RJDNMD, **18**(4):347-354 *http://www.jrdiabet.ro*

THE LINK BETWEEN DIABETES, DIABETES TREATMENT AND CANCER

Laurenţiu Ene [1], ***Oana Alexandru*** [1,2], ***Raluca Budiu*** [3], ***Ada Maria Georgescu*** [4], ***Anica Dricu*** [2, ✉]

[1] Clinical Hospital of Neuropsychiatry Craiova, Dep. of Neurology
[2] University of Medicine and Pharmacy, Craiova, Romania
[3] Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine and Magee Women's Research Institute, Pittsburgh, PA 15213, USA
[4] University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania

received: September 09, 2011 *accepted*: November 11, 2011

available online: December 15, 2011

Abstract

Diabetes mellitus (DM) and cancer are serious diseases, representing a great social burden worldwide and their association has been studied over the years. Several risk factors are common to both DM and cancer and results of epidemiological studies suggest that DM is linked to cancer incidence. However, several types of cancer (e.g. liver, pancreas, endometrial) are more frequent in type 2 DM patients while other neoplasm's (e.g. breast, colon, rectum, kidney or bladder) represent a smaller risk. Several in vivo *and* in vitro *studies indicate that some anti-diabetic drugs, like insulin analogs, potentate tumor genesis. However, the results of the most of these studies are still under discussion. Some authors suggest that insulin therapy may increase risk for cancer, this phenomenon being mediated by IGF-1R signaling. A mild increase of cancer risk and mortality in DM (mostly type 2) patients has also been suggested. In this review we aim to summarize the current data concerning the association between DM and cancer.*

key words*: cancer, diabetes, insulin, insulin-like growth factor*

Introduction

The association between cancer and DM has been the subject of debate for many years. Both cancer and DM are serious diseases, representing a great social burden worldwide.

Over the years, scientists conducted many epidemiological studies of which results are still under discussion. However most of the authors consider that there is a mild increase of cancer risk and mortality in diabetic (mostly type 2) patients [1, 2].

Several types of cancer like liver [3], pancreas [4] or endometrial [5] are more frequent in diabetic patients. The same category of patients have a smaller risk of developing other cancers like breast [6], colon [7], rectum [8], kidney [9] or bladder [10]. It

✉ Petru Rares street, No2, 200349, Craiova, Romania;
corresponding author e-mail: anicadricu@webmail.umfcv.ro, anica.dricu@live.co.uk

was also observed that in diabetic men, the incidence of prostate cancer is reduced [11].

The high incidence of hepato cellular carcinoma in type 2 diabetic patients might be explained by the increased insulin concentrations in the liver cells, due to the portal circulation. It is already known that these patients have insulin resistance and hyper insulinemia. The mechanism is not present in type 1 DM which makes it nonspecific. Therefore, it is possible that DM related factors like steatosis, cirrhosis or nonalcoholic fatty liver disease are involved in liver carcinogenesis. The neoplastic process in the liver might also be favored by viral infections with hepatitis B or C viruses [3, 12, 13].

The association between DM and pancreatic cancer is complicate. It is known that both hyperglycemia and DM are consequences of pancreatic cancer. Therefore, in the epidemiological studies were enrolled only patients diagnosed with DM at least 5 years prior to pancreatic cancer diagnosis. The biological mechanisms involved are not yet much elucidated. One possible cause may also be hyperinsulinemia. The mechanism is not explained in diabetic patients treated with insulin [14, 15].

Common risk factors for diabetes and cancer

Most of the reported common risk factors for DM and cancer are divided into two classes: modifiable and unmodifiable (Figure 1).

Between the unmodifiable risk factors are: age (both diabetes and cancer became more frequent with age), sex (men are more exposed to both cancer and diabetes than women), and race (african americans are at higher risk for developing cancer, and have higher risk of DM than hispanics, non-hispanic whites, native americans and asian americans) [8, 11].

