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ANTIDIABETIC TREATMENT, OBESITY, AND CANCER RISK IN ALGERIAN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract – *Objective:* *Several studies have shown that antidiabetic drugs and obesity can modulate the risk of developing cancer. The objective of this study was to assess the impact of the use of antidiabetic drugs and obesity on the risk of developing cancers in type 2 diabetics.*

Materials and Methods: *Data for 1220 patients were collected from the processing of files and a pre-established questionnaire. The anthropobiological parameters and the associated treatment type have been unspecified.*

Results: *Women (OR=17.26; 95% CI=2.88-103.45,* p*<0.01), overweight individuals (OR=4.81; 95% CI=1.63-14.14,* p*<0.01) and hypertensive diabetic subjects (OR=3.82; 95% CI=1.39-10.49,* p*<0.01) are more exposed to cancers. It is interesting to note that diabetic subjects treated with insulin have a reduced risk of developing cancer (OR=0.22; 95% CI=0.07-0.67,* p*<0.01). Diabetic subjects treated with metformin have a four and a half times higher risk of developing cancer (OR=4.61; 95% CI=1.48-14.37,* p*<0.01).*

Conclusions: *In type 2 diabetic subjects, cancer is significantly linked to overweight, to the presence of essential hypertension in individuals under hypotensive as well as in patients treated with metformin.*

KEYWORDS: *Type 2 diabetes mellitus, Cancer, Overweight, Insulin, Metformin.*

INTRODUCTION

One of the less known and controversial diabetes complications is the occurrence of cancer[1,2]. Many studies and meta-analyses have demonstrated an association between diabetes and several cancer types, in particular with obesity, overweight[3], hyperinsulinism, hyperglycemia, or chronic inflammation[2]. In addition, the existence of an insulinoresistance seems to be correlated to a greater cancer aggression and increased mortality[4-6].

The potential biological links between the two diseases are not fully understood. In addition, observational studies suggest that certain drugs used to treat hyperglycemia are associated with an increased or reduced risk of cancer[7]. In many cancer models, it was possible to show a overexpression of 2 to 6 times insulin receptors compared to non-cancer cells[4,8].

Thus, it has been suggested that obesity and overweight combined with insulin resistance may promote carcinogenesis[7,9,10].

The objective of this study was to assess the association between diabetes and cancer as well as the risk impact of the use of oral antidiabetics (metformin), insulin, and the presence of high blood pressure cancer occurrence.

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PATIENTS AND METHODS

The cross-sectional analytical study included 1220 type 2 diabetic patients divided into two groups: diabetic cancer patients. Breast cancer ranks first (40%) followed by colon cancer (33.34%); lung cancer has a significant percentage of (20%) followed by gastric cancer (6.66%). Considered cases were 256 individuals, and non-cancer diabetics as controls were 964 individuals. Participants were admitted to the Tlemcen University Hospital Center from March 2017 to March 2019.

The data had been selected from files examination and from a pre-established questionnaire. The parameters studied related to age, sexes, type of cancer, diabetes family history, or cancer, the consanguinity degree, and obesity had been assessed by body mass index (BMI) calculation. Diabetes associated treatment type, and the nature of the treatment were noted: analogs of slow insulin (Glargine and detemir), rapid insulin analog mixture, and slow insulin (Insulin aspartate protamine and insulin lispro protamine), rapid insulin analogs (insulin aspartate and insulin glulisine). For oral antidiabetics, metformin. For the associated essential hypertension, the treatments reported were mainly inhibitor of the enzyme of conversion into monotherapy. Participation in this study was voluntary and all subjects gave their written, informed consent. This study had been reviewed and approved by the Ethics and Professional Conduct Committee Tlemcen University.

Statistical analysis

Results are expressed as mean±standard deviation and percentage. A Student *t* test was used for averages comparison, and a Chi-square test was used to compare percentages. We performed binary logistic regressions to identify diabetic patients at risk of developing cancer (breast cancer, colon cancer, lung cancer, and gastric cancer) using the factors measured [11]. The response variable is denoted here as Y, which counts diabetic subjects with cancer (C) and controls (T), (C) being the reference value. We plotted the Receiver Operating Characteristic (ROC) curves and calculated the Area Under Curve (AUC) to determine the predictive capacities of the formulated logistic models. The results were considered statistically significant from a *p*-value ≤ 0.05. Data processing was performed using Minitab 18 software.

RESULTS

1220 subjects from the far west of Algeria, aged 35 to 70, were recruited. 42% patients treated with metformin monotherapy were selected. The rest of the patients were treated with insulin without any combination of drugs. The diabetic cancer patients average BMI is 26.60±4.85 kg/m^2 *vs.* 25.51±4.53 kg/m^2 in non-cancer diabetics. Arterial hypertension is more common in diabetic cancer patients (60%) compared to non-cancer patients (17.64%).

Regarding the analytical study, Table 1 gives a summary of the factors used in the logistic model.

Regarding the sex factor in the logistic model, women are seventeen times more exposed to cancers compared to men (OR=17.26; 95% CI=2.88-103.45, $p<0.01$).

