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ORIGINAL ARTICLE

Systemic cortisol correlates with poor prognosis parameters in women with breast cancer and excessive body fat

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KEYWORDS
Breast cancer;
Cortisol;
Poor prognosis

Abstract
Introduction: Excessive body fat can lead to systemic hormonal deregulation associated with poor cancer prognosis. This study analyzed the relationship between systemic cortisol levels and clinicopathological parameters in breast cancer patients categorized by body mass index (BMI).
Material and methods: Peripheral blood samples were collected from 223 women with or without breast cancer to investigate daytime cortisol levels. Circulating cortisol was measured using an enzyme immunoassay kit and correlated with clinicopathological data. The Cancer Genome Atlas (TCGA) data were collected to visualize cortisol axis-related gene expression in breast tumors (n = 1215).
Results: No significant difference in cortisol levels was found concerning breast cancer diagnosis. However, when breast cancer patients were stratified by BMI, cortisol levels were significantly higher in obese patients compared to eutrophics. Eutrophic patients exhibited lower cortisol levels when they had Luminal A tumors compared to those with HER2-amplified tumors. Obese patients with Luminal B tumors had higher cortisol levels than those carrying Luminal A, HER2, or triple-negative tumors. Additionally, lymph node metastasis correlated with high cortisol levels and obesity, as did the presence of blood clots.

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Conclusions: These findings suggest that obesity and systemic cortisol levels in breast cancer patients should be further explored to understand their relationship with clinicopathological parameters.

PALABRAS CLAVE
Cáncer de mama;
Cortisol;
Mal pronóstico

El cortisol sistémico se correlaciona con los parámetros de peor pronóstico en las mujeres con cáncer de mama y exceso de grasa corporal

Resumen
Introducción: El exceso de grasa corporal puede conducir a una desregulación hormonal sistémica asociada con un mal pronóstico del cáncer. Este estudio analizó la relación entre los niveles sistémicos de cortisol y los parámetros clinicopatológicos en pacientes con cáncer de mama categorizadas según el índice de masa corporal (IMC).
Material y métodos: Se recolectaron muestras de sangre periférica de 223 mujeres con o sin cáncer de mama para investigar los niveles diurnos de cortisol. El cortisol circulante fue medido mediante un kit de inmunoensayo enzimático y correlacionado con los datos clinicopatológicos. Se recopilaron datos del *Cancer Genome Atlas* (TCGA) para visualizar la expresión génica relacionada con el eje del cortisol en tumores mamarios (n = 1215).
Resultados: No se encontró una diferencia significativa en los niveles de cortisol en relación con el diagnóstico de cáncer de mama. Sin embargo, al estratificar a las pacientes con cáncer de mama por IMC, los niveles de cortisol fueron significativamente más altos en pacientes con obesidad en comparación con las eutróficas. Las pacientes eutróficas presentaron niveles más bajos de cortisol cuando tenían tumores Luminal A en comparación con aquellas con tumores HER2-amplificados. Las pacientes obesas con tumores Luminal B mostraron niveles más altos de cortisol que aquellas con tumores Luminal A, HER2 o triple negativo. Además, la metástasis en ganglios linfáticos se correlacionó con niveles elevados de cortisol y obesidad, al igual que la presencia de coágulos sanguíneos.
Conclusiones: Estos hallazgos sugieren que la obesidad y los niveles sistémicos de cortisol en pacientes con cáncer de mama deben ser explorados más a fondo para comprender su relación con los parámetros clinicopatológicos.

Introduction

Breast cancer has the highest incidence and mortality among women in the world. Several clinico-pathological parameters are important for the staging, treatment, progression and prognosis of this disease. Among them, we have the molecular subtypes, the degree of invasiveness, the presence of lymph node metastasis, age at diagnosis and BMI. The latter is an important parameter for assessing the presence of excess body fat, defined as overweight or obesity.[1,2]

Obesity is the basis of several diseases that cause significant comorbidities, including cancer. Excessive body fat has been related to cancer prognosis by mechanisms that include changing cellular signaling,[3] sex steroid hormone and metabolism imbalance[4] and immune system deregulation,[5] such as the presence of high levels of adipokines and pro-inflammatory factors.[6] Furthermore, obesity provides a low-grade chronic inflammation affecting all stages of carcinogenesis, in addition to being associated with recurrence in breast cancer patients.[7,8]

Furthermore, it has been well-established that breast cancer and obesity alter the cortisol levels, associated with cancer progression.[9] Although breast cancer is the most common malignant neoplasm diagnosed in women, little is known about the effect of obesity on cortisol levels and its correlation with clinicopathological features.

