REVIEW ARTICLE

Diabetes and cancer: A comprehensive review

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Diabetes mellitus (DM) is a common worldwide endocrine disorder characterized by hyperglycemia resulting from defects in insulin secretion and insulin action or both. A number of clinical studies have investigated diabetes and its causal relation with neoplasm. Several epidemiological studies have found that diabetic patients have an increased risk of different types of cancers, for example liver, pancreas, gastric (stomach), colorectum, kidney, and breast, and it is predicted that hyperglycemic state observed in diabetic milieu enhances the cancer risk in prediabetic and diabetic individuals. To explore the strength of evidence and biases in the claimed associations between type 2 DM (T2DM) and risk of developing cancer, an umbrella review of the evidence across published meta-analyses or systematic reviews is performed. The concurrence of T2DM with the growing burden of cancer globally has generated interest in defining the epidemiological and biological relationships between these medical conditions. Through this review, it was found that diabetes could be related to cancer. Yet, the results from most of the studies are obscure and conflicting and need a robust research so that the link between diabetes and cancer could be firmly and impeccably documented.

Key words: Breast neoplasms, diabetic complications, gastric neoplasms, hepatic neoplasms

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INTRODUCTION

Diabetes is emerging as one of the most prevalent human ailments next to cardiovascular diseases and is the sixth leading cause of death worldwide (WHO). Etiologically, diabetes mellitus (DM) is a heterogeneous disorder characterized by abnormal glucose homeostasis and insulin resistance. The root cause of diabetes involves complex mechanisms. Diabetes is of two types – Type 1 and Type 2. Type 1 DM is juvenile diabetes/insulin-dependent DM (IDDM) characterized by pancreas failure to produce insulin on account of beta cell destruction. It is prevalent in young age like in children, adolescents and young adults. On the other hand, type 2 DM (T2DM) is adult-onset diabetes and is called as non-IDDM resulting due to inability of cells/tissues to respond properly to the action of insulin. Apart from these, other factors such as genetic and metabolic abnormalities are also accountable.[1] A number of studies has related diabetes to cancer risk. Furthermore, growing evidences suggested an abnormal glucose homeostasis as an independent risk factor for the development of specific neoplasms and affecting the prognosis of cancer.[2,3] Several epidemiological studies have found that diabetic patients have an increased risk of different types of cancers, for example, liver, biliary tract, pancreas, stomach, colorectum, kidney, bladder, breast, and endometrium.[4-12] Contrarily, a reduced incidence of prostate cancer has been reported in individuals with diabetes.[13] In recent years, spectacular advances took place in interpreting the etiology of diabetes and cancer. Novel cancer biomarkers (CBs) are studied to evaluate the risk of cancer in prediabetic and nondiabetic individuals. Therefore, challenge in the cancer research would be the identification of novel CBs that could be used as prognostic and diagnostic tools. CBs are present in tumor tissues or fluids and include a wide variety of molecules such as DNA, mRNA, transcription factors, cell surface receptors, secreted proteins, and small metabolites.

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observational, cohort, case studies, and meta-analysis studying the correlation between diabetes and different neoplasms has been performed. Around 9 published studies on pancreatic cancer, 8 on gastric cancer and 17 on hepatic cancer, 6 colorectum cancer, 8 breast cancer, and 2–3 articles on prostate cancer extracted from the survey were profoundly studied from the total of 77 references included in the review [Table 1]. The largest proportion of cancer cases attributable to the increase in prevalence of diabetes and high body mass index (BMI) was in low-income and middle-income countries like Asia and sub-Saharan Africa.[14]

