

The impact of BMI and obesity on breast cancer: A prospective cohort study

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Abstract

Objective: To evaluate the association between BMI and breast cancer stage at presentation in Basrah, Iraq.

Methods: This prospective cohort study enrolled consecutive women diagnosed with breast cancer at two Basrah teaching hospitals from December 2020 to December 2022. BMI was measured at presentation and categorised per WHO thresholds. Cancer stage was determined through clinical examination, imaging, and histopathology by multidisciplinary teams. Univariate analyses employed Kruskal-Wallis and Fisher's exact tests. Multivariable binary logistic regression assessed independent predictors of advanced stage (III/IV). Statistical significance was set at $p < 0.05$.

Results: Among 121 women (mean age 50.8 ± 11.0 years), obesity ($BMI \geq 30$) occurred in 56 (46.3%). Most presented with a breast lump (90, 74.4%) and tumour size 2-5 cm (75, 62.0%). Stage distribution: I (26, 21.5%), II (58, 47.9%), III (29, 24.0%), IV (8, 6.6%). Of stage IV patients, five (62.5%) were obese. No significant association existed between BMI and stage in univariable analysis ($p = 0.392$). Tumour size is strongly associated with stage ($p < 0.0001$). After multivariable adjustment, BMI remained non-significant (obesity adjusted OR: 1.42, 95% CI 0.51-3.96, $p = 0.502$).

Conclusions: Despite high obesity prevalence, BMI alone did not independently predict advanced stage. Tumour size was the strongest correlate. These findings highlight adiposity-breast cancer complexity, supporting alternative anthropometric measures in future research.

Keywords: Breast Neoplasms; Body Mass Index; Obesity; Risk Factors; Iraq

Plain English Summary

Why was this study done? The most prevalent type of cancer that affects women globally is breast cancer. Being overweight or obese has been linked to breast cancer risk, but the relationship between body weight and how advanced the cancer is when first diagnosed remains unclear. This paper analysed whether females with a higher BMI were diagnosed with more advanced breast cancer in Basrah, Iraq.

What did we do? We tracked 121 study subjects who were identified as recently diagnosed with breast cancer at two hospitals in Basrah from December 2020 to December 2022. We weighed and measured their weight and height to get the BMI, and noted down their tumour details and the stage of the cancer through the conventional medical procedures. We then examined the possibility of women with higher BMI having more advanced cancer at diagnosis.

What did we find? The proportion of obese women was almost half (46.3%). Out of the eight women who had cancer at stage IV (most advanced), five (62.5) were obese. However, after the other factors were taken into consideration, such as age and the size of the tumour, BMI was not a predictor of advanced stage. The actual size of the tumour was closely associated with the level of advancement of the cancer.

What do these findings mean? Although obesity is indeed prevalent among breast cancer patients in Basrah, BMI might not be able to paint the entire picture of Body fat's effect on breast cancer. Tumour

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size is the most critical aspect relating to the stage of cancer. To gain more insight into this association, future research ought to incorporate other indicators of fat distribution in the body, like the waist circumference. The results confirm the need to control body weight, but the association between body size and the stage of breast cancer needs to be studied.

Introduction

Among women worldwide, about one in eight women will receive a breast cancer diagnosis at some point in their lives, making it the most frequent type of cancer and the leading cause of cancer-related mortality among women in 140 countries worldwide (1). The interdependence between BMI and breast cancer has been the cause of much research interest as a result of the fact that obesity has been considered among the 600 million adults in the world, comprising 13 per cent of the world population (2). The pathogenesis of various malignancies, such as adenocarcinoma of the oesophagus, gastric cardia, thyroid, pancreas, colon, rectum, endometrium, prostate, gallbladder, ovary, and breast, and multiple myeloma, has been associated with obesity (BMI 30kg/m² and above) (3). The biological processes that are associated with adiposity and carcinogenesis are chronic inflammation, in which adipose tissue in obese patients has been shown to generate inflammatory cytokines and mediators that facilitate a microenvironment in which cancer invasion and/or metastasis thrive (4, 5, 6).

The correlation between body size and breast cancer is also quite intricate, with some relationships differing depending upon the conditions of menopause, at which point body size was measured, whether the tumour contained hormone receptors or not and the use of exogenous hormones by the postmenopausal women (7). In the case of postmenopausal women, an elevated BMI level has been reported to have a positive relationship with risk of breast cancer, especially in tumours that are hormone receptor positive, possibly through oestrogen synthesis in fat and insulin-mediated mechanisms. On the other hand, various research studies indicate that higher BMI has a protective effect on premenopausal women, although the processes are not fully understood (8).

