

Type 2 diabetes mellitus and cancer



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Abstract

The question whether diabetes mellitus is associated with an increased risk for development of cancer cannot be clearly answered. The mechanism(s) responsible for this association is yet not fully understood. It remains controversial whether chronic hyperglycaemia in people with type 2 diabetes mellitus (T2DM) itself is a main factor increasing risk for cancer or whether the risk of neoplastic transformation correlates with other biochemical abnormalities and pharmacological treatment of diabetes.

Evidence from experimental and clinical studies indicates insulin resistance and related abnormalities (e.g. hyperin-

sulinism and obesity) as a major risk factors. Therefore, it is suggested that insulin sensitizers, such as metformin or glitazones may diminish the risk of cancer. On the other hand, insulin secretagogues are suggested to increase a chance for cancer development since it was demonstrated that insulin in high concentration may influence cell proliferation and apoptosis and thus play a role in carcinogenesis. The aim of this review is to summarize current state of knowledge about T2DM and cancer association.

key words: type 2 diabetes mellitus, cancer, insulin, oral hypoglycaemic drugs

Introduction

Results of the large prospective mortality study recently conducted in USA suggest that diabetes may be

an independent risk factor for death from cancers of colon, liver, pancreas, and female breast and, in men, of the liver and bladder [1]. On the other hand, it is estimated that approximately 8–18% of people with malignancies have diabetes [2]. Some, but not all, epidemiological studies have indicated that people with T2DM are at higher risk of developing a variety of cancers, including breast, pancreatic, liver, kidney, endometrial, and colon cancer. Interestingly enough, patients with type 1 diabetes are more likely to develop cervical and stomach cancers [3].

Although major advances have been made in clarifying the relation between diabetes and cancer, the quest-

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ion whether diabetes mellitus is associated with an increased or a reduced risk for the development of cancer cannot be answered. In addition, the exact mechanism (s) of diabetes — cancer interaction if it really exists — remains incompletely understood. Neoplastic transformation in people with T2DM seems to be a complex, multistep process, which may be influenced by many factors. Among proposed biological mechanisms, explaining diabetes-cancer correlation, there are observations that higher levels of insulin resistance and related abnormalities (i.e. hyperglycaemia, hyperinsulinism, obesity) may have an impact on cell differentiation, proliferation and apoptosis and thus play a key role in carcinogenesis. In addition, there is also evidence that some hypoglycaemic drugs that increase insulin levels, may promote cancer development at various sites.

Hyperglycaemia

Hyperglycaemia was first described in patients with cancer in 1885 [4]. However, results from epidemiological studies of the association between abnormal glucose tolerance and cancer are mixed. Several studies did not find any association between diabetes and cancer [5]. In contrary, Saydah has found that impaired glucose tolerance is an independent predictor for cancer and cancer mortality [6]. Stattin et al. have reported results of a large prospective cohort study, with a 18-year duration of follow-up, exploring the link between chronic hyperglycaemia and cancer. The obtained results provide further evidence for this comorbidity relationship [7].

There are at least few possible mechanisms underlying the association between hyperglycaemia and cancer. One possible explanation is that elevated blood glucose level acts directly as a carcinogenic factor. At a cellular level, glucose may lead to activation of energy sensing mechanisms, which in turn favour cellular growth and proliferation. Another potential mechanism is an elevated glucose concentrations that may stimulate cancer growth through increased formation of advanced glycation end-products [8]. In an experimental study, high glucose itself was shown to induce DNA damage [9]. It has also been demonstrated that hyperglycaemia is associated with increased production of free radicals in mitochondria and may contribute to greater oxidative damage to DNA [10]. Free radicals are formed disproportionately in people with diabetes by autooxidation of glucose, sorbitol pathway activation, increased mitochondrial production of superoxide anions, and oxidative degradation of advanced glycation end-products [11]. The accumulation of free radicals, mainly reactive oxygen species (ROS) and nitrogen reactive species (NOS), may lead to the activation of pathways that con-

trol cell differentiation and apoptosis. These very active species may also cause damage to various biological macromolecules, including lipids, proteins and both nuclear and mitochondrial DNA. It has been suggested that mitochondrial DNA damage is more extensive and persists longer than nuclear DNA damage due to limited ability to repair [12, 13]. Nuclear and mitochondrial DNA damage may promote a great number of mutations, which in turn may lead to malignant transformation. The role of free radicals and the oxidative stress in the carcinogenesis is a well-known [14]. Recently, we have shown that type 2 diabetes mellitus may be associated not only with an elevated level of oxidative DNA damage but also with the increased susceptibility to mutagens and decreased efficacy of DNA repair [15]. It was also found that glucose at high concentrations may inhibit the expression of the DNA repair protein XPD induced by insulin [16]. Therefore, both an elevated level of DNA damage in diabetics and insufficient DNA repair processes may be considered as important cancer risk factors. It was shown that the extent of DNA damage correlates with blood glucose concentration and DNA damage was significantly higher in poorly-controlled diabetics than in well-controlled diabetics both in men and women [6, 17–20].

