Diabetes, insulin and cancer risk

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Abstract

There is a consensus that both type 1 and type 2 diabetes are associated with a spectrum of cancers but the underlying mechanisms are largely unknown. On the other hand, there are ongoing debates about the risk association of insulin use with cancer. We have briefly reviewed recent related research on exploration of risk factors for cancer and pharmacoepidemiological investigations into drug use in diabetes on the risk of cancer, as well as the current understanding of metabolic pathways implicated in intermediary metabolism and cellular growth. Based on the novel findings from the Hong Kong Diabetes Registry and consistent experimental evidence, we argue that use of insulin to control hyperglycemia is unlikely to contribute to increased cancer risk and that dysregulations in the AMP-activated protein kinase pathway due to reduced insulin action and insulin resistance, the insulin-like growth factor-1 (IGF-1)-cholesterol synthesis pathway and renin-angiotensin system, presumably due to reduced insulin secretion and hyperglycemia, may play causal roles in the increased risk of cancer in diabetes. Further exploration into the possible causal relationships between abnormalities of these pathways and the risk of cancer in diabetes is warranted.

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Key words: Diabetes; Insulin; Cancer; Hyperglycemia; Cholesterol synthesis pathway; Renin-angiotensin system; adenosine 5’-monophosphate -activated protein kinase pathway

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INTRODUCTION

The prevalence of diabetes has been rapidly increasing in China over the past decades, i.e., from 0.9% in 1980, to 3.1% in 1994 and further increased to 9.7% in 2008. In addition to cardiovascular disease and renal disease, type 1 and type 2 diabetes are also associated with a spectrum of cancers, except for prostate cancer with reports showing conflicting results. Since the first few reports on increased incidence of cancer in insulin-treated patients, there are ongoing debates regarding the risk association of insulin use with cancer. In 2010, the American Diabetes Association and the American Cancer Society reviewed the state of science concerning a number of issues regarding the association between diabetes and cancer, including diabetes treatment and cancer risk, and published a joint consensus report but without conclusions about many of these issues, including insulin usage and cancer risk. Further contention about
insulin usage and cancer risk has important implications since millions of people require insulin to control hyperglycemia. To address this issue, we need to consider two fundamental questions. Firstly, does endogenous insulin play a causal role in cancer development? Secondly, does insulin usage play a causal role in cancer development? Many authors suspect that insulin and insulin analogues may promote tumor proliferation but the data from the Hong Kong Diabetes Registry and experimental evidence suggests a different story.

HYPERGLYCEMIA AND CANCER RISK AMONG INSULIN USERS COMPARED TO NON USERS
52% (HR: 0.48, 95% CI: 0.32-0.73) reduction of cancer in anerobic conditions which thrive better than normal cells by obtaining energy latter can independently promote growth of cancer cells portantly, insulin use is indicated for hyperglycemia. The hypothesis of cancer with insulin use were flawed with biases which glycemia. Many of the cohort studies on the association insulin action and may require insulin to control hyper glycemia. To address this issue, we need to consider two implications of insulin-sufficient mice, which was reversed by insulin therapy.

HYPERINSULINEMIA AND CANCER IN NON-DIABETIC SUBJECTS
Circulating insulin levels in non-diabetic or prediabetic subjects are associated with some cancer subtypes. This is often attributed to hyperinsulinemia due to obesity-associated insulin resistance which can promote carcinogenesis through several mechanisms. The adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK) pathway is a gatekeeper for energy metabolism intimately related to cell cycles, and is considered a therapeutic target for diabetes, metabolic syndrome and cancer. Insulin resistance is associated with inhibition of the LKB1-AMPK pathway which promotes energy storage and obesity. In experimental studies, inhibition of the LKB1-AMPK was associated with protein synthesis and cancer development, while its activation by metformin reduced cancer risk. Many tumor cells express insulin and insulin growth factor (IGF-1) receptors which can activate the protein kinase B (Akt) and mitogen-activated protein kinase signaling networks in neoplastic tissues. Although more evidence is needed to confirm these mechanisms, they are supported by the association of cancer risk with circulating levels of insulin and IGF-1 in population-based studies.

INSULIN USE AND CANCER IN DIABETIC SUBJECTS
However, these mechanisms are not likely to be relevant to people with diabetes, who often have insufficient insulin action and may require insulin to control hyperglycemia. Many of the cohort studies on the association of cancer with insulin use were flawed with biases which can only be addressed by randomized clinical trials. Importantly, insulin use is indicated for hyperglycemia. The latter can independently promote growth of cancer cells which thrive better than normal cells by obtaining energy from glycolysis rather than the tricarboxylic acid cycle in anerobic conditions. In this regard, we reported a 52% (HR: 0.48, 95% CI: 0.32-0.73) reduction of cancer risk among insulin users compared to non users, using a validated approach largely free of drug use indication bias, prevent user bias and immortal time bias.

