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Retrospective Study Reveals Association between Type 2 Diabetes Mellitus and Certain Types of Cancer

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ABSTRACT
Background: Type 2 diabetes mellitus (T2DM) alters the risk of developing a variety of cancers, and certain types of cancers impact on developing T2DM. **Objective:** To investigate the relationship between type 2 DM and cancer, in predicting potential risk factors common to both cancer and diabetes including aging, sex, obesity, and analyze risks of site-specific malignancies associated with T2DM. **Patients and methods:** This study enrolled a group of patients (2000 patients) who visited Clinical Oncology and Nuclear Medicine Department of Mansura University Hospital divided into 2 group, first group (1000 patients) cancer patients with type 2 diabetes mellitus (group I) and second group (1000 patients) cancer patients without diabetes (group II). **Results:** There was a statistical significant difference as regards of increasing certain type of cancers in T2DM than non-diabetic patients as colorectal carcinoma, cancer breast, uterine carcinoma and hematological malignancy ($p < 0.05$). However, other types of cancers as cancer prostate, lung cancer and gastric carcinoma were more in non-diabetic patients than T2DM ($p < 0.05$). **Conclusion:** Because of changes in lifestyle, the prevalence of diabetes and cancer is increasing at an alarming rate throughout the globe. The relationship between diabetes and cancer development informs us that diabetic individuals have an increased risk of developing cancer, and cancer may cause diabetes through a variety of mechanisms. As a result, research should focus on developing more preventive and therapeutic options for diabetes and cancer patients.
Keywords: Association, Cancer, Obesity, T2DM.

INTRODUCTION
Diabetes mellitus is a group of metabolic illnesses characterized by extended episodes of hyperglycemia (high blood glucose) [(1)]. Diabetic type 2 (T2D) (predominantly resulting from insulin resistance, rendering target cells unable to effectively respond to insulin and so unable to utilise blood glucose for energy) [(2, 3)].

In the year 2018, over 9.6 million fatalities were linked to cancer, making cancer the second highest cause of death globally. Cancer is responsible for roughly one in every six deaths throughout the globe[(4)]. The link between diabetes and carcinogenesis has been shown in several studies, with the strongest association being seen in patients with type 2 diabetes (T2DM) [(5)].

Furthermore, in addition to a direct correlation between impaired glucose tolerance/diabetes and the initiation of cancer, hyperglycemia has been shown to be associated with cancer proliferation and invasiveness. A large number of epidemiological studies have shown that diabetes is positively associated with a variety of cancers. Obesity and type 2 diabetes, "Obesity is a new concept for diabetes that affects people who are obese," have become much more common throughout the world, and both are commonly associated with metabolic disorders[(6, 7)].

Both are also linked to a higher incidence and mortality rate, which can hasten the progression of cancer. In addition, diabetes has been linked to the formation and increased risk of a variety of various malignancies, including breast, hematological, and others [(8, 9)].

The aim of the present study was to investigate the relationship between type 2 DM and cancer, in predicting potential risk factors common to both cancer and diabetes including aging, sex, obesity, and analyze risks of site-specific malignancies associated with T2DM.

PATIENTS AND METHODS
Type of the study: This study was a retrospective study, which is depended on database.

Patients: 2000 patients with established cancer above 35 year old were enrolled in this study, they presented to Clinical Oncology and Nuclear Medicine Department of Mansura University Hospital. Patients were divided into 2 group, first group (1000 patients) cancer patients with type 2 diabetes mellitus (group I) and second group (1000 patients) cancer patients without diabetes (group II). The data of this study have been collected since 2013. Outpatients or in-patients were included in the study.

Ethical consent:

An approval of the study was obtained from Mansura University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria: Patients with established T2DM diagnosed by clinical manifestation and biochemical investigations above 35 year old with cancer.

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Exclusion criteria: Patients less than 35-years-old, patients with cancer pancreas, patients with advanced liver disease, patients with end stage renal diseases, pregnant patients and type 1 DM were excluded.

