CHARACTERIZATION OF INVASIVE DUCTAL CARCINOMA (IDC) IN PRE-AND POSTMENOPAUSAL WOMEN

KHALID MAHDI SALIH

Al-Musatnsirihya University/ College of Science/ Department of Biology.

Khalid.salih11@yahoo.com

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Abstract

Background: Previous findings reported that the majority of BC in Iraqi women is invasive ductal carcinoma (IDC) and the most frequent subtype is estrogen receptor (ER+) and/or progesterone receptor (PR+) expressed.

Objective: The present study is aimed to determine the association of age, BMI, and the levels of estradiol and progesterone hormones as well as their receptors in pre- and postmenopausal women with IDC that may ultimately help identify high-risk women who would benefit from increased screening or chemoprevention.

Methodology: Forty premenopausal and fifty eight (58) postmenopausal women with IDC, previously identified their ER and PR expression, are involved in this study. Age, BMI, and serum levels of estradiol and progesterone are determined.

Results: Both pre- and postmenopausal patients are presented at advanced age (45.8 ± 0.76, 59.1 ± 0.72 year) respectively. The average of BMI in both groups is within overweight category, but without significant difference between pre- and postmenopausal patients (27.3 ± 045, and 26.7±0.38 kg/m^2 respectively). Both estradiol and progesterone serum levels are significantly higher in premenopausal patients (290.1± 6.5 pg/ml, and 2.55± 0.38 ng/ml respectively) than those in postmenopausal patients (264.1± pg/ml, and 0.75± ng/ml respectively). Just postmenopausal patients showed significant reverse association between E2 levels and the positively expression of ER (r= - 0.289), and PR (r= - 0.386), while progesterone levels showed significant association with age of pre- and postmenopausal, and with BMI of postmenopausal.

Conclusion: Collectively, age, estradiol level, and expression of ER and PR are the main factors associated with the diversity of breast cancer in pre- and postmenopausal women and ultimately they may help in identifying high-risk women who would benefit from increased screening or chemoprevention.

Introduction

Breast cancer (BC) is a highly heterogeneous disease due to its diverse morphological features, the variable clinical outcome and the response to different therapeutic options [1]. Based on WHO classification in 2003, 70%– 80% of the all breast cancers will eventually belong to either one of the two major histopathological classes, namely invasive ductal carcinomas (IDCs) or invasive lobular carcinoma (ILC) [2]. Also it has been classified according to expression of estrogen receptor(ER), progesterone receptor (PR) and human epidermal growth factor receptor (HER2) into at least three major subtypes, each of these subtypes has different risk factors for incidence, response to treatment, risk of disease progression, and preferential organ sites

of metastases [3,4]. On the other hand, The actual cause of cancer is unknown but several factors are known to increase the risks of developing breast cancer, for instances; the risk of getting breast cancer increases with age, a woman is more than 100 times more likely to develop breast cancer in her 60s than in her 20s [5], but breast cancer tends to be more aggressive in younger people [6]. Furthermore, the estimated decrease in risk per five year delay in menarche is 22 % [7], while late menopause increases the risk of breast cancer by almost 3% for each year older at menopause, so that a women who has the menopause at 55 rather than 45 years age, has approximately 30% higher risk [8]. Moreover, studies showed that post-menopausal women with the highest levels of estrogen and testosterone have 2-3 times the risk of women with the lowest levels [9]. Also overweight post-menopausal women, as measured by body mass index (BMI), have a 10-20% increased risk of breast cancer, and obese post-menopausal women a 30% increase in risk when compared to lean (BMI 22.5-24.9) women. In contrast, obese pre-menopausal women have a 20% reduction in breast cancer risk, and women with a BMI under 22.5 have a 15% reduction in risk compared to women with a BMI of 22.5-24.9 kg/m^2 [10]. Since our previous study found that the majority of BC in Iraqi women was invasive ductal carcinoma (IDC) that constitute 88.3% and the most frequent subtype was Luminal-like carcinoma (80.6%) [11], thus the present study is aimed to determine the association of age, BMI, and the levels of estradiol and progesterone hormones as well as their receptors in pre- and postmenopausal women with invasive ductal carcinoma (ICD) that may ultimately help identify high-risk women who would benefit from increased screening or chemoprevention.

