The Prevalence and Significance of Oestrogen Receptor (ER) Positivity in Breast Cancer at the University Hospital of the West Indies, Jamaica

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ABSTRACT

Objective: *To identify the prevalence of oestrogen receptor (ER) positivity, and determine the relationship of ER status with patient and tumour characteristics, in patients with breast cancer.*

Subjects and Methods: *A retrospective review was conducted regarding the prevalence and clinical significance of ER in patients with breast cancer at the University Hospital of the West Indies (UHWI). Oestrogen receptor status results of 243 patients treated at UHWI were collected for the period January 1, 2002 to December 31, 2009. One hundred and ninety-nine were available for review.*

Results: *Oestrogen receptor status was positive in 125 (63%) and negative in 74 (37%) patients. Mean age at diagnosis was 52.6 ± 13.0 years for the ER positive group and 58.5 ± 14.23 years for the ER negative group. Postmenopausal women accounted for 55.2% and 64.9% of the ER positive and negative groups, respectively. Mean BMI was 28.0 kg/m^2 and 29.6 kg/m^2 for the ER positive and negative groups, respectively. Menarche occurred mainly between ages 12 and 13 years for both groups. Mean age at 1st parity was 23.4 years for the ER positive and 21.4 years for the ER negative group with median parity of two for both groups. The most prevalent risk factors were oral contraceptive pill (OCP) use (24.3% for the ER positive group, 17.1% for the ER negative group), family history of breast cancer (12.0%; 13.4%) and previous smoking (8.4%; 6.9%). Tumour node metastasis (TNM) stage was Stage II in most cases (46%; 49%). Infiltrating ductal histology was most common (81.5%; 87.7%). Her 2/ neu status was negative for most patients (91.3%; 91.5%). Most patients were disease free (77.6%; 70.0%) after an average follow-up period of 3.5 years. More persons in the ER negative group had locoregional recurrence (8%) and metastases (22%).*

Conclusions: *Oestrogen receptor positive cohort was more prevalent. The ER negative group was older (*p = *0.003).*

Keywords: Breast cancer, oestrogen receptor

Prevalencia y Significación de la Positividad del Receptor de Estrógeno (RE) en el Cáncer de Mama en el Hospital Universitario de West Indies, Jamaica

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RESUMEN

Objetivo: *Identificar la prevalencia del receptor de la positividad de receptor de estrógeno (RE), y determinar la relación del estatus de RE con el paciente y las características del tumor, en las pacientes con cáncer de mama.*

Sujetos y métodos: *Se realizó un estudio retrospectivo con respecto a la prevalencia e importancia clínica del RE en los pacientes con cáncer de mama en el Hospital Universitario de West Indies (UHWI). Se recogieron los resultados del estatus del receptor de estrógeno de 243 pacientes tratados en UHWI en el periodo del 1 de enero de 2002 al 31 de diciembre de 2009. Ciento noventa y nueve estuvieron disponibles para examen.*

Resultados: *El estatus del receptor de estrógeno fue positivo en 125 (63%) y negativo en 74 (37%) pacientes. La edad promedio al momento del diagnóstico fue 52.6 ± 13.0 años para el grupo de RE positivo y 58.5 ± 14.23 años para el RE grupo negativo. Las mujeres menopáusicas representaron el 55.2% y el 64.9% del RE de los grupos positivos y negativos respectivamente.*

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El índice de masa corporal (IMC) promedio fue 28.0 kg/m2 y 29.6 kg/m2 para el RE de los grupos positivos y negativos respectivamente. La menarquia ocurrió principalmente entre las edades de 12 y 13 años para ambos grupos. La edad promedio en la primera paridad fue 23.4 años para el grupo de RE positivo y 21.4 años para el de RE negativo, siendo la paridad mediana igual a dos para ambos grupos. Los factores de riesgo de mayor preponderancia fueron el uso de anticonceptivos orales (ACO) (24. 3% para el grupo de RE positivo, 17.1% para el grupo RE negativo); historia familiar de cáncer de mama (12.0%; 13.4%); y hábito de fumar con anterioridad (8.4%; 6.9%). De acuerdo con la estadificación tumor-nódulo-metástasis (TNM), se trataba de la Etapa II en la mayor parte de los casos (46%; 49%). La histología ductal infiltrante fue la más común (81.5%; 87.7%). El estatus Her2/neu *fue negativo para la mayoría de las pacientes (91.3%; 91.5%). La mayoría de las pacientes se hallaban libres de enfermedad (77.6%; 70.0%) después de un periodo promedio de seguimiento de 3.5 años. En el grupo de RE negativo había más personas con recurrencia locoregional (8%) y metástasis (22%).*
Conclusiones: *La cohorte positiva del receptor de estrógeno positiva fue más prevaleciente. El grupo negativo de RE fue de mayor edad (*p = *0.003).*

