Obesity, Type 2 Diabetes, and Cancer: The Insulin and Insulin-Like Growth Factor Connection

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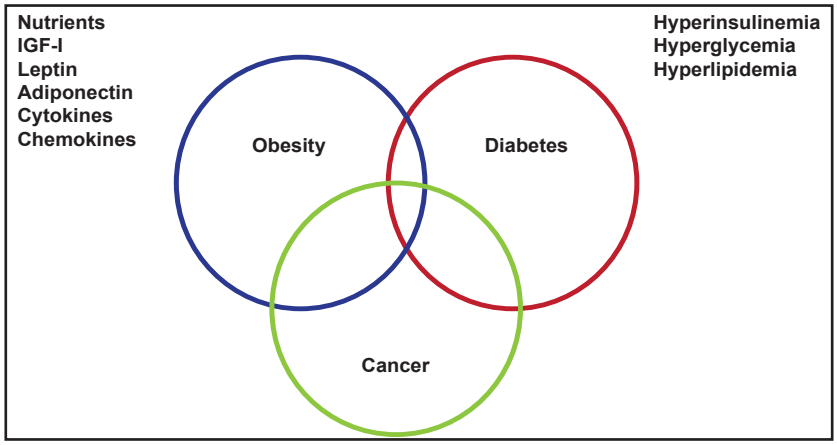
The worldwide epidemic of obesity has triggered a concomitant surge in cases of type 2 diabetes. Both are related to cancer through IGF-1, hyperinsulinemia, and other factors (Figure 1). Derek LeRoith, MD, PhD, Mount Sinai Medical Center, New York, USA, recipient of the Gerald D. Aurbach Award, spoke about the association between obesity, diabetes, and cancer and their connection to insulin and IGFs.

Figure 1. Impact of Diabetes and Obesity on Cancer Development.



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Obesity is one of the most serious public health problems of this century [Scott and Batterham. *Am J Physiol Regul Integr Comp Physiol* 2011]. In the United States alone, it affects about 12 million (16.9%) children aged 2 to 19 years and over 75 million (33.7%) adults [American Heart Association 2011]. Worldwide, an estimated 17.6 million children aged <5 years are overweight, and some 400 million adults are obese.

Statistics show that 58% of diabetes cases can be attributed to a body mass index >30 kg/m^2 [World Heart Federation 2011] and that at least 20 different cancers are associated with obesity [Hemminki K et al. *Eur J Cancer Prev* 2011] (Table 1). The majority of patients with type 2 diabetes are overweight or obese [Ross SA et al. *Curr Med Res Opin* 2011].

Table 1. Cancers Associated with Obesity.

In Women	In Men
• Breast (postmenopausal)	• Prostate
• Endometrium	• Stomach
• Cervical	• Colorectal
• Uterine	• Kidney
• Ovarian	• Liver/Gall Bladder
• Colorectal	• Pancreatic
• Kidney	• Esophageal
• Liver/Gall Bladder	• Hematopoietic
• Pancreatic	
• Esophageal	
• Hematopoietic	

Together, the widespread epidemics of obesity and type 2 diabetes have underscored the importance of these disorders as risk factors for cancer and renewed interest in the study of the involvement of hyperinsulinemia and IGF-IR signaling in the development and progression of cancer.

Dr. LeRoith discussed the mechanisms that involve the insulin/IGF-1 system and cancer and type 2 diabetes, with a focus on IGF-IR, hyperinsulinemia, and insulin receptors (IRs) in cancer. IGF-I and IGF-II, along with insulin, play key roles in cell survival, growth, and proliferation, as well as in the metabolic effects of insulin.

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Two features demonstrate the relationship between the IGF system and cancer: most epithelial cancers and cancer cell lines demonstrate increased expression of IGF-1R compared with adjacent normal tissue, and epidemiological studies show an increased relative risk of developing prostate, colon, breast, and other cancers when circulating IGF-1 is in the upper quartile of the normal range.

