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The intricate relationship between obesity, type 2 diabetes and female breast cancer: A retrospective study of 335 women

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Abstract

Background: Type 2 diabetes (T2D) is a risk factor for female breast cancer (FBC). Obesity has also been associated with FBC, also depending on menopausal status. This study aimed to evaluate the impact of obesity and T2D on the development, aggressiveness, and invasiveness of FBC.

Methods: Demographic, clinical, and histopathological data from 335 women with FBC were collected, and analyzed according to weight category (102 normal weight, 117 overweight, and 116 living with obesity) and the presence/absence of T2D.

Results: Age at oncologic diagnosis was not statistically significantly different for body weight; women with overweight or obesity were more likely to have an oncologic diagnosis after menopause than normal weight ($p < 0.001$). The presence of overweight/obesity and T2D seemed to be associated with a higher incidence of metastasis, recurrence, and triple-negative breast cancer (TNBC) subtype ($p < 0.001$). Excess body weight was also associated with high histologic grade (G3) ($p < 0.005$).

Conclusions: These results confirm excess body weight and T2D as unfavorable prognostic factors in terms of the presence of the TNBC subtype, tumor metastasis, recurrence, and aggressiveness (G3 and Ki-67 > 20%). This study highlights the importance of prevention in all women, with early screening, and adequate nutritional programs.

KEYWORDS
breast cancer, histology, menopause, obesity, type 2 diabetes

1 | INTRODUCTION

Female breast cancer (FBC) is one of the most commonly diagnosed cancers, with 2.3 million new cases diagnosed in 2020,[1] and the highest incidence and mortality rates in most countries. In women, approximately 24.5% of all cancer cases and 15.5% of cancer deaths are attributed to FBC.[2]

Over time, the heterogeneity of FBC has been explored by modern molecular pathology, which has identified biomarkers such as estrogen (ER) and progesterone (PR) receptors, and human epidermal growth factor receptor (HER2). These markers have allowed the classification of FBC into subtypes: luminal A, luminal B, HER2-enriched, and triple-negative breast cancer (TNBC). Triple-negative breast cancer, due to the absence of hormonal receptor expression (ER, PR, and HER2), is a malignant subtype of FBC that cannot respond to endocrine and targeted therapies, and has intense mitotic activity and an unfavorable prognosis. Furthermore, for proliferation biomarkers, Ki-67 has been identified as another clinical biomarker to differentiate luminal A from luminal B subtypes.[3]

The pathophysiology of FBC is complex, and includes genetic, hormonal, and environmental factors. The most important non-modifiable risk factors for developing FBC are genetic mutations (BRCA1 and BRCA2 gene) and family history of the disease; other non-genetic modifiable factors contribute to the etiology of the disease.[4] It has been suggested that the higher incidence rates of FBC are associated with greater exposure to risk factors for FBC, such as hormonal factors (e.g., early age at menarche, advanced menopause, advanced maternal age, shorter periods of breastfeeding, and later marriage) and lifestyle risk factors (e.g., low physical activity, poor diet, alcohol intake).[1] These hormonal and environmental factors are often associated with obesity.

According to the International Agency for Research on Cancer, excess body weight has been associated with an increased risk of at least 13 different cancers (esophageal adenocarcinoma, renal cell carcinoma, pancreatic cancer, gastric cancer, liver cancer, meningioma, multiple myeloma, colon and rectal cancer, postmenopausal breast cancer, ovarian cancer, uterine cancer, gallbladder cancer, and thyroid cancer).[5,6]

In 2016, the World Health Organization (WHO) established that approximately 2 billion adults had a body mass index (BMI) >25 kg/m2, and of these, 650 million (13%) suffered from obesity. According to this linear trend, one billion people are expected to be living with obesity by 2030. Therefore, the global increase in obesity rates is a cause for concern owing to the close relationship between obesity and various pathologies including tumors.[7,8]

Approximately 90% of people with Type 2 diabetes (T2D) are living with overweight or obesity.[9] Its role in increasing the risk of several cancers, including colorectal, prostate and FBC, has also been recognized.[10] This association was confirmed by a comprehensive review of the evidence across meta-analyses of observational studies of T2D with risk of developing several cancers and cancer mortality, showing a higher incidence of several types of cancer, including FBC, in people living with T2D.[11] It has also been shown that the association between T2D and FBC remained significant after adjustment for age and the presence of obesity.[10]

In addition, women with diabetes have been reported to have a greater risk of developing subtypes of FBC associated with poorer prognosis, including PR/HER2-negative and TNBC, than women without diabetes.[12]

For all these reasons, overweight/obesity, and T2D have been recognized as the main factors responsible for increased FBC risk and mortality.

