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# Diabetes Mellitus: A Potential Risk for Developing Cancer

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## Abstract

Epidemiological studies have clearly indicated diabetes as a risk factor for cancer initiation and progression. Both diabetes and cancer are influenced by multiple factors of known and unknown origin. The magnitude to which these diseases impact the health and economy of the population is colossal. In this review, we will focus on the link between diabetes (Type 2 Diabetes Mellitus) and cancers of varying origins. A number of meta-analyses with and without adjusting confounding factors have been performed implying that diabetes could probably be one of the unregulated perils giving rise to cancer directly, or indirectly promoting pre-existing tumorigenesis. At the molecular level, signaling pathways regulated by insulin and its analogs are considered to be the basis for abnormal cellular proliferation and inhibition of apoptosis. Controlling diabetes and diabetic-induced complications, and therapeutic intervention that can reduce the risk of cancer initiation might aid in protecting the diabetic population from developing cancer.

**Keywords:** Diabetes; Cancer; Insulin; Insulin-like growth factors

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## Introduction

Diabetes Mellitus (DM, Type 2) is one of the fastest growing medico-economic problems worldwide. Current statistical estimate presents around 29.1 million Americans as diabetic and approximately 8.1 million of these individuals go undiagnosed and untreated making DM the 7th leading cause of death in people (www.diabetes.org/diabetes-basics/statistics). DM patients might develop cancer due to factors like sex, age, obesity, ethnicity, tobacco, alcohol, diet, physical activity levels; and relative experimental studies are gradually contributing towards the knowledge to gain further insights into the interrelationship between DM and cancer. Insulin resistance, hyperinsulinemia and chronic inflammation associated with diabetes mellitus are all strongly correlated with cancer [1].

In women with DM, the varying levels of estrogens and progesterone can aid in developing cancers of the breast, ovaries and endometrium, depending on the bioavailability of ovarian steroid hormones [2-10]. Both cancer and diabetes are multi-factorial, heterogeneous and chronic diseases with severe complications. With cancer already making a large impact on mortality in our population, extensive research specific to diabetes as a risk for cancer is warranted. Due to their frequency, even minor influences have a major impact on the population. Throughout the world, the exponential growth in DM prevalence is responsible for most morbidity and mortality [11].

Diabetes and cancer are becoming epidemic in nature influenced by many factors, both genetic and environmental. Co-relation between these two conditions has long been speculated and under investigation. Factors like adipocytokines, insulin, growth factors and epigenetic changes are implicated in the pathogenesis of cancer amongst diabetes patients [12]. The biological factors that favour cancer in diabetes patients include diabetes duration, different therapeutic drugs, varying levels of

metabolic molecules and presence of chronic complications. Epidemiological evidence clearly indicates that the risk of developing several types of cancer appear to be associated with T2DM, thereby increasing the mortality rate in diabetic patients [13-19]. The association between diabetes and cancer have to be investigated extensively and requires reinterpretation because DM is not a single disease but a group of metabolic disorders characterized by hyperglycemia.

In general, diabetes has been shown to increase the risk for heart disease by 2-fold [20] and is equivalent to the risk for Myocardial Infarction (MI) in non-diabetic individuals who have previously had a MI [21]. Emerging data are now correlating diabetes with increased risk of certain types of cancer [22-39]. The complications of diabetes, which include heart disease, kidney disease, blindness, and increased risk for amputations, are as serious as they are diverse [23].

## Cancers associated with Diabetes

A series of recent research and meta-analyses have revealed a relatively strong correlation between some types of cancer and diabetes. In diabetic patients, cancer may be favoured by general mechanisms that promote cancer initiation or progression in any organ due to alterations (hyperglycemia, hyperinsulinemia, drugs) that affect all tissues; or site-specific mechanisms supporting carcinogenesis of a particular organ (such as liver [30], pancreas [31], biliary tract [32], stomach [33], kidney [34], colorectum [35], breast [36], bladder [37] and endometrium [38]. Mortality is moderately increased with diagnosis of diabetes in patients with cancer. Several confounding factors having general or site-specific relevance make it difficult to assess cancer risk in diabetic patients.