In this context, we analyzed the systemic cortisol levels in patients diagnosed with breast cancer according to their BMI and correlated them with parameters used to determine disease prognosis.

Material and methods

Evaluation of cortisol-related gene expression

To investigate the panel of expression concerning cortisol-related genes, we used the TIMER (TIMER2.0) database applied to the expression profiles of the Cancer Genome Atlas (TCGA) cohort available at http://timer.cistrome.org/. We used the Gene_DE and Gene_corr modules available to 1215 breast cancer tumors. Data concerning the expression of CRH (corticotropin-releasing hormone); CRHR1 e CRHR2 (corticotropin-releasing hormone receptors); NR3C1 e NR3C2 (glucocorticoid receptors genes); MC2R (melanocortin 2 receptors) genes were included.

Study population

This was a cross-sectional observational study involving 223 women, aged 15–86 years, recruited between 2015 and 2017 at the Cancer Hospital of Francisco Beltrão (CEONC), Paraná, Brazil. Of these, 88 had benign breast conditions (control group) and 135 had breast cancer. Women were included after signing consent terms. The study is approved by the Institutional Ethics board under the register CAAE 35524814.4.0000.0107, ethics opinion number 6.129.064.

All patients underwent surgery to collect biopsy materials. After breast biopsy analysis by a pathologist, the patients were categorized as controls or breast cancer patients. Posteriorly, women were categorized according to their BMI into eutrophic (BMI $\leq$ 24.9 kg/m^2), overweight (BMI $\geq$ 25.0 kg/m^2 or $\leq$29.9 kg/m^2), or obese (BMI $\geq$ 30.0 kg/m^2) and plasma samples was collected. and clinicopathological information. For breast cancer patients, clinicopathological data also were collected.

We applied the following criteria for women to be included in our study: (1) patients referred to CEONC with imaging exams indicating breast cancer (Breast Imaging Reporting and Data System (BI-RADS) 4–5) and who underwent biopsy surgery and (2) female patients. Participants were excluded if: (1) it was impossible to calculate BMI due to lack of accurate weight and/or height information and (2) those who did not present clinicopathological data collected from the patient's medical records.

Sample collection and circulating-unbound cortisol measurements

This study aimed to measure the circulating-unbound cortisol levels in the blood collected in the afternoon, outside the morning peak of secretion. At the time the participants underwent biopsy surgery for breast cancer investigation, peripheral blood samples (10 mL) were collected through a venous puncture in tubes with an anticoagulant (EDTA) between 2 pm and 5 pm. The samples were then subjected to 5-min centrifugation at 4000 rpm, and the plasma was frozen until analysis. Circulating-unbound cortisol levels were measured at 450 nm using a commercial colorimetric enzyme-linked kit (AccuBind ELISA kit, USA) and expressed in μg/dL.

Clinicopathological data

For breast cancer patients, clinicopathological data were collected from patient's medical records. Patients were categorized as carrying tumors into the following molecular subtypes: luminal A for positive estrogen and/or progesterone receptor with Ki67 index under 14%; luminal B for positive estrogen and/or progesterone receptor with Ki67 index equal or above 14%; human epidermal growth factor 2 receptor-amplified (HER2) for those with negative estrogen and progesterone receptors, any Ki67 value, and HER2-amplified; and triple-negative when estrogen, progesterone, and HER2 were negative, for any Ki67 value. Patients were also categorized according to the histological grade of the tumor (grade I, grade II, and grade III), lymph node metastasis (presence or absence), and intratumoral clots (presence or absence). Other parameters, such as age ($\leq$50 or >50 years) and the presence or absence of menopause at diagnosis, were also considered. A pathologist evaluated all biopsies and IHC slides.

Statistical analysis

Cortisol levels were compared between the control and breast cancer groups. Subsequently, cortisol levels of breast cancer patients categorized according to BMI were compared within each variable, and the results are presented as mean ± standard error. GraphPad Prism software (version 7.0) was used to analyze the quantitative variables. Data distribution and group normality were evaluated using the Levene and Shapiro–Wilk tests. Data were assessed using the Grubbs test to verify outliers. We applied the Student's *t*-test (parametric data) or Mann–Whitney test (non-parametric data). Correlation analysis was performed using Spearman's test in the R language program (https://cran.r-project.org/web/packages/corrplot/corrplot.pdf) and is shown as a heatmap. Statistical significance was set at $p \leq 0.05$.

