Chapter 8

Diabetes and Cancer: Is there a Link?

Andra-Iulia Suceveanu, Adrian-Paul Suceveanu, Andreea-Daniela Gheorghe and Laura Mazilu

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.72081

Abstract

Cancer and diabetes are two major health problems worldwide, and incidence is increasing globally for both diseases. Type 2 diabetes is characterized by hyperinsulinemia and insulin resistance and the effect of insulin and insulin growth factor I on cancer development and progression have been demonstrated in animal and human studies. The relationship between diabetes and cancer was reported for more than 60 years. Many epidemiological studies conducted over time suggested the association between diabetes and cancer. Epidemiological studies show an increased risk in type 2 diabetic patients for colon, breast, liver, pancreas, bladder cancers and non-Hodgkin's lymphoma, and a decrease risk for prostate cancer. Lung cancer does not appear to be related to diabetes and for renal cancer data are inconclusive. Diabetes, beside the fact that it is an independent risk factor for different type of cancer, can also have an impact on prognosis of cancer, and studies shown an increased cancer mortality in patients with diabetes.

Keywords: diabetes, cancer, hyperinsulinemia, insulin resistance

1. Introduction

Cancer and diabetes are two major health problems worldwide, and incidence is increasing globally for both diseases. In 2012, 14.1 million new cancer cases and 8.2 million death occurred worldwide, and the number of cases and deaths is expected to grow as populations adopt lifestyle behaviors that increase the cancer risk [1, 2]. Diabetes is also an important health problem associated with severe complications, and its growing worldwide In 2014 was estimated that 422 million adults were living with diabetes, the prevalence of diabetes globally is 8.5% in adult population and caused 1.5 million death in 2012 [3]. Globally, cancer is the 2nd cause of death, and diabetes is 12th cause of death [4]. The economic growth is accompanied

by lifestyle westernization, characterized by physical inactivity, high-calorie diet and obesity and may explain this change in incidence and mortality of lifestyle related diseases such as diabetes, cancer and cardiac disease.

The relationship between diabetes and cancer was reported for more than 60 years. Theodore Tuffier, a French surgeon, is probably the first one to hypothesize the existence of a relationship of type 2 diabetes mellitus and cancer risk in the second half of nineteenth century. He observed that patients with type 2 diabetes have a greater risk of certain cancers than those without diabetes and formulated some key questions: could diabetes affect the incidence of cancer? could diabetes influence the natural history of cancer? and could cancer affect the natural history of diabetes? [5].

Many epidemiological studies conducted over time suggested the association between diabetes and cancer. Studies show an increased risk in type 2 diabetic patients for colon, breast, liver, pancreas, bladder cancers and non-Hodgkin's lymphoma [6–12], and a decrease risk for prostate cancer [13]. Lung cancer does not appear to be related to diabetes and for renal cancer data are inconclusive [14].

Diabetes, beside the fact that is an independent risk factor for different type of cancer, can also have an impact on prognosis of cancer, and studies shown an increased cancer mortality in patients with diabetes. A meta-analysis of 23 studies comparing the overall survival in cancer patients with or without diabetes showed that diabetic patient have an increased mortality, HR of 1.41 (95% CI, 1.28 to 1.55) compared to non-diabetic patients in all cancer types [15].

The majority of the studies that explore the relation between diabetes and cancer do not make the difference between type 1 and type 2 diabetes. It is important to make that distinction, because type 1 diabetes is an autoimmune disease and it is caused by destruction of pancreatic β cells with resultant insulin deficiency and hyperglycemia, and on the other hand type 2 diabetes it appears because of peripheral insulin resistance and it is characterized by hyperinsulinemia and β cell hyperplasia. These 2 entities differ also in the age of onset, type 2 diabetes occurs in adults patients, while type 1 diabetes is usually observed in young people. Considering the differences in the physiopathology of these two diseases, it is important to make diagnostic distinction before any conclusion is made about the association of diabetes and cancer. But, the large majority of patients with diabetes have type 2 diabetes and most study have been conducted on patients with diabetes at older age, this can extrapolate that the majority of diabetic patients who develop cancer are patients with type 2 diabetes.

One Swedish study was conducted on patients with type one diabetes, but did not found an increased risk for pancreatic, breast or colorectal cancer in this patients [16, 17].

2. Diabetes and cancer – common risk factors

Diabetes and cancer very often coexist in the same patients; up to 18% of patients with cancer have also diabetes. Risk factors that are common for both diseases, diabetes and cancer are age, obesity and overweight, physical inactivity, smoking [18]. An important problems is whether

the association of diabetes with different type of cancer is related to common risk factor for both diseases or diabetes with metabolic modification like insulin resistance and hyperinsulinemia is responsible for the increased risk of cancer. More studies are needed to understand the role of each component of lifestyle independent of other, to understand the relation between diabetes and cancer.

2.1. Age

More than 60% of cancers are diagnosed in patients aged 60 years or more, and the prevalence of diabetes is 17% in this age group; the coexistence of cancer and diabetes is expected to raise as life expectancy increases [19, 20].

2.2. Obesity

Diabetes is known to be related with overweight and obesity, studies shown over the years a strong association between obesity, insulin resistance and type 2 diabetes and early age diagnosis of diabetes is reported to be linked directly to obesity severity [21, 22]. Cancers most frequently associated with obesity and overweight are breast cancer in postmenopausal women, colon, pancreas, endometrium, gallbladder and liver, and may increase mortality in prostate cancer [23, 24].

The association between weight loss and decreased risk of diabetes was strengthened by numerous studies. A randomized, prospective, multicenter Diabetes Prevention Trial, shown that lifestyle intervention and physical activity was associated with 58% reduction in incidence of diabetes in high risk individuals [25].

The relation between weight loss and cancer risk is not that clear, and most data are derived from breast cancer studies, and in this studies association observed was very weak [26]. The Nurses' Health Study shown a statistical significant association between weight loss and decrease incidence of breast cancer, if the weight loss is maintained for more than 4 years [27].

