BREAST CANCER

Changing Trends in Estrogen Receptors/Progesterone Receptors/Human Epidermal Growth Factor Receptor 2 Prevalence Rates Among Jordanian Patients With Breast Cancer Over the Years

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abstract

PURPOSE Estrogen receptors (ERs), progesterone receptors (PRs), and human epidermal growth factor receptor 2 (HER2) are the mainstay of breast cancer management, and their prevalence rates vary among different populations possibly related to ethnic/genetic and/or socioeconomic status. In a previous study conducted at the King Hussein Cancer Center (published 2006), Jordan ER/PR/HER2 rates for patients diagnosed in 2003-2004 were 50.8%/57.5%/17.5%, respectively. The aim of this study is to revisit the prevalence rates to see if they have changed over the years with changing socioeconomic status.

MATERIALS AND METHODS We retrieved clinicopathologic data of all patients (1,185) diagnosed with breast cancer during 2018. The data included age, histologic type, grade, and ER/PR/HER2 status as determined by immunohistochemistry and/or fluorescence in situ hybridization for HER2.

RESULTS The mean age of patients was 52 (median = 51, range = 25-92) years, and the majority (73.2%) had invasive carcinoma of no special type. ER/PR/HER2 were 77.0%/72.4%./23.8%, respectively. Triple-negative breast cancers were 10.1%. In comparison with previous results of 2006, the changes are statistically significant. Similar changes were seen in other Middle Eastern populations. The current rates are close to those of Western populations.

CONCLUSION Rates of ER/PR/HER2 expression have significantly changed and are close to those of Western populations for ER/PR. We propose that such changes are secondary to the adoption of a westernized lifestyle and socioeconomic changes.

INTRODUCTION

Breast cancer is the most common cancer in Jordan and the third leading cause of cancer death after lung and colorectal cancers. Similarly, breast malignancies are among the leading causes of cancer deaths among women globally.[1,2]

Breast cancer is a heterogeneous hormone-dependent tumor. The molecular mechanisms of this hormone dependence have been the focus of studies in the past few decades, primarily to understand the predictive role and prognostic value of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) in breast cancer management. This is because many breast cancers rely on ER and/or PR for growth, and this effect requires the presence of ER-expressing/PR-expressing cells. Binding of ER and/or PR hormone to its receptor results in unmasking of the DNA-binding sites on the receptor, migration into the nucleus, and binding to specific estrogen response elements near the genes responsible for the physiologic actions of the hormone.[3,4,6]

ER–(estrogen receptor-negative)/PR–(progesterone receptor-negative) tumors tend to be diagnosed at later stages and show aggressive pathologic features (eg, high nuclear grade, poor histologic differentiation, and high proliferative index).[4] It has been estimated that 75%-85% of ER+ (estrogen receptor-positive) and PR+ (progesterone receptor-positive) patients are likely to respond to hormone therapy, whereas those with ER– and PR– tumors are not likely to respond to endocrine therapy.[5] ER status also predicts benefit from second-line and subsequent hormone therapy. ER/PR status, therefore, represents an important intermediate end point that predicts both prognosis and response to treatment.[7] On the other hand, HER2 is expressed in

CONTEXT

Key Objective

Have the expression rates of estrogen receptor/progesterone receptor and human epidermal growth factor receptor 2 in Jordanian breast cancer significantly changed over a period of 15 years?

Knowledge Generated

The rates of estrogen receptor/progesterone receptor/human epidermal growth factor receptor 2 in breast cancer have significantly changed over a 15-year period from 50.8%/57.5%/17.5%, respectively, to 77.0%/72.4%./23.8%. Similar changes were seen in other Middle Eastern populations. The current rates are close to those of Western populations.

