

## The Risk of Cancer in Diabetes Patients: A Review

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### ABSTRACT

Diabetes and cancer are complicated, severe, homogenous and chronic fatal disease with tremendous impact on worldwide. One of the theory why diabetes and cancer link may exist is that high level of circulating insulin can promote the growth of tumours. The people with diabetes are more risk of many forms of cancer in which cancer is the second leading cause for death and diabetes is the seventh leading cause to death. The common risk factors that link diabetes and cancer is age, sex, obesity, physical activity, increased calorie intake, alcohol and smoking. The mechanism that increases the risk of cancer in diabetic patient is insulin resistance and hyperglycemia which leads to progression of cancer. The risks of cancer are shown to be higher in type II diabetes patients because in type II diabetes the body produces more insulin than normal. Thus we have concluded that diabetes is a high-risk state for several types of cancer. It is increased according to age, sex, obesity and decreased physical activity. The diabetes and cancer risk is higher in obese patients. However, most diabetes is not associated with the risk of cancer. Therefore, we can provide awareness of preventive strategies and public health policies to avoid overlapping burden of both diseases that already have tremendous impact on people health and economy. By providing awareness we can overcome the mortality rate of the both disease.

**Key Words:** diabetes, cancer, risk, chronic fatal disease.

### INTRODUCTION

Diabetes is a common disease that affects our body's ability to produce or respond to the hormone insulin is impaired. Cancer is a disease caused by an uncontrolled division of abnormal cells in a part of the body. Diabetes and cancer are complicated, severe, homogenous and chronic fatal disease with tremendous impact on worldwide. One of the theory why diabetes and cancer link may exist is that high level of circulating insulin can promote the growth of tumors. [1] The people with diabetes are more risk to many forms of cancer in which cancer is the second leading cause for death and diabetes is the seventh leading cause for death. The common risk factors that link diabetes and cancer is age, sex, obesity, physical activity,

increased calorie intake, alcohol and smoking. [2] The mechanism that increases the risk of cancer in diabetic patient is insulin resistance and hyperglycemia which leads to progression of cancer. The risks of cancer are likely to be higher in type II diabetes patients than in type I diabetes because in type II diabetes the body produces more insulin than normal. [3]

### SITE SPECIFIC CANCER RISK IN DIABETES

The diabetes link with cancer varies among cancer types of which type II diabetes patients are more risk to pancreatic cancer, liver cancer, endometrial cancer but smaller increased risk of colorectal cancer, bladder cancer, breast cancer, blood cancer

and type 1 diabetes patient are risk to stomach cancer and cervical cancer. [4]

### **Pancreatic cancer**

Pancreatic cancer is when cells start being produced in the pancreas in an uncontrolled fashion by the body. Pancreatic cancer is the most dangerous form of cancer. Pancreatic cancer is twice as likely to occur in people with diabetes or new onset diabetes because both share the same risk factors such as poor diet, physical inactivity, obesity and aging. [5] The mechanism behind the pancreatic cancer and diabetes is that normal levels of circulating insulin and increased pressure on the pancreas to produce insulin is the possible reasons for diabetes leading to a higher risk of pancreatic cancer. [6] The recent meta-analysis which included 6,657 female and 7,742 male patients with an average age of 66.5 years, from which 4,080 pancreatic patients were reported with type II diabetes and 9,721 patients without type II diabetes which resulted that the patients with type II diabetes are more risk to pancreatic cancer than the patients without type II diabetes. [7] The BMI and HbA1C range was higher (25 kg/m<sup>2</sup> and 7.41%) in both diabetic and non-diabetic patients with pancreatic cancer and there was no difference in range when the studies were compared. They also compared the influence of diabetes history and its duration on the incidence of pancreatic cancer which resulted that people with longer duration (>5 years) of type II diabetes are more risk to pancreatic cancer than the patient with shorter duration (< 5 years) of diabetes. The risk of pancreatic cancer is also higher in patients with recent onset diabetes. Studies that linked pancreatic cancer in people with type 1 diabetes have produced a conflicting result that some studies show the increased risk and others showing no increased risk. The reason behind these mixed results is that some studies have an unclear definition and selection criteria of people with type I diabetes. [8]