2.3. Physical inactivity

Data from epidemiologic observational studies shown that physical activity is associated with lower risk of colon, breast and endometrial cancers, and may help to prevent lung or prostate cancer, but in this case the link is not yet established [28–31].

A protective role of increased physical activity in diabetes metabolism and outcomes has been demonstrated in studies. Data from observational studies suggest that approximately 30 to 60 minutes of moderate-intensity physical activity, at least 5 days per week reduces substantially, with 25–36%, the risk of developing type 2 diabetes [18, 32].

2.4. Smoking

Smoking is a well-known risk factor for lung cancer incidence and mortality. Other types of cancer that is known to be associated with cigarette smoking are cancer of larynx, upper

digestive tract, bladder, pancreas, liver, kidney and uterine cervix. Studies have shown that smoking is an independent risk factor for diabetes, and it is well known to act as an adverse effect on diabetes complications [33, 34].

2.5. Alcohol consumption

Alcohol consumption increases the risk of many type of cancers, oral cavity, pharynx, colon, liver and female breast. For diabetes, increased alcohol consumption is a considered a risk, but moderate consumption was associated with reduced incidence of diabetes in both men and women [35, 36].

3. Mechanisms underlying diabetes and cancer

Carcinogenesis is a very complex process in which normal cells must undergo multiple genetic modification in order to appear malignant phenotype and invasion and metastasis occurs. This process of carcinogenesis is divided in three steps. First step is initiation, this is the irreversible step toward cancer, second step is promotion, the stimulation of growth of initiated cells, and the third step is progression. Any factors that have the capability to affect one of these steps could be associated with cancer incidence and mortality.

Diabetes may have an effect on carcinogenesis process by multiple mechanisms: hyperinsulinemia, either is exogenous due to administration of insulin or endogenous due to insulin resistance, hyperglycemia or chronic inflammation [18].

There are many epidemiologic evidence that support the link between diabetes and cancers. Diabetes and cancer may be related simply because these two diseases share common risk factors such as obesity, diet, physical inactivity, but several biologic mechanism have been described that may strengthen this link between diabetes and cancer.

Information regarding biologic mechanism is from in vivo and in vitro studies, research is ongoing currently to provide more clear understanding of these possible mechanisms, and the information from these studies may be important for prevention of the disease and management of the patient.

3.1. Hyperinsulinemia

Insulin and insulin-like growth factor (IGF) receptors form a complex network of cell surface receptors and majority of cancer cells express these receptors. The A isoform is commonly expressed on cells, and can stimulate insulin-mediated mitogenesis, even in cells that do have a deficiency in IGF-I receptors, and in addition to this function, the insulin receptor is capable to stimulate cell proliferation and to promote metastasis [18, 37, 38]. Interaction of insulin receptors or IGF-I receptors with their ligands activate multiple pathways, that can stimulate proliferation, resistance to apoptotic stimuli, invasion and metastasis. IGF-I have more

important anti-apoptotic and mitogenic activities than insulin, and could act as growth factor in pre-neoplastic or cancer cells that express insulin and IGF-I receptors. In cancer cells these receptors are over-expressed and many cancer cell lines have been shown to be very responsive even to the mitogenic effect of normal concentrations of IGF-I [39–41].

High levels of IGF-I have been associated with an increased risk of postmenopausal breast cancer, colon and prostate cancer [18, 42, 43].

It is also possible that hyperinsulinemia may promote carcinogenesis by indirect mechanisms. Insulin reduces the hepatic production of insulin growth factor binding protein (IGFBP) and this will lead to increased levels of circulating free IGF-I.

Hyperinsulinemia have an indirect effect on reduction in hepatic production and blood levels of sex-hormone binding protein, which increase bioavailability of estrogen in both man and women and also increase bioavailability of testosterone in women which is also link to cancer, but not in man [18, 44].

In postmenopausal women, body fat is the primary site of estrogen synthesis, and obesity is related to high levels of serum estrogen this will increase the risk for breast and endometrial cancers in women who do not use hormonal replacement therapy [45].

3.2. Hyperglycemia

The link between effect of hyperglycemia and cancer is still unclear. Hyperglycemia increases production of free radicals which could lead to oxidative damage to DNA and mutation in oncogenes and tumor suppressor genes [18]. Research is still unclear about whether high levels of circulating glucose fuels malignant growth.

The recent interest in Warburg hypothesis emphasize the dependence of many cancers on glycolysis, creating a high requirement for glucose, so called "glucose addiction," because ATP generation glycolysis requires more glucose than oxidative phosphorylation. This is the basis for F-flurodeoxyglucose—positron emission tomography (PET) of cancer, that detects tissues with high glucose uptake [46].

Studies correlating hyperglycemia with cancer do not indicate that the high level of glucose itself mediate this correlation, because chronic hyperglycemia is associated with insulin resistance and often with excess of body fat, and hyperglycemia may act as surogate [18].

3.3. Chronic inflammation

Type 2 diabetes and obesity are characterized by chronic inflammation that increases the production of free radicals. This can disrupt insulin signaling and damage DNA. Adipose tissue is an active endocrine organ and is producing interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), adiponectin, leptin and tumor necrosis factor-α (TNF-α). All of these factors may play a role in malignant transformation and cancer progression, and some of these roles are well known [47].

4. Diabetes treatment and cancer

Type 2 diabetes is treated with different types of medications, so it may be a link between these drugs and the risk of cancer. Anti-diabetic medication includes drugs that increase insulin in circulation (insulin and sulfonylureas) and drugs that improve insulin action and decrease insulin levels (metformin, thiazolidinediones). The central goal of diabetes management is glucose control, this minimize morbidity and mortality related to diabetes by reducing diabetes associated complications. When selecting antidiabetic therapies, physician and patients consider several factors, these includes type of diabetes, glucose-lowering potential of the antidiabetic agent, adverse effect of treatment, costs, patient characteristic and comorbidities.

Type 2 diabetes represent the majority of diabetic population and account for 95% of diabetic population and majority of studies were conducted on this patients. It is generally associated with obesity and overweight in almost 80% of cases. In type 2 diabetes insulin resistance and hyperglycemia are progressive [48, 49].