Relevance

This finding may provide valuable epidemiologic and etiologic factors for purposes of prevention and management of breast cancer in emerging populations.

approximately 15%-20% of high-grade invasive breast cancers and is associated with rapid tumor growth, increased risk of recurrence after surgery, poor response to nontargeted therapy (chemotherapy), and shortened survival.[8]

The prevalence of ER/PR/HER2 and the distribution of surrogate molecular subtypes of breast cancer vary considerably between racial/ethnic groups.[9] In the Middle East, initial studies have shown that Arabic women are more likely to be diagnosed with tumors that are negative for ER/PR receptors compared with their western (Western European/American) counterparts.[9-15] However, recently, similar studies conducted on Arabic patients with breast cancer reported ER/PR expression rates that are comparable with those of female populations in the West.[16-23]

In this study, our primary objective is to examine whether the expression rates of ER/PR and HER2 in Jordanian breast cancer significantly differed from the rates previously published by Sughayer et al[10] and investigate the factors that might have influenced the disparity.

MATERIALS AND METHODS

Clinicopathologic data of a cohort of 1,185 Jordanian patients with breast cancer diagnosed in 2018 were collected from the archives of the Department of Pathology at the King Hussein Cancer Center. Histopathologic records were reviewed for patients' age, histologic type of breast carcinoma, grade of carcinoma, hormone receptors (HRs), and HER2 status. The archived specimens included in this study were all originally received as either surgical specimens fixed in 10% buffered formalin or as paraffin-embedded blocks. The breast carcinomas were classified according to WHO classification of breast tumors into invasive carcinoma of no special type (NST), lobular, or other types. The HR and HER2 status was determined using either immunohistochemical methods (IHC) alone (for ER and PR) or IHC and fluorescence in situ hybridization for equivocal HER2 cases (cases scored as 2+).

It is worth mentioning that we used unpublished data from our previously published study[10] for comparison of triple-negative breast cancer (TNBC) numbers.

The Institutional Review Board at the King Hussein Cancer Center approved collection of the data presented in this article and its publication (No. 20 KHCC 30).

Immunostaining

Immunostaining was performed using the Ventana 1E2 antibody clone for PR (rabbit monoclonal primary antibody, prediluted; Ventana Medical Systems, Tucson, AZ), Ventana SP1 antibody clone for ER (rabbit monoclonal primary antibody, prediluted; Ventana Medical Systems), and Ventana Pathway (4B5) antibody clone for HER2 (rabbit monoclonal primary antibody, prediluted; Ventana Medical Systems) as per the manufacturer's instructions and run on the Ventana Benchmark Ultra system using the OptiView detection system. Positive controls were included on the same slide for each immune stain. Immunoreactivity was evaluated by two pathologists separately using the College of American Pathologists/ASCO 2010 guidelines for ER/PR and 2013 for HER2.[24,25] Evaluation of HER2 by fluorescence in situ hybridization was performed in the IHC equivocal cases (2+) using a commercially available kit (Path Vysion; Vysis Inc, Downers Grove, IL).

Approximation of Molecular Subtypes

Approximation of the molecular subtypes on the basis of the ER/PR/HER2 status was adopted from the 13th St Gallen consensus,[26] however, with minor changes because of the lack of the Ki-67 marker for most cases. Another adaptation was the inclusion of low ER/PR (< 10%) as a criterion for the luminal B (HER2−) subtype. Cases were classified as follows:

1. Luminal A: if both (ER and PR)+ and HER2−
2. Luminal B (HER2+ [human epidermal growth factor receptor 2-positive]): if ER or PR+ and HER2+ or luminal B (HER2− [human epidermal growth factor receptor 2-negative]) if HER2− and either ER or PR is low positive (< 10%) or negative (but not both negative)