Metabolic abnormalities common to both obesity and T2D, such as insulin resistance and adipose tissue alteration, have been recognized as the likely mechanistic links that may contribute to cancer development and progression.[13]

Several studies have analyzed the relationship between BMI and FBC with discordant results, suggesting an inverse association based on menopausal status, different countries,[6,13–15] or cancer subtypes.

For example, weight gain and higher BMI appeared to be associated with an increased risk of postmenopausal FBC, especially ER- and PR-positive FBC, while an inverse association appeared to exist with the incidence of premenopausal FBC.[12] In addition, the presence of obesity in European and American premenopausal women has been suggested to decrease the risk of FBC, while studies have reported a positive association in Asian premenopausal women with obesity.[14]

If there is strong evidence to consider obesity as a significant modifiable risk factor in the pathogenesis of FCB,[6] there are conflicting results in describing an association between excess weight and FCB development.[10]

This study aimed to investigate the demographic, clinical, and histopathologic characteristics, and menopausal status of women with FBC to evaluate the impact of body weight and T2D on the development, aggressiveness, and invasiveness of FBC.

2 | MATERIAL AND METHODS

2.1 | Study design

A retrospective analysis of 335 women who were normal weight, overweight, or with obesity, with a diagnosis of FBC, was performed between January 2020 and October 2023 in the Breast Unit of the Santa Maria Goretti Hospital at the Sapienza University, Polo Pontino, in Latina, Italy.

A detailed review of the medical records was conducted to obtain information regarding weight, BMI, presence or absence of T2D, age at the FBC diagnosis, presence or absence of metastases, age at menarche, age at menopause, and pathological characteristics of the tumor (histological type and lymph node status). Data were collected from all patients diagnosed with FBC who presented to the Breast Unit during the previously mentioned period. The authors considered as relapses both those that occurred during the data collection period, and those reported by patients who had already been diagnosed with cancer.

Since it has been reported in the literature that the average age of natural menopause internationally is 45–55 years,[16] and in developed countries it is generally accepted that the average age at menopause is about 51 years,[17,18] an age of >50 years was used as representative of postmenopausal status for women with unspecified menopausal status.

The histological classification of FBC was based on the latest WHO (2019) guidelines. The tumor grade was defined according to the Elston and Ellis grading system.

Molecular classification was based on the identification of ER and PR receptors, HER2 status, and Ki-67 proliferation index. The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, treatment, and follow-up of early FBC recognize a cut-off of >20% to differentiate between low and high proliferation.[19]

Body mass index was calculated using the Quetelet Index[20] and categorized according to the WHO criteria that classifies BMI into four groups as underweight, normal weight, overweight, and with obesity (BMI <18.5, 18.5–24.9, 25–29.9, and ≥30 kg/m^2, respectively). T2D was diagnosed according to the ADA/EASD guidelines.[21]

2.2 | Statistical analysis

The mean (± standard deviation) was used to represent baseline variables. Percentages were used to represent categorical variables. The means and medians of the variables were calculated using descriptive statistics. Analysis of variance and Pearson's chi-squared test or Fisher's exact test were used to compare patient and tumor characteristics according to BMI groups. Both methods were used for categorical variables. Independent Student's *t*-test was used to compare continuous between the groups with or without T2D, whereas Pearson's chi-squared test (or Fisher's exact test) was used to compare categorical variables. A $p < 0.05$ (5%) was considered significant in all statistical analyses performed with IBM SPSS Statistics software for Windows, version 21.0.

3 | RESULTS

Of the 335 women evaluated, 102 were of normal weight, 117 were overweight, and 116 were with obesity.

Examination of the clinical and demographic data showed an older age in overweight women than in women living with obesity and normal weight, although this difference was not significant. However, women with overweight/obesity more frequently presented an oncological diagnosis after menopause, whereas women with normal weight were more likely to have an oncological diagnosis before menopause. In fact, the percentages of premenopausal status were 33.3%, 11.9%, and 10.3% in women of normal weight, overweight, or with obesity, respectively. No significant differences were observed in the age at menarche (Table 1).