Methods:

For all studied cases, they were subjected to the following:

I- Proper history taking: with careful attention to: Age, sex, diabetes mellitus (type -duration –treatment-controlled or not presence of other diabetic complications), type of cancer, and drug history

II- Clinical examination: Blood pressure (BP), pulse, temperature and respiratory rate, body mass index (BMI), cardiac examination, chest examination, abdominal examination, and lymph node examination.

III- Laboratory investigations: Complete blood count, liver biochemical profile (Aspartate aminotransferase [AST], alanine aminotransferase [ALT], total and direct bilirubin and serum albumin), kidney function tests (serum creatinine and blood urea), tumor markers, and Hb A1c.

IV- Imaging studies: Pelvi-abdominal ultrasonography in addition to CT scan on body and /or MRI on body.

V- Histopathological studies: Tissue biopsy was needed to confirm cancer type.

Data management:

The collected data were revised, coded, tabulated using Statistical Package for the Social Sciences (Version 25.0. Armonk, NY: IBM Corp.). Data were presented and suitable analysis was done according to the type of data obtained for each parameter. Kolmogorov Smirnov test was done to test the normality of data distribution. Descriptive statistics were expressed as mean, standard deviation (± SD) for parametric numerical data, and frequency and percentage of qualitative data. Student T Test was used to assess the statistical significance of the difference between two study group means. Chi-Square test was used to examine the relationship between two qualitative variables, Fisher's exact test: was used to examine the relationship between two qualitative variables when the expected count was less than 5 in more than 20% of cells and Effect size: Effect size is the magnitude of the difference between groups. For t test; Cohen's d thresholds for small, moderate, and large effect sizes were 0.20-0.5, 0.5-0.8, and >0.80. For chi square test' Phi (φ) or Cramer's V thresholds for small, medium, and large effect sizes were 0.1-0.3, 0.3-0.5 and >0.5.

RESULTS

Comparison of age, gender and BMI (according to DM status) and (according to each type of cancer versus other cancer types):

Statistically significant differences in age distribution were found across the analysed groups. In both groups, the majority of patients were between the ages of 51 and 65 (Table 1).

Mean age of each type of cancer versus other cancer types is shown in table 2. There was significant p value (<0.05) for cancer lung, stomach, HCC, brain, thyroid, prostate and significant p value (<0.001) for cancer breast, uterus, ovary.

Regarding the gender distribution; type 2DM in cancer patients was significantly more common in females than males collectively, but with comparison of gender of each type of cancer versus other cancer types there was significant p value for cancer stomach, thyroid, bladder, colorectal cancer, lung, multiple myeloma, brain, and HCC. This means male gender is more likely for cancer incidence than female, but female genital cancer are widely recently spread (Table 1 and Table 2).

Obese patients were more in type 2 DM in comparison with over weighted and normal weight but in non DM patients, normal weighted were more with percent in comparison with over weighted and obese with highly significant p (Table 1).

According to average BMI in each type of cancer versus other cancer types there was significant p value for cancer uterus, leukemia, HCC, colorectal cancer, stomach, lymphoma, and breast (Table 2).

Table (1): Comparison of age, gender and BMI according to DM status

		DM N=1000		Non DM N=1000		Effect size	P
Age (years)	Mean±SD	57.5	9.6	58.5	9.7	d=0.103	0.028
35-50	N, %	258	25.8%	237	23.7%	V=0.027	0.699
51-65	N, %	504	50.4%	510	51.0%		
66-75	N, %	217	21.7%	232	23.2%		
>75	N, %	21	2.1%	21	2.1%		
Males	N, %	385	38.5%	476	47.6%	φ=0.092	<0.001
Females	N, %	615	61.5%	524	52.4%		
BMI (kg/m^2)	Mean±SD	31.4	6.5	25.6	4.7	d=1.082	<0.001
Normal weight	N, %	155	15.5%	490	49.0%	V=0.403	<0.001
Overweight	N, %	304	30.4%	305	30.5%		
Obese	N, %	541	54.1%	205	20.5%		

BMI= body mass index; DM = diabetes mellitus; SD= standard deviation.