The majority of studies on antidiabetic treatment and cancer risk have limitations, one limitation is that diabetic patients are treated with more than one antidiabetic agent, because of the progressive nature of type 2 diabetes. In this case is very difficult to assess an association between a specific antidiabetic drug and cancer risk [18].

There are 14 diabetes drugs available at this time, and data suggest a higher risk of cancer development with pioglitazone, insulin and insulin secretagogues [50–53]. Metformin have been identified in several studies in the past few years to improve survival in patient diagnosed with cancer and diabetes and to reduced cancer risk [54]. Insulin has been shown in studies to have a direct proliferative effect; for the insulin analogues, further studies are needed to determine the potential role in cancer proliferation.

5. Diabetes and site – specific cancer

5.1. Diabetes and breast cancer

Breast cancer is the leading cause death among females worldwide. An estimated 1.7 million new cases and more than 500,000 deaths occurred in 2012 [2]. Risk factors for breast cancer include age greater than 50 years, family history, genetics, female gender, Caucasian and African American Race, obesity and hormonal factors such as menstrual history, nulliparity and use of hormone replacement therapy [55].

The association of diabetes and breast cancer was studied extensively and appears to be connected via activation of insulin-IGF pathway through hyperinsulinemia and dysregulation of sex hormones [56, 57]. Cell proliferation in both normal human cell and in breast cancer cell has been shown to be influence by insulin. Insulin stimulates cell cycle progression and DNA synthesis of MCF-7 breast cancer cells in vitro [58, 59].

One mode of action of breast cancer gene 1 (BRCA-1) is a tumor suppressor activity which depends on its ability to mimicry a cellular low-energy status, which is also known to block tumor cell anabolism and suppress the malignant phenotype. Studies shown that increased physical activity and normal weight in young women and adolescence have been associated with significantly delayed breast cancer onset for Ashkenazi Jewish women carrying BRCA-1 gene mutations [60].

Similar to animal model, human studies demonstrated a link between hyperinsulinemia and the risk for breast cancer. One study, although was conducted on postmenopausal women without diabetes, the Women's Health Initiative, reported that fasting insulin levels, independent of obesity, were strongly associated with breast cancer risk [61]. Studies conducted on women with diabetes, demonstrated also the association between hyperinsulinemia and risk for breast cancer. The Nurses' Health Study was conducted on women with type 2 diabetes and concluded that women with type 2 diabetes had an elevated incidence of breast cancer, independent of body adiposity and also that the risk was observed on women with estrogen receptor positive breast cancer [62].

Other studies explored the relationship between type 2 diabetes and breast cancer mortality and reported positive association. For example, prospective cohort study conducted by Coughlin et al. [63] showed that diabetic patient had an increased risk of breast cancer mortality in comparison with controls. Several factors may contribute to the increased mortality in diabetic breast cancer patients, these include delayed cancer diagnosis, suboptimal cancer treatments, direct tumor promoting effects of hyperinsulinemia, and adverse effects of diabetes-related comorbidities or certain antidiabetic medications [64].

In conclusion, several studies have demonstrated an increased risk of breast cancer and breast cancer mortality in patients with type 2 diabetes and this may be related to biological effect of diabetic state.

5.2. Diabetes and endometrial cancer

Worldwide in 2012, more than 500,000 women were diagnosed with uterine cancer, and the mortality rate was 1.7 to 2.4 per 100,000 women [65]. In developed countries, uterine cancer is the most common gynecologic neoplasia, counting over 50,000 new cases and over 10,000 deaths from this disease every year [66–68].

An important and well known risk factor for endometrial cancer is obesity. Other risk factors are reproductive factors, hypertension, physical activity, exposure of endometrium to estrogen unopposed by progesterone and diabetes.

In vitro studies have shown that endometrial cancer cells have an increased proliferation by activation of IGF-I, activation of insulin, and through the ovarian steroid hormone signaling pathways, such as estrogen and androgen [68, 69]. Although is not known to exist a direct correlation with insulin or IGF levels in endometrial cancer, additional factors such as ovarian steroid hormones or inflammatory cytokines make difficult to confirm if there is a single effect of insulin or IGF activation through insulin or IGF serum levels. Estrogen can activate IGF-I receptor on endometrial cancer cells, this will increase cellular proliferation through PI3K signaling, a link to IGF-I receptor activation [70]. The androgen receptor (AR) activated

by the binding with androgen could also increase the proliferation of endometrial cells by the Notch signaling pathway [66, 71]. Insulin resistance increases C-reactive protein (CRP) levels and was associated with an increased risk of endometrial cancer in postmenopausal women [66, 72]. This show that endometrial cancer could be associated with the chronic inflammation that present in type 2 diabetes.

Obesity is a well-established risk factor form endometrial cancer, and due to close relationship between obesity and type 2 diabetes it is important to distinguish and there a very few studies that examined the effect of diabetes in endometrial cancer by body weight, and the findings in this studies is inconsistent [73]. There are many studies that examine the association between diabetes and the incidence of endometrial cancer, but only three studies adjusted for body mass index (BMI) and one study reported a significant association of endometrial cancer risk and diabetes [74, 75].

Association between diabetes and incidence of endometrial cancer and the potential effect of modification by obesity and physical activity was prospectively examined in the Swedish Mammography Cohort Study. Diabetes was associated with an increased risk for endometrial cancer, and combination of diabetes with obesity and low physical activity was associated with a further increased risk for endometrial cancer [76]. Interventions to reduce body weight and increase physical activity may have important implications in terms of endometrial cancer and future management of diabetic subjects.

5.3. Diabetes and colorectal cancer

In 2012, there were an estimated 1.4 million new colorectal cancer cases and 693,900 deaths. The highest colorectal cancer incidence rates in both males and females are in Japan, followed by Europe, Oceania, and North America. The lowest rates are found in Africa, some Asian countries, and Latin America and the Caribbean [2].

Type 2 diabetes was suggested as a risk factor for colorectal cancer [77]. Mechanisms implicated in this association are a slower bowel transit in patient with diabetes, that lead to increased exposure to toxins, increased production of carcinogenic bile acids and hyperinsulinemia [78].

