Breast Cancer Molecular Subtypes in Oman: Correlation with Age, Histology, and Stage Distribution – Analysis of 542 Cases

I. Mehdi, A. A. Monem, B. Al Bahrani, F. A. Ramadhan

Abstract

Background

Breast cancer (BC) is one of the most common malignancies and a foremost health issue throughout the world. BC accounted for 23.1% of cancer cases diagnosed in Oman in 2009. BC is a heterogeneous disease, and immunohistochemical (IHC) markers are used to further classify it into distinct subtypes, which are biologically discrete and display different behaviors. IHC testing of the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (Her-2); can sub-classify BC into 4 principal molecular subtypes. These subtypes are luminal A (ER+ and/or PR+, HER2−), luminal B (ER+ and/or PR+, HER2+), basal like (BCL - ER−, PR−, HER2−), and Her2/neu (ER−, PR−, HER2+). Previous studies have shown preliminary evidence and high probabilities of molecular differences across ethnic and geographic groups which may be responsible for disparities in presentation, biological behavior, treatment response and outcome.

Patients and Methods

BC data from 2006-2010 at the National Oncology Center – The Royal Hospital, Oman were retrospectively retrieved from the electronic patient record system (Al-Shifa). Data were analyzed with respect to ER, PR, and Her-2 status and tumours were classified on molecular basis. Molecular subtypes were correlated with age, histology and treatment outcome. The results were compared with published regional and international data.

Results

There were 542 cases of BC accessible for evaluation. Luminal A subtype was the most common and the BCL subtype was highest among Omani females. Age was a significant factor in basal-like (63.8% younger than 50 years vs. 36.2% older than 50 years) and Her2+ve tumours (60.9% vs. 39.1%). High grade tumors were mostly observed (41%) in basal tumors and were lowest in luminal A (19%). A higher stage at presentation (Stage III and IV) was observed in Her2+ tumours (59%), and a higher (22.4%) mortality was detected in basal like/TN tumours.

Conclusions

The molecular classification and sub-typing of BC have revealed ethnic and geographic variation. Luminal A subtype is the most common among