



Frequency and Risk Factors of Association of Breast Cancer and Diabetes Type 2 in Constantine, the Eastern City of Algeria

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Abstract: *Background:* Breast cancer and type 2 diabetes mellitus (T2DM); two worrying public health problems of our century and frequently in our country, have many risk factors in common as well as pathophysiological links. The main objective of the present study is to estimate the frequency of the T2DM-breast cancer association in women in the city of Constantine, while looking for risk factors for breast cancer in this population. *Patients and methods:* A prospective multicenter descriptive study was conducted from January 1, 2019 until December 31, 2020, in women with T2DM associated with newly diagnosed breast cancer. The patients had answered a questionnaire and underwent a clinical and laboratory examination. *Results:* 901 women with breast cancer were seen during the study period, 152 of whom were type 2 diabetics (17%). Their average age was 64 ± 10 years. The age of discovery of T2DM and breast cancer were 53 ± 9.75 years and 62 ± 10 years, respectively. As for the mean duration of diabetes, it was 11 ± 8 years. Insulin was taken over an average of nine years with a calculated average dose of 93 u/d. For the cancer stage, the majority were in stages IIIA (41.5%) and IIIB (32.3%). The common risk factors for T2DM and breast cancer found were sedentary lifestyle (78% of patients), overweight or obesity (81.5%), abdominal obesity (86.5%), low HDLc (70%), hypertriglyceridemia (72.5%). Diabetic imbalance was found in 61.4% of patients. In addition, overweight and obesity were correlated with cancer severity (OR: 1.237; $p = 0.0001$) as well as abdominal obesity (OR: 1.162; $p = 0.0001$). *Conclusion:* The noted frequency of the association of type 2 diabetes and breast cancer requires a targeted cancer screening strategy as well as joint management of risk factors, the only guarantee of a better prognosis for this cancer.

Keywords: Type 2 Diabetes Mellitus, Breast Cancer, Association, Frequency and Risk Factors

1. Introduction

Diabetes mellitus and cancer are two diseases whose incidence continues to grow. Thus, the consequence is an

increase in the number of deaths directly related to these 2 conditions.

Indeed, cancers have become the second leading cause of death and diabetes mellitus is recorded as the twelfth worldwide [1]. Several epidemiological studies have

reported an increase in the incidence of cancer, including breast cancer in diabetic subjects, and several have strengthened the link between breast cancer risk and diabetes [2, 3]. Hyperinsulinism and hyperglycemia, which together with dyslipidemia represent the three main metabolic disturbances occurring in type 2 diabetes, can be considered with obesity [4] as risk factors and triggers of cancer phenotypes [5]. On the other hand, several molecules commonly used in the treatment of diabetes have favorable or unfavorable effects on the appearance and evolution of cancers, including breast cancer compared to other hypoglycemic treatments.

The objectives of this work are to estimate the frequency of the association of type 2 diabetes and breast cancer in women on the one hand, to identify the risk factors for breast cancer in this population, in particular obesity, sedentary lifestyle, metabolic syndrome, hyper-insulinism, insulin resistance, to investigate the impact of antidiabetic treatment on breast cancer and to participate in the implementation of prevention measures.

2. Patients and Methods

This is a prospective multicenter descriptive study, taking place from the first January 2019 to 31th December 2020 concerning all women with type 2 diabetes regardless of the antidiabetic treatment received, with or without complications of diabetes, carrying a newly diagnosed malignant tumor in the breast; histologically proven with or without metastases.

These women are recruited from the registers of the various services taking care of these patients with breast cancer at the level of the university hospital structures of the city of Constantine, namely, the Regional University Military Hospital (HMRUC), the Doctor BENBADIS University Hospital Center, the DIDOUCHE Mourad hospital establishment.

Our patients were sorted during a consultation, a control for their breast cancer, or during a hospitalization and this from the questionnaire of the study and the anatomopathological, biological, and radiological assessments brought back. For those who died, transferred, or lost sight of our study, information was collected from their records. The statistical analysis was performed using SPSS version 26 software. The tool for managing the bibliographic references collected from the PubMed site was Endnote 20. The output style chosen was that of the journal BMC Surgery.

