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STUDY ON THE PREVALENCE OF VARIOUS FORMS OF CANCER IN DIABETIC PATIENTS HOSPITALIZED IN THE NATIONAL INSTITUTE OF DIABETES, NUTRITION AND METABOLIC DISEASES "PROF. N.C. PAULESCU"

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Abstract

Background and aims: *Epidemiological evidence suggests that people with diabetes have a significantly increased risk of developing various cancers. The aim of the study was to assess the frequency of various cancers in diabetic patients admitted in the National Institute of Diabetes Nutrition and Metabolic Diseases "Prof. N.C. Paulescu" between 01.01.2011 and 01.09.2014.* ***Material and methods****: The study analyzed a total of 24.104 admissions, corresponding to a total of 13.960 patients. A total of 520 hospitalizations with a diagnosis of cancer and diabetes were indentified. Finally, 298 patients meeting the inclusion and exclusion criteria were included in the study. For these patients, personal history, clinical and laboratory data were assessed.* ***Results:*** *The prevalence of cancer in hospitalized diabetic patients was 2.13%. The most frequent types of cancer (number of cases) were: breast - 63 patients, colorectal - 45 patients, pancreatic - 37 patients, lung - 31 patients and prostate - 20 patients.* ***Conclusions:*** *Our data showed that the most common form of cancer associated with diabetes was breast cancer (21%), followed by colorectal cancer (15.10%) and pancreatic cancer (12.42%). Further prospective studies are needed in the long term on larger study groups to evaluate the incidence and prevalence of various forms of cancer in the diabetic population.*

key words: cancer, diabetes mellitus, obesity, hyperglycemia, metformin

Background and Aims

Diabetes mellitus (DM) and cancer are two heterogeneous chronic diseases with increasing prevalence and mortality in all ages, irrespective of sex and population, that are influenced by both genetic and environmental factors.

Chronic diseases are the leading cause of mortality worldwide, in 2012 reaching a total of 58 million deaths, of which 38 million (65.5%)

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were due to major chronic diseases (Noncommunicable Diseases - NCDs) [1]. Moreover, 80% of deaths were due to the following four major chronic diseases: cardiovascular disease caused 17.5 million deaths (46.2% of NCD deaths), malignant tumors 8.2 million deaths (21.7% of NCD deaths), pulmonary chronic disease (including asthma and chronic obstructive pulmonary disease) 4 million deaths (10.7% of NCD deaths) and diabetes 1.5 million deaths (4% of NCD deaths). In 2012, 52% of the premature deaths (before the age of 70 years) were due to NCD. The mortality from chronic diseases increased from 31 million deaths in 2000 to 38 million in 2012, and is supposed to increase to 52 million by 2030 [1].

According to the International Diabetes Federation (IDF), the worldwide prevalence of diabetes mellitus (DM) in 2013 was 382 million people (5.4%), with an expected increase to 592 million in 2035). The prevalence of prediabetes in 2013 was 316 million (4.4%), and in 2035 it will reach 471 million people [2,3]. It is assumed that in 2013 there were 175 million people with undiagnosed diabetes worldwide [2]. In 2014 over 18% of the world population was overweight (Body Mass Index – BMI between 25-29.99 kg/m^2) and over 8.3% of the world population was obese (BMI ≥ 30 kg/m2) [4-6].

According to the PREDATORR (National study on the prevalence of diabetes, prediabetes, overweight, obesity, dyslipidemia, hyperuricemia and chronic kidney disease in Romania) study data, diabetes prevalence in Romania in 2013 in the adult population (20-79 years) was 11.6%. Prediabetes prevalence was 18.4% while 34.6% of patients were overweight and 31.4% were obese [7]. Thus, in Romania the prevalence of glucose metabolism disorders is about 30%, and that of excessive weight (BMI ≥ 25kg/m2) is about 66% [7].

In 2012, the worldwide 5-year prevalence of all cancer types was 32.5 million, the first four places being represented by: breast cancer (6.3 million cases), prostate cancer (3.9 million cases), colorectal cancer (3.5 million cases) and lung cancer (1.9 million cases) [8]. In 2012 the global cancer incidence was 14.1 million cases and there were 8.2 million cancer deaths [8].

Epidemiological evidence suggests that there is a moderate increase in cancer risk in diabetic patients and in subjects with impaired glucose tolerance [9,10], especially for liver, pancreas, colon, breast and endometrium, but a decreased risk for prostate cancer [11], the overall prevalence of cancer in diabetic patients being higher than in the general population. The risk is greater (about 2 times higher) for liver, pancreas, and endometrium cancer, approximately 1.2-1.5 times higher for colorectal, breast and bladder cancer [12]. The risk is similar for lung cancer [12].

