

**Diabetes and Cancer: A Review**

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**Abstract**

Diabetes and cancer are common chronic conditions, and their co-existence in the same individual is not frequent. Type 2 diabetes mellitus is an independent risk factor for several types of cancers such as that of pancreatic, liver, colorectal, breast, endometrial, renal and female reproductive organs. Several epidemiological cohort and case control studies have clearly supported it but relative risk of prostate cancer is decreased in male patients. Many other factors that influence the risk of cancer in diabetes are hyperinsulinemia, hyperglycemia, obesity, increased oxidative stress while anti-diabetic drugs have minor effect on cancer risk (except biguanide eg. metformin). This review article will summarize the evidence of link between diabetes and cancer and its causes.

**Keywords:** Diabetes mellitus, cancer, insulin, metformin.

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**Introduction**

The World Health Organization Diabetes Programme has stated that the worldwide prevalence of diabetes mellitus was 346 million in 2011 and will increase to approximately 366 million in 2030 [1]. In the United States, it is estimated that 29.1 million people or 9.3% population have diabetes. Among that 21.0 million are diagnosed and 8.1 million or 27.8% of people with diabetes are undiagnosed in 2012. According to World Health Organization criteria 1985, 70.3% cases of newly diabetes had recognized between aged 25-64 years in China. The prevalence of diabetes in China is three times higher than ten years ago [2]. Diabetes mellitus (DM) is a serious and rapidly growing health problem worldwide and is also associated with severe acute and chronic complications that negatively influence the quality of life and survival of affected individuals both. Diabetes and cancer are common, multifactorial, chronic diseases which co-exist in same patient is not common. Diabetes is associated with high risk of cardiovascular and microvascular complications and also increased cancer risk [3, 4]. Type 2 diabetes mellitus is a group of metabolic disorders characterized by impaired fasting glucose level, hyperinsulinemia, hyperglycemia which has been linked to elevation of tumor cell proliferation and migration in vitro. Hyperglycemia include reduced insulin secretion, decreased glucose utilization and increased glucose production which leads to damage, dysfunction and failure of organs like eyes, kidney, nerves, heart and blood vessels. Symptoms of hyperglycemia include polyuria, polydipsia, weight loss, polyphagia, blurred vision and also uncontrolled

diabetes leads to ketoacidosis or nonketotic hyperosmolar syndrome. Diabetic patients are also related with hormonal and metabolic disorders like insulin growth factor, exogenous insulin, insulin analogs, insulin secretions but drugs that decreased the cancer risk are metformin and thiazolidinediones [5-7]. Many environmental risk factors such as obesity, inactive lifestyle, stress and smoking are intended to increase the chances of oncological comorbidities [8,9].

The relation between diabetes and cancer has been studied broadly and found that diabetes is associated with increased risk of many types of cancer like liver, pancreatic, breast, endometrial, kidney, bladder, colorectal cancers and non-Hodgkin's lymphoma but the risk of prostate cancer is decreased [10-12,22]. This review article will summarize the evidence of link between diabetes and cancer, types of cancer and its causes and relation with diabetes treatment.

**Classification of diabetes and cancer risk**

On the basis of the pathogenesis process, diabetes mellitus can be divide into

Two broad categories:

**Type I DM:** Insulin-dependent diabetes mellitus (IDDM)

Result of complete or near-total insulin deficiency.

Hyperglycemia is associated with an absolute deficiency of endogenous insulin secretion and the absolute necessity for exogenous insulin therapy.

**Type II DM:** Noninsulin- dependent diabetes mellitus (NIDDM)

Group of disorders like insulin resistance, impaired insulin secretion and increased glucose production.

Hyperglycemia and hyperinsulinemia coexist for a long time because of insulin resistance, when beta cell become dysfunctional completely then patient require insulin treatment because of endogenous insulin deficiency.

#### **Gestational DM:**

Characterized by high blood glucose levels first recognized during pregnancy. The condition occurs in 4% of all pregnancy.

The epidemiological study between the association of diabetes and cancer have done in type II diabetic patients (90%). The difference between these types depends upon young patient, insulin therapy in type I and insulin-independent in type II. Type I diabetic patients need exogenous insulin because of autoimmune destruction of pancreatic beta cells which cannot produce endogenous insulin. Insulin plays a major role in cancer growth, experiment was done in rats and mice [13]. In type II diabetes mellitus, hyperglycemia is associated with endogenous increased insulin level caused by insulin resistance.