### **Liver cancer**

Liver cancer is also known as hepatocellular carcinoma. It is a term that refers to either primary liver cancer that originates in the liver and secondary liver cancer that spreads to the liver from another part of the body such as the bowel. Hepatocellular carcinoma is the second most serious cancer in the worldwide. In addition to pancreatic cancer the association between the liver cancer and diabetes has been reported as the strongest cancer death. [9] The exact cause of liver cancer is unknown, but it is strongly linked to scarring and inflammation of liver called cirrhosis, which is caused by alcohol misuse and hepatitis B & C virus. Type II diabetes is the most common form of diabetes mellitus that leads to increased risk of liver cancer due to its strong association with obesity. The exact mechanism for the underlying risk is unknown but some hypothesis has shown that hyperinsulinemia and increased IGF can promote cell proliferation which inhibit the apoptosis and promote carcinogenesis. [10] The recent study done in 2015 about 10,794 diabetes cases with primary liver cancer were included. Among them, 4497 cases were male and 6223 cases were female with an age group number (10-70 years). The incidence included both men and women, which resulted that men with diabetes are higher risk to liver cancer than female. The increase in age can result in improved liver cancer in diabetes patients. In these 10,794 patients, 317 patients have diabetes and hepatitis from which 37 patients had a risk of liver cancer. A correlation study was also done between the duration of diabetes and the liver cancer in which the duration was divided into 0-5 years, 5-10 years, 10-20 years and 20 years above in which it results that the diabetes patients with the duration of 5-10 years and 10-20 years are more risky to liver cancer. However the risk of liver cancer was increased in male with increased duration and age than in females with diabetes. [11]

### **Endometrial cancer**

Endometrial cancer is otherwise known as uterine cancer (cancer of the uterus or womb). It is the most common form of cancer in women and one that affects the female reproductive system. Cancer of the uterus is considered as the earliest stage of womb cancer which develops in the cells located in the lining of the uterus (womb) called the endometrium. The women who have not gone through menopause, the endometrium grows and thickens each month before being shed from the womb as a monthly period. A high level of estrogens in the body can cause the cells of the endometrium to divide and increase the risk of endometrial cancer. [4] A prospective study was done which included 36,773 women in the cohort for 7 years, of which 225 endometrial cancer cases were diagnosed. The potential risk factors of endometrial cancer in diabetic and non-diabetic patients were compared in which the individuals who were diagnosed with diabetes patients were older, lower physical activity, less education and tended to have used less post-menopausal hormone treatment and oral contraceptives were also not used these characteristic were lower in non-diabetic patients but some characteristic were similar between the diabetic and non-diabetic patients. These characteristic increase the risk of endometrial cancer in diabetic patients. [12] Additional adjustment were made for unobserved exposure such as postmenopausal hormone use, oral contraceptive use, parity, age at menopause, education, smoking and total energy intake but these did not show any result. The diabetic and non-diabetic patients were compared according to the BMI and physical activity of the women which confirmed that women with high BMI and low physical activity were at increased risk of endometrial cancer than with low BMI and high physical activity. [13]

### **Bladder cancer**

Bladder cancer occurs when tumour occur in the bladder. It may be non muscle invasive bladder tumour which grow in the

lining of bladder that affect the 70% of person or muscle invasive bladder cancer which grow among the muscle around the bladder but this is more serious cancer it can spread to other parts of the body. Bladder cancer is the sixth most common form of cancer and has increased incidence of bladder cancer which have been linked with type II diabetes. Evidence put forward that diabetes mellitus is associated with increased risk of bladder cancer. [14] According to recent meta-analysis that included 19 cohort studies, 9 case control studies and 8 cohort studies that were conducted in Europe, North America, Asia and two in multiple countries consisted of men and women with diabetes. Among these 36 studies, 18 studies did not demonstrate increase in bladder cancer risk in diabetes patients. In random effect the patients with diabetes were compared the patient with non- diabetes which resulted in that the patient with diabetes are more risk to bladder cancer than the patients with non-diabetes. [15] Fourteen studies were compared for the incidence of bladder cancer with diabetes according to the sex which shown that men was associated with increased risk of bladder cancer than in female. The three studies in the meta-analysis compared risk of bladder cancer with the duration of diabetes (<5 and >5 years). It resulted that the patient with shorter duration of diabetes are higher of developing bladder cancer than patients with longer duration of diabetes. [16]

### **Breast cancer**

Breast cancer refers to cancer that is uncontrollable growth and spread of new cells that originates from breast tissue. As cancer develops in different parts of the breast, there are various different types of breast cancer. Some remain inside the breast and are known as non-invasive breast cancers, while most have the ability to spread outside the breast and are commonly referred to as invasive breast cancer. The causes of breast cancer in diabetes patient is that age, hormone activity, hormone replacement therapy, family history, post-

menopausal obesity and type II diabetes. Four major mechanisms that may contribute to the association between type II diabetes mellitus and breast cancer is the activation of the insulin pathway, activation of the insulin-like growth factor-1 pathway, altered regulation of endogenous sex hormones and altered regulation of adipocytokines. [17] Recent meta-analysis which included 40 independent risk estimates were reported in 40 articles of these 15 case control study, 3 cross sectional studies (18 retrospective studies) and 22 were prospective studies were conducted in north America, south America, Europe and in Asia which included 56,111 breast cancer cases. The association between diabetes and breast cancer is restricted in post-menopausal women. The risk of breast cancer is increased in obese post-menopausal women than in pre-menopausal obese women. The women with increased body weight are more risk to breast cancer. [18]

