia might generate carcinogenesis indirectly, through its effects on the insulin-like growth factor (IGF-I) (Schoen, 2005). Insulin and IGF factors form a complex network of surface cell receptors. Homodimers and heterodimers of the insulin receptors, as well as IGF, on the cell surface, mediate the insulin and IGF response. Isoform A can stimulate the *insulin-mediated mitogenesis*, even in the cells that are lacking IGF-I receptors. Besides, apart from its metabolic functions, insulin receptors are able to stimulate the proliferation of cancerous cells and the appearance of metastasis.

Since the glucose intake by cancerous cells is done in high quantities in a manner dependent to the connection to the insulin receptor, the effects of the activation of the insulin receptor are rather linked to the cell survival and mitogenesis than to the increased glucose intake (Schoen, 2012). The increase of the circulating insulin level has a series of indirect effects, among which we may find the decrease of liver production and of the blood levels of the gender-hormone binding globulin, thus increasing the level of estrogen both at women and at men, as well as testosterone at women but not at men (Le, 2012). The ovarian androgen synthesis and possible the one existing at the level of suprarenal glands is increased by the hyperinsulinemia in the case of women at pre-menopause (Pinheiro, 2005). The increased endogenous levels of sexual hormones are associated with a high risk of breast cancer, endometrial cancer and possibly other types of cancer at women, during post-menopause (Eliassen, 2006 and La Vecchia *et al*., 2011). Due to the molecular heterogeneity of different types of cancer, the hypothesis through which hyperglycemia favors the increase of tumoral subsets remains valid, and adequate anti-diabetic therapy limits the increase of cancerous cells.

The adipose tissue is an active endocrine organ that produces free bile acids, interleukin 6 (IL-6), chemotactic proteins for monocytes, plasminogen activator inhibitor -1 (PAI-1), adiponectin, leptin, tumor growth factor (Robertson *et al*., 2007). Each of them can play an etiologic role in the malign transformation process or in cancer progress. For example, through PAI-1, the plasminogen system is correlated with the unfavorable prognostic of breast cancer, the activation of the encoding signal and of protein transcription via cytokines (IL-6) increase proliferation, survival and invasion of cancerous cells and decreases the antitumor immunity of the host (Orgel, 2013 and Federico *et al*., 2007). The main objective of this study was to assess the prevalence of neoplastic disorders at patients with DM type 2, as well as to establish the possible correlations between the studied parameters (age, weight status, DM evolution duration, cardiovascular risk) and neoplastic disorders. Besides, we have also investigated the relationship between the used antihyperglicemic therapy and the types of neoplastic disorders in the study group.

MATERIALS AND METHODS

Study description

Our study included 3094 patients with DM type 2 treated through the Center for Diabetes Timișoara, during 2013-2015: 1723 women (55,7%) and 1371 men (44,3%), mean age 66,2 ± 10 (41-82) years and mean evolution duration of DM of 10,6 ± 5,7 (1-29) years.

Studied parameters

The following parameters have been evaluated: gender, age (years), weight status: body mass index (BMI - BMI), expressed in kg/m^2, circumference of the abdomen (CA) expressed in cm. In addition, we have collected data related to alcohol consumption, smoking, presence of arterial hypertension (AHT), type of the antihyperglicemic therapy.
The lipid profile of the patients included in study was also determined: CT (mg/dl), HDLc (mg/dl), TG (mg/dl), LDLc (mg/dl).

The quality of the glycemic control was quantified through the value of HbA1c (%).

Statistical analysis

Data were collected and analyzed using SPSS v.17 software suite (SPSS Inc. Chicago, IL, USA) and are presented as mean ± standard deviations (for continuous variables with Gaussian distribution), or percentages (categorical variables). In order to assess the significance of the differences between groups, t-student (means, Gaussian populations), Mann-Whitney U (not-Gaussian populations), and chi-square with Yates correction (proportions) tests were used. Continuous variable distributions were tested for normality using Shapiro-Wilk test and for equality of variances, with Levene's test. A p value <0.05 was considered the threshold for statistical significance.