TABLE 1. Distribution of ER/PR/HER2 in Breast Cancer Types

Feature	Invasive Carcinoma of NST, No. (%)	Lobular Carcinoma, No. (%)	P	Other Types, No. (%)	Total, No. (%)
ER+	670 (77.2)	81 (96.4)	< .0001	161 (69.1)	912 (77.0)
PR+	634 (73.0)	74 (88.1)	.0016	150 (64.4)	858 (72.4)
HER2+	225 (25.9)	3 (3.6)	< .0001	53 (22.8)	281 (23.7)
ER or PR+	708 (81.7)	81 (96.4)	.0006	182 (78.1)	974 (82.2)
TPBC	110 (12.7)	2 (2.4)	.005	19 (8.2)	131 (11.1)
Low ER/PR	87 (10.0)	7 (8.3)	.62	28 (12.0)	122 (10.3)
TNBC	86 (9.9)	2 (2.4)	.03	32 (13.7)	120 (10.1)
Total	868 (73.3)	84 (7.1)		233 (19.7)	1,185

Abbreviations: ER, estrogen receptor; ER+, estrogen receptor-positive; HER2+, human epidermal growth factor receptor 2-positive; NST, no special type; PR+, progesterone receptor-positive; TNBC, triple-negative breast cancer; TPBC, triple-positive breast cancer.

3. HER2-enriched: if only HER2 is positive
4. TNBC if each of ER, PR, and HER2 are negative

In addition, a fifth category was added.

1. Triple-positive breast cancer if ER, PR, and HER2 are all positive

Statistical Handling

Descriptive statistics were used to describe the findings. In addition, chi-square and Student's t-tests were used to compare sets of data. A P value of ≤ .05 was considered to be statistically significant.

RESULTS

ER/PR/HER2 in Various Types

Patients' age ranged between 26 and 93 years (median = 51, mean = 52.0 years), with 528 (44.67%) patients being age < 50 years. Of the total, 868 (73.2%) of the cases were invasive carcinoma of NST of various histologic grades, 670 (77.2%) of which were ER+, 634 (73.0%) PR+, 225 (26%) HER2+, and 86 (9.9%) triple-negative. On the other hand, lobular carcinomas were observed in 84 (7.1%) of all cases, 81 (96.4%) of which were ER+, 74 (88.1%) PR+, 4 (4.8%) HER2+, and two (2.4%) triple-negative (Table 1).

As expected, the rates of ER, PR, and HER2 expression were statistically significantly different between the invasive carcinoma of NST and the lobular types where more of the lobular were likely to be ER+/PR+ (P value ≤ .0001 and

.0016, respectively) and less likely to be HER2+ (P value ≤ .0001).

Approximating Molecular Subtypes

Approximating the molecular subtypes on the basis of IHC is shown in Table 2. Around 50% of all cases were luminal A, whereas luminal B ranged from 21% to 40% depending on the histologic subtype. Most of the lobular carcinomas (78%) were luminal A. The HER2-enriched and TNBC subtypes in the entire cohort were approximately 8% and 10%, respectively.

Other types of breast carcinomas (including mixed type, mucinous, micropapillary, apocrine, tubular, cribriform, and metaplastic carcinoma) constituted 233 cases (19.7%), of which 32 (13.7%) were triple-negative and 161 (69.1%), 150 (64.4%), and 53 (22.8%) were ER+, PR+, and HER2+, respectively.

Of the total cases, 33 (2.8%) had low ER expression (1%-9%), whereas those with the low PR (1%-9%) were 89 (7.5%). In total, the number of cases with low expression of both ER and PR HRs status was 4 (0.3%).

Of the entire group, the number of triple-positive cases was 131 (11.1%). These overlap with (are part of) the luminal B HER2+ group, which is around 16%.