#### **How to diagnosis Diabetes mellitus?**

Fasting plasma glucose  $\geq 7.0$  mmol/L (126 mg/dL).  
Random blood glucose  $\geq 11.1$  mmol/L (200 mg/dL).  
HbA1c  $> 6.5\%$   
2-hr values in oral glucose tolerance test (OGTT)  $\geq 11.1$  mmol/L (200mg/dL).

#### **Relation between diabetes and cancer**

Several studies and multiple meta-analysis have confirmed that risk of cancer in association of diabetes patients such as liver, pancreas, endometrium, colorectal, breast, kidney, bladder and non- Hodgkin's lymphoma is increased but prostate cancer is decreased [14-22,30,65]. However, lung cancer is not associated with diabetes mellitus.

#### **Diabetes and Pancreatic Cancer**

Meta- analysis of 35 cohort studies suggested that risk of pancreatic cancer is increased in diabetes mellitus patients with relative evidence (relative risk RR= 1.94) [23]. Increased risk was also independent of BMI causing metabolic syndrome and obesity and insulin resistance [24]. Several meta-analysis also showed independent association between BMI and

pancreatic cancer in both male and female [25]. Another meta-analysis of 36 case-control and cohort studies indicated that sex and age accustomed odd ratios for pancreatic cancer with diabetic patients were 1.8(95%CI1.7-1.9) [4].

The pre-diabetic form was also considered for risk factor for pancreatic cancer. The mechanism remained unclear and hyperinsulinemia is possible cause as exocrine pancreatic cells lead to pancreatic cancers due to high insulin concentrations and common blood supply with islets of insulin.

#### **Diabetes and Liver Cancer**

The mechanism underlying this relationship is still unclear although inflammation of liver, liver cell damage and repair are likely to associate the increase chance of liver carcinoma in diabetic patients. It also includes hepatitis B & C virus infections in diabetic patients. The risk of liver cancer is also due to non-alcoholic steatohepatitis which leads to liver cirrhosis and cancer and also depends upon age, sex, alcohol and tobacco consumption, history of hepatitis, BMI. Liver cancer is cause by metabolic imbalance of liver which is the main organ in the body [26-29]. The risk of liver disease remained significant in comparison between 2061 patients with hepatocellular carcinoma with 6183 controls after excluding the fatty liver disease patients. So it cannot be entirely omitted that hyperglycemia or hyperinsulinemia independently subsidized the liver cancer risk [30].

#### **Diabetes and Colorectal Cancer**

Type II diabetes and colorectal cancer association reveal confounding by variables of exposure that independently influence both colon cancer and type II diabetes like age, sex, BMI, smoking, alcohol use, menopause, estrogen therapy, visceral fat, physical activity, high consumption of red meat, low intake of dietary fiber, use of medicine aspirin, family history of colorectal carcinoma [18,31].

Several studies have supported the relation between colorectal carcinoma and type II diabetes. The increased risk of colon cancer in diabetes patients has recently supported by meta-analysis of 15 studies, 6 case-control and 9 cohort studies, including 2.5 million patients, relative risk (RR)=1.3 in relation to non-diabetic patients [15]. Other studies also showed increased risk of cancer in diabetic patients rather than non-diabetic [18, 32].

#### **Diabetes and Breast Cancer**

The risk of breast cancer is increased in diabetic women, this risk factor is independent from obesity. Several meta-analysis of 20 case-control study and

cohort study have shown significant 20% increased risk of breast cancer (RR 1.20; 95% CI 1.12-1.28) [21,69]. A relative risk in diabetic women was 1.27 in comparison with non-diabetic patients adjusting age, sex, race, BMI, smoking and alcohol consumption [11]. The relation between risk of breast cancer and diabetes was studied separately among postmenopausal women or among women of postmenopausal age, a supportive result was observed in both case-control and cohort studies, relative risk was 1.19 [33-35]. Also hormonal replacement therapy with estrogen increased the risk of breast cancer in lean postmenopausal women but the cancer risk was not increased in obese women [36, 69].