In this section, we will elaborate on the various cancers that have been bracketed with onset of diabetes. Whether diabetes and metabolic complications owing to diabetes could be a sole risk factor for the initiation of cancer is debatable; a number of studies are indicative of an association of diabetes with cancer. Most studies are epidemiologic in nature; molecular evidence needs to be garnered and therapeutic intervention to prevent initiation and progression of cancer in diabetics is essential.

## Pancreatic Cancer

Several meta-analyses indicate that the strongest association between DM and increased cancer risk is with pancreatic and liver cancer. A recent meta-analysis of 35 cohort studies documented a 94% (95% CI, 66-127%) increase in the risk of pancreatic cancer in individuals with diabetes relative to those without diabetes [31]. Subgroup analyses revealed that the increased risk of pancreatic cancer was independent of study design, sex, geographic location, body mass index, alcohol consumption and smoking status [13]. Interpretation between diabetes and pancreatic cancer is complicated due to abnormal glucose metabolism, which might be a consequence of pancreatic cancer. However this meta-analysis also found that diabetes was associated with a 1.83-fold (95% CI, 1.38-2.43) increased risk of pancreatic cancer in general [39].

The frequency of diabetes diagnosis among patients with pancreatic cancer has gradually and continuously increased for 3 years preceding cancer detection [40, 41]. Similar tendency was found regarding FPG levels, with an inverse relation to BMI [42]. Diabetes, predominantly new onset, was estimated to have more than 40% prevalence among pancreatic cancer [43].

## Breast cancer

Breast cancer is currently the most common malignancy affecting women in industrialized countries [44]. Epidemiologic evidence suggests a modest relation between Type-2 diabetes and breast cancer. Breast cancer shares some risk factors with diabetes, such as age and obesity [45, 46]. Female diabetic patients were more likely to have increased risk of and mortality from breast cancer [47-49]. A meta-analysis of 20 studies (5 case-control and 15 cohort studies) showed a 20% (95% CI, 12-28%) increased risk of breast cancer in diabetic women [32]. Majority of Type-2 diabetics have shown a statistically significant 20% higher risk of developing breast cancer (RR 1.20; 95% CI 1.2-1.28) than non-diabetic women,

and risk was more prominent among Type-2 diabetes and postmenopausal women [50].

Hormonal changes in diabetics are attributed towards augmented breast cancer risk; including insulin, insulin-like growth factors, estrogens, cytokines and steroid sex hormones. Most of these hormones and growth factors are known to play an important role in carcinogenesis. The interaction of these hormonal factors in diabetic state is complex and known to be involved in the promotion of cancer [51].

## Prostate Cancer

Prostate cancer differs from other cancers in its association with diabetes. In contrast to increased risk of numerous forms of neoplasia, a reduced incidence of prostate cancer has been reported in diabetic patients [13]. A meta-analysis of 19 studies (9 case-control and 10 cohort studies) showed a significant decreased risk of prostate cancer [39]. The suggested mechanism underlying this inverse association is thought to be reduced (16%) testosterone levels in diabetic men. The diverse use of medications such as metformin and statins; and changes in lifestyle and diet, to control diabetes has been hypothesized as elements potentially contributing to the inverse association between diabetes and prostate cancer [13].

## Liver Cancer

Hepato Cellular Carcinoma (HCC) is the second most frequent cause of death in men worldwide with cancer. In addition to pancreatic cancer it has been studied most extensively in association with DM [52]. Epidemiological evidence has suggested a significant association between diabetes and liver cancer, after taking important confounding factors into account, specifically alcohol consumption and hepatitis B or C virus infection [30, 53]. HCV-positive individuals were more than three times more likely to have T2DM [54] and HCV core protein has been shown to induce insulin resistance [55, 56]. Some recent studies strongly support a positive association between diabetes and the risk of hepato cellular carcinoma. Diabetes patients were at 1.86-fold (95%CI, 0.99-3.51) increased risk of liver cancer [53].