Table (2): Comparison of age, gender and BMI according to each type of cancer versus other cancer types

Cancer type	Age	P	Gender		P	BMI	P
	mean± SD		Male (N=861)	Female (N=1139)		mean±SD	
Colorectal	58.1±11	0.801	19.3%	13.5%	0.001	29.6 ± 6.4	0.001
Lung	59.1±10.2	0.049	16.4%	10.4%	<0.001	28 ± 6	0.189
HCC	59.3±7.1	0.048	15.6%	5.8%	<0.001	27.5 ± 5.4	0.016
Stomach	59.3±9	0.018	10.8%	7.6%	0.014	25.7 ± 4.4	<0.001
Lymphoma	58.6±8.9	0.421	10.7%	7.7%	0.022	27 ± 5.3	0.001
Thyroid	62±7.1	0.004	3.3%	1.8%	0.030	27.9 ± 6.4	0.523
Bladder	58.6±10.8	0.672	3.5%	1.9%	0.031	27.7 ± 5	0.333
Brain	54.1±10.4	0.005	4.2%	1.1%	<0.001	26 ± 5.2	0.007
Leukemia	57±10.9	0.324	4.8%	3.4%	0.131	26.4 ± 3.9	0.002
Breast	54.4±9.6	<0.001	-	22.5%	-	31.8 ± 7.9	<0.001
Uterus	60±8.1	<0.001	-	11.9%	-	31.4 ± 7.2	0.002
Ovary	53.8±8.6	0.001	-	12.3%	-	28.9 ± 6.3	0.195
Multiple myeloma	60.4±6.8	0.082	5.6%	-	<0.001	27.3 ± 3.7	0.146
Prostate	61.8±8.2	<0.030	6.0%	-	-	26.7 ± 4	0.627

BMI= body mass index; SD= standard deviation; HCC= hepatocellular carcinoma.

Comparison of present history and laboratory parameters according to DM status:

Our study demonstrated that type 2 DM with cancer patients prone to obesity and comorbidities (Hypertension (HTN), IHD and high serum creatinine level) in comparison to non-DM cancer patients as a part of metabolic syndrome in T2DM (Table 3).

Table (3): Comparison of present history and laboratory parameters according to DM status

	DM N=1000		Non DM N=1000		Effect size (φ)	P
	N	%	N	%		
Non hypertensive	769	76.9%	878	87.8%	0.143	<0.001
Hypertensive	231	23.1%	122	12.2%		
No IHD	934	93.4%	961	96.1%	0.061	0.007
IHD	66	6.6%	39	3.9%		
Normal creatinine	901	90.1%	933	93.3%	0.058	0.009
High creatinine	99	9.9%	67	6.7%		

DM = diabetes mellitus; IHD= ischemic heart disease.

Comparison of cancer types according to DM status:

Incidence of colorectal cancer, breast cancer, cancer uterus, multiple myeloma and leukemia (hematological malignancy) increased significantly with type 2 DM than non DM. But incidence of cancer lung, cancer stomach, and cancer prostate decreased significantly with type2 DM than non DM (Table 4).

