

## FACTORS THAT MAY INFLUENCE THE RISK OF CANCER IN DIABETES

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### Abstract

Several studies revealed a frequent association with increased cancer risk in diabetes. The results of these studies indicate that some types of cancer develop more commonly in patients with diabetes; the relative risks are greater for liver, pancreas, and endometrium cancer and less for colon, rectum, breast, and bladder cancer. Lung cancers do not appear to be associated with an increased risk in diabetes, and the evidence for kidney cancer or non-Hodgkin lymphoma is inconclusive. Prostate cancer occurs less often in men with diabetes. Most of the epidemiological data on cancer incidence and mortality has been obtained for type 2 diabetic patients and these findings cannot be extended to type 1 diabetic subjects. Obesity, the quality of metabolic control, the administered drugs, the possible presence of chronic complications, the increased oxidative stress and the potential role of inflammatory cytokines are some of the factors present in diabetic patients, that may influence the association between diabetes and cancer.

### Rezumat

Studii recente publicate în literatura de specialitate au relevat incidența crescută de apariție a cancerului la pacienții diabetici. Cele mai frecvent întâlnite tipuri de neoplasme au fost identificate la nivelul ficatului, pancreasului și endometriului și mai puțin la nivelul colonului, rectului, glandelor mamare și vezicii biliare. Cancerul pulmonar, renal și limfoamele non-Hodgkin nu au fost corelate semnificativ cu diabetul. Cele mai multe date din literatură corelează incidența apariției cancerului cu diabetul de tip 2, și mai puțin cu diabetul de tip 1. Factorii ce favorizează dezvoltarea neoplasmelor la pacienții diabetici sunt: obezitatea, stresul oxidativ, precum și prezența citokinelor pro-inflamatorii.

**Keywords:** diabetes mellitus, cancer, risk factors

### Introduction

Diabetes mellitus has been epidemiologically associated with an increased risk of cancer [1,2,3,4]. The results of several studies indicate that

some cancers develop more commonly in patients with diabetes (predominantly type 2); the relative risks are greater (about twofold or higher) for liver, pancreas, and endometrium cancer, and lesser (about 1.2–1.5 fold) for cancers of the colon and rectum, breast, and bladder. Lung cancers do not appear to be associated with an increased risk in diabetes, and the evidence for kidney cancer or non-Hodgkin lymphoma is inconclusive. Prostate cancer occurs less often in men with diabetes. The large majority of the epidemiological data on cancer incidence and mortality has been obtained for type 2 diabetic patients and the data cannot be extended to type 1 diabetic subjects [5].

A new Expert Consensus Statement of the American Diabetes Association and the American Cancer Society was published in July 2010 in *Diabetes Care*. The consensus statement addresses four questions: “Is there a meaningful association between diabetes and cancer incidence or prognosis?” (1), “What risk factors are common to both diabetes and cancer?” (2), “What are the possible biologic links between diabetes and cancer risk?” (3), and “Do diabetes treatments influence the risk of cancer or cancer prognosis?” (4) [6].

The experts specify that “Diabetes has been consistently associated with an increased risk of several of the more common cancers, but for many, especially the less common cancers, data are limited or absent and more research is needed. Potential risk factors, common to both cancer and diabetes, include aging, sex, obesity, physical activity, diet, alcohol, and smoking. Diabetes may influence the development of cancer by several mechanisms, including hyperinsulinemia, hyperglycemia, increased oxidative stress or chronic inflammation. The potential role of anti-diabetic drugs in favoring cancer is unclear and data are not conclusive because the large majority of diabetic patients change the drug dosage and/or the type of drug many times during the course of the disease. Epidemiological studies on this issue are inconclusive and therefore difficult to interpret [6].

### **Factors that may influence the risk of cancer in diabetes**

#### **Nonmodifiable risk factors**

##### **Age.**

The incidence of most cancers increases with age. The relationship between cancer and aging is unclear, but the increased risk of cancer in old age is possibly due to: poor cellular repair mechanisms, activation of genes that stimulate cancer and suppression of genes that prevent cancer and life time exposure to carcinogens [7,8].

The prevalence of diabetes mellitus increases with age and the National Health and Nutrition Examination Survey (NHANES III) demonstrated that, in the population over 65 years old, almost 18% to 20% have diabetes [9].