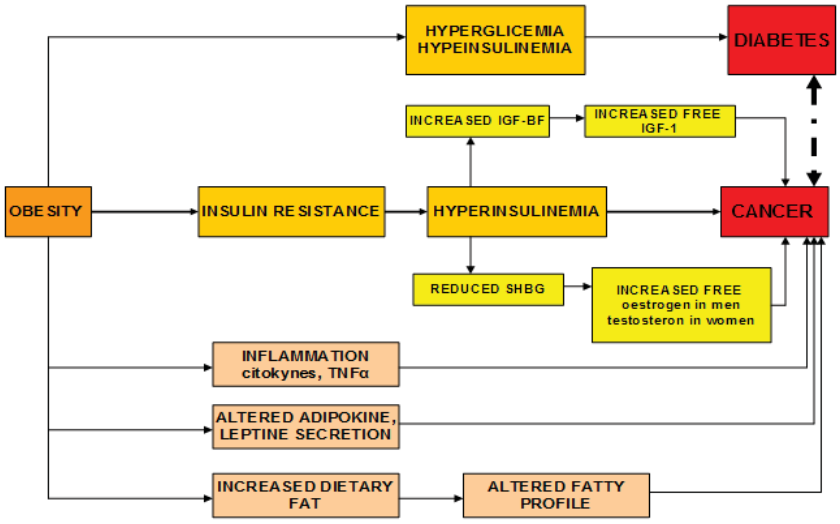

Figure 1. Common risk and pathogenic factors between diabetes and cancer.

The most common modifiable risk factors are: overweight, obesity and weight change, diet, alcohol consumption, tobacco smoking and physical activity.

Several studies have shown that obesity is a common factor for diseases like DM and cancer. The association between obesity and a higher incidence of type 2 DM has also been reported. It is also well known that weight loss

decreases DM incidence. Similar to type 2 DM, there are several types of cancer associated with overweight or obesity: breast, colo-rectal cancer, endometrial, liver, pancreas and gallbladder. A diet based on fruits, vegetables, hole graines and low in processed meats and red meats may be protective against both cancer and type 2 diabetes [16, 17, 18, 19].

Moderate alcohol consumption reduces DM incidence but increases the risk of cancer [20]. Tobacco smoking is also a risk factor for many types of cancer and for DM [21]. Physical activity reduces the risk of developing type 2 DM, and is associated with lower risk of developing cancer or improving survival of patients with cancer.

The neoplastic process may be determined by mechanisms like hyperinsulinemia, hyperglycemia or chronic inflammation [1].

Insulin along with IGF-1 and IGF-2 are ligands which belong to the IGF system. The IGF family is a complex system involved in the processes of proliferation, apoptosis and transformation of the cells. Besides the 3 ligands, this system has 3 receptors which are associated with the ligands (IR, IGF-1R and IGF-2R) and 6 binding proteins (IGFPB 1-6) [22].

The insulin ligand is mostly involved in cellular metabolism and glucose regulation. The endogenous insulin is produced by the β-pancreatic cells and after the synthesis, the protein reaches the liver cells by portal vessels. Here, most of insulin is retained and degraded. Only 1/10 up to 1/3 of endogenous insulin received by the liver will arrive to the peripheral tissues [23].

Type 1 DM is characterized by the autoimmune destruction of the β-pancreatic cells, which leads to lack of endogenous secretion of the insulin, which, in turn, leads to increased level of glucose in blood and urine. In consequence, these patients need exogenous insulin from the very beginning [1].

Type 2 DM patients have hyperglycemia which is associated with hypeinsulinemia (caused by insulin resistance).

The 2 type DM patients are not dependent on exogenous insulin in the first stage of the disease. However, with the disease progresses, the patients require a combination of multiple oral agents and finally exogenous insulin requires to regulate the level of the glucose [1].