Comparison With the Previous Study

Table 3 displays comparison between the current study and the 2006 study[10] in terms of the rates of HR and HER2

TABLE 2. Approximation of Molecular Subtypes of Breast Carcinoma

Molecular Subtype	Invasive Carcinoma of NST, No. (%)	Lobular Carcinoma, No. (%)	Other Variants/Subtypes, No. (%)	Total, No. (%)
Luminal A	445 (51.3)	65 (77.4)	92 (39.5)	602 (50.8)
Luminal B (HER2+)	152 (17.5)	3 (3.6)	36 (15.5)	191 (16.1)
Luminal B (HER2–)	112 (12.9)	14 (16.7)	56 (24.0)	182 (15.4)
HER2-enriched	73 (8.4)	0 (0.0)	17 (7.3)	90 (7.6)
TNBC	86 (9.9)	2 (2.4)	32 (13.73)	120 (10.1)
Total	868	84	233	1,185

Abbreviations: HER2, human epidermal growth factor receptor 2; HER2–, human epidermal growth factor receptor 2-negative; HER2+, human epidermal growth factor receptor 2-positive; NST, no special type; TNBC, triple-negative breast cancer.

TABLE 3. Comparison Between the Current Study and the 2006 Cohort

	Invasive Carcinoma of NST			Lobular Carcinoma		
Feature	Current Study, No. (%)	2006 Cohort, No. (%)	P	Current Study, No. (%)	2006 Cohort, No. (%)	P
ER+	670 (77.2)	122 (50.8)	< .001	81 (96.4)	15 (68.2)	< .001
PR+	634 (73.0)	138 (57.5)	< .001	74 (88.1)	20 (90.8)	.71
HER2+	225 (25.9)	42 (17.5)	.006	4 (4.8)	3 (13.6)	.14
TNBC	86 (9.9)	50 (21.0)	< .001	2 (2.4)	1 (4.5)	.58
Total	686	240		84	22	

Abbreviations: ER+, estrogen receptor-positive; HER2+, human epidermal growth factor receptor 2-positive; NST, no special type; PR+, progesterone receptor-positive; TNBC, triple-negative breast cancer.

positivity in each of the invasive carcinomas of NST and lobular carcinoma. The rates are significantly higher in the current study for all three markers in the invasive carcinoma of NST subtype (P value for ER+/PR+ < .001, and for HER2+ .006) and significantly higher only for ER (P value < .001) in the lobular type. The TNBC rate was much less in the invasive carcinoma of NST in the current study than the previous one. Assuming that the cutoff for the ER and PR positivity was 10% in the previous study, which is now 1%, the difference will still be significant for all three markers in the invasive carcinoma of NST and the ER in the lobular type.

Age

Patients older than 50 years had higher percentages of ER+ and HER2+ cases than patients who are younger than 50 years; however, this association was not significant (P value = .47; Table 4).

DISCUSSION

Breast malignancies have significant differences in ER/PR expression and HER2 status around the world with regard to race and ethnicity. The causes of these differences are likely to be multifactorial including socioeconomical factors and biologic differences reflected from genetic influences and differences in lifestyle, nutrition, or environmental exposure.[27]

This study consisted of 1,185 patients with breast cancer, which, to our knowledge, is the largest cohort for a study of this type in the Middle East.

The present work comes as an update study to a previously published one by the same group[10] and conducted in the same cancer facility, King Hussein Cancer Center, which treats 70%-80% of Jordanian patients with breast cancer. The aim was to re-evaluate the prevalence of the ER/PR and HER2 status in the Jordanian population, given the current changes in socioeconomic status, changes in lifestyle and nutrition, and advancements in diagnostic techniques.

The average age for this cohort was 52 years (median = 51 years, range = 25-92 years), which is considered quite young compared with the mean age upon diagnosis in American populations as reported by Parise et al (mean = 59 years) and by Jiagge et al who reported a mean age at diagnosis of 60 and 62 years for African and White Americans, respectively.[9,28] However, the age reported in Jordan is comparable with other countries in the same region or in the same income category: Peru (mean = 50.5)[17] and Egypt (mean = 49.5),[22] and close to some European countries such as Poland where the mean age of luminal A and B subtypes is 56.3 years.[29]

ER, PR, and HER2 are important predictive and prognostic biomarkers that can be used to approximate the molecular subtypes. Studies conducted over the past few years

