Incidence and clinicopathological characteristics of breast cancer patients from a single center study

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ABSTRACT

Chronic diseases may be associated with adverse clinical characteristics of breast cancer outcomes. This study determined the descriptive association of some chronic diseases and clinicopathological characteristics of breast cancer patients in women diagnosed in a single center in Jeddah, KSA. Retrospective data of 196 patients diagnosed with breast cancer (from 2015-2021) was analyzed. Demographics, patients' health conditions, and tumor properties were investigated. Most women diagnosed with breast cancer were 40-69 years of age. Women with a body mass index (BMI) classification of overweight/obese were extremely significantly more than those who were classified as lean. The tumors reported show that a significant number of samples (87.0%) had tumors between T1 and T2. Significantly more tumors (61.0%) were of grade V, and ~81.0% were histopathologically classified as invasive ductal carcinoma. A significant majority of breast cancers in this population were human epidermal growth factor receptor 2 negative (70%), progesterone receptor positive (58%), and non-triple negative (~93%). In these patients, a BMI classification of overweight/obese is possibly associated with breast cancer. Awareness and knowledge about the correlation of breast cancer with obesity may help to reduce or delay its presence.

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Introduction

Breast cancer is the most common form of cancer and is the leading cause of death from cancer in women globally. In 2020, there were roughly 2.3 million new instances of breast cancer and 685,000 breast cancer deaths worldwide. Interestingly, its prevalence and fatality rates differed per country.[1] Between January 1 and December 31, 2018, the total number of newly diagnosed cancer cases reported to the Saudi Cancer Registry was 20,131, of which 15,933 cases were reported in Saudi nationals and 8840 (56.4%) were reported in Saudi women. Breast cancer was the most prevalent type of cancer in Saudi females, with 2814 diagnosed cases representing 17.7% of all cancer types in Saudi Arabia and 31.8% of all cancer types in Saudi Arabian women. Most cases were diagnosed among women between 45 and 59 years of age (40.6%). In the Makkah region, 32% of all cancer cases (2288) were due to breast cancer, ranking it as the leading type of cancer. In fact, the Makkah region was the third of the highest five regions with an age-standardized rate of 36.9 cases per 100,000. The median age at diagnosis was 51 years and ranged from 17 to 99.[2]

Breast cancer is a complicated disease caused by a mixture of genetic variations and environmental risk factors. Variance in clinical outcomes, histopathologic appearance, and molecular abnormalities signify its diversity, its subtypes, and its different etiologies.[3]

Women who are diagnosed with breast cancer often share several characteristics, such as the age of cancer onset, age of menarche and menopause, family history of breast cancer, lifestyle choices, and use of oral contraceptives.[4,5] Nonetheless, these factors manifest differently in

various groups of women where specific lifestyle patterns and socioeconomic factors have been linked to an increased risk of breast cancer. Accordingly, from the perspective of epidemiological research, examining the most common risk factors in a particular group of women can provide guidance in breast cancer prevention.[5]

Numerous studies examined the role of diabetes, hypertension, and obesity in increasing the risk of breast cancer, while other studies investigated the poor prognosis and decreased survival of breast cancer in premenopausal or postmenopausal patients.[6,7] More specifically, studies show that obesity increases the risk of the occurrence of breast cancer and lowers the survival rate once diagnosed.[8] Furthermore, postmenopausal women who have elevated body mass index (BMI) scores have a higher chance of developing hormone receptor-positive breast cancer.[9,10]

About 15% of all invasive breast cancers have the triple-negative immunophenotype, which is defined as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER) 2 negative.[11]

According to a study by Yang *et al*., breast cancer can be classified into several molecular subtypes based on gene expression profiling analysis.[12] These subtypes are then confirmed by a panel of immunohistochemical (IHC) markers, which include cytokeratins 5/6, PR, HER2, proliferation marker Ki-67, and epidermal growth factor receptor. This study shows that molecular subtypes identified in expression studies, suggesting etiologic and heterogeneity of breast cancer may have a differing effect on breast cancer risk factors.[12] Accordingly, HER2, PR, and ER are among several prognostic and predictive biomarkers that have been endorsed and are presently used in routine clinical practice in the diagnosis, categorization, and decision regarding the treatment of breast cancer.[13] More importantly, the use of such biomarkers can shed light on the factors affecting the patterns of the different subclasses of breast cancer. For example, the most aggressive forms of breast cancer are labeled as "triple-negative" for the molecular presence of ER, PR, and HER2 on its cells when evaluated using IHC.[11]