A recent subgroup and meta-analysis of 18 cohort studies reveals a significant association between diabetes and an increased risk of hepatocellular carcinoma by 101% (95% CI, 61-151%) and mortality by 56% (95% CI,30-87%) in diabetic individuals compared to non-diabetics [30]. Many other studies suggest a link between diabetes and liver cancer, which may be mediated through higher risk of non-alcoholic steatohepatitis, leading to cirrhosis and liver cancer [30].

## Biliary Tract Cancer

Diabetes patients may have a greater risk of biliary tract cancer. Diabetes was independently associated with an increased risk of biliary stones [57]. Biliary stones might act as an intermediate factor between diabetes and tract cancer and is considered to be a major risk factor for biliary tract cancer [58]. A meta-analysis of 8 case-control and 13 cohort studies reveals that diabetes was associated with an increased risk of biliary tract cancer, as compared to non-diabetic patients (RR 1.43; 95% CI, 1.18-1.72). These evidences indicate a greater risk of biliary tract cancer in diabetic patients [32].

## Gastric Cancer

Meta-analysis evidence linking diabetes to gastric cancer has not shown any significant association in men with diabetes. However, meta-analysis of 4 case-control and 17 cohort studies in women has shown significant association with a 1.18-fold (95% CI, 1.01-1.39) increased risk of gastric cancer [33]. There was a strong evidence of heterogeneity among the studies in this meta-analysis. Another study demonstrated that diabetes was significantly associated with an increased incidence (61%) of gastric cancer (95% CI, 2-154%) in women, whereas the association was not significant in men (RR 1.23; 95% CI,0.98-1.54), after adjusting for potential confounding factors, such as dietary factors, body mass index, physical activity and smoking status [59].

## Colorectal Cancer

A number of cohort studies taking into consideration life style factors (such as a lack of exercise and obesity) have

shown an increased risk of colorectal cancer in diabetes patients [60]. Meta-analysis of 30 cohort studies documented that diabetes was associated with an increased incidence of colorectal cancer (RR 1.27; 95% CI, 1.21-1.34) and relative mortality from colorectal cancer (RR 1.20; 95% CI, 1.03-1.40). A strong evidence of heterogeneity among the studies in subgroup analysis, meta-analysis and meta-regression analysis showed an elevated risk of colorectal cancer in individuals with diabetes compared to individuals without diabetes [61]. Colorectal cancer with diabetes was independent of physical activity, body mass index, cancer start-site, geographic location, sex, smoking and family history of colorectal cancer [62]. Diabetes was positively associated with colorectal cancer mortality [61, 62].

## Bladder Cancer

Meta-analysis of 16 studies, 7 case-control showed that diabetes was associated with a risk of bladder cancer when compared with no diabetes (RR=1.24, 95% CI 1.08-1.42) [58]. Of the conducted case-control studies and cohort studies, cohort studies with diabetic patients suggest that individuals with diabetes may have a modestly increased risk of bladder cancer [63].

## Renal Cancer

Number of studies on renal cancer is small with diabetes cases and meta-analysis has not been performed. But epidemiological studies suggest a higher risk of renal cell cancer in diabetic patients [12].

## Blood Cancer

Meta-analysis involving 13 case-control and 13 cohort studies was performed to correlate diabetes with different types of blood cancer. Outcome was reported as the Odds Ratio (OR). The OR for non-Hodgkin lymphoma was increased at 1.22 (95% CI, 1.07-1.39; P < .01) but the OR for Hodgkin lymphoma did not show any difference. There was an increased OR for peripheral T-cell lymphoma (OR = 2.42, 95% CI, 1.24-4.72; P = .009), however other non-Hodgkin lymphoma subtypes did not change. The OR for leukemia was 1.22 (95% CI, 1.03-1.44; P = .02) and the OR for myeloma was 1.22 (95% CI, 0.98-1.53; P = .08). In conclusion, excluding confounder consequences, patients with Type-2 DM showed a 20% increased risk for developing certain types of blood cancer [64].

## Type 1 Diabetes Mellitus and Cancer

In a population-based study, researchers found that people with Type 1 diabetes had a modest overall increase in cancers compared to non-diabetics. However, certain cancers showed a much higher risk. For example, Type 1 diabetics had nearly double the risk for developing stomach and cervical cancer and almost three times the risk for developing cancer of the uterus [65]. The plausible reason attributed to this is the high numbers of Helicobacter pylori infection among people with Type 1 diabetes. Inflammation caused by H. pylori -- the bacteria that cause stomach ulcers -- is believed to play a role in stomach cancer.

