

Does Type 2 diabetes increase the risk of developing cancer?



“Understanding the relationship between Type 2 diabetes and cancer remains one of the biggest challenges for the medical community...”



Philippe Froguel^{*1,2,3,4,5} Amélie Bonnefond^{1,2,3}

Over the past 30 years, a plethora of epidemiologic studies have demonstrated a marked and consistent association between Type 2 diabetes (T2D) and the overall risk for cancer (and its mortality) in various populations [1–4]. However, it was also demonstrated that the strength of this association depended on the cancer site [1,3]. Indeed, the incidence of hepatocellular and pancreatic cancers is doubled in patients presenting with T2D [1,3]. Endometrial cancer risk is also doubled in women with T2D [1,3], while risk of postmenopausal (but not premenopausal) breast, colorectal, kidney, biliary tract and bladder cancers, non-Hodgkin's lymphoma, leukemia, and myeloma is 'only' 20–50% higher in patients presenting with T2D [1,3,5]. Notably, the risk of prostate cancer, by contrast, is approximately 15% lower in men with T2D [1,3].

Various assumptions have been made to elucidate direct or indirect mechanisms explaining the association between T2D and cancer. This research has not been very successful so far as both common disorders

are markedly complex and heterogeneous, and several risk factors (e.g., aging, male sex, ethnicity, overweight/obesity, visceral adiposity, tobacco smoking, alcohol consumption, sedentary lifestyle, poor diet – excessive red/processed meat intake and low vegetable/fruit/wholegrain intake – microvascular complications, hypertension, socioeconomic status and family history) have to be considered as confounding factors in the assessment of cancer risk in patients with T2D [1,4,6].

The inverse association between T2D and prostate cancer may be explained by the lower levels of testosterone in men with T2D; elevated circulating levels of testosterone have been associated with a higher risk of prostate cancer [1,3]. Consequently, the protection from prostate cancer in men presenting with T2D may be due to a lower exposure of the prostate to testosterone [1,3].

For the other T2D-associated cancers, there are two leading hypotheses attempting to explain the contribution of T2D to cancer development: insulin resistance

“...there are two leading hypotheses attempting to explain the contribution of Type 2 diabetes to cancer development: insulin resistance and consequent hyperinsulinemia; and chronic hyperglycemia...”

¹CNRS-UMR8199, Lille Pasteur Institute, Lille, France

²Lille II University, Lille, France

³European Genomic Institute for Diabetes (EGID), Lille, France

⁴Department of Genomics of Common Disease, School of Public Health, Imperial College London, Hammersmith Hospital, London, UK

⁵Qatar Biomedical Research Institute, Qatar Foundation, Doha, Qatar

*Author for correspondence. philippe.froguel@good.ibl.fr

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and consequent hyperinsulinemia; and chronic hyperglycemia [1,4,6].

The first hypothesis is supported by several epidemiologic studies demonstrating that high circulating levels of endogenous insulin are associated with increased cancer incidence and mortality [7]. Insulin is known to be an important growth factor (in both healthy and malignant tissues) and can promote cell proliferation and tumorigenesis via various mechanisms, including an increase in the levels of IGF-1 [8]. Hyperinsulinemia (related to high endogenous insulin levels and/or insulin therapy) leads to excessive insulin/IGF-1 action in cells or tissues expressing the insulin/IGF-1 receptors (including cancer cells that are highly sensitive to insulin), which activates the PI3K/AKT/PTEN and MAPK signaling pathways via IRS1 and, consequently, promotes cell proliferation and tumor cell growth [7,8]. Notably, several drug candidates that target IGF-1 and/or insulin signaling networks were reported to have antineoplastic activity in humans [8]. Furthermore, hyperinsulinemia has been found to decrease the hepatic synthesis of SHBG, leading to an increase in serum estrogen, which is involved in the onset of both breast and endometrial cancers [1,4]. It is noteworthy that the big controversy about the putative cancer-inducing effect of long-acting insulin analogs in diabetic patients has not been conclusive so far; although it is believed that T2D itself, rather than exogenous insulin, causes cancer [1,4].