Thus, a better understanding of specific factors that are distinctive to breast cancer patients in the city of Jeddah allows for enhancement in the application of preventive strategies and enhanced clinical decision-making. So, this study investigates the incidence, specific factors in patients, and clinicopathological characteristics of breast cancer in women from Jeddah city.

Materials and Methods

Study design and data collection

This is a retrospective single-center study of 196 patients diagnosed with breast cancer as the only inclusion criterion. All consecutive data between the years of 2015 and 2021 was collected from records of King Abdulaziz University Hospital. The study aims to describe various factors, including demographics, conditions, and tumor properties in breast cancer patients in Jeddah. Demographic data consisted of age, nationality, and marital status; conditions consisted of the presence of diabetes, hypertension, heart disease, lung disease, and BMI; and tumor properties consisted of its size, location, grade, histopathology classification, number of lymph nodes, and IHC markers (HER2, PR, and ER).

Statistical analysis

Chi-Squared goodness-of-fit was used to produce descriptive statistics of sample demographics and evaluate multiple response questions where applicable, followed by post hoc examination using data partitioning. The squared test for association and Fisher's exact tests were used to evaluate multiple variables, while Cramer's V or φ and Kindall's tau values were used to express the strength of the association.

Results

Descriptive statistics show that gender, age, and marital status significantly deviated from equal distribution. Here we note that most women diagnosed with breast cancer in the study ranged in age between 40 and 69 ($p<0.001$), married ($p<0.001$), and of Saudi Arabian nationality ($p<0.001$) (Table 1). Descriptive statistical exploration of conditions possibly associated with breast cancer, namely diabetes, hypertension, heart disease, or lung disease, revealed no significant associations. However, the frequency of women with a BMI classification of overweight or obese was extremely significantly higher than those who were classified as lean ($p<0.001$) (Table 2).

Analysis of the tumors reported in this study shows that a significant number of samples, nearly 87%, had tumors that ranged between T1 and T2 ($p<0.001$) and were equally located in the left or right breast, 51% and 47.4%, respectively. Significantly more tumors, 61%, were of grade V and nearly

Table 1. Descriptive analysis of demographics.

Descriptive	Classification	n (%)	X^2 score
Age	20-39 years old	25 (12.8)	176.83***
	40-69 years old	**153 (78.1)**[f]	
	Above 70 years old	18 (9.2)	
Marital status	Married	**159 (87.8)**	103.70***
	Unmarried	22 (12.2)	
Saudi national	No	74 (37.8)	11.76***
	Yes	**122 (62.2)**	

Numbers in bold indicate a significantly higher-than-expected frequency; [f]significant in *post hoc* analysis of data using partitioned Chi-squared test at a Bonferroni-adjusted α; ***extreme significant difference from a normal distribution.

81% were histopathologically classified as invasive-ductal carcinoma (IDC) ($p<0.001$). Furthermore, nearly 76% of women had 1 to 3 lymph nodes ($p<0.001$). A significant majority of breast cancer patients in this population, nearly 70%, tested negative for the presence of HER2 ($p<0.001$), 58% of the patients tested positive for PR ($p<0.05$), and fortunately 93% of the patients tested negative for all three markers ($p<0.001$) (non-triple negative) (Table 3).

Discussion

Although the population of women in the Makkah region is largely diverse, breast cancer is one of the most prevalent types of cancer among them and in Saudi Arabia.[14] It is important to identify the possible determining factors of breast cancer in this region. Jeddah is one of the main cities in this region and the most populous, and so was selected to be the source of a sample to represent breast cancer cases in this population.

Analysis of demographics in this study shows that age and marital status significantly deviated from an equal distribution. The women diagnosed with breast cancer included in the study were between 40 and 69 years old, married, and of Saudi Arabian nationality.