Hyperinsulinemia has been associated with insulin resistance, increased levels of growth factors, including IGF-1, and alterations in NF-_B and peroxisome proliferator-activated receptor signaling, which may promote colon cancer through their effects on colonocyte kinetics and was explored in most studies.

The Nurses' Health Study shown that patients with type 2 diabetes included in the study had a relative risk for colorectal cancer of 1.43 [79]. Several studies shown an increased risk for colorectal cancer in diabetic patients using insulin therapy [80] and also reported increased mortality in diabetic patients with colorectal cancer aged over 30 [77].

In conclusion, both colorectal cancer risk and mortality appear to be increased in patients with type 2 diabetes and hyperinsulinemia is mediating this association.

5.4. Diabetes and pancreatic cancer

Cancer of the pancreas is one of the deadliest cancer types. Based on the GLOBOCAN 2012 evaluation it is estimated that pancreatic cancer is responsible for more than 330,000 deaths per year, putting pancreatic cancer on the seventh place of leading causes of cancer death in both sexes together. Worldwide, according to data available, more than 330,000 people had pancreatic cancer in 2012, making it the 11th most common cancer, and the highest incidence and mortality rates due to pancreatic cancer are found in developed countries [2].

The causes of pancreatic cancer are still insufficiently known, but certain risk factors have been identified to have an impact in the development of pancreatic cancer. Risk factors implicated in pancreatic cancer are smoking, obesity, genetics, diabetes, diet, physical inactivity [81].

Diabetes mellitus is associated with an increased risk of pancreatic cancer; data in literature shown that both type I and type II diabetes have doubled the risk of pancreatic cancer [82]. Diabetes may be a risk factor for pancreatic cancer, but may also be the result of pancreatic cancer itself. Mechanism implicated is hyperinsulinemia, insulin has been shown to promote growth in pancreatic cell line and insulin resistance may enhance pancreatic carcinogenesis through enhanced proliferation of islet cells and increase cell turnover [83]. In type 2 diabetes exocrine pancreatic cells are exposed to high levels of insulin, and insulin act as mitogen leading to tumor growth. But this does not explain the increased risk of pancreatic cancer in type 1 diabetic patients and in patients treated with insulin therapy [84]. On the other hand, pancreatic cancer can be the cause of diabetes, through islet cell destruction and insulin resistance. It is not clear how pancreatic cancer can determine insulin resistance, but has been shown that diabetic patients with pancreatic cancer have increased plasma levels of islet amyloid polypeptide, a hormonal factor secreted by pancreatic cells that may cause insulin resistance [85].

Insulin resistance may appear early in pancreatic cancer, and patients may be diagnosed with diabetes long before developing sign or symptoms of pancreatic cancer. This concept was introduced by Gullo et al. [86]

In conclusion, further studies are necessary to explain this complicated association between diabetes and pancreatic cancer.

5.5. Diabetes and prostate cancer

Unlike others cancers that were discussed before, prostate cancer have been shown to have a decreased incidence among type 2 diabetic patients, studies show a decreased risk for prostate cancer in diabetic patients (9–16%) [87, 88].

High testosterone levels are associated with prostate cancer and type 2 diabetic patients commonly have low levels of testosterone, are obese and elderly and both are associated with low levels of testosterone, and this may be one of the reason that can explain the negative association with prostate cancer.

Some studies have suggested that the link between prostate cancer and diabetes is mediated by the effect of hyperinsulinemia on testosterone levels [89]. Other studies have shown a negative association between hyperglycemia, hyperinsulinemia and prostate cancer. For example, Stocks and colleagues [90] in their prospective study reported that increased insulin resistance and low glycemic control is associated with low risk for prostate cancer in diabetic patients.

Despite the fact that prostate cancer risk may be low in diabetic patients, they may have higher risk for cancer related mortality than non-diabetic patients.

Prostate cancer is an important example of the complexity of carcinogenesis associated with diabetes. On the one hand, an association between diabetes, IGF-1, hyperinsulinemia and insulin resistance appears plausible, but on the other, these features can be somewhat counterbalanced as well and can reduce the risk for the development of one of the leading cancer entities worldwide.

5.6. Diabetes and hepatic cancer

Hepatocellular carcinoma (HCC) represents the most common form of primary liver cancer. The association between HCC and type 2 diabetes was reported first 30 years ago, when Lawson documented that type 2 diabetes is more prevalent in patients with HCC, irrespective of viral hepatitis, alcoholic cirrhosis or hemochromatosis [91].

Since then, multiple studies have shown an association between type 2 diabetes and HCC, and documented the increased risk for HCC in diabetic patients, independent of age, sex, obesity, smoking, hypertension, presence of cirrhosis and hepatic steatosis [92–94].

The exact pathophysiological mechanisms linking type 2 diabetes and HCC are not completely understood, but the understanding of HCC pathophysiology has improved in recent years.

It is well known that type 2 diabetes is associated with increased hepatic and peripheral insulin resistance, lipotoxicity, increased oxidative stress and chronic low-grade inflammatory state, and several studies suggest that all these factors may contribute to the development of HCC by promoting hepatic cellular growth/proliferation and by inhibiting cellular apoptosis. In addition, in the presence of insulin resistance, insulin levels rise in blood, resulting in increased insulin-like growth factor-1 (IGF-1) production that is capable to stimulate hepatic cellular growth and proliferation and inhibit cellular apoptosis in the liver. Hyperinsulinemia also stimulates insulin receptor substrate-1 (IRS-1), which plays an important role in the activation of some intracellular cytokine signaling pathways implicated in hepatic carcinogenesis [95, 96].

There are ongoing studies trying to improve our knowledge about the pathophysiology of HCC. Recently, we have evidence that suggest that gut microbiota alteration may play a role in pathogenesis of type 2 diabetes [98], other studies reported some epigenetic alterations that might be also important for HCC development, for example, the hypermethylation of the E-cadherin-1 (CDH-1) gene has been related to increased incidence of NAFLD-related HCC [95–97].

http://dx.doi.org/10.5772/intechopen.72081

6. Conclusions

Diabetes and cancer are common and serious global health problems, and incidence of both diseases is increasing all over the world. Many studies have suggested the relationship between diabetes and cancer and the fact that diabetes, may affect the risk of developing a variety of cancers, and this association is also biological plausible.