3. Results

3.1. General Characteristics of the Population

From first January 2019 to 31th December 2020, during the study period, 901 women with breast cancer were consulted, 152 of whom were type 2 diabetics. As a result, a frequency of 17% was noted. The overall average age (\pm type deviation) of

our type 2 diabetic patients with breast cancer was 64 ± 10.45 years, with extremes ranging from 37 to 89 years. The largest percentage of our patients either 78% were sedentary, the majority or 49.3% are from Constantine, 64.5% were married, and 83.5% had an average socio-economic level. Regarding their level of education, 39.5% had no level. As for personal background, 73 patients (48%) had them. Of these, 45 patients (62%) had cardiovascular disease and 14 (19%) had dyslipidemia.

62 of the 152 patients (41%) had female relatives with breast cancer and 26 (or 42%) of them reported that they were first-degree relatives. As for diabetics in the family, 102 of our patients (67%) reported having diabetes with 38% and 42%, respectively, in first and second degree relatives. The average menarche age of our patients was $12 \text{ years} \pm 1 \text{ year}$ and a half.

The largest part of our patients with a percentage of 69.4% were married between 15 and 25 years old with an average age of first pregnancy of 24 ± 6 years. 78 women (51.3%) had received contraceptive treatment and 35 patients (45%) were on estrogen. On the other hand, most of them, 69.7% had breastfed their children. As for menopause, 127 of our patients (84.11%) are menopausal with an average age of menopause of 49 ± 4 years.

3.2. Number of Women Recruited Per Institution Per Year

We were able to recruit from the medical oncology department of the Constantine Regional University Military Hospital (HMRUC), 18 patients in 2019 (20%) and 13 (21%) in 2020. Similarly, 43 patients (48%) were recruited in 2019 and 34 patients (55%) in 2020 from the medical oncology department of the DIDOUCHE Mourad hospital. As well as 44 patients were recruited from the radiotherapy department of the Constantine University Hospital Center, including 29 (32%) in 2019 and 15 (24%) in 2020.

3.3. History of Diabetes

3.3.1. Age of Discovery of Diabetes

The overall average (\pm standard deviation) age of discovery of diabetes in our patients is 53 ± 9.75 years with extremes ranging from 30 to 89 years. 54 patients (35.8%) became diabetic in the 50-59 age group, 44 patients (29.1%) between 40 and 49 years of age and 30 patients (19.8%) between 60 and 69 years of age (Figure 1).

3.3.2. Duration of Evolution of Diabetes

The course of the disease is less than ten years in 81 patients (53.64%) with an average duration of 11.05 ± 8 , 26 years (Figure 2).

3.3.3. Previous Treatment of Diabetes

98 patients (67.1%) were on oral antidiabetic drugs, 17 patients (11.64%) were on a diet alone, as were patients who were on oral antidiabetic drugs (ADO) and insulin, while 14 patients (9.6%) were on insulin alone. Note that 6 patients (3.9%) were not on any treatment or diet.

As for the average duration of taking ADO alone, insulin

alone, and ADO plus insulin, the results were 7 years \pm 6.9 years, \pm 6.65, and 7 years \pm 4.67 respectively.