Diabetes and total cancer

There are strong evidences linking cancer with diabetes. A number of epidemiological studies has investigated the association between diabetes and cancer risk.[15] In a European study on 17 varied populations, cancer mortality rate was 1.12, 1.28, 1.57 in prediabetes, newly diagnosed diabetes, and known diabetes cases, respectively.[16] Gender-related differences in cancer and diabetes were inconspicuous.[17] Some studies found increased risk of cancer in diabetes while others did not. A recent analysis by Qi *et al*. 2019 investigated the risk of 23 common types of cancer among patients with T2DM on a large sample size (8485) in mainland China. The standardized incidence ratios of total cancer were 1.34 and 1.62 among males and females, respectively. Enhanced risk of cancer of the prostate, blood, skin, thyroid, kidney, liver, pancreas, lung, colorectum, and stomach was found in T2DM males and greater risks of cancer of the nasopharynx, liver, esophagus, thyroid, lung, pancreas, lymphoma/leukemia, uterus, colorectum, breast, cervix, and stomach among females with T2DM. In contrast, there was significantly decreased risk of gallbladder cancer in females with T2DM.[18] Diabetes as a risk factor for all-site cancer in both women and men, with an excess risk of cancer slightly greater for women than men was reported by Ohkuma *et al*., 2018.[19] In addition, it is predicted that hyperglycemic state observed in diabetic milieu enhances the cancer risk in prediabetic individuals. An increased incidence of cancer mortality with fasting blood glucose in the prediabetic individuals (6.1–6.9 mmol/L) was reported in a Korean study.[20] Hence, epidemiological studies provide evidence that diabetes and prediabetes are associated with an increased risk of total cancer.

Pancreatic cancer

Ductal adenocarcinoma of the pancreas (DPAC) is the fifth leading cause of death related to cancer in developed countries and is the thirteenth most common type of cancer worldwide.[21] Approximately, 80% of the pancreatic cancer are associated with diabetes and impaired glucose tolerance.[22] A recent meta-analysis of 88 cohort studies documented a 94% increase in the risk of pancreatic cancer in individuals with diabetes compared to nondiabetic individuals.[23,24] The link between pancreatic cancer and diabetes is intricated due to the fact that abnormal glucose homeostasis may be underlying factor for the onset of such cancers. In a recent large pooled analysis in Asian individuals, chen *et al*., 2017 showed an increased mortality risk for pancreatic cancer in diabetic subjects.[25] According to recent reviews, patients with T2DM has thrice the tendency to develop pancreatic cancer compared to nondiabetic individuals.[25-27] Several studies had hypothesized that the diabetes is a consequence of asymptomatic pancreatic cancer while some had conflicting observations proving that DM (type 2) is really a cause, not a consequence of pancreatic cancer. Nevertheless, Gullo *et al*., 1994 reported that the T2DM could be consequence of pancreatic cancer and is more stronger in recently diagnosed individuals.[28] Diabetes duration <1 year was reported to carry the highest risk for DPAC as reported by Ben *et al*. 2011.[29]

Gastric cancer

Studies examining the relationship between DM and the risk of gastric cancer-related mortality have produced inconsistent results. A meta-analysis of twenty-two cohort studies reporting data on 8,559,861 participants observed diabetes as a predisposing factor that increased the risk of gastric cancer in men.[30] Parallely, a prospective study in Japan involving 97,771 volunteers, examined approximately 61% increase in cancer risk in diabetic males. However, other studies reported contradictory results with respect to cancer risk in females.[31] In a meta-analysis by Ge *et al*., 2011, a subgrouped analysis revealed 18% increased risk of gastric cancer in diabetic women compared to diabetic men.[7] In an investigation by Jee *et al*., 2005 increased fasting serum glucose and diabetes were considered as independent risk factors for gastric cancer, and the relative risk tends to increase accompanying an increased fasting serum glucose level.[20] Likewise, significant association between diabetes and the higher risk of gastric cancer has been documented by Lin *et al*.[32] According to Lin *et al*., 2011 hyperglycemia may account for generation of imbalance in the energy/metabolism and impairment of immune system that could progressively lead to gastric cancer. While many studies and meta-analysis reported significant difference between diabetic and nondiabetic individuals, several other studies reported diversified results. In a cohort by Chodick *et al*., 2010 they concluded no significant correlation between incidence of gastric cancer and diabetes.[33] In addition, in a study reported by Xu *et al*., 2015 there was no significant correlation obtained in risk of gastric cancer with diabetes in both genders.[34]

Hepatic cancer

There are some intriguing findings from the previous literature on the association of diabetes with liver cancer.