The aim of the study was to assess the frequency of various cancers in patients with diabetes admitted in the National Institute of Diabetes Nutrition and Metabolic Diseases (NIDNMD) "Prof. N.C. Paulescu" from 01.01.2011 to 01.09.2014.

Materials and Method

This was a retrospective study analyzing a total of 24.104 admissions corresponding to a total of 13.960 patients hospitalized of which 524 had a diagnosis of both diabetes and cancer as shown in Figure 1. To investigate all patients hospitalized from 01.01.2011 to 01.09.2014 in the NIDNMD “Prof. N.C. Paulescu” the ProMedic computer software was used. The inclusion criteria were: presence of diabetes and cancer concomitantly, and age above 18 years. The exclusion criteria were: age below 18 years and the lack of a clear diagnosis of diabetes and/or cancer. In addition, incomplete

observation sheets were excluded. After exclusion of patients not fulfilling all the inclusion/exclusion criteria, a total of 298 patients with diabetes and various cancers represented the final study group. The following parameters were registered for the study group: demographic data (age, gender, body mass index - BMI, waist circumference), data regarding diabetes (type of diabetes, duration, complications including hypertension, coronary heart disease, chronic kidney disease, retinopathy and neuropathy) and cancer (location), biological data (glycosylated hemoglobin- HbA1c, high density lipoprotein cholesterol-HDL, triglycerides – TG, etc.). Finally, the type of antidiabetic treatment (diet alone, oral antidiabetic therapy - OAD, and insulin) was also recorded.

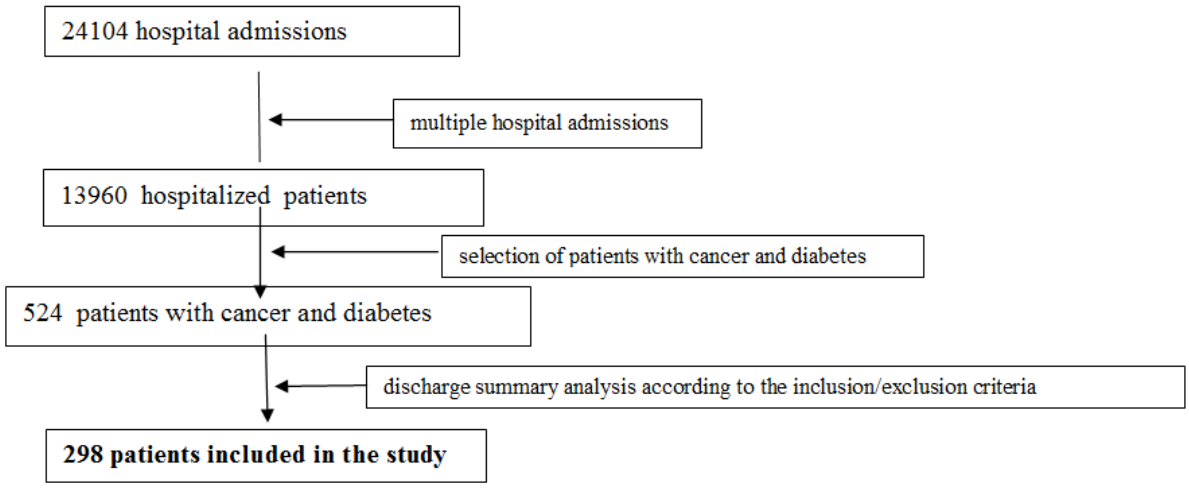

Figure 1. *Flow chart of patient study enrolment.*

Statistical analysis

All variables were introduced in an Excel database (Microsoft® Office 2013), after which they were analyzed using the SPSS (Statistical Package for the Social Sciences) version 19 software. Quantitative variables were analyzed using ANOVA (Analysis of variance) and t-test and qualitative variables with the chi-square test. A p-value < 0.05 was considered to be statistically significant.