### **Diabetes and Endometrial Cancer**

A meta-analysis of 16 studies, 13 case-control and 3 cohort studies, revealed a significant increased risk of endometrial cancer in diabetic patients, relative risk 2.10, (95% CI 1.75-2.53) [17]. A strong relation between type I diabetes and endometrial cancer was noted. It is independent from obesity [3]. Mainly sex hormone abnormalities and hyperinsulinemia, which increase estrogen secretion by decreasing sex hormone binding globulin concentration and stimulate androgen production in ovarian stroma are the mechanism to cause cancer. Others mechanism like delayed menarche in type I diabetes women have higher chances of irregular menstrual cycle, nulliparity and fertility disorders.

### **Diabetes and Renal Cancer**

The increased risk of renal cancer in diabetes patients was shown by studies but till now no meta-analysis has been performed [3]. The relative risk of renal cancer is more in obese patients (3.2; 95% CI=1.9-5.1) [16].

### **Diabetes and Bladder Cancer**

Meta-analysis of 16 studies showed that the risk of bladder cancer was increased in diabetes than non-diabetes (RR=1.24, 95% CI 1.08-1.42) [19].

### **Diabetes and Prostate Cancer**

In diabetic male patients, the risk of pancreatic cancer is lower than non-diabetic patients, supported by a meta-analysis of 19 studies, 7 case-control and 12 cohort studies, result as RR=0.84 [22]. The range of testosterone is in lower level in diabetes mellitus so risk of prostate cancer is decreased. The latest meta-analysis revealed significant inverse relation between diabetes and prostate cancer, which includes 14 studies and showed slight decreased risk of prostate cancer in diabetes patients with relative risk 1.91[37].

Again the relative risk was confirmed as 0.84 in another meta-analysis [22].

### **Other risk factors for diabetes and cancer**

More than 80% diabetes patients are obese. Obesity and BMI are related with higher incidence and higher mortality in cancer. Cancer related with obesity and overweight are pancreas, liver, gall-bladder, kidney, colorectal and endometrium [14, 38].

Fat distribution is also important in the body, central obesity (upper body) increased the risk and worsen the outcome of cancer than gynoid obesity. Many studies suggested that the association between diabetes and cancer are influenced by high prevalence of obesity in diabetic patients, both obesity and diabetes are characterized by hyperinsulinemia. Many other factors associated in this mechanism are diet, nutritional factors, hormonal and metabolic abnormalities. A tight relation have been studied between obesity, estrogen levels and the breast cancer that showed increased risk mainly in obese postmenopausal women. Obese postmenopausal women usually present an increase in estrone and estradiol both due to increase activity of adipose tissue [12, 39]. Adipose tissues produces cytokines, predominatly IL-6 which play major role in regulating mitogenic activity. Adipose tissue is an active endocrine gland which produces free fatty acids, monocyte chemoattractant protein, plasma activator inhibitor-I, adiponectin, leptin and tumor necrosis factor-alpha [40]. These all factor play a role in cancer cell proliferation and enhanced apoptosis, also animal studies had proved that cancer are more prone to obese animals than lean animals [41].

Hyperinsulinemia and hyperglycemia both are present in diabetic patients. It is well known that high intake of sugar, carbohydrates and high blood glucose levels and impaired glucose tolerance are associated with cancer risk. Hyperinsulinemia increases the level of circulating IGF-I to stimulate cell proliferation in many organs like liver, pancreas, colon, ovary, and breast with increased cancer risk in diabetic patients. The role of increased insulin is to bind and activate IGF-I receptor. Insulin-like growth –factor-binding protein- (IGFBP-1 and IGFBP-2) produced by liver is reduced by insulin which stimulates cancer cells [42,43]. Hyperinsulinemia in premenopausal women increases the androgen synthesis in ovaries and may decrease sex-hormone-binding globulin concentration and elevated endogenous sex steroid levels increase the cancer risk of postmenopausal cancers like breast and endometrium [14]. The role of an abnormal energy balance and disorder of hyperglycemia impair the

effects of ascorbic acid and decrease the immune system effectiveness. Hyperglycemia regulate the level of reactive oxygen species. These species are sensitive to hyperglycemia. Hyperglycemia supplies more glucose to cancer cells, resistance to apoptosis and tumor cell and promote malignant cancer cell proliferation [12, 44].