### **Gender**

Certain cancers are gender-specific (cervical, endometrium, ovarian, testicular, prostate), or nearly so (breast), overall cancer occurs more frequently in men [6].

### **Modifiable risk factors**

#### **Obesity**

Diabetes is often linked to obesity, and obesity is known to increase the risk of cancer. According to the American Cancer Society, obesity increases the risk of: breast (after menopause) cervical, colon or rectal, esophageal, gall bladder, kidney, liver cancer, multiple myeloma, non-Hodgkin lymphoma, ovarian, pancreas, endometrial cancer [10,11]. The relationship between obesity and cancer is complex and not fully understood.

Obesity affects estrogen levels. After menopause, estrogen, progesterone and ovarian androgens are diminished due to adult-onset ovarian failure. Estrone is the dominant form of estrogen during menopause. It is produced in small quantities by the ovary and the adrenal glands, and is mainly derived from by the peripheral conversion of androstenedione in adipose tissue. The biological effects of estrogen had to be mediated by a receptor protein- estrogen receptor. There are two types of estrogen receptor (ER): ER, which is a member of the nuclear hormone receptors family, and the estrogen G protein-coupled receptor (GPER), which is a G protein-coupled receptor [12]. There are two different forms of the estrogen receptor,  $\alpha$  and  $\beta$ , each encoded by a separate gene. The ER $\alpha$  protein is expressed in endometrium, breast cancer cells, ovarian stroma cells, and the hypothalamus. In males, ER $\alpha$  protein is found in the epithelium of the efferent ducts. The ER $\beta$  protein is expressed in kidney, brain, bone, heart, lungs, intestinal mucosa, prostate and endothelial cells [13-15]. Estrogen and ER have been implicated in breast, ovarian, endometrial, colon and prostate cancer. The colon cancer is associated with a loss of ER $\beta$ , the predominant ER in colon tissue. Two hypotheses have been proposed to explain the tumorigenesis induced by estrogen:

- estrogen binding to the ER stimulates proliferation of mammary cells with the increase in cell division and deoxyribonucleic acid (DNA) replication, leading to mutations.
- estrogen metabolism produces genotoxic waste [12].

Increased proliferation rates raise the probability that mutations accumulate in proto-oncogenes and tumor suppressor genes. Impairment of apoptosis may allow cells that have harbored such mutations to survive and eventually to expand clonally, thus allowing them to accumulate additional mutations until full malignancy is reached. Finally, proliferative stimuli may also enhance the growth of established tumors [17,18,19]. ER $\alpha$  is associated with more differentiated tumors, while the evidence that ER $\beta$  is involved, is controversial [16].

Obesity-related effects on insulin levels and the insulin-like growth factor-1 (IGF-1) axis may be important contributors to the increased risk for cancer development and progression. Several studies have consistently shown a strong association between obesity and both insulin resistance and hyperinsulinemia. A number of mechanisms may link elevated insulin to cancer development. There is evidence that insulin can act as a growth factor, with effects similar to those of insulin like growth factor I (IGF-I). Tumor tissues, generally have increased levels of IGF-I receptors, and increased insulin receptor content has also been reported. The A isoform of the insulin receptor is commonly expressed and this isoform can stimulate insulin-mediated mitogenesis [20,21]. Elevated insulin increases IGF-I and possibly IGF-II activity by suppressing gene expression of insulin-like growth factor binding protein-1 (IGFBP-1) and possibly IGFBP-2 [22]. *In vitro* experiments have proved indeed that insulin is a key regulator of IGFBP-1 gene expression and its production in the liver [23], and that it may also reduce IGFBP-1 synthesis in other tissue types, including endometrium [24]. IGF-I has more potent mitogenic and anti-apoptotic activities than insulin and could act as a growth stimulus in preneoplastic and neoplastic cells that express insulin, IGF-I, and hybrid receptors [6]. Insulin stimulates the ovarian (and possibly also adrenal) androgen synthesis. Insulin is a key regulator of the hepatic synthesis and plasma levels of sex hormone binding globuline (SHBG), down-regulating SHBG levels, and is thus a direct determinant of 17 beta-estradiol unbound to SHBG [25].