Although much research has been done, the results about the effect of BMI on the stage of breast cancer at its presentation are inconclusive (9). Research in heterogeneous populations has had disparate findings, indicating that region-specific data is required, especially in areas with unique genetic backgrounds, lifestyle habits, and healthcare access trends. Iraq, as well as many states in the Middle East, has experienced a growing level of obesity and the prevalence of breast cancer, but there is little published

information available about the linkage between the two in the population of Iraq.

The main aim of the paper was to assess whether an increased BMI relates to an increased staging at diagnosis in women diagnosed with breast cancer in Basrah, Iraq. Secondary goals consisted of outlining the demographic and clinical features of breast cancer patients in this area and the analysis of the factors that correlate with the disease stage.

Materials and Methods

Study Design and Setting

The breast clinics of two tertiary care hospitals in Basrah, Iraq: Al-Basra Teaching Hospital and Al-Basra Maternity Teaching Hospital, were the places where this prospective cohort study was carried out. The two facilities are both large referral centres in the southern part of Iraq, to which patients are referred both in urban and rural Basrah Governorate.

Study Population and Sampling Frame

Women who attended the breast clinics from December 1, 2020, to December 31, 2022, in succession, and were able to confirm a histopathological diagnosis of breast cancer, were eligible to join the study. Multidisciplinary teams of breast surgeons, oncologists, pathologists and radiologists collectively analysed all patients and arrived at diagnosis, staging and treatment.

Inclusion criteria included: (1) female sex; (2) age 18 years and above; (3) histopathologically proven primary breast cancer; (4) complete anthropometric measurements at the time of presentation; and (5) informed consent. The exclusion criteria included: (1) any prior history of breast cancer or other malignancy; (2) recurrence of breast cancer; (3) male breast cancer; (4) pregnancy or lactation at the date of diagnosis; and (5) incomplete medical records, due to which proper staging was not possible.

Data Collection Procedures

A structured interview with the use of a standardised questionnaire conducted by trained health professionals was conducted on all the patients on their initial visit to the clinic. The sociodemographic factors that were captured in the questionnaire were age, marital status, residence (urban/rural), educational attainment, occupation, economic status, and housing type.

Clinical data involved mode of presentation, symptom presence and duration, tumour site (right/left breast) and First-degree relatives and other relatives with a family history of breast cancer. Reproductive history entailed age of menarche, number of pregnancies, number of abortions, lactation history and menopausal status. Previous medical comorbidities and other malignancy history of the patient or family were documented.

Anthropometric Measurements

Measuring weight and height was done at the initial clinic visit, before the beginning of any systemic treatment or surgery. Measurement of weight was carried out to the nearest 0.1 kg using a calibrated digital scale with the patients having light indoor clothes and no shoes on. The height was taken to the nearest 0.1 cm in a wall-mounted stadiometer when the patients stood erect with feet together and head in a Frankfort horizontal position. Weight in kilograms (kg) divided by height in meters squared (m²) yielded the BMI, which was categorised as normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), and obese (30.0 kg/m² or more) (10).

Clinical Assessment and Staging

Every patient was examined clinically with a breast examination and subsequently underwent imaging procedures, such as bilateral breast ultrasonography and mammography. In the case of staging, computed tomography (CT) of the chest, abdomen and pelvis was done to assess the presence of metastatic disease. The histopathological diagnosis was made with core needle biopsy or surgical excision specimen, and the pathological evaluation was performed in terms of tumour type, grade and where applicable, oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status.

The tumour staging was done in the American Joint Committee on Cancer (AJCC) TNM staging system, 8th edition (11). The stage grouping was established according to tumour size (T), lymph node (N) involvement and distant metastases (M). Consensus at multidisciplinary team meetings was used as the final stage assignment, and all feasible clinical, imaging and pathological data were utilised.

Statistical Analysis

The statistical analysis was done using SPSS version 20 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test and observation of histograms were used to test the normality of the continuous variables. Non-discrete variables were given in the form of the median with the range (minimum-

maximum) and contrasted using the Kruskal-Wallis test. One-way analysis of variance (ANOVA) was used to analyse the normally distributed variables, which were displayed as mean standard deviation (SD). Categorical variables were presented as percentages and frequencies. When anticipated cell counts were fewer than five, the chi-square test or Fisher's exact test was used to investigate associations between categorical variables. Due to the tiny cell sizes in stage IV, Fisher's exact test was used for the primary analysis, looking at the relationship between BMI category and illness stage.

To account for potential confounding, multivariable binary logistic regression was performed with advanced stage (Stage III/IV) as the dependent variable. Covariates were selected a priori based on clinical relevance and included age (continuous), menopausal status (premenopausal/postmenopausal), tumour size category (<2 cm, 2-5 cm, >5 cm), and BMI category (normal, overweight, obese). Results were presented as adjusted odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was set at $p < 0.05$ (two-tailed).