Results

After eliminating patients not meeting the inclusion and exclusion criteria, a total of 298 patients were analyzed: 164 females and 134 males with a mean age of 67.09±11.27 years. Most of them (n=246) came from urban areas. Type 2 diabetes mellitus (T2DM) was the most frequent (n=274. 91.94%) form of diabetes, followed by type 1 diabetes (T1DM) with 17 cases (5.70%). We also found one case of latent autoimmune diabetes in adults (LADA) (0.34%) and one case of maturity-onset diabetes of the young (MODY) (0.34%). In five patients the diabetes was secondary to pancreatectomy**.** T2DM patients had a mean HbA1c of 8.91±2% and a mean BMI of 28.23±7.36 kg/m^2. Obese patients (BMI>30 kg/m^2) represented 26.64% (73 out of 274) of T2DM patients. Almost half of them were women and had breast cancer (29 patients).

The frequency of various types of cancer in our inpatient diabetic population was 2.13%. The most frequent types of cancer in hospitalized diabetes patients were breast cancer– (63 cases - 21%), colorectal cancer (45 cases-15.1%), pancreatic cancer (37 cases – 12.41%), lung

cancer (31 cases - 10.4%), prostate cancer (20 cases - 6.7%), urinary bladder cancer (13 cases - 4.4%), uterine cervix cancer (13 cases - 4.4%) and endometrial cancer (10 cases - 3.4%), as detailed in Figure 2.

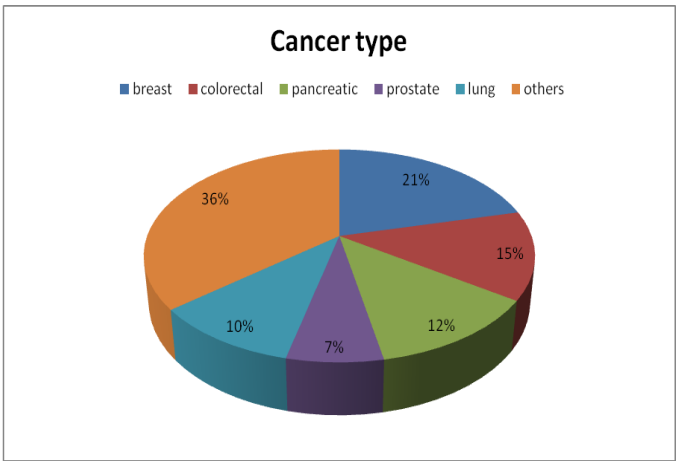

Figure 2. *Cancer type distribution in the study population.*

Table 1. Cancer distribution by sex.

No.	CANCER TYPE			
	MALE	No.	FEMALE	No.
1.	Colorectal	31	Breast	63
2.	Pancreatic	21	Pancreatic	16
3.	Prostate	20	Pulmonary	15
4.	Pulmonary	16	Colorectal	14
5.	Hepato-cellular	5	Uterine cervix	13
6.	Urinary Bladder	4	Endometrial	10
7.	Baso-cellular	4	Urinary Bladder	9

To be noted, sixty-one of sixty-three patients with breast cancer had type 2 diabetes. We are showing in Table 1 the most frequent malignancies in diabetic patients according to sex.

A hundred and ten patients had the diagnosis of cancer after the diagnosis of DM as shown in Figure 3. The mean time elapsed between the two diagnoses was 11.5±8.14 years while 25 patients had the two diseases diagnosed in the same year.

We are giving in Table 2 the mean time between the onset of diabetes and diagnosis of cancers for the most frequent malignancies recorded in the study group.

Table 2. Mean time for cancer diagnosis after DM.

Cancer TYPE	No. cases	Mean (years)
Others	32	10.40
Breast	24	11.96
Colorectal	20	14.35
Pancreatic	13	11.00
Pulmonary	11	11.82
Prostate	10	9.00
Total	110	11.42

Stratifying patients by cancer type, we found no significant difference in mean HbA1c, but HDL-cholesterol had much lower values in

patients with hepatocellular, biliary, ovary and testicular cancer (p=0.01) compared to other cancer types. BMI was higher in females with genital neoplasia, as shown in Table 3. No diabetes complications were associated particularly with any form of cancer.

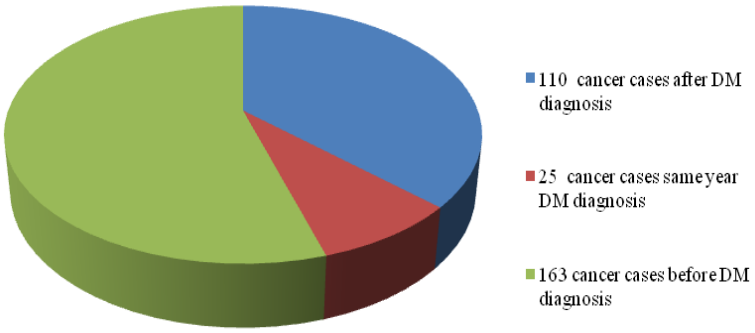

Figure 3. *Cancer diagnosis and DM diagnosis.*

Table 3. Cancer type distribution by various parameters values.