### **Colorectal cancer**

Colon cancer is also known as bowel cancer or colorectal cancer is the third most common form of cancer. Colon cancer occurs when cells of the glands in the colon start to grow in an uncontrolled way, and therefore tumours develop. If it is left untreated the cancer will grow into the muscle wall of the colon and it can spread to neighboring organs. Colon cancer is linked with diet factors, obesity and people with type II diabetes and they were found to have a higher chance of developing colon cancer. Colon cancer is most commonly diagnosed in older people as the risk increase with age. [19] A meta-analysis in which 21 studies was conducted which included 216,981 participants. There were 7 prospective cohort studies including 3 prospective mortality study and other studies were retrospective cohort studies. All studies were limited to patients with invasive colorectal cancer, except one that included 124 out of 1853 patients with non-invasive colon cancer. Ten of the studies were population-based, one was cohort based on

a multicenter trial, and eleven studies included only patients who undergone surgery and all others were from single institutions. There were twelve studies where outcomes were not adjusted for age of the patient or for tumor stage. By these studies it have been resulted that patient with diabetes have an increased risk of colorectal cancer with significant increase in all-cause mortality and cancer specific mortality. The risk of developing colorectal cancer is higher in type II diabetic patient's than in non-diabetic patient. [20]

### **Prostate cancer**

Prostate cancer can develop when the cells starts to grow in an uncontrolled way. Prostate cancer grows slowly and may not cause any problem. The majority of men with low grade prostate cancer lives for many years without symptoms, without spreading but becoming life-threatening and while high grade disease spreads quickly and can be lethal. [21] Recent meta-analysis included 733 articles from which 17 cohort studies were analyzed for the association of diabetes and the prostate cancer that had 274,677 male patients. This study included only prospective and retrospective studies. The studies were then examined for the association between diabetes and prostate cancer specific mortality and all-cause mortality in patients. The association between the pre-existing diabetes and the prostate cancer showed that 30% increase in prostate cancer mortality and 68% increase in all-cause mortality in patients with prostate cancer. Five studies which found the association between the prostate cancer and the pre-existing type II diabetes which resulted in increase in all-cause mortality in patients with prostate cancer and not associated with the prostate cancer specific mortality. This meta-analysis suggests that prostate cancer may worse the prognosis of men. [22]

### **Gastric cancer**

Gastric cancer is the cancer that starts in the stomach also known as stomach cancer. It tends to develop slowly over many years. Before a true cancer can

develop, pre-cancerous changes often occur in the inner lining of the stomach. These changes rarely cause symptoms and therefore often cannot be detected. Cancer starting in the different area can result in different symptoms and tend to have different outcomes. Infection with bacteria is the common cause of gastric cancer. [4] A recent meta-analysis was done which included 2,130 articles; from these 21 studies were analyzed for the association of diabetes mellitus and gastric cancer. The participants included where 8,559,861 individuals and reported with 13,538 new gastric cancer cases and 2,140 died due to gastric cancer. The studies were conducted in Asia, Europe, USA and the study were using self-administered questionnaire, medical records and blood glucose test were used. Among these 15 studies reported that diabetes was not associated with a change in gastric cancer risk but change in character was detected and 9 studies reported that there was association between the diabetes and gastric cancer mortality. There were eleven studies for men and ten studies of women in the association of diabetes and gastric cancer risk, six and five studies for association between the diabetes and gastric cancer mortality in men and women, which reported that there was no association of diabetes, and gastric cancer risk and mortality, both in men and women. A subgroup analysis was conducted which suggested that diabetes was associated with an increase in impact on gastric cancer incidence and mortality, it might increase the risk of gastric cancer incidence in men and increased risk of gastric cancer mortality in women but the study was not adjusted for smoking and alcohol consumption, it might increase the risk of gastric cancer mortality in men with diabetes according to age(<55 years) and there was no gender difference for gastric cancer incidence and mortality. [23]

#### **Kidney cancer**

Kidney cancer is the cancer that develops in the kidney which is the part of the urinary system. The type of they develop

depends upon the type of cell the cancer develops. Around 50 out of 100 the kidney cancer is diagnosed in the people aged 70 years and it is rare in people around age 50 years. The recent meta-analysis which included 15 studies, from this nine cohort studies were included in this four studies were conducted in Europe, three in Asia and two in North America. From these nine studies, six studies had both men and women, two studies included only men and only one study included women. The studies that were analyzed showed that diabetes patients have an increased risk of kidney cancer than in patients without diabetes. The studies according to the sexes resulted that women are more risk to kidney cancer than the men. [24]

#### **CONCLUSION**

Thus we have concluded that diabetes is a high-risk state for several types of cancer. It is increased according to age, sex, obesity and decreased physical activity. The risk of cancer is mostly increased in type II diabetic patients. The diabetes and cancer risk is more high obese patients. However, most diabetes is not associated with the risk of cancer. Therefore, we can provide awareness of preventive strategies and public health policies to avoid overlapping burden of both diseases that already have tremendous impact on people health and economy. By providing awareness we can overcome the mortality rate of both diseases.

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