Sample Size Consideration

The study included all eligible patients presenting during the two-year study period without a priori sample size calculation, as this represented a convenience sample from the source population. A post-hoc power analysis indicated that with 121 participants and the observed distribution of BMI categories and stage, the study had 80% power to detect an odds ratio of approximately 2.5 for the advanced stage, comparing obese to non-obese patients, assuming a two-tailed alpha of 0.05.

Results

Sociodemographic and Anthropometric Characteristics

A total of 121 female patients with newly diagnosed breast cancer were enrolled during the study period. The anthropometric and sociodemographic features of the study population are shown in Table 1. The average age was 50.75 ± 11.02 years, with a median age of 50 and a range of 26-80 years. The majority of participants lived in cities (68, 56.2%) and were married (103, 85.1%).

Educational attainment varied considerably, with 12 (9.9%) women being illiterate, while 35 (28.9%) had completed tertiary education. Notably, 100 (82.6%) women were employed, and only 21 (17.4%) were unemployed. The economic status was mainly rated to be accepted (63, 52.1) with lower numbers reporting middle (27, 22.3), poor (23, 19.0) and very good (8, 6.6).

Only a little more than half (62, 51.2%) owned their home.

In terms of BMI classification, 28 (23.1) women were normal weight, 37 (30.6) of them were

overweight, and 56 (46.3) were obese. This distribution suggests that three-quarters of the study population (76.9) were overweight or obese during the diagnosis of breast cancer.

Table 1: Anthropometric and sociodemographic information on the study population.

Variable	Mean $\pm$ SD	Median (Min.-Max.)
Age	50.75 $\pm$ 11.02	50 (26-80)
	Frequency	Percent
Marital status		
Single	18	14.9
Married	103	85.1
Residence		
Urban	68	56.2
Rural	53	43.8
Level of education		
Don't read and write	12	9.9
Primary school	13	10.7
Intermediate school	15	12.4
Secondary school	15	12.4
A graduate of technical institutes	31	25.6
Tertiary education	35	28.9
The job of the patient		
Employee	100	82.6
Unemployed	21	17.4
Economic state		
Very good	8	6.6
Middle	27	22.3
Accepted	63	52.1
Poor	23	19
Housing		
Owned	62	51.2
Rented	46	38
Others	13	10.7
BMI		
Normal (18.5-24.9 kg/m ²)	28	23.1
Overweight (25.0-29.9 kg/m ²)	37	30.6
Obese ($\geq$ 30.0 kg/m ²)	56	46.3
Total	121	100

Cancer-Relevant Medical History

Table 2 is a summary of reproductive history, comorbidities and family history of cancer. The median value of the number of pregnancies was 4 (range 0-15), where the mean was 4.22-2.91. The majority of women (99, 81.8) indicated that they had breastfed. Concerning the menopausal status, 52 (43.0%) women were postmenopausal and 69 (57.0) were premenopausal.

Medical comorbid conditions were chronic in 37 (30.6) women, and 84 (69.4) women reported having no chronic diseases. 30 (24.8) women had a positive family history of breast cancer, and 20 (16.5) had a family death as a result of breast malignancy. Twenty-eight (23.1) and 29 (24.0) women reported breast cancer in their friends or relatives and other malignancies in friends, respectively.

Table 2: Cancer-relevant medical history of the study population

Variable	Mean $\pm$ SD	Median (Min.-Max.)
Number of pregnancies	4.22 $\pm$ 2.91	4 (0-15)
Number of abortions	0.55 $\pm$ 1.02	0 (0-5)
	Frequency	Percent
Presence of lactation		

Yes	99	81.8
No	22	18.2
Menopausal status		
Postmenopausal	52	43
Premenopausal	69	57
Chronic disease		
Yes	37	30.6
No	84	69.4
Family history of breast cancer		
No	91	75.2
Yes	30	24.8
Family death due to breast malignancy		
No	101	83.5
Yes	20	16.5
Breast cancer in friends or relatives		
No	93	76.9
Yes	28	23.1
Any other malignancy in friends		
Yes	29	24
No	92	76
Total	121	100

Clinical Presentation and Tumour Characteristics

Table 3 shows the features of the history of the present and tumour appearance. The most frequent symptom on presentation was a breast mass alone, which was reported by 90 (74.4) women. Another 12 (9.9) had a mass accompanied by pain, and 19 (15.7) had other symptoms such as nipple discharge, skin changes or axillary masses.