Epigenetic changes in the IGF receptors family are not only involved in cancer progression and staging but in metabolic diseases also, including type 2 DM. The most common symptoms associated with type 2 DM include insulin resistance and obesity and the patients often develop chronic complications including neuropathy, nephropathy and retinopathy [24]. Using genetically alerted mice, it has been shown that genetic changes in insulin receptor (IR) or IGF1R are fallowed by impaired insulin signaling and decreased insulin dependent glucose transport [25]. Nikoshkov et al., 2011 [26], evaluated the epigenetic methylation in the promoters of both IR and IGF1R genes in diabetic db/db mice versus control mice [26]. Their main finding was that the methylation level is increased in the *IGF1R* but not in the *IR* promoter [26]. This increase was seen only in the skeletal muscle and with a higher frequency in the male db/db mice versus females [26]. The sex related differences can be explained by the fact that estrogen receptor (ER) signaling can regulate *IGF1R* gene expression through the binging of ER-Sp1

complex to the *IGF1R* promoter. The authors suggested that the binding of ER-Sp1 complex to the *IGF1R* promoter in female mice, may protect Sp1 binding sites from methylation [26].

The insulin receptor (IR) is a tyrosine-kinase receptor, mostly expressed in liver cells, muscles and adipocites. IR has 2 isoformes: IR-A and IR-B. An increased expression of IR was observed in various neoplasms like: breast, thyroid or miosarcomas [27].

Insulin binding by it's receptor, normally determines several metabolic effects (glucose uptake and the inhibition of gluconeogenesis in the liver) through the activation of PI-3 kinase pathway [23]. In hyperinsulinemic subjects, these metabolic effects of insulin are attenuated. IRS-1 phosphorylation to serine 312 leads to the inhibition of PI3 kinase recruitement. In addition, high level of IRS-2 induces an increase in RAF-1 expression which in turn leads to ERK overactivation. Therefore, in contrast to the attenuation of the metabolic effects, an overactivation of the mitogenic effects of insulin is observed. in hyperinsulinemic patients [28, 1].

Hyperinsulinemia also determines an increase of estrogen bioavailability in men and women and an increase of testosterone bioavailability in women. Also, the androgen synthesis in ovary and adrenal glands is increased. The elevated levels of endogenously secreted sex steroids are associated with higher risk of postmenopausal breast and endometrial cancer [17, 29].

Hyperglycemia is another potential mediator of the neoplastic transformation. Several studies have found many correlations between glucose level and the neoplastic transformation of the cells [30].

A series of factors secreted by the adipose tissue, such as: free fatty acids, cytokines, adiponectin, leptin, tumor necrosis factor-alpha or monocyte chemo attractant protein or plasminogen activator inhibitor-1, might also play a role in the malignant transformation, neoplastic progression, insulin resistance and DM [17, 31, 32].

It is also known that oxidative stress determines a proinflammatory condition that reduces the anti-oxidant capacity of the cells, making them vulnerable to malignant transformation. DM was demonstrated to determine metabolic transformations that increase oxidative stress [33].

Diabetes therapy and cancer

Ninety percent of all diabetic patients are diagnosed with type 2 DM. These patients are mainly treated with oral medication, but, 40-80% of them will receive insulin therapy during their lifetime. The rest are patients with type 1 DM, treated with insulin from the time of diagnostic [34, 35].

The insulin used to treat diabetic patients exists in several formulations like: human insulin (short-acting and intermediate-acting) or analogs of human insulin –synthetic insulin (rapid-acting and long-acting). Both types of insulin are administrated subcutaneous. The difference between human and synthetic insulin resides in their time of action (which is longer in the case of synthetic insulin) and their affinity to the IGF-1R, which seems to be higher in the case of insulin analogs [36]. Several *in vitro* studies performed in the last years, showed that some insulin analogs have a mitogenic potency in breast cancer and osteosarcoma. However, the current data is not conclusive. Therefore, for patients with a very high risk of cancer incidence more attention it

may be needed when choosing between various types of insulin [37-39].

Type 2 diabetic patients are treated for years with oral drugs. There are 3 major types of oral anti-diabetic drugs that are currently available: biguanides, sulphonylureas and thiazolidinediones (TZD).

The biguanides are insulin sensitizers that reduce the levels of circulating glucose and insulin in patients with type 2 DM, presenting hyperinsulinemia and insulin resistance. The most used drug from this class is metformin. Several *in vitro* and *in vivo* studies demonstrate the antineoplastic activity of the drug, but they cannot be used in patients with renal insufficiency or liver disease [40, 41, 42].

