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TYPES OF DIABETES MELLITUS INTERLINKED WITH CANCER, OTHER DISEASES, AND COMPLICATIONS WITH OR WITHOUT CANCER

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Abstract:

Cancer and type 2 diabetes are both common illnesses around the globe. Diabetes patients clearly have a much higher incidence of cancer. According to epidemiologic research, people with diabetes are much more likely to develop common malignancies such as gastric, pancreatic, urinary tract, breast, liver, colorectal, and female reproductive cancers. Patients with diabetes have a somewhat higher risk of dying from cancer than those without the disease. Though the underlying processes of this putative relationship have not yet been completely explored, there is mounting evidence that some malignancies and diabetes are related. Insulin is a powerful growth agent that stimulates cell division and the development of cancer either directly or indirectly via insulin-like growth factor 1. (IGF1). IGF binding protein-1 is inhibited by hyperinsulinemia, increasing the bioactivity of IGF-1. A more plausible and believable reason for the development of cancer is hyperglycemia. High glucose levels may encourage the development of cancer cells both directly and indirectly. Additionally, persistent inflammation is seen as a characteristic of cancer development. The many medications used to manage diabetes seem to alter the cancer risk. To improve the prognosis of diabetic cancer patients, early cancer detection screenings and proper cancer therapy are crucial. The links between diabetes and common malignancies are outlined in this research along with potential explanations and practical consequences for medical practice.

Keywords: *Cancer, Diabetes, Association, Mechanism*

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INTRODUCTION:

Diabetes mellitus (DM) is becoming more common everywhere. 8.3% of persons globally, according to the International Diabetes Federation, have type II diabetes (T2DM). T2DM incidence varies by country and area. The greatest rates are 10.5% in the United States, 8.7% in Southern Asia, 6.7% in Europe, and 4.3% in Africa. By 2030, diabetes is expected to affect 552 million people globally [1].

Cancer and diabetes mellitus (DM) are typically detected in the same patient [2]. A higher incidence of many malignancies, including gastric, pancreatic, breast, liver, urinary tract, colorectal, and female reproductive cancers, is reportedly linked to DM. For malignancies of the liver, pancreas, and endometrium, the relative risk is 2.0 to 2.5; for cancers of the breast, colon, and bladder, it is 1.2 to 1.5 [3]. It is important to remember that DM is a widespread health issue. Even if the DM-related risk increase for cancer incidence and death is minimal, the impact on the population as a whole would be substantial [4].

The mechanism of DM linked to cancer is yet unknown and requires additional investigation. According to certain theories, the mechanism behind the association between diabetes and cancer is essentially linked to hormonal [insulin and insulin-like growth factor (IGF)-1] or metabolic (hyperglycemia) elements of the DM, as well as several medications [5]. Anti-diabetic medication may have an impact on cancer risk. Metformin and thiazolidinediones (TZDs), two insulin sensitizers, have been associated to HER2-positive breast cancer [7] and prostate cancer [6] in diabetic patients, according to mounting evidence. Compared to diabetic individuals using metformin, those receiving insulin or insulin secretagogues had a higher risk of developing cancer [8].

In this article, we discuss the epidemiologic studies that have shown links between diabetes and cancer as well as potential causes, causes, and consequences for medical practice.

RELATIONSHIPS BETWEEN DIABETES AND CANCER RISK:

Insulin Sensitivity: In T2DM, when the amount of circulating insulin is regularly elevated, insulin resistance is highly prevalent. The increased risk and development of cancer linked with diabetes are significantly influenced by the insulin/IGF axis. Insulin and IGF-1 receptors are overexpressed in cancer cells [2]. Insulin resistance is characterized by hyperinsulinemia. The processes through which hyperinsulinemia could connect cancer and diabetes have been studied and explored in great detail. Through ligand interaction with the β cells (IR) and/or indirectly by raising circulation IGF-1 levels, hyperinsulinemia may affect the development of cancer [9]. Two IR isoforms, IR-A and IR-B, facilitate insulin signal transduction [10]. IGF2 has a greater affinity for IR-A recognition than IGF-1, while IR-B is insulin-specific and primarily engaged in glucose control. Insulin directly promotes mitogenic development by binding with IR-A. IGF-1 receptor activation follows an increase in IGF-1 hepatic expression, which further promotes cell proliferation when insulin levels are raised [11]. The majority of tissue samples and cancerous cells exhibit the IR-A and IGF-1 receptors [12].