In recent years evidence has accumulated indicating that both fasting and postprandial hyperglycaemia increase the risk of various type of cancer. Yamagata et al. have found that even a modest increase in fasting plasma glucose (FPG) is a risk factor for gastric cancer in men and women and that hyperglycaemia is a possible cofactor increasing the risk posed by *Helicobacter pylori* infection [21].

The large Korean and Austrian cohort study have also found statistically significant association of fasting plasma glucose levels with risk of pancreatic cancer, as well as of endometrial cancer, and twofold increase of risk of malignant melanoma among women aged < 49 years, an increase in breast cancer risk correlated with high fasting glucose level was observed. Interestingly, among Paris policemen, isolated postchallenge hyperglycaemia (IGT) was not associated with increased coronary heart disease, but with increased risk of malignancy, the 10-year death rate from cancer increasing from 3 to 5 to 8% and the 20 year risk increasing from 10 to 16 to 31% in normal versus isolated postload IGT versus isolated postload diabetes, respectively [22, 23].

The Nurses' Health Study has shown that diet with a high glycaemic load was associated with an increased risk of pancreatic cancer. These results confirm previous observations indicating that high postprandial blood glucose level may increase the risk of cancer in women who already have an underlying degree of insulin resistance [24, 25].

As it was mentioned above, hyperglycaemia both acute and chronic leads to an elevated level of oxidative

stress that in turn activates nuclear factor- κ B (NF- κ B) and several pro-inflammatory mediators such as tumor necrosis factor α (TNF α) and interleukin 6 (IL-6). The increase level of proinflammatory cytokines expresses a low grade chronic inflammatory process that is often seen in people with T2DM. It is suggested that inflammation is an important event in carcinogenesis, however, the exact pathway of this transition has not been clarified until now. TNF α and IL-6 are recognized mediators of insulin resistance and play, mainly TNF α , a crucial role in the proliferation of certain tumors and metastatic spread [26]. In addition, TNF α may also reduce the expression of the major histocompatibility (MHC) class I molecule on the cell surface allowing malignant cells to be unrecognized by immune system [27]. The association inflammation-cancer has been confirmed in few clinical studies. Therefore, it can not be also excluded that chronic low grade inflammatory process induced by hyperglycaemia may increase the risk of neoplastic transformation. This hypothesis is supported by clinical observations. Ujpal et al. reported possible correlation between oral inflammation and precancerous lesions (leukoplakia and erythroplakia), and tumors in patients with diabetes related periodontitis and the atrophic lesions [28]. Gatti et al. suggested that *Helicobacter pylori* infection in people with diabetes can increase the risk of gastric adenocarcinoma [29].

Insulin resistance/hiperinsulinism

Among the major mechanisms that have been linked with the increased risk of cancer in T2DM patients, insulin resistance and related factors such as: compensatory hyperinsulinemia, obesity, hyperglycaemia and hormonal abnormalities can be found. It is suggested that some of these factors are important in the early cancer development, whereas others may be important for tumor progression [30]. Apart from effects on carbohydrates, lipids, and proteins metabolism, insulin may also act as a growth promoting hormone with mitogenic effects in both normal and malignant tissue [31, 32]. Hyperinsulinemia may affect the development of cancer directly or through insulin-like growth factor or stimulation of insulin-like growth factor receptors. It has also been shown that insulin suppresses IGF binding protein-1 and thus increases the free fraction of IGF-1.

Epidemiologic studies have observed an elevated risk of colorectal cancer associated with high circulating insulin and C-peptide concentrations [33]. Therefore, it is likely that insulin and its precursors, that have been shown to have some homology to the insulin-like growth factors, may influence cell proliferation and apoptosis and thus play a role in carcinogenesis [34]. Association between

insulin and IGF-I levels and colorectal cancer suggests that a diet inducing high blood glucose levels and an elevated insulin response in people with insulin resistance may contribute to tumor growth [25]. A diet with a high dietary glycaemic load may increase the risk of colorectal cancer in women. Ogihara et al. have demonstrated that insulin enhances the stimulatory effects of epidermal growth factor on the proliferation of cultured gastric epithelial cells. This observation supports the indirect effect of insulin on cell proliferation that may predisposes to genetic alterations and, therefore, to carcinogenesis [35].

Majority of T2DM patients are overweight or obese. Therefore, the term of diabetes have been recently introduced. It has been shown that overweight and obesity are associated with increased risk for breast, colon, endometrium, esophagus, gallbladder, liver, prostate, ovarian, pancreas, and kidney cancer [36–39]. Calle et al. suggest that obesity may account for 14% of cancers in men and 20% of cancers in women, and in this cohort the heaviest men and women were 52 and 62%, respectively, more likely to die of cancer [40].

Several biological mechanisms have been proposed to link diabetes with some types of cancer, among them are the observations that majority of people with obesity have higher levels of insulin-resistance and other biochemical abnormalities.