Obesity is characterized by altered production of adipokines by adipocytes, that may be important contributors to the increased risk for cancer development and progression. The adipose tissue is an active endocrine organ producing proinflammatory and anti-inflammatory factors, including the adipokines leptin, adiponectin, resistin, visfatin, plasminogen activator inhibitor-1 as well as cytokines and chemokines, such as interleukin-6, tumor necrosis factor- $\alpha$  [26]. Leptin, the most extensively studied adipokine, acts on the hypothalamus to decrease food intake and increase energy expenditure. The obese state is associated with high

circulating leptin levels suggesting that obese individuals are insensitive to the effects of leptin. The resistance to leptin seems to explain the inability of exogenous leptin administration to prevent weight gain. Leptin can stimulate proliferation of preneoplastic and cancer cells *in vitro*; *in vivo* the role of leptin in carcinogenesis is unclear [27]. Adiponectin, is the most abundant transcript in adipocytes and has antidiabetic and anti-inflammatory properties. Low levels of adiponectin are associated with an increased risk of breast cancer and animal studies show that the exogenous adiponectin inhibits tumor growth and tumor angiogenesis [28]. Plasminogen activator inhibitor-1 functions as a fibrinolytic inhibitor and plays an important role in signal transduction, cell adherence, and cell migration. There is clinical evidence implicating plasminogen activator inhibitor-1 as a key factor in tumour invasion and metastasis [29,30]. The relationship of resistin levels with breast carcinogenesis has been well characterized [31]. Resistin is expressed in human prostate cancers and the adipokine induces prostate cancer cell proliferation through phosphatidylinositol-3 kinases (PI3K)/Akt signalling pathways. The proliferative effect of resistin on prostate cancer cells may account in part for prostate cancer progression [32]. Resistin and visfatin levels were significantly higher in patients with colorectal cancer and they may be good biomarkers of colorectal malignant potential and stage progression [33]. The inflammatory cytokine tumor necrosis factor- $\alpha$ , is an important tumor promoter in a variety of experimental animal models. This cytokine is also produced by the malignant cells of advanced cancers and its presence is associated with a poor prognosis [34]. Interleukin-6, is relevant to prostate cancer and advanced/metastatic cancer patients have higher levels of interleukin-6 [35].

### **Diet**

As scientific research progresses, there is evidence that dietary patterns are closely associated with the risk for several types of cancer. Current research indicates that diets low in fat and high in fiber, fruits, vegetables, and grain products are associated with reduced risks for cancer [36].

### **Physical activity**

Epidemiologic studies consistently show that physical activity is associated with a lower risk of colon, postmenopausal breast, and endometrial cancer [6]. Physical activity may improve cancer survival for breast and colorectal cancers [6]. Physical activity may protect against cancer and tumor development through its role in energy balance, hormone metabolism and by decreasing the time of exposure to potential carcinogens. Physical activity has also been found to alter a number of inflammatory and

immune factors, some of which may influence cancer risk. The protective association of physical activity after diagnosis and survival in other cancers are inconsistent [37].

#### **Tobacco smoking**

Tobacco smoking is associated with trachea, bronchus, lung, larynx, upper digestive tract, bladder, kidney, pancreas, liver, stomach, uterine cervix cancers and leukemia [6].

#### **Alcohol**

Alcohol is associated with an increased risk of mouth, esophagus, pharynx and larynx, colorectal, liver, stomach, breast and ovarian cancer. The International Agency for Research on Cancer of the World Health Organization has classified alcohol as a group 1 carcinogen [38].

### **Interactions between diabetes, diabetes treatments, and cancer**

#### **Hyperglycemia**

The Warburg effect consists of the "observation that most cancer cells predominantly produce energy by a high rate of glycolysis followed by lactic acid fermentation in the cytosol, rather than by a comparatively low rate of glycolysis followed by oxidation of pyruvate in mitochondria like most normal cells. Malignant rapidly-growing tumor cells typically have glycolytic rates that are up to 200 times higher than those of their normal tissues of origin; this occurs even if oxygen is plentiful" [39].