Results

Initially, we verified the differential expression of genes involved in the regulation of the HPA axis in women with breast cancer and we observed that for all genes analyzed, there was a lower expression in the tumors compared to normal tissues (CRH, CRHR1, CRHR2, NR3C1, NR3C2 – $p < 0.001$; MC2R – $p < 0.01$) (Fig. 1).

In the population study, 223 women were recruited, 88 with benign breast condition (control) and 135 with breast cancer. After categorizing these patients according to BMI, we found in the control group: 36 eutrophic, 19 overweight and 18 obese. The breast cancer group was formed by 35 eutrophic, 56 overweight and 35 obese. In both groups, some women were excluded because they did not meet the necessary criteria (15 in the control group and 9 in the breast cancer group).

We determined the circulating cortisol levels in all patients' plasma samples by comparing control (Fig. 2A, 11.09 ± 0.58 μg/dL) and cancer patients (11.28 ± 0.49 μg/dL) and no differences were found (p = 0.8133). When we compared the controls categorized according to BMI, also we did not observe any statistically significant difference (11.47 ± 0.97 μg/dL for eutrophic; 9.90 ± 1.22 μg/dL for overweight; and 10.90 ± 1.28 μg/dL for obese; p = 0.730 eutrophic vs. obese; p = 0.332 eutrophic vs. overweight; p = 0.574 overweight vs. obese). Furthermore, when breast cancer patients were categorized according to their BMI, we did not observe any statistically significant difference among groups despite the obese group having higher cortisol levels than the eutrophic group (10.02 ± 0.88 μg/dL for eutrophics; 11.98 ± 0.84 μg/dL for overweight; and 12.46 ± 0.90 μg/dL for obese; p = 0.058 for eutrophic vs. obese; p = 0.127 eutrophic vs. overweight, and p = 0.7107 overweight vs. obese). No significant differences were observed when comparing patients in each BMI category between controls and breast cancer patients.