Of the 26 (21.5) women, 75 (62.0) and 20 (16.5) had a tumour size of less than 2 cm, between 2 and 5 cm, and larger than 5 cm, respectively. Tumours were slightly more on the right hand (70, 57.9) than on the left hand (51, 42.1). The first consultation was done at private clinics (53.4% of 53 women) and in the public breast clinics (68.56.2-68.56.2% of 68 women).

The mean time from the first symptom to consultation was quite wide: 21 (17.4) women reported it and proceeded to visit the doctor within 1-7 days, 25 (20.7) within 1-4 weeks, and 75 (62.0) over one month. When questioned

about whether they felt that they had waited to seek care, 41 (33.9) people answered in the affirmative, and 80 (66.1) denied that they had delayed seeking care. Only a minority (21, 17.4) had tried medication before seeking consultation; this was usually antibiotics or anti-inflammatory drugs that were self-obtained.

In terms of beliefs about breast cancer, 100 (82.6) per cent of women believed that breast cancer is treatable, and 108 (89.3) per cent of the women said that they would still accept mastectomy in case it is recommended.

The metastasis of lymph nodes was found in 79 (65.3) women with no nodal involvement in 42 (34.7) women. At the time of diagnosis, local metastasis (skin involvement or chest wall involvement) was reported to occur in 30 (24.8) women and distant metastasis in 6 (5.0) women. Distribution of the patients indicated that a majority of the patients had Stage I disease: Stage I in 26 (21.5%), Stage II in 58 (47.9%), Stage III in 29 (24.0%), and Stage IV in 8 (6.6%).

Table 3: The present history of cancer among the study participants

Variable	Frequency	Percent
Presenting symptoms		
Mass	90	74.4
Mass and pain	12	9.9
Others	19	15.7
Size of mass		
Less than 2 cm	26	21.5
From 2 to 5 cm	75	62
More than 5 cm	20	16.5

Site of malignancy		
Right	70	57.9
Left	51	42.1
Site of first consultation		
Private clinic	53	43.8
Public breast clinic	68	56.2
Duration from first symptoms to consultation		
1-7 days	21	17.4
1-4 weeks	25	20.7
One or more months	75	62
Does she think she is delayed?		
Yes	41	33.9
No	80	66.1
Did she try medication?		
Yes	21	17.4
No	100	82.6
Do you think breast cancer is curable?		
Yes	100	82.6
No	21	17.4
Accept mastectomy?		
Yes	108	89.3
No	13	10.7
Lymph node metastasis		
Yes	79	65.3
No	42	34.7
Local metastasis		
Yes	30	24.8
No	91	75.2
Distant spread		
Yes	6	5
No	115	95
Stage of the disease		
Stage I	26	21.5
Stage II	58	47.9
Stage III	29	24
Stage IV	8	6.6

Age Distribution by Disease Stage

The age distribution in the various stages of the disease is shown in Table 4. The mean age also rose and rose with increasing stage: Stage I (49.65±8.48 years), Stage II (50.17±10.54 years), Stage III (51.03±13.30 years), and Stage

IV (57.50±12.48 years). The Kruskal-Wallis test showed that there was no statistically significant age difference in different stages ($p=0.382$), which showed that age did not play a significant role in disease stage in this cohort.

Table 4: Age distribution by stage of disease

Stage of the disease		Age (years)
Stage I	F	26
	Mean	49.65
	Median	49.5
	SD	8.476
	Min	36
	Max	71
Stage II	F	58
	Mean	50.17
	Median	50

Stage III	SD	10.535
	Min	26
	Max	80
	F	29
	Mean	51.03
Stage IV	Median	53
	SD	13.295
	Min	26
	Max	75
	F	8
P-value*	Mean	57.5
	Median	53.5
	SD	12.479
	Min	43
	Max	80
P-value*		0.382
*Kruskal-Wallis Test		

Association Between BMI and Disease Stage

Table 5 examines the relationship between BMI category and disease stage. Among normal-weight women (n=28), stage distribution was: Stage I (8, 30.8%), Stage II (15, 25.9%), Stage III (5, 17.2%), and Stage IV (0, 0.0%). Overweight women (n=37) showed: Stage I (8, 30.8%), Stage II (14, 24.1%), Stage III (12, 41.4%), and Stage IV (3, 37.5%). Obese women (n=56) demonstrated: Stage I (10, 38.5%), Stage II (29,

50.0%), Stage III (12, 41.4%), and Stage IV (5, 62.5%).

Importantly, out of the eight patients with Stage IV, five (62.5) patients were obese, two (25.0) patients were overweight, and none were of normal weight. Nonetheless, the exact test by Fisher did not show a statistically significant correlation between the BMI category and stage of the disease (p=0.392), which means that the identified distribution might have been observed due to chance.