Palabras claves: Cáncer de mama, receptor de estrógeno

West Indian Med J 2012; 61 (8): 796

INTRODUCTION

In Jamaica, breast cancer is amongst the leading cancers with the highest mortality rates (1). The calculated lifetime risk for breast cancer in females is 1 in 20; while in males it is 1 in 3333 (2). Breast cancer therefore remains a major health problem. In the parish of Kingston and St Andrew, 4981 persons were diagnosed with cancer for the period 2003 to 2007; 2344 of these were females, of whom 720 were diagnosed with breast cancer, mostly in the age range of 25 to 59 years (3).

Breast cancer treatment has undergone several changes in the past decades due to the discovery of specific prognostic and predictive biomarkers that enable the application of more individualized therapies to different molecular subgroups (4). These include oestrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor, also known as ErB-2, and heat shock protein. Oestrogen receptor refers to a group of receptors that are activated by the hormone 17β-oestradiol. It is a DNA-binding transcription factor that regulates gene expression. Oestrogen receptor α is the predominant subtype expressed by more than two-thirds of human breast cancers (5). Tamoxifen is targeted against it.

Local studies have revealed the absence of established risk factors in a significant number of affected women, which makes it evident that there are other risk factors, such as genetic factors to be elucidated. Brady-West and Graham (6) found that, even in subjects younger than 35 years, there was no greater prevalence of nulliparity, previous atypia on histology or family history, compared to older subjects; most women were diagnosed with stages II and III breast cancer. The five-year survival data for 62 patients with stage I breast cancer treated at the University Hospital of the West Indies (UHWI) between 1982 and 1988 was 66.7%, below that quoted from international multicentre studies, suggesting that clinical staging may have been inadequate (7).

Prognostic information is useful for clinicians in determining whether net benefits can be obtained from administering adjuvant therapy, and also for policy-makers to determine the cost-effectiveness of different prognosis-based treatment protocols (8). These factors allow one to distinguish which patients are likely to have recurrences after treatment of their primary tumour from those with low risk of recurrence. The Nottingham Prognostic Index is based on tumour size, lymph node status, and histological grade (9, 10). The College of American Pathologists has added response to neoadjuvant therapy, oestrogen receptor/progesterone receptor status and *Her 2/neu* gene amplification and/or over-expression, also endorsed by the National Comprehensive Cancer Network. It has been shown that conventional pathologic diagnosis gives limited data about prognosis and the response of the tumour to specific therapy (11). Patients with ER negative and PR negative status and *Her 2/neu* gene over-expressing have poor survival (12). The triple-negative immunophenotype, *ie* ER/PR/*Her 2/neu* negative, constitutes approximately 15% of all invasive breast cancers (14), and carries the poorest prognosis (13).

Breast cancer remains the leading cancer among Jamaican women, and deserves the attention of those who plan healthcare programmes. Targeted therapy is the new paradigm for breast cancer management. Focus has been placed on the oestrogen receptor, the presence of which has prognostic and therapeutic implications. The American Society of Clinical Oncology guidelines recommends ER testing in all patients with newly diagnosed invasive breast cancer (14), hence the scientific basis and justification for this study.

SUBJECTS AND METHODS

Ethics approval was granted by the Ethics Committee of the University Hospital of the West Indies/University of the West Indies/Faculty of Medical Sciences. We conducted a retrospective review of the prevalence and clinical significance of ER positivity at the UHWI, Jamaica, in breast cancer patients.

The aims of this study were to identify the prevalence of ER positivity at UHWI, to determine its relationship with patient age and tumour grade, histological type and presence of metastases and to compare the clinical characteristics of the cohorts of ER positive patients and ER negative cases.