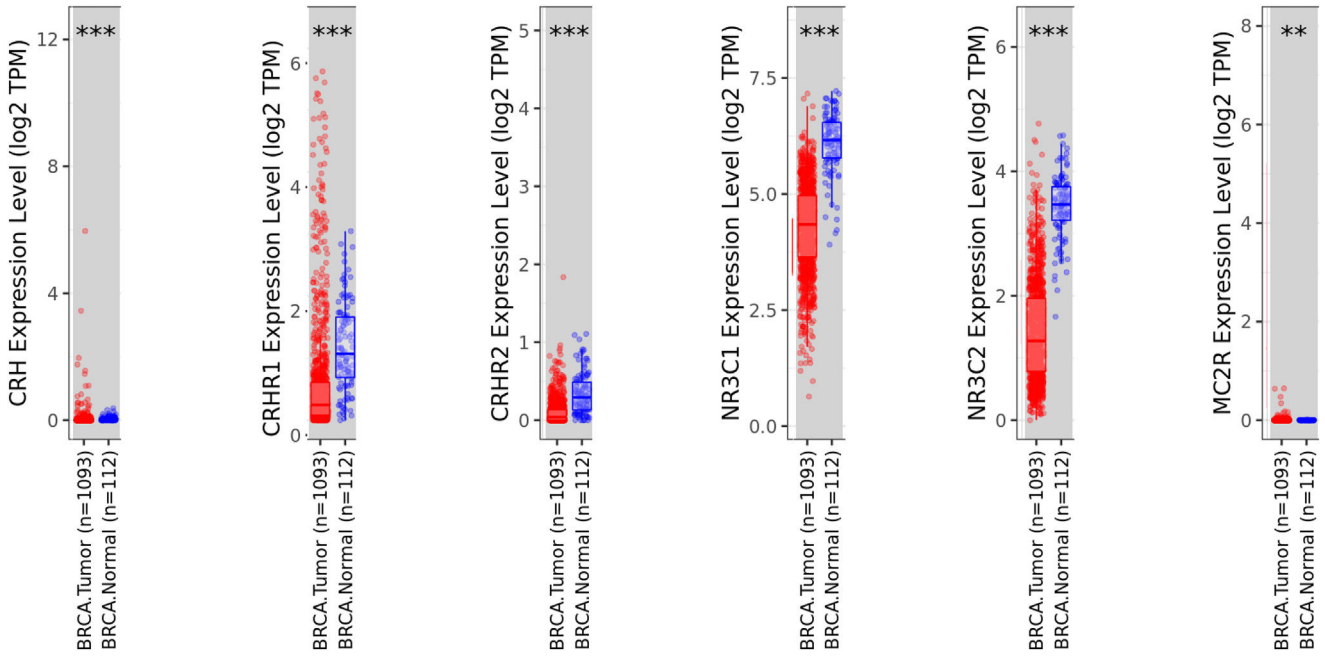

Figure 1 Differential gene expression between tumor and adjacent normal tissues from patients diagnosed with breast cancer for the CRH, CRHR1, CRHR2, NR3C1, NR3C2, MC2R genes according to The Cancer Genome Atlas (TCGA) data collection via the TIMER 2.0 tool. The distributions of the gene expression levels are displayed using box plots. The statistical significance computed by the Wilcoxon test is annotated by the number of stars (*: p value <0.05; **: p value <0.01; ***: p value <0.001).

All data collected on the clinicopathological characteristics of women with breast cancer are demonstrated in Table 1. Most of the patients in all groups were aged >50 years and were menopausal at diagnosis. Luminal B was the molecular subtype that was predominant for eutrophic, Luminal A for overweight, and triple-negative for obesity. Regarding histological grade, the predominance was grade 2 for eutrophic, grade 1 for overweight, and grade 3 for obesity. In relation to lymph node metastasis, all groups showed a predominance of absence, as well as the presence of clots, with the exception of the obese group, in which the number of women with presence or absence was equal. No differences were observed concerning age at diagnosis and menopausal status at diagnosis (Table 2).

We found significant differences in cortisol concentrations among breast cancer patients categorized according to BMI, among the different molecular subtypes in the group obese (Fig. 2B–D). In this group, statistically significant difference was observed between the luminal B subtype (16.78 ± 1.13 μg/dL) and luminal A subtype (9.53 ± 15.0 μg/dL, p = 0.0015), and between the luminal B subtype and triple-negative (10.62 ± 1.69 μg/dL, p = 0.0188), in both conditions, patients with the Lumina B subtype had higher cortisol levels. The luminal B subtype has higher cortisol levels than the HER2 subtype (12.6 ± 1.74 μg/dL, p = 0.0572).

Obese patients showed a statistically significant difference in cortisol levels between tumor grade I (15.15 ± 1.51 μg/dL) and grade III tumors (10.21 ± 1.19 μg/dL, p = 0.0171, Fig. 2E–G). When we compare cortisol levels in obese patients in relation to histological grade, we observed a reduction in cortisol with increasing histological grade, with those with lower histological grade having higher levels of systemic cortisol. In contrast, cortisol levels between eutrophic and overweight patients did not differ according to the histological grade of the tumor (Fig. 2D–F).

Regarding the presence of intratumoral clots (Fig. 3A), obese women (14.05 ± 1.22 μg/dL) carrying tumors with clots when compared to eutrophic presented statistically significant difference in cortisol levels (8.14 ± 1.52 μg/dL for eutrophic, p = 0.0060). Obese patients with clots (14.05 ± 1.22 μg/dL) had higher cortisol levels than those without clots (10.25 ± 1.41 μg/dL, p = 0.0501).

No difference in plasma cortisol levels was observed between overweight patients with the presence (11.86 ± 1.52 μg/dL) and absence of lymph node metastasis (11.70 ± 1.08 μg/dL, p = 0.9324, Fig. 3B) similarly between obese patients with the presence (13.82 ± 1.15 μg/dL) and absence of lymph node metastasis (11.51 ± 1.41 μg/dL, p = 0.2248). When we compared eutrophic patients with lymph node metastasis (7.60 ± 1.75 μg/dL) to those without (12.48 ± 1.27 μg/dL), we observed a significant difference between the groups (p = 0.0322). Obese patients with lymph nodal invasion presented a statistically significant difference in cortisol levels (13.82 ± 1.15 μg/dL) in relation to the eutrophic patients (7.60 ± 1.75 μg/dL, p = 0.0052, Fig. 3B).

Spearman's correlations are shown as heatmaps (Fig. 3C–E) and highlight that the three groups have a distinct pattern concerning the crosslinks among clinicopathological parameters.