RESULTS

By analyzing the prevalence of neoplastic disorders in the group included in our study, we have seen it was of 3,5%, as 109 of the patients included in the study had a certain form of cancer (Figure 1).
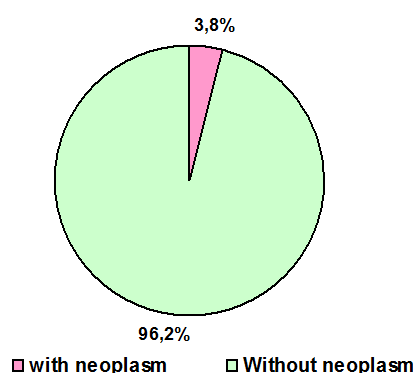

Figure 1. Prevalence of neoplastic disorders at patients with DM type 2

As per genders, we have seen a higher cancer prevalence in the case of women: 3,8% and 3,2% men respectively (p=0,102) (Figure 2).
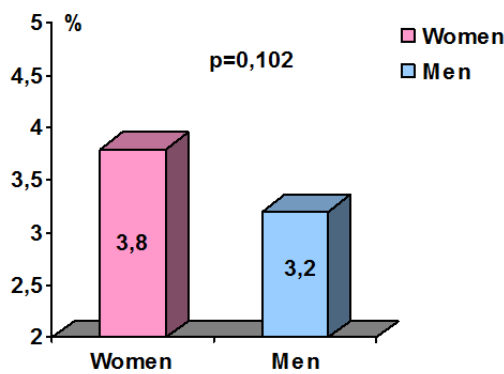
Figure 2. Prevalence of neoplastic disorders, per genders, in the studied group

By analyzing the type of cancer, we found that 52 patients (1,7%) were diagnosed with breast cancer, 31 patients (1%) with colorectal cancer, 14 patients (0,4%) with Hodgkin and Non-hodgkin lymphoma and 12 patients (0,4%) with other types of cancer (pulmonary, urinary bladder, scuamocelular epithelium).

% (p<0.01). Patients were also subdivided based on the type of antihyperglicemic therapy they were undergoing, as follows: those with non-insulin treatment, insulin and oral antidiabetic drugs in association and those treated only with insulin. Table 2 shows cancer prevalence, based on the antihyperglicemic treatment. In the studied group, the prevalence of neoplastic disorders has been higher at patients treated with insulin, and the sub-group treated with SU had a neoplasm prevalence twice as high as compared with the sub-group treated with metformin in monotherapy (Table 2).

DISCUSSIONS

The presence of DM creates an environment that is favorable for the development of cancerous cells and the potential favoring factors of this process are: hyperglicemia, the increase of the production of reactive oxygen species (ROS), the creation of advanced glycation end products (AGE) and their interaction with RAGE receptors, hypoactivation of the *Phosphoinositide 3-kinase/protein kinase B* axis. In the presence of this micro-climate precancerous cells trigger the mechanisms involved in their malignant transformation, based

Table 1. Characteristics of patients with DM type 2 with and without neoplasm

Parameter	With neoplasm	Without neoplasm	p
Mean age (years)	68,9±11,7	63,5±9,2	p<0,001
Mean BMI (kg/m^2)	33,7±5,2	31,2±4,7	p<0,001
Mean duration of DM (years)	11,6±5,7	9,6± 4,9	p<0,001
CA men (cm)	112,6±12,8	104,6±10,4	p<0,01
CA women (cm)	105,6±11,6	99,2±9,8	p<0,001
HbA1c (%)	8,3±1,4	7,9±1,1	p<0,01
CT (mg/dl)	229,5±49,2	227,0±49,4	p=0,72
HDLc (mg/dl)	44,5±10,0	47,5±11,4	p=0,07
LDLc (mg/dl)	143,7±37,2	140,7±34,4	p=0,55
TG (mg/dl)	206,5±69,7	193,9±64,3	p=0,18

