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ARTICLE

Prevalence of Hormone Receptors and HER2/neu in Breast Cancer Cases in Jordan*

Maher A SUGHAYER,¹ Maha M AL-KHAWAJA,¹ Suleiman MASSARWEH,² Mahmoud AL-MASRI³

Departments of ¹Pathology, ²Medical Oncology, and ³Surgical Oncology, King Hussein Cancer Center, Amman, Jordan

The management and prognosis of breast cancer nowadays require the evaluation of Estrogen (ER). Progesterone Receptors (PR) and HER2/neu. Ethnic variation in the expression of these receptors is well documented. The aim of this study is to determine the prevalence of ER, PR and HER2/neu among Jordanian women with breast cancer of ductal and lobular types. A retrospective analysis was performed on 267 cases of breast cancer referred for treatment at King Hussein Cancer Center, Jordan between the period of June 2003 and June 2004. Standard immune stains were used for evaluation of hormone receptors and HER2/neu. In addition, evaluation of HER2/neu was done by FISH in selected cases. Of these 267 cases, 240 (89.9%) were ductal carcinomas of various histological grades, 122

Key words: breast cancer, hormone receptors, HER2/neu

Introduction

Breast cancer is one of the most common malignancies in women. The tumor is highly heterogeneous, with a wide range of biological, pathological and clinical characteristics. Of these characteristics, hormone receptors and HER2/neu status have a great influence on the clinical outcome. Estrogens have a crucial role in the proliferation and progression of breast cancer.¹ Estrogen is the major steroid mitogen for the luminal epithelial cell population (the usual target for neoplastic transformation).² The role of hormone receptors

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(50.8%) of which were ER-positive, 138 (57.5%) PRpositive and 42 (17.5%) HER2/neu-positive. Twentytwo (8.2%) of all cases were lobular carcinomas, 15 (68%) of which were ER-positive, 20 (90.9%) PRpositive and 3 (13.6%) HER2/neu-positive. Five (1.9%) of the total cases were of mixed lobular and ductal types, 4 (80%) of which were ER-positive, 3 (60%) PR-positive and none were positive for HER2/neu. The prevalence of hormone receptor positivity in breast cancer of Jordanian women is lower than that of the western populations and close to other populations such as the Chinese and the minor ethnic groups of Northern America (African Americans). (Pathology Oncology Research Vol 12, No 2, 83–86)

as prognostic and therapeutic tools has widespread acceptance in the management of breast cancer. The expression of estrogen receptor (ER), in particular, is thought to be of great importance, predicting an approximately 50% to 75% response rate to hormonal therapy.^{3,4} The association between HER2/neu gene (C-erbB2) amplification and poor prognosis was first determined in 1987 by Salmon et al,⁵ whose results showed that amplification of the HER2/neu gene was strongly correlated with time to relapse (diseasefree survival) and overall survival. Not only is the identification of HER2 status important for determining the prognosis of breast cancer patients, but it is also important for selecting those with metastasis for therapy with trastuzumab (Herceptin).^{6,7} The aim of this study was to determine the prevalence of ER, progesterone receptor (PR) and HER2/neu among Jordanian women with breast cancer, and to compare them with those reported in the literature in other populations. Correlation between hormone receptor status and patients' age, histological type and grade of breast cancer was also attempted.

Correspondence: Maher A SUGHAYER, MD, Department of Pathology, King Hussein Cancer Center, Queen Rania AlAbdullah Str., P.O. Box: 1269, Amman 11941 Jordan. Tel.: +962-777491216, fax: +962-6-5342567

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Materials and Methods

The archived files of the Department of Pathology at King Hussein Cancer Center were reviewed for the period between June 2003 and June 2004. Two hundred sixtyseven patients with primary or recurrent ductal or lobular carcinoma were studied. The pathology reports were reviewed for patients' age, histological type of breast carcinoma, grade of carcinoma, hormone receptors and HER2/neu status. The cases studied were received originally either as surgical specimens fixed in 10% buffered formalin or in form of paraffin-embedded blocks. The specimens received were mastectomies, lumpectomies, trucut biopsies, wide local excisions or chest wall skin biopsies. The surgical specimens were processed for routine hematoxylin and eosin staining.