## Signaling pathway from Diabetes to Cancer

The most plausible explanation deduced from various studies suggesting diabetes as a risk factor for cancer is through the insulin signaling pathway. The pathway will be discussed in detail in this section.

A common factor that cannot be ignored for diabetes and cancer association is obesity. Cancers consistently associated with obesity include those of pancreas, breast, renal cell, oesophagus, liver and colorectum [66]. Some epidemiologic studies have reported that diabetes and obesity are linked to increased risk of certain cancers through enhanced expression of insulin, C-peptide and Insulin like Growth Factor-1 (IGF-1) [67-79]. A correlation between cancer and diabetes can be established by measuring insulin, C-peptide, IGF-1, IGF-binding protein levels and also by genetic mutations in the gene encoding insulin, insulin receptor, IGF-1, IGF-2, IGF-binding proteins, Insulin Receptor Substrates (IRS) [80]. Studies involving animal models demonstrated that aberrant insulin, IGF-1 and IGF-2 signaling lead to enhanced tumorigenesis, while abrogating their expression had reverse effects [81].

Therapies targeting diabetic-induced signaling pathways to fight cancer are under clinical trials.

Elevated plasma insulin is associated with poorer outcomes of cancer. Meta-analysis shows excess risks of colorectal, breast and pancreatic cancers associated with higher levels of circulating C-peptide/ insulin and markers of glycaemia. Insulin itself exerts a mitogenic effect through IGF-1 receptor on various tissues including breast cancer cell lines. Interestingly, breast cancer cells appear to have high levels of insulin receptors compared to normal breast tissue [82]. The direct effect of insulin on endometrial cancer cells is probably through ERK1/2 and glycogen synthase kinase-3β Ser9 phosphorylation, thereby promoting carcinogenesis [83]. It is also possible that hyperinsulinemia promotes carcinogenesis indirectly through the effects of IGF-1. Insulin reduces the production of IGF binding protein-1 and consequently increases the bioactive IGF-1. IGF-1 has more potent mitogenic and anti-apoptotic effects than insulin and could act as a stimulus for growing pre-neoplastic and neoplastic cells.

## Insulin and IGF-1 Signaling

Insulin is produced mainly by the pancreatic β cells, while IGF-1 is synthesized largely in the liver in response to the action of growth hormones on the growth hormone receptor. Insulin increases the expression of growth hormone receptors and enhances post-receptor signalling; hyperinsulinemia may lead to increased production of IGF-1 [82], present in T2DM-related obesity and associated with increased cancer and mortality risk [84-90]. Insulin signals primarily through the insulin receptor, while IGF-1 signals primarily through the IGF-1 receptor. Insulin receptor signalling mainly mediates metabolic effects, while IGF-1 signaling leads to growth and proliferation [91]. The insulin receptor and IGF-1 receptor have a similar structure with α and β subunit joined to another α and β subunit by disulfide bonds. Cells that express both the insulin receptor and IGF-1 receptor can also express hybrid receptors, consisting of α and β subunits from insulin receptor bound to an α and β subunit of an IGF-1 receptor [65]. Insulin has a high affinity for insulin receptor-A and receptor-B and low affinity for IGF-1 receptor and does not bind to hybrid receptors. IGF-1 signals through IGF-1 receptor as well as hybrid receptors. IGF-2 binds to insulin receptor-A, IGF-1/ insulin receptor and IGF-1 receptor. Binding of insulin to insulin receptor-A leads to different signaling activation compared with IGF-2 binding (Figure 1).