Table 2. Prevalence of neoplastic disorders in relation with the used antihyperglycemic therapy

Treatment	Prevalence of neoplasm	p	Treatment	Prevalence of neoplasm	p
Non-insulin	3,4%	0.030*	Met in monotherapy	3,9%	0.008*
			Met + SU	2.2%	
			Met + SU + incretins	6,7%	
			SU	8.1%	
			SU + incretins	5.8%	
			Met + TZD (n=2)!	50%	
Oral+insulin	1,5%		Insulin + Met	1.3%	0.691
			Insulin + SU	0%	
			Insulin + Met + SU	2,8%	
Only insulin	5,6%				

* Differences are significant at α=0.05 treshold
MET= Metformin; SU= Sulphonylureas; TZD= Thiazolidinediones

The patients included in the study have been divided into two sub-groups: with and without neoplasm, thus performing a comparison between the main characteristics of the two sub-groups. The main characteristics that we have researched are presented in Table 1. Mean age of patients with neoplasm has been significantly higher as compared to those without neoplasm: 68.9±11.7 years versus 63.5±9.2 years (p<0.0001). Besides, such statistically significant differences were also observed between the mean values of the CA: 112.6±12.8 cm at men with neoplasm, as compared to 104.6±10.4 cm at those without neoplasm (p<0.01); 105.6 ± 11.6 cm at women with neoplasm, and 99.2 ± 9.8 cm at women without neoplasm (p<0.0006). As for the quality of glycemic control, it has been observed that the value of HbA1c was statistically significant higher at the group with neoplastic disorder 8.3 ± 11.4 %, as compared to the group without neoplastic disorders 7.9 ± 1.1

on their characteristic proprieties: increase of glycemia and of the gycolytic activity with the release of lactic acid (Warburg effect), decrease of the mitochondrial activity and oxidative phosphorylation, reduction of energy losses and acceleration of the phospholipid turnover. The results of multiple meta-analysis have been published until now, demonstrating that some forms of cancer develop more frequently at patients with DM. An international study which included data from 6 European countries and included a 549.944 people in total, 49% men, mean age upon study start of 45 years – they have been tracked for a period of 11,3 years. This study has shown that an increase of the fasting glycemia by 1 mmol/l is followed by an RR of 1,05 at men and of 1,11 at women as related to cancer incidence (Stocks, 2009). Another study conducted in Korea during a period of 10 years which included

1.298.385 patients, 64% men, has shown a significant increase of the incidence of all types of cancer at patients with DM: 1,24 (95%, CI; 1,20-1,28) at men and 1,33 (1,25-1.41) at women (Stocks, 2009). There is an obvious association between DM and colorectal cancer, Berster and Goke concluding that the risk of neoplasm at patients with DM is 30-40% higher, the smallest risk being at patients with a HbA1c value lower than 5%; for each 1% increase of the HbA1c, this risk increases by 34% (Berster, 2008). A meta-analysis which included 24 studies (8 control cases and 16 cohorts) has demonstrated the direct connection between the risk of colorectal cancer (the most frequent type of cancer of the digestive tract in modern society) and DM, with a RR of 1,26 (95% CI; 1,20-1,31), and this risk increases directly proportional with the duration of evolution of DM (18,19,20). A cohort study conducted in Germany, which included 742 people, has shown the inverse relation between the duration of evolution of DM and the risk of neoplasm (Hense *et al*., 2011).

Data from two large retrospective studies conducted in Belgium (4012 patients with DM type 2) and China (7950 patients with DM type 2) have demonstrated that hyperglicemia and DM significantly increase the risk of neoplasm (Geraldine, 2012 and Zhang *et al*., 2012), Moreover, it seems that the increase of the levels of IGF-1, hyperinsulinemia and the increase of HbA1c over 7,5% is associated with the increased occurrence of adenomatous polyps at young ages, (Schoen *et al*., 2005 and Siddiqui *et al*., 2008). Slow intestinal transit and constipation, very frequent at diabetic patients, determine a longer exposure of the colic mucous membrane to different toxins and carcinogens (Larsson *et al*., 2005). A study conducted in Italy has shown that diabetic women with the age of over 40 years have a risk 3 times higher for endometrial cancer as compared to women without DM and this risk increases when it is associated with obesity and sedentarity, (Friberg *et al*., 2007). It has been found that the risk of breast cancer is correlated with the level of hyperinsulinism, evaluated through the values of C peptide: women with higher values of the C peptide have a higher risk of breast cancer as compared with women with lower values of this peptide.