TABLE 4. Comparison of ER/PR/HER2 Between Patients on the Basis of Age

		ER+, No. (%)	PR+, No. (%)	HER2+, No. (%)	Low ER/PR, No. (%)	TNBC, No. (%)
Subtype				Age < 50 Years		
Total	528	397 (75.19)	386 (73.11)	135 (25.57)	47 (8.90)	63 (11.93)
Invasive carcinoma of NST	403	308 (76.43)	303 (75.19)	114 (28.29)	33 (8.19)	43 (68.25)
Lobular carcinoma	27	27 (100.00)	26 (96.30)	0 (0.00)	2 (7.41)	0 (0.00)
				Age ≥ 50 Years		
Total	657	515 (78.40)	472 (71.84)	146 (31.40)	75 (11.42)	57 (8.68)
Invasive carcinoma of NST	465	362 (77.90)	331 (71.18)	111 (23.87)	54 (11.61)	43 (9.25)
Lobular carcinoma	57	54 (94.74)	48 (84.21)	3 (5.26)	5 (8.77)	2 (3.51)

Abbreviations: ER, estrogen receptor; ER+, estrogen receptor-positive; HER2+, human epidermal growth factor receptor 2-positive; NST, no special type; PR, progesterone receptor; PR+, progesterone receptor-positive; TNBC, triple-negative breast cancer.

TABLE 5. Breast Carcinoma ER/PR/HER2 Profiles in Middle Eastern Populations

	Jordan		Egypt		Saudi Arabia		Lebanon	
Feature	Current Study, %	Sughayer et al, 2006, %[10]	Aiad et al, 2014, %[22]	Dey et al, 2010, %[15]	Khabaz, 2014, %[21]	Amr et al, 1995, %[13]	El Saghir et al, 2014, %[19]	Abadjian, 1996, %[14]
ER+	76.96	50.8	73	68.9	75.50	42.9	74.40	43
PR+	72.41	57.50	63	58.1	59	38.1	69	43
HER2+	23.80	17.50	37	NA	32	NA	23.80	65

Abbreviations: ER+, estrogen receptor-positive; HER2+, human epidermal growth factor receptor 2-positive; NA, not applicable; PR+, progesterone receptor-positive.

reported a wide range of proportion of patients expressing these markers. This disparity is usually largely attributed to racial/ethnic differences.[29-35]

The most prominent breast cancer histologic subtype in our current cohort is invasive carcinoma of NST (73.3%) followed by other variants of breast cancer types (19.7%). On the other hand, the most frequent molecular subtype in this study is luminal A (50.8%) followed by luminal B HER2+ (16.1%), and the least common subtype is HER2-enriched (7.6%).

In addition, ER/PR and HER2 rates for the patients in the current study were considerably higher than the percentages published in a previous study by the same group in 2006 (Tables 3 and 5). Both studies were conducted in the same institute, and IHC evaluation was also performed by the same group of pathologists; that being said, the deployed methods (manual v automated), detection methods, and primary antibody clones were different (Table 6). In addition, in 2009, the laboratory became College of American Pathologists–accredited and has since participated in External Quality Assessment Systems/proficiency testing programs that cover immunohistochemical predictive biomarker testing.

In regard to the antibody clones/assays used, it has been shown that the currently used antibodies/assays for ER/PR/HER2 in our study are more sensitive than those used in the previous study[36-40] and so tend to yield more positive results. These studies have shown that the SP1 antibody clone for ER used in our current study (Table 6) is more sensitive than 1D5 used previously.[38,39] Also, other studies have demonstrated differences and similarities between different antibody clones and assays for ER/PR[37] and HER2.[40] For the latter, the Ventana Pathway assay for HER2 appears to be more sensitive than the Dako HercepTest that we used in our study. Another point concerning the IHC methodology is the manual versus automated techniques used where it is thought that automated methods are likely to be more sensitive and specific[36] although some studies[37] showed that this is not necessarily true.

