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ARTICLE

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

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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 (50.8%) of which were ER-positive, 138 (57.5%) PR-positive and 42 (17.5%) HER2/neu-positive. Twenty-two (8.2%) of all cases were lobular carcinomas, 15 (68%) of which were ER-positive, 20 (90.9%) PR-positive 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)

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 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 (disease-free 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.

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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 sixty-seven 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 positive 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

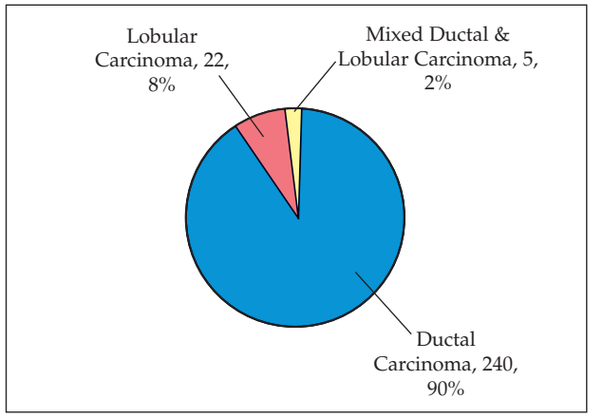

Figure 1. *Distribution of breast carcinoma according to histological type*

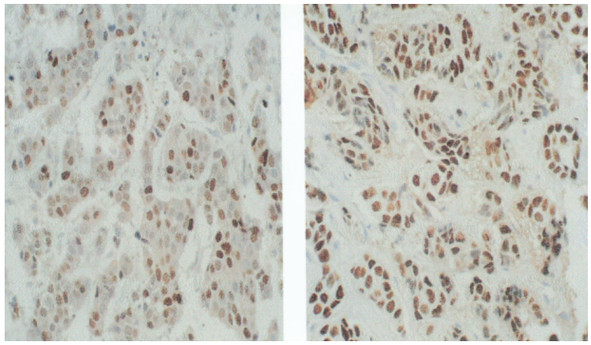

Figure 2. *Estrogen and progesterone receptor positivity in ductal carcinoma*

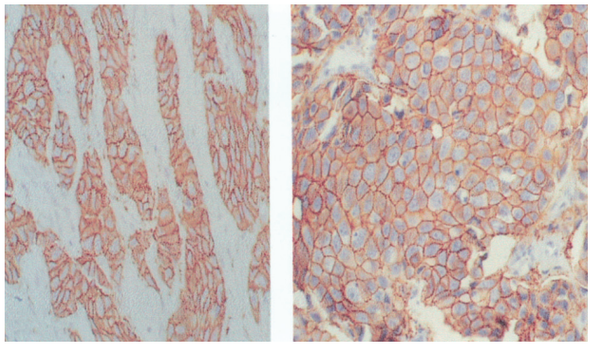

Figure 3. *HER 2/neu positive (+3) cases of ductal carcinoma*

Table 1. **Ductal carcinoma cases**

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

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%) PR-positive 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/neu-positive 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

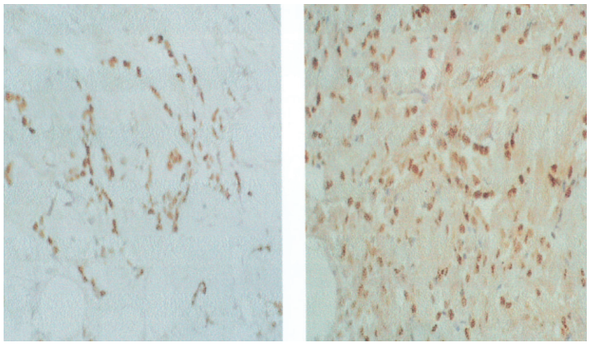

Figure 4. *Estrogen and progesterone receptor positivity in lobular carcinoma*

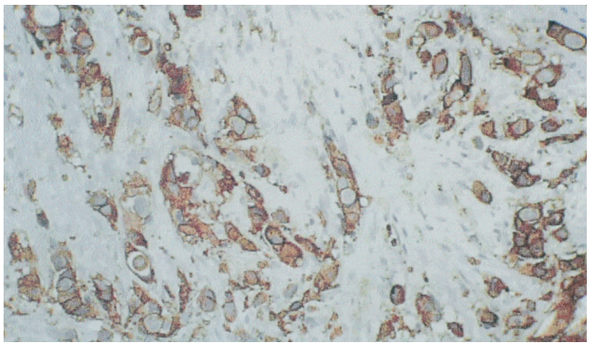

Figure 5. *A case of HER 2/neu positive (+3) pleomorphic lobular carcinoma*

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 Egypt[27] 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 women[29] compared to only 39% of Jordanian females[30] 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.