Inclusion Criteria

Females with tissue histology that confirmed invasive breast carcinoma for the period January 2002 – December 2009. They must have been treated at the centre studied: UHWI, and ER results available.

Exclusion Criteria

Cases whose medical records were not available for interrogation, ductal carcinoma *in situ*, males and cases with no ER results were excluded.

During the period reviewed, ER testing at the Department of Pathology, University of the West Indies (UWI) was done *via* immunohistochemistry using mouse monoclonal antibodies 1D5, on formalin-fixed, paraffin-embedded breast tissue following antigen retrieval. Any nuclear reactivity for ER was considered a positive result. *Her 2 /neu* testing was done *via* the Biogenex Her 2 HSP cytoplasmic c-erbB-2 protein staining kits and Hercep Test kits at UHWI, using immunohistochemistry. Positivity was graded from 1^+ to 3^+ based on the strength of staining. Fluorescence *in situ* hybridization (FISH) is not offered at the UWI.

All medical records were kept confidential. An ID number was used for identification purposes, with a document containing corresponding patient hospital registration number being kept separately in a secure location with only the researcher and collaborators having access to this information.

Data collected were entered into Microsoft Excel software. Stastical Package for the Social Science was used to analyse data collected. Continuous variables were summarized as ranges along with means and standard deviation. Categorical data were summarized as proportions. The relationship between clinical variables was assessed using Pearson's product moment correlation coefficients and Chi-square testing, or their respective non-parametric analogues, as appropriate for continuous and categorical data. The prevalence of ER positivity was calculated. Multivariate logistic regression determined associations between patient tumour characteristics and ER negative and ER positive breast cancer. Odds ratios (OR) and 95% confidence intervals (CI) from the multivariate logistic regression analyses was adjusted for race, body mass index (BMI) and age (≤ 50 or > 50 years). As it was hypothesized that the proportion of ER positive would have been 0.65 (65%) in one group and 0.45 (45%) in the other, 106 subjects per group were needed to have an 80% chance of rejecting the hypothesis of no difference at the 0.05 level.

RESULTS

A total of 1230 ER tests were performed at UHWI between January 2002 and December 2009, 640 of which were for patients registered at the UHWI. Only 357 of these names were found in the medical records computer log. Only 243 of these patient records were found and based on availability of data and exclusion criteria, 199 were included in the study. Oestrogen receptor status was positive in 125 (63%) and negative in 74 (37%) patients.

Mean age at diagnosis was 52.6 ± 13.0 years (range 28–87; median = 52; IQR = 43–61) for the ER positive group and 58.5 ± 14.23 years (range 32–90; median = 56.5; IQR = 48–71) for the ER negative group (95% CI: 1.96, 9.74). Postmenopausal women accounted for 55.2% and 64.9% of the ER positive and negative groups, respectively with mean age at menopause being 48.8 years and 49.7 years, respectively. Mean BMI was 28.0 kg/m^2 and 29.6 kg/m^2 for the ER positive and negative groups, respectively (95% CI: -0.60, 3.77). Menarche occurred mainly between ages 12 and 13 years for both groups (IQR = 12–13 years for the ER positive and 12–14 years for the ER negative group (95% CI: -0.32, 0.53)). Mean age at 1st parity was 23.4 years for the ER positive group and 21.4 years for the ER negative group with median parity being two for both groups. The most prevalent risk factors were oral contraceptive pill (OCP) use (24.3%) for the ER positive group (17.1% for the ER negative group); family history of breast cancer (12.0%; 13.4%) and previous smoking (8.4%; 6.9%).

Most persons had tumour node metastasis (TNM) stage II (46% for ER positive group; 49% for ER negative group) and stage III (38.0%; 29.0%) breast cancer, with grade II. Infiltrating ductal histology was most common (81.5%; 87.7%). *Her 2/neu* status was negative for most patients (91.3%; 91.5%). Most patients with early breast cancer remained disease free (77.6%; 70.0%) after an average follow-up period of 3.5 years (Figure). More persons in the ER negative group had locoregional recurrence (8%) and metastases (22%).