The incidence of metastases and relapses was significantly higher in overweight or women with obesity ($p < 0.001$). Tumor aggressiveness, expressed as a tumor proliferation index Ki-67 > 20%, and lymph node invasiveness (pN1-2) was higher in women living with overweight/obesity, but the difference was not significant. For histological grade, the results showed a significant ($p < 0.001$) growing trend regarding the presence of a high histological grade (G3) in patients who were overweight (16.2%) compared with those who were normal weight (11.7%), and remained higher in women living with obesity (13.0%) (Table 2).

Data obtained from 335 patients with FBC showed a prevalence of TNBC of 4.8% ($N = 16/335$). Specifically, the presence of TNBC subtype was 3.9% ($N = 4/102$) in the normal weight group, 5.9% ($N = 7/117$) in the overweight group, and 6.0% ($N = 7/116$) in the group with obesity ($p < 0.001$). No significant difference was present in the mean age of patients (Table 2).

The prevalence of T2D was 22.2% (46/207), which was consistent with that in people living with overweight/obesity of both sexes.[11] In the analysis of the two subgroups (women with T2D vs. women without T2D), a significant difference was observed in the presence of metastases, relapses, and TNBC subtypes (higher in women with T2D). No significant differences were observed in the age at oncological diagnosis and age at menarche, and menopausal status (Table 3).

4 | DISCUSSION

The study investigated 335 women who were treated for FBC in a single center to evaluate the demographic, clinic, and pathological characteristics, and menopausal status of women suffering from FBC. The influence of obesity and T2D was correlated with the onset, progression, and severity of FBC. No significant differences were present between women with normal weight, overweight, and obesity regarding their age at oncological diagnosis. However, women living with overweight/obesity more frequently presented an oncological diagnosis after menopause, whereas women of normal weight were more likely to have an oncological diagnosis before menopause. According to these results, which are consistent with observational data in the literature, the existence of an overweight/obesity condition after menopause could be a possible risk factor for FBC, confirming the complexity of the interaction between obesity, T2D, and FBC.[13,22]

For example, a meta-analysis comprising 34 datasets that included >2.5 million women who were assessed for a possible association between FBC risk and BMI, showed an overall reduction in the risk of FBC by approximately 8% for every 5 kg/m^2 increase in BMI in premenopausal women, whereas the risk increased after menopause.[23] The Million Women Study, which followed 1.2 million women aged 50–64 for an average of 5.4 years, of whom 45,037 had FBC, found an approximately 30% increased risk of FBC in postmenopausal women with obesity compared with women without obesity.[24]

TABLE 1 Demographic and clinical data of women with FBC.

	Normal weight (BMI 18.5–24.9)	Overweight (BMI 25–29.9)	Obesity (BMI >30)	*P*
Number	102	117	116	
BMI (kg/m^2)	22.7 ± 0.29	27.6 ± 1,34	34.2 ± 3.6	0.001
Age at oncological diagnosis (year)	59.9 ± 10.5	62.3 ± 11.6	59.6 ± 11.5	n.s.
Menarche age (year)	12.4 ± 1.6	12.4 ± 1.5	12.0 ± 1.6	n.s.
Menopause age (year)	47.1 ± 10.2	49.2 ± 4.8	49.0 ± 4.2	n.s.
Postmenopausal status (N, %)	68/102, 66.6%	103/117, 88.0%	104/116, 89.6%	0.001
Premenopausal status (N, %)	34/102, 33.3%	14/117, 11.9%	12/116, 10.3%	0.001

TABLE 2 Histopathological characteristics of tumors in women with normal weight, overweight, and obesity.

	Normal weight (BMI 18.5–24.9)	Overweight (BMI 25–29.9)	Obesity (BMI >30)	*P*
Metastasis (N, %)	0	9/117, 7.7%	12/116, 10.3%	0.001
Relapses (N, %)	5/102, 4.9%	11/117, 9.4%	10/116, 8.6%	0.001
TNBC (N, %)	4/102, 3.9%	7/117, 5.9%	7/116, 6.0%	0.001
Histological grade G3 (high) (N, %)	12/102, 11.7%	19/117, 16.2%	15/116, 13.0%	0.005
Lymph node invasion (pN1-2) (N, %)	21/89, 23.6%	23/92, 25%	18/80, 22.5%	n.s.
High proliferation (Ki 67 > 20%) (N, %)	40/102, 39.2%	50/117, 42.7%	60/116, 51.7%	n.s.