Several studies have postulated that low diet in red and processed meat and high fiber diet in vegetables, fruits and whole grains decrease the cancer risk. Several meta-analysis also showed that high diet in vegetables, fruits, whole grain cereals, monounsaturated fatty acids and dietary fiber protect against type II diabetes by improving insulin level and also protect against cancer in type II diabetes. Regular physical exercises also decrease cancer risk in colon, breast and endometrial cancer as shown in many studies. Physical exercise also decrease risk of diabetes. Smoking and alcohol consumption are independent risk factor for diabetes and cancer [45]. Leptin is also secreted by adipose tissue cytokine. Leptin is increased in obesity and diabetes exclusively of body mass index. Leptin is also involved in local invasion of tumor metastasis. It is associated with insulin and C-peptide levels and associated with metabolic syndrome and increased C-reactive protein (CRP), inflammation marker. Insulin, fasting serum leptin and triglycerides are increased in breast cancer after adjusting BMI and age [46-48]. Adiponectin is also secreted by adipocytokine and its plasma concentration is inversely related to BMI. Studies had proved that increased adiponectin reduce the cancer risk in diabetic patients. Adiponectin showed an anti-proliferative effect in breast cancer cells [49].

Epigenetic process influences gene expression and it includes DNA methylation, histone modification, chromatin remodeling, non-coding RNAs and microRNAs. These gene expression increase or decrease according to environmental influences. Epigenetic process increased the cancer risk occurrence [50]. It is a common path between gene and environment. Diet is a major epigenetic processes that affects the level of DNA methylation and histone modification depending upon the availability of methyl donors like folate, choline and methionine [51].

#### **Effects of anti-diabetic drugs and cancer risk**

Increased insulin level is responsible for increased risk of cancer in diabetes. Metformin (biguanide) is used as a first line drug therapy for type II diabetic patients. The studies showed that decreased cancer

risk in treatment group compared to untreated patients odds ratio=0.86 [52]. Metformin reduces the level of insulin through the mechanism by the stimulation of an enzyme AMP-activated protein kinase through the tumor suppressor protein liver kinase B1 (LKB1) and suppressed hepatic gluconeogenesis and glucose output from liver. It is independent of decrease in hyperinsulinemia [53]. A number of studies showed that metformin has a protective role in occurrence of cancers in diabetic patients. UK Prospective Diabetes Study (UKPDS) has proved that diabetic patients treated with metformin has lower risk of cancer. Meta-analysis of 15 studies showed a significant effect of metformin in cancer of colon [54].

Thiazolidinediones are selective agonists for the nuclear peroxisome proliferator-activated receptor gamma (PPAR  $\gamma$ ), enhance the transcription of many insulin related genes. Meta-analysis showed no effect of this drugs on cancer risk [55, 56, 68].

The other drug group sulphonylureas causes more insulin secretion that leads to hyperinsulinemia and related with increase cancer risk. One case-control study showed that patient treated with glibenclamide but not with gliclazide has increased risk of cancer than other oral hypoglycemic drugs [57]. The retrospective cohort study of metformin therapy was lowest in cancer risk than sulphonylureas, RR=1.08 (95% CI 0.96-1.21), the colorectal cancer risk was increased with sulphonylureas, RR=1.36 (95% CI 1.19-1.54) and with insulin, RR=1.42 (95% CI 1.27-1.60) [58].

For both type I and type II diabetes, insulin is most important factor to treat hyperglycemia. Insulin and insulin-like growth factor I (IGF-1) have similar signal pathways and also metabolic and mitogenic effects of hormones were overlapped partially. Both insulin and IGF-1 work as growth factor. The new meta-analysis of observational studies showed the association between insulin and the cancer risk especially in colorectal cancer related with insulin therapy (**Table 1**) [59].

Incretin therapies: Glucagon-like peptide-I (GLP-1) is secreted by small intestine, provides nutrients and improves insulin secretion and delays gastric emptying. Dipeptidyl-peptidase-4 (DDP-4) inactivates GLP-1. Recent studies showed that GLP-1 therapies induce pancreatic ductal hyperplasia and increase the risk of chronic pancreatitis that leads to pancreatic cancer [60].

