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Assessment of Predictive Confounders for the Prevalence of Breast Cancer among Iraqi Population: A Retrospective Study from Baghdad, Iraq

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***Abstract*—**Although breast cancer prevalence continues to increase, mortality has been decreasing as a result of early detection and improvement in adjuvant systemic therapy. Nevertheless, this disease required further efforts to understand and identify the associated potential risk factors that could play a role in the prevalence of this malignancy among Iraqi women. The objective of this study was to assess the perception of certain predictive risk factors on the prevalence of breast cancer types among a sample of Iraqi women diagnosed with breast cancer. This was a retrospective observational study carried out at National Cancer Research Center in College of Medicine, Baghdad University from November 2017 to January 2018. Data of 100 patients with breast cancer whose biopsies examined in the National Cancer Research Center were included in this study. Data were collected to structure a detailed assessment regarding the patients' demographic, medical and cancer records. The majority of study participants (94%) suffered from ductal breast cancer with mean age 49.57 years. Among those women, 48.9% were obese with body mass index (BMI) 35 kg/m^2. 68.1% of them had positive family history of breast cancer and 66% had low parity. 40.4% had stage II ductal breast cancer followed by 25.5% with stage III. It was found that 59.6% and 68.1% had positive oestrogen receptor sensitivity and positive human epidermal growth factor (HER2/neu) receptor sensitivity respectively. In regard to the impact of prediction of certain variables on the incidence of ductal breast cancer, positive family history of breast cancer ($P < 0.0001$), low parity ($P< 0.0001$), stage I and II breast cancer ($P = 0.02$) and positive HER2/neu status ($P < 0.0001$) were significant predictive factors among the study participants. The results from this study provide relevant evidence for a significant positive and potential association between certain risk factors and the prevalence of breast cancer among Iraqi women.

***Keywords*—**Ductal breast cancer, hormone sensitivity, Iraq, risk factors.

I. Introduction

BREAST cancer is the most frequent malignancy among women worldwide and regarded as a second leading cause of cancer death in women after lung cancer [1]. Breast cancer prevalence continues to increase; however, mortality rate has been decreasing principally as a result of early detection and highly improvement in treatment options regarding adjuvant systemic therapy [2], [3]. This malignant tumour tends to arise from the glandular tissue of the breast [4]. Numerous etiological and risk factors contribute to this malignancy including increasing age, family history, obesity, exposure to radiation, early menarche, delay menopause and low parity [5]. Additionally, certain gene mutations particularly BRCA 1 and BRCA 2 genes can increase the risk of breast cancer, these mutations pass from parents to children [6], [7].

Breast cancer can be classified based on the tumour cells which can arise from mainly ductal and lobular cell carcinoma [8], [9].

Many different tumour markers have been characterized and are used for the differentiation and diagnosis of breast cancer [10]. These in clinical consideration are serum tumour markers including glycolytic enzymes such as LDH, milk proteins such as lactoalbumin and tissue tumour marker including hormone receptors such as ER or PR and oncoproteins such as HER-2 or CerbB-2 or neu [11], [12]. Furthermore, samples used are tumor tissue biopsy or body fluid (serum).

Breast cancer cells that receive signals from oestrogen and promote the growth of these cells are categorized as oestrogen receptor positive (ER+). Similarly if these cells receive signals from progesterone and promote its growth, they are categorized as progesterone receptor positive (PR+). This type of classification is of importance for the assessment of cancer prognosis, prediction and helps in deciding treatment options and response. Breast cancers diagnosed as hormone positive (ER positive and/or PR positive) are slightly slower growing and have a slightly better prognosis than hormone negative breast cancers (BCs) [13]-[15]. If the tumor is ER+ve and/or PR+ve, then the cancer can be treated with a hormone therapy [16]. For this reason, these tumors are also sometimes referred to as "hormone sensitive." Immunohistochemical assays (IHC) are used to detect oestrogen and progesterone tumour biomarkers which stain the nuclei of tumor cells if they express hormone receptors. They are directly applied on the cancer biopsy slides and read under light microscope [17]. The aim of this study was to explore and understand the perception of specific predictive confounding factors on the prevalence of BC types among a sample of Iraqi women diagnosed with BC in Baghdad, Iraq.

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II. Methods

A. Study Design

The study was designed as a retrospective; single-centre analysis. Patients were surveyed from November 2017 through January 2018. Approval of the study was granted from the Ethical Committee of College of Pharmacy-Mustansiriya University. The research was conducted at National Cancer Research Center in College of Medicine, Baghdad University, Baghdad Province, Iraq.

B. Participants and Data Collection

Women with BC diagnosis admitting during the aforementioned period to National Cancer Research Centre were recruited in this study. Women over the age of 18 years old, those with BC were included and used to estimate the sample size of this study, while those with missing enough clinical data were excluded. Data for each participant were extracted and used to structure a detailed assessment for the patients. The data included information related to baseline characteristics (age, education level categorized as primary; secondary or university level; smoking habits), clinical records (BMI, parity classified as low parity (less than 3) and multiparity (more than 3), family history of BC and previous medical conditions). Cancer related data were also collected and included (BC type whether ductal or lobular, cancer stage, receptor type whether oestrogen or progesterone, receptor status whether positive, negative or mixed, human epidermal growth factor 2-HER2/neu status whether positive or negative).