The discovery that down-regulating IRs in LCC6 cells lowers xenograft tumor development in athymic mice and prevents lung metastasis [10,12] supports the IR's independent activity. Inhibition of the IGF-1 receptor has also been associated with a decrease in the growth of breast cancer cells [11,13]. Additionally, hyperinsulinemia increases bioactive IGF-1 levels by boosting bioactive IGF-1 and lowering IGF-binding protein-1 levels [14]. The engagement of IRs or IGF-1 receptors with their ligands results in the activation of a number of downstream signaling cascades. The phosphorylation of adaptor proteins initiates two important pathways: (1) the Ras/MAPK/extracellular signal-related kinase 1/2 pathway, which is essential for the growth and development of cancer cells, and (2) the PI3K/Akt/forkhead box O, PI3K/Akt/mTOR, and PI3K/Akt/forkhead box O pathways [12].

Hyperglycemia:

Traditional thinking has seen hyperglycemia as a minor cause of cancer whereas hyperinsulinemia has been viewed as the main one [15] The risk of cancer and hyperglycemia are positively correlated, according to several case-control and large cohort studies [16]. In a tumor-prone animal study, it was shown that insulin-deficient hyperglycemic mice developed more and larger liver tumors than insulin-sufficient animals, and their levels of apoptosis were lower. Insulin treatment was able to stop this behavior [17]. However, in vivo research has shown that T1DM, which is characterized by hyperglycemia, slows the development of tumors. This result refutes the hypothesis that hyperglycemia accelerates tumor development, at least when an insulin shortage is present. According to a recent study, tumors continue to absorb large quantities of glucose regardless of the level of blood glucose. Improved glycemic management does not lower cancer risk in diabetic

individuals, according to a recent meta-analysis. An independent variable's potential risk for cancer is hyperglycemia. To assess the proportional contributions of insulin and glucose, further research is required. The "indirect impact" and "direct effect" are two potential ways through which hyperglycemia raises the chance of developing cancer. The "indirect influence" of activity in other organs would therefore have an impact on tumor cells by boosting the production of inflammatory cytokines and growth hormones like insulin and IGF-1 in the blood. The "direct impact" is the influence that is directly forced onto tumor cells, improving invasion and migration, inducing abnormalities, boosting migration and invasion, and rewiring cancer-related signaling pathways. By enabling nuclear preservation and the accumulation of transcriptionally active -catenin without being affected by hyperinsulinemia, adipokines, or inflammation, high hyperglycemia enhances this signaling pathway. Wnt/-catenin signaling has recently been recognized as a key cancer-related pathway.

Persistent irritation:

The dysregulated metabolism in poorly controlled diabetes results in a long-lasting pro-inflammatory state characterized by high levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF), C-reactive protein, and other markers of chronic inflammation. An increasing amount of evidence shows that chronic inflammation is associated with an increased chance of getting cancer [18] and that it may promote genetic instability. The conventional evidence that quasi-anti-inflammatory medicines may lower the incidence of several malignancies also lends weight to this conclusion. It is unclear exactly how inflammation in diabetes people promotes tumor growth. Chronic oxidative stress and chronic inflammation are mutually exclusive. Oxidants have an influence on the release of inflammatory cytokines, environmental sensing by innate immune receptors from the Toll-like and DNA polymerase oligomerization domain-like receptor families, and signaling that initiates the adaptive range of cellular responses to such signals [40]. Prior to the onset of the carcinogenesis process, reactive oxygen species may damage DNA, proteins, and lipids. Nuclear factor-kappa B (NF-B), which is significantly triggered by chronic inflammation and is associated with high levels of TNF, aids in the development and spread of various malignancies. In addition to promoting angiogenesis and metastasis, NF-B also undermines adaptive immunity, modulates responses to hormonal and/or chemotherapeutic drugs, and is implicated in the growth and survival of cancerous cells. As a result, persistent exposure to oxidative stress and chronic inflammation increases the likelihood that sensitive cells may advance toward malignant transformation.