HYPERGLYCEMIA AND CANCER
Several large cohort or case-control studies have reported a positive association between hyperglycemia and cancer. To date, none of the randomized clinical trials of blood-glucose lowering drugs have included cancer as a predefined clinical endpoint. In a prospective cohort, including new insulin users with carefully matched non-insulin users, we first reported the marked reduction in cancer risk in insulin users and an 18% increase in cancer risk for every 1% increase in glycated hemoglobin (A1c). These novel findings were corroborated by a meta-analysis of blood glucose lowering trials where intensive glycemic control with 0.3%-0.9% reduction in A1c was associated with 9% (95% CI: 0.79-1.05) reduction in cancer risk, although individual trials of intensive glycemic control did not observe a reduction in cancer risk. In a tumor-prone animal model, researchers have reported an increased number and size of liver tumors with reduced apoptosis in insulin-deficient hyperglycemic animals compared to insulin-sufficient mice, which was reversed by insulin therapy.

AMPK PATHWAY AND CANCER RISK
The risk association of A1c with cancer has led us to further examine the possible associations of lipids with the risk of cancer, which are tightly linked with glucose metabolism. Using a well characterized prospective cohort, the Hong Kong Diabetes Registry, we first reported the V-shaped risk associations of cancer with various lipid parameters, including low density lipoprotein cholesterol (LDL-C) levels < 2.80 mmol/L and ≥ 3.80 mmol/L, high density lipoprotein cholesterol (HDL-C) levels < 1.0 mmol/L and ≥ 1.30 mmol/L and triglyceride < 1.70 mmol/L.

Here, the risk association of cancer with low HDL-C has been reported in the general population and may be causal. There are consistent reports that show a protective effect of metformin on the risk of cancer and cancer mortality. In Chinese type 2 diabetic patients, we have further reported the anti-cancer effects of metformin which is enhanced among patients with low HDL-C < 1.0 mmol/L. Since both apolipoprotein (Apo) A-I, the main lipoprotein of HDL-C, and metformin can increase insulin sensitivity by activating the AMPK pathway, the interactive effects of metformin and HDL-C on cancer risk suggest that an abnormal AMPK pathway may link diabetes and cancer.

INFLAMMATION, THE RENIN ANGIOTEN-SIN SYSTEM AND THE CHOLESTEROL SYNTHESIS PATHWAY
Although the risk association of low LDL-C and cancer has been reported in the general population, its nature remains elusive. In Chinese type 2 diabetic patients, the presence of albuminuria or low triglyceride (< 1.7 mmol/L) greatly enhanced the low LDL-C-cancer associations but not low LDL-C alone. This low LDL-C-associated cancer risk was markedly attenuated by use of...
CONFOUNDING EFFECTS OF OBESITY IN EXAMINATION OF INSULIN LEVELS AND USAGE FOR CANCER

The associations between obesity and cancer incidence and mortality in general populations have been repeatedly reported for a member of site-specific cancers[64-66]. In type 2 diabetes, the association between body mass index (BMI) and cancer is not a simple linear one but in a V-shaped manner[67]. Both type 2 diabetic patients with BMI < 24.0 kg/m² and ≥ 27.6 kg/m² are at increased risk of cancer compared to those who have a BMI at ≥ 24.0 kg/m² and < 27.6 kg/m²[68]. Obesity impairs insulin action and results in insulin resistance and compensatory hyperglycemia[69]; thus potentially confounding the association between insulin levels and cancer, as well as that between insulin usage and cancer. In this regard, one study reported that the association between obesity and cancer is mediated via the AMPK pathway[70], although many authors believe that insulin and the IGF axis may play a role in obesity-related high cancer risk[71]. With the Hong Kong Diabetes Registry, we reported that insulin usage is associated with a reduced risk of cancer[72] and the hazard ratio is unchanged after further adjusting for the non-linear association between BMI and cancer (unpublished data). Obesity and type 2 diabetes share common characteristic changes in lipid profiles: high triglyceride, low HDL-C and increased concentration of small dense LDL-C particles[68-69]. What is interesting among type 2 diabetes is that low HDL-C but not high triglyceride predicts cancer[65-67,69]. Thus, the lipid-cancer risk associations may only partially explain the obesity-cancer association because the V-shaped association between BMI and cancer among type 2 diabetes was observed after adjusting for the non-linear associations of lipids and cancer risk[68]. To this end, the observed insulin usage and reduced cancer risk is independent of BMI-cancer and lipid-cancer associations[18].

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