For eutrophic women (Fig. 3C), significant correlations were found regarding histological grade II and absence of metastasis (R = 0.900 and p < 0.001), presence of menopause at diagnosis and histological grade II (R = 0.780 and p < 0.001), age at diagnosis >50 years and presence of menopause at diagnosis (R = 0.720 and p < 0.001),

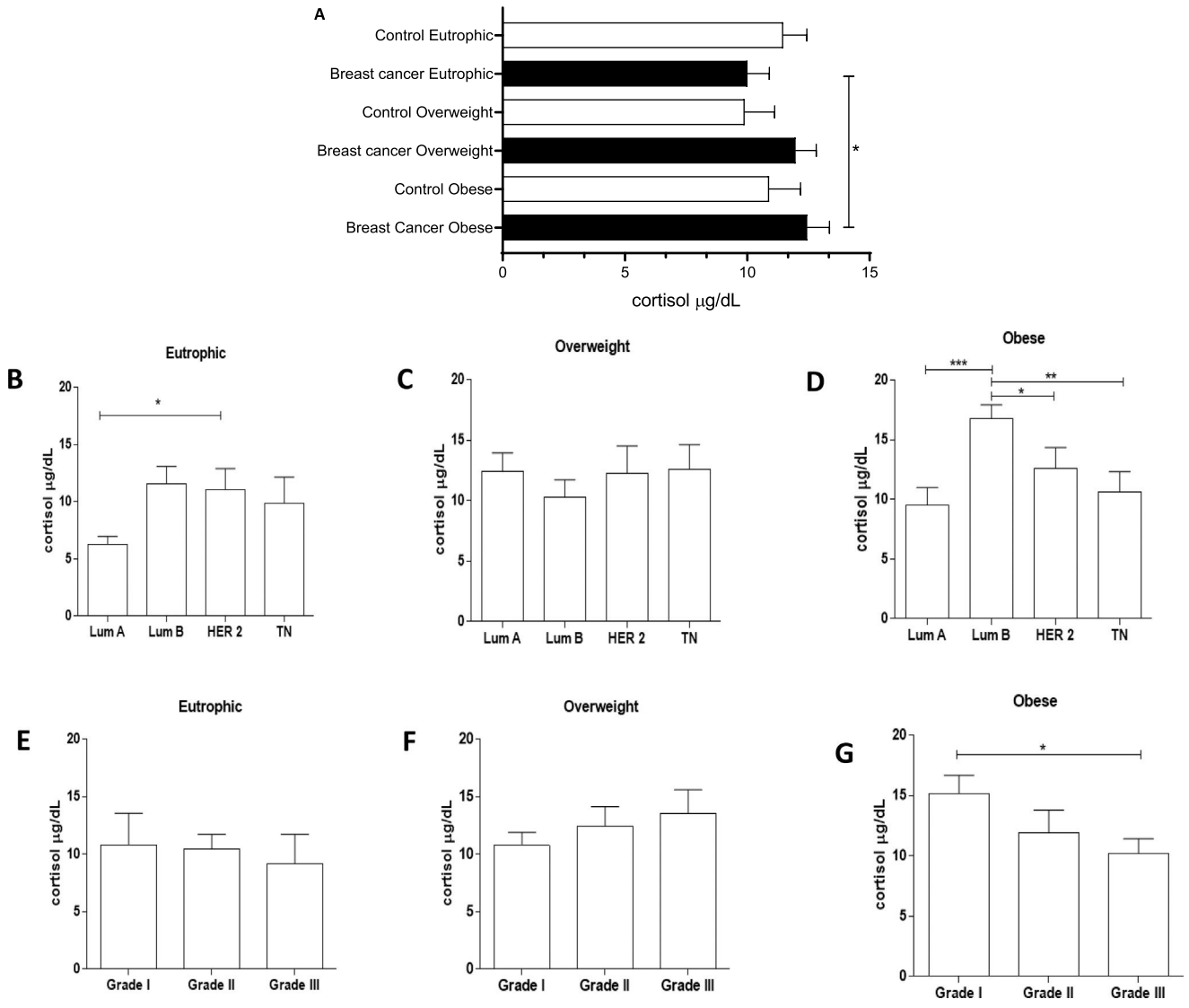

Figure 2 Circulating-unbound cortisol levels regarding controls versus breast cancer (A), molecular subtypes (B–D) and tumor grade (E–G) based on body mass index (BMI) categories. Lum A = Luminal A tumors, Lum B = Luminal B tumors, HER2 = human epidermal growth factor receptor 2-amplified tumors, TN = Triple-negative tumors. * indicates statistical significance (*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$).

histological grade III and metastasis ($R = 0.890$ and $p < 0.01$), histological grade I and absence clots ($R = 1.00$ and $p < 0.001$), and subtype luminal B and presence of menopause at diagnosis ($R = -0.720$ and $p < 0.01$).