Table (4): Comparison of cancer types according to DM status

	DM N=1000		Non DM N=1000		Effect size (φ)	P
	N	%	N	%		
Colorectal	192	19.2%	128	12.8%	0.233	<0.001
Lung	100	10.0%	160	16.0%	0.087	<0.001
HCC	108	10.8%	92	9.2%	0.089	0.233
Stomach	60	6.0%	120	12.0%	0.027	<0.001
Lymphoma	100	10.0%	80	8.0%	0.105	0.118
Thyroid	20	2.0%	28	2.8%	0.026	0.242
Bladder	32	3.2%	20	2.0%	0.038	0.092
Brain	20	2.0%	28	2.8%	0.026	0.242
Leukemia	56	5.6%	24	2.4%	0.082	<0.001
Breast	156	15.6%	100	10.0%	0.035	<0.001
Uterus	80	8.0%	56	5.6%	0.075	0.033
Ovary	80	8.0%	60	6.0%	0.036	0.080
Multiple myeloma	32	3.2%	16	1.6%	0.024	0.019
Prostate	12	1.2%	40	4.0%	0.056	<0.001

DM = diabetes mellitus; HCC= hepatocellular carcinoma

DISCUSSION

The present study aimed to assess relationship between T2DM and certain types of cancer and investigate role of obesity according to BMI in T2DM in cancer patients in addition to comparison of comorbidities (HTN, IHD and high serum creatinine level) between T2 DM with cancer patients and non DM cancer patients.

Gender is recognized to play a role in cancer incidence and progression, besides anatomical and hormonal disparities, genetic differences should be considered when assessing the effects of gender on cancer[(10)].

In this study there was significant statistical difference between different groups as regards mean age and gender as female category was predominated in diabetic cancer patients collectively, due to female genital cancer are widely spread recently, but male gender was more likely for other cancer incidence than female. Increased levels of blood glucose and serum insulin result in a reduction in the synthesis of sex hormone binding globulin (SHBG), which in turn enhances the production of free estrogen and testosterone in the body. Cancers such as breast, endometrial, and prostate cancers are connected with elevated amounts of free estrogen and testosterone in the body and the majority of patients in our research were between the ages of 51 and 65, demonstrating that the risk of cancer decreases with age. In agreement with our findings, a prior research was conducted **[(10)].**

There were 60.56±13.6 years between the DM and non-DM groups, with the DM cohort being older than the non-DM cohort by 13.7 years. The majority of participants were between the ages of 51 and 65 (37.4 percent in both groups), however type 2 diabetes in cancer patients was more frequent in men than in women.

As regards BMI, our study found a significant statistical increase in BMI in T2 DM with cancer patients (group I) than non DM cancer patients (group II). This means that obese patients were more in group I with incidence of increasing BMI in certain types of cancer than others. Obesity was observed (BMI > 30 kg/m^2) in cancer uterus and breast and overweight in cancer ovary, colorectal and lymphoma with significant p value and the least BMI cancer patients were observed with cancer stomach, brain, and leukemia with significant increasing of BMI. Adipose tissue is an essential organ for the generation of adipokines, inflammatory cytokines, and enzymes, all of which are dysregulated in obesity and type 2 diabetes, which may contribute to tumour development and metastasis in these conditions.

In accordance to our results, a previous study by **Williams *et al.*[(11)]** reported that obese patients were more in type 2 DM with percent 41% in comparison with overweighted 36% , normal weighted 16% and under weighted 2% but in non DM patients, normal weighted were 32% in comparison with overweighted 34%, under weighted 5% and obese 15% with highly significant p value. The results of another study by **Recalde *et al.*[(12)]** found that having a higher BMI was associated with a higher risk of 26 cancer types. A prospective study that included 3,658,417 participants and 202,837 cancer cases discovered that having a higher BMI was associated with a higher risk of 18 types, although these relationships differed in terms of direction. BMI was positively associated with risk of cancers of the corpus uteri, kidneys, gallbladder and biliary tract, thyroid, colon, and breast. BMI was shown to be connected with the risk of prostate cancer in an inverted U-shaped way, as well as with the risk of four other malignancies in an L-shaped pattern (head and neck, esophagus, larynx, and trachea, bronchus, and lung). So, it is obvious from our study and other studies that obesity is considered a principal factor of most cancer types development, which is also its responsibility for insulin resistance (type 2 DM) and metabolic syndrome.