Table 1: Summary of included studies involving the association between diabetes and cancer risk

Cancer	References	Design	Characteristic findings
Pancreatic cancer	Chen *et al*., 2017	Cohort (19)	Increased risk of pancreatic cancer in diabetes
	Ogunleye *et al*., 2009	Cohort	
	Batabyal *et al*., 2014	Meta-analysis of 88 cohort	
	Gupta *et al*., 2006	Cohort	
	Pannala *et al*.	Case–control	
	Ben *et al*., 2011	Meta-analysis	
Gastric cancer	Chen *et al*., 2017	Cohort (19)	Positive association between diabetes and gastric cancer
	Miao *et al*., 2017	Meta-analysis	
	Inoue *et al*., 2006	Cohort	
	Kuruki *et al*., 2007	Case control	
	Ge *et al*., 2011	Meta-analysis	
	Xu *et al*.	Cohort	No significant association between diabetes and gastric cancer
	Codick *et al*., 2015	Cohort	
Liver cancer	Davila *et al*., 2005	Case–control	Positive correlation of diabetes with HCC
	Lagiou *et al*., 2000	Case–control	
	Ogunleye *et al*., 2009	Cohort	
	Li *et al*., 2017	Case–control	
	Wang *et al*., 2017	Meta-analysis	Risk of hepatic cancer increased in diabetes associated with HBV, HCV, or alcoholic cirrhosis
CRC	Zhu *et al*., 2017	Meta-analysis	Patients with diabetes has a 5-year shorter survival (18%) in CRC compared to nondiabetic patients
	Zelenko *et al*., 2014	Meta-analysis	Increased risk of CRC in diabetes compared to nondiabetic patients
	Guraya *et al*., 2015	Meta-analysis of cohort (8)	Diabetic females has greater risk of developing CRC than men
Breast cancer	Hardefeldt *et al*., 2012	Meta-analysis (43)	Significantly increased risk of breast cancer in diabetes women compared to men and nondiabetic females
	Larsson *et al*., 2007	Meta-analysis	A 20% enhancement in the risk of breast cancer in type 2 diabetes
Prostate cancer	Lee *et al*., 2016	Meta-analysis	A 29% increase in prostate cancer-specific mortality was observed in preexisting diabetes
	Bonvas *et al*., 2004	Meta-analysis	People with diabetes have a significant decrease in risk of developing prostate cancer

CRC=Colorectal cancer; HCV=Hepatitis C virus; HBV=Hepatitis B virus; HCC=Hepatocellular carcinoma

In a study in US on 2061 hepatocellular carcinoma (HCC) and 6183 control, 2.8-fold enhancement in the risk of hepatic cancer in diabetic individuals was reported.[35] Similar findings were obtained in Greece. They examined 333 cases of HCC and 363 controls. Diabetic patients were at a 1.86-fold (95% confidence interval [CI], 0.99–3.51) higher risk of liver cancer.[36] These findings strongly evident the correlation of diabetes with HCC. A three-fold increased risk of liver cancer has been reported in earlier investigations after adjustment of confounding factors such as alcoholism and viral hepatitis.[37,38] Several studies have elucidated the relationship between diabetes and HCC with different etiologies. An extensive US-based study on hepatoma revealed profound results; the hepatoma risk was elevated in diabetic individuals manifested with hepatitis B virus (HBV), hepatitis C virus (HCV) infection, or with alcoholic cirrhosis.[39] Contrarily, subsequent studies analyzed that the risk of HCC increased in diabetic individuals independent of alcoholism and/or viral hepatitis.[40,41] In view of the above contradictions, studies exploring the relationships between diabetes and hepatocellular carcinomas with different etiologies have been analyzed separately. Risk of HCC was found to double in diabetic individuals in China with chronic hepatitis as speculated by Li *et al*., 2017.[42] Parallelly, a study in Europe investigating on the risk of HCC in diabetes in association with chronic hepatitis C observed that HCC incidence was 11.4% and 5.0% in diabetic and nondiabetic individuals, respectively.[43] Contrary observations were speculated in cohort involving 54,979 individuals, wherein increased HCC risk was found in HCC-negative individuals.[44] There is discrepancy in the observations on the risk of HCC in diabetes and need further research to be clearly understood. The underlying mechanism probably linking the risk of HCC and diabetes involves many intricated mechanisms. It has been suggested that low insulin and hyperglycemia in diabetes may account for increased virological response and impairment in HCV eradication leading to fibrosis which progresses to cirrhosis in patients with T2DM and HCV.[45-48]