Overweight individuals have an almost five times higher risk of developing one of the cancers compared to subjects with other levels of BMI (Normal and obese) (25 <BMI <30) (OR=4.81; 95% CI=1.63-14.14, $p<0.01$).

Concerning diabetic hypertensive subjects, they are practically four times more exposed to cancer compared to normotensive subjects (OR=3.82; 95% CI=1.39-10.49, $p<0.01$).

It is interesting to note that diabetic subjects treated with insulin have a reduced risk of developing cancer (OR=0.22; 95% CI=0.07-0.67, $p<0.01$). However diabetic subjects treated with oral antidiabetics have a four and a half times higher risk of developing cancer (OR=4.61; 95% CI=1.48-14.37, $p<0.01$) than those treated with insulin.

The analytical part aim is to present two prediction models which support current data and suggest that diabetes increases the risk of occurrence of several types of cancer. We also intend to assess the various treatments used impact on the management of type 2 diabetes and their potential risks in the occurrence of cancers.

The first logistic model (Table 1) shows a statistically significant association between cancers (breast, gastric, colon, and lung) on the one hand, and sex, overweight, arterial hypertension, and insulin treatment seem to be exerted minor or no effect on the occurrence of cancers.

The second logistic model (Table 2) shows a statistically significant association between cancers (breast, gastric, colon, and lung). Sex, overweight, hypertension arterial, and treatment with oral antidiabetics seems associated with an increased risk of these types of cancer.

Treatments appear to have a divergent influence on cancer occurrence.

TABLE 1. Results of the logistic regression model study.

Predictor	*Coefficient*	*Z (Wald)*	p-*value*	*OR*	*95% CI*
Constant	-4.64985	-4.46	0.0001		
Sexe	2.84816	3.12	0.002	17.26	2.88-103.45
Overweight	1.57004	2.85	0.004	4.81	1.63-14.14
Arterial hypertension	1.34045	2.60	0.009	3.82	1.39-10.49
Insulin	-1.52920	-2.64	0.008	0.22	0.07-0.67

OR: odds ratio; **CI**: confidence interval.

TABLE 2. Results of the logistic regression model study.

Predictor	*Coefficient*	*Z (Wald)*	p-*value*	*OR*	*95% CI*
Constant	-6.17905	-5.20	0.0001		
Sexe	2.84816	3.12	0.002	17.26	2.88-103.45
Overweight	1.57004	2.85	0.004	4.81	1.63-14.14
Arterial hypertension	1.34045	2.60	0.009	3.82	1.39-10.49
Metformin	1.52920	2.64	0.008	4.61	1.48-14.37

OR: odds ratio; **CI**: confidence interval.

The adjustment adequacy test by Pearson method, a sum of the squares of difference, Hosmer-Lemeshow, and by the two Brown methods (general alternative and symmetric alternative) accepts the logistic model with a *p*-value greater than 0.05 (Table 3).

For models 1 and 2 (Table 4) forecast capacities, there is a very high percentage of matching pairs (86.2%). Somers' D, Goodman-Kruskal's Gamma, and Kendall's Tau-a are summaries of the table of concordant and discordant pairs. The higher values indicate that the model has better forecasting capabilities. In our case, the first two measures worth 0.75 and 0.78 imply a strong forecasting capacity. The Kendall Tau-a gives a relatively low forecasting capacity.

ROC curve

The ROC curve relates the true positive rate (sensitivity) to the false positive rate (1– Specificity) in a graph (point cloud). Usually, we compare *p* (w) to a threshold S=0.5 to make a prediction y (w). We can thus construct the confusion matrix and extract the 2 mentioned indicators.

The ROC curve generalizes this idea by varying over the whole continuum of the possible values of the threshold Sentre 0 and 1. For each configuration, the confusion matrix is constructed, and the true positive rate and the false positive rate are calculated.

In the first model (Figure 1) we get AUC=0.78, the value of AUC allowed us to indicate that

TABLE 3. Fit adequacy tests.

Method	*Chi-square*	*DF*	*p-value*
Pearson	14.2240	23	0.920
Somme des carrés d'écart	17.4663	23	0.786
Hosmer-Lemeshow	2.8982	7	0.894
Brown:			
General Alternative	2.1157	2	0.347
symetric Alternative	1.6413	1	0.200

DF: degre of freedom.

TABLE 4. Association measures (between the response variable and the probability forecasts).

Pairs	*Number*	*Percentage*	*Summary measurement*	
Concordant	2870	86.2	D de Somers	0.75
Discordant	362	10.9	Gamma de Goodman-Kruskal	0.78
Ex aequo	98	2.9	Tau a de Kendall	0.25
Total	3330	100.0		

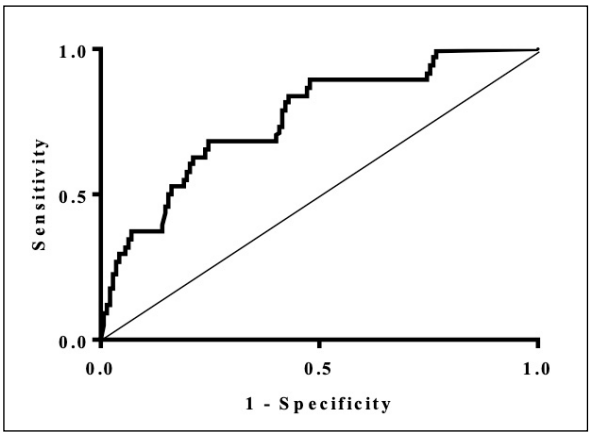

Fig. 1. First model (insulin).

this logistic model has acceptable discrimination. Whereas in the second model (Figure 2) AUC=0.68, therefore the discrimination of this model is acceptable.