Nevertheless, the difference in the rates between the two studies is greater than that would be anticipated on the basis of technical reasons alone, especially considering that this trend of change in the biomarker rates is observed among similar Middle Eastern cohorts (Table 5). Therefore, other factors are more likely to be involved in the causation of this trend, which may also be applicable to other countries in the Middle East. Hence, we propose that adoption of a more westernized lifestyle by women in our region, more exposure to industrial estrogens, and increase in the life expectancy among women, which may play a role in the increase of ER+/PR+ cancers among older women, are among those factors leading to improved socioeconomic status and the observed trend of change.

We propose that the improved socioeconomical factors are directly related to the adoption of westernized lifestyle as

TABLE 6. Detection Method and Clone Comparison Between 2006 and 2018 Studies

Technical Feature	Jordan—2018 (current study)	Jordan—2006 (study by Sughayer et al[10])
Detection method	Ventana Benchmark Ultra system using the OptiView detection system	Avidin-biotin-peroxidase manual method
Primary antibody clone	PR: Ventana 1E2 antibody clone (rabbit monoclonal primary PR antibody, prediluted; Ventana Medical Systems, Tucson, AZ) ER: Ventana SP1 antibody clone (rabbit monoclonal primary ER antibody, prediluted; Ventana Medical Systems, Tucson, AZ) HER2: Ventana Pathway (4B5) antibody clone (rabbit monoclonal primary HER2 antibody, prediluted; Ventana Medical Systems, Tucson, AZ)	PR: Monoclonal Mouse Anti-Human PR, clone PR 636 ER: Monoclonal Mouse Anti-Human ER clones 1D5 Dako company (Glostrup, Denmark). HER2: HercepTest (rabbit polyclonal antibody; Dako company [Glostrup, Denmark])
EQAS	CAP	None

Abbreviations: CAP, College of American Pathologists; EQAS, External Quality Assessment Systems; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor.

manifested by the dramatic rise in obesity rates related to changes in dietary habits associated with the introduction of nontraditional high-fat foods and decreased fertility rates, and the increased age at first pregnancy[41-43] might have contributed to the changes in the prevalence of hormonal receptors in breast cancer among Jordanian women. Reproductive factors and risk of ER+/PR+ breast cancers are previously documented.[44]

The observed rates in this study are comparable with the percentages found in studies of Western White cohorts and similar to those published by Middle Eastern scholars in recent years (Table 5).[10-21] The current proportion of HR+ cases in Jordan (82.9%) is very close to that in United States, which is 84%-85%. Similarly, the TNBC in Jordan proportion is currently at 10.1% comparable with 11.4% in the United States. The only difference is in the HER2, which is 23.8% in Jordan compared with 15.5% in the United States.[45,46]

However, the proportion of cases expressing HRs and HER2 is lower in patients from African and/or Hispanic descents compared with their non-Hispanic White counterparts. Looking back at studies recently conducted in the United States and Canada, we see that although a racial disparity is still pronounced, the rate of expression is much higher in the groups living in the United States and Canada than the reported percentages from less-developed countries in Africa, Asia, and the southern American continent.[17,28,32-35] These findings support the aforementioned argument that the adoption of a westernized lifestyle by our emerging communities, increased life expectancy, and exposure to exogenous estrogens are more likely responsible factors than others in explaining this trend. This is by no means intended to underestimate the genetic predisposition of certain ethnic groups for some types of breast cancer such as TNBC and the role of improved IHC techniques and different antibody clones in increasing the sensitivity and therefore detection rates of ER/PR/HER2.

In conclusion, a significant increase in the rates of ER, PR, and HER2 is observed over a period of 15 years (first cohort from 2003 to 2004[10] and the current one from 2018). Apart from the improved detection techniques, the reasons for this change are not entirely clear in this study. This change may be secondary to multiple factors, with adoption of a more westernized lifestyle by Jordanian women probably being a major player.

Nevertheless, further epidemiologic and socioeconomic studies discussing these associations in the Middle Eastern population are warranted.

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