It is important as a clinician to take in consideration all aspects when treating a cancer patient who has diabetes. It is important to consider all complications, cardiac, neurologic and renal complications that are commonly associated with diabetes. Continued improvement of cancer outcomes may be dependent also by the control of diabetes. Taking in consideration the results of numerous epidemiologic and clinical studies involving diabetes and cancer, clinicians must also pay attention to the increased risk of new or longstanding diabetics for some tumor entities by regularly screening diabetic patients for early development of cancer.

The association between diabetes and cancer is complex and need further studies.

It is an important health problem worldwide, and scientists, clinicians and politicians have to develop national policies for early diagnosis and prevention of diabetes and cancer more effectively, otherwise both diseases with their biologic and sociologic relationships could overwhelm health systems.

Author details

Andra-Iulia Suceveanu[1]*, Adrian-Paul Suceveanu[2], Andreea-Daniela Gheorghe[3] and Laura Mazilu[3]

*Address all correspondence to: andrasuceveanu@yahoo.com

1 Faculty of Medicine, Department of Gastroenterology, Emergency Hospital of Constanta, Ovidius University, Constanta, Romania

2 Faculty of Medicine, Department of Internal Medicine, Emergency Hospital of Constanta, Ovidius University, Constanta, Romania

3 Faculty of Medicine, Department of Oncology, Emergency Hospital of Constanta, Ovidius University, Constanta, Romania

References

[1] International Agency for Research on Cancer Section of Cancer Surveillance. Cancer-Mondial [cited 12-01-2015]. Available from: http://www-dep.iarc.fr/

[2] Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. [cited 30-07-2015]. Available from: http://globocan.iarc.fr

[3] Global report on diabetes, World Health Organization. 2016. http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf

[4] Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: Systematic analysis of population health data. Lancet. 2006; **367**:1747-1757. DOI: 10.1016/S0140-6736(06)68770-9

[5] Tuffier T. Diabete et neoplasmes. Archives Generales de Medecine. 1888;**7**:129-140

[6] Jiang Y, Ben Q, Shen H, Lu W, Zhang Y, Zhu J. Diabetes mellitus and incidence and mortality of colorectal cancer: A systematic review and meta-analysis of cohort studies. European Journal of Epidemiology. 2011;**26**:863-876 [PubMed]

[7] Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: A meta-analysis. International Journal of Cancer. 2007;**121**:856-862 [PubMed]

[8] Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, Zhang H, Li Z. Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of cohort studies. European Journal of Cancer. 2011; **47**:1928-1937 [PubMed]

[9] Wang C, Wang X, Gong G, Ben Q, Qiu W, Chen Y, Li G, Wang L. Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: A systematic review and meta-analysis of cohort studies. International Journal of Cancer. 2012;**130**:1639-1648 [PubMed]

[10] Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: A meta-analysis. Diabetologia. 2007;**50**:1365-1374 [PubMed]

[11] Larsson SC, Orsini N, Brismar K, Wolk A. Diabetes mellitus and risk of bladder cancer: A meta-analysis. Diabetologia. 2006;**49**:2819-2823

[12] Mitri J, Castillo J, Pittas AG. Diabetes and risk of non-Hodgkin's lymphoma: A meta-analysis of observational studies. Diabetes Care. 2008;**31**:2391-2397. [PMC free article] [PubMed]

[13] Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. Cancer Epidemiology, Biomarkers & Prevention. 2006;**15**:2056-2062 [PubMed]

[14] Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocrine-Related Cancer. 2009;**16**:1103-1123. Abstract/FREE Full TextGoogle Scholar

[15] Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL, Wolff AC, Brancati FL. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: A systematic review and meta-analysis. JAMA. 2008;**300**:2754-2764. [PMC free article] [PubMed]

[16] Zendehdel K, Nyrén O, Östenson C-G, Adami H-O, Ekbom A, Ye W. Cancer incidence in patients with type 1 diabetes mellitus: A population-based cohort study in Sweden. JNCI: Journal of the National Cancer Institute. December 2003;**95**(23):1797-1800. DOI: 10.1093/jnci/djg105

[17] Cannata D, Fierz Y, Vijayakumar A, LeRoith D. Type 2 diabetes and cancer: What is the connection? Mount Sinai Journal of Medicine. 2010;**77**:197-213. DOI: 10.1002/msj.20167

[18] Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D. Diabetes and cancer: A consensus report. CA: a Cancer Journal for Clinicians. 2010;**60**:207-221. DOI: 10.3322/caac.20078

[19] Aziz NM, Rowland JH. Trends and advances in cancer survivorship research: Challenge and opportunity. Seminars in Radiation Oncology. 2003;**13**:248-266. DOI: 10.1016/S1053-4296(03)00024-9

[20] CDC, Lance Armstrong Foundation. A National Action Plan for Cancer Survivorship: Advancing Public Health Strategies. Atlanta, Georgia: U.S. Department of Health and Human Services, CDC; 2004 Available at http://www.cdc.gov/cancer/survivorship/overview.htm

[21] Schienkiewitz A, Schulze MB, Hoffmann K, Kroke A, Boeing H. Body mass index history and risk of type 2 diabetes: Results from the European prospective investigation into cancer and nutrition (EPIC)-Potsdam study. The American Journal of Clinical Nutrition. 2006; **84**:427-433 PubMed

[22] Wei M, Gaskill SP, Haffner SM, Stern MP. Waist circumference as the best predictor of noninsulin dependent diabetes mellitus (NIDDM) compared to body mass index, waist/hip ratio and other anthropometric measurements in Mexican Americans–a 7-year prospective study. Obesity Research. 1997;**5**:16-23. DOI: 10.1002/j.1550-8528.1997.tb00278