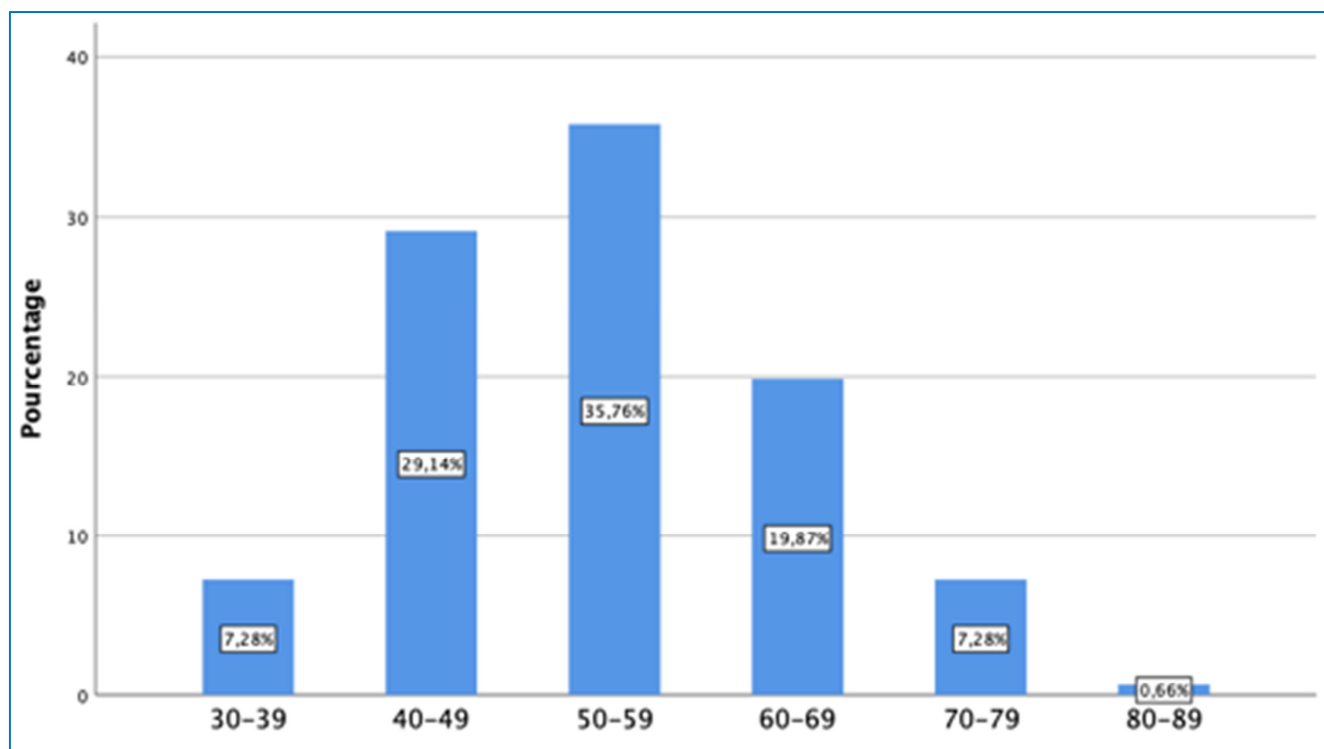


Figure 1. Distribution of patients by age of discovery of diabetes.