**Table 1: Oral hypoglycemic drugs**

Group	Generation	Drugs	Mechanism
Biguanides		Metformin	Do not cause insulin release
Sulfonylureas	1 <sup>st</sup> generation	Tolbutamide, Chlorpropamide	Release of insulin.
	2 <sup>nd</sup> generation	Glibenclamide, Glyburide Glipizide, Gliclazide, Glimepiride	
Meglitinide / phenylalanine analogues		Repaglinide Nateglinide	Short acting insulin releases.
Thiazolidinediones		Rosiglitazone Pioglitazone	Reverse insulin resistance, entry of glucose into muscle and fat is improved.
Alpha-glucosidase inhibitors-		Acarbose Miglitol	Decreases & slows down digestion and absorption of polysaccharides and sucrose without increasing insulin levels.

## Discussion

Several epidemiological studies and meta-analysis suggested that diabetes mellitus increase the risk of cancer depending on the cancer site, increase more in pancreatic cancer, liver, colorectal, endometrium, breast but the cancer risk is decreased in prostate cancer [14-22, 30, 65]. Although after adjustment of age, sex and races diabetes mellitus type II and cancer co-exist frequently [12]. Also some studies have shown that cancer risk is increased by a group of metabolic and hormonal disorders such as hyperglycemia, hyperinsulinemia, obesity, hypertension, dyslipidemia and gout in diabetes patients and also affected by other risk factors such as diet, stress, exercise, smoking, alcohol consumption [14]. Several meta-analysis and systemic review showed that diabetes was related with increased risk of cancer incidence [61].

A meta-analysis of cohort studies showed the increased risk of liver and pancreatic cancer in both sexes as 2.01 and 1.94 in diabetic patients [23, 62]. Liver cancer is most common in type II diabetes mellitus due to hyperinsulinemia, hepatitis B & C infections, steatosis, non-alcoholic fatty liver diseases and liver cirrhosis. The risk of colorectal cancer was also increased in diabetes patients by bowel disorders, constipation, high fecal bile concentration, hydroxy-fatty acids, biliary tract cancer and cholelithiasis [63]. The research supported the proof of the effect of fatty acids and their metabolites, which stimulate DNA transcription factor, peroxisome proliferator activated receptor gamma (PPAR-  $\gamma$ ) and increased expression has been found in rat and human colon carcinoma cell [64].

A newly published meta-analysis reported that diabetes is also related with increased risk of bladder and kidney cancers [19,65]. Obesity is the main cause for these both cancers, there is also a relation between diabetes and non-Hodgkin's lymphoma. The risk of breast cancer is also increased in diabetes patients due to sex hormones abnormalities and increased insulin level. It also increases the level of bioactive estrogen hormone by lowering sex hormone-binding globulins concentration and stimulates androgen growth in female [21]. But the association between diabetes and prostate cancer is decreased in male patients due to reduced testosterone levels, imbalanced insulin, use of drugs like metformin and diet control [22].

The most important factor in association between diabetes and risk of cancer is insulin resistance, hyperinsulinemia, it has a mitogenic effect by activating insulin-like growth factor. Hyperinsulinemia and hyperglycemia stimulate tumor cell proliferation and metastasis in type II diabetes [66, 67]. The drug metformin biguanide lowers the risk of cancer in diabetes patients than insulin or sulphonylurea [58]. Also adipose tissue produces inflammatory cytokines, interleukin-6, and monocyte chemoattractant protein and plasminogen activator inhibitor-I, which play a major role in carcinogenesis, cancer progression and poor outcome.

## Conclusions

From all these review and meta-analysis, we conclude that diabetes and cancer are associated with each other with several confounding factors such as

metabolic syndrome, hormonal imbalance, hyperinsulinemia, hyperglycemia, hypertension, dyslipidemia, obesity as risk factors of cancer in diabetes patients. Including all these disorders and also cardiovascular disease, diabetes are increasing rapidly all over the world due to increasing trend of population and life style so diabetes patients are strongly encouraged to go for cancer screenings as it is one of the major health issues in society.

### Conflict of Interest

The authors declare no potential conflicts of interest in this manuscript.

### Abbreviations

BMI=body mass index,

DM=diabetes mellitus,

HbA1c= glycated hemoglobin,

IL-6=interleukin-6,

IGF=Insulin like growth factor

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