Table 5: BMI category by stage of disease

BMI category	Stage I	Stage II	Stage III	Stage IV	Total	P-value
Normal	8 30.80%	15 25.90%	5 17.20%	0 0.00%	28 23.10%	0.392*
Overweight	8 30.80%	14 24.10%	12 41.40%	3 37.50%	37 30.60%	
Obese	10 38.50%	29 50.00%	12 41.40%	5 62.50%	56 46.30%	
Total	26 100.00%	58 100.00%	29 100.00%	8 100.00%	121 100.00%	

*Fisher's Exact Test

Association Between Tumour Size and Disease Stage

As shown in Table 6, tumour size and disease stage show a statistically significant association (p<0.0001, Fisher's exact test). Among tumours less than 2 cm (n=26), most of the tumours were of Stage I (15, 57.7%), then followed by Stage II (7, 12.1%), Stage III (3, 10.3%), and Stage IV (1, 12.5%). Stage II (45, 77.6%), Stage III (16, 55.2%), Stage I (10, 38.5%), and Stage IV (4, 50.0%) had

the highest percentage of tumours in Stage II, Stage III, Stage I and Stage IV, respectively (n=75). Stage III (10, 34.5% and 3, 37.5%) and Stage IV (3, 37.5% and 1, 3.8%) were most common, with Stage III (n=20), followed by Stage II (n=6), and Stage I (n=1). This trend supports the fact that the size of the tumour during presentation is highly linked to the higher level of the disease.

Table 6: Tumour size by stage of disease

Tumour size	Stage I	Stage II	Stage III	Stage IV	Total	P-value*
<2 cm	15 57.70%	7 12.10%	3 10.30%	1 12.50%	26 21.50%	<0.0001

2-5 cm	10	45	16	4	75
	38.50%	77.60%	55.20%	50.00%	62.00%
>5 cm	1	6	10	3	20
	3.80%	10.30%	34.50%	37.50%	16.50%
Total	26	58	29	8	121
	100.00%	100.00%	100.00%	100.00%	100.00%

*Fisher's Exact Test

Association Between Menopausal Status and Disease Stage

Table 7 evaluates the connection between disease stage and menopausal status. In postmenopausal women (n=52), the distribution of the stages was the following: Stage I (10, 38.5%), Stage II (27, 46.6%), Stage III (13, 44.8%), and Stage IV (2, 25.0%). In

premenopausal women (n=69), the distribution was: Stage I (16, 61.5%), Stage II (31, 53.4%), Stage III (16, 55.2%), and Stage IV (6, 75.0%). The exact test by Fisher showed no statistically significant relationships between the menopausal status and the stage of the disease (p=0.7).

Table 7: Menopausal status by stage of disease

Menopausal status	Stage I	Stage II	Stage III	Stage IV	Total	P-value*
Postmenopausal	10	27	13	2	52	0.7
	38.50%	46.60%	44.80%	25.00%	43.00%	
Premenopausal	16	31	16	6	69	57.00%
	61.50%	53.40%	55.20%	75.00%	57.00%	
Total	26	58	29	8	121	100.00%
	100.00%	100.00%	100.00%	100.00%	100.00%	

*Fisher's Exact Test

Multivariable Analysis of Factors Associated with Advanced Stage

The binary logistic regression was done to control for possible confounding by taking the advanced stage (Stage III/IV) as the dependent variable. Table 8 shows adjusted odds ratios of factors that are related to advanced stage at presentation.

Adjusted with age, menopause and tumour size, BMI category was not significant. The adjusted odds ratio of advanced stage in overweight and obese women was 1.18 (95% CI 0.41-3.40, p=0.762) and 1.42 (95% CI 0.51-3.96, p=0.502), respectively, as compared to normal-weight

women. Age, premenopausal status was not significantly linked with advanced stage compared with post menopausal status (OR 1.53, 95% CI 0.65-3.62, p=0.331).

The only notable independent predictor of advanced stage was the size of the tumour. The adjusted odds ratio of advanced stage with a tumour size below 2 cm, 2-5 cm, and above 5 cm was 4.55 (95% CI 1.56-13.25, p=0.005), 26.32 (95% CI 5.92-117.01, p<0.0001), respectively. These results validate the fact that presentation tumour size is the predominant factor that is linked with disease stage, regardless of the presence of BMI and other covariates.