The TZDs are peroxizome proliferator-activated receptor (PPAR) gamma agonists that activate PPAR-gamma receptors and improve insulin sensitivity in the peripheral tissues. They can be used in patients with renal insufficiency. Some *in vitro* studies indicate that TZDs have an anti-neoplastic activity by activating 5′ adenosine monophosphate – activated protein kinase (AMPK). However, *in vivo* animal studies indicate that the drugs can potentiate tumor genesis. Thus, the results are controversial and there is a need for further population studies to elucidate the drug effects [43, 44].

Sulphonylureas are insulin secretagogues along with the rapid-acting insulin secretion compounds glinides. They stimulate the β-pancreatic cells to release insulin. Some observational studies reported a higher risk of cancer incidence and mortality in patients treated with these drugs [45, 46].

Cancer therapy and diabetes

Many of the patients diagnosed with cancer have DM or pre-diabetes status. It is already known that the modern anti-cancer strategies include the inhibition of the IGF system. The inhibition influences the mitogenic and the metabolic effects of the system compounds. The IGF system can be inhibited by:

– direct targeting of the IGF-1R – with monoclonal antobodies and protein kinases inhibitors;
– inhibition of IGF-1R signaling at the enzymatic level.

The IGF-1R signaling occurs *via* several pathways including: phosphatidylinositol 3-kinase (PI3K), AKT, mTOR, or cABL. All the inhibitors of these proteins increase the glucose levels, especially mTOR and cABL inhibitors. Those increse the levels of glycemia in 20% of the treated patients. Therefore, it is very important to monitorize the levels of glycemia in all patients diagnosed with cancer and treated with these agents [27, 47].

Conclusions

Many epidemiological publications, from observational studies, have suggested that type 2 DM is also associate with increased risk of cancer. This co-occurrence was found in various cancers, including liver, pancreas, endometrial, colorectal, breast and bladder.

There are also studies suggesting that degree of hyperglycaemia, and treatment modalities for this condition influence the risk of cancer. However, the evidences are not strong enough to conclude this link. To give an answer to those questions, long-term fallow-ups of hyperglycaemic treatments is

required to ensure that such therapies are or not associated with increased risk of cancer.

Understanding the mechanisms that link DM and cancer has a great clinical significance, given the fact that both are serious diseases, with life threatening complications. Because of the complex biology and heterogeneity of both diseases, more preclinical and clinical studies are required to elucidate the link between DM and cancer and to establish the cause of elevated risk of cancers in subjects with DM.

Conflict of interest: No conflict of interest.

REFERENCES

1. **Vigneri P, Frasca F, Sciacca L, Pandini G and Vigneri R.** Diabetes and cancer. *Endocr Relat Cancer*, 16(4), 1103-1123, 2009.

2. **Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL, Wolff AC and Brancati FL.** Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA*, 300(23), 2754-2764, 2008.

3. **Davila JA, Morgan RO, Shaib Y, McGlynn KA and El-Serag HB.** Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. *Gut* 54(4), 533-539, 2005.

4. **Bonovas S, Filioussi K and Tsantes A.** Diabetes mellitus and risk of prostate cancer: a meta-analysis. *Diabetologia* 47(6), 1071-1078, 2004.

5. **Folsom AR, Anderson KE, Sweeney C and Jacobs DR Jr.** Diabetes as a risk factor for death following endometrial cancer. *Gynecol Oncol* 94(3), 740-745, 2004.

6. **Lipscombe LL, Goodwin PJ, Zinman B, McLaughlin JR and Hux JE.** The impact of diabetes on survival following breast cancer. *Breast Cancer Res Treat* 109(2), 389-395, 2008.

7. **Wolpin BM, Meyerhardt JA, Chan AT, Ng K, Chan JA, Wu K, Pollak MN, Giovannucci EL and Fuchs CS.** Insulin, the insulin-like growth factor axis, and mortality in patients with nonmetastatic colorectal cancer. *J Clin Oncol* 27(2), 176-185. 2009.

8. **Jemal A, Siegel R, Ward E, Hao Y, Xu J and Thun MJ.** Cancer statistics, 2009.*CA Cancer J Clin* 59(4), 225-249.