In pre- and post-menopausal women, obesity is associated with increased plasma concentration of testosterone and reduced levels of sex hormone binding globulins (SHGBs). As a consequence, the amount of free and biologically active androgens increases. Obesity leads also to a rise in endogenous estrogen levels. Testosterone possesses higher affinity for SHGBs than estrogens, consequently plasma concentrations of free estrogens increase. In addition, it should be pointed out that androgens are converted into estrogens by peripheral adipose tissue. Moreover, higher levels of insulin reduce serum concentration of insulin-like growth factor binding proteins (IGFBP-1 and IGFBP-3). Reduction of IGFBPs increases plasma level of IGF-1. Insulin and IGF-1 exert a gonadotropic activity, which potentiates the synthesis of steroids in the ovary, mainly androgens, and inhibits the hepatic production of SHGB. Hyperinsulinemia may elevate free plasma estrogen levels through SHBG inhibition, which may be particularly relevant in women with low estrogen levels. Estrogens alter the expression of different members of the IGF family, such as IGFR-1 and IGFR-2, IGF-2 and, IGFBPs. Expression of IGFs is essential for the estrogen-mediated growth. Thus, estrogens increasing the sensitivity of neoplastic cells to insulin may stimulate their growth [41].

The first direct evidence of an association between elevated visceral adipose tissue level and colorectal cancer was reported by Schoen et al. [37]. An increase risk

for both T2DM and cancer in people with obesity, possibly through a common mechanism of insulin resistance, was shown in some other studies [42, 43]. However, results from epidemiological studies of the association of obesity/diabetes and different types of cancer are mixed. For example, Garmendia et al. reported no association between obesity and breast cancer in women at any age [44]. These observations are in concordance with those reported by Stattin et al. [7]. This may suggest that other factors connected with T2DM may play a role in the development of cancer. For example, the existence of non-alcoholic fatty liver in diabetics and a high incidence of viral hepatitis should also be taken into consideration, because its role in developing liver cirrhosis and primary liver cancer [45].

Hypoglycaemic drugs

Insulin

Insulin is the only therapy which is efficacious in T2DM once β -cell failure has supervened. It has been postulated that insulin treatment might be responsible for coexistence of T2DM and cancer through the disturbances in the insulin signalling pathway. It has been established that binding insulin to the specific region of a subunit of insulin receptor (IR) causes the structural changes of IR and autophosphorylation of tyrosine residues in the intracellular β subunit. Metabolic effects of insulin are related with insulin receptor substrate 1 (IRS-1) and insulin receptor substrate 2 (IRS-2). Activation of IRS by phosphorylation of tyrosine residues stimulates two pathways: the phosphatidylinositol-3-kinase pathway and the mitogen-activated protein-signalling pathway (MAPK). MAPK promotes cell growth and proliferation. It is worth emphasizing that in case of insulin resistance the MAPK pathway is not inhibited [46]. Interestingly, it was observed that long-term insulin therapy is associated with an increased risk of colorectal cancer among T2DM patients [33, 37, 47]. An increased incidence of malignancies of colon and rectum in insulin-treated patients with diabetes mellitus was also noted in The JEVIN-trial [48].

Yang et al. observed 197 cases of colorectal cancer in insulin users per 100,000 p-year compared with 124 per 100,000 person year in T2DM patients not receiving insulin. The age- and sex-adjusted HR of colorectal cancer associated with ≥ 1 year of insulin use was 2.1 (95% CI: 1.2–3.4, $P = 0.005$). Patients who received ≥ 3 years of cumulative insulin therapy had 3 times higher risk of colorectal cancer (adjusted OR, 3.4; 95% CI: 1.5–7.7, $P = 0.004$) compared with patients who received no insulin. Interestingly, Yang et al. have found no corre-

sponding association of cancer with metformin, sulphonylureas, or their combination. The multivariable OR associated with 3 or more years of therapy was 1.0 (95% CI: 0.6–1.7), 0.8 (95% CI: 0.5–1.2) and 1.2 (95% CI: 0.7–2.2) for metformin, sulphonylureas and their combination, respectively [47].

On the other hand, Chuang et al. demonstrated that T2DM patients who received insulin had a lower risk of developing of non-melanoma skin cancer (NMSC) compared with non-insulin users (1.40% vs. 2.35%, $P = 0.11$) [49]. Skin keratinocytes express the IGFR-1, but they do not synthesize IGF-1 [50]. Dermal fibroblasts support the proliferation of keratinocytes in the epidermis by secreting IGF-1. As dermal fibroblasts age, their ability to produce IGF-1 is severely diminished. Chuang et al. believed that decrease in IGF-1 expression with aging is a major component of an increase in NMSC seen in geriatric patients. Thus, an increased activation of IGFR-1 might have given some protection against skin cancer development. Insulin, which is structurally very similar to IGF-1, will bind and activate IGFR-1. Thus, increased serum level of insulin in T2DM may increase the activation of IGFR-1 in skin and decrease the risk of NMSC.

It should also be pointed out that Kath et al. showed no altered risk for malignancies as a function of insulin dosage, the duration of diabetes or insulin therapy, the quality of diabetes control or the prevalence of long-term complications of the disease in subject with diabetes [51].

