Estrogen, Progesterone & Human Epidermal Growth Factor 2 testing in breast cancer at Kenyatta National Hospital

Andrew Gachii, MD
Consultant Histopathologist, Med Path (UoN), FC Path (ECSA)
Head of Department-Lab Medicine, Kenyatta National Hospital, Kenya
I have been sponsored by Roche Kenya Ltd to attend the IAP-2018 congress
Background

Statistics

- Kenya population: 50 Million
- Cancer is 3rd leading cause of death in Kenya (after infectious and cardiovascular disease)
- 37,000 new cases in 2012
- 28,500 cancer deaths annually
- 60% of cancer patients are < 60 years
- 70-80% of cancer is diagnosed in late stages

breast (34/100000)  
cervical(25/100000)  
oesophagus

Prostate  
Kaposi sarcoma  
Oesophagus

In LMIC 48% of deaths are premature(<70years) Vs 26% in developed countries
BREAST CARCINOMA

• Cancer of breast is a leading cause of death in women all over the world. In Kenya, it is the leading cause of cancer death among women, although the actual incidence is not known due to lack of maintenance of proper records including registry and surveillance. However the reported incidence is 34/100,000.

• The cause is unknown though certain risk factors have been identified. This includes age, genetics and periods of prolonged oestrogen exposure.
BREAST CARCINOMA

• It has long been recognized that breast cancer is not a single disease, breast cancer is a heterogeneous disease with varying clinical outcomes in histologically similar tumors.

• Micro array gene profiling has identified several breast cancer subtypes which include luminal A, Luminal B, Basal, and Her2 subtype. These subtypes show variable prognosis and response to therapy and are identified in tissue using surrogate immunohistochemical markers.
BREAST CARCINOMA

• Oestrogen, Progesterone receptor positivity as well as HER 2 receptor over expression have been identified as important prognostic indicators in Carcinoma of breast. Accurate determination of estrogen and progesterone receptors and human epidermal growth receptor 2 (HER2) protein over expression are widely accepted as the basis for treatment of breast cancer.

• Immunohistochemical determination of estrogen receptors, progesterone receptors and human epidermal growth receptors (HER-2) oncoprotein

• expression are usually required by oncologists in deciding optimal management options of these patients
Background

Breast Cancer and Africa

Search in Pubmed (Oct.2018)
Breast AND Cancer AND Carcinoma AND Pathology
Background

Breast Cancer and Africa

Search in Pubmed (Oct. 2018)
Africa AND Breast AND Cancer AND Carcinoma AND Pathology

49,360 vs. 292
Background

Breast Cancer and Africa

N° OF PUBLICATIONS

Search in Pubmed (Oct.2018)
Africa AND Breast AND Cancer AND Carcinoma AND Pathology
Background

Breast Cancer and Africa

N° OF PUBLICATIONS

Search in Pubmed (Oct.2018)
Kenya AND Breast AND Cancer AND Carcinoma AND Pathology

7

VS.

292
Breast cancer pathogenesis and histologic vs. molecular subtypes

<table>
<thead>
<tr>
<th>Histological subtypes</th>
<th>Ductal</th>
<th>Lobular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preinvasive cancer</td>
<td>Ductal carcinoma in situ (DCIS)</td>
<td>Lobular carcinoma in situ (LCIS)</td>
</tr>
<tr>
<td>25%</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>Cells limited to basement membrane</td>
<td>May spread through ducts and distort duct architecture</td>
<td>Does not distort duct architecture</td>
</tr>
<tr>
<td></td>
<td>1% progress to invasive cancer per year</td>
<td>Same genetic abnormality as ILC - E-cadherin loss</td>
</tr>
<tr>
<td></td>
<td>Usually unilateral</td>
<td>1% progress per year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Can be bilateral</td>
</tr>
<tr>
<td>Invasive cancer</td>
<td>Invasive ductal carcinoma (IDC)</td>
<td>Invasive lobular carcinoma (ILC)</td>
</tr>
<tr>
<td>75%</td>
<td>79%</td>
<td>10%</td>
</tr>
<tr>
<td>Extension beyond the basement membrane</td>
<td>Usually from DCIS precursor</td>
<td>Usually from LCIS precursor</td>
</tr>
<tr>
<td></td>
<td>Cause fibrous response, producing a palpable mass on examination</td>
<td>Minimal fibrous response, presents less often with palpable mass</td>
</tr>
<tr>
<td></td>
<td>Metastasis through lymphatics and blood</td>
<td>Metastasis through abdominal viscera to GI, ovaries, uterus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Molecular subtypes</th>
<th>Triple negative</th>
<th>HER2+</th>
<th>Luminal B</th>
<th>Luminal A</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of breast cancers</td>
<td>15-20%</td>
<td>10-15%</td>
<td>20%</td>
<td>40%</td>
</tr>
<tr>
<td>Receptor expression</td>
<td>HER2</td>
<td>ER+/PR+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histologic grade</td>
<td>I light (grade III)</td>
<td>Low (grade I)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prognosis</td>
<td>Poor</td>
<td>Good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response to medical therapy</td>
<td>Chemotherapy</td>
<td>Trastuzumab</td>
<td>Endocrine</td>
<td></td>
</tr>
</tbody>
</table>

Normal breast stem cells or progenitor cells transform into breast cancer cells. The cancer cells are similar in phenotype to the normal basal and luminal cells of the ductal structure.

Basal or myoepithelial cells
- Contractile cells for milk ejection
- Estrogen receptor –
- Progesterone receptor –

Luminal or epithelial cells
- Respond to hormonal stimulation for milk production
- Estrogen receptor +
- Progesterone receptor +/-

Cancer cell phenotype
- Basal
- Basoluminal
- Luminal

Robbins RE.
# Triple Negative Breast Cancer

What is the truth?

<table>
<thead>
<tr>
<th>Year</th>
<th>REFERENCES</th>
<th>COUNTRY</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>J Clin Oncol</td>
<td>NIGERIA</td>
<td>507</td>
<td>28%</td>
</tr>
<tr>
<td>2012</td>
<td>Diagn Pathol</td>
<td>MOROCCO</td>
<td>390</td>
<td>13,60%</td>
</tr>
<tr>
<td>2012</td>
<td>BMC Res Notes</td>
<td>MOROCCO</td>
<td>366</td>
<td>12,60%</td>
</tr>
<tr>
<td>2012</td>
<td>ONCOLOGY</td>
<td>MALI</td>
<td>114</td>
<td>46%</td>
</tr>
<tr>
<td>2012</td>
<td>BREAST CANCER RES TREAT</td>
<td>NIGERIA</td>
<td>308</td>
<td>48,10%</td>
</tr>
<tr>
<td>2012</td>
<td>PATHO RES PRACTICE</td>
<td>EGYPT</td>
<td>274</td>
<td>28,50%</td>
</tr>
<tr>
<td>2014</td>
<td>Annals Diagn Pathol</td>
<td>EGYPT</td>
<td>125</td>
<td>16%</td>
</tr>
<tr>
<td>2014</td>
<td>BMC Res Notes.</td>
<td>TANZANIA</td>
<td>52</td>
<td>38,40%</td>
</tr>
<tr>
<td>2014</td>
<td>BREAST</td>
<td>KENYA</td>
<td>301</td>
<td>20,20%</td>
</tr>
<tr>
<td>2014</td>
<td>Pan Afr Med J.</td>
<td>NIGERIA</td>
<td>226</td>
<td>34%</td>
</tr>
<tr>
<td>2015</td>
<td>BREAST DISEASE</td>
<td>ALGERIA</td>
<td>3014</td>
<td>20,80%</td>
</tr>
<tr>
<td>2015</td>
<td>Breast J.</td>
<td>GHANA</td>
<td>223</td>
<td>58,30%</td>
</tr>
<tr>
<td>2015</td>
<td>Ann Surg Oncol.</td>
<td>GHANA</td>
<td>147</td>
<td>61%</td>
</tr>
<tr>
<td>2016</td>
<td>BMC Women’s Health</td>
<td>MOROCCO</td>
<td>279</td>
<td>17,60%</td>
</tr>
<tr>
<td>2016</td>
<td>Pathobiology</td>
<td>NIGERIA</td>
<td>835</td>
<td>47,65%</td>
</tr>
<tr>
<td>2016</td>
<td>Asian Pac J Cancer Prev.</td>
<td>IVORY COAST</td>
<td>302</td>
<td>32,10%</td>
</tr>
</tbody>
</table>

Mean SSA: 3015, 40%
Mean North Africa: 4448, 20%
Mean Africa: 7463, 28%
OBJECTIVE OF THE STUDY AT
AT KNH

- Objective: To determine the proportion of breast cancer subtypes at Kenyatta National Hospital, the largest national public referral hospital in the East African Region.

- Study Design & setting: Cross sectional study of specimens for breast cancer received in the pathology department at Kenyatta National Hospital between February 2017 and 2018.

- Methods: 273 cases were analyzed using immunohistochemistry markers for Estrogen receptor (ER), Progesterone receptor (PR) and HER2 to identify the molecular subtypes. The subtype definition was: Luminal A (ER and/or PR positive Her2 negative), Luminal B (ER, PR, and HER2 positive), Her 2 enriched (ER and PR negative, HER2 positive,), and Triple Negative (ER, PR, and HER2 negative).

- Other clinicopathological characteristics including age, menopause status, and tumor size, grade and stage where available were recorded for each sub type.
IMH-NEGATIVE STAINING-POSITIVELY STAINING GLAND SERVE AS POSITIVE CONTROL
IMH-POSITIVE STAINING-ER POSITIVE
IHC interpretation

HER2

*image courtesy, Roche Diag. EMEA-LATAM, Scanned on Roche DP200
Results:
- Oestrogen Receptor positivity -- constituting 64.8%
- Progesterone positivity 56.0%
- HER 2 constituting 26.7%
MOLECULAR SUBTYPES

• LUMINAL A -42 %
• LUMINAL B -23 %
• TRIPPLE
• NEGATIVE -21%
• HER 2
• ENRICHEDE -19.8%
FREQUENCY OF ER, PR, HER-2 COMBINATIONS

- ER – PR – HER-2-VE: 21%
- ER-VE/PR-VE/HER2: 42%
- ER+/PR+/HER2+: 6.8%
- ER+/PR-/HER2-VE: 6.6%
- ER-/PR+VE/HER2+: 22.2%
- ER_+VE/PR+/HER2-VE: 1.4%
LUMINAL A SUBTYPES
Correlation of the receptors with age

• Age 21-30: 10 cases (5ER⁺/5PR⁺/6HER2⁺);
• Age 31-40: 56 cases (35ER⁺/29PR⁺/12HER2⁺);
• Age 41-50: 91 cases (43ER⁺/46PR⁺/24HER2⁺);
• Age 51-60: 55 cases (26ER⁺/25PR⁺/13HER2⁺);
• Age 61-70: 41 cases (25ER⁺/21PR⁺/16HER2⁺);
• Age 71-80: 21 cases (14ER⁺/13PR⁺/4HER2⁺);
• Age 81-90: 5 cases (3ER⁺/2PR⁺/2HER2⁺).
LUMINAL A CASES PER AGE GROUP
DISCUSSION

• The results indicate a progressive rise in the incidence of breast case which peak at the perimenopausal period and then a decrease thereafter.

• The hormone receptor positivity (ER/PR or both) was highest in the pre-menopausal period constituting a total of 52.2% and with the decade of 40-50 years registering a significant level of 30.3%.
DISCUSSION

• The prevalence of breast cancer subtypes appears to be similar to that which has been recently published from Kenya and other countries (1).

• The HER 2 over expression was seen in 57/273 or 21% of the total number of cases analyzed; again with progressive increase in positivity up to menopause. This is in keeping with other studies that indicate that 20% to 25% of breast cancers will over express the HER2/NEU protein; with some authors suggesting that HER2 over expression is associated with age (2); our study showed similar significant relationship between HER2 over expression and patient’s age.
DISCUSSION

• The least common combination is oestrogen – ve/progesterone +ve/Her2+ constituting 1.4%. In a study involving 275 breast cancer cases Parise et al(4) recorded an incidence of 1.1 %.

• Of significance was the incidence of triple negative case i.e eostrogen –ve/progestone –ve/Her 2 –ve which constitute 27% of the total case. The reported incidence worldwide is 12-20% of all cancers although it is widely accepted that these prevalences vary by race and age. The young and blacks are more likely to be triple negative (3).
CONCLUSION

• Routine determination of hormone receptors is extremely important for appropriate targeted therapy.

• For practising clinician especially in Countries with limited or stressed health care budgets use of ER, PR and Her 2 studies for subtyping is valuable for therapeutic and prognostication purposes.

• Where resources are available, more elaborate molecular testing including gene expression profiling and latest generation genomic testing would be recommended in addition to routine testing of biomarkers.


• 4. Lund, M., Lund M., Butler, E., Hair, B., Ward, K. Andrews, A., Bayakly, S., Regan, R.O., and Elly,