Materials & Methods

This study has been conducted upon Iraqi women in different centres and hospitals for early detection of breast cancer and gynecology in Baghdad. Patients involved in this study include 40 premenopausal and 58 postmenopausal women with invasive ductal carcinoma (IDC) based on histopathological and immunohistochemistry result obtained from our previous study which confirmed the class of BC and the expression of ER and PR gene [11]. Age, height, body weight for all women were recorded and the body mass index (BMI) was calculated as their body mass divided by the square of their height-with the value universally being given in units of kg/m^2. A BMI from 18.5 up to 24.9 indicate optimal weight, lower than 18.5 suggests the person is underweight, a value from 25 up to 29.9 may indicate the person is overweight, and a value from 30 upwards suggests the person is obese [12]. About 5 ml blood were aspirated by using peripheral vein punctures and dispensed in a plane tube (without anticoagulant), and left for 15 minutes at 4^0C to clot. Then, it was centrifuged at 3000 rpm for 10 minutes to collect serum which stored in -20^0C until be used for determination of estradiol and progesterone levels by using a commercially AccuBind ELISA Micro wells kit (Monobind Inc, USA) based on delayed competitive enzyme immunoassay, in which the essential reagents required for enzyme immunoassay include antibody, enzyme-antigen conjugate and native antigen. Upon mixing the biotinylated antibody with a serum containing the antigen (estradiol or progesterone), a reaction results between the antigen and the antibody, then after a short incubation, the enzyme conjugate (antigen analogue-horseradish peroxidase conjugate in a protein-stabilizing matrix red with dye) is added, thus competition reaction results between the analogue and the antigen in the sample occurs for a limited number of antibody binding sites not consumed in the first

incubation. As a result, the enzyme activity in the antibody bound fraction is inversely proportional to the native antigen concentration [13].

Descriptive data were expressed as percentage values, whereas measurable data were expressed as mean ± standard error (M ± SE). Differences among groups were analyzed either by using Chi-square test for descriptive values or by using one-way analysis of variance (ANOVA). The correlation coefficient (r) between two parameters was carried out by Pearson correlation coefficient test. The P values of difference < 0.05 were considered significant [14].

Results

Data illustrated in Table-1 showed that premenopausal patients were presented at an average age of 45.8 year which is significantly higher than that in postmenopausal patients (59.1 year). However, the average of BMI in both groups was within overweight category, but without significant difference between pre- and postmenopausal patients (27.3, and 26.7 kg/m^2 respectively). Concerning with estradiol and progesterone, their levels were significantly higher in premenopausal patients (290.1 pg/ml, and 2.55 ng/ml respectively) than those in postmenopausal patients (264.1 pg/ml, and 0.75 ng/ml respectively).

Table-1: Characterization of pre- and postmenopausal patients with IDC

Parameter M ± SE	Menopause Period		Significance of differences by ANOVA
	Premenopausal (n=40)	Postmenopausal (n=58)	
Age (year)	45.8 ± 0.76	59.1 ± 0.72	P < 0.0001
BMI (kg/m^2)	27.3 ± 0.45	26.7 ± 0.38	P = 0.294
E2 (pg/ml)	290.1 ± 6.5	264.1 ± 6.9	P = 0.01
Pr (ng/ml)	2.55 ± 0.20	0.75 ± 0.01	P < 0.0001

When frequency of various BMI categories (normal, overweight, and obese) are calculated, results revealed non-significant differences between pre- and postmenopausal patients as shown in Table-2.

Table-2: Percentages of BMI categories in IDC women

BMI category	Menopause Period		Significance of association by X^2
	Premenopausal	Postmenopausal	
Normal (18.5-24.9)	n=11 (27.5%)	n=16 (27.6%)	X^2= 0.716 P = 0.698
Overweight (25-29.9)	n=21 (52.5%)	n=34 (58.6%)	
Obese (≥ 30)	n=8 (20%)	n=8 (13.8%)	

Furthermore, significant association in the expression of ER and PR was found between pre- and postmenopausal patients (Table-3), in which the majority of premenopausal patients (94.2%) are positively expressed ER and/or PR and the rest (5.2%) have negative expression for both ER and PR. However, 77.5% of

postmenopausal patients are positively expressed ER and/or PR and the rest (22.5%) are negative for both ER and PR.