Metformin

If hyperinsulinemia plays a role in cancer pathogenesis, interventions that improve insulin sensitivity such as exercise and dietary modifications or usage of so-called insulin-sensitizers (metformin and thiazolidinediones) may be expected to lower the risk of tumor growth [52, 53]. Pharmacologic therapies that increase insulin sensitivity in type 2 diabetes, such as metformin, may have a beneficial effect not only on diabetes outcomes, but also on cancer-related mortality.

Metformin is an oral hypoglycaemic drug that does not increase plasma insulin levels. Metformin reduces hepatic glucose production through the inhibition of gluconeogenesis and glycogenolysis. The inhibition of respiratory chain diminishing gluconeogenesis and the activation of expression of glucose transporters consuming glucose in the hepatic mitochondria are primary mechanism of metformin action. It has been shown that metformin increases insulin sensitivity in hepatocytes, adipocytes and, muscle cells by activation of protein kinase $\alpha 2$ activated by AMP (AMP activated protein kinase, AMPK), this leads to increased consumption of glucose and storage of glycogen in skeletal muscle cells. The AMPK is activated by serine/threonine kinase

11 (SKT11, LKB1), which is also a well-known tumor suppressor [54, 55]. Activation of AMPK by metformin and physical activity requires LKB1, and this would also explain why exercise is beneficial in the primary and secondary prevention of certain cancers [56]. Based upon these observations Evans et al. hypothesized that metformin use in T2DM patients may reduce their risk of cancer development. This assumption has been supported by findings that people with T2DM treated with metformin had lower risk of cancer (OR 0.79; CI: 0.67–0.93) that those using other hypoglycaemic agents [57].

Thiazolidinediones (TZDs)

Thiazolidinediones are synthetic ligands of the intracellular peroxisome-activated receptor γ (PPAR γ). PPAR γ is a nuclear receptor/transcription factor found in adipocytes, skeletal muscle cells and hepatocytes. Thiazolidinediones activates PPAR γ and regulates transcription by two mechanisms:

- transactivation; DNA dependent, PPAR γ forms a heterodimer with the retinoid X receptor (RXR) and recognizes specific DNA response elements called PPAR response elements (PPRE) in the promotor region of target genes: lipoprotein lipase, fatty acids transporters protein, fatty acyl coenzyme A synthase and insulin dependent glucose transporters GLUT-4;
- transrepression: DNA independent, PPAR γ inhibits transcription negatively interfering with other signal-transduction pathways, such as the NF- κ B signalling pathway [58].

The main biological effect of TZDs on adipose tissue is to increase fatty acids uptake, thus lowering triglycerides and non-estrified fatty acids. Thiazolidinediones decreases insulin resistance in skeletal muscle by the facilitation of glucose uptake and utilization (through the facilitation of glucose transport, glycogen synthesis and glucose oxidation). Thiazolidinediones increase the number of small adipocytes and the subcutaneous adipose-tissue mass [59].

Some in vitro studies showed anti-neoplastic action of particular member of TZDs class. For example, troglitazon inhibited the growth of human cancer cell lines in lung, colon (HTC-116), breast (MCF-7) and prostate (PC-3) in immunodeficient mice [60–64].

The molecular mechanisms are still not clear and several possible mechanisms of anticarcinogenic action of TZDs are suggested:

- stimulation of cell differentiation; Ohta et al. have demonstrated that PPAR γ agonists induce increase of differentiation markers: E-cadherin and carcinoembryonic antigen, what stimulate pancreatic cancer cell differentiation (BxPC-3) [65]. TZD not only inhibits cell and clonal growth, but also induces G1 cell cycle arrest through the induction of p21WAF-1 and upre-

gulation of differentiation markers. According to this Li et al. have demonstrated that TZD promoted terminal differentiation and morphological changes to well-differentiated and less malignant state [66, 67];

- antiproliferative action/cell cycle arrest: Troglitazone caused G1 cell cycle arrest in human hepatocarcinoma cell line (Huh7 i Hep3B) by the induction of p27. p27 is an inhibitor of cyclin D/cyclin-dependent kinase (Cdk) 4 and cyclin E/Cdk2, which kinases govern cell cycle progression at the restriction and late transition points of G1 [68, 69];
- apoptosis induction: activation of PPAR γ was associated with decreased Bcl-2 and NF- κ B in human colon cancer and neuroblastoma cells [70–72]. Bcl-2 family, such as: Bcl-X_L, Bcl-w, Mcl-1, A1, are responsible for cell survival. Whereas, the lack of them cause tissue decay, what was observed in Bcl-w $-/-$ mice [73]. PPAR γ agonists induce proapoptotic proteins, such as: Bax, Bid, Bak and Bad that lead to apoptosis [73, 74];
- angiogenesis inhibition: leptin induces the migration of smooth muscle cells through the activation of two pathways: PI3K \rightarrow Akt \rightarrow eNOS and ERK1/MAPK. Troglitazone and ciglitazone suppressed the leptin-induced migration by decrease of expression of this hormone [75];
- inhibition of invasion: activation of PPAR γ inhibits gelatinase B (MMP-9) and the migration of macrophages and muscle cells. Liu et al. have demonstrated that TZD suppressed the migration of invasive breast cancer [76].