DISCUSSION

The combination between type 2 diabetes and cancer (breast, gastric, colon, and lung cancers) appears undeniable, a causal relationship by having sex; also, overweight plays an essential role, and in the presence of high blood pressure and hyperglycemia treatments appear to be linked to cancer in our study population[12].

It is well established that breast cancer is the most common female cancer in the world. It represents 23% of women's cancers and 10.9% of all human cancers in the world[13].

Numerous clinical studies have suggested a link between diabetes and cancer forms variety, including breast[14], colorectal[15] endometrial[16], and pancreatic[17,18].

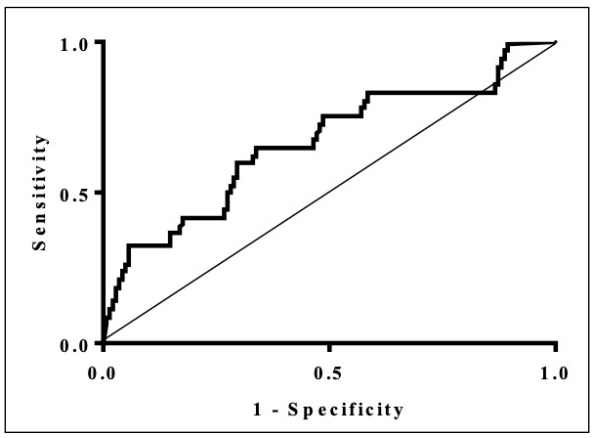

Fig. 2. Second model (oral antidiabetic).

Our study shows a statistically significant association between the risk of developing cancer in type 2 diabetes females, a risk multiplied by 17 (OR=17.26; p=0.002).

Furthermore, the relationship may be due in whole or in part to the sharing of a common relationship predisposing conditions, such as obesity[7]. Overweight and obesity are associated with the risk of developing type 2 diabetes in the population of the far west of Algeria[19]. This risk is multiplied almost 5 times (OR=4.81) and is very significantly linked to cancer (p=0.004) in both models.

The link between high blood pressure and cancer has been the subject of numerous studies. Those two diseases are more frequent with the age[20]. Several studies reported the risk of breast cancer associated with the long-term use of antihypertensive drugs[21]. Some studies have limited the risk to men, while others have shown that hypertension is also a risk factor for cancer in women[22,23]. In our study, the cancers studied revealed a statistically significant association with high blood pressure, regardless of the type of hypoglycemic agent used. This risk is multiplied by 4 (OR=3.82; p=0.009) when hypertensive diabetics are on insulin. Likewise, this risk is multiplied by 3 (OR=2.60; p=0.009) when hypertensive diabetics are on oral antidiabetics, all sexes combined.

Our logistic model also significantly shows oral antidiabetic drugs as a risk factor for the occurrence of cancers in diabetics. This risk is multiplied by 5 (OR=4.61; p=0.008). While the diabetes treatment with insulin seems to not affect on the occurrence of cancers in our study population (OR=0.22; p=0.008). Insulin seems to have rather a protective effect.

The potential increased risk of cancer associated with diabetes medication may result from direct or indirect effects on insulin and circulating insulin levels or other mechanisms[24,25].

However, the data remains contradictory[26,27]. Metformin, the most common treatment used in people with type 2 diabetes, may have a protective effect against cancer, possibly due to a reduction in glucose and insulin levels[28]. This is not the case in this study.

CONCLUSIONS

Although cancers and diabetes have many risk factors in common including obesity and overweight as well as the presence of hypertension, our case-control study assumes that treatment with metformin may potentiate the occurrence of cancers.

The ROC curve justifies that the logistics model has a very high-capacity forecast.

Author contributions:

Nouria DENNOUNI-MEDJATI: conceptualization, data curation, formal analysis, methodology, writing original draft; Majda DALI-SAHI: conceptualization, methodology, supervision, validation; Baya GUERMOUCHE: methodology, visualization, writing original draft; Hamza Naguib MERAD BOUDIA: methodology, visualization, writing original draft; Youssouf KACHEKOUCHE: formal analysis, methodology, visualization, writing review and editing.

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Ethical standards:

This study was conducted according to Helsinki declaration together with the laws of Algeria.

Data availability:

Data are not available due to confidentiality agreement with collaborators.

Conflict of Interest:

Authors have not a direct or indirect interest (financial or nature) with a private, industrial or commercial organization relationship with presented subject.

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