# Type 2 Diabetes Mellitus, Insulin Resistance, Obesity, there is Any Association with Liver Cancer?

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## Introduction

Hepatocellular carcinoma (HCC) accounts for 70 – 85 % of primary liver cancers, ranking fifth among the most common malignancies worldwide and third as a cause of cancer death. Dominant etiological factors of HCC show great variations according to different geographic areas. In Asia, vertically transmitted hepatitis. B infection is a major contributor to HCC, which may emerge in non-cirrhotic livers due to direct oncogenic properties of the hepatitis B virus. In sub-Saharan Africa, dietary exposure to aflatoxin may synergize with the carcinogenic effects of chronic hepatitis B infection. In the Western world, HCC most often complicates cirrhosis evolving from chronic viral hepatitis B and C, alcoholic injury, or inherited disorders such as hemochromatosis [1,2].

## Liver Cancer and Diabetes

There is now a large body of evidence indicating a strong and consistent increased risk of incident cancer associated with diabetes [3]. For type 2 diabetes, the strength of the association depends on the specific cancer site, with the strongest relationships observed for liver and pancreatic cancers, followed by endometrial, postmenopausal breast, colorectal, bladder, non-Hodgkin's lymphoma, and kidney cancer [4]. For stomach cancer, there was an increased risk in a Japanese population [5], but it is not known if this extends to other populations, most of which have a much lower incidence of stomach cancer. The literature also consistently demonstrates a 10–20% decreased risk of prostate cancer among men with diabetes, due, in part, to the reduced levels of circulating testosterone levels in these individuals [6].

For other, rarer malignancies, the number of studies is small, and more importantly, they usually lack adequate power to reliably explore these associations. Similarly, for studies of cancer mortality, positive associations have been shown for cancers of the pancreas, liver, colon and rectum, and bladder [7]. However, there is little data for mortality of rare cancer outcomes. For type 1 diabetes, evidence is limited and variable. Cohort studies have shown a 10–37% increased risk for the incidence of all cancers combined, whereas case-control studies showed no association [8]. Studies are rarely large enough to explore site-specific cancer incidence. However, there is evidence to suggest an increased risk for cancers of the pancreas, liver, and stomach. The evidence of cancer-specific mortality among type 1 diabetic cohorts is even more limited.

## Possible Mechanisms

The higher risk of HCC among people with diabetes could potentially be related to exposure of the liver to high insulin concentrations in the portal circulation that are particularly elevated among people with insulin resistance and type 2 diabetes, particularly if the tumor cells remain sensitive to insulin. Hyperinsulinemia could increase risk of HCC by increasing synthesis of insulin-like growth factor-1 (IGF-1) which promotes cell growth and proliferation and inhibits apoptosis with evidence for this mechanism provided by in vitro studies, animal models, and epidemiologic studies (reviewed in reference. A further possible biological mechanism for the association between diabetes and liver cancer is that up to 80% of people with type 2 diabetes are thought to have non-alcoholic fatty liver disease which increases risk of non-alcoholic steato-hepatitis, cirrhosis and subsequent HCC.

Experimental and clinical observations on the ability of anti-diabetic medications to alter cancer risk by improving insulin resistance are accumulating [9]. Metformin, an activator of AMP-activated protein kinase, and thiazolidinediones, agonists of peroxisome proliferator-activated receptor may effectively reduce circulating glucose and insulin levels and limit their systemic effects on oncogenic pathways. In addition, metformin and thiazolidinediones reduce the extent of hepatic lipid accumulation, further limiting the organ-specific molecular events that may contribute to hepatocarcinogenesis [10]. The observations of Lai et al. [11] provide valuable additional evidence that properly controlled glucose and lipid homeostasis may help avoid or delay diabetes-associated complications, an unfortunately long list that

In conclusion, old age, low serum TG levels and high serum GGT levels may predict risk of HCC in diabetic patients who do not have chronic viral hepatitis or alcoholic cirrhosis. Scoring system

using these parameters may be useful in identifying subgroups of the diabetic population who are at an increased risk of HCC. In clinical practice, clinicians are increasingly required to manage and treat patients with both T2DM and HCC. Although there are still important gaps in our knowledge(s), the use of metformin may be associated with a lower incidence of HCC. To date, studies reporting on the effect of glucose-lowering medications other than metformin on HCC prognosis are both scant and difficult to interpret, owing to the complexity of pharmacotherapy for T2DM, and the many sources of bias that this complexity may generate. Further research is required to clarify the variables that contribute to the complexity of the associations between T2DM, hyperglycemia, diabetes treatment and HCC risk.

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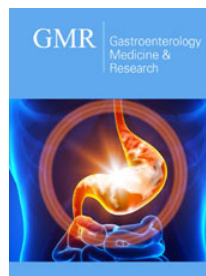
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