More and more clinic and epidemiological studies have demonstrated the link between DM and the increase of the pancreas risk, the relationship between the two disorders being extremely complex, since we are talking about a so-called „causality" relationship (Brodovicz, 2012). Numerous pharmaceutical agents used in the treatment of DM type 2 intervene in the carcinogenesis process after a different exposure period (Dankner *et al*., 2012). The protective role of metformin has been proven towards the increased risk that the insulin of sulphonylurea therapies have on the risk of cancer (Gallagher, 2011). Metformin reduces glycemia and hyperinsulinemia at patients with resistance to insulin, especially through the reduction of the production of glucose by the liver; it induces apoptosis and the activation of the metabolic pathways (proteinkinase AMP that activates LKB1/AMP); it inhibates cellular proliferation, thus reducing the creation of colonies with the partial blocking of the cellular cycle in the lines of cancerous cells; it reduces the production of ROS, thus blocking mutagenesis in somatic cells (Rocha, 2011). Besides, the metformin therapy improves the results of chemotherapy at patients with breast or pulmonary cancer, being considered as an independent survival factor at patients with colorectal cancer, (Lee *et al*., 2012). Besides, it amplifies

the anticancer effects (blocks tumor growth, prolongs remission, induces a complete response) of some agents of chemotherapy such as doxorubicin and paclitaxel (Hirsch *et al*., 2009 and Rocha *et al*., 2011). Some observational studies have revealed an increased risk of cancer at patients treated with sulfonylurea derivatives, yet it seems that the gliclazide therapy determines a lower risk due to the reduction of oxidative stress (Bowker *et al*., 2006). Insulin treatment determines a significant, exaggerated increase of circulating insulin as compared to endogenous insulin, thus amplifying the link between hyperinsulinemia and the risk of cancer (Currie, 2009). A series of epidemiological studies have analyzed the potential connection between the use of insulin and insulin analogs and the risk of neoplasm (Janghorbani, 2012). Data from a randomized clinical trial, conducted over a period of 5 years, glargine versus NPH, has not indicated a higher risk of cancer due to any localization of glargine insulin (Hekens, 2009).

Conclusions

The prevalence of neoplastic diseases was of 3,5% at the patients included in the study, 1,5 times higher as compared to the general population of Timiş counties. By genders, we have determined a higher prevalence in the case of women as compared to men. The following limitations of the study were identified: not having included all patients with cu DM type 2 registered at the Center of Diabetes Timişoara, a low number of cases which, according to the estimations of the study group, could lead to a β type error, and the neoplasm diagnosis was determined by consulting the county's register of oncology. We have determined a higher prevalence of neoplasm at patients with DM type 2 that underwent insulin treatment, this fact was probably influenced by other factors as well, such as: age of the patients, longer duration of evolution of DM, the presence of overweight and obesity. Patients treated with sulfonylurea derivatives had a prevalence of neoplastic disorders twice as high as compared to patients treated with metformin in monotherapy.

Competing Interest: The authors declare that they have no competing interests

Author's Contribution

OANA ALBAI- conceived of the study, and participated in its design and coordination and helped to draft the manuscript, participated in the sequence alignment.

ROMULUS TIMAR- participated in the sequence alignment. All authors read and approved the final manuscript.

REFERENCES

Berster, J.M., Goke, B. 2008. Type 2 diabetes mellitus as risk factor for colorectal cancer. *Arch. Physiol. Biochem*, 114, 84–98

Bowker, S.L., Majumdar, S.R., Veugelers P, and Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. Diabetes Care, 2006; 29:2, 254–258.

