FACTORS THAT MAY INFLUENCE THE RISK OF CANCER IN DIABETES

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Abstract

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

Keywords: diabetes mellitus, cancer, risk factors

Introduction

Diabetes mellitus has been epidemiologically associated with an increased risk of cancer [1,2,3,4]. The results of several studies indicate that
some cancers develop more commonly in patients with diabetes (predominantly type 2); the relative risks are greater (about twofold or higher) for liver, pancreas, and endometrium cancer, and lesser (about 1.2–1.5 fold) for cancers of the colon and rectum, breast, and bladder. Lung cancers do not appear to be associated with an increased risk in diabetes, and the evidence for kidney cancer or non-Hodgkin lymphoma is inconclusive. Prostate cancer occurs less often in men with diabetes. The large majority of the epidemiological data on cancer incidence and mortality has been obtained for type 2 diabetic patients and the data cannot be extended to type 1 diabetic subjects [5].

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

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

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

**Nonmodifiable risk factors**

**Age.**

The incidence of most cancers increases with age. The relationship between cancer and aging is unclear, but the increased risk of cancer in old age is possibly due to: poor cellular repair mechanisms, activation of genes that stimulate cancer and suppression of genes that prevent cancer and lifetime exposure to carcinogens [7,8].
The prevalence of diabetes mellitus increases with age and the National Health and Nutrition Examination Survey (NHANES III) demonstrated that, in the population over 65 years old, almost 18% to 20% have diabetes [9].

**Gender**

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

**Modifiable risk factors**

**Obesity**

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

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

- estrogen binding to the ER stimulates proliferation of mammary cells with the increase in cell division and deoxyribonucleic acid (DNA) replication, leading to mutations.
- estrogen metabolism produces genotoxic waste [12].
Increased proliferation rates raise the probability that mutations accumulate in proto-oncogenes and tumor suppressor genes. Impairment of apoptosis may allow cells that have harbored such mutations to survive and eventually to expand clonally, thus allowing them to accumulate additional mutations until full malignancy is reached. Finally, proliferative stimuli may also enhance the growth of established tumors [17,18,19]. ERα is associated with more differentiated tumors, while the evidence that ERβ is involved, is controversial [16].

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

Obesity is characterized by altered production of adipokines by adipocytes, that may be important contributors to the increased risk for cancer development and progression. The adipose tissue is an active endocrine organ producing proinflammatory and anti-inflammatory factors, including the adipokines leptin, adiponectin, resistin, visfatin, plasminogen activator inhibitor-1 as well as cytokines and chemokines, such as interleukin-6, tumor necrosis factor-α [26]. Leptin, the most extensively studied adipokine, acts on the hypothalamus to decrease food intake and increase energy expenditure. The obese state is associated with high
circulating leptin levels suggesting that obese individuals are insensitive to the effects of leptin. The resistance to leptin seems to explain the inability of exogenous leptin administration to prevent weight gain. Leptin can stimulate proliferation of preneoplastic and cancer cells in vitro; in vivo the role of leptin in carcinogenesis is unclear [27]. Adiponectin, is the most abundant transcript in adipocytes and has antidiabetic and anti-inflammatory properties. Low levels of adiponectin are associated with an increased risk of breast cancer and animal studies show that the exogenous adiponectin inhibits tumor growth and tumor angiogenesis [28]. Plasminogen activator inhibitor-1 functions as a fibrinolytic inhibitor and plays an important role in signal transduction, cell adherence, and cell migration. There is clinical evidence implicating plasminogen activator inhibitor-1 as a key factor in tumour invasion and metastasis [29,30]. The relationship of resistin levels with breast carcinogenesis has been well characterized [31]. Resistin is expressed in human prostate cancers and the adipokin inhibits prostate cancer cell proliferation through phosphatidylinositol-3 kinases (PI3K)/Akt signalling pathways. The proliferative effect of resistin on prostate cancer cells may account in part for prostate cancer progression [32]. Resistin and visfatin levels were significantly higher in patients with colorectal cancer and they may be good biomarkers of colorectal malignant potential and stage progression [33]. The inflammatory cytokine tumor necrosis factor-α, is an important tumor promoter in a variety of experimental animal models. This cytokine is also produced by the malignant cells of advanced cancers and its presence is associated with a poor prognostic [34]. Interleukin-6, is relevant to prostate cancer and advanced/metastatic cancer patients have higher levels of interleukin-6 [35].

Diet

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

Physical activity

Epidemiologic studies consistently show that physical activity is associated with a lower risk of colon, postmenopausal breast, and endometrial cancer [6]. Physical activity may improve cancer survival for breast and colorectal cancers [6]. Physical activity may protect against cancer and tumor development through its role in energy balance, hormone metabolism and by decreasing the time of exposure to potential carcinogens. Physical activity has also been found to alter a number of inflammatory and
immune factors, some of which may influence cancer risk. The protective association of physical activity after diagnosis and survival in other cancers are inconsistent [37].