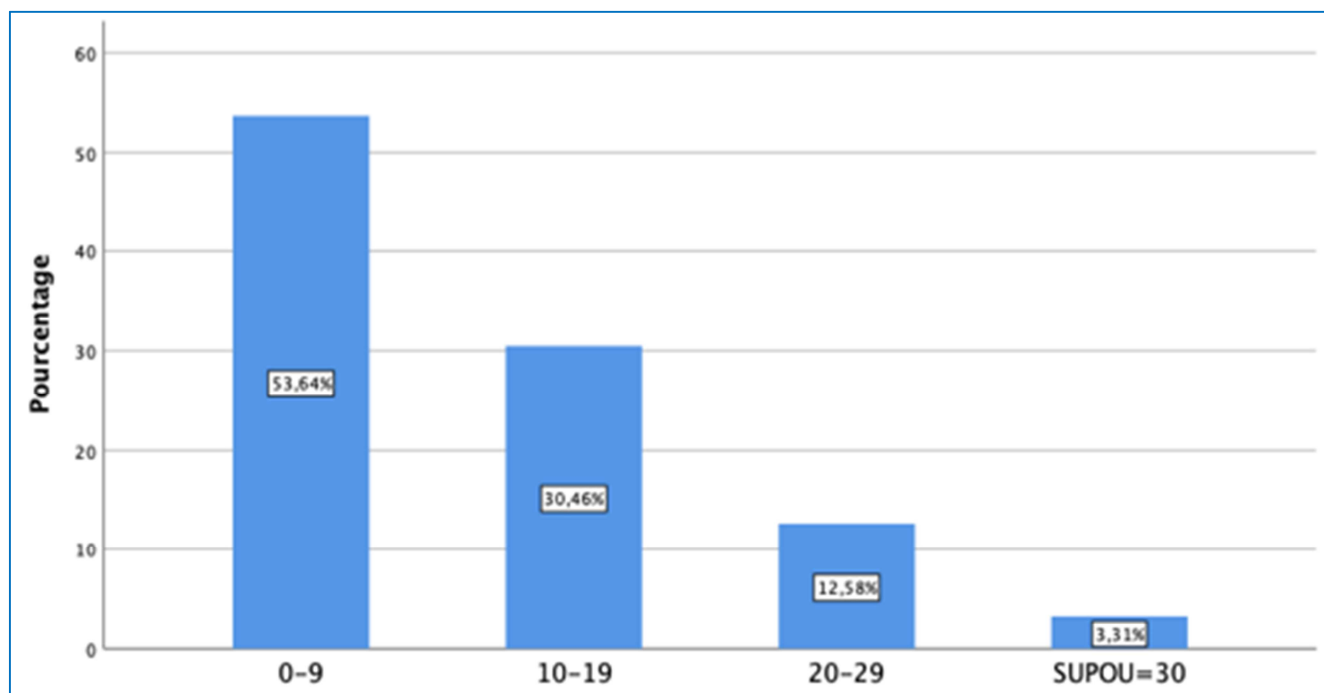


Figure 2. Distribution of patients by duration of diabetes progression.

3.3.4. Current Treatment for Diabetes

63 patients (42%) are on ADO and insulin, 57 (or 38%) are on ADO, 30 patients (or 20%) are on insulin alone and 2 patients have stopped all antidiabetic treatment.

3.3.5. Complications of Diabetes

93 out of 149 patients (63.2%) who brought back their fundus, did not have diabetic retinopathy. 34 out of 152 patients (22%) had diabetic nephropathy. In our series, 91 patients (60%) did not have diabetic neuropathy. (Table 1).

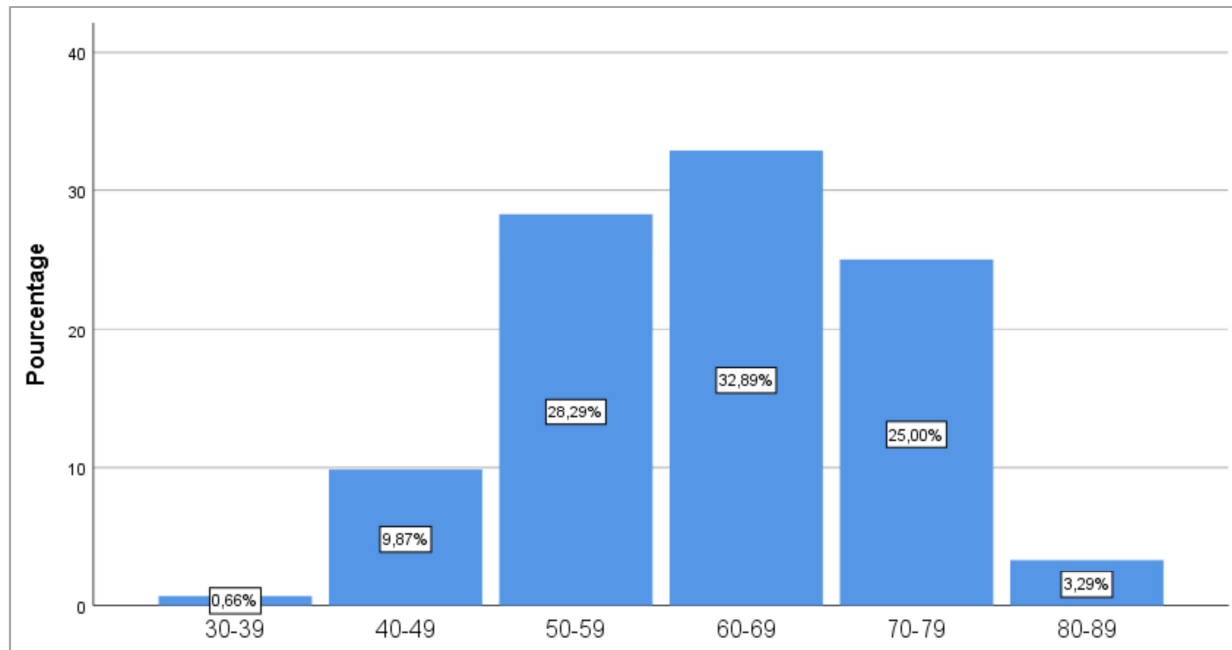


Figure 3. Age of discovery of breast cancer in our patients.