TABLE 3 Demographic, clinical and histopathological data in women with or without diabetes.

	Women without diabetes	Women with diabetes	*P*
Number	161	46	
Weight (kg)	77.9 ± 12.8	80.9 ± 12.4	n.s.
BMI (kg/m^2)	30.4 ± 4.8	31.2 ± 4.7	n.s.
Age at oncological diagnosis (year)	60.2 ± 11.9	63.9 ± 10.1	n.s.
Menarche age (year)	12.1 ± 1.4	12.4 ± 1.7	n.s.
Menopause age (year)	49.1 ± 6.0	49.1 ± 4.8	n.s.
Postmenopausal status (N, %)	145/161, 90.1%	41/46, 89.1%	n.s.
Premenopausal status (N, %)	16/161, 9.9%	5/46, 10.9%	n.s.
Metastasis (N, %)	13/161, 8.0%	7/46, 15,2%	0.001
Relapses (N, %)	12/161, 7.4%	10/46, 21.7%	0.001
Lymph node invasion (pN1-2) (N, %)	30/161, 18.6%	8/46, 17.4%	n.s.
TNBC (N, %)	12/161, 7.4%	5/46, 10.8%	0.001

Several probable mechanisms that could explain the relationship between obesity and FBC, involving the role of estrogens, insulin deregulation, and chronic inflammation, have been hypothesized.[23]

To explain the intricate relationship observed in the literature between excess body weight and FBC based on menopausal status, it has been hypothesized that the increase in visceral adipose tissue after menopause may affect circulating estrogens and potentially increase the risk of FBC, probably due to the presence of aromatase, an enzyme that converts androstenedione to estrone (E1), which is subsequently reduced to E2.[25–27] In fact, higher E2 levels have been observed in postmenopausal women with obesity, whereas lower E2 levels have been found in premenopausal women who are living with overweight/obesity.[28]

Several theories have been proposed to explain the lower risk of FBC observed in premenopausal women living with overweight/obesity: the combination of longer anovulatory menstrual cycles and lower progesterone levels in the late phase of the menstrual cycle,[22] the negative feedback on the hypothalamic-pituitary axis due to the increased estrogen production by the ovaries and partly by the adipose tissue,[29] and the hyperplastic expansion of adipose tissue with an increase in the number of adipocytes that characterizes early onset obesity, in contrast to the hypertrophic expansion of adipose

tissue during adulthood characterized by an increase in adipocyte volume.[30,31] Adipocyte hypertrophy is in fact linked with adipose tissue dysfunction and insulin resistance, leading to the suppression of serum sex hormone binding globulin (SHBG) concentrations, and subsequent increases in systemic levels of free estrogen and free testosterone.[28]

It should also be added that the occurrence of premenopausal cancers appears to be regulated by differences in genomic profiles, with differential expression of several types of genes in ER + tumors before and after menopause,[32] which may suggest an independent role, at least in part, of obesity. However, a probable role of obesity in genetic mutation or epigenetic regulation of the FBC profile has been reported.[33] Overall, further studies are needed, especially in premenopausal FBC.

According to previous studies, obesity correlates with advanced and adverse cancers, including greater lymph node invasiveness, recurrence and metastasis, higher prevalence of TNBC tumors, high histopathological grade and Ki-67 index, and death. In fact, biologically aggressive cancers appear to be correlated with adverse biochemical features.[34,35] Consistent with these data, the results confirmed a greater and significant presence of metastases, relapses, and high histological grades in women living with excess weight (overweight/obesity). Furthermore, tumor aggressiveness, expressed as Ki-67 > 20%, and lymph node invasiveness, were also higher in women living with overweight/obesity, although the differences were not significant.