The breast carcinomas were classified according to WHO classification of breast tumors.⁸ Two hundred forty cases were ductal, 22 were lobular and 5 were mixed. The carcinomas were graded using modified Bloom and Richardson method.

The hormone receptor and HER2/neu status was determined using either immunohistochemical methods (IHC) alone (for ER and PR), or IHC and fluorescence in situ hybridization (FISH) (for cases of +2 HER2/neu). The avidin-biotin-peroxidase method was used for immunohistochemical staining. The primary antibodies used were obtained from Dako company (Glostrup, Denmark). Appropriate positive controls were included for each immune stains.

Immunoreactivity was evaluated by two pathologists separately, by estimating the percentage of positively stained nuclei for ER and PR and the membranous staining for HER2/neu. Cases with strong complete membranous staining in more than 10% of the tumor cells were considered positive (+3), those with weak to moderate complete membranous staining in more than 10% of the tumor cells were considered equivocal (+2), and cases with no or faint incomplete membranous staining were considered negative (0 or +1). Evaluation of HER2/neu by FISH was done in the equivocal cases (+2), using a commercially available kit (Path Vysion; Vysis, Inc., Downers Grove, USA).

Results

A total of 267 cases were studied. Of these, 240 (89.9%) were ductal, 22 (8.2%) lobular and 5 (1.9%) mixed ductal and lobular carcinomas (*Figure 1*). Patients' age ranged from 27 to 89 years. Minor types were excluded (one case of mucinous carcinoma). The ductal carcinoma cases were of various grades: 7 (2.9%) of cases were of grade I, 71 (29.6%) grade II and 162 (67.5%) grade III. One hundred twenty-two (50.8%) were ER-positive (*Figure 2*), 138 (57.5%) PR-positive and 42 (17.5%) HER2/neu-positive (*Figure 3*). One hundred six (44.2%) of the ductal carcinoma cases were pos-

itive for both ER and PR, 16 (6.7%) were ER+PR-, 32 (13.3%) were ER-PR+, and 86 (35.8%) were negative for both receptors. All grade I cases were either ER- or PR-positive, and none of them were positive for HER2/neu. Fifty-seven (80.2%) of grade II cases were positive for either ER or PR, 10 (14.0%) of them were positive for HER2/neu. Ninety (55.5%) of the grade III cases were positive for either



Figure 1. Distribution of breast carcinoma according to histological type



Figure 2. Estrogen and progesterone receptor positivity in ductal carcinoma



Figure 3. HER 2/neu positive (+3) cases of ductal carcinoma

	Age < 50 years		Age > 50 years		Total
	No.	%	No.	%	No.
ER +	59	48.4%	63	51.6%	122
ER – Total	82 141	69.5%	36 99	30.5%	118 240

Table 1. Ductal carcinoma cases

ER: estrogen receptor, PR: progesterone receptor

ER or PR, and 32 (19.8%) were positive for HER2/neu. Eighty-two of 118 (69.5%) ER-negative cases were below the age of 50 years (Table 1). Eleven (26.2%) of the HER2/neu-positive cases were also positive for both hormone receptors, 27 (64.3%) were negative for both hormone receptors, and 4 (9.5%) of the cases were positive for either ER or PR, but not for both. In the lobular carcinoma cases, 15 (68.2%) were ER-positive (Figure 4), 20 (90.9%) PRpositive and 3 (13.6%) HER2/neu-positive. Four (18.2%) of the lobular carcinoma cases were of grade I, 15 (68.2%) grade II and 3 (13.6%) grade III. Two of the three HER2/neupositive cases were PR+ER-, and one case was negative for both receptors. All of the HER2/neu-positive cases were of grade III, pleomorphic type (Figure 5). In the mixed lobular and ductal carcinomas, 4 (80%) of cases were ER-positive, 3 (60%) PR-positive, while none of them showed positivity for HER2/neu.