Diabetes' effects on cancer:

Insulin resistance, hyperinsulinemia, hyperglycemia, and dyslipidemia are the major characteristics of DM. Since obesity is linked to inflammation and hyperinsulinemia as well, it has been challenging to discern between diabetes and obesity's separate roles in the development of cancer. The relative significance of these elements might be clarified by research using transgenic diabetic mice. Quasi-diabetic mice (A-ZIP/F-1) produced more tumors in a transgenic model of cutaneous and mammary carcinogenesis than wild-type controls [19]. Female mice with T2DM had faster mammary gland growth and breast tumor growth in MKR animal models of mammary tumorigenesis, irrespective of obesity and inflammation. The initial breast tumor development and subsequent lung metastasis were both aided by hyperinsulinemia. Following therapy with anti-insulin medications, tumor development was prevented by a drop in blood insulin levels. Animal research results taken together provide evidence that diabetes and cancer development are linked.

The results of epidemiology:

The findings of a study of 12 cohort studies showed that diabetes increased the risk of all cancer incidence for all persons, with a pooled adjusted RR of 1.14 (1.06-1.23) for men and 1.18 (1.08-1.28) for women. According to research, diabetes is associated with a variety of cancers, including tumors of the pancreas, liver, breast, colon, urinary tract, stomach, and female reproductive systems. An overview of the meta-analyses on the connections between diabetes and site-specific cancer is given in Table 1.

Colorectal cancer:

With a cumulative RR of 1.27, a meta-analysis of 30 cohort studies revealed that diabetes was linked to a higher risk of prostate cancer (1.21-1.34). For both men and women, this connection persisted. In contrast to rectal cancer, colon cancer was reported to have a substantial connection with diabetes in our prior retrospective cohort analysis. This result demonstrated a subsite-specific link between T2DM and colorectal cancer. Intramucosal adenocarcinomas have been attributed to general variables including hyperinsulinemia and IGF-1. Patients with diabetes have slower bowel movements and more frequent constipation, which increases their exposure to intestinal toxins and possible carcinogens. Increased fecal bile acid concentrations have been shown to be

able to cause colorectal carcinogenesis in animal models [20].

Bladder Cancer:
Diabetes was strongly linked to an elevated risk of kidney cancer, according to a meta-analysis that included eleven cohort studies [RR = 1.39 (1.09-1.78)]. Compared to males, women had a somewhat greater connection (RR = 1.47 (1.18-1.83); men, 1.28 (1.10-1.48). The two most frequent comorbidities of DM, hypertension and late-stage renal illness, enhance the risk of kidney cancer. The kidney becomes more vulnerable to carcinogens and the development of tumors as a consequence of impaired renal function, which raises the amounts of toxins and carcinogens in the blood as well as immunological suppression. According to the results of a meta-analysis of 29 cohort studies, people with DM had a higher chance of developing bladder cancer [RR = 1.29 (1.08-1.54)]. Only males show a favorable connection [RR = 1.36 (1.05-1.77)]. In addition to general causes, diabetes patients' recurrent urinary tract infections may also play a role [21].