Table 8: Multivariate logistic regression estimates of factors that are related to advanced stage (Stage III/IV)

Variable	Adjusted Odds Ratio	95% Confidence Interval	P-value
Age (per year)	1.02	0.98-1.06	0.385
Menopausal status			
Postmenopausal	Reference		
Premenopausal	1.53	0.65-3.62	0.331
BMI category			
Normal weight	Reference		
Overweight	1.18	0.41-3.40	0.762
Obese	1.42	0.51-3.96	0.502
Tumour size			
<2 cm	Reference		
2-5 cm	4.55	1.56-13.25	0.005
>5 cm	26.32	5.92-117.01	<0.0001

Hosmer-Lemeshow goodness-of-fit test: $\chi^2=6.24$, df=8, p=0.620

Discussion

This is a prospective cohort study of 121 women with breast cancer diagnoses in Basrah, Iraq, that showed a very high number (76.9) of overweight and obese women who were previously diagnosed with breast cancer, which is in line with current trends in the world where the prevalence of obesity is increasing, and it may affect the epidemiology of breast cancer (12). The main result, that the adiposity type did not significantly correlate with the stage of disease presentation after the multivariate correction, adds to the current debate on the connection between the adiposity levels and the severity of breast cancer.

The fact that 62.5 per cent of the stage IV patients were obese, with 37.5 per cent being overweight and none of them normal weight, at first indicates the likelihood of the existence of a correlation between an increased BMI and a more advanced disease. Nevertheless, there is no statistical significance ($p=0.392$) and the non-association of the same after multivariate adjustment, which suggests that this effect could be due to the high background prevalence of obesity in the population of the study and is not necessarily biological. This observation has corroborated several recent reports, which have found no null relationships between BMI and breast cancer stage following proper confounder adjustment (13, 14).

Interpretation of Findings in the Context of Existing Literature

There has been extensive research on the relationship between BMI and the stage of breast cancer, with contradicting findings. According to a large meta-analysis by Liu et al. (15), obesity was found to increase the risk of advanced diagnosis by 30%, especially in postmenopausal women. Nonetheless, such an association subsided once tumour characteristics and factors of access to healthcare were incorporated. Conversely, the study of the relationship between obesity and the poorer outcomes was found by GC-Estévez et al. (16) to be not the same in all populations, indicating that genetic background, healthcare systems, and the definition of obesity might have affected the results.

Since tumour size is the leading predictor of stage (adjusted OR 26.32, tumours larger than 5 cm versus tumours smaller than 2 cm) is biologically plausible and is expected to occur in clinical results, since tumour size directly impacts the T staging of the TNM system. The positive correlation is also a good control that ensures that our staging methodology and statistical methodology are valid (17).

There is no significance between the status of menopause and the stage ($p=0.7$), which is not in line with studies that have indicated premenopausal women present with advanced disease (18). This could, however, be due to the relatively young age of our cohort (mean 50.8 years) and equal distribution of the premenopausal (57%) and postmenopausal (43%). Pizzato et al. (19) also found similar results in the EPIC cohort, menopausal effects of stage depending on tumour subtype and not equally observed across European populations.

Occupational and Educational Observations

The most interesting was that the number of employed women (82.6%), and women with higher education (54.5% with technical institute or tertiary education) was high among our breast cancer cohort. Although this could indicate the relation between socioeconomic status and the risk of breast cancer, other reasons should be taken into account. Working and educated women also could be more health-aware and seek medical care earlier, which could result in a higher incidence being detected and not actually increased (20). Other researchers have reported similar trends in South Africa (21) and Canada (22), where occupational determinants and education level affected the rate of breast cancer diagnosis by processes such as access to screening, health literacy and on-job exposures. The fact that the median time between the onset of the symptoms and the consultation was over one month in 62 per cent of patients indicates the existence of serious waiting times in seeking medical attention, even though the level of education is rather high. Such a paradox, learned women with significant delays, implies that knowledge is not enough to encourage women to seek care in time, and that psychosocial, cultural, and health system obstacles can also carry the same weight (23). Similar results were indicated by Jiang et al. (24), who found that education was a predictor of breast cancer incidence and not stage at diagnosis in a Chinese cohort, suggesting that the education-stage relationship is moderated by many other factors that were not health knowledge.

Biological Mechanisms and Complexities

The fact that our study did not find a direct association between BMI stage and breast cancer development does not rule out the already existing biological connections between adiposity and breast cancer development. Obese adipose tissue releases inflammatory cytokines such as interleukin-6, tumour necrosis factor-alpha, and leptin and releases less adiponectin that produces a pro-inflammatory, pro-angiogenic

microenvironment capable of supporting tumour growth and metastasis (25). The fact that the aromatase activity is present in adipose tissue means that obese women have elevated levels of circulating oestrogen, which can encourage hormone receptor-positive tumours (26).

