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Risk Assessment of Type 2 Diabetes and Women Cancer in Egypt

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Abstract

Background: Type 2 diabetes mellitus (T2DM) and cancer, leading global causes of death and disability, exhibit a notable association in females, with gynecologic malignancies sharing frequent mechanisms like elevated insulin levels, IGF signaling, and dysregulated ovarian steroid hormones. This research purposed to evaluate the common risk factors between T2DM and women cancer and to explore the possible links between these two common diseases. **Methods:** This study conducted a retrospective analysis of adult females medical records admitted to the Hematology and Oncology unit within the Internal Medicine Department. The data encompassed 532 women diagnosed with breast, uterine, or ovarian cancer between June 2020 and June 2022. Women were divided into two groups: diabetic and non-diabetic. For each woman, data on age, BMI, medical history (including DM, HTN, IHD, etc.), as well as laboratory and imaging results, was collected. **Results:** Breast cancer was detected in 48.1% of cases, uterine cancer in 25.6%, and ovarian cancer in 26.3%. The incidence of breast and uterine cancer was notably higher during the 6th decade of life (post-menopausal) for both diabetic and non-diabetic individuals. Breast, uterine, and ovarian cancer occurrence was significantly greater between diabetic and obese patients. In the breast cancer group, the incidence of hypertension and high creatinine levels, both associated with diabetes, was higher than in the non-diabetic group. However, in uterine cancer patients, non-diabetics had a significantly higher IHD incidence than diabetics. However, among ovarian cancer patients, diabetic status was related to a significantly greater IHD incidence. **Conclusion:** T2DM women face a higher developing cancer risk, particularly breast, uterine, and ovarian cancer. Postmenopausal DM women are at an elevated breast, ovarian, and uterine cancer risk and should undergo timely screenings for these conditions.

Introduction:

Cancer and type 2 diabetes mellitus (T2DM) rank among the top global causes of mortality and disability [1]. Clinical research indicates that breast, uterine, and ovarian cancer are influenced by pathogenic factors associated with T2DM [2]. In T2DM females, there is an elevated gynecologic malignancies prevalence and occurrence that share frequent pathways with T2DM, involving elevated insulin concentrations, ovarian steroid hormones and Insulin Growth Factor (IGF) signalling dysregulation [3].

Women with breast cancer and diabetes exhibit hormonal imbalances characterized by heightened estrogen and androgen production and decreased hepatic formation of Sex Hormone Binding Globulin (SHBG) [4]. This increased availability of estrogen promotes estrogen receptor (ER)-positive or estrogen-dependent breast cancer cells proliferation [5]. Hyperinsulinemia, a common condition in T2DM, leads to increased ER expression and binding capacity [6]. Moreover, ER activation enhances the cell growth-promoting effects of insulin by activating Phosphoryl Inositol-3 Kinase (PI3K) and augmenting the function of Insulin Receptor Substrate-1 (IRS-1) [7].

Multiple studies have identified common modifiable risk factors between T2DM and endometrial cancer, including a sedentary lifestyle and obesity [8]. IGF-1, insulin, and ovarian steroid hormone signaling pathways activation, particularly androgen and oestrogen pathways, can stimulate endometrial cancer cell lines growth [9].

Estrogen ability to activate Insulin Growth Factor 1 Receptors (IGF1R) on endometrial cancer cells increases cellular multiplication via the IGF1R-activating PI3K signaling pathway [10]. Moreover, the interaction between testosterone and the androgen receptor (AR) may promote endometrial cancer cells multiplication by activating the Notch signaling system [11].

Elevated C-reactive protein (CRP), a marker of inflammation triggered by Interleukin-6 (IL-6), is linked to insulin resistance and raises endometrial cancer risk in postmenopausal women [12]. This implies a potential link between endometrial cancer and chronic inflammation in T2DM.

Several studies have linked T2DM with a greater ovarian cancer risk. This connection is mainly attributed to elevated serum androgen concentrations and reduced serum progesterone concentrations, rather than changes in serum estrogen concentrations [13, 14]. These hormonal fluctuations commonly seen in diabetes may contribute to the elevated ovarian cancer risk.