#### **Increased oxidative stress**

Oxidative stress is caused by the presence of reactive oxygen species (superoxide anion radical, singlet oxygen, hydrogen peroxide, highly reactive hydroxyl radical) that the cell is unable to counterbalance. The result is the damage of biomolecules including DNA, ribonucleic acid (RNA), proteins and lipids. Oxidative stress has been implicated in the natural aging process as well as a variety of disease states: neoplastic, metabolic and neurological diseases. Oxygen-free radicals, known as reactive oxygen species (ROS) have dual role. ROS act within cells as secondary messengers in intracellular signaling cascades, which induce and maintain the oncogenic phenotype of cancer cells. ROS can also induce cellular apoptosis and can function as anti-tumorigenic species. The ROS activated signal pathways are regulated by two protein families – the mitogen activated protein kinase (MAPK) and the redox sensitive kinases. MAPK are serine/threonine kinases that phosphorylate their specific substrates - serine and/or threonine residues. MAPK consist of three family members: the extracellular signal-regulated kinase, the c-Jun NH2-terminal kinase and the p38 MAPK. The MAPK signaling pathways modulate gene

expression, mitosis, proliferation, metabolism, and programmed cell death. Of the three subfamilies, the extracellular signal-regulated kinase pathway has been associated with the regulation of cell proliferation. Activation of the extracellular signal-regulated kinase, the c-Jun NH<sub>2</sub>-terminal kinase and p38 subfamilies has been observed in response to changes in the cellular redox balance. Activation of MAPK directly leads to increased activator protein -1 (AP-1) activity resulting in increased cell proliferation. One of the genes regulated by AP-1 is cyclin D1 and AP-1 activates this promoter, resulting in the activation of cyclin-dependent kinase (cdks), which promotes the cell division cycle. c-Jun stimulates the progression into the cell cycle by induction of cyclin D1 and suppression of a protein that inhibits cell cycle progression. NF- $\kappa$ B activation has been linked to the carcinogenesis process, because it regulates several genes involved in cell transformation, proliferation, and angiogenesis. Tumor cells of colon, breast, and pancreas carcinoma have been reported to express activated NF- $\kappa$ B. The second family consists of signaling factors that use cysteine motifs as redox-sensitive sulfhydryl switches to modulate specific signal transduction cascades regulating downstream proteins. The redox-sensitive signaling cascade involves the cytoplasmic factors, nuclear signaling and transcription factors. Redox-sensitive signaling factors regulate multiple processes including proliferation, anti-apoptotic signaling pathways and neoplastic transformation [40-44].

#### **Free fatty acids**

Deregulation of fatty acid synthase activity, could also play a role in the pathogenesis of insulin resistance, diabetes, and cancer. Fatty acid synthase expression is increased in cancer cells, and fatty acid synthesis is important for membrane remodeling during cell migration and proliferation, and for lipid-based post-translational modifications of intracellular proteins in highly proliferating cells [5].

#### **Diabetes treatments**

##### **The mitogenicity of insulin**

Insulin and insulin analogues have metabolic and mitogenic activities in the cell, and the mitogenic activities *in vitro* resemble to be mediated through the insulin-like growth factor-I (IGF-I). The IGF-I plays an important role in cell growth. The biological actions of IGF-I are mediated by its receptor, a tyrosine kinase receptor-IGF-IR. The binding of ligand to the IGF-IR leads to receptor autophosphorylation of tyrosines 1131, 1135, and 1136 in the kinase domain of the receptor [44]. This induces the phosphorylation of juxtamembrane tyrosines and carboxyl-terminal serines that form binding sites for docking proteins including

insulin receptor substrates and Src homology and collagen domain protein. These molecules activate signaling *via* the phosphatidylinositol-3-kinase (PI3K)-Akt (responsible for metabolic actions and involved in apoptosis) and ras-raf-mitogen-activated protein kinase (MAPK) pathways (responsible for the proliferation and prevention of apoptosis). IGF signaling plays a role in growth, and is a well-established mediator of the malignant phenotype [45-47]. Many tumors show altered expression of the IGF-IR, its ligands and tumors can express the insulin receptors isoform A and hybrid receptors. The insulin receptors isoform A is a fetal isoform and the overexpression of this isoform is a major mechanism of IGF system overactivation in cancer. Insulin forms hybrid receptors is commonly overexpressed in cancer. By binding to hybrid receptors, insulin may stimulate specific IGF-IR signaling pathways. Preclinical studies indicate that IGF-IR overexpression induces tumor formation and metastasis [48-51].

Insulin stimulates cell proliferation through IGF-IR but there is an important distinction between mitogenicity and carcinogenicity, which refers to the ability or tendency to transform cells and promote tumor growth [52]. The investigations of Weinstein *et al.* assessed the *in vitro* mitogenic and anti-apoptotic activities of insulin analogues, and regular human insulin in multiple cancer cell lines showed that insulins like glargine, detemir, and lispro, unlike regular insulin, displayed proliferative and anti-apoptotic effects in a number of malignant cell lines [53]. The ideal experiment in order to establish that insulin displays carcinogenetic behavior is a large, prospective randomized clinical trial, with a lengthy follow-up period. Resulting data should be interpreted cautiously in light of all other presently available scientific evidence [52].