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

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

Interactions between diabetes, diabetes treatments, and cancer

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

Increased oxidative stress
Oxidative stress is caused by the presence of reactive oxygen species (superoxide anion radical, singlet oxygen, hydrogen peroxide, highly reactive hydroxyl radical) that the cell is unable to counterbalance. The result is the damage of biomolecules including DNA, ribonucleic acid (RNA), proteins and lipids. Oxidative stress has been implicated in the natural aging process as well as a variety of disease states: neoplastic, metabolic and neurological diseases. Oxygen-free radicals, known as reactive oxygen species (ROS) have dual role. ROS act within cells as secondary messengers in intracellular signaling cascades, which induce and maintain the oncogenic phenotype of cancer cells. ROS can also induce cellular apoptosis and can function as anti-tumorigenic species. The ROS activated signal pathways are regulated by two protein families – the mitogen activated protein kinase (MAPK) and the redox sensitive kinases. MAPK are serine/threonine kinases that phosphorylate their specific substrates - serine and/or threonine residues. MAPK consist of three family members: the extracellular signal-regulated kinase, the c-Jun NH2-terminal kinase and the p38 MAPK. The MAPK signaling pathways modulate gene
expression, mitosis, proliferation, metabolism, and programmed cell death. Of the three subfamilies, the extracellular signal-regulated kinase pathway has been associated with the regulation of cell proliferation. Activation of the extracellular signal-regulated kinase, the c-Jun NH2-terminal kinase and p38 subfamilies has been observed in response to changes in the cellular redox balance. Activation of MAPK directly leads to increased activator protein-1 (AP-1) activity resulting in increased cell proliferation. One of the genes regulated by AP-1 is cyclin D1 and AP-1 activates this promoter, resulting in the activation of cyclin-dependent kinase (cdks), which promotes the cell division cycle. c-Jun stimulates the progression into the cell cycle by induction of cyclin D1 and suppression of a protein that inhibits cell cycle progression. NF-κB activation has been linked to the carcinogenesis process, because it regulates several genes involved in cell transformation, proliferation, and angiogenesis. Tumor cells of colon, breast, and pancreas carcinoma have been reported to express activated NF-κB. The second family consists of signaling factors that use cysteine motifs as redox-sensitive sulfhydryl switches to modulate specific signal transduction cascades regulating downstream proteins. The redox-sensitive signaling cascade involves the cytoplasmic factors, nuclear signaling and transcription factors. Redox-sensitive signaling factors regulate multiple processes including proliferation, anti-apoptotic signaling pathways and neoplastic transformation [40-44].

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

Diabetes treatments
The mitogenicity of insulin
Insulin and insulin analogues have metabolic and mitogenic activities in the cell, and the mitogenic activities in vitro resemble to be mediated through the insulin-like growth factor-I (IGF-I). The IGF-I plays an important role in cell growth. The biological actions of IGF-I are mediated by its receptor, a tyrosine kinase receptor-IGF-IR. The binding of ligand to the IGF-IR leads to receptor autophosphorylation of tyrosines 1131, 1135, and 1136 in the kinase domain of the receptor [44]. This induces the phosphorylation of juxtamembrane tyrosines and carboxyl-terminal serines that form binding sites for docking proteins including
insulin receptor substrates and Src homology and collagen domain protein. These molecules activate signaling via the phosphatidylinositol-3-kinase (PI3K)-Akt (responsible for metabolic actions and involved in apoptosis) and ras-raf-mitogen-activated protein kinase (MAPK) pathways (responsible for the proliferation and prevention of apoptosis). IGF signaling plays a role in growth, and is a well-established mediator of the malignant phenotype [45-47]. Many tumors show altered expression of the IGF-IR, its ligands and tumors can express the insulin receptors isoform A and hybrid receptors. The insulin receptors isoform A is a fetal isoform and the overexpression of this isoform is a major mechanism of IGF system overactivation in cancer. Insulin forms hybrid receptors is commonly overexpressed in cancer. By binding to hybrid receptors, insulin may stimulate specific IGF-IR signaling pathways. Preclinical studies indicate that IGF-IR overexpression induces tumor formation and metastasis [48-51].

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

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

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

Preclinical studies have shown that thyroid C cells express GLP-1 receptors whose activation induces C cell hyperplasia and medullary thyroid cancer (MTC). Animal models develop spontaneously age-induced nodular hyperplasia of C cells frequently. Sporadic MCT has a frequency of 0.5-1%, in animal models, higher in males secondary to ageing. In humans, MCT
represents 3-10% of thyroid cancer and approximately 75% are either sporadic, with 25% being part of a multiple endocrine neoplasia, or familial.

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

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

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

On July 21st 2011, the European Medicines Agency recommended new contra-indications and warnings for pioglitazone, considering a risk of bladder cancer.
Secretagogues, including sulfonylureas and glinides, stimulate beta-cells to release insulin by binding to specific cell receptors. A small number of observational studies found a higher risk of cancer among individuals with diabetes treated with sulfonylureas compared with those treated with other diabetes medications. There is no published data to support the association between glinide and cancer risk [6].

Conclusion

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

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

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

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References

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