Breast cancer:
A conceptual analysis of 20 cohort studies found a correlation between diabetes and breast cancer, with a summary RR of 1.23 (1.12-1.34). Diabetic women had a greater risk of endometrial cancer, according to a meta-analysis of 15 cohort studies (RR = 1.81 (1.38-2.37)). Hyperinsulinemia may raise the amounts of reactive estrogens in diabetic women by decreasing the quantity of circulating androgens protein. It is generally known that bioactive estrogens raise the risk of cancer in female reproductive organs. Increased levels of bioactive oestrogen will encourage the expansion of endometrial and breast cells and inhibit apoptosis, raising the risk of developing cancer.

Liver cancer:
The largest risk for cancer has been observed for liver cancer in several research looking at the relationship between DM and cancer. According to a meta-analysis, those with diabetes had a 2.0-fold higher chance of having hepatocellular carcinomas (HCC) than people without the disease. And both men and women showed evidence of this connection. High levels of insulin generated by the body are delivered via the portal vein into the liver. IGF-1 is produced in response to hyperinsulinemia, which further encourages cellular proliferation and prevents apoptosis in the liver. In vitro, in vivo, and epidemiological investigations have all shown the critical role that hyperinsulinemia and IGF-1 play in the development of hepatic carcinogenesis. Diabetes patients are more likely to have cirrhosis, hepatitis, and liver steatosis, which are all well-known possible causes of HCC. Insulin resistance increases the formation of steatosis and inflammation as well as future liver cancer by inducing the production of several pro-inflammatory cytokines identified a dose-responsive connection between fasting glucose and the chance of developing liver cancer but also reported a causal link. Additionally, in people with hepatic steatosis, T2DM-induced hyperglycemia triggers the production of TNF and IL-6 and accelerates the development of cancer.

Pancreatic cancer:
A 3-year follow-up research found that persons with new-onset DM had a 7.94 higher risk of acquiring pancreatic cancer than those without the condition. A meta-analysis of 35 cohort studies found that both men and women with DM had an increased risk of pancreatic cancer. But the question of "reverse causation," or whether diabetes is a cause of pancreatic cancer rather than a risk factor, comes into play. Pancreatic cancer may lead to diabetes because the pancreatic beta cells are harmed. According to in vitro studies, insulin resistance is brought on by blocked insulin receptors, reduced insulin activity, and impaired glucose transport in a pancreatic cancer model. However, the newly developed diabetes brought on by pancreatic cancer is caused by peripheral insulin resistance rather than damaged pancreatic beta cells. On the other hand, because of their closeness to islets that secrete insulin, exocrine pancreatic cells in individuals with T2DM are exposed to extremely high insulin levels. Cancer cells develop more quickly when insulin is present. As a result, hyperinsulinemia may be to blame for T2DM patients' increased risk of pancreatic cancer.

Prostate Cancer:
Patients with diabetes tend to have a lower chance of developing prostate cancer. According to an updated meta-analysis, there was an inverse relationship between diabetes and prostate cancer risk in American research but not in data from other nations. In a separate meta-analysis, the preventive influence of DM was also identified in various levels or phases of prostate cancer. Low levels of testosterone have been seen in diabetic males, which may be one cause. Prostate cell development is stimulated by the transformation of androgen to dihydrotestosterone [22].

Table 1: Combined Relative Risk And 95% Confidence Interval in Cohort Studies Evaluating Diabetes Individuals' Risk Of Cancer In Several Organs

Cancer	Studies	RR	Confidence Interval (95 %)	RR (Male)	Confidence Interval (95 %)	RR (Female)	Confidence Interval (95 %)
Gastric	11	1.2	1.08-1.34	1.1	0.97-1.24	1.24	1.01-1.52
Prostate	25	0.92	0.81-1.05	0.92	0.81-1.05	NA	N/A
Bladder	29	1.21	1.02-1.45	1.36	1.05-1.77	1.28	0.75-2.19
Kidney	11	1.2	1.08-1.34	1.28	1.10-1.48	1.47	1.18-1.73
Colon-rectum	30	0.92	0.81-1.05	1.25	1.17-1.33	1.23	1.13-1.33
Endometrium	15	1.29	1.08-1.54	NA	N/A	1.81	1.38-2.37
Breast	20	1.39	1.09-1.78	NA	N/A	1.23	1.12-1.34
Liver	18	1.27	1.21-1.34	1.96	1.71-2.24	1.66	1.14-2.41
Pancreas	35	1.81	1.38-2.37	1.7	1.55-1.87	1.6	1.43-1.77
Non-Hodgkin's lymphoma	11	1.21	1.02-1.45	1.13	0.96-1.34	1.24	0.97-1.58