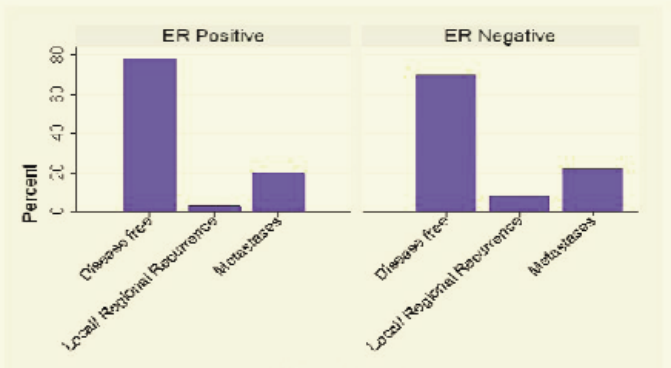

Figure: Outcomes by oestrogen receptor (ER) status for patients with early breast cancer after an average follow-up of 3.5 years.

Comparison of ER Positive and Negative Patients

Table 1 summarizes a comparison of demographic characteristics between the two groups. It was observed that:

- Patients in the ER positive group were, on average, significantly younger than those in the ER negative group
- There was no significant difference in average BMI, median parity or average age at menarche between the two groups
- There was no significant association between menopausal status, family history and ER status
- OCP use collected as part of the "Other" variable – no test conducted as data were missing for some subjects

Table 2 summarizes a comparison of clinicopathological characteristics between the two groups. It was observed that there was no significant association between any of the clinicopathological characteristics (stage, lymphovascular invasion (LVI), grade, histology and *Her 2/neu* status) and ER status.

Note that for combining *Her 2 /neu* (HER) status and ER status, the four subgroups considered were:

ER positive/HER positive grade III-10;

ER positive/HER negative-105;

ER negative/HER positive grade III-6 and

ER negative/HER negative-65.

Numbers were quite low in the HER POS grade III group so statistical analyses were not performed for these subgroups.

Table 1: Summary of demographic characteristics by oestrogen receptor (ER) status

	ER Positive	**ER Negative**	***p*-value**
Number of patients	125	74	–
Age at Diagnosis (years)			
Mean ± SD	52.6 ± 13.0	58.4 ± 14.2	0.003*
Range	28 – 87	32 – 90	(*t*-test)
Median (IQR)	52 (43 – 61)	56.5 (48 –71)	
Age Groups at Diagnosis (years)			
< 35	9 (7.2%)	2 (2.7%)	0.030*
35 – 50	50 (40.0%)	22 (29.7%)	(Chi-square test)
51 – 65	45 (36.0%)	25 (33.8%)	
> 65	21 (16.8%)	25 (33.8%)	
BMI (kg/m^2)	n = 85	n = 44	
Mean ± SD	28.0 ± 6.3	29.6 ± 5.1	0.153
Range	15.4 – 45.3	20.5 – 43.3	(*t*-test)
Parity (no.)	n = 104	n = 55	
Median	2	2	0.549
IQR	1 – 3	1 – 4	(Wilcoxon Rank
Range	0 – 13	0 – 8	Sum)
Age at Menarche (years)	n = 124	n = 72	
Mean ± SD	12.9 ± 1.4	13.0 ± 1.5	0.624
Range	11 – 18	11 – 18	(*t*-test)
Menopausal Status			
Pre	56 (44.8%)	26 (35.1%)	0.181
Post	69 (55.2%)	48 (64.9%)	(Chi-square test)
OCP Use	26	12	–
Family History	n = 117	n = 67	
Yes	14 (12.0%)	9 (13.4%)	0.772
No	103 (88.0%)	58 (86.6%)	(Chi-square test)

*$p < 0.05$ result deemed significant

BMI: body mass index; IQR: interquartile range; OCP: oral contraceptive pill

Table 2: Summary of clinicopathological characteristics – breakdown by oestrogen receptor (ER) status