CANCER TYPE		HbA1C	HDL cholesterol	Triglycerides	BMI
BAZOCELLULAR		8.7	48	176.7	33.30
BRAIN		8.8	41.2	197.6	22.81
UTERINE CERVIX		9.3	50.6	209.1	25.50
COLORECTAL		9.1	41.8	172.9	28.01
ENDOMETRIAL		7.9	54.1	193.3	33.83
GASTRIC		8	43.4	149.1	28.84
SUDORIPARY GLAND		6.2	60.7	123.3	28.0 7
HEPATOCELLULAR		10.6	25.1	108.6	22.78
LARYNGEAL		10.5	44.5	166.5	25.9
BREAST		9	45.4	176.2 5	31.42
MELANOMA		7.2	44.5	227.3	26.31
BONE		8.9	40.4	205.5	23.84
OVARY		10.1	26.3	170.6	28.71
PANCREATIC		9.4	38.9	158.6	24.1
PROSTATE		9.9	43.4	223.6	27.2
PULMONARY		9.6	38.1	184.1	27.29
KIDNEY		7	39	180.6	26
RETROPERITONEAL		7.1	98	53	21.2
NASOPHARYNGEAL		6.7	34.6	160	35.4
ADRENAL		7.4	31	185	44
URINARY BLADDER		8.8	43.1	145.5	28.1
Total	Mean	9.1	42.4	176.9	28.66
	N	226	232	217	183
	Minimum	5.5	12.4	42	14
	Maximum	16.4	98	1216	54.7

There wasn't any difference between patients who were treated with insulin or oral treatment in terms of cancer prevalence (n=221 with insulin treatment, n=77 without insulin; p=0.388), except for metformin. Patients not receiving metformin have a higher prevalence of cancer (n=94 with metformin treatment, n=204 without metformin, p=0.028).

Discussions

The 5-year cancer prevalence in the Romanian general population was estimated at 0.83% by Globocan [8] while in our study group of hospitalized diabetic patients it was 2.13%. Epidemiological studies (retrospective, prospective but also meta-analyses) showed a

risk of cancer in diabetic patients between 1.14 and 1.84 times higher [13]. The increased prevalence of cancer in diabetic patients in our study may be explained by the fact that patients were selected from the inpatients admitted in the NIDNMD "Prof. NC Paulescu" and not from the outpatient department, hospital addressability being particularly higher for the metabolically unbalanced diabetic patients due to the presence of cancer. Another explanation is that the study group did not include all age groups, the minimum age of cancer diagnosis being 33 years, while it is well known that the cancer risk increases with age [14,15].

In our study, the average time of cancer appearance in diabetic patients was 11.5 years. In other studies, the time duration between exposure to a carcinogenic factor and cancer appearance was 20-50 weeks in animal models, and 20-50 years in humans [16].

Epidemiological evidence suggests that there is a moderate increase in the risk of cancer in diabetic patients for various sites: pancreas, breast, uterine, colorectal and liver, but a protective effect for prostate cancer. In our study the most common form of cancer associated with diabetes was breast cancer, almost all cases being recorded in females with T2DM.

Over 90% of diabetics are T2DM patients [17] and T2DM is associated with obesity. In obese subjects, the adipose tissue secretes excess inflammatory cytokines and leptin but there is decreased adiponectin [18,19]. Leptin acts by activating (stimulating) mitogen activated protein kinase (MAPK) in exerting tumour proliferative effects [18,20,21] and by increasing the expression and activity of aromatase (which increases conversion of androgens to estrogens) and activates estrogen receptor-ERα [18,22]. Hyperinsulinemia associated with obesity is accompanied by excessive ovarian androgen secretion (in premenopausal women) and decreased hepatic synthesis of sex hormone binding globulin (SHBG), leading to increased bioavailability of estrogen and testosterone in women and only estrogen in men [23,24]. These hormonal changes explain the increased prevalence of breast cancer and endometrial cancer in obese diabetic patients, but also the protective effect of diabetes on prostate cancer [24]. In our study, BMI was associated with increased breast and uterine cancer.