[23] Ma J, Li H, Giovannucci E, et al. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: A long-term survival analysis. The Lancet Oncology. 2008;**9**:1039-1047. DOI: 10.1016/S1470-2045(08)70235-3

[24] Pischon T, Lahmann PH, Boeing H, et al. Body size and risk of colon and rectal cancer in the European prospective investigation into cancer and nutrition (EPIC). Journal of the National Cancer Institute. 2006;**98**:920-931. DOI: 10.1093/jnci/djj246

[25] Knowler WC, Barrett-Connor E, Fowler SE, et al. Diabetes prevention program research group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. The New England Journal of Medicine. 2002;**346**:393-403. DOI: 10.1056/NEJMoa012512

[26] Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. JAMA. 2006;**296**(2):193-201. DOI: 10.1001/jama.296.2.193

[27] Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. JAMA. 2006;**296**:193-201

[28] Lee IM. Physical activity and cancer prevention–data from epidemiologic studies. Medicine and Science in Sports and Exercise. 2003;**35**:1823-1827. DOI: 10.1249/01.MSS.0000093620.27893.23

[29] Friedenreich CM, Orenstein MR. Physical activity and cancer prevention: Etiologic evidence and biological mechanisms. The Journal of Nutrition. 2002;**132**:3456S-3464S. PubMed

[30] Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. JAMA. 2005;**293**(20):2479-2486. DOI: 10.1001/jama.293.20.2479

[31] Meyerhardt JA, Giovannucci EL, Holmes MD, et al. Physical activity and survival after colorectal cancer diagnosis. Journal of Clinical Oncology. 2006;**24**:3527-3534. DOI: 10.1200/JCO.2006.06.0855

[32] Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care. 2006;**29**:2102-2107. DOI: 10.2337/dc06-0560

[33] Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: A systematic review and meta-analysis. JAMA. 2007;**298**:2654-2664 [PubMed]

[34] Haire-Joshu D, Glasgow RE, Tibbs TL. Smoking and diabetes. Diabetes Care. 1999;**22**:1887-1898. DOI: 10.2337/diacare.22.11.1887

[35] Howard AA, Arnsten JH, Gourevitch MN. Effect of alcohol consumption on diabetes mellitus: A systematic review. Annals of Internal Medicine. 2004;**140**:211-219. DOI: 10.7326/0003-4819-140-6-200403160-00011

[36] Baliunas DO, Taylor BJ, Irving H, et al. Alcohol as a risk factor for type 2 diabetes: A systematic review and meta-analysis. Diabetes Care. 2009;**32**:2123-2213. DOI: 10.2337/dc09-0227

[37] Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. Nature Reviews. Cancer. 2008;**8**:915-928. DOI: 10.1038/nrc2536

[38] Zhang H, Pelzer AM, Kiang DT, Yee D. Down-regulation of type I insulin-like growth factor receptor increases sensitivity of breast cancer cells to insulin. Cancer Research. 2007;**67**:391-397. DOI: 10.1158/0008-5472.CAN-06-1712

[39] Frasca F, Pandini G, Scalia P, Sciacca L, Mineo R, Costantino A, Goldfine ID, Belfiore A, Vigneri R. Insulin receptor isoform a, a newly recognized, high-affinity insulin-like growth factor II receptor in fetal and cancer cells. Molecular and Cellular Biology. 1999;**19**:3278-3288. [PMC free article] [PubMed]

[40] De Meyts P, Christoffersen CT, Urso B, Wallach B, Gronskov K, Yakushiji F, Shymko RM. Role of the time factor in signaling specificity: Application to mitogenic and metabolic signaling by the insulin and insulin-like growth factor-I receptor tyrosine kinases. Metabolism. 1995;**44**(10 Suppl 4):2-11 [PubMed]

[41] Papa V, Pezzino V, Costantino A, Belfiore A, Giuffrida D, Frittitta L, Vannelli GB, Brand R, Goldfine ID, Vigneri R. Elevated insulin receptor content in human breast cancer. The Journal of Clinical Investigation. 1990;**86**:1503-1510. DOI: 10.1172/JCI114868

[42] Chen W, Wang S, Tian T, et al. Phenotypes and genotypes of insulin-like growth factor 1, IGF-binding protein-3 and cancer risk: Evidence from 96 studies. European Journal of Human Genetics. 2009;**17**(12):1668-1675. DOI: 10.1038/ejhg.2009.86

[43] Major JM, Laughlin GA, Kritz-Silverstein D, Wingard DL, Barrett-Connor E. Insulin-like growth factor-I and cancer mortality in older men. The Journal of Clinical Endocrinology and Metabolism. 2010;**95**(3):1054-1059. DOI: 10.1210/jc.2009-1378

[44] Calle EE, Kaaks R. Overweight, obesity and cancer: Epidemiological evidence and proposed mechanisms. Nature Reviews. Cancer. 2004;**4**:579-591. DOI: 10.1038/nrc1408

[45] World Cancer Research Fund, American Institute for Cancer Research. Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective. American Institute for Cancer Research: Washington, D.C.; 2007. DOI: 10.1126/science.1160809

[46] van Kruijsdijk RC, van der Wall E, Visseren FL. Obesity and cancer: The role of dysfunctional adipose tissue. Cancer Epidemiology, Biomarkers & Prevention. 2009;**18**:2569-2578. DOI: 10.1158/1055-9965.EPI-09-0372

[47] Wu Y, Antony S, Meitzler JL, Doroshow JH. Molecular mechanisms underlying chronic inflammation-associated cancers. Cancer Letters. 2014;**345**(2):164-173. DOI: 10.1016/j.canlet.2013.08.014

[48] Abbour S. Primary care physicians and insulin initiation: Multiple barriers, lack of knowledge or both? International Journal of Clinical Practice. 2008;**62**:845-847. DOI: 10.1111/j.1742-1241.2008.01757.x

[49] Richard M et al. Type 2 diabetes: Assessing the relative risks and benefits of glucose-lowering medications Bergenstal. The American Journal of Medicine. **123**(4):374. e9 - 374.e18. DOI: 10.1016/j.amjmed.2009.07.017