Possible repercussions for medical practice:

Patients with a history of diabetes must undergo cancer screening: The research mentioned above demonstrate that people with DM are more likely to have certain forms of cancer. A balanced diet, regular exercise, and weight control may decrease the likelihood and enhance the prognosis of DM and certain cancers. A consensus study from the American Diabetes Association and the American Cancer Society [23] backed up this claim. Early DM-related cancer screening is crucial for T2DM patients in order to enhance prognosis. At-risk people and groups should start cancer screening tests that have been shown to be beneficial for malignancy (breast, colon, endometrial cancer, etc.) comparatively sooner than the general public. Based on current guidelines, further cancer examinations should be conducted. Specific guidelines for cancer screening, nevertheless, have yet to be developed in relation to DM.

The effect of diabetes medications on cancer risk:

The main DM medication groups work in diverse ways to replace circulating insulin, lower hyperglycemia, or lessen the resulting obesity. Metformin and TZDs are two examples of insulin sensitizers, which are oral diabetes medications that reduce insulin resistance by changing signaling along the AKT/mTOR pathway. With confidence, metformin has been used to treat T2DM. There is growing evidence that metformin has an anti-cancer impact from studies done on people and in a preclinical context. In individuals with or at risk for diabetes, metformin usage was associated with a clinically meaningful 39% lower risk of cancer than metformin use alone, according to a meta-analysis of 17 randomized controlled trials. In certain cancer cell lines, metformin may reduce cell growth and trigger apoptosis [24]. Metformin usage has not been linked to increased survival in patients with advanced pancreatic cancer, according to a recent retrospective cohort research [25]. While metformin usage has been linked to a decreased risk of breast, colon, liver, pancreatic, and other cancers, it has not been linked to a higher risk of prostate cancer. TZD-based medication has been linked to a possible cancer risk, particularly pioglitazone with bladder cancer, as well as a protective function in breast, lung, and colorectal cancers. The majority of research revealed that metformin treatment reduces specific cancer risks in T2DM whereas insulin and insulin secretagogues marginally enhance those risks. However, it would be premature to limit the use of metformin and TZDs to those as of yet unconfirmed cancer indications.

Taking care of cancer patients with diabetes:

Cancer patients may struggle to manage their diabetes. Diabetes may have a deleterious effect on both the risk of cancer and the results of cancer therapy. It is obvious that comorbidities may influence the clinical results in cancer patients. Clinicians should focus more on comorbidities while caring for cancer patients with T2DM. Therefore, strict and multifaceted techniques should be used to manage diabetes in individuals receiving therapy for cancer. Cancer patients who have poor glycemic control had higher morbidity and death rates. Therefore, it's crucial to treat hyperglycemia in cancer patients. It's important to keep an eye on both hypoglycemia and hyperglycemia's symptoms. Cancer patients with DM and their families should keep an eye out for these symptoms and treat them as needed as soon as they appear. Aggressive glycemic control is required for

hospitalized patients with acute concomitant problems in order to enhance the prognosis.

CONCLUSIONS:

An increase in cancer risk and death as well as mounting evidence for certain location malignancies are all supported by prior research. The molecular processes underlying the link between diabetes and the development of cancer are currently being studied. The processes of metabolic, inflammatory, and endocrine aspects have been highlighted in this study as potential explanations for this connection. According to the health risk profile of each patient, guidelines specifically for diabetic individuals should include both medication in medical settings and broad screening for certain tumors.

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