Colorectal cancer was the second form of malignancy associated with diabetes in our study. The correlation with diabetes could be explained by high levels of insulin-like growth factor 1 (IGF1), hyperinsulinemia, higher BMI or even autonomic diabetic neuropathy that slows intestinal transit time, and thus increasing contact of colon mucosa with various toxins [13].

Pancreatic cancer, the third in frequency in our study, was previously reported to be associated with diabetes independent of sex, age, ethnicity, alcohol consumption, smoking status and BMI [13]. The association is possibly explained by hyperglycemia and hyperinsulinemia [13].

The pathophysiological mechanisms that may explain the link between the two chronic diseases is complex. Thus, hyperglycemia predisposes to an imbalance between production and use of reactive oxygen species (ROS), and thus increases oxidative stress and leads to genomic instability and DNA (deoxyribonucleic acid) mutations which have been associated with various cancers types [13,25]. Hyperglycemia can also exert a favorable effect on tumor growth by direct action (glucose and glutamine being the main energy sources of tumor cells) and by increasing the formation of advanced glycation end products (AGE) [13,26].

Persistent subclinical chronic inflammation present in diabetes, by increasing levels of

inflammatory cytokines (IL-6 - interleukin 6, TNF - tumor necrosis factor, PAI-1-plasminogen activator inhibitor 1) that are secreted by the adipose tissue and activating certain intracellular transmission pathways like the Janus tyrosine kinase (JAK pathway / STAT) [27] or nuclear factor κB (NF-κB) pathway [18,27]) increases the risk of malignant transformation and progression [18,28,29].

The central pathophysiological defect in T2DM, metabolic syndrome (MS) and obesity is represented by impaired insulin / type 1 insulin growth factor (IGF1) axis due to insulin resistance and it is associated directly and indirectly with the risk of cancer. Hyperinsulinemia exerts its effects directly or through a decreased activity of insulin-like growth factor-binding protein 1 and 2 (IGFBP1, IGFBP2) which leads to increased bioavailability of free IGF1 [30,31]. Insulin and IGF1 receptors act through the tyrosine kinase family, the insulin receptor (IR) or the IGF1 receptor (IGF-1R), which triggers an extremely complex cascade of cellular signaling mediated by the insulin receptor substrate (IRS) family proteins [30]. Insulin exerts its metabolic effects through the phosphatidylinositol 3-kinase PI3K / AKT (Protein kinase B -PKB, also known as Akt) pathway and its mitogenic effects through the MAPK pathway (Ras / Raf / MEK / ERK-a MAPK signaling cascade chain of proteins in the cell), the two signaling pathways being interconnected. The two pathways finally converge on a common pathway, the mammalian target of rapamycin - mTOR / P70S6K (Phospho-p70 S6 Kinase) [30].

In our study, patients receiving metformin treatment were diagnosed less frequently with cancer, in fact metformin being associated with a decreased risk of cancer in many epidemiological studies [32-35]. Metformin decreases the risk of cancer through several mechanisms: either indirectly in peripheral tissues (liver and muscle) by lowering insulin levels, either directly through a mechanism involving the LKB1 (liver kinase B1) / AMPK (adenosine monophosphate-activated protein kinase) and PI3K / AKT / mTOR signaling (P3IK / AKT / mTOR) [34].

Our study has several limitations. Thus, patients were followed during a single hospitalization, retrospectively without being followed for a specified period of time (follow-up) and without being able to make a clear correlation between the incidence of various cancers types and diabetes duration. There is a lack of histology reports for a positive diagnosis of cancer and for the histological type of cancer. Moreover, there was a lack of complete anamnestic, clinical and laboratory data in some patients sheets, especially for some confounding factors (such as degree of physical activity, smoking, heredity, alcohol consumption, etc.) Finally, there is a need for a larger group of patients for a better correlation of cancer incidence with diabetes duration.

Conclusions

Cancer and diabetes are two complex diseases with strong multifactorial epidemiological associations. By their negative potential (increased morbidity and mortality), they captivated the attention of researchers and have been extensively discussed in the literature. However, no clear causal link between the two conditions has been identified yet.

Although our study had many limitations, it could highlight in a relatively short period of time the prevalence of various forms of cancer in diabetic hospitalized patients. The most common form of cancer associated with diabetes in our diabetic population was breast cancer (21%), colorectal cancer (15.10%) and pancreatic cancer (12.42%), highlighting the association between breast cancer obesity and T2DM.

Further prospective studies with a long duration are needed on large datasets of patients to evaluate the incidence and prevalence of various forms of cancer in diabetic population.

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