[50] Blin P, Lassalle R, Dureau-Pournin C, et al. Insulin glargine and risk of cancer: A cohort study in the French National Healthcare Insurance Database. Diabetologia. 2012;**55**(3):644-653. DOI: 10.1007/s00125-011-2429-5

[51] Hemkens LG, Grouven U, Bender R, et al. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: A cohort study. Diabetologia. 2009;**52**(9):1732-1744. DOI: 10.1007/s00125-009-1418-4

[52] Chang C-H, Lin J-W, Wu L-C, Lai M-S, Chuang L-M. Oral insulin Secretagogues, insulin, and cancer risk in type 2 diabetes mellitus. The Journal of Clinical Endocrinology & Metabolism. July 2012;**97**(7):E1170-E1175. DOI: 10.1210/jc.2012-1162

[53] Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. Diabetes Care. Feb 2006;**29**(2):254-258. DOI: 10.2337/diacare.29.02.06.dc05-1558

[54] Monami M, Colombi C, Balzi D, et al. Metformin and cancer occurrence in insulin-treated type 2 diabetic patients. Diabetes Care. 2011;**34**(1):129-131. DOI: 10.2337/dc10-1287

[55] Key TJ, Verkasalo PK, Bancks E. Epidemiology of breast cancer. The Lancet Oncology. **2**(3):133-140. DOI: 10.1016/S1470-2045(00)00254-0

[56] Xue F, Michels KB. Diabetes, metabolic syndrome, and breast cancer: A review of the current evidence. The American Journal of Clinical Nutrition. 2007 Sep;**86**(3):s823-35

[57] Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: A meta-analysis. International Journal of Cancer. 2007;**121**:856-862. DOI: 10.1002/ijc.22717

[58] Ish-Shalom D, Christoffersen C, Vorwerk P, et al. Mitogenic properties of insulin and insulin analogues mediated by the insulin receptor. Diabetologia. 1997;**40**(Suppl 2):S25. DOI: 10.1007/s001250051393

[59] Chappell J, Leitner JW, Solomon S. Effect of insulin on cell cycle progression in MCF-7 breast cancer cells. Direct and potentiating influence. The Journal of Biological Chemistry. 2001 Oct 12;**276**(41):38023-80. Epub 2001 Aug 10

[60] Brunet J, Vazquez-Martin A, Colomer R, Graña-Suarez B, Martin-Castillo B, Menendez JA. BRCA1 and acetyl-CoA carboxylase: The metabolic syndrome of breast cancer. Molecular Carcinogenesis. 2008;**47**:157-163. DOI: 10.1002/mc.20364

[61] Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE, Li J, Ho GY, Xue X, Anderson GL, Kaplan RC, Harris TG, Howard BV, Wylie-Rosett J, Burk RD, Strickler HD. Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. JNCI: Journal of the National Cancer Institute. January 2009;**101**(1):48-60. DOI: 10.1093/jnci/djn415

[62] Michels KB, Solomon CG, Hu FB, Rosner BA, Hankinson SE, Colditz GA, Manson JAE. Type 2 diabetes and subsequent incidence of breast cancer in the nurses' health. Study Diabetes Care. Jun 2003;**26**(6):1752-1758. DOI: 10.2337/diacare.26.6.1752

[63] Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. American Journal of Epidemiology. June 2004;**159**(12):1160-1167. DOI: 10.1093/aje/kwh161

[64] DeCensi A, Gennari A. Insulin breast cancer connection: Confirmatory data set the stage for better care. Journal of Clinical Oncology. 2011;**29**(1):7-10

[65] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA: a Cancer Journal for Clinicians. 2015;**65**:87

[66] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA: a Cancer Journal for Clinicians. 2016;**66**:7

[67] Joung KH, Jeong J-W, Ku BJ. The association between type 2 diabetes mellitus and women cancer: The epidemiological evidences and putative mechanisms. BioMed Research International. 2015;**2015**:920618. DOI: 10.1155/2015/920618

[68] Mu N, Zhu Y, Wang Y, Zhang H, Xue F. Insulin resistance: A significant risk factor of endometrial cancer. Gynecologic Oncology. 2012;**125**(3):751-757. DOI: 10.1016/j.ygyno.2012.03.032

[69] Bruchim I, Sarfstein R, Werner H. The IGF hormonal network in endometrial cancer: Functions, regulation, and targeting approaches. Frontiers in Endocrinology. 2014;**5**:76. DOI: 10.3389/fendo.2014.00076

[70] Syed V, Ulinski G, Mok SC, Ho S-M. Reproductive hormone-induced, STAT3-mediated interleukin 6 action in normal and malignant human ovarian surface epithelial cells.

JNCI: Journal of the National Cancer Institute. April 2002;**94**(8):617-629. DOI: 10.1093/jnci/94.8.617

[71] Wang T, Rohan TE, Gunter MJ, et al. A prospective study of inflammation markers and endometrial cancer risk in postmenopausal hormone nonusers. Cancer Epidemiology, Biomarkers and Prevention. 2011;**20**(5):971-977. DOI: 10.1158/1055-9965.EPI-10-1222

[72] Crosbie EJ, Zwahlen M, Kitchener HC, Egger M, Renehan AG. Body mass index, hormone replacement therapy, and endometrial cancer risk: A meta-analysis. Cancer Epidemiology, Biomarkers & Prevention. 2010;**19**(12):3119-3130. DOI: 10.1158/1055-9965.EPI-10-0832

[73] Friberg E, Mantzoros CS, Wolk A. Diabetes and risk of endometrial cancer: A population-based prospective cohort study. Cancer Epidemiology, Biomarkers & Prevention. 2007;**16**(2):276-280. DOI: 10.1158/1055-9965.EPI-06-0751

[74] Terry P, Baron JA, Weiderpass E, Yuen J, Lichtenstein P, Nyrén O. Lifestyle and endometrial cancer risk: A cohort study from the Swedish twin registry. International Journal of Cancer. 1999;**82**:38-42. DOI: 10.1002/(SICI)1097-0215(19990702)82:1<38::AID-IJC8>3.0.CO;2-Q