#### **Safety of other class of pharmacological agents with antihyperglycemic actions**

Incretin mimetics are a new class of pharmacological agents with antihyperglycemic actions that mimic the actions of incretin hormones originating in the gut, such as glucagon-like peptide (GLP)-1. GLP-1 is rapidly degraded by dipeptidyl peptidase 4 (DPP-4). Two alternative pathways have been thought to overcome this shortcoming: the development of GLP-1 analogs resistant to DPP-4 named incretin mimetics or the development of DPP-4 inhibitors.

Preclinical studies have shown that thyroid C cells express GLP-1 receptors whose activation induces C cell hyperplasia and medullary thyroid cancer (MTC). Animal models develop spontaneously age-induced nodular hyperplasia of C cells frequently. Sporadic MCT has a frequency of 0.5-1%, in animal models, higher in males secondary to ageing. In humans, MCT

represents 3-10% of thyroid cancer and approximately 75% are either sporadic, with 25% being part of a multiple endocrine neoplasia, or familial

In 2009 the Regulatory Committee of Food and Drug Administration (FDA) has communicated that preclinical toxicological studies with Liraglutide<sup>®</sup>, a GLP-1 analogue developed by Novo Nordisk, Denmark have reported that C cell hyperplasia and MTC incidence increase with drug exposure. Clinical studies with liraglutide that monitored safety issues have revealed a small number of patients with an increase in calcitonin level during the treatment. There have been reported few cases of papillary thyroid carcinoma during the clinical development program of liraglutide, but data suggested these cannot be directly related to the GLP-1 agonist [54].

Dipeptidyl peptidase-4 (DPP4), also known as adenosine deaminase complexing protein 2 or CD26 is an antigenic enzyme expressed on the surface of most cell types and is associated with immune regulation, signal transduction and apoptosis. DPP4 appears to work as a suppressor in the development of cancer and tumors and is useful as a marker for various cancers [55-58]. In theory, DPP-4 inhibitors may influence cancer development and progression but large, prospective randomized clinical trials with a lengthy follow-up period are necessary for confirming or infirming this theory.

Thiazolidinediones are insulin-sensitizing peroxisome proliferator-activated receptor (PPAR) $\gamma$ . Some *in vitro* studies indicated that PPAR $\gamma$  agonists have several anti-cancer activities, such as inhibiting growth and inducing apoptosis and cell differentiation while other studies using animal models indicated that PPAR $\gamma$  agonists can potentiate tumorigenesis [59,60]. Some epidemiological evidence that suggest a link between the pioglitazone, and an increased risk of bladder cancer have been analyzed by the United States Food and Drug Administration (FDA). The announcement, published on September 17 2010, stresses that at the moment, the agency has not concluded that pioglitazone caused the increase in the risk of bladder cancer among patients who either used the drug for more than 2 years or those whose accumulative intakes of this drug over the years were the highest is no clear evidence that the drug. The FDA said an analysis of data collected during a 5-year period from an ongoing 10-year observational study conducted by the manufacturer, Takeda Pharmaceuticals North American Inc in San Diego.

On July 21<sup>st</sup> 2011, the European Medicines Agency recommended new contra-indications and warnings for pioglitazone, considering a risk of bladder cancer.

Secretagogues, including sulfonylureas and glinides, stimulate beta-cells to release insulin by binding to specific cell receptors. A small number of observational studies found a higher risk of cancer among individuals with diabetes treated with sulfonylureas compared with those treated with other diabetes medications. There is no published data to support the association between glinide and cancer risk [6].

### Conclusion

Diabetes has been associated with an increased risk of several of the more common cancers.

Several potential factors present in diabetic patients (obesity, quality of metabolic control, the administered drugs, the possible presence of chronic complications, increased oxidative stress, and the potential role of inflammatory cytokines) may influence the association between diabetes and cancer.

Prospective, randomized clinical trials should address any direct relationship between class of pharmacological agents with antihyperglycemic actions and cancer, because the clinical relevance of the *in vitro* studies is unclear.