Table 1. Distribution of cases with microangiopathic complications.

Variables	Results n (%)
Diabetic retinopathy (DR)	
Yes/Non	56 (36,8%)/93 (63,2%)
Stage of DR	
debutante DR	22 (31,3%)
Minimal DR	11 (19,6%)
Moderate DR	12 (21,4%)
Pre- proliferant DR	3 (5,4%)
Proliferant DR	5 (8,9%)
Macular edema	3 (5,4%)
Diabetic nephropathy (DNe)	
Yes/No	34 (22,4%)/118 (77,6%)
Stage DNe	
Stage 3	17 (50%)
Stage 4	10 (29,4%)
Renal failure	7 (20,6%)
Diabetic nephropathy (DN)	
Yes/No	61 (40%)/91 (60%)
Sensitive	39 (63,9%)
Motor	3 (4,9%)
CAN	2 (3,3%)
Vesical	16 (26,8%)
Upper digestive tract	1 (1,1%)

ACN: autonomic cardiac neuropathy.

3.4. History of Cancer

3.4.1. Age of Discovery of Cancer

The average age of our patients when discovering their cancer is 62 years \pm 10.28 with extremes ranging from 37 to 87 years (Figure 3).

3.4.2. Hormone Receptors and Stages of Cancer

106 of our patients (69.7%) have ROEs while PR were

negative in 114 patients (75%). On the other hand, in 122 patients in our series (80%), HER2 receptors are negative. As for the stage of breast cancer, the majority are in stages IIIA and IIIB with 41.5% and 32.3%, respectively (Table 2).

Table 2. Distribution of our patients by presence or absence of hormone receptors and UICC stages.

Variables	Results
Hormone Receptors	
RE+/-	106 (69,7%) /46 (30,3%)
RP+/-	38 (25%) /114 (75%)
RHER2+/-	30 (19,7%)/122 (80,3%)
UICC stages	
Stage I	0 (0%)
Stage IIA	5 (3,3%)
Stage IIIB	12 (7,9%)
Stage IIIA	63 (41,5%)
Stage IIIB	49 (32,3%)
Stage IV	23,15%)

3.4.3. Treatment

Of the 116 (76%) whose treatment contained chemotherapy, 52 (or 45%) had received a 3 FAC / 3 TXT-based protocol. 32 patients (27.6%) had received 6 FAC. 93 (or 61%) of the 152 patients had received hormone therapy, of which 62% had received Anastrozole, 27% Letrozole, and 8.6% Tamoxifen. 103 of the patients (68%) had received radiotherapy sessions. 58 of them (56%) had received 55 Grays divided into 25 sessions. 33 patients (or 32%) had received 50 Grays over 25 sessions. 121 patients in our series (80%) had received surgery, 97% of whom had PATEY and 3% had conservative treatment supplemented by lymph node dissection. 32 patients (21%) had been put on targeted therapy. 69% of them had received Trastuzumab.

