Diabetes and Cancer

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KEYWORDS

- Diabetes mellitus • Obesity • Metabolic syndrome • Cancer • Hyperinsulinemia
- Hyperglycemia • Inflammation

KEY POINTS

- Type 2 diabetes, obesity, and the metabolic syndrome are associated with an increased risk of cancer development.
- Proposed mechanisms to link type 2 diabetes and cancer include insulin resistance, hyperinsulinemia, insulin-like growth factor-1, hyperglycemia and dyslipidemia, inflammatory cytokines, and adipokines.
- Hyperinsulinemia, insulin receptor expression, and insulin receptor signaling are associated with increased tumor growth and metastasis.
- Hyperglycemia can contribute to the development and progression of cancers by promoting transformation of cancer cells, providing an energy source and allowing for cell survival and resistance to chemotherapy.
- Chronic inflammation leads to increased levels of circulating interleukin (IL)-1β, IL-6, and tumor necrosis factor-α that can promote invasion of tumor cells.

INTRODUCTION

Type 2 diabetes (T2D) and obesity are both associated with reduced life expectancy and have been correlated with an increased risk of cancer development. Obesity, the metabolic syndrome, and T2D are also associated with more advanced stage of certain cancers at presentation, resistance to therapy, and recurrence; factors that contribute to greater cancer mortality.[1–4] There are many biologic factors common to obesity and T2D that may contribute to cancer risk. In this review, we discuss the links between T2D and cancer and the various biologic mechanisms associated with T2D, the metabolic syndrome, and obesity that may be promote cancer development, growth, and metastases.

EPIDEMIOLOGY OF DIABETES AND CANCER
Diabetes, Obesity, and the Metabolic Syndrome

The prevalence of T2D has been growing steadily over the past decade. In 2004, it was predicted that the number of people diagnosed with T2D would rise to 366 million by 2030; however, the numbers are rising more rapidly than predicted. Current estimates from the International Diabetes Federation (IDF), report that 366 million people worldwide had diabetes in 2011, and the projected number of people with diabetes by 2030 is 552 million. Many years before the development of hyperglycemia, the hallmark of diabetes, insulin resistance develops in metabolic tissues and consequently hyperinsulinemia occurs, due to beta cell compensation.[5,6] Eventually, beta cell failure occurs and patients develop hyperglycemia.[7] At this point, diabetes may be diagnosed, although the individual has most likely had insulin resistance and hyperinsulinemia for many preceding years.

Type 1 diabetes mellitus (T1D) results from the autoimmune destruction of the insulin-producing beta cells, which leads to severe insulin deficiency. T1D accounts for about 5% to 10% of diabetes. Various epidemiologic studies have been conducted to investigate the link between T1D and overall cancer incidence.[8] A study conducted in Denmark found that there was no overall increase in cancer cases among individuals with T1D,[8] whereas a Swedish study found a 17% increase in cancer risk in individuals with T1D.[9] This study reported an increased risk of leukemia and skin and stomach cancers.[9] A follow-up study by the same group observed an association between early-onset leukemia and T1D.[10] The highest incidence of acute myeloid leukemia and acute lymphoblastic leukemia in patients with T1D was observed in patients diagnosed with T1D between the ages of 10 and 20 years.[10] Whether the increase in cancer in these patients with T1D is due to a viral etiology or insulin therapy remains to be determined.[10]

The metabolic syndrome is a syndrome of insulin resistance that is associated with a greater risk of developing T2D. The metabolic syndrome is diagnosed by dyslipidemia and hypertension, in addition to abdominal obesity and abnormal glucose homeostasis.[11] The dyslipidemia and hypertension associated with the metabolic syndrome are thought to occur as a consequence of insulin resistance.[11] The Metabolic Syndrome and Cancer (Me-Can) Project in Austria, Sweden, and Norway has examined the association between the syndrome as a whole and its components with cancer risk. The investigators have reported that a higher composite metabolic syndrome score is associated with increased risk of liver cancer as well as bladder cancer in men and postmenopausal breast cancer in women.[12–14] They have also reported an increase in the risk of certain cancers associated with higher glucose levels, hypertriglyceridemia, and hypertension.[15–17]

Obesity, whether defined as a body mass index (BMI) of 30 kg/m^2 or higher or by increased waist circumference ($\geq$102 cm in men or $\geq$ 88 cm in women),[18] also is associated with an increased risk of certain cancers.[19] In 2008, the World Health Organization (WHO) reported that 10% of men and 14% of women worldwide were obese. In the WHO Region of the Americas, 26% of individuals were obese (www.who.int). Obesity is associated with many comorbid conditions, including the metabolic syndrome and T2D. The risk of developing T2D increases with higher BMI levels and with longer duration of obesity. Abdominal obesity is specifically associated with insulin resistance and the metabolic syndrome.[11] A meta-analysis of 221 datasets found that a 5 kg/m^2 increase in BMI was associated with an increased risk of developing esophageal, thyroid, colon, and renal carcinoma and multiple myeloma in men and women, in addition to hepatocellular and rectal cancer, and malignant melanoma in men, and endometrial, gallbladder, postmenopausal breast, and pancreatic cancer and leukemia in women.[19] The