Table-3: Percentages of estrogen receptor (ER) and progesterone receptor (PR) in IDC women

Receptor types (n), (%)	Menopause Period		Significance of association by X^2
	Premenopausal	Postmenopausal	
ER+ and/or PR+	n=31 (77.5%)	n=55 (94.8%)	X^2= 9.72 P = 0.021
ER- / PR-	n=9 (22.5%)	n=3 (5.2%)	

After analysis the correlation between estradiol levels and other tested parameters by using Pearson correlation test (Table-4), results showed non-significant association between E2 levels and all of the other parameter (age, BMI, ER+, and PR+) in premenopausal patients. However, postmenopausal patients showed significant reverse association between E2 levels and the positively expression of ER (r= - 0.289, p= 0.033) and PR (r= - 0.386, p= 0.002).

Table-4: Correlation of E2 levels versus age, BMI, receptor expression of pre- and postmenopausal BC women

Character	Correlation of E2 level (r) versus	
	Premenopausal	Postmenopausal
Age	r = - 0.159 P = 0.327	r = - 0.081 P = 0.545
BMI	r = 0.006 P = 0.970	r = 0.239 P = 0.070
ER+	r = 0.151 P = 0.352	r = - 0.289 P = 0.033
PR+	r = - 0.033 P = 0.839	r = - 0.386 P = 0.002

In contrast, progesterone levels revealed strong significant negative association with the age of both premenopausal patients (r= - 0.759, p < 0.00001) and postmenopausal patients (r= - 0.48, p= 0.0001), while other tested parameters showed non-significant correlation except BMI which is positively correlated with Pr levels of postmenopausal women only (r= 0.299, p= 0.022) (Table-5).

Table-5: Correlation of Progesterone levels versus age, BMI, receptor expression of pre- and postmenopausal BC women

Character	Correlation of Pr level (r) versus	
	Premenopausal	Postmenopausal
Age	r = - 0.759 P < 0.00001	r = - 0.48 P = 0.0001
BMI	r = - 0.002	r = 0.299

	P = 1	P = 0.022
ER	r = 0.299 P = 0.060	r = - 0.062 P = 0.643
PR	r = 0.189 P = 0.242	r = 0.025 P = 0.852

Discussion

Despite age at menopause, result of this study found that BC Iraqi women were presented at advanced age whether they are premenopausal (45.8 ± 0.76 year) or postmenopausal (59.1 ± 0.72 year). These results were compatible with world-wild survey and with the Iraqi Cancer Registry data during the period 2000-2009, which reported that the incidence of all female breast cancer in Iraq (all ages) has risen in Iraq, and there is rapidly increasing in the age specific incidence rate among women at age 60-69 years [15]. Supporting evidence indicated that most women become menopausal between the ages of 45 and 54 years, thus early menarche and late menopause are known to increase women's risk of developing breast cancer [16]. Although our results found strong negative correlation between age and progesterone levels in both pre- and postmenopausal women (Tabel-5), no significant correlation observed between age and estradiol levels (Table-4). Since breast cancer is a typical hormone-dependant tumor, therefore longer exposure to estrogen results in an increased risk of developing breast cancer, and endogenous estrogen are thought to play a major role in breast cancer carcinogenesis [17].

