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Diabetes and cancer

Annamaria Colao*, Pasquale Vitale and Antongiulio Faggiano

Department of Endocrinology and Molecular and Clinical Oncology, Federico II University of Naples, Italy
**Correspondence: colao@unina.it*

The hypothesis that diabetes mellitus (DM) is associated with an increased risk of cancer is a deep-rooted suggestion, formulated probably during nineteenth century, surely very far away from knowledge of the pathogenic mechanisms of both diseases. Nowadays, numerous meta-analysis demonstrate the strong positive correlation existing between DM and site-specific cancer. In addition, patients developing cancer with pre-existing DM are reported to experience higher short- and long-term mortality. Anyway, the increased risk of cancer development in subjects with an alteration of glucose metabolism is not yet explained: this lack could be addressed to the overlapping risk factors of both diseases like physical inactivity and overalimentation or to the confounding factor represented by anti-diabetic treatments.

The strongest association between DM and site-specific cancer regards liver and pancreatic cancer. Liver cells are exposed to high levels of insulin and, consequently, to its mitogenic effect due to portal circulation. However, this event occurs both in diabetic and non-diabetic subjects, so limiting the relevance of this mechanism to explain the high frequency of liver cancer in DM. On the other hand, diabetic patients are more prone to develop cirrhosis, steatosis, and non-alcoholic fatty liver disease (NAFLD) and these conditions are surely correlated to liver cancer. The relationship between DM and pancreatic cancer is very difficult to prove because it is arduous to establish which condition begins firstly between cancer or hyperglycemia (like the question of the chicken and the egg). However, lots of reported findings give support to consider DM as risk factor for pancreatic cancer; actually, deeper researches are necessary to clarify the mechanism and the implication of this intriguing connection.

Another of the main site-specific cancer frequently associated with DM is breast cancer (BC), the most common cause of death due to cancer in European women. Around one in five women with BC is affected also by DM and probably their coexistence could be explained by similar risk factors like obesity, dyslipidemia, and hyperinsulinemia, although the mechanism underlying this articulated relation needs to be clarify. Several longitudinal and retrospective cohort studies demonstrate that the frequency of BC is significantly increased in postmenopausal women with DM; furthermore, they reveal that the prognosis of women with BC and DM is worse and overall mortality is higher in comparison with non-diabetic patients.

An increase of the development of other organ cancers in correlation with DM is reported, although in some cases studies are not so numerous or well built. They include endometrial, colorectal, and bladder cancer in which the most recent evidence underline not only a raise in the prevalence in the cohort of patients with DM but also an increased mortality.

As all the rules that must be respected, the positive correlation between DM and cancer has an exception represented by prostate cancer. In contrast with the other evidences, in fact, recent meta-analysis report a reduced frequency of prostate cancer in men affected by DM. Even though insulin can play a role also in the progression and the prognosis of this specific cancer, especially during the androgen deprivation therapy, diabetes-related hypogonadism seems to represent the pivotal determining of the decreased risk of developing this neoplasm.

Focusing on the possible pathogenic mechanism that sustained this linkage, the metabolic disequilibrium that characterize a diabetic person contains various elements of interest able to explain several aspects of the increased risk of neoplasm or tumoral progression in these patients. These are represented by hyperglycemia, hyperinsulinemia and insulin resistance, obesity and chronic inflammation which are singularly or contemporary present in DM.

By definition, cancer cells have a very sustained proliferation and need more glucose than other cells; DM and correlated hyperglycemia are optimal conditions for sustaining this metabolic change occurring in cancer cells, that, opportunely, increase the expression of glucose membrane transporters. This abnormal activation of glucose catabolism leads to an increased production of lactate that reduced ph of extracellular matrix, causing the death of non-tumoral cells and promoting the activation of matrix collagenases which make easier the development of metastasis. In addition, hyperglycemia cause the accumulation of advanced glycation end-products (AGEs) which are responsible for oncogenic DNA damaging through the production of reactive oxygen species (ROS).

In non-type I DM, insulin levels are almost always elevated upon the upper range limit and it is associated with the intensification of its pro-proliferative effect. Several studies in literature confirm the mitogenic effect of insulin that could be considered as a peculiar growth factor; this peculiarity became stronger if we consider that insulin can activate non-only its proper receptor (IR), which results in anti-apoptotic activities, but also insulin-like growth factor 1 receptor (IGF-1R) whose pathway play an essential role in cell multiplication and immortalization. The importance of the function of insulin in the development of cancer in diabetic patients is confirmed by the significantly increased expression of IR and IGF-1R in tumoral cells.

A significant percentage of patients affected by DM has a BMI compatible with the diagnosis of obesity. Apart from the induced hyperinsulinemia and insulin resistance, typical in these patients, peptide hormones secreted by adipose tissue can represent the keystones to explain the mechanism by which obesity favors cancer in diabetic patients. Adiponectin and leptin are in fact probably involved in regulating carcinogenesis; the first has an anti-inflammatory activity and stimulate the glucose metabolism, increasing the insulin sensitivity. Leptin, on the other hand, is been demonstrated having a pro-inflammatory

effect which finally results in the stimulation of neoplastic transformation, cell proliferation, and neo-angiogenesis.

The multiform relation between DM and cancer is far away to be definitively understood and all the studies of the next years will have to reckon with the complexity of both DM and neoplasms and consider the heterogeneity of the population involved. But, in the third millenium medicine, all the scientist are called to make an effort in order to give a solution to the emerging health questions of our society. This is the mission they are expected to accomplish.

I am hopeful.

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