Discussion

The survival of women with breast cancer varies with racial background and geographical location. The hormone receptor status and responsiveness of tumor to hormone therapy is an important parameter in breast cancer management and patient survival. Most of the studies conducted to evaluate the hormone receptors and HER2/neu status were done in western countries. The aim of this study is to establish data about the hormone receptor and HER2/neu values in Jordan.

Numerous studies have demonstrated differences in hormone receptor status and histology by race and ethnicity among women living in the United States.^{9,10,11,12} In a study conducted by Li et al, it was demonstrated that relative to non-Hispanic whites, African Americans, Native Americans, Filipinos, Chinese, Koreans, Vietnamese, Indians/ Pakistanis, Mexicans, South/Central Americans and Puerto Ricans living in the United States had 1.4 to 3.1-fold elevated risks of presenting with ER-PR- breast cancer.¹³ In another study, 63.9% of white American women with breast cancer were ER+PR+, 19.8% ER-PR-, 12.8% ER+PR- and 3.6% ER-PR+, while among black American women 48.3% were ER+PR+, 34.8% ER-PR-, 11.8% ER+PR- and 5% ER-PR+.¹⁴

In Austria, ER was positive in 80.6% and PR was positive in 61.3% of primary breast cancer patients.¹⁵ Hormone receptor determination of 1052 Chinese breast cancer patients revealed that ER was positive in 53% of premenopausal and 61.6% of postmenopausal women. PR was positive in 51.5% and 46.2%, respectively.16 In Thai females with breast cancer, 53.4% were ER-positive and 42.1% were PR-positive.¹⁷ In a study done on Nigerian women with breast cancer, 24% were positive for ER and 13.9% were positive for PR.18 Limited data are available from the Arab countries. In a study done on 88 Iraqi women with locally advanced or metastatic breast cancer, 34.2% of cases were ER+PR+ and 43.8% ER-PR-.¹⁹ In a study done in Lebanon, 43% of breast cancer cases showed positively for estrogen and progesterone receptors.²⁰ In Saudi females, one study showed 33.3% positivity and 52.4% negativity for both hormone receptors.²¹ In a study done in Tunisia. ER was found to be positive in 14% of inflammatory and 32% of non-inflammatory breast cancer cases.²²

Regarding lobular carcinoma, a study done on American patients with infiltrating lobular carcinoma showed 92.7% of the tumors as positive for ER and 67.4% as positive for PR.²³ HER2/neu gene amplification or HER2/neu protein overexpression has been identified in 10-34% of invasive breast cancers according to a series of 52 published studies including more than 16,000 patients.²⁴ Ethnic variation in HER2



Figure 4. Estrogen and progesterone receptor positivity in lobular carcinoma



Figure 5. A case of HER 2/neu positive (+3) pleomorphic lobular carcinoma

codon 655 genetic polymorphism was noticed.²⁵ In different studies done in multiple Arab countries, HER2/neu was found to be amplified in 25% of primary breast cancer cases in Tunisia,⁶ 40% in Egypt²⁷ and in 65% of cases in Lebanon.²⁰ The HER2/neu gene product is rarely detected immunohistochemically in classical in situ or invasive lobular carcinomas, but it is present in most invasive pleomorphic lobular carcinomas.²⁸ All the HER2/neu-positive cases of lobular carcinoma in our study were of the pleomorphic type.

Although our sample is small, our results reveal that in comparison with white American women, the Jordanian females with breast cancer have lower hormone receptor positivity rates. Our results are more close to those of black Americans and Chinese. This could be partially explained by the age at diagnosis of breast cancer. About 77% of American women²⁹ compared to only 39% of Jordanian females³⁰ with breast cancer are over the age of 50 at diagnosis. In our study, 69.5% of the ER-negative cases were below the age of 50 years. Biological and lifestyle factors are also likely to contribute to these findings. A comprehensive study of hormone receptors and other important tumor parameters like grade and the recently described DNA microarray for gene expression is recommended in order to understand the factors leading to such differences. This may provide further insight into breast cancer etiology in different ethnic populations.

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