Additionally, research has found a positive association among elevated serum IGF-1, IGF-1R, and Insulin Growth Factor Binding Protein 2 (IGFBP-2) concentrations in ovarian cancer women [15]. In a specific study, IGF-1 in human ovarian cells, particularly OVCAR-3 cells, was shown to stimulate KCl cotransport (KCC) formation, which is linked to ovarian cancer cell proliferation and invasiveness [16].

The objective of this study was to evaluate the shared risk factors between T2DM and cancer in women, as well as to investigate potential connections between these prevalent conditions.

2- Subjects and Methods

2.1. Study Design: This study involved a retrospective analysis of medical records from adult female patients aged 35 and above who were admitted to the Hematology and Oncology unit within the Internal Medicine Department.

2.2. Data Collection: The data were gathered from 532 women who had been diagnosed with either breast, uterine, or ovarian cancer. This data was extracted from the Hematology and Oncology unit's database, spanning from June 2020 to June 2022. The subjects under investigation were categorized into two groups: group I (316 patients) consisted of cancer patients with T2DM, while group II (216 patients) comprised cancer patients without diabetes.

2.3. Ethical consent: Approval for this study was granted by the Academic and Ethical Committee. [approval No. 1017] The research adhered to the ethical guidelines outlined in The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving human participants.

2.4. Inclusion criteria: Female patients above 35-year-old with established breast, uterine or ovarian cancer.

2.5. Exclusion criteria: Patients who were less than 35 years old, those with pancreatic cancer, individuals with advanced liver disease, patients in the end stage of renal disease, pregnant patients, and those diagnosed with T1DM.

2.6. For all subjects the following was recorded: age and Body Mass Index (BMI), with patients classified as normal (18.5-24.9), overweight (25-29.9), or obese (≥30); medical history, including diabetes, hypertension (HTN), heart disease, and other comorbidities; laboratory results, encompassing Complete Blood Count (CBC), Liver Function Test (LFT), Kidney Function Test (KFT) with renal impairment considered if creatinine exceeded 1.2 mg/dl, tumor markers, and Glycated Hemoglobin (HbA1c); and imaging results from Pelvi-abdominal ultrasonography, Computed Tomography (CT) scans, and/or Magnetic Resonance Imaging (MRI) scans of various body regions.

Statistical Analysis: The acquired data underwent statistical analysis utilizing the software programs "Microsoft Excel" and "Statistika-12". Descriptive statistics, including arithmetic mean (M), standard deviation (SD), and sample size (n), were employed to summarize the findings. Statistical significance between values was evaluated utilizing Student's t-test, with significance established at $P < 0.05$. To assess the risk associated with the recorded data, calculations were performed for the Odds ratio (OR), 95% confidence interval, as well as the positive and negative predictive values.

Results:

4.1. Basic Information of the Studied Population:

The study comprised 532 women, with 316 classified as diabetic and 216 as non-diabetic. Among them, 256 (48.1%) had breast cancer (156 diabetic and 100 non-diabetic), 136 (25.6%) had uterine cancer (80 diabetic and 56 non-diabetic), and 140 (26.3%) were diagnosed with ovarian cancer (80 diabetic and 60 non-diabetic). No statistically substantial change was seen between the two groups ***(Table 1)***.

Table 1: Basic information of the studied population:

Cancer type		Diabetic status				
		Diabetic 316	Non-diabetic 216	P value	OR	95% CI
Breast cancer	256(48.1%)	156 (49.4)	100 (46.3)	0.48	1.233	1.049-1.456
Uterine cancer	136(25.6%)	80 (25.3)	56 (25.9)	0.87	1.125	0.929-1.361
Ovarian cancer	140(26.3%)	80 (25.3)	60 (27.8)	0.52	1.080	0.894-1.304

4.2. Relation between different age and BMI groups according to their diabetic status in studied Population: A statistically substantial change (p-value < 0.05) was seen in the cases of uterine and ovarian cancer with respect to the diabetic status within each group. The incidence of breast and uterine cancer was notably higher during the sixth decade of life (post-menopausal) in both diabetic and non-diabetic individuals. Conversely, ovarian cancer showed a higher incidence in diabetic patients aged between 35 and 50 years. In terms of BMI, a highly significant statistical difference was noted between the various cancer types studied (breast, uterine, and ovarian) and diabetic status, as these cancers occurrence was markedly higher in diabetic and obese patients **(Table 2).**

Table 2: Relation between different age and BMI groups according to their diabetic status among the studied groups:

	Breast cancer (256)		Uterine cancer (136)		Ovarian cancer (140)	
mean±SD	54.39±9.65		60.0±8.27		53.86±8.75	
Age(years)	DM (156)	NO DM (100)	DM (80)	NO DM (56)	DM (80)	NO DM (60)
35 – 50	60(38.5)	40(40.0)	12(15.0)	12(21.4)	40(50.0)	16(26.7)
51 – 65	80(51.3)	40(40.0)	40(50.0)	40(71.4)	32(40.0)	40(66.7)
66 - 75	12(7.7)	16(16.0)	24(30.0)	4(7.1)	8(10.0)	4(6.7)
> 75	4(2.6)	4(4.0)	4(5.0)	0(0.0)	0	0
P	0.20		0.01*		0.007**	
mean±SD	54.39±9.65		54.39±9.65		54.39±9.65	
BMI (kg/m^2)	DM (156)	NO DM (100)	DM (80)	NO DM (56)	DM (80)	NO DM (60)
Normal weight	8(5.1)	56(56.0)	4(5.0)	28(50.0)	12(15.0)	32(53.3)
Overweight	32(20.5)	20(20.0)	16(20.0)	16(28.6)	20(25.0)	20(33.3)
Obese	116(74.4)	24(24.0)	60(75.0)	12(21.4)	48(60.0)	8(13.3)
P	<0.001**		<0.001**		0.008**	

4.3. Relation between comorbidities (HTN, IHD & high creatinine level) and the diabetic status in studied Population:

While no statistically significant difference was observed, it is noteworthy that in the breast cancer group, the incidence of HTN and elevated creatinine levels associated with diabetes tended to be higher compared to non-diabetic individuals. Conversely, among uterine cancer patients, non-diabetics exhibited a significantly higher incidence of IHD than diabetics. In the case of ovarian cancer patients, diabetic status was notably associated with a significantly higher incidence of IHD ***(Table 3).***

Table 3: Relation between different comorbidities and diabetic status among the studied groups:

	HTN			IHD			High creatinine		
	DM (72)	NO DM (24)	P	DM (4)	NO DM (4)	P	DM (16)	NO DM (12)	P
	No (%)	No (%)		No (%)	No (%)		No (%)	No (%)	
Breast cancer	36(50)	8(33.3)	0.16	0 (0)	0 (0)	-	8 (50.0%)	8 (66.7%)	0.35
Uterine cancer	20(27.8)	8(33.3)	0.61	0 (0)	4(100)	0.005**	8 (50.0%)	4 (33.3%)	0.79
Ovarian cancer	16(22.2)	8(33.3)	0.28	4(100)	0 (0)	0.005**	0 (0.0)	(0.0)	-

HTN: Hypertension, IHD: Ischemic Heart Disease, DM: Diabetes Mellitus.

Discussion

Cancer is a significant global public health concern, and its prevalence, particularly among women, is increasing due to advancements in screening, diagnosis, therapy, and an aging population [17]. Existing research has indicated a noteworthy occurrence of comorbid diabetes in women with cancer. In fact, diabetes is more prevalent among women with cancer than those without, potentially attributed to shared risk factors like advanced age, smoking, and obesity [18]. This study aims to evaluate common risk factors between T2DM and cancer in women, as well as investigate potential links between these prevalent conditions.

This study found a high prevalence and elevated risk of breast, uterine, and ovarian cancer among women with T2DM in our region, aligning with numerous studies that have reported increased cancer risk in T2DM patients. Our results were consistent with El Hammady et al.'s study [19] in the Mansoura region of Egypt, as well as Vatseba T. S.'s research [20] on reproductive system cancer prevalence in women with T2DM in Ukraine, and Fernández-Arce L et al.'s investigation [21] into all-cause mortality among Spanish women with breast cancer. Yang et al. [18] also confirmed similar findings when reviewing diabetes incidence in cancer patients compared to cancer-free controls. We observed a noteworthy correlation between age and various cancer types in our study groups, with breast, uterine, and ovarian cancers being more prevalent in the 51-65 age group, regardless of