	ER Positive (n = 125)	ER Negative (n = 74)	*p*-value
Stage	n = 115	n = 69	
I	10 (8.7%)	8 (11.6%)	0.559
II	53 (46.1%)	34 (49.3%)	(Chi-square test)
III	44 (38.3%)	20 (29.0%)	
IV	8 (7.0%)	7 (10.1%)	
LVI	n = 115	n = 64	
Yes	36 (31.3%)	20 (31.3%)	0.994
No	79 (68.7%)	44 (68.7%)	(Chi-square test)
Grade	n = 111	n = 63	
I	19 (17.1%)	7 (11.1%)	0.212
II	75 (67.6%)	40 (63.5%)	(Fisher's Exact test)
III	15 (13.5%)	16 (25.4%)	
IV	1 (0.9%)	–	
VI	1 (0.9%)	–	
Histology	n = 124	n = 73	
Infiltrating ductal	101 (81.5%)	64 (87.7%)	0.170
Infiltrating lobular	19 (15.3%)	5 (6.9%)	(Fisher's Exact test)
Histology	**ER Positive**	**ER Negative**	
Other	4 (3.2%)	4 (5.5%)	
***Her 2/neu* Status**	n = 115	n = 71	
Positive	10 (8.7%)	6 (8.5%)	0.954
Negative	105 (91.3%)	65 (91.5%)	(Chi-square test)

LVI – lymphovascular invasion

DISCUSSION

Receptor status is becoming increasingly important in breast cancer research because of its impact on prognosis, treatment and survival, and because of its relation to breast cancer subtypes (15). The usefulness of this study lies in the fact that by comparing the cohorts of ER negative to ER positive patients, one can accurately identify which clinical variables bear clinical significance in this population and are affected by ER status, as well as impact patient outcome. Regional data are needed across the Caribbean, with a role for documentation of patient outcome and prognostic models at a regional level.

Looking at the two cohorts combined: late menarche, early menopause, nulliparity, family history of breast cancer and oral contraceptive use were not prevalent. The population was overweight, and mostly postmenopausal. There is limited evidence that controlling obesity, participating in exercise and adopting a diet low in fats and high in fruit and vegetables will alter risk at this age (16). Most other known risk factors demonstrated in previous literature (17) were not seen in this population studied. This may be the case as risk factors vary by menopausal status and the premenopausal group was not as dominant in the population studied (18). More risk factors will have to be sought in this population. The introduction of genetic testing, for example breast cancer genes (BRCA-1 and BRCA-2), in at-risk populations will be useful (19).

Age at diagnosis bore clinical significance when both cohorts were compared according to ER status. The ER negative group was statistically significantly older than the ER positive group with the age range 35–50 years being most prevalent for the latter and age over 50 years being most prevalent for the former. The US Preventive Services Task Force has also reported an association between the younger age group and ER negativity and older age group and ER positivity (20). This was not reflected in the population studied.

A prognostic factor is any measurement that correlates with disease-free or overall survival in the absence of systemic adjuvant therapy and, as a result, is able to correlate with the natural history of the disease. These include axillary lymph node status, tumour size and grade, LVI, age at diagnosis, ER and *Her 2/neu* status. In contrast, a predictive factor is any measurement associated with response to a given therapy, such as ER and H*er 2/neu* status. Age is regarded as a prognostic factor. Early stage breast cancer seen in premenopausal women less than 35 years of age at diagnosis, although likely ER positive, is still associated with a worse five-year survival when compared to older patients, in terms of relapse-free survival, cause-specific survival, distant metastases and breast and regional node recurrence. However, the adverse effect of young age on outcome appears to be limited to node-negative patients. Such patients will likely benefit from not only hormonal therapy and surgery but also adjuvant systemic chemotherapy (21, 22).

The NSABP B-06 trial randomized women with early-stage breast cancer to mastectomy, lumpectomy alone, or lumpectomy followed by radiation therapy. No adjuvant systemic therapy was administered. The women with ER-positive tumours had a five-year disease free survival (DFS) of 74% and overall survival (OS) of 92%, while the women with ER-negative tumours had a five-year DFS and OS of 66% and 82%, respectively (23).

Studies with longer follow-up, however, suggest that the prognostic significance of hormone receptors may not persist long-term. Hilsenbeck *et al* demonstrated an improved prognosis for ER-positive tumours during the first three years of follow-up but not after three years. It is possible that the presence of oestrogen or progesterone receptors merely predicts for a more indolent, slower growing tumour with longer times to disease recurrence (24).