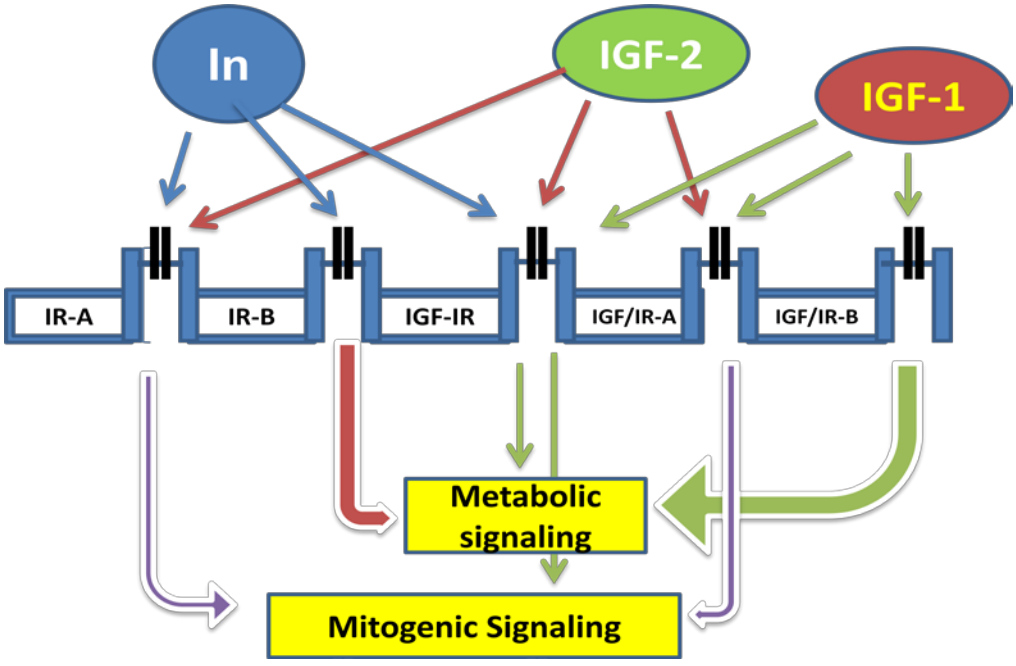

**Figure 1: Insulin ligand – receptor interactions.** Schematic showing the insulin (In) receptors (IR-A and IR-B), the insulin like growth factor-1 receptor (IGF-1R), the hybrid receptors (IGF-1R/IR-A and IGF-1R/IR-B) and their respective ligands. Adapted from Emily J. Gallagher et al., Endocr Pract 2010. The pathway from diabetes and obesity to cancer: On the route to targeted therapy. 16(5), 864-873.

Binding of insulin to insulin receptor-A and IGF-1 or IGF-2 to IGF-1 receptor leads to autophosphorylation of β sub-unit of the receptors and phosphorylation of residues on IRS and adaptor proteins (Gab1, Shc, and APS). Phosphorylation of IRS leads to activation of p85, a regulatory subunit of Phosphatidylinositol-3-Kinase (PI3K), which results in activation of protein kinase B (Akt). Akt, in turn, inhibits apoptosis and induces protein synthesis facilitating cell cycle progression and eventually cell proliferation [91]. The autophosphorylation of IGF-1 receptor activates MAPK pathway and recruitment of adaptor protein Shc and then Grb2 (Growth factor receptor bound protein 2) which results in activation of Ras and Raf-1/MEK/ERK pathway that leads to cellular proliferation [92-95] (Figure 2). Cancerous cells show an increased expression of insulin receptor-A, hybrid receptors or IGF-1 receptors. Hence enhanced insulin, IGF-1 or IGF-2 levels allow for increased activation of mitogenic signaling pathways, thereby promoting carcinogenesis [94].