[75] Anderson KE, Anderson E, Mink PJ, Hong CP, Kushi LH, Sellers TA, Lazovich D, Folsom AR. Diabetes and endometrial cancer in the Iowa women's health study. Cancer Epidemiology, Biomarkers & Prevention. 2001;**10**(6):611-616. [PubMed]

[76] Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: A metaanalysis. Diabetologia. 2007;**50**:1365-1374

[77] Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: A meta-analysis. JNCI: Journal of the National Cancer Institute. November 2005;**97**(22):1679-1687. DOI: 10.1093/jnci/dji375

[78] Will JC, Galuska DA, Vinicor F, Calle EE. Colorectal cancer: Another complication of diabetes mellitus? American Journal of Epidemiology. May 1998;**147**(9):816-825. DOI: 10.1093/oxfordjournals.aje.a009534

[79] Yakar S, Nunez NP, Pennisi P, Brodt P, Sun H, Fallavollita L, Zhao H, Scavo L, Novosyadlyy R, Kurshan N, Stannard B, East-Palmer J, Smith NC, Perkins SN, Fuchs-Young R, Barrett JC, Hursting SD, Le Roith D. Increased tumor growth in mice with diet-induced obesity: Impact of ovarian hormones. Endocrinology. December 2006;**147**(12):5826-5834. DOI: 10.1210/en.2006-0311

[80] Yang YX, Hennessy S, Lewis JD. Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. Gastroenterology. 2004. DOI: 10.1053/j.gastro.2004.07.011

[81] Bosetti C, Bertuccio P, Negri E, La Vecchia C, Zeegers MP, Boffetta P. Pancreatic cancer: Overview of descriptive epidemiology. Molecular Carcinogenesis. 2012;**51**:3-13. DOI: 10.1002/mc.20785

[82] Batabyal P, Vander Hoorn S, Christophi C, Nikfarjam M. Association of diabetes mellitus and pancreatic adenocarcinoma: A meta-analysis of 88 studies. Annals of Surgical Oncology. 2014;**21**:2453-2462. DOI: 10.1245/s10434-014-3625-6

[83] Silverman DT, Schiffman M, Everhart J. Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. British Journal of Cancer. 1999;**80**:1830-1837. DOI: 10.1038/sj.bjc.6690607

[84] Stevens RJ, Roddam AW, Beral V. Pancreatic cancer in type 1 and young-onset diabetes: Systematic review and meta-analysis. British Journal of Cancer. 2007;**96**:507-509. DOI: 10.1038/sj.bjc.6603571

[85] Permert J, Larsson J, Westermark GT, Herrington MK, Christmanson L, Pour PM, Westermark P, Adrian TE. Islet amyloid polypeptide in patients with pancreatic cancer and diabetes. The New England Journal of Medicine. 1994, February 1994;**330**:313-318. DOI: 10.1056/NEJM199402033300503

[86] Gullo L, Pezzilli R, Morselli-Labate AM, the Italian Pancreatic Cancer Study Group. Diabetes and the risk of pancreatic cancer. The New England Journal of Medicine. 1994, July 1994;**331**:81-84. DOI: 10.1056/NEJM199407143310203

[87] Bonovas S, Filioussi K, Tsantes A. Diabetes mellitus and risk of prostate cancer: A meta-analysis. Diabetologia. 2004;**47**:1071. DOI: 10.1007/s00125-004-1415-6

[88] Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. Cancer Epidemiology, Biomarkers & Prevention. November 2006;**15**(11):2056-2062. DOI: 10.1158/1055-9965.EPI-06-0410

[89] Grossmann M, Thomas MC, Panagiotopoulos S, Sharpe K, MacIsaac RJ, Clarke S, Zajac JD, Jerums G. Low testosterone levels are common and associated with insulin resistance in men with diabetes. The Journal of Clinical Endocrinology & Metabolism. May 2008;**93**(5):1834-1840. DOI: 10.1210/jc.2007-2177

[90] Stocks T, Lukanova A, Rinaldi S, Biessy C, Dossus L, Lindahl B, Hallmans G, Kaaks R, Stattin P. Insulin resistance is inversely related to prostate cancer: A prospective study in northern Sweden. International Journal of Cancer. 2007;**120**:2678-2686. DOI: 10.1002/ijc.22587

[91] Lawson DH, Gray JM, McKillop C, et al. Diabetes mellitus and primary hepatocellular carcinoma. The Quarterly Journal of Medicine. 1986;**61**:945-955. [PubMed]

[92] Romeo S, Kozlitina J, Xing C, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nature Genetics. 2008;**40**(12):1461-1465. DOI: 10.1038/ng.257

[93] Falleti E, Fabris C, Cmet S, Cussigh A, Bitetto D, Fontanini E, Fornasiere E, Bignulin S, Fumolo E, Bignulin E, Pirisi M, Toniutto P. PNPLA3 rs738409C/G polymorphism in cirrhosis: Relationship with the aetiology of liver disease and hepatocellular carcinoma occurrence. Liver International. 2011;**31**:1137-1143. DOI: 10.1111/j.1478-3231.2011.02534.x

[94] Evans JMM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. BMJ British Medical Journal. 2005;**330**(7503):1304-1305. DOI: 10.1136/bmj.38415.708634.F7

[95] Donadon V, Balbi M, Mas MD, Casarin P, Zanette G. Metformin and reduced risk of hepatocellular carcinoma in diabetic patients with chronic liver disease. Liver International. 2010;**30**:750-758. DOI: 10.1111/j.1478-3231.2010.02223.x

[96] Dapito DH, Mencin A, Gwak G-Y, et al. Promotion of hepatocellular carcinoma by the intestinal microbiota and TLR4. Cancer Cell. 2012;**21**(4):504-516. DOI: 10.1016/j.ccr.2012.02.007

[97] Liu YL, Patman GL, Leathart JB, et al. Carriage of the PNPLA3 rs738409 C>G polymorphism confers an increased risk of non-alcoholic fatty liver disease associated hepatocellular carcinoma. Journal of Hepatology. 2014;**61**:75-81. DOI: 10.1016/j.jhep.2014.02.030

IntechOpen