Mutations in tumor suppressor genes that are commonly found in cancers may explain the enhanced expression of the IGF-IRs [Lane DP and Hupp TR. *Drug Discov Today* 2003]. Tissue and cell culture studies indicate higher expression of IGF-1R in cancer cells. This increase is the result of both enhanced promoter activity and increased translation.

The IGF-IR promoter is a downstream target for tumor suppression action. Enhanced promoter activity is seen in many cancer cells that express mutated tumor suppressor gene products, such as p53 and WT1. Enhanced translation is seen with deletion or mutation of PTEN, another common tumor suppressor that is mutated in cancers.

Blocking the activation of IGF-1R inhibits cancer growth both *in vitro* and *in vivo*. This has led to the development of numerous humanized IGF-1R-blocking antibodies and a number of tyrosine kinase inhibitors of IGF-IR signaling that have entered various phases of preclinical and clinical testing in various epithelial cancers and sarcomas.

Insulin Promotes Cancer in Obesity and Type 2 Diabetes

Data show that type 2 diabetes increases breast cancer risk and mortality, and hyperinsulinemia has been identified as a major factor that links these two diseases. Conversely, early administration of insulin-sensitizing therapy may reduce breast cancer risk and mortality in patients with type 2 diabetes [Fierz et al. *Diabetes* 2010].

According to Dr. LeRoith, an animal model of insulin resistance has demonstrated the direct causality between endogenous hyperinsulinemia and cancer growth and metastases. Results show that inhibiting tyrosine kinase reduces mammary tumors, despite marked hyperinsulinemia

Overexpression of IRs in cancer cells may explain their increased sensitivity to hyperinsulinemia. In addition, isoform A (IR-A), together with autocrine production of its ligand, IGF-II, is emerging as an important mechanism of normal and cancer stem cell expansion and is a feature of several malignancies [Belfiore A and Malaguarnera R. *Endocrin Relat Cancer* 2011].

The Role of Obesity and Type 2 Diabetes

The association between obesity, type 2 diabetes, and certain types of cancers is well established. For example, half of all patients with pancreatic cancer are diabetic at the time of diagnosis [Magruder JT et al. *Pancreas* 2011], but it remains unclear whether diabetes that is associated with pancreatic cancer is a cause or an effect of the condition. Increased weight is also known to worsen glycemic control and increase the risk of diabetes progression. However, results from large, prospective clinical trials have shown that weight reduction significantly improves glycemic control in type 2 diabetes patients and lowers the risk of progression of diabetes, as well as cancer [Ross SA et al. *Curr Med Res Opin* 2011].

Tackling the Problem

Complex genetic, endocrine, and biological forces tend to limit the efficacy of cancer therapy. For example, *de novo* activation of the IR-A/IGF-II autocrine loop represents a mechanism of resistance to anticancer therapies [Belfiore A and Malaguarnera R. *Endocr Relat Cancer* 2011]; treatment-related weight gain is a side effect of many oral antidiabetes agents and insulin; and several anticancer treatments may induce or worsen insulin resistance. In addition, diabetes treatments may influence the risk of cancer independently of their effect on glycemia and complicate investigation of the association between diabetes and cancer [Wild SH. *Diabetologia* 2011].

Increasing knowledge of the IR role in cancer has important implications for cancer prevention, which should include control of insulin resistance and hyperinsulinemia in the population and meticulous evaluation of new antidiabetic drugs for their metabolic:mitogenic ratio. Future anticancer therapies need to target the IR-A pathway to inhibit the tumor-promoting effect of IR without impairing the metabolic effect of insulin.

The prevention and treatment of obesity and type 2 diabetes are equally vital. Type 2 diabetes is a global public health crisis that threatens the economies of all nations, particularly developing countries. Epidemiological studies and randomized clinical trials show that type 2 diabetes is largely preventable through diet and lifestyle modifications [Hu FB. *Diabetes Care* 2011].

Translating these findings into practice, however, requires fundamental changes in public policies, the food and built environments, and health systems [Hu FB. *Diabetes Care* 2011]. To curb the escalating epidemics of obesity, diabetes, and cancer, primary prevention through the promotion of a healthy diet and lifestyle needs to be a global public health priority.