Regarding the TNBC, this study suggested an increase in TNBC in women living with overweight/obesity who were mostly postmenopausal. This result is in line with several studies which have found an association between obesity and the development and progression of postmenopausal TNBC. This FBC subtype is one of the most aggressive that is most likely to metastasize, and it represents 15%–20% of FBC cases. The poor clinical outcomes, including increased recurrence and decreased survival, are due to the lack of treatments able to target cancer cells.[36]

Several studies have recognized visceral adipose tissue as an endocrine organ capable of releasing proinflammatory cytokines and substances associated with insulin resistance, T2D, and metabolic syndrome,[25,37] conditions that have been confirmed to be associated with higher risk of FBC in postmenopausal women by a recent large meta-analysis.[27]

Although obesity appears to have an intricate role in conferring protection in premenopausal women, and a poor prognosis in postmenopausal women, T2D is recognized as an unfavorable factor in both premenopausal and postmenopausal women.[6] The impact of T2D on the development and progression of FBC has been explored in several studies, suggesting a 23% higher risk of FBC and a more advanced stage in women with T2D than in women without T2D.[13] The results of this study agree with these observations, indicating that the presence of T2D increases the development of metastases, relapses, and the diagnosis of TNBC tumors, thus worsening the prognosis of women with FBC. The presence of menopausal status, age at oncological diagnosis and age at menarche were not significantly different between women with and without T2D.

Although the impact of T2D on FBC prognosis requires further clarification,[37] several factors associated with T2D may contribute to cancer progression, including hyperinsulinemia, hyperglycemia, dyslipidemia, insulin-like growth factor, adipokines, and cytokines that are common in obesity.[10] However, a review of the epidemiologic evidence, supported by laboratory studies that have observed a reduction in plasma SHBG in women with hyperinsulinemia, a known biomarker of high T2D risk, has concluded that T2D appears to play its own distinct role in the etiology of FBC.[38] This may explain why the presence of obesity did not differ between women with and without T2D in this study.

Studies suggest screening for FBC in women with diabetes to be proactive to detect cancer at the earliest possible stage, in addition to lifestyle modifications including physical activity, and dietary changes, which have shown utility in breast cancer populations experiencing several physical and psychological benefits.[39]

This study has several limitations related to the real-world retrospective cohort. Therefore, the results should be interpreted in relation to these concerns. External confounders (e.g., alcohol use, smoking, socioeconomic status, drug therapies, chemotherapy, hormonal contraceptives, hormone measurement, breast-feeding, parity, family history of cancer) were not included in the collected data. In addiction, BMI was used as a metric to define anthropometric height/weight characteristics for classification into groups. However, as noted above, BMI has limitations because it does not measure body fat distribution, which is probably a more important guide to the risk of excess adiposity than BMI itself.[40]

Nevertheless, this was a large retrospective study using real-world data, which increases the validity of the findings and the hypotheses that can be generated. This makes the retrospective data a valuable resource for generating important knowledge.

This study also provides a complete description of the case studies in terms of demographic and anthropometric data of the patients, menopausal status, and histological data of the tumors, including molecular subtype of FBC, aggressiveness, relapses, and metastasis, both for women living with overweight/obesity, and for women living with diabetes, compared to normal weight and normoglycemic women.

5 | CONCLUSIONS

Obesity is a pathological condition that has a significant impact on women, increasing the risk of many comorbidities such as T2D and cardiovascular diseases, as well as increasing the risk of malignant tumors such as FBC. The results of the study, consistent with data in the literature, showed an association between excess body weight and the risk of premenopausal FBC.

However, no clinical approach can suggest weight gain as a therapeutic strategy, and FBC screening programs should be performed regularly at every age. This study highlights the need to consider the comorbidity related to excess fat, and the danger of maintaining an overweight condition during the menopausal transition, which are conditions related to more aggressive tumors.

Furthermore, overweight/obesity and T2D are often associated, which is confirmed as a further risk factor for the development, progression and unfavorable prognosis of FBC, both before and after menopause.

Globally, these results could also encourage clinicians to promote a "culture of prevention" through early screening and adequate nutritional programs for all women, to mitigate the recurrence and invasiveness of tumors, but also to benefit from early diagnosis.

Further studies are needed to explore these complex relationships, particularly to confirm the association between body weight, type 2 diabetes, and menopausal status, and to elucidate possible pathways involved, including hormonal and molecular pathways.

AUTHOR CONTRIBUTIONS

IM wrote the first draft of the manuscript and developed the methodology. CG, GG, and MC contributed to the data analysis and methodology. RP, EB, and AM acquired and curated the data acquisition and curation. SP and FR performed the project administration. EDF and AC performed formal analysis and investigation. FL edited, supervised, and validated the manuscript. DC conceived the study, and reviewed, edited, and supervised the manuscript. All authors proofread the manuscript and agreed with the submission and publication.

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CONFLICT OF INTEREST STATEMENT

We have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

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