Association between diabetes and hepatitis B-related HCC also seems to remain unclear. Increased risk (2–3 fold) of HCC in diabetic patients positive for HBV was reported in a Taiwan-based study.[49] Supportingly, a study by Amano

et al., 2014 on HCC patients with HBV infection found T2DM to be significantly related to HCC in HBV patients.[50] Contradictorily, a cross-sectional study on cirrhotic patients with HBV with and without HCC found that diabetes was not a significant risk factor for HCC.[51] Similarly, Gao *et al*., 2013 found that diabetes was analyzed to be independent of the prospect of HCC in cirrhotic patients with HBV infection.[52] Involvement of nonalcoholic fatty liver and alcohol abuse also need to be accounted as they contribute significantly as risk factors for HCC in diabetes. Several reports and reviews suggested diabetes could be risk factor for nonalcoholic fatty liver disease and subsequent cryptogenic HCC.[53]

Colorectal cancer

It is the third most commonly diagnosed cancer in global incidence (1.8 million cases and 10.2% of the total cancer) being higher in males compared to females.[54] The association between diabetes and colorectal cancer (CRC) has been elucidated in numerous epidemiological studies and meta-analysis have been published.[55] Diabetic individuals are highly prone to CRC in comparison with nondiabetics. A systemic analysis of 8 selected studies showed a robustic correlation of T2DM with the 1.21-fold enhanced risk. The analysis resulted in spectacular findings where diabetic women exhibited greater risk of developing CRC than men.[56] Affirmative results linking CRC with diabetes in the above analysis can be thus a compelling evidence. Intriguing results were obtained in a meta-analysis report wherein the risk of cancer was found to be independent of geographic location, sex, family history of CRC, smoking, physical activity, and BMI.[57,58] Zhu *et al*., 2017 analyzed 36 cohort studies with 2,299,012 participants to explore the interrelationship between diabetes and CRC. The meta-analysis revealed that the patients with diabetes will have a 5-year shorter survival in colorectal, colon, and rectal cancer with a 18%, 19%, and 16% decrease in overall survival (OS), respectively, compared to nondiabetic individuals. The aforementioned studies indicates that diabetes had a negative effect on CRC in OS.[59] The biological mechanism linkage between diabetes and CRC prognosis is still unclear. Currently, it is hypothesized that hyperglycemia, insulin resistance, and insulin/insulin like growth factors (IGF) are probably involved in the progression of diabetes to CRC.

Breast cancer and other sex related cancers

A positive association between diabetes and risk of breast cancer has been reported in females. Breast cancer has emerged as the most common ailment affecting the morbidity and mortality among females worldwide.[60] Insulin resistance, hyperinsulinemia, and changes in the signaling of growth hormones and steroid hormones associated with diabetes may affect the risk of breast neoplasm. A 20% enhancement in the risk of breast cancer and T2DM have been surveyed.[11] Similarly meta-analysis by Hardefeldt *et al*., 2012 on 43 studies including 40 and 6 studies investigating breast cancer in women and in men, respectively, found significantly increased risk of breast cancer in Diabetic women. However, increased risk of breast cancer in males was not statistically significant, and it was concluded that diabetes is an independent risk factor for breast cancer.[61] Several factors are responsible in etiology underlying the breast cancer. Obesity and diabetes are considered as some of the risk factors for the onset of breast cancer. Furthermore, increased estrogen in females is thought to be a possible link between breast cancer and diabetes in female individuals.[62] Obesity is considered as one of the predisposing factors for cancer even in nondiabetic individuals with impaired fasting glucose levels.[63] Other sex-related cancers such as endometrial and prostate cancer are also studied, yet the results of most of the studies are inconclusive. A strong positive association of diabetes with increased risk of endometrial cancer has been reported in females in meta-analysis of 13 case–control and 3 cohort studies.[12] Hyperinsulinemia and hyperestrogenemia associated with low sex hormone-binding globulin (SHBG) levels are considered as etiological factors responsible for stimulating the proliferation of endometrial cells causing cancer.[64] A high risk estimate of risk ratio (RR) 1.65, 95% CI 1.50–1.81 in a meta-analysis is corroborative with the assumptions linking endometrial cancer with T2DM. Yet the results are nonconvincing due to heterogeneity among the clinical studies.[65] Contradictory reports were found in case of breast and ovarian cancer. The outcome in these studies were supported by a lower risk estimate in a meta-analysis (RR 1.21, 95% CI 1.10–1.32 and RR 1.19, 95% CI 1.06–1.34, respectively) and were associated with low heterogeneity among the studies.[66,67]