Interestingly, a study completed in the city of Makkah that investigated breast cancer in Saudi Arabian women concluded that age, marital status, family history, parity, age at first full-term pregnancy, menopausal status, breastfeeding, and BMI played an important role in the development of breast cancer. Their study also indicated that most breast cancer cases were

Table 2. Descriptive analysis of conditions.

Descriptive	Classification	n (%)	X^2 score
BMI	Lean	33 (17.0)	84.45***
	Overweight/obese	**161 (83.0)**	
Diabetes	No	**143 (73)**	41.32***
	Yes	53 (27)	
Hypertension	No	**158 (80.6)**	73.47***
	Yes	38 (19.4)	
Heart disease	No	**194 (99)**	188.08***
	Yes	2 (1)	
Lung disease	No	**193 (98.5)**	184.18***
	Yes	3 (1.5)	

BMI, body mass index. Numbers in bold indicate a significantly higher-than-expected frequency; ***extreme significant difference from a normal distribution.

Table 3. Descriptive analysis of tumor properties.

Descriptive	Classification	n (%)	X^2 score
Size	T1	**76 (43.2)**[ǂ]	94.73***
	T2	**76 (43.2)**[ǂ]	
	T3	18 (10.2)	
	T4	6 (3.4)	
Location	Left	**99 (51.0)**[ǂǂ]	88.59***
	Right	**92 (47.4)**	
	Bilateral	3 (1.5)	
Grade	IV	76 (39.0)	9.48**
	V	**119 (61.0)**	
Histopathology classification	IDC	**144 (80.9)**[ǂ]	182.44***
	Lobular	23 (12.9)	
	Papillary	11 (6.2)	
Number of lymph nodes	1-3	**138 (75.8)**[ǂ]	161.06***
	4-9	42 (23.1)	
	>10	2 (1.1)	
HER2 positive	No	**135 (69.9)**	30.72***
	Yes	58 (30.1)	
Estrogen receptor Positive	No	96 (50.3)	0.005NS
	Yes	95 (49.7)	
Progesterone receptor positive	No	79 (42.0.)	4.79*
	Yes	**109 (58.0)**	
Triple negative	No	**182 (92.9)**	144.00***
	Yes	14 (7.1)	

HER2, human epidermal growth factor receptor 2. Numbers in bold indicate a significantly higher than expected frequency; [ǂ]significant in *post hoc* analysis of data using partitioned Chi-squared test at a Bonferroni-adjusted α; [ǂǂ]although frequencies are significantly high in *post hoc* testing, it is not when the bilateral sample was excluded from the statistical test; ***extreme significant difference from a normal distribution; [NS]no significance.

found among women between 41 and 50, married, and with a BMI>30.[15]

Furthermore, a study by Bendardaf *et al.* examined the incidence and clinicopathological features of breast cancer in women from the Northern Emirates and found that only 20% of these women diagnosed with breast cancer were younger than 40 years.[16] Moreover, data from a study by Lara-Medina *et al*., analyzing data between the years 1998 and 2008, reported that the age at diagnosis of triple-negative breast cancer (TNBC) in Hispanic women in Mexico City was between 38 and 62 years.[17] Along with recent findings from this study and such results from other studies, geographically near or far from Jeddah, confirm that the wider age range for diagnosis of breast cancer is between 40 and 69 years. Accordingly, this age group must be the target for strong awareness campaigns and screening programs for an early diagnosis, treatment, and eventually a favorable prognosis.

In this study, statistical exploration of possible conditions associated with breast cancer, namely diabetes, hypertension, heart disease, or lung disease, revealed no significant associations. However, the frequency of women with a BMI classification of overweight or obese was of extreme significance more than those who were classified as lean.