Brodovicz G, Kou TD, Alexander CM, *et al*. Impact of diabetes duration and chronic pancreatitis on the association between type 2 diabetes and pancreatic cancer

risk. Diabetes, Obesity & Metabolism, 2012; 14:12, 1123–1128.

Currie CJ, Poole CD, Gale EAM. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia, 2009; 52:9, 1766–1777.

Dankner R, Balicer R, Boffetta P, *et al*. Diabetes, glucose control, glucose lowering medications, and cancer risk: a 10-year population-based historical cohort. BMC Cancer. 2012; 12: 364.

Deng L, Gui Z, Zhao L, Wang J, and Shen L. Diabetes mellitus and the incidence of colorectal cancer: an updated systematic review and meta-analysis. Digestive Diseases and Sciences, 2012; 57:6, 1576–1585.

Eliassen H, Colditz GA, Rosner B, Willett WC, and Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. *The Journal of the American Medical Association,* 2006; 296:2, 193–201.

Federico A, Morgillo F, Tuccillo C, Ciardiello F, and Loguercio C. Chronic inflammation and oxidative stress in human carcinogenesis. *International Journal of Cancer*, 2007; 121:11, 2381–2386.

Friberg E, Mantzoros CS, Wolk A. Diabetes and Risk of Endometrial Cancer: A Population-Based Prospective Cohort Study. Cancer Epidemiol Biomarkers Prev, 2007; 16: 276-280.

Gallagher EJ and LeRoith D. Diabetes, cancer, and metformin: connections of metabolism and cell proliferation. Annals of the New York Academy of Sciences, 2011; 1243: 54–68.

Garg SK, Maurer H, Reed K, Selagamsetty R. Diabetes and cancer: two diseases with obesity as a common risk factor. Diabetes Obes Metab. 2014; 16: 97–110.

Geraldine N, Marc A, Carla T, *et al*. Relation between diabetes, metformin treatment and the occurrence of malignancies in a Belgian primary care setting. Diabetes Research and Clinical Practice, 2012; 97:2, 331–336.

Giovannucci E, Harlan DM, Archer MC, *et al*. Diabetes and cancer: a consensus report. Diabetes Care. 2010; 33: 1674–1685.

Hekens LG, Grouven U, Bender R, *et al*. Risk of malignancies in patients with diabetes treated with human ibsulin or insulin analogues: a cohort study. Diabetologia, 2009; 52: 1732-1744.

Hense HW, Kajuter H, Wellmann J, and Batzler WU. Cancer incidence in type 2 diabetes patients—first results from a feasibility study of the D2C cohort. Diabetology & Metabolic Syndrome, 2011; 3:15.

Hense HW, Kajuter H, Wellmann J, and Batzler WU. Cancer incidence in type 2 diabetes patients—first results from a feasibility study of the D2C cohort, Diabetology & Metabolic Syndrome, 2011; 3:15.

Hirsch HA, Iliopoulos D, Tsichlis PN, and Struhl K. Metformin selectively targets cancer stem cells, and acts together with chemotherapy to block tumor growth and prolong remission. *Cancer Research*, 2009; 69:19, 7507–7511.

Janghorbani M, Dehghani M, and Salehi-Marzijarani M. Systematic review and meta-analysis of insulin therapy and risk of cancer. *Hormones & Cancer*, 2012; 3:4 137–146.

Jutta MB, Burkhard G. Type2 diabtes mellitus as risk factor for colorectal cancer. Archives of Physiology and Biochemistry, 2008; 114: 84-98.

La Vecchia C, Giordano SH, Hortobagyi GN, and Chabner B. Overweight, obesity, diabetes, and risk of breast cancer: interlocking pieces of the puzzle. *Oncologist,* 2011; 16;6, 726–729.

Larsson SC, Orsini N, and Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *Journal of the National Cancer Institute,* 2005; 97:22, 1679–1687.