Govindarajan et al. conducted a retrospective analysis of a database from 10 Veteran Affairs medical centers to assess the influence of TZD used to treat diabetes mellitus on risk cancer. Data on male patients 40 years and older diagnosed to suffer from diabetes mellitus between 1997–2003 and subsequent diagnoses of colorectal, lung, and prostate cancer and use of TZD, other antidiabetic agents, and insulin were analyzed. They have found 33% reduction in lung cancer risk among TZD users (RR 0.67; 95%; CI: 0.51–0.87) [77].

Sulphonylureas

Association between sulphonylureas therapy of T2DM patients and risk of cancer is well known. Available clinical trial are unequivocal. On the one hand, Bowker et al. showed that T2DM patients using insulin and sulphonylureas had increased risk of death because of cancer [78]. Patients with type 2 diabetes exposed to sulphonylureas and exogenous insulin had a significantly increased risk of cancer-related mortality compared with patients exposed to metformin. It is uncertain whether this increased risk is related to a deleterious effect of sulphonylurea and insulin or a protective effect of metformin or due to some unmeasured effect related to both therapy modalities and cancer risk. Cancer mortality

over follow-up was 4.9% for sulphonylurea monotherapy users, 3.5% for metformin users and 5.8% for insulin users. However, the authors have postulated that T2DM increased the risk of cancer by metabolic syndrome or insulin resistance [78]. On the other hand, Yang et al. have found that sulphonylurea therapy in T2DM was not connected with risk of colorectal cancer [47]. Moreover, sulphonylureas are very diverse group of drugs, and effects of action of particular drug are rather drug specific, but not class specific. Monami et al. performed a retrospective observational cohort study on a consecutive series of 568 outpatients (282 women, 286 men) with type 2 diabetes treated with either glibenclamide (n = 378) or gliclazide (n = 190). Information on all-cause mortality and on causes of death up to 31 December 2004 was obtained by the City of Florence Registry Office. Mean follow-up was 5.0 ± 1.6 and 4.4 ± 2.0 years for death and cardiac events, respectively; during follow-up, 33 and 11 deaths were observed in the glibenclamide and gliclazide groups, with a yearly mortality rate of 4.3 and 2.2%, respectively ($P < 0.05$). Mortality for malignancies was significantly higher in patients treated with glibenclamide after adjustment for age, sex, BMI, and insulin and metformin treatment, [OR 3.6 (1.1–11.9); $P < 0.05$] [79]. Interestingly, we have found that gliclazide decreased the level of DNA damage induced by free radicals. Therefore, we can speculate that the risk of cancer in subjects with T2DM treated by gliclazide may be reduced [80].

Conclusions

Up to now, the studies involving diabetes mellitus and malignancies show controversial results: many of them have found cases of malignancies that were comparable or even lower than those in nondiabetic subjects; others conclude that diabetes mellitus is linked to a higher incidence of malignancies and/or a predictor of mortality due to cancer.

The association between T2DM and increased risk of some types of cancer is not completely understood. Several biological mechanisms have been postulated to account for this association. Chronic hyperglycaemia — the main feature of T2DM—leads to increased oxidative stress by enhanced glucose flux through the polyol pathway, formation of advanced glycation end-products (AGEs), activation of protein kinase C (PKC), and stimulation of the hexosamine pathway. It is postulated that elevated level of oxidative DNA damage may be responsible for increased cancer risk in T2DM patients. Moreover, diabetic patients have decreased efficacy of DNA repair and insufficient endogenous antioxidant system (reduced amount of free radical scavengers). Disturbances in DNA

repair process may form mutations and genome instability bringing neoplastic transformation. The results both experimental and epidemiological studies indicate the important role of insulin-resistance and related disorders in carcinogenesis in people with T2DM. It is also suggested that hypoglycaemic drugs may have an impact on the risk of cancer in people with diabetes and this problem is under intensive investigations. The association between diabetes and cancer is complex and warrants further study as the general population ages and the magnitude of both health problems continues to grow.