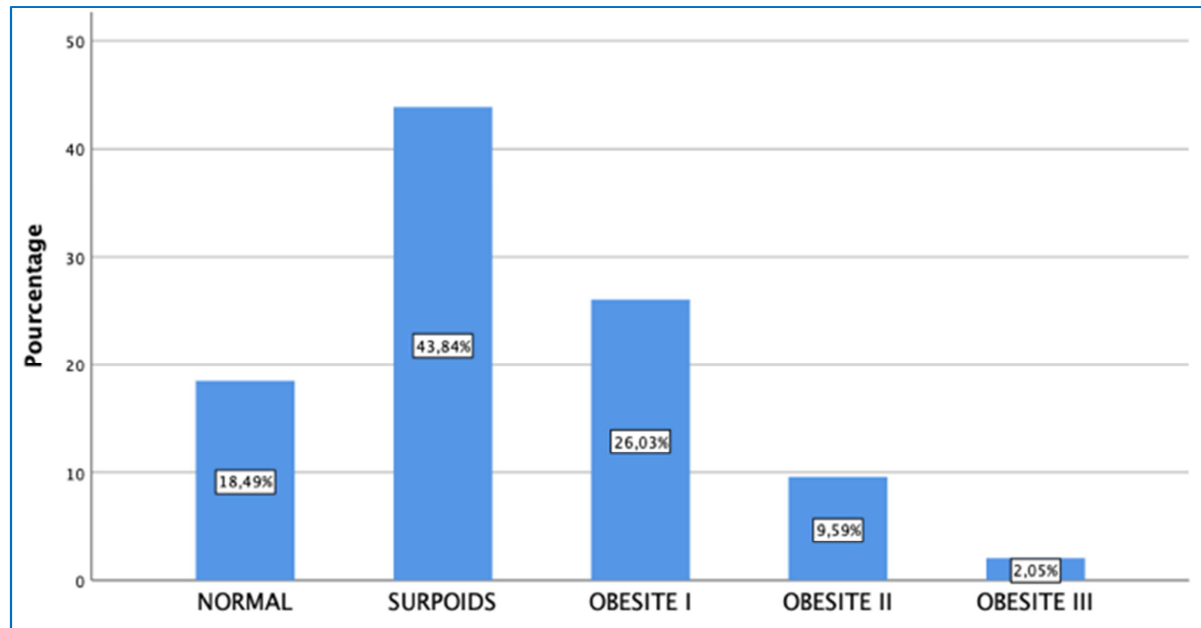


Figure 4. Distribution of patients in our series by BMI.

3.5. Clinical Characteristics of the Study Population

3.5.1. BMI

Our patients had normal BMI in 18.5% and overweight in 44% of cases. It is observed that 26% had grade I obesity, 9.6% had grade II obesity, and 2% morbid obesity. ($p < 0.001$) (Figure 4).

3.5.2. Waist Circumference

The waist circumference of 141 patients was measured. Thus, the average waist circumference in our population is $99.77 \text{ cm} \pm 16.43$ with a minimum of 70 cm and a maximum of 116 cm.

Biological characteristics of the study population, 145 of the 152 patients brought us the results of their HbA1c. The average HbA1c in our population was $7.57\% \pm 1.38$ with a minimum of 5% and a maximum of 13.9%. Thus, 61.38% of our patients had an HbA1c greater than 7%. Comparing this percentage with those with an HbA1c of less than 7%, the p

was < 0.001 . Regarding total cholesterol, 130 of our patients made the assessment we requested and whose results came back to an average of $1.99 \text{ g/L} \pm 0.69$, a minimum of 0.74 g/L and a maximum of 5.65 g. As a result, 50% of our patients had cholesterol levels $\geq 2 \text{ g/L}$.

In addition, 135 patients out of 152 reported on HDLc levels. The average HDLc of these patients was $0.46 \text{ g/L} \pm 0.20$ with a minimum of 0.20 g/L and a maximum of 1.60 g/L. Thus, 70% of our patients had an HDLc level $\leq 0.5 \text{ g/L}$. On the other hand, 132 of our patients have returned their assessment regarding the level of LDLc. The mean LDLc was $1.26 \text{ g/L} \pm 0.54$ with a minimum of 0.20 g/L and a maximum of 3.02 g/L. 28.8% of our patients had an LDLc level $\geq 1.6 \text{ g/L}$. As for triglycerides, 132 patients brought us their assessment. The mean triglycerides were $1.78 \text{ g/L} \pm 0.56$ with a minimum of 0.7 g/L and a maximum of 3.19 g/L. 95 patients in our series (72.5%) had triglyceride levels $> 1.5 \text{ g/L}$ (Table 3).

