Diabetol Int (2015) 6:190–192
DOI 10.1007/s13340-015-0227-x

COMMENTARY

Diabetes and risk of cancer

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Received: 12 July 2015 / Published online: 2 August 2015

Recent epidemiological studies have revealed the association of elevated cancer risk and diabetes mellitus [1–13]. Because the prevalence of diabetes mellitus and cancer is increasing worldwide, understanding the higher risk of specific types of cancer is important in management of diabetic patients. The American Diabetes Association (ADA) and the American Cancer Society (ACS) produced a consensus report on the increased risk of liver, pancreas, endometrial, colorectal, breast, and bladder cancer among diabetic patients [14]. In 2013, the joint committee of the Japan Diabetes Society (JDS) and the Japanese Cancer Association (JCA) reported the association of diabetes and cancer, including colorectal, liver, and pancreatic cancer, among Japanese diabetic patients [15]. Although the mechanisms underlying this association are not fully understood, several potential mechanisms which promote oncogenesis in diabetes have been discussed. Chronic inflammation, insulin resistance associated with hyperinsulinemia, and hyperglycemia have been suggested as potential mechanisms. These factors may lead to increased risk of cancer in diabetes and promote oncogenesis in different ways. Numerous studies have suggested the effect of insulin and chronic inflammation on cancer progression in diabetes. The experimental and epidemiological evidence is most consistent with the hyperinsulinemia and chronic inflammation hypothesis. In particular, progression of hepatocellular carcinoma seems to be closely associated with chronic inflammation and insulin resistance related to hyperinsulinemia. In a large scale cohort study in Japan, diabetes led to a high risk of hepatocellular carcinoma [16]. A meta-analysis also showed that diabetes increases the risk of hepatocellular carcinoma [12] and diabetes is risk factor for hepatocellular carcinoma among patients with nonalcoholic fatty liver disease (NAFLD) [17]. A recent clinical review suggested that NAFLD and nonalcoholic steatohepatitis (NASH) patients, especially those with diabetes, should be monitored for the onset of hepatocellular carcinoma [18]. However, the involvement of hyperglycemia in cancer development is less clear and few studies have shown the contribution of hyperglycemia to cancer progression and metastasis.

Cancer cells maintain an abnormally high rate of glycolysis, even in the presence of oxygen, a phenomenon called the Warburg effect [19]. Enhanced glucose uptake in cancer is revealed by positron emission tomography (PET) scans, a widely used method of cancer detection, and clinical use of PET scans is well established. Despite many years of investigation, the specific regulatory mechanisms responsible for the Warburg effect are not fully understood. Increased expression of glucose transporter 1 has been observed, and this enables cancer cells to absorb extracellular glucose [20]. Increased type 2 hexokinase activity in cancer has also been demonstrated [21–23]. Although hexokinase is involved in the first irreversible stage of glycolysis, it is not the late limiting enzyme of the process. Fructose 2,6-bisphosphate (F2,6BP) is a powerful allosteric activator of 6-phosphofructo-1-kinase (PFK-1), which is the rate-limiting enzyme of glycolysis [24]. F2,6BP increases the affinity of PFK-1 for fructose 6-phosphate and reduces the inhibitory effect of ATP. Previous work has revealed markedly elevated levels of F2,6BP in several cancer cell lines [25–27]. The intracellular concentration of F2,6BP depends on the activity of the bifunctional enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFK-2/FBPase) [28]. At least four

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genes have been identified that encode PFK-2/FBPase. Inducible PFK-2 has the highest kinase activity ratio of all PFK-2/FBPase isoforms and is a powerful activator of glycolysis [29, 30]. Activation of glycolytic genes by hypoxia-inducible-factor-1 (HIF-1) is believed to be critical for metabolic adaptation of cancer cells to hypoxia. Minchenko et al. demonstrated that expression of iPFK-2 mRNA is increased in response to hypoxia and HIF-1 is required for this induction in mouse fibroblasts [31]. Furthermore, high expression of iPFK-2/FBPase has been demonstrated in human cancers, suggesting the association of F2,6BP (iPFK-2/FBPase)-mediated activation of glycolysis and the Warburg effect [32]. To determine the effect of hyperglycemia on intracellular glycolysis, F2,6BP levels in peripheral blood mononuclear cells obtained from patients with diabetes were measured. F2,6BP levels in peripheral blood mononuclear cells from diabetic subjects were significantly higher than in those from age-matched normal control subjects. A significant positive correlation between intracellular F2,6BP levels and HbA1c was observed. These results suggest that hyperglycemia increases intracellular F2,6BP, leading to activation of glycolysis [33]. High glucose also activates a variety of signaling pathways that control cancer cell proliferation, migration, invasion, and recurrence [34]. The memory effect of hyperglycemia might also be associated with epigenetic alteration of oncogenic pathways [35]. Hyperglycemic conditions lead to permanent activation of oncogenic pathways in cancer cells, even after hyperglycemic conditions have been normalized to euglycemic conditions [36, 37]. Thus hyperglycemia might promote enhanced glycolysis in cancer tissue and lead to the elevated risk of cancer progression for diabetic patients. However there is no evidence, so far, that glycemic control reduces cancer proliferation and metastasis among diabetic patients. Some studies have been shown that inadequate maintenance of blood glucose in diabetic patients is a significant risk factor for poor survival of cancer patients [38, 39].

It has also been suggested that cancer and diabetes have risk factors in common, for example aging, obesity, an inappropriate diet, and/or exercise. High body mass index is associated with increased risk of several cancers. Therefore, healthy diet, exercise, body weight control, smoking cessation, and reducing alcohol intake should be encouraged to reduce the risk of diabetes and cancer, as described in the report of the joint committee of the JDS and the JCA [15]. Management of obesity should be a major aspect of preventive care. However, a cohort study revealed increased cancer risk for men with BMI less than 21 kg/m^2, suggesting the importance of appropriate body weight [15]. Furthermore, diabetic patients should be encouraged to undergo screening as required depending on their sex and age [15]. It is necessary to communicate this message to individual patients and to share the information from clinical findings. It may minimize the progression of malignant disease among diabetic patients.

Compliance with ethical standards

Conflict of interest The author has no conflicts of interest to report.

Ethics policy This article does not contain any studies with human or animal subjects performed by any of the authors.

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