These biological impacts, however, might not reflect in a simple linear correlation between the BMI and stage at presentation due to several reasons. To begin with, BMI is not a perfect way of assessing adiposity since it does not differentiate between subcutaneous and visceral fat, which possess different metabolic phenotypes (27). Second, it is important how weight gain occurs concerning the diagnosis of cancer; weight loss in the recent past because of cancer cachexia may be incorrectly classified as normal weight in previously obese women (28). Third, the relationship itself can be altered by tumour biology, in which obesity can have more effects on certain subtypes (e.g., hormone receptor-positive, luminal tumours) than others (29).

Strengths and Limitations

There are a number of strengths in this research. The prospective design meant a systematic collection of data at presentation, thus reducing the chances of recall bias. Trained personnel measured the anthropometric data using standardised procedures without the use of self-reported weight and height. Staging Multidisciplinary teams made sure that AJCC criteria were applied consistently. The sample size of the two large referral centres further increases the generalisability of the sample to the rest of the Basrah population.

Nevertheless, several significant shortcomings should be noted when these results are considered. To start with, 121 patients were not a big sample due to which statistical power was constrained regarding subgroup analyses, and it might have been too small to reveal significant but modest correlations between BMI and stage. The post-hoc power analysis showed that the study was powered to identify relatively large effects ($OR \geq 2.5$) and thus smaller but clinically significant associations could have been missed (type II error).

Second, tumour receptor (ER, PR, HER2) and histologic grade were not available to be analysed. These are key effect modifiers in the obesity-breast cancer interaction, where hormone receptor-positive tumours are mostly affected by the hormone receptor-related hormones and inflammatory processes triggered by obesity (30). The lack of these data makes it impossible to perform stratified analyses that could reveal associations hidden in the general cohort.

Third, the cross-sectional aspect of the measurement of BMI at the time of presentation does not allow for differentiating between long-standing obesity and those that are due to weight changes. It is also possible that patients have been experiencing weight loss because of the symptoms of cancer before presentation, and that this may bias associations to the null (31). Fourth, unmeasured confounding factors such as physical activity, diet, and detailed reproductive history might also have been residual confounding factors.

Fifth, it was done at two hospitals in one city in Iraq, and this may not be generalisable to other regions where ethnic makeup is different, lifestyle is different, and access to healthcare varies. Sixth, body fat distribution was not examined as there were no measures of central adiposity or waist circumference, which could be more important to breast cancer biology compared to overall BMI (32).

Implications for Clinical Practice and Future Research

Notwithstanding these shortcomings, there are a number of implications to our findings. The obesity rate among breast cancer patients is also high in Iraq and other similar countries, which is why clinicians and healthcare professionals in the mentioned area need to value and promote the use of weight management as a form of holistic treatment of the specified disease. Nevertheless, BMI is not correlated with the stage, which is an indication that every woman, irrespective of body size, needs the same attention when it comes to the screening of breast cancer and early detection.

The close relation between the size of the tumour and stage illustrates the extreme significance of early diagnosis. The very long wait times to care observed in this cohort (62% waits more than 1 month) are a target that can be addressed using public health interventions. The educational campaigns are not to create awareness on breast cancer alone, but also the obstacles to healthcare seeking promptly; such barriers may be in the form of fear, stigma, and logistical factors (33).

The weaknesses of this study should be overcome in future research by employing larger, multi-centre prospective cohorts with extensive data collection of tumour receptor status, histologic grade and a measure of central adiposity (waist circumference, waist-hip ratio). Literature on research in the Middle East and North Africa region is still underrepresented in the world literature, even though the incidence of breast cancer is increasing, and these populations have some unique aspects (34). The sample size of a sufficiently powered subgroup

analysis could be achieved through collaborative networks in the Iraqi governorates.

Study Limitations and Future Directions

Several limitations are to be considered in detail to inform the interpretation and future research. The lack of tumour subtype results is the greatest drawback since the biological pathways between obesity and breast cancer vary fundamentally between hormone receptor-positive and -negative tumours (35). Obese women with breast cancer that has hormone receptors would be able to exhibit higher stages of the disease as a result of the tumour promotion by oestrogen, and no relationship would have been anticipated between triple-positive or HER2-positive tumours. The key aspect in future research should be to collect complete receptor status data to facilitate biologically meaningful analysis. Another methodological issue is the time of BMI measurement. The weight at the time of cancer diagnosis might be unrelated to adiposity before the disease, and, specifically, in patients with symptomatic tumours leading to weight loss or poor appetite. Ideally, it is preferable to get pre-diagnosis records of weight or to get detailed records of weight history, but this is not feasible in normal clinical practice. The introduction of maximum lifetime weight or weight at age 18-20 years could be more successful in terms of long-term exposure to obesity, which is important to breast carcinogenesis (36).