Table 3. Biological parameters of patients in our series.

Variables	N	Minimum	Maximum	Average	Standard deviation
HbA1c	145	5,0	13,9	7,579	1,3860
Total Cholesterol	130	0,74	5,65	1,9940	0,69256
HDLc	135	0,20	1,60	0,4647	0,20520
LDLc	132	0,20	3,02	1,2614	0,54600
Triglyceride	132	0,70	3,19	1,7825	0,56925
Uree	133	0,10	1,47	0,292	0,17449
Creatinine	137	4,0	52,0	10,363	4,6766
Microalb of 24H	111	1	4000	153,69	488,643

4. Discussion

Compared with the 9 studies, our results regarding the frequency of the DT2-breast cancer combination are almost

identical to those of Wolf [6] (16%) and are close to those of Maskarinec [7] (13.38%). Sanderson [8] posted the largest result in the association of T2D and CS with a percentage of 24.73%. (Figure 5).

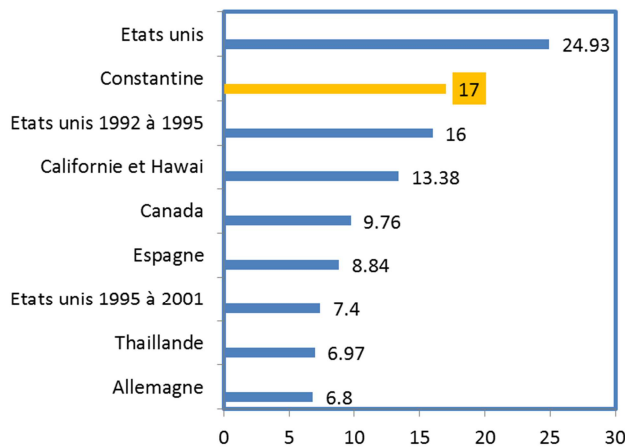


Figure 5. Comparison of the frequency of the combination of T2D and breast cancer in our series.

Regarding the risk factors in common between T2D and

breast cancer, patients in our series aged over 50 years accounted for 93%. This is the age category where women are rather postmenopausal or peri-menopausal. The average age of the patients in our series, which is 64 years \pm 10, is close to that of De Mascarinec et al. [7] which reports an average age of 60 and a half years and similar to that found by Wolf et al. [6]. Whose average age is 64.9 years \pm 10 and that of the Cleveland et al. study (63.6 years) [9].

The conclusions drawn are that postmenopausal women with diabetes had an increased risk of developing breast cancer [OR = 1.35; 95% confidence interval (CI) = 0.99-1.85]. In addition, the work of S. Hannat in Setif has led to results close to ours. Indeed, patients in his series aged over 50 years accounted for 75% with an average age of 61 years \pm 12.5. As for the weight of our patients, our results suggest that overweight and menopausal status should be considered risk factors for breast cancer in women with type 2 diabetes in the wilaya of Constantine. (Table 5).

Table 4. Comparison of our patients' IMBs with that of studies.

Studies	Total of patients (n)	BMI (kg/m ²) < 25	BMI 25- 30	BMI >30
Wu	90	49 (54,4%)	>25 41 (45,5%)	
Jordan	42	30 (72%)	\geq 25 12 (28%)	
Shrauder	254	68 (24,6%)	92 (33,3%)	94 (42,1 %)
Esquinas	81	14 (17,3%)	29 (35,8%)	38 (46,9%)
Mascarinec	1013	180 (18%)	357 (35%)	476 (47%)
Hannat (Setif)	16	5 (31%)	9 (56%)	2 (13%)
Our Study	152	28 (18,5%)	67 (44%)	57 (37,5%)

Regarding the duration of diabetes progression, we obtained a result of 11.05 \pm 8.26 years. A duration longer than that of Maskarinec et al [7], Esquinas et al [10]. and Cleveland et al [9]. which obtained results of 8 and a half years, respectively \pm 5.3 years, 8.73 years and 7 years. For glycemic imbalance, our results revealed that of the 145 patients who had brought back their HbA1c, 61.38% of them had a value greater than 7%, witnessing the imbalance of our patients; compared to other studies that considered their patients' HbA1c levels and had different results than ours [11, 12]. 67% of our patients were

on ADO alone, 11.6% on diet alone.