For overweight women (Fig. 3D), significant correlations were found regarding histological grade II and subtype luminal B ($R = 0.760$ and $p < 0.001$), age at diagnosis >50 years and presence of menopause at diagnosis ($R = 0.820$ and $p < 0.001$), HER2/luminal HER and absence of metastasis ($R = 0.750$ and $p < 0.05$), histological grade II and triple-negative ($R = -0.780$ and $p < 0.01$), and subtype luminal A and HER2 /luminal HER ($R = -0.700$ and $p < 0.05$).

For obese women with breast cancer (Fig. 3E), significant correlations were found between histological grade I and grade II ($R = 0.750$ and $p < 0.01$), age at diagnosis >50 years and presence of menopause at diagnosis ($R = 0.780$ and $p < 0.001$).

Discussion

In the present study, we analyzed the combined impact of breast cancer and excessive body fat on circulating cortisol levels and our findings indicate that these factors alter cortisol levels in patients, especially correlated with clinicopathological features linked to poor prognosis. To the best of our knowledge, this represents the first report showing such an association in the literature.

Cortisol plays a crucial metabolic role in the human body, along with its anti-inflammatory functions and impact on the immune system. Its secretion is regulated by the hypothalamic–pituitary–adrenal (HPA) axis, which is influenced by various internal and external factors. For efficient communication within this axis, several protein hormones are expressed and secreted. The hypothalamic paraventricular nucleus, in response to various stimuli, secretes CRH,

Table 1 Clinicopathological data of breast cancer patients categorized according to their body mass index (BMI).

	Eutrophic	Overweight	Obese	Total
Number of individuals	*N* = 35 (27.78%)	*N* = 56 (44.44%)	*N* = 35 (27.78%)	*N* = 126 (100%)
Age at diagnosis				
≤50 years	16 (45.7%)	23 (41.1%)	15 (42.9%)	54 (42.86%)
>50 years	19 (54.3%)	33 (58.9%)	20 (57.1%)	72 (57.14%)
Histological grade				
Grade I	04 (11.4%)	27 (48.2%)	11 (31.4%)	42 (35.29%)
Grade II	19 (54.3%)	17 (30.3%)	11 (31.4%)	47 (39.50%)
Grade III	07 (20.0%)	11 (19.6%)	12 (34.3%)	30 (25.21%)
Molecular subtype				
Luminal A	05 (14.3%)	19 (33.9%)	07 (20.0%)	31 (25.41%)
Luminal B	12 (34.3%)	16 (28.6%)	08 (22.9%)	36 (29.51%)
HER2-amplified	07 (20.0%)	09 (16.1%)	06 (17.1%)	22 (18.03%)
Triple-negative	09 (25.7%)	10 (17.9%)	14 (40.0%)	33 (27.05%)
Lymph node metastasis				
Absence	16 (45.7%)	34 (60.7%)	18 (51.4%)	68 (62.96%)
Presence	09 (25.7%)	16 (28.6%)	15 (42.9%)	40 (37.04%)
Clots				
Absence	18 (51.4%)	28 (50.0%)	16 (50.0%)	62 (57.41%)
Presence	10 (28.6%)	20 (35.7%)	16 (50.0%)	46 (42.59%)
Menopause at diagnosis				
Absence	09 (25.7%)	20 (35.7%)	11 (31.4%)	40 (33.06%)
Presence	23 (65.7%)	35 (62.5%)	23 (65.7%)	81 (66.94%)

which acts on the corticotropin-releasing hormone receptors in the anterior pituitary. This gland then secretes adrenocorticotropic hormone, which controls the secretion of cortisol in the adrenal cortex through MC2R. Cortisol performs its functions through glucocorticoid receptors, encoded by the NR3C1 and NR3C2 genes.[10]

From Fig. 1, we verified the differential expression of genes involved in the regulation of the HPA axis between women with breast cancer and those with normal breast tissue. We observed a negative regulation of NR3C genes in tumor tissue, compromising cortisol function, corroborating previous studies.[11]

Initially, no significant differences in circulating cortisol concentrations were observed between women with and without breast cancer. The literature contains conflicting information about such changes, likely due to differences in methodology for measuring cortisol levels or the disease stage. Alterations in cortisol levels have been reported in advanced-stage breast cancer patients, correlating with disease spread and early mortality.[12]