Reference

1. *Lazennec G, Bresson D, Lucas A, et al:* ER beta inhibits proliferation and invasion of breast cancer cells. Endocrinology 142: 4120-4130, 2001
2. *Anderson E, Clarke RB, Howell A:* Estrogen responsiveness and control of normal human breast proliferation. Review. J Mammary Gland Biol Neoplasia 3: 23-35, 1998
3. *Osborne CK, Yochmowitz MG, Knight WA 3rd, McGuire WL:* The value of estrogen and progesterone receptors in the treatment of breast cancer. Cancer 46: 2884-2888, 1980
4. *Wittliff JL:* Steroid-hormone receptors in breast cancer. Cancer 53 (3 Suppl): 630-643, 1984
5. *Slamon DJ, Clark GM, Wong SG, et al:* Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235: 177-182, 1987
6. *Shak S:* Overview of the trastuzumab (Herceptin) anti-HER2 monoclonal antibody clinical program in HER2-overexpressing metastatic breast cancer. Herceptin Multinational Investigator Study Group. Review. Semin Oncol 4 Suppl 12: 71-77, 1999
7. *Cobleigh MA, Vogel CL, Tripathy D, et al:* Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 9: 2639-2648, 1999
8. *Tavassoli FA, Devilee P (Eds.):* World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. IARC Press: Lyon, 2003
9. *Pegoraro RJ, Karnan V, Nirmul D, Joubert SM:* Estrogen and progesterone receptors in breast cancer among women of different racial groups. Cancer Res 46: 2117-2120, 1986
10. *Ruder AM, Lubin F, Wax Y, et al:* Estrogen and progesterone receptors in breast cancer patients. Epidemiologic characteristics and survival differences. Cancer 64: 196-202, 1989
11. *Gapstur SM, Dupuis J, Gann P, et al:* Hormone receptor status of breast tumors in black, Hispanic, and non-Hispanic white women. An analysis of 13,239 cases. Cancer 77: 1465-71, 1996
12. *Joslyn SA:* Hormone receptors in breast cancer: racial differences in distribution and survival. Breast Cancer Res Treat 73: 45-59, 2002
13. *Li CI, Malone KE, Daling JR:* Differences in breast cancer hormone receptor status and histology by race and ethnicity among women 50 years of age and older. Cancer Epidemiol Biomarkers Prev 7: 601-607, 2002
14. *Chu KC, Anderson WF, Fritz A, et al:* Frequency distributions of breast cancer characteristics classified by estrogen receptor and progesterone receptor status for eight racial/ethnic groups. Cancer 92: 37-45, 2001
15. *Stierer M, Rosen H, Weber R, et al:* Immunohistochemical and biochemical measurement of estrogen and progesterone receptors in primary breast cancer. Correlation of histopathology and prognostic factors. Ann Surg 218: 13-21, 1993
16. *Chow LW, Ho P:* Hormonal receptor determination of 1,052 Chinese breast cancers. J Surg Oncol 75: 172-175, 2000
17. *Lertsanguansinchai P, Chottetanaprasith T, Chatamra K, et al:* Estrogen and progesterone receptors status in Thai female breast cancer patients: an analysis of 399 cases at King Chulalongkorn Memorial Hospital. J Med Assoc Thai 85, Suppl 1: S193-202, 2002
18. *Ikpatt OF, Ndoma-Egba R:* Oestrogen and progesterone receptors in Nigerian breast cancer: relationship to tumour histopathology and survival of patients. Cent Afr J Med 49: 122-126, 2003
19. *al-Alwan NA, al-Kubaisy W, al-Rawaq K:* Assessment of response to tamoxifen among Iraqi patients with advanced breast cancer. East Mediterr Health J 6: 475-82, 2000
20. *Abadjian G, Antoun R:* Breast carcinoma: evaluation of hormone receptors and pS2, erb-B2, P-glycoprotein and Ki-67 markers. J Med Liban 44: 10-15. 1996 in French
21. *Samir S Amr, Abdul Rahman M. Sa'di, Fazal Ilahi, et al:* Spectrum of Breast Diseases In Saudi Arab Females: A 26 Year Pathological Survey At Dhahran Health Center. Ann Saudi Med 15: 125-132, 1995
22. *McCarthy NJ, Yang X, Linnoila IR, et al:* Microvessel density, expression of estrogen receptor alpha, MIB-1, p53, and c-erbB-2 in inflammatory breast cancer. Clin Cancer Res 8: 3857-3862, 2002
23. *Arpino G, Bardou VJ, Clark GM, Elledge RM:* Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. Breast Cancer Res 6: 149-156, 2004
24. *Ross JS, Fletcher JA:* HER-2/neu (c-erb-B2) gene and protein in breast cancer. Am J Clin Pathol 112(Suppl 1): S53-67, 1999
25. *Ameyaw MM, Tayeb M, Thornton N, et al:* Ethnic variation in the HER-2 codon 655 genetic polymorphism previously associated with breast cancer. J Hum Genet 47: 172-175, 2002
26. *Sellami M, Gamoudi M, Krichen K, et al:* Incidence of amplification of the C-erb B2/Her-2/neu gene in human breast cancer (in French). Arch Inst Pasteur Tunis 68: 33-41, 1991
27. *el-A Helal T, Khalifa A, Kamel AS:* Immunohistochemical expression of p53 and c-erbB2 proteins in breast cancer in Egypt. Anticancer Res 20: 2145-2150, 2000
28. *Middleton LP, Palacios DM, Bryant BR, Krebs P, Otis CN, Merino MJ:* Pleomorphic lobular carcinoma: morphology, immunohistochemistry, and molecular analysis. Am J Surg Pathol 24: 1650-1656, 2000
29. *Feuer EJ, Wun LM:* DEVCAN: Probability of Developing or Dying of Cancer. Version 4.0. Bethesda MD: National Cancer Institute. 1999.
30. *Al-Kayed S, Al-Hijawi B, Al-Haliq T:* Incidence of cancer in Jordan 2001. National Cancer Registry, Ministry of Health/Jordan, 2001