### Acknowledgements

This work was supported by CNCSIS –UEFISCSU, project number PNII – IDEI code 2177/2008

### References

1. Kuriyama S, Tsubono Y, Hozawa A, Shimazu T, Suzuki Y, Koizumi Y, Ohmori K, Nishino Y, Tsuji I. Obesity and risk of cancer in Japan. *Int J Cancer* 113: 148–157, 2005.
2. Larsson SC, Orsini N, Wolk A. Body mass index and pancreatic cancer risk: A meta-analysis of prospective studies. *Int J Cancer* 120: 1993–1998, 2007.
3. Larsson SC, Wolk A. Epidemiology of obesity and diabetes: prevalence and trends. In *Obesity and Diabetes*, Mantzoros C (ed) pp 15–36. Boston: Humana Press, 2006.
4. Larsson SC, Wolk A. Obesity and the risk of gallbladder cancer: a meta-analysis. *Br J Cancer* 96: 1457–1461, 2007.
5. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R: Diabetes and cancer. *Endocr Relat Cancer* 16: 1103–1123, 2009.
6. Edward Giovannucci, David M. Harlan, Michael C. Archer, Richard M. Bergenstal, Susan M. Gapstur, Laurel A. Habel, Michael Pollak, Judith G. Regensteiner, Douglas Yee. Diabetes and Cancer: A Consensus Report, *Diabetes Care*, 33:1674-85, 2010.
7. Garcia M, Jemal A, Ward EM, Center MM, Hao Y, Siegel RL, Thun MJ. *Global Cancer Facts & Figures 2007*. Atlanta, Georgia, American Cancer Society, 2007.
8. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 59: 225–249, 2009.
9. Harris MI, Flegal KM. Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose and impaired glucose tolerance in US adults. *Diabetes Care*, 21:518-524, 1998.

10. American Cancer Society. *ACS report calls for greater cancer prevention efforts*. Retrieved July 1, 2010, from <http://www.cancer.org/Cancer/news/acs-report-calls-for-greater-prevention-efforts> 2010.
11. Obesity Society. (n.d.). *Cancer and obesity*, 2010, [http://www.obesity.org/information/cancer\\_obesity.asp](http://www.obesity.org/information/cancer_obesity.asp), 2010.
12. Dahlman-Wright K, Cavailles V, Fuqua SA, Jordan VC, Katzenellenbogen JA, Korach KS, Maggi A, Muramatsu M, Parker MG, Gustafsson JA. "International Union of Pharmacology. LXIV. Estrogen receptors". *Pharmacol. Rev.* 58 (4): 773–81, 2006.
13. Yaghmaie F, Saeed O, Garan SA, Freitag W, Timiras PS, Sternberg H. Caloric restriction reduces cell loss and maintains estrogen receptor- $\alpha$  immunoreactivity in the pre-optic hypothalamus of female B6D2F1 mice. *Neuro Endocrinol. Lett.* 26 (3): 197–203, 2005.
14. Hess, RA. Estrogen in the adult male reproductive tract: a review. *Reproductive Biology and Endocrinology* 1 (52): 52, 2003.
15. Babiker FA, De Windt LJ, van Eickels M, Grohe C, Meyer R, Doevendans PA. Estrogenic hormone action in the heart: regulatory network and function. *Cardiovasc. Res.* 53 (3): 709–19, 2005.
16. Deroo BJ, Korach KS. Estrogen receptors and human disease.. *J. Clin. Invest.* 116 (3): 561–7, 2006.
17. Cohen S. M., Ellwein L. B. Genetic errors, cell proliferation, and carcinogenesis. *Cancer Res*, 51: 6493-6505, 1991.
18. Preston-Martin S., Pike M. C., Ross R. K., Jones P. A., Henderson B. E. Increased cell division as a cause of human cancer. *Cancer Res*, 50: 7415-7421, 1990.
19. Cory S., Vaux D. L., Strasser A., Harris A. W., Adams J. M. Insights from Bcl-2 and Myc: malignancy involves abrogation of apoptosis as well as sustained proliferation. *Cancer Res*, 59: 1685s-1692s, 1999.
20. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. *Nat Rev Cancer*. 8: 915–928, 2008.
21. Denley A, Carroll JM, Brierley GV, Cosgrove L, Wallace J, Forbes B, Roberts CT Jr. Differential activation of insulin receptor substrates 1 and 2 by insulin-like growth factor-activated insulin receptors. *Mol Cell Biol*, 27: 3569–3577, 2007.
22. Renehan AG, Frystyk J, Flyvbjerg A. Obesity and cancer risk: the role of the insulin-IGF axis. *Trends Endocrinol Metab*, 17: 328–336, 2006.
23. Rechler M. M. Insulin-like growth factor binding proteins. *Vitam. Horm*, 47: 1-114, 1993.
24. Lee P. D., Giudice L. C., Conover C. A., Powell D. R. Insulin-like growth factor binding protein-1: recent findings and new directions. *Proc. Soc. Exp. Biol. Med*, 216: 319-357, 1997.
25. Franks S., Kiddy D. S., Hamilton-Fairley D., Bush A., Sharp P. S., Reed M. J. The role of nutrition and insulin in the regulation of sex hormone binding globulin. *J. Steroid Biochem. Mol. Biol*, 39: 835-838, 1991.
26. Fantuzzi G. Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol*, 115:911-9, 2005.
27. Fenton JI, Hord NG, Lavigne JA, et al. Leptin, insulin-like growth factor-1, and insulin-like growth factor-2 are mitogens in Apc<sup>Min/+</sup> but not Apc<sup>+/+</sup> colonic epithelial cell lines. *Cancer Epidemiol Biomarkers Prev*, 14: 1646–52, 2005.
28. Brakenhielm E, Veitonmaki N, Cao R, et al. Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis. *Proc Natl Acad Sci USA*, 101: 2476–81 2004.
29. Bajou K. Role of PAI-1 plasminogen activator inhibitor in tumor invasion and angiogenesis]. *Bull Mem Acad Roy Med Belg* 157: 313–318, 2002.
30. Bajou K, Maillard C, Jost M, Lijnen RH, Gils A, Declerck P, Carmeliet P, Foidart JM, Noel A. Host-derived plasminogen activator inhibitor-1 (PAI-1) concentration is critical for *in vivo* tumoral angiogenesis and growth. *Oncogene* 23: 6986–6990, 2004.