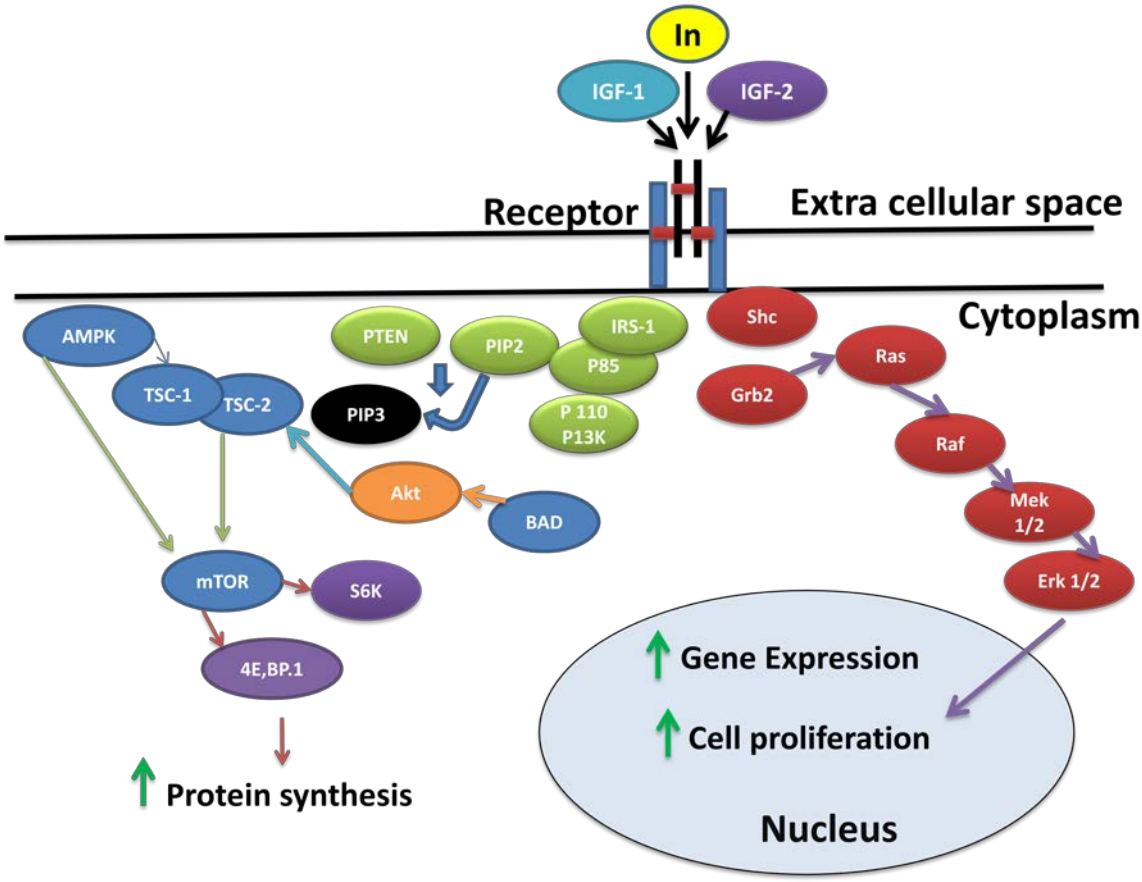


**Figure 2: Insulin and Insulin-like growth factor-1 and -2 signaling pathways.** Insulin (In) and IGF-1 and IGF-2 signal through Ras-Raf-Mek pathway or PI3K pathway or mTOR pathway in a cell. Overexpression of these ligands due to diabetic condition or drugs could possibly lead to enhanced aberrant signaling facilitating in neoplasm and cancer development. Overexpression of Insulin and IGF receptors is seen in many cancers. Adapted from Emily J. Gallagher et al., Endocr Pract 2010. The pathway from diabetes and obesity to cancer: On the route to targeted therapy. 16(5), 864-873.

## Conclusion

Epidemiologic evidence suggests that individuals with diabetes are at significantly higher risk for many forms of cancers. The theory of reverse causation has been established where pancreatic cancer can induce a diabetic state and is supported. Many in vitro and in vivo studies have shown evidence that the rate of insulin secretion among individuals may influence the risk and progression of cancer. Additionally, insulin and IGF-1 levels in cancer patients are proportional to cancer-related mortality. In cancer cells, insulin or IGF-1 increased cell proliferation and reduced apoptosis. On the other hand, insulin signaling deficiency caused by the down regulation of IRs inhibits cell proliferation. Further studies are necessary to determine the effect of blocking or disrupting receptor activity on tumor growth and metastasis. Early diagnosis of diabetes and continuous monitoring can aid in prognostic measures for cancer. Further investigation is needed to develop a more rational approach to cancer prevention and treatment among individuals with diabetes.

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