According to a previous study that examined causes of breast cancer in women in the Makkah region of Saudi Arabia, obesity and breast cancer were significantly correlated ($p<0.05$). However similar to my findings, diabetes, hypertension, and hyperlipidemia did not affect the incidence of breast cancer.[14]

A study that examined the incidence and clinicopathological features of breast cancer in women from the Northern Emirates showed that 71.3% of breast cancer cases were overweight or obese, close to the prevalence obtained in my study (83%).[16] Such regional findings emphasize that increasing BMI may be strongly associated with the incidence of breast cancer. According to the study by Alshamsan *et al.*, the prevalence of obesity and excess weight in newly diagnosed non-metastatic breast cancer patients aged over 40 years (59.1%) was higher than that of younger Saudi women (41.6%).[18] When compared to non-obese patients, obese patients had lower rates of HER2+ breast cancer and were more likely to be over 40 years old. In the same study, HER+ status, obesity, and lack of screening for breast cancer were independent predictors of advanced-stage presentation.[19]

A study investigated the prognostic impact of diabetes and obesity on the prognosis of early-stage breast cancer by factorially categorizing patients into four groups based on the presence or absence of the two conditions. Obese patients with diabetes had larger tumors at diagnosis (more than 2 cm), were older, and had worse outcomes overall. These findings suggest that metabolic health influences the prognosis of patients and may be affected by early breast cancer.[20] Furthermore, individuals with diabetes have a higher risk of developing cancer than the general population, a higher incidence of breast cancer, and a higher mortality rate.[21] In fact, women with type 2 diabetes have a marginally elevated risk of breast cancer. Organs with high levels of ER, such as the breasts, the endometrium, and the ovaries, are more susceptible to cancer when there is a decreased level of estrogen due to insulin resistance. Healthcare professionals can investigate ways to support improved screening and lifestyle modifications to reduce the mitogenic effects of insulin-like growth factors by being aware of these relationships.[21]

A study conducted in Louisiana looked at the relationship between diabetes and obesity and the state's incidence of breast cancer. The data came from primary invasive breast cancer records found in the Tumor Registry between 2010 and 2015. The results of the study showed that diabetes and obesity are separate risk factors for breast cancer and that luminal A breast cancer was also linked to patients being overweight. In subgroup analyses, diabetes was linked to an increased risk for TNBC and for luminal A breast cancer in women ≥50 years of age. Further, obesity and diabetes have been found to be risk factors for breast cancer; these findings highlight the complexity and potential variation in comorbid risk by molecular subtype of the condition. In fact, diabetes was found to be significantly correlated with the incidence of HER2+ breast cancer, TNBC, and luminal A breast cancer in Louisiana.[19] These findings support results from this study which show the correlation of overweight as a risk factor for breast cancer. While Hossain *et al*. found a significant correlation between diabetes and the incidence of HER2+ breast cancer, this may explain why outcomes of this study had no significant correlation between diabetes and breast cancer in the population as the majority of incidences were HER2-.

The correlation between disease characteristics and BMI and its outcomes in women with non-metastatic breast cancer was determined in Saudi Arabia by Alshamsan *et al*. Their analysis showed that patients over 40 years of age had a higher obesity rate (59.1% *versus* 41.6%; $p<0.001$). Although being over 40 years old was a risk factor for obesity on its own, age, however, did not correlate with a more advanced clinical stage. In fact, regardless of age or menopausal status, advanced tumor stage III *versus* stage I/II was more strongly associated with obesity.[18] The findings by Alshamsan *et al.* match the results from this research, which looked at the association of breast cancer between obesity and the advanced stage more than stage I/II within Saudi women in Jeddah city aged 40 years and over regardless of menopausal status.

Stead *et al.* examined the clinical and pathologic features of breast cancers in an unselected series of patients from a tertiary care hospital serving a diverse population.[22] The study focused on TNBC and was conducted on female patients with invasive breast cancer diagnosed between 1998 and 2006. According to the study, black women of diverse backgrounds, regardless of age or BMI, have three-times as many triple-negative tumors as non-black women.[22] Additionally, black women's poorer prognosis for breast cancer is probably due in part to the higher prevalence of TNBC tumors in black women across all age and weight categories. When considering all patients, the percentage of TNBC tumors dropped as BMI rose.[22] Therefore, these findings, along with data from this study, may help to further explain the relationship between a higher BMI and a decrease in the proportion of TNBC tumors in Jeddah. The reason for this is that my data only shows 7% of TNBC out of all the cases in the study, whereas TNBC generally accounts for 10-15% of all breast cancer cases.[23,24]