The second hypothesis on the putative contribution of hyperglycemia to cancer development is supported by large epidemiological studies that showed a continuous association between fasting plasma glucose levels and cancer incidence or mortality [1,4,9]. It was believed for a long time that neoplastic cells required huge amounts of glucose to thrive and proliferate as these cells are unable to use efficient anaerobic glycolysis (known as the Warburg effect) [7], and a recent study has demonstrated that high concentrations of glucose (11 mM) promote tumor progression *in vitro*, with or without insulin in the culture medium [10]. However, a study based on tomography scans of patients who took a traceable analog of glucose, demonstrated that tumors continue to burn huge amounts of glucose, even if the patients presented with low plasma glucose levels [7]. Furthermore, a recent meta-analysis of major randomized controlled trials demonstrated that cancer incidence was

not reduced in T2D patients with an intensified glycemic control [11]. Therefore, the data support the first hypothesis with the key role of insulin and IGF-1, and turn against the second ‘hyperglycemia’ hypothesis.

Notably, the association between T2D and both pancreatic and liver cancers appears to be more complex than expected due to some degree of reverse causality [1,3,12]. Both the liver and the pancreas are exposed to high endogenous insulin levels as insulin is secreted from the pancreatic β -cells and is subsequently transported through the portal vein to the liver. However, abnormal glucose metabolism may be caused by pancreatic cancer, which can destroy pancreatic islets [12]. In fact, a sudden onset of diabetes in adult subjects is considered to be an indicator to investigate for an early manifestation of pancreatic cancer [3]. With regard to liver cancer, steatosis, nonalcoholic fatty liver disease and cirrhosis markedly enhance the susceptibility for this cancer, and are, therefore, important confounding factors for patients at risk of T2D [12]. However, epidemiologic studies demonstrated that reverse causality did not account for the totality of the association between T2D and both pancreatic and liver cancers [1,3,12].

Genetics may provide some clues about T2D and cancer. Genome-wide association studies (GWAS) have detected some shared susceptibility genes between T2D and cancer (with, however, a modest effect that is characteristic of GWAS): *CDKN2A/B*, *JAZF1*, *KLF14* and *HNF1B* [13]. With regard to *HNF1B*, the alternative alleles at the same genetic variants showed opposing effects on T2D and prostate cancer risk, which corroborates epidemiologic data [14]. However, no rigorous genetic studies (e.g., Mendelian randomization, which analyzes the effect of genes on both cancer and T2D-related traits that are known to be associated with cancer) involving GWAS data have been able to establish a causality between T2D and cancer (which may be due to lack of statistical power or difficulties in obtaining data for a large cohort on cancer, T2D status and various metabolic traits). A recent study showed that germline mutations in the gene encoding the tumor suppressor *PTEN* homolog cause a cancer predisposition state, as well as a profound constitutive insulin sensitization that apparently occurs in association with obesity [15]. The authors suggested that *PTEN* mutations have a paradoxical divergent effect: enhancement of

risks of both cancer and obesity/adiposity, and a decrease in the risk of T2D (through increased insulin sensitivity) [15].

With regard to complex events affecting DNA stability, two large studies have demonstrated a strong relationship between large chromosomal clonal mosaic events (CME; detected in blood or saliva) and aging and cancers (particularly blood cancers) [16,17]. These CME can lead to gain or loss of large chromosomal segments (or even the entire chromosome), copy-neutral loss of heterozygosity or uniparental disomy in a subset of cells (between 5 and 95% of cells that clonally proliferate). Given the link between T2D and both aging and cancers (including hematological cancers), we assessed the putative relationship between T2D and CME in blood [18]. We found a marked association between CME occurrence and a severe form of T2D, characterized by vascular complications and normal weight (with an odds ratio of 5) [18]. We suggested that the development of age-dependent CME may be strongly accelerated by the T2D state, especially in the presence of vascular complications, which

in turn would contribute to the T2D effect on premature aging and cancer [18]. However, further studies involving several longitudinal studies examining cancer, T2D and its vascular complications are needed to clearly understand the causality between CME, T2D (with its vascular complications) and further cancer.

Understanding the relationship between T2D and cancer remains one of the biggest challenges for the medical community [1]. Rigorous large observational and collaborative studies (with a good design and high quality available data) are necessary to disentangle the pieces of the puzzle.

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