The presence of oestrogen or progesterone receptors is, however, a powerful predictive factor for the likelihood of benefit from adjuvant endocrine therapy with drugs such as tamoxifen and the aromatase inhibitors. The most recent Early Breast Cancer Trialists' Collaborative Group update of randomized trials using adjuvant tamoxifen demonstrated that five years of adjuvant tamoxifen led to proportional reductions in the risk of recurrence and mortality of 47% and 26%, respectively, of patients with ER-positive tumours.

This proportional reduction in mortality was similar for node-negative and node-positive patients (25).

Worse prognosis is associated with axillary lymph node positivity, tumour size > 3 cm, LVI, tumour grade III, age at diagnosis < 35 years, *Her 2 /neu* over-expression and ER negative status. Such patients would likely receive adjuvant systemic chemotherapy. The Oxford Overview Analysis demonstrates that adjuvant hormonal therapy and polychemotherapy reduce the risk of recurrence and death from breast cancer. Adjuvant systemic therapy, however, has associated risks and it would be useful to be able to optimally select patients most likely to benefit (26).

In this study, most subjects from both groups remained disease free at the end of treatment and for the period studied, and their pathological features did not differ significantly. Most persons were diagnosed at stage Π of their disease which may explain the good outcome. Also most persons had absence of LVI.

Oestrogen receptor positivity was 63% of the population studied. *Her 2/neu* negativity was also prevalent so that can also explain the good outcome as demonstrated in previous literature.

Her 2/neu over-expression is associated with increased tumour aggressiveness, increased rates of recurrence, and increased mortality in node-positive patients, while the influence in node-negative patients is more variable (27). Retrospective studies have suggested that *Her 2/neu* over-expression may also have a predictive role for response to chemotherapy (particularly anthracycline-based as opposed to alkylator-based) and endocrine therapy (28). The presence of *Her 2/neu* over-expression predicts for response to a humanized monoclonal antibody, trastuzumab (Herceptin™). Mass *et al* demonstrated that *Her 2/neu* amplification, as determined by FISH, may be a better predictor of response to trastuzumab (29).

Recently, the American Society of Clinical Oncology (ASCO) and the Canadian National Comprehensive Cancer Network (NCCN) guidelines recommend that the Onco*type* DX assay can be used to predict the risk of recurrence in patients with node-negative, ER-positive tumours (that are larger than 1 cm or defined as T1B with unfavourable characteristics disease) and to identify patients likely to obtain the most benefit from adjuvant tamoxifen alone *versus* addition of chemotherapy.

The future of biomarkers lies in p53, Bcl-2 and thymidine labelling index for node-negative breast disease (30, 31). From the above, one can infer the following:

Other risk factors need to be elucidated in larger and prospective studies.

- ER kits should also be more accessible at the government hospitals as results impact on patient treatment and outcome.
- Anti-oestrogen therapy, including aromatase inhibitors, should be more readily accessible in the government pharmacies and a wider range provided at lower costs to patients in this population because of the high prevalence of ER receptor positivity.
- Benefit can also be derived from making FISH testing and trastuzumab therapy more readily available and affordable to this population.
- More local data need to be obtained with regards to which biomarkers will determine outcome of patients. Also more prospective studies need to be done locally to determine whether or not there is a unique set of genetic biomarkers specific to the local population that can be used as prognostic and predictive factors, when making national treatment protocols.

Limitations of the study were: the small sample size, unavailability of some patients' files, poor record keeping, a single centre study and the subjectivity and variation of immunohistochemistry staining results.

CONCLUSION

This study has highlighted a difference in the population studied as compared to the internationally reported norm in terms of demographics of patients diagnosed with invasive breast cancer. Looking at the two cohorts combined: late menarche, early menopause, nulliparity, family history of breast cancer (in a first degree relative), and oral contraceptive use were not prevalent. The population was overweight, which has been described in prior literature as being a risk factor for breast cancer. Oestrogen receptor positivity was 63%. The population treated had a fairly good outcome.

ACKNOWLEDEMENTS

Gratitude is owed to the Departments of Medicine and Pathology and the staff of Medical Records office for assistance in data collection and documentation. Heartfelt thanks are also due to the statistician, Dr C A Walters and my supervisors.

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