9. **Lindblad P, Chow WH, Chan J, Bergstrom A, Wolk A, Gridley G, McLaughlin JK, Nyren O and Adami HO.** The role of diabetes mellitus in the aetiology of renal cell cancer. *Diabetologia* 42(1), 107-112, 1999.

10. **Larsson SC, Orsini N, Brismar K and Wolk A.** Diabetes mellitus and risk of bladder cancer: a meta-analysis. *Diabetologia* 49(12), 2819-2823, 2006.

11. **Nicolucci A.** Epidemiological aspects of neoplasms in diabetes. *Acta Diabetol* 47(2), 87-95.

12. **Postic C and Girard J.** The role of the lipogenic pathway in the development of hepatic steatosis. *Diabetes Metab* 34(6 Pt 2), 643-648, 2008.

13. **Chen HF, Li CY, Chen P, See TT and Lee HY.** Seroprevalence of hepatitis B and C in type 2 diabetic patients. *J Chin Med Assoc* 69(4), 146-152, 2006.

14. **Hsu C and Saif MW.** *Diabetes and Pancreatic Cancer.* Highlights from the "2011 ASCO Annual Meeting". Chicago, IL, USA; June 3-7, *JOP*, **12**(4), 330-333. 2011.

15. **Kang SP and Saif MW.** Clinical outcome of pancreatic cancer patients with diabetes mellitus: is diabetes a poor prognostic factor? Highlights from the "2010 ASCO Annual Meeting". Chicago, IL, USA. June 4-8, *JOP*, **11**(4), 334-335. 2010.

16. **Chow WH, Gridley G, Fraumeni JF, Jr and Jarvholm B.** Obesity, hypertension, and the risk of kidney cancer in men. *N Engl J Med* 343(18), 1305-1311, 2000.

17. **Cleary MP and Grossmann ME.** Minireview: Obesity and breast cancer: the estrogen connection. *Endocrinology* **150**(6), 2537-2542, 2009.

18. Pischon T, Lahmann PH, Boeing H, Friedenreich C, Norat T, Tjonneland A, Halkjaer J, Overvad K, Clavel-Chapelon F, Boutron-Ruault MC, Guernec G, Bergmann MM, Linseisen J, Becker N, Trichopoulou A, Trichopoulos D, Sieri S, Palli D, Tumino R, Vineis P, Panico S, Peeters PH, Bueno-de-Mesquita HB, Boshuizen HC, Van Guelpen B, Palmqvist R, Berglund G, Gonzalez CA, Dorronsoro M, Barricarte A, Navarro C, Martinez C, Quiros JR, Roddam A, Allen N, Bingham S, Khaw KT, Ferrari P, Kaaks R, Slimani N and Riboli E. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* 98(13), 920-931, 2006.

19. Vigneri P, Frasca F, Sciacca L, Frittitta L and Vigneri R. Obesity and cancer. *Nutr Metab Cardiovasc Dis* 16(1), 1-7, 2006.

20. Baliunas DO, Taylor BJ, Irving H, Roerecke M, Patra J, Mohapatra S and Rehm J. Alcohol as a risk factor for type 2 diabetes: A systematic review and meta-analysis. *Diabetes Care*, 32(11), 2123-2132, 2009.

21. Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L and Cogliano V. A review of human carcinogens--Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol* 10(11), 1033-1034, 2009.

22. Mardilovich K, Pankratz SL and Shaw LM. Expression and function of the insulin receptor substrate proteins in cancer. *Cell Commun Signal*, **7**, 14, 2009.

23. Ferrannini E and Cobelli C. The kinetics of insulin in man. II. Role of the liver. *Diabetes Metab Rev* 3(2), 365-397, 1987.

24. Golden SH. Emerging therapeutic approaches for the management of diabetes mellitus and macrovascular complications. *Am J Cardiol* 108(3 Suppl), 59B-67B, 2011.

25. Leroith D and Accili D. Mechanisms of disease: using genetically altered mice to study concepts of type 2 diabetes. *Nat Clin Pract Endocrinol Metab* 4(3), 164-172, 2008.

26. Nikoshkov A, Sunkari V, Savu O, Forsberg E, Catrina SB and Brismar K. Epigenetic DNA methylation in the promoters of the Igf1 receptor and insulin receptor genes in db/db mice. *Epigenetics* 6(4), 405-409, 2011.

27. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. *Nat Rev Cancer* 8(12), 915-928, 2008.

28. Corbould A, Zhao H, Mirzoeva S, Aird F and Dunaif A. Enhanced mitogenic signaling in skeletal muscle of women with polycystic ovary syndrome. *Diabetes* 55(3), 751-759, 2006.

29. Keating NL, O'Malley AJ and Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 24(27), 4448-4456, 2006.

30. Dankner R, Chetrit A and Segal P. Glucose tolerance status and 20 year cancer incidence. *Isr Med Assoc J* 9(8), 592-596, 2007.

31. Hudgins LC, Hellerstein MK, Seidman CE, Neese RA, Tremaroli JD and Hirsch J Relationship between carbohydrate-induced hypertriglyceridemia and fatty acid synthesis in lean and obese subjects. *J Lipid Res* 41(4), 595-604, 2000.

32. Kern PA, Ranganathan S, Li C, Wood L and Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. *Am J Physiol Endocrinol Metab* 280(5), E745-751, 2001.

33. Federico A, Morgillo F, Tuccillo C, Ciardiello F and Loguercio C. Chronic inflammation and oxidative stress in human carcinogenesis. *Int J Cancer* 121(11), 2381-2386. 2007.

34. Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* 58(4), 773-795, 2009.

35. Bergenstal RM, Bailey CJ and Kendall DM. Type 2 diabetes: assessing the relative risks and benefits of glucose-lowering medications. *Am J Med* 123(4), 374 e 379 -318.

36. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG and Yee D. Diabetes and cancer: a consensus report. *CA Cancer J Clin* 60(4), 207-221.

37. Hemkens LG, Grouven U, Bender R, Gunster C, Gutschmidt S, Selke GW and Sawicki

PT. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. *Diabetologia* 52(9), 1732-1744, 2009.

38. Weinstein D, Simon M, Yehezkel E, Laron Z and Werner H. Insulin analogues display IGF-I-like mitogenic and anti-apoptotic activities in cultured cancer cells. *Diabetes Metab Res Rev* **25**(1), 41-49, 2009.

39. Home PD and Lagarenne P. Combined randomised controlled trial experience of malignancies in studies using insulin glargine. *Diabetologia* 52(12), 2499-2506, 2009.

40. Zakikhani M, Blouin MJ, Piura E and Pollak MN. Metformin and rapamycin have distinct effects on the AKT pathway and proliferation in breast cancer cells. *Breast Cancer Res Treat* 123(1), 271-279.

41. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD and Evans JM. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. *Diabetes Care* 32(9), 1620-1625, 2009.

42. Bodmer M, Meier C, Krahenbuhl S, Jick SS and Meier CR. Long-term metformin use is associated with decreased risk of breast cancer. *Diabetes Care* 33(6), 1304-1308.

43. Lewis JD, Capra AM, Achacoso NS, Ferrara A, Levin TR, Quesenberry CP Jr and Habel LA. Thiazolidinedione therapy is not associated with increased colonic neoplasia risk in patients with diabetes mellitus. *Gastroenterology*. 135(6), 1914-1923, 1923 e1911. 2008.

44. Govindarajan R, Ratnasinghe L, Simmons DL, Siegel ER, Midathada MV, Kim L, Kim PJ, Owens RJ and Lang NP. Thiazolidinediones and the risk of lung, prostate, and colon cancer in patients with diabetes. *J Clin Oncol* 25(12), 1476-1481. 2007.

45. Monami M, Lamanna C, Balzi D, Marchionni N and Mannucci E. Sulphonylureas and cancer: a case-control study. *Acta Diabetol* 46(4), 279-284, 2009.

46. Bowker SL, Majumdar SR, Veugelers P and Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin: Response to Farooki and Schneider. *Diabetes Care* 29(8), 1990-1991, 2006.

47. LoPiccolo J, Blumenthal GM, Bernstein WB and Dennis PA. Targeting the PI3K/Akt/mTOR pathway: effective combinations and clinical considerations. *Drug Resist Updat* 11(1-2), 32-50, 2008.