In the present study, aggravated comorbidities (HTN, IHD and high serum creatinine level) were significantly more in the type 2 DM than in non-DM cohorts. That was stated by **Williams *et al.*[(11)]** who found comorbidities (HTN ,IHD and high serum creatinine level) between the type 2 DM to non-DM cohorts were 66%, 16% and 2% respectively to 41%, 9% and 1% respectively with significant p value.

In the current study, a comparison of certain types of cancer (we work on 14 type of cancer after exclusion of pancreatic cancer) according to DM status between type 2DM patients and non DM patients showed that incidence of colorectal cancer, breast cancer, cancer uterus, multiple myeloma and leukemia (hematological malignancy) increased significantly with type2 DM than non DM as mentioned above, in addition to increased incidence of HCC, cancer bladder, cancer ovary and lymphoma with type2 DM than non DM with non-significant P value in this study.

But there was significant decrease of incidence of cancer lung, cancer stomach, and cancer prostate with type2 DM than non DM as mentioned above, in addition to insignificant decrease incidence of cancer thyroid and brain cancer with type2 DM than non DM.

This was agreed by another study **Bjornsdotti *et al.*[(13)]**, who reported that type 2 diabetes had a higher risk for all cancer, hazard ratio (HR) 1.10 (95% CI 1.09–1.12), with highest HRs for liver (3.31), pancreas (2.19) and uterine cancer (1.78). There were lesser increases in risk for breast (1.05) and colorectal cancers (1.20). Type 2 diabetes patients experienced a higher HR 1.23 (1.21–1.25) of overall post-cancer mortality and mortality from prostate, breast, and colorectal cancers**.** For the most common cancer sites, risks HR were above one at 1.05 (95% CI = 1.01–1.09) for breast cancer and 1.20 (95% CI = 1.16–1.23) for colorectal cancer. They were lower for prostate cancer, and no different for lung cancer.

This also concordant with a previous study by **Lo *et al.*[(10)]** among type 2 diabetes patients, a retrospective cohort research comprising an Asian population was

done in order to assess the risk of developing many main forms of cancer. According to the findings of the study, the National Health Research Institute in Taiwan used a countrywide population-based database from 1996 to 2009 to conduct its research. The incidence and hazard ratios (HRs) for distinct forms of cancer were estimated, and the results suggest that cancer occurrences were more prevalent in the liver, the colorectum, and the lung. A modest increase in cancer risk was observed in 13 sites, with the liver having the highest hazard ratio (HR) of 1.78 (95 percent confidence interval = 1.73–1.84), followed by the pancreas (HR = 1.52, 95 percent confidence interval = 1.40–1.65), and the uterus and corpus (HR = 1.38, 95 percent confidence interval = 1.22–1.55). Other types of cancer, such as head and neck cancer, thyroid cancer, stomach cancer, colorectal cancer, gallbladder cancer, extrahepatic bile duct cancer, kidney cancer, bladder cancer, breast cancer, and skin cancer, were found to be more common in diabetics, whereas esophageal and lung cancers were found to be less common in diabetics. In addition, cancer risks are stratified based on the number of years of follow-up. After a lengthier time of follow-up, the risk of cancer rose modestly in the majority of the locations. The most significant shift was in non-lymphoma, Hodgkin's where the hazard ratio rose from 0.94 (95 percent confidence interval = 0.82–1.08) within 3.5 years to 1.17 (95 percent confidence interval =1.03–1.33) after 3.5 years [(10)].

CONCLUSION

Because of changes in lifestyle, the prevalence of both type 2 diabetes and cancer is increasing at an alarming rate throughout the globe. The association between diabetes and cancer development informs that diabetic individuals have an enhanced risk of developing cancer and cancer may cause diabetes by several mechanisms. Moreover, presence of diabetes mellitus increases risk of cancer morbidity and mortality even with low risk cancer type incidence in DM. Our present study showed increase risk of colorectal cancer, breast cancer, uterine carcinoma and hematological malignancy in DM than cancer prostate and lung cancer.

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