31. Hou Wk, Xu YX, Yu T, Zhang L, et al. Adipocytokines and breast cancer risk. *Chin Med J*, 120:1592-6, 2007.
32. Ionică FE, Pisoschi C, Negreş S, Nikos RF, Tărăță M, Popescu F, Atorvastatin influence on glycemic control in patients with type 2 diabetes mellitus., *Farmacia*, 2010, 58(6), 728-734
33. Takako Eguchi Nakajima, Yasuhide Yamada, Tetsutaro Hamano et al. Adipocytokines as new promising markers of colorectal tumors: Adiponectin for colorectal adenoma, and resistin and visfatin for colorectal cancer. *Cancer Science*, 101:1286-1291, 2010.
34. Szlosarek P, Charles KA, Balkwill FR. Tumour necrosis factor- $\alpha$  as a tumour promoter. *Eur J Cancer* 42: 745-50, 2006.
35. Smith PC, Hobisch A, Lin DL, Culig Z, Keller ET. "Interleukin-6 and prostate cancer progression". *Cytokine Growth Factor Rev*. 12 (1): 33-40, 2001.
36. Engeset Dagrun, Dyachenko Alina, Ciampi Antonio, Lund Eiliv. Dietary patterns and risk of cancer of various sites in the Norwegian European Prospective Investigation into Cancer and Nutrition cohort: the Norwegian Women and Cancer study. *European Journal of Cancer Prevention*, 18: 69-75, 2009.
37. Lee I, Oguma Y. Physical activity. In: Schottenfeld D, Fraumeni JF, editors. *Cancer Epidemiology and Prevention*. 3rd ed. New York: Oxford University Press, 2006.
38. Paveliu MS, Bengea S, Paveliu FS, Individualized drug response related to genetic variations of cytochrome P450 isoforms and other enzymes, *Farmacia*, 2010, 58(3), 245-254
39. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* 324: 1029-1033, 2009.
40. Wada T, Penninger JM. Mitogen-activated protein kinases in apoptosis regulation. *Oncogene*. 23:2838-49, 2004.
41. Klaunig JE, Kamendulis LM. The role of oxidative stress in carcinogenesis. *Annu Rev Pharm Toxicol*;44:239-267, 2004.
42. Cook JA, Gius D, Wink DA, Krishna MC, Russo A, Mitchell JB. Oxidative stress, redox, and the tumor microenvironment. *Semin Radiat Oncol*. 14:259-66, 2004.
43. Totan A, Greabu M, Mitrea N, Mohora M, Arsene AL, Relationships between erythrocyte Na<sup>+</sup>/K<sup>+</sup>-ATPase activity, oxidative stress and high blood pressure in hypertensive diabetic patients, *Farmacia*, 2010, 58(3), 322-331
43. Denisa Margină, Daniela Grădinaru, Niculina Mitrea - Development of a potentiometric method for the evaluation of redox status in human serum, *Revue Roumaine de Chimie*, 54 45-48, 2009.
45. Charlotte M. Boney<sup>2</sup>, Hiroko Sekimoto, Philip A. Gruppuso and A. Raymond Frackelton, Jr. Src Family Tyrosine Kinases Participate in Insulin-like Growth Factor I Mitogenic Signaling in 3T3-L1 Cells *Cell Growth & Differentiation*, 12 379-386, 2001.
46. Baserga R, Peruzzi F, Reiss K. The IGF-1 receptor in cancer biology. *Int J Cancer*, 107:873-7, 2003.
47. Manning BD, Cantley LC. AKT/PKB signaling: navigating downstream. *Cell*, 129:1261-74, 2007.
48. Johnson GL, Lapadat R. Mitogen-activated protein kinase pathways mediated by ERK, JNK, and p38 protein kinases. *Science*, 298:1911-2, 2002.
49. Belfiore A The role of insulin receptor isoforms and hybrid insulin/IGF-I receptors in human cancer. *Curr Pharm Des*, 13(7):671-86, 2007.
50. Lopez T, Hanahan D. Elevated levels of IGF-1 receptor convey invasive and metastatic capability in a mouse model of pancreatic islet tumorigenesis. *Cancer Cel*, 1 1:339-53. 2002.
51. Jones RA, Campbell CI, Gunther EJ, et al. Transgenic overexpression of IGF-IR disrupts mammary ductal morphogenesis and induces tumor formation. *Oncogene*, 26:1636-44, 2007.
52. Yuen JS, Macaulay VM. Targeting the type 1 insulin-like growth factor receptor as a treatment for cancer. *Expert Opin Ther Targets*, 12:589-603, 2008.