Le N, Nestler JE, Strauss JF, and Wickham EP. gender hormone-binding globulin and type 2 diabetes mellitus. Trends in Endocrinology and Metabolism, 2012; 23:1, 32–40.

Lee JH, Kim II T, Jeon SM, Hong SP, Cheon JH, and Kim WH. The effects of metformin on the survival of colorectal cancer patients with diabetes mellitus. International Journal of Cancer, 2012; 131:3, 752–759

Leroith D, Novosyadlyy R, Gallagher EJ, *et al*. Obesity and Type 2 diabetes are associated with an increased risk of developing cancer and a worse prognosis; epidemiological and mechanistic evidence. Experimental and Clinical Endocrinology & Diabetes, 2008; 116; 1, S4–S6.

Noto H, Goto A, Tsujimoto T, Osame K, Noda M. Latest insights into the risk of cancer in diabetes. J Diabetes Investig. 2013; 4: 225–232.

Orgel E, Mittelman SD. The links between insulin resistance, diabetes, and cancer. Curr Diab Rep. 2013; 13: 213–222.

Pinheiro SP, Holmes MD, Pollak MN, Barbieri RL, Hankinson SE. Racial differences in premenopausal endogenous hormones. *Cancer Epidemiol Biomarkers Prev* 2005; 14*:* 2147–2153

Robertson R, Zhou H, Zhang T, and Harmon JS. Chronic oxidative stress as a mechanism for glucose toxicity of the beta cell in type 2 diabetes. Cell Biochemistry and Biophysics, 2007; 48:2-3, 139–146.

Rocha GZ, Dias MM, Ropelle ER, *et al*. Metformin amplifies chemotherapy-induced AMPK activation and antitumoral growth. *Clinical Cancer Research*, 2011; 17:12, 3993–4005.

Rocha GZ, Dias MM, Ropelle ER, *et al*. Metformin amplifies chemotherapy-induced AMPK activation and antitumoral growth. Clinical Cancer Research, 2011; 17:12, 3993–4005.

Saydah H, Platz EA, Rifai N, MN Pollak, Brancati FL, and Helzlsouer KJ, Association of markers of insulin and glucose control with subsequent colorectal cancer risk. Cancer Epidemiology Biomarkers & Prevention, 2003; 12:5, 412–418.

Schoen RE, Weissfeld JL, Kuller LH *et al*. Insulin-like growth factor-I and insulin are associated with the presence and advancement of adenomatous polyps. Gastroenterology, 2005; 129:2, 464–475.

Schoen RE, Weissfeld JL, Kuller LH *et al*. Insulin-like growth factor-I and insulin are associated with the presence and advancement of adenomatous polyps. *Gastroenterology,* 2005; 129:2, 464–475.

Siddiqui AA, Maddur H, Naik S, Cryer B. The association of elevated HbA1c on the behavior of adenomatous polyps in patients with type-II diabetes mellitus. *Digestive Diseases and Sciences*, 2008; 53:4, 1042–1047.

Stocks T, Rapp K, Bjørge 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 Medicine, 2009; 6:12, DOI: 10.1371/journal.pmed.1000201

Tan BX, Yao WX, Ge J, *et al*. Prognostic influence of metformin as first-line chemotherapy for advanced nonsmall cell lung cancer in patients with type 2 diabetes. Cancer, 2011; 117:22, 5103–5111.

Vigneri P, Frasca F, Sciacca L *et al*. Diabetes and cancer. *Endocr Relat Cancer*. 2009; 16: 1103–1123.

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Prevalence and correlation with the antihyperglicemic Therapy

Xu CX, Zhu HH, Zhu YM. Diabetes and cancer: Associations, mechanisms, and implications for medical practice. *World J Diabetes.* 2014; 5:3 72–380.

Zhang PH, Chen ZW, Lv D, *et al*. Increased risk of cancer in patients with type 2 diabetes mellitus: a retrospective cohort study in China. *BMC Public Health*, 2012; 12: 567.

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