References

1. Coughlin SS, Calle EE, Teras LR. et al. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. *Am J Epidemiol* 2004; 159: 1160–1167.
2. Ko C, Chaudhry S. The need for a multidisciplinary approach to cancer care. *J Surg Res* 2002; 105: 53–57.
3. Psarakis HM. APRN. Clinical challenges in caring for patients with diabetes and cancer. *Diabetes Spectrum* 2006; 19: 157–162.
4. Freund E. Zur diagnose des carcinoms. *Wiener Medizinische BI* 1985; 8: 268–269.
5. Shaw JE, Hodge AM, de Courten M. et al. Isolated post-challenge hyperglycaemia confirmed as a risk factor for mortality. *Diabetologia* 1999; 42: 1050–1054.
6. Saydah SH, Loria CM, Eberhardt MS, Brancati FL. Abnormal glucose tolerance and the risk of cancer death in the United States. *Am J Epidemiol* 2003; 157: 1092–1100.
7. Stattin P, Bjor O, Ferrari P. et al. Prospective study of hyperglycaemia and cancer risk. *Diabetes Care* 2007; 30: 561–567.
8. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 2004; 4: 579–591.
9. Lorenzi M, Montisano DF, Toledo S, Barrioux A. High glucose induces DNA damage in cultured human endothelial cells. *J Clin Invest* 1986; 77: 322–325.
10. Dandona P, Thusu K, Cook S. et al. Oxidative damage to DNA in diabetes mellitus. *Lancet* 1996; 347: 444–445.
11. Caimi G, Carollo C, Lo Presti R. Diabetes mellitus: oxidative stress and wine. *Curr Med Res Opin* 2003; 19: 581–586.
12. Yakes FM, Van Houten B. Mitochondrial DNA damage is more extensive and persists longer than nuclear DNA damage in human cells following oxidative stress. *Proc Natl Acad Sci USA* 1997; 94: 514–519.
13. Bandy D, Davison AJ. Mitochondrial mutations may increase oxidative stress: implications for carcinogenesis and aging? *Free Radic Biol Med* 1990; 8: 523–539.
14. Seril DN, Liao J, Yang GY, Yang CS. Oxidative stress and ulcerative colitis: associated carcinogenesis: studies in humans and animal models. *Carcinogenesis* 2003; 3: 353–362.
15. Blasiak J, Arabski M, Krupa R. et al. DNA damage and repair in type 2 diabetes mellitus. *Mutat Res* 2004; 554: 297–304.
16. Merkel P, Khoury N, Bertolotto C, Perfetti R. Insulin and glucose regulate the expression of the DNA repair enzyme XPD. *Mol Cell Endocrinol* 2003; 201: 75–85.
17. Dincer Y, Akcay T, Alademir Z, Ilkova H. Assessment of DNA base oxidation and glutathione level in patients with type 2 diabetes. *Mutat Res* 2002; 505: 75–81.
18. Song F, Jia W, Yao Y. et al. Oxidative stress, antioxidant status and DNA damage in patients with impaired glucose regulation and newly diagnosed type 2 diabetes. *Clin Sci Lond* 2007; 112: 599–606.

19. Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. *Gastroenterology* 2007; 132: 2208–2225.
20. Schiel R, Beltschikow W, Steiner T, Stein G. Diabetes, insulin, and risk of cancer. *Methods Find Exp Clin Pharmacol* 2006; 28: 169–175.
21. Yamagata H, Kiyohara Y, Nakamura S. et al. Impact of fasting plasma glucose levels on gastric cancer incidence in a general Japanese population: the Hisayama study. *Diabetes Care* 2005; 28: 789–794.
22. Jee SH, Ohrr H, Sull JW. et al. Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* 2005; 293: 194–202.
23. Rapp K, Schroeder J, Klenk J. et al. Fasting blood glucose and cancer risk in a cohort of more than 140,000 adults in Austria. *Diabetologia* 2006; 49: 945–952.
24. Michaud DS, Liu S, Giovannucci E. et al. Dietary sugar, glycemic load, and pancreatic cancer risk in a prospective study. *J Natl Cancer Inst* 2002; 94: 1293–1300.
25. Higginbotham S, Zhang ZF, Lee IM. et al. Women's Health Study. Dietary glycemic load and risk of colorectal cancer in the Women's Health Study. *J Natl Cancer Inst* 2004; 96: 229–233.
26. Tsuji S, Kawai N, Tsujii M. et al. Review article: inflammation-related promotion of gastrointestinal carcinogenesis — a perigenetic pathway. *Aliment Pharmacol Ther* 2003 (1 Suppl): 82–89.
27. Holden RJ, Pakula IS, Mooney PA. Tumour necrosis factor- α : a continuum of liability between insulin-dependent diabetes mellitus, non-insulin-dependent diabetes mellitus and carcinoma (review). *Med Hypotheses* 1999; 52: 319–323.
28. Ujpál M, Matos O, Bibok G. et al. Diabetes and oral tumours in Hungary epidemiological correlations. *Diabetes Care* 2004; 27: 770–774.
29. Gatti LL, Burbano RR, de Assumpção PP. et al. Interleukin-1 β polymorphisms, *Helicobacter pylori* infection in individuals from Northern Brazil with gastric adenocarcinoma. *Clin Exp Med* 2004; 4: 93–98.
30. Stocks T, Lukanova A, Rinaldi S. et al. Insulin resistance is inversely related to prostate cancer: a prospective study in Northern Sweden. *Int J Cancer* 2007; 120: 2678–2686.
31. van der Burg BB, Rutteman GR, Blankenstein MA. et al. Mitogenic stimulation of human breast cancer cells in a growth-defined medium: synergistic action of insulin and estrogen. *J Cell Physiol* 1988; 134: 101–108.
32. Barker BE, Fanger H, Farnes P. Human mammary slices in organ culture. I. Methods of culture and preliminary observations on the effects of insulin. *Exp Cell Res* 1964; 35: 437–448.
33. Kaaks R, Toniolo P, Akhmadkhanov A. Serum C-peptide, insulin-like growth factor (IGF-1), IGF-binding proteins, and colorectal cancer risk in women. *J Natl Cancer Inst* 2000; 92: 1592–1600.
34. Rosenfeld RG. Insulin-like growth factors and the basis of growth. *N Engl J Med* 2003; 349: 2184–2186.
35. Ogihara S, Yamada M, Saito T. et al. Insulin potentiates mitogenic effect of epidermal growth factor on cultured guinea pig gastric mucous cells. *Am J Physiol* 1996; 271: 104–112.
36. Calle EE, Thun MJ, Petrelli JM. et al. Body-mass index and mortality in a prospective cohort of US adults. *N Engl J Med* 1999; 341: 1097–1105.
37. Schoen RE, Tangen CM, Kuller LH. Increased blood glucose and insulin, body size, and incident colorectal cancer. *J Natl Cancer Inst* 1999; 91: 1147–1154.
38. Bianchini F, Kaaks R, Vainio H. Overweight, obesity, and cancer risk. *Lancet Oncol* 2002; 3: 565–574.
39. Bray GA. The underlying basis for obesity: relationship to cancer. *J Nutr* 2002; Suppl 11: 3451–3455.
40. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *N Engl J Med* 2003; 348: 1625–1638.
41. Guastamacchia E, Resta F, Triggiani V. et al. Evidence for a putative relationship between type 2 diabetes and neoplasia with particular reference to breast cancer: role of hormones, growth factors and specific receptors. *Curr Drug Targets Immune Endocr Metabol Disord* 2004; 4: 59–66.
42. Nelson R, Persky V, Davis F, Becker E. Excess risk of primary liver cancer in patients with diabetes mellitus [letter]. *J Natl Cancer Inst* 1997; 89: 327–328.
43. Nelson R, Persky V, Davis F. Diabetes mellitus and risk of large bowel cancer [letter]. *J Natl Cancer Inst* 1997; 89: 1232.
44. Garmendia ML, Pereira A, Alvarado ME, Atalah E. Relation between insulin resistance and breast cancer among Chilean women. *Ann Epidemiol* 2007; 17: 403–409.
45. Kaklamani E, Trichopoulos A, Tzonou A. et al. Hepatitis B and C viruses and their interaction in the origin of hepatocellular carcinoma. *JAMA* 1991; 265: 1974–1976.
46. De Fea K, Roth RA. Modulation of insulin receptor substrate-1 tyrosine phosphorylation and function any mitogen-activated protein kinase. *J Biol Chem* 1997; 272: 31400–31406.
47. Yang Y, Hennessy S, Lewis JD. Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. *Gastroenterology* 2004; 127: 1044–1050.
48. Schiel R, Müller UA, Braun A. et al. Risk of malignancies in patients with insulin-treated diabetes mellitus: results of a population-based trial with 10-year follow-up (JEVIN). *Eur J Med Res* 2005; 10: 339–344.
49. Chuang TY, Lewis DA, Spandau DF. Decreased incidence of nonmelanoma skin cancer in patients with type 2 diabetes mellitus using insulin: a pilot study. *Br J Dermatol* 2005; 153: 552–557.
50. Tavakkol A, Elder JT, Griffiths CE. et al. Expression of growth hormone receptor, insulin-like growth factor 1 (IGF-1) and IGF-1 receptor mRNA and proteins in human skin. *J Invest Dermatol* 1992; 99: 343–349.
51. Kath R, Schiel R, Müller UA, Höffken K. Malignancies in patients with insulin-treated diabetes mellitus. *J Cancer Res Clin Oncol* 2000; 126: 412–417.
52. Kacalska O, Krzyczkowska-Sendrakowska M, Milewicz T. et al. Molekularne podstawy antynowotworowego działania uwrażliwaczy na insulinę. *Endokrynologia Polska* 2005; 56: 309–313.
53. Berstein LM. Clinical usage of hypolipidemic and antidiabetic drugs in the prevention and treatment of cancer. *Cancer Letters* 2005; 224: 203–212.
54. Hawley SA. et al. Complexes between the LKB1 tumour suppressor, STRAD α/β and MO25 α/β are upstream kinases in the AMP-activated protein kinase cascade. *J Biol* 2003; 2: 28.
55. Lizcano JM, Göransson O, Toth R. et al. LKB1 is a master kinase that activates 13 kinases of the AMPK subfamily, including MARK/PAR-1. *EMBO J* 2004; 23: 833–843.
56. Bauman AE. Updating the evidence that physical activity is good for health: an epidemiological review 2000–2003. *J Sci Med Sport* 2004; Suppl 1: 6–19.
57. Evans JM, Donnelly LA, Emslie-Smith AM. et al. Metformin and reduced risk of cancer in diabetic patients. *BMJ* 2005; 330: 1304–1305.
58. Yki-Jarvinen H. Grud therapy. Thiazolidinediones. *NEJM* 2004; 351: 1106–1118.
59. Miyazaki Y, Mahankali A, Matsuda M. et al. Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. *J Clin Endocrinol Metab* 2002; 87: 2784–2791.
60. Elstner E, Müller C, Koshizuka K. et al. Ligands for peroxisome proliferators-activated receptor γ and retinoic acid receptor inhibit growth and induce apoptosis of human breast cancer cells in vitro and in BXN mice. *Proc Natl Acad Sci USA* 1998; 95: 8806–8811.