C. Statistical Analysis

The SPSS version 23 was used for statistical analysis. Descriptive analysis was used to describe the study population, and the results were expressed in numbers, percentages, means, and standard deviations. Association between categorical variables was assessed using either Chi-square or corrected Chi-square. The level of significance used for the statistical analysis was $P < 0.05$.

III. Results

Table I presents the baseline characteristics of the study participants based on the differences between the prevalence of BC (ductal and lobular). Of the recruited study participants who met the inclusion criteria of this study, 100 women with BC were identified. Regarding the baseline characteristics, mean age of the study participants was 49.58 ± 9.47 years. The majority of study participants (94%) suffered from ductal BC. All of the study participants (100%) reported no history of smoking and 44% had a secondary education level.

Regarding the clinical characteristics reported in this study, 48.9% of the ductal BC women were obese with BMI 35 kg/m^2, while 51.1% were overweight with BMI 27.09 kg/m^2. 68.1% of them had positive family history of BC and 89.4% had no previous medical conditions. In addition, 66% of the ductal BC women had low parity.

With regard to the cancer characteristics of women diagnosed with ductal BC, 40.4% had stage II BC followed by 25.5% with stage III. It was found that 59.6% had positive ER sensitivity. However, no considerable difference was observed for receptor status whether positive or negative regarding PR sensitivity (51% and 49%) respectively or mixed ER/PR sensitivity (51% and 49%) respectively (Table I). For HER2/neu status, 68.1% had positive receptor sensitivity (Table I).

TABLE I
Baseline Characteristics of Study Population Based on the Differences between the Prevalence of BC (Ductal and Lobular)

Variable	Ductal BC N=94	Lobular BC N=6
Age mean± SD (year)	49.57±9.7	49.67±5.24
BMI: 25–29.9 (Kg/m^2), (n,%)	27.09±1.6, 48 (51.1)	--------
BMI: ≥30 (Kg/m^2), (n,%)	35.0±3.8, 46 (48.9)	32.23±3.94, 6 (100)
Family history, (n,%)		
Yes	64 (68.1)	46 (100)
No	30 (31.9)	0
Medical Conditions, (n,%)		
Yes	10 (10.6)	0
No	84 (89.4)	0
Parity, (n,%)		
Low parity	62 (66)	4 (66.7)
Multiparity	32 (34)	2 (33.3)
BC Stage at Diagnosis, (n,%)		
Stage I	20 (21.3)	0
Stage II	38 (40.4)	2 (33.3)
Stage III	24 (25.5)	4 (66.7)
Stage IV	12 (12.8)	0
ER status, (n,%)		
6Positive	56 (59.6)	4 (66.7)
Negative	38 (40.4)	0
PR status, (n,%)		
Positive	48 (51)	4 (66.7)
Negative	46 (49)	0
ER/ PR status, (n,%)		
Positive	46 (49)	4 (66.7)
Negative	48 (51)	0
HER2/neu status, (n,%)		
Positive	64 (68.1)	4 (66.7)
Negative	30 (31.9)	0

TABLE II
Predictive Factors for the Prevalence of Ductal Breast Cancer

Predictive Variable	Ductal BC N=94	Chi square value	P-value
Age (year) >49 vs. <49	44/50	0.38	0.53 NS
BMI			
Overweight vs. Obese	48/46	0.04	0.83 NS
Family history			
Yes vs. No	64 /30	12.29	<0.0001
Medical Conditions			
Yes vs. No	10/84	68.25	<0.0001
Parity			
low parity vs. multiparity	62/32	9.57	<0.0001
BC Stage at Diagnosis			
Stage I + II vs. Stage III+IV	58/36	5.13	0.02
Estrogen receptor status			
Positive vs. Negative	56 /38	3.44	0.06 NS
PR status			
Positive vs. Negative	48/46	0.04	0.83 NS
ER/ PR status			
Positive vs. Negative	46 /48	0.04	0.83 NS
HER2/neu status			
Positive vs. Negative	64 /30	12.29	<0.0001

NS=not significant

Table II shows the impact of prediction of certain variables

on the prevalence of ductal BC. According to this and with regard to the demographic data of the study participants, it was found that positive family history of BC ($P < 0.0001$) was one of the significant predictive factors for the prevalence of ductal BC. About the clinical characteristics, low parity ($P < 0.0001$) was also a significant predictive factor for the prevalence of ductal BC. With regard to the cancer characteristics of the study participants, stage I and II BC ($P = 0.02$) and positive HER2/neu status ($P < 0.0001$) were significant predictive factors for the prevalence of ductal BC. Although 56 (59.6%) out of 94 ductal BC women had positive ER sensitivity, there was no significant finding ($P = 0.06$) regarding the predictive effect of ER status. In addition, there was no significant findings regarding age younger and older 49 years old ($P = 0.53$), BMI (overweight vs. obese; $P = 0.83$), PR sensitivity (positive vs. negative; $P = 0.83$) and mixed ER/ PR sensitivity (positive vs. negative; $P = 0.83$).