diabetic status. These findings are consistent with several studies. For instance, Fernández-Arce L et al. [21] noted a high incidence of breast cancer at the age of 60 in diabetics and 69 in non-diabetics. Hossain et al. [22] also reported a higher occurrence of breast cancer in the 60-69 age group, whether diabetic or not. In a meta-analysis, Wang et al. [23] found that ovarian cancer was more common in diabetic females aged 44-62, while Liu et al. [24] discovered that uterine cancer was frequent in diabetic women aged 50-59 in Taiwan. Our results align with various other studies [18, 22, 23, 25], which demonstrate a strong association between an increased risk of malignancy and higher BMI, particularly among diabetic women. Notably, there was a significant link between obesity and the incidence of breast, uterine, and ovarian cancers in the diabetic group. Similar findings were reported in a study conducted at Benha University Hospital by Ali et al. [26]. Obesity is recognized as an independent risk factor for several cancers, including breast, uterine, and ovarian cancer [27].

Obesity triggers a systemic inflammatory response that releases multiple cytokines and activates signaling pathways, thereby promoting tumor initiation, survival, and evasion of the immune system [28]. It's important to note that T2DM frequently accompanies obesity, and studies investigating the connection between obesity and cancer risk or outcomes often fail to distinguish between obesity with and without T2D.

Numerous studies provide strong evidence of complex associations between diabetes and various types of cancer, including breast, uterine, and ovarian cancer [29]. Women with diabetes have been found to face a higher risk of developing cancer compared to those without diabetes [30]. A multitude of factors associated with obesity, metabolic syndrome, and T2D can independently or concurrently contribute to cancer progression. These factors encompass hyperinsulinemia, hyperglycemia, dyslipidemia, insulin-like growth factor, adipokines, cytokines, as well as the composition of the gut microbiome [31].

Our findings indicate a positive correlation between various comorbidities (hypertension, ischemic heart disease, and impaired kidney function) and breast, uterine, and ovarian cancer among our study groups, whether they had diabetes or not. This aligns with numerous other studies [32, 33, 34, 35, 36]. It's worth noting that our results revealed a significant association between ischemic heart disease (IHD) and a limited number of our participants, including none in the breast cancer group, four in diabetic ovarian cancer patients, and four in non-diabetic uterine cancer patients. This can be attributed to the fact that both cancer and IHD are leading causes of mortality, and individuals with both conditions often have a reduced life expectancy.

Breast, uterine, and ovarian cancers have been linked to an elevated risk of diabetes and cardiovascular diseases, along with their shared

comorbidities such as nephropathy, coronary artery disease, heart failure, and renal failure. The connection between cardiovascular diseases and cancer is thought to arise from common risk factors like aging, smoking, obesity, hypertension, diabetes, hyperlipidemia, and physical inactivity. These shared risk factors can increase both short- and long-term cardiovascular mortality and morbidity [37].

Inflammation plays a significant role in the development and progression of both tumors and cardiovascular conditions [38]. Cancers can disrupt the coagulation cascade, potentially leading to hypercoagulability and thromboembolic diseases. These factors hold considerable importance in the domain of cardio-oncology [39].

Study Limitation:

This study has several limitations, including its retrospective observational design, which allows for associations to be identified but not causation. The small number of cases in the study population has likely reduced the statistical power of the models. Limited data availability prevented the assessment of risk factors based on pre or postmenopausal status. Although BMI classification followed WHO guidelines, it did not distinguish between Class I (30≤ BMI<34.9), Class II (35≤ BMI<39.9), and Class III (BMI≥40) obesity; instead, these categories were merged into one. Diabetes and other comorbidities were defined solely by indications in medical records, lacking information on duration, medications, or disease control, which could impact risk. Lastly, this analysis was restricted to data from Benha University Hospital and did not account for other established risk factors related to lifestyle (e.g., diet, physical activity), reproductive history, or social determinants of health not available in the database.

Conclusion:

Women with T2DM face an elevated risk of cancer, particularly breast, uterine, and ovarian cancer. Various metabolic abnormalities associated with T2DM may account for this increased risk. Postmenopausal women with T2DM should undergo timely screenings for breast, ovarian, and uterine cancer due to their heightened risk. The high cancer incidence in obese women underscores the importance of addressing weight issues. Enhanced understanding of the links between these conditions can aid in identifying contributing factors and designing personalized prevention strategies. Ultimately, the goal is to promote healthy aging and prevent cancer and other diseases associated with T2DM, which are major causes of disability and mortality worldwide.

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