53. C. Kazda, L. Sliker, L. Ilag, R. Byrd, T. Rees, M. Prince. Appraising the mitogenicity of insulin analogues relative to human insulin—response to: Weinstein D, Simon M, Yehezkel E, Laron Z, Werner H. Insulin analogues display IGF-I-like mitogenic and anti-apoptotic activity in cultured cancer cells. *Diabetes Metab Res Rev*, 26(3): 145–9, 2010.
54. Weinstein D, Simon M, Yehezkel E, Laron Z, Werner H. Insulin analogues display IGF-I-like mitogenic and anti-apoptotic activities in cultured cancer cells. *Diabetes Metab Res Rev*, 25:41–49, 2009.
55. Drucker D, Sherman S, Grelick F, Bergenstal R, Sherwin R, Buse J. Terapiile pe baza de incretine in diabetul zaharat tip 2: evaluarea riscurilor si beneficiilor. *Diabetes Care.* , 3(2): 117-123, 2010.
56. Pro B, Dang N. CD26/dipeptidyl peptidase IV and its role in cancer. *Histol Histopathol* 19 (4): 1345–51, 2004.
57. Masur K et al. DPPIV inhibitors extend GLP-2 mediated tumour promoting effects on intestinal cancer cells". *Regul Pept.* 137 (3): 147–55, 2006.
58. Wesley UV et al. Dipeptidyl peptidase inhibits malignant phenotype of prostate cancer cells by blocking basic fibroblast growth factor signaling pathway" *Cancer Res.* 65 (4): 1325–34, 2005.
59. Havre PA, Abe M, Urasaki Y, Ohnuma K, Morimoto C, Dang NH. The role of CD26/peptidyl peptidase IV in cancer. *Front. Biosci.* 13: 1634–45, 2008.
60. Ohta K, Endo T, Haraguchi K, Hershman JM, Onaya T. Ligands for peroxisome proliferator-activated receptor gamma inhibit growth and induce apoptosis of human papillary thyroid carcinoma cells. *J Clin Endocrinol Metab*, 86: 2170–2177, 2001.

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*Manuscript received: January 22<sup>nd</sup> 2011*