The absence of information on physical activities and eating is an opportunity cost to investigate behavioural variables that can change the relationship between obesity and cancer. Exercise has direct impacts on the risk and prognosis of breast cancer that can be connected to the following mechanisms: insulin sensitivity, decreased inflammation, and an increase in immunity (37). The future research must include the validated questionnaires to evaluate the lifetime and recent physical activity, and diet patterns through the regionally applicable food frequency questionnaires.

The future research designs should prioritise central adiposity measures. Visceral fat is captured in the waist circumference and waist-to-hip ratio and is metabolically more active than subcutaneous fat and is more closely linked to insulin resistance, inflammation and hormonal dysregulation (38). There is a growing body of evidence indicating that such measures can potentially do better than BMI at predicting the outcomes of breast cancer, especially in a population in which BMI distribution is not equal to that of Western cohorts (39).

Iraq has a complex healthcare system setting that has both challenges and opportunities for the research of breast cancer. The study period of

two years was in line with the prevailing economic and infrastructural issues that could have influenced access to healthcare and diagnostic delays. Future research ought to be systematic in evaluating the factors of the healthcare system, such as the distance to the treatment centres, the time to travel, and the out-of-pocket costs, which could be significant determinants of the stage at presentation without necessarily involving individual patient factors (40).

Lastly, qualitative studies on the causes of diagnostic delay in Iraqi women would potentially inform interventions that would be culturally sensitive. The interaction of knowledge, beliefs, fear, family life, and navigation of the healthcare system would add to quantitative results and inform the development of strategies in the field of public health based on the local situation (41).

Conclusion

This Basrah, Iraq-based prospective cohort study of 121 women diagnosed with breast cancer revealed that although obesity was very prevalent (46.3) among the patients, the category of BMI was not significantly correlated with the stage of the disease at presentation when adjusted with tumour size and other covariates. The most satisfactory predictor of the stage was the tumour size, with the larger the tumour size, the higher the likelihood of advanced disease, with tumours greater than 5 cm having 26-fold higher odds than those less than 2 cm. Prolonged delays towards seeking care were also common, with 62% of women taking more than one month to see any doctor after the development of signs and symptoms.

The findings indicate that the BMI might not be adequate to reflect the complicated association based on adiposity and breast cancer biology in the absence of tumour receptor status data. The prevalence of obesity in this group justifies the relevance of weight management in preventing breast cancer and in general health, and the high tumour size-stage correlation justifies the urgency of early detection efforts. Further studies in the Iraqi and other regional populations must include adiposity measurements such as the waist circumference, full characterisation of tumours, their receptor status, and measurement of the healthcare system factors that may lead to delayed diagnosis. There is a need to conduct multicentre collaborative studies with sufficient participant numbers to help unravel the complicated relationship between body composition, tumour biology and breast cancer outcomes in this underresearched population.

List of Abbreviations

AJCC: American Joint Committee on Cancer

ANOVA: Analysis of Variance

BMI: Body Mass Index

CI: Confidence Interval

CT: Computed Tomography

Df: Degrees of Freedom

ER: Oestrogen Receptor

HER2: Human Epidermal Growth Factor Receptor 2

HRT: Hormone Replacement Therapy

IRB: Institutional Review Board

MDT: Multi-Disciplinary Team

MeSH: Medical Subject Headings

OR: Odds Ratio

PR: Progesterone Receptor

SD: Standard Deviation

SPSS: Statistical Package for Social Sciences

TNM: Tumour, Node, Metastasis

WHO: World Health Organisation

Declarations

Ethics Approval and Consent to Participate

The University of Basrah's College of Medicine's Research Ethics Committee accepted the study, which was conducted in accordance with the Declaration of Helsinki (reference number: 45/2020, approved November 15, 2020). Before enrollment, written consent was obtained from each participant. The right to withdraw at any moment without having an impact on their clinical care was explained to the participants. Before analysis, all data were anonymised by substituting distinct study numbers for personal identifiers.

Consent for Publication

The final paper has been reviewed by all authors, who have approved its publication. The Creative Commons Attribution Non-Commercial 4.0 license is used to publish the work.

Data Availability

The corresponding author can provide the datasets created and examined for this study upon reasonable request. Data are stored at the College of Medicine, University of Basrah, and will be shared with qualified researchers following institutional data sharing policies and with appropriate ethical approvals.

Competing Interests

The writers affirm that they have no conflicting interests. There are no recognised financial or non-financial interests that could affect the work presented in this manuscript.

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Author Contributions

KAZ: Conceptualisation, Methodology, Investigation, Writing – Original Draft, Supervision, Project administration

AMZA: Investigation, Data Curation, Formal Analysis, Writing – Review & Editing, Validation, Resources

All authors read and approved the final manuscript.

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