Similarly, 11.6% of our patients were on ADO and insulin combined. 9.6% were on insulin alone. Our results are close to those of Esquinas et al. with rates of 56.8%, 24.7%, and 17.3% of patients who are, respectively, on ADO alone, ADO + insulin and diet alone [10]. For Sanderson et al., only the percentage of patients on diet only (8.5%) is close to our results [8], while 46.8% and 44.7% of their patients were respectively on ADO and insulin combined and ADO alone (Table 6).

Table 5. Comparison of previous diabetes treatments taken by our patients' studies.

Studies	Diet alone N (%)	ADO alone N (%)	Insulin salone N (%)	ADO + insulin n (%)
Sanderson	4 (8,5%)	21 (44,7%)	22 (46,8%)	
Esquinas	14 (17,3%)	46 (56,8%)	-	20 (24,7%)
Our Study	17 (11,64%)	98 (67,1%)	14 (9,6%)	17 (11,64%)

For our patients, of the 98 who were on oral anti-diabetics, the majority, 82 in number (or 83.67%), were taking metformin. Thus, the safety of using metformin as a protective factor against breast cancer cannot be proven here. In addition, the average dose of insulin calculated in our patients was 93 units per day. Hannat in Setif reported an average dose of 36.2 \pm 15.31U/d.

Majority of our patients are in stages IIIA and IIIB of the pTNM classification with 41.5% and 32.3%, respectively. Our findings are all at odds with the international literature

and studies conducted on breast cancer. Indeed, 88.8% of our patients are in stages III-IV (IIIA: 41.5%, IIIB: 32.3%, IV: 15%) with 21.5% in stage III and 78.4% in stages I and II for Shrauder et al. [13]. and 31% in stages III-IV of the Maskarinec et al. study [7]. This is probably due to the very advanced awareness and screening campaigns in Germany and the United States. This campaign is evolving in Algeria and stages I and II are just beginning to appear in some cities of the country (Table 4).

Table 6. Comparison of UICC stages in our patients' studies.

Studies	Stages UICC,
Shrauder	Stage 1: 30 (11,5%),
	Stage 2: 174 (66,9%),
	Stage 3: 56 (21,5%)
Maskarinec	Stage 1-2: 590 (58%),
	Stage 3-4: 316 (31%),
	Missed: 107 (11%)
Our study	Stage IIA: 5 (3,3%),
	Stage IIB: 12 (7,9%),
	Stage IIIA: 63 (41,5%),
	Stage IIIB: 49 (32,3%),
	Stage IV: 23 (15%)

Through our study, we estimated the frequency of the association of type 2 diabetes and breast cancer and identified risk factors both common and that due to the presence of diabetes, duration and treatment. However, the protective role of metformin is not formally demonstrated, nor were the harms of prolonged exposure to exogenous insulin and insulin secretagogues. Understanding these complex relationships would require more prospective population studies. It would be interesting to continue using our data in the future to assess the results on the impact of risk factors on breast cancer mortality and prognosis and to continue to monitor these patients over the long term. This is the first study that clarified the frequency of the association of type 2 diabetes and breast cancer in Algeria. Similarly, the Arab countries, namely, in the Maghreb and Africa, have not carried out such a study.

5. Conclusion and Outlook

The possible relationship between the occurrence of cancer and the presence of diabetes has been the subject of a debate of ideas and questions for decades. However, the benefit of the cancer prevention efforts undertaken over the past thirty years could be erased in the coming years by the increase in the incidence of obesity. As for type 2 diabetes, it increases the risk of occurrence of various types of cancer due to a community of risk factors and because of the increase in the life expectancy of diabetic subjects.

Multidisciplinary consultation meetings where multidisciplinary is preferred should necessarily involve specialists from organs of different specialties such as endocrinology-diabetology to better follow these patients whose disease has a rather complex mechanism and requires the intervention of everyone for optimal management of the disease.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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