61. Kubota T, Koshizuka K, Williamson EA. et al. Ligand for peroxisome proliferators-activated receptor gamma (troglitazone) has potent antitumour effect against human prostate cancer both in vitro and in vivo. *Cancer Res* 1998; 58: 3344–3352.
62. Sarraf P, Mueller E, Jones D. et al. Differentiation and reversal of malignant changes in colon cancer through PPAR gamma. *Nat Med* 1998; 4: 1046–1052.
63. Tsubouchi Y, Sano H, Kawahito Y. et al. Inhibition of human lung cancer cell growth by the peroxisome proliferators-activated receptor-gamma agonists through induction of apoptosis. *Biochem Biophys Res Commun* 2000; 270: 400–405.
64. Keshamouni VG, Reddy RC, Arenberg DA. et al. Peroxisome proliferators-activated receptor-gamma activation inhibits tumour progression in non-small-cell lung cancer. *Oncogene* 2004; 23: 100–108.
65. Ohta T, Elnemr A, Yamamoto M. et al. Thiazolidinedione, a peroxisome proliferators-activated receptor-gamma ligand, modulates the E-cadherin/beta-catenin system in a human pancreatic cancer cell line, BxPC-3. *Int J Oncol* 2002; 21: 37–42.
66. Elnemr A, Ohta T, Iwata K. et al. PPAR gamma ligand (thiazolidinedione) induces growth arrest and differentiation markers of human pancreatic cancer cells. *Int J Oncol* 2000; 17: 1157–1164.
67. Grommes C, Landreth GE, Heneka MT. Antineoplastic effects of peroxisome proliferators-activated receptor gamma agonists. *Lancet Oncol* 2004; 5: 419–429.
68. Polyak K, Lee MH, Erdjument-Bromage H. et al. Cloning of p27Kip1, a cyclin-dependent kinase inhibitor and a potential mediator of extracellular antimitogenic signals. *Cell* 1994; 78: 59–66.
69. Yu J, Qiao L, Zimmermann L. et al. Troglitazone inhibits tumour growth in hepatocellular carcinoma in vitro and in vivo. *Hepatology* 2006; 43: 134–143.
70. Chen GG, Lee JF, Wang SH. et al. Apoptosis induced by activation of peroxisome-proliferator activated receptor-gamma is associated with Bcl-2 and NF-kappaB in human colon cancer. *Life Sci* 2002; 70: 2631–2646.
71. Chen F, Wang M, O'Connor JP. et al. Phosphorylation of PPAR gamma via active ERK1/2 leads to its physical association with p65 and inhibition of NF-kappa-beta. *J Cell Biochem* 2003; 90: 732–744.
72. Kim EJ, Park KS, Chung SY. et al. Peroxisome proliferators-activated receptor-gamma activator 15-deoxy-Delta12,14-prostaglandin J2 inhibits neuroblastoma cell growth through induction of apoptosis: association with extracellular signal-regulated kinase signal pathway. *J Pharmacol Exp Ther* 2003; 307: 505–517.
73. Print CG, Loveland KL, Gibson L. et al. Apoptosis regulator bcl-w is essential for spermatogenesis but appears otherwise redundant. 1998; 95: 12424–12431.
74. Zhang Z, Kumar R, Santen RJ, Song RX. The role of adapter protein Shc in estrogen non-genomic action. *Steroids* 2004; 69: 523–529.
75. Goetze S, Bungenstock A, Czupalla C. et al. Leptin induces endothelial cell migration through Akt, which is inhibited by PPAR gamma-ligands. *Hypertension* 2002; 40: 748–754.
76. Liu H, Zang C, Fenner MH. et al. PPAR gamma ligands and ATRA inhibit the invasion of human breast cancer cells in vitro. *Breast Cancer Res Treat* 2003; 79: 63–74.
77. Govindarajan R, Ratnasinghe L, Simmons DL. et al. Thiazolidinediones and the risk of lung, prostate, and colon cancer in patients with diabetes. *J Clin Oncol* 2007; 12: 1476–1481.
78. 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* 2006; 29: 254–258.
79. Monami M, Balzi D, Lamanna C. et al. Are sulphonylureas all the same? A cohort study on cardiovascular and cancer-related mortality. *Diabetes Metab Res Rev* 2007; Mar 23: [Epub ahead of print].
80. Sliwinska A, Blasiak J, Drzewoski J. Effect of gliclazide on DNA damage in human peripheral blood lymphocytes and insulinoma mouse cells. *Chem Biol Interact* 2006; 162: 259–267.