Our results did not indicate a difference in systemic cortisol levels among women without breast cancer, but in the group with breast cancer, obese patients had higher cortisol levels than eutrophic patients. This suggests that both the presence of a tumor and obesity are factors that contribute to the increase in plasma cortisol observed in this study. Excess body fat influences tumor development through several mechanisms, such as increased leptin and decreased adiponectin secretion.[13] Furthermore, obesity in women with breast cancer is associated with increased tumor growth,[14] a highly inflammatory tumor microenvironment,[15] tumor progression,[16] reduced disease-free survival, and increased mortality.[17]

Several studies demonstrate the relationship between obesity and the HPA axis, as well as circulating cortisol concentrations. Pro-inflammatory mediators secreted by fatty tissues hyperstimulate the HPA axis.[18,19] Studies demonstrate that adipocytes convert cortisone to cortisol through increased activation of the 11beta-hydroxysteroid dehydrogenase axis, altering its systemic concentration.[20,21]

We investigated circulating cortisol levels and molecular subtypes according to patient BMI. Obese patients with the luminal B subtype had significantly increased cortisol levels compared with those with other subtypes. Eutrophic patients with luminal A subtype tumors had significantly lower cortisol levels than those with HER2-amplified tumors. The literature extensively discusses the role of cortisol in these subtypes. Malignant cells have more corticosteroid

Table 2 Circulating-unbound cortisol levels (μg/dL) in patients with breast cancer, according to age at diagnosis and menopausal status at diagnosis according to body mass index (BMI) categories.

	Age at diagnosis		*P*-value
	≤50 years	>50 years	
Eutrophic	10.24 ± 1.374[a,b]	10.33 ± 1.230[d,e]	$p = 0.9616$
Overweight	11.99 ± 1.339[a,c]	11.70 ± 1.093[d,f]	$p = 0.8679$
Obese	12.63 ± 1.525[b,c]	11.79 ± 1.180[e,f]	$p = 0.6597$
	Menopause at diagnosis		
	No	**Yes**	
Eutrophic	11.64 ± 2.134[g,h]	10.12 ± 1.087[j,k]	$p = 0.5363$
Overweight	12.45 ± 1.506[g,i]	11.49 ± 1.043[j,l]	$p = 0.5912$
Obese	13.60 ± 1.587[h,i]	11.66 ± 1.174[k,l]	$p = 0.3448$