Diabetes and prostate cancer

In relation to diabetes, contrasting results were obtained for prostate cancer compared with other type of cancer. In a meta-analysis studies by Kasper and Giovannucci, it was found that diabetic men were at a significantly decreased risk of developing prostate cancer.[13] The presence of low levels of testosterone and SHBG in diabetic men could be responsible for this conflicting results.[68]

To eliminate the bias in the stage of diagnosis of cancer and its risk, a meta-analysis was performed by Lee *et al*., 2016. They investigated the incidence of death due to prostate cancer in men in preexisting diabetic individuals.[69] Preexisting diabetes are patients diagnosed with diabetes before the diagnosis of the prostate cancer. Conflicting results were obtained in a meta-analysis studying the correlation between preexisting diabetes and the death incidence in prostate cancer patients. A 29% increase

in prostate cancer-specific mortality was observed in preexisting diabetes. Further, focusing on subgroup analysis in T2DM in particular, no significant correlation was obtained between preexisting T2DM and prostate cancer-related mortality. Based on heterogeneity in the findings, further investigations should be undertaken to ascertain the link between diabetes and prostate cancer.

Kidney cancer

There has been remarkable increase in the incidence of kidney cancer over the past few decades. Factors such as hypertension, obesity, and smoking are identified as risk factors underlying renal carcinoma and T2DM. Several evidences across epidemiological studies showed diabetic patients to have an increased risk of cancer at several sites, yet diabetes as a risk factor for kidney cancer remains unclear. In a meta-analysis by Larsson and Wolk, 2011 on 9 cohort studies revealed significant data. Patients with diabetes exhibited significant increase in the risk of cancer compared to nondiabetic individuals indicating association between diabetes and kidney cancer.[9] Like other cancers, there has been disparity in findings in the studies linking diabetes and kidney cancer, especially in terms of gender. A recent analysis on a large cohort of 117,570 women and 48,866 men in US studying the risk of diabetes and renal cell carcinoma (RCC) revealed astonishing results. Women with diabetes had an increased risk of RCC compared to nondiabetes women with no significant association in men. T2DM was found independently associated with a greater risk of RCC in women but not in men.[70]

Lung cancer

Lung cancer has also emerged as one of the leading causes of cancer-related death and the second most common malignancy in men and women in USA.[71] A case–controlled study analyzed cancer survival among lung cancer patients with and without diabetes and found the interplay between lung cancer and diabetes increased the 5-year OS for lung cancer patients without DM (OS - with diabetes 20; without diabetes 29%) concluding diabetes not causing adverse impact on lung cancer survival.[72]

Link between diabetes and cancer

A number of assumptions and mechanisms responsible for etiology underlying diabetes have been reported. Many factors are considered responsible for the cause/relationship of diabetes with cancer. Nevertheless, conditions such as hyperinsulinemia, hyperglycemia, and inflammation are considered to be of prime significance in progression of diabetes to cancer. Hyperinsulinemia is suggested to be involved in carcinogenesis directly by promoting cancer initiation and progression and indirectly through IGF-1. IGF-1 has powerful mitogenic and antiapoptotic activities and plays a pivotal role in triggering cancer initiation.[73,74]

Correlation of diabetes with oxidative stress is another area of concern that needs thorough investigation. Increased oxidative damage in diabetes is considered responsible for DNA damage, mutational changes in oncogenes and eventually to cancer.[75] The link between cancer and diabetes is still obscure. To add to better understanding and to elucidate the role of hyperglycemia with cancer, parallelly, we conducted a case–controlled study on T2DM individuals in Saudi population. Intriguingly, we found raised levels of CBs in T2DM individuals compared to nondiabetic controls. However, the correlation of CBs with hyperglycemic state was not noteworthy in our study with an exception to certain marker (unpublished data).

CONCLUSION

Based on the survey of the published data, analysis from this review indicates that diabetic individuals have an enhanced risk of developing cancer. Yet, whether diabetes lead to cancer or cancer causes diabetes is still obscure. Further research needs to be undertaken so that the etiology behind diabetes and cancer could be explicitly obtained.

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