IV. Discussion

BC is becoming one of the most prevalent health threats and constituting the major and highest malignancy among Iraqi females since 1986. It is associated with a mortality rate of 23% after cardiovascular diseases [18]. The exact causes of BC are not yet fully known, but based on the findings of earlier studies, it is considered as a disease of wide variety of risk factors. Literature showed that classifying invasive BCs into distinct subtypes based on tumour histology is relevant and they differ in associations with multiple risk factors. These could be considered as predictive of subsequent BC risk such as reproductive, lifestyle and anthropometric factors [19], [20]. Results of this study revealed that the majority of study participants suffered from ductal BC. These findings are consistent with earlier studies which showed that BC cases were 75% ductal carcinomas and 15% were of the lobular type [21]-[25]. In many instances, the prevalence of ductal BC is more strongly associated with certain risk factors such as family history of a first-degree relative with BC, nulliparity obesity and elevated BMI [26]. BC prevalence rates become increasingly common with increasing age as it begins to rise at around the age of 30 and continues to increase thereafter [27]. This is of a particular concern in the populations of developing countries, including Iraqi population as ageing is largely a disease of older people. In addition, unhealthy lifestyle patterns are considered as one of the contributory factors which expose women to higher individual risk [28]. In this study, the mean age of patients diagnosed with BC was around 50 years and this coincides with [29] which reported that women over 50 years of age accounted for approximately 78% of new BC cases. These findings are coincide with earlier results published by the Iraqi Cancer Registry [18] which reported that the highest BC frequency was observed between 45 and 49 years old with the peak incidence between 50-54 years old. Obesity is considered as one of the most important public health problems and has a considerable impact on BC prevalence. Earlier studies reported that overweight and obesity are associated with higher risks of diverse types of cancers such as ovary and BCs since adipose tissue of obese individuals produces inflammatory cytokines and mediators, creating an environment that promotes cancer invasion and metastasis [30]-[32]. The proposed mechanisms for the development of BC in obese women could be related to the excessive aromatization activity of the adipose tissue produced by overexpression of estrogen levels, pro-inflammatory cytokines, hyperactivation of insulin-like growth factors (IGFs) alongside insulin resistance, adipocyte-derived adipokines, hypercholesterolemia and overexpression oxidative stress and reactive oxygen species [33]. These are in agreement with the findings of our study which demonstrated that 48.9% were obese and 51.1% were overweight among patients with ductal BC.

It is well known that there is a strong correlation of BC risk with family history. Furthermore, the perception for BC risk is associated with family history of any cancer in family parents [34]. In this study, family history significantly and strongly correlated as predictive risk factor in patients with ductal BC ($P < 0.0001$) suggesting that it constituted a twofold increase in risk of BC developing for women in their first-degree family, and a larger increase in a first-degree relative diagnosed before age 50 [35]-[37]. These are in accordance with [38] which reported that family history is considered as one of the strongest risk factors for BC development. Family history of cancer and its association with BC risk perception was studied by [39] which found that risk perception of BC was associated with the presence of BC family history, the type of cancer found in the first-degree relatives. Moreover, the study also found that maternal history of BC was associated with a modest increase in the net number of repeat mammograms. Controversial studies regarding the effect of multiparity on the prevalence of BC risk whether it could possess a high or low protective effect are of significant concern. Nulliparity has been associated with an increased risk of ER-positive but not ER-negative BC. Women who had at least one full-term pregnancy before the age of 30 will get a reduced risk of BC by 25% compared with nulliparous women, while multiparity could show more protective effect as the number of deliveries increased [40]. Nkondjock and Ghadirian study showed that women with eight or nine deliveries have about 30% reduced risk compared to those with five births [41]. These are in strong agreement with the findings of our study which showed that 66% of the ductal BC women had low parity. Furthermore, in this study it was observed that low parity was significantly associated with a high risk of ductal BC ($P < 0.0001$), suggesting it as another potential predictive factor among women with BC risk. Hormone receptor expression is a critical part of the pathological evaluation of BC and is considered as the main indicator of potential responses to hormonal therapy; where approximately 70% of BC cases are hormone-dependent especially ER-positive expression that is also associated with amplification or overexpression of HER2/ neu in 10-34% of invasive BC cases [42]-[44]. This is also in agreement with the results of our study which showed that 59.6% of patients diagnosed with ductal BC had ER-positive expression and significantly correlated with the expression of

HER2/neu status ($P < 0.0001$) indicating another predictive factor for the prevalence of ductal BC among the study participants.

V. Conclusion

Since BC is a worldwide health problem, it is necessary to carefully evaluate the potential risk factors among Iraqi populations and hence women can get more awareness about the impact and potential of these associated risk factors while, additional cohort studies are needed to better provide more evidences in order reduce the prevalence of this cancer type.

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