According to the BMI status, the present study showed non-significant differences between two groups whether in the average of BMI (Table-1) or in its categories (Table-2), in which only one quarter of pre- and postmenopausal women (27.5%, and 27.6% respectively) have normal BMI and the majority of them are either overweighed (52.5%, and 58.6% respectively) or obese (20%, and 13.8% respectively). In addition, our results demonstrated non-significant correlation between BMI and estradiol levels in both pre- and postmenopausal women (Table-4), while progesterone levels were significantly increased with increasing BMI just in postmenopausal women (Table-5). These results were consistent with other studies that didn't find association between BMI and BC risk in premenopausal women [18, 19]. However, several epidemiological evidences suggested that higher body mass index (BMI) was positively associated with increased BC risk in postmenopausal women [20, 21], but inversely reduced BC risk in premenopausal women [22-24]. This heterogeneity in the acting of BMI as BC risk factor has been discussed in several opinions. In premenopausal women, it was reported that there were more frequent an ovulatory cycles in obese which possibly protect against BC risk [25], and the clearance of free estrogen in liver was faster in obese than in lean women [26]. In contrast, among postmenopausal women, the excess of adipose tissue may elevate the production of endogenous estrogen and decrease sex-hormone-binding globulin (SHBG), these events along with the effect of increased formation of oestrone and testosterone may finally promote cellular proliferation and inhibit apoptosis in breast [27]. Moreover, a meta-analysis study suggested that the relationship between body weight and risk of BC may vary based on the menopausal status or estrogen receptor (ER) and progesterone receptor (PR) status [28]. However, it was reported that people who are obese or overweight from childhood (hereditary) do not actually show any increase risk of breast cancer [29]. Recent study found that the higher risk of breast cancer with increased BMI in postmenopausal women is likely due to

higher levels of estrogen because after menopause, fat tissue becomes the most important source of estrogen instead of the ovaries [30], and the heterogeneous association of BMI and BC risk in different ethnicity may partly due to different genetic background in postmenopausal women [31].

In respect to the estradiol and progesterone levels and their receptors, our study found that their levels in premenopausal women were significantly higher than postmenopausal women (Table-1), but only estradiol levels in both groups were further than normal range, while progesterone levels are still within normal range. Also the positive expression of both ER and/or PR was significantly higher than that in premenopausal women (Table-3) and negatively correlated just with the increasing levels of estradiol levels (Table-4) but not with progesterone levels (Table-5). Therefore, it can be suggested that estradiol plays pivotal role in the development of breast cancer in postmenopausal women. Substantial prospective data have studied circulating estrogens and breast cancer risk in postmenopausal women. It was found that increasing quintiles of circulating estradiol level as well as other estrogens were positively associated with breast cancer risk [9, 31-33]. Thus, these studied provides strong evidence that circulating sex hormones are truly a marker of increased risk in postmenopausal women because even in postmenopausal hormone users, plasma estradiol levels appear to be at least modestly associated with risk and not simply a result of tumor-related hormone production [34, 35]. Consistent with our results, no association of postmenopausal circulating progesterone and breast cancer risk was observed, however assessment of the association between plasma hormones and breast cancer risk by estrogen and progesterone receptor status of the tumor showed strong positive associations for ER+/PR+ tumors, and weak or no association noted for ER+/PR− and ER−/PR− tumor types [35, 36].

In contrast to the rapidly accumulating data on postmenopausal women, relatively few studies on circulating sex steroids levels and breast cancer have been conducted in premenopausal women who are largely due to the variation in hormone levels, particularly estrogen levels, over the menstrual cycle. It was found that only follicular total and free estradiol were significantly associated with breast cancer risk particularly among ER+/PR+ cases but no association was observed with estrone, estrone sulfate, or progesterone in both luteal and follicular phases of the cycle [37-39]. Comparable with our results, it was reported that ER and PR are expressed in 80% and 60% of breast cancer cases respectively for sustaining cancerous breast epithelium [40]. Whilst the expression of hormone receptors depends on many host and tumor characteristics (i.e. age, BRCA- 1/2 mutation, BMI, parity, grade, HER-2 expression), the PR is induced by an active estrogen–ER pathway [41]. Another study confirms an age-related inverse relationship between HER-2/neu and PR only in women age > 45 years but not in women age < or = 45 years [42]. Therefore, tumors with high levels of ER and PR are highly sensitive to endocrine therapy irrespective of menopausal status, and most postmenopausal patients with tumors expressing very high levels of ER can be optimally treated with adjuvant hormonal therapy alone, and can safely forego the rigors of chemotherapy [43].

In conclusion, these findings indicate that age, estradiol level, and expression of ER and PR are the main factors associated with the diversity of breast cancer in pre- and postmenopausal women, but need further investigation of another markers particularly HER-2 receptors.

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