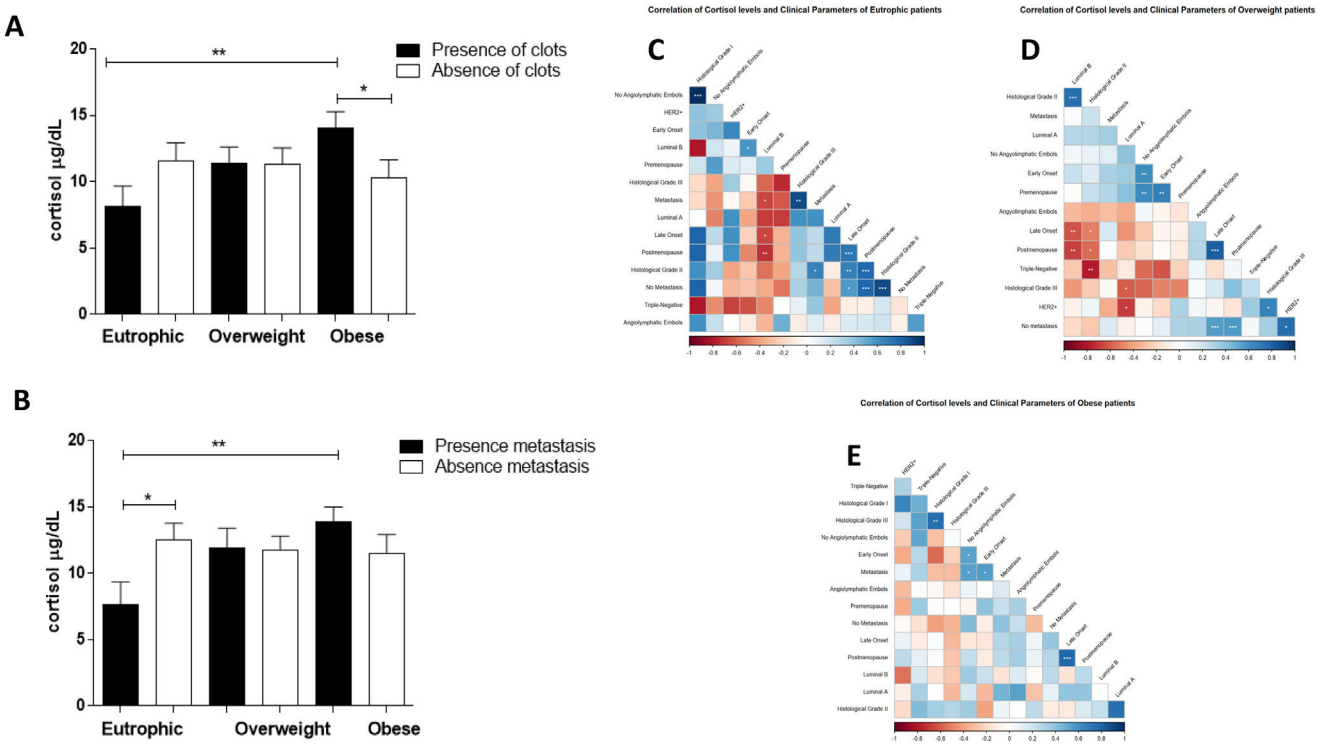

Figure 3 Circulating-unbound cortisol levels concerning intratumoral clots (A), lymphnodal metastasis (B) based on body mass index (BMI) categories. * indicates statistical significance (*$p \leq 0.05$; **$p \leq 0.01$). Heatmaps of correlation among circulating-unbound cortisol levels and clinical parameters of patients with breast cancer categorized according to body mass index (BMI) in eutrophic (C), overweight (D), or obese (E). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$).

receptors than benign cells,[22] making them more responsive to cortisol. Our findings suggest that further studies should investigate how cortisol behaves in each molecular subtype according to BMI.

Tumor proliferation is linked to cumulative genomic instability and differentiation, with higher-grade and more aggressive cancers being more undifferentiated.[23] Cortisol influences cancer progression by affecting tumor nuclear grade.[24] Our data showed increased cortisol levels in obese patients with grade I tumors compared with those with grade III tumors. The reduction in cortisol may be related to its consumption in obese breast cancer patients with grade III tumors. Furthermore, obese patients with grade I tumors, due to high cortisol levels, may be more vulnerable to histological alterations.

Metastasis, a key factor determining patient survival is linked to changes in cortisol levels.[25] High BMI increases the risk of metastasis in a dose–response relationship.[26] We found that obese women with breast cancer and lymph node metastasis had higher plasma cortisol levels than eutrophic patients, a difference not observed in non-metastatic cases. Higher mean diurnal cortisol concentrations in patients with metastatic breast cancer correlate with significantly suppressed immune function,[27] potentially promoting lymph node metastasis. Glucocorticoid receptors also control the mesenchymal-epithelial transition process in breast cancer, which is critical for metastasis.[25]

Our heatmaps revealed distinct correlations for obese patients compared to other BMI groups, with mostly weak correlations. Eutrophic and overweight women had several significant positive correlations, highlighting breast cancer's multifactorial and heterogeneous nature, where a single risk factor like obesity can alter clinicopathological feature relationships.

The main limitations of our study include the relatively small sample size, the absence of repeated cortisol measurements, and the lack of evaluation in alternative biological samples such as saliva or tumor tissue. Additionally, while a single-point cortisol analysis offers a snapshot of hormone levels, it may not reliably reflect long-term activity of the hypothalamic–pituitary–adrenal (HPA) axis. Despite this, there are few reports on the association between circulating cortisol levels and breast cancer prognosis, which becomes our findings relevant and novelty.

In conclusion, these results indicate that obesity and the cortisol levels may have a negative effect on disease breast cancer prognosis. Thus, for further investigation and evidence, the BMI and plasma cortisol dosage calculation in these patients may be used as parameters to evaluate the prognosis of breast cancer and consequently influence medical conduct.

Declaration of competing interest

The authors declare that there are no conflicts of interest that could impair the impartiality of the research reported.

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Author contributions

WRP and CP designed the experiments and analyzed the data. ACBK performed the cortisol measurements and collected the data. JCS and EM performed the cortisol measurements. DR assisted with patient selection. TBS and FTP analyzed the data. All authors reviewed and edited the manuscript as well as the final approval of the submitted version.

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