A study by Bendardaf *et al*. investigated the incidence of breast cancer in women from the Northern Emirates, taking into account patient-specific factors such as clinicopathological features.[16] Their findings demonstrated that IDC accounted for approximately 84% of all cases of breast cancer in this study, and approximately 36.8% of women over 40 had HER2 overexpressing tumors. In addition, approximately 80% of breast cancer cases in this population tested negatively

for the expression of HER2 on their cells, 61% of the cases expressed PR on their cells, and nearly 65% of cases expressed ER on their cells.[16] These results are nearly the same as the findings of this study, which showed that the majority of breast cancer in the study population was HER2 negative, nearly 70%, PR positive, 58%, and non-triple negative, nearly 93%. This may clarify receptor status in overweight breast cancer in this region, which may help with early detection or treatment plans. In their study, interestingly, Bendardaf *et al.* conclude the mean age diagnosed with breast cancer women a decade younger than in developed countries.[16]

Moreover, Zekri *et al.* state that the purpose of their study was to evaluate the clinical features and prognoses of patients with HER2-positive disease as well as to ascertain the frequency of HER2 over-expression in newly diagnosed breast cancer patients in Saudi Arabia between 2007 and 2013 at 3 hospitals located in the country's three largest cities.[25] According to their findings, approximately 29.9% of breast cancer patients had overexpressed HER2, the median age at diagnosis was 46 years, 92.5% of Saudi patients were hormone receptor-negative, 42.4% had tumors in stage IV, and 13.1% of patients had these abnormalities. The most common pathology (92.9%) was infiltrating ductal carcinoma, with an average tumor size of 3.5±2.5 cm.

This study provided similar results to those of Zekri *et al.* regarding HER2 overexpression in breast cancer in one of the largest cities in Saudi Arabia, as the HER2 overexpression rate is about 30%, which is within the range reported in previous studies. Patient average tumor size in this study was significant between T1 and T2, which matches with the average tumor size of 3.5±2.5 cm in Zekri *et al*. Also, I found that IDC was the most common pathology (81%) compared to the other types which matches Zekri *et al*.'s findings.

A study conducted in Mexico City between 1998 and 2008 examined the risk factors and prevalence of TNBC among Hispanic women. They found that the median patient age at diagnosis (± standard deviation) was 50±12 years which is similar to studies done in Saudi Arabia with a mean age of 48.8±12.2 years.[17,26] These findings also align with the average age in this study. However, Hispanic women with breast cancer had a median age at diagnosis that was 11 years younger than average in the United States.[17] Compared to white women with breast cancer, the study population had a higher prevalence of TNBC.[17]

Moreover, the objective of the study by Alabdulkarim *et al*. was to investigate the demographics of patients who had surgery for breast cancer in Riyadh, Saudi Arabia between 2005 and 2012. In general, the patients in their study were younger than those in Western countries who had breast cancer. Nevertheless, in contrast to Western nations, being young was not linked to worse outcomes.[26] Additionally, the majority of patients (92.6%) had invasive disease, with an average tumor size of 3.4±2.4 cm at presentation, according to the findings regarding disease characteristics; only the size of the primary tumor was significantly correlated with recurrence. According to Alabdulkarim *et al*., the tumor size was 3 cm or T2. Given that large tumors increase the risk of lymph node invasion, their size may have played a role in the low percentage of stage I disease.[26] These findings align with the results of this study, which show that nearly 87%, had tumors that ranged between T1 and T2, and nearly 76% of women had 1 to 3 lymph nodes.

According to Alabdulkarim *et al*., generally, patients in our region had breast cancer at a younger age than those in Western countries.[26] Therefore, routine screening and early detection may contribute to minimizing the harmful effects and increasing the effectiveness of therapeutic strategy plans.

Conclusions

To conclude this study's findings, the average age of women diagnosed with breast cancer in Jeddah was between 40 and 69 years. Additionally, the BMI classification of these patients indicates that being overweight or obese is possibly linked with breast cancer. Moreover, HER2 negative and PR positive were the majority of breast cancer in this population, while 7% of non-triple negative breast cancer cases. So, this suggests that awareness and knowledge about the correlation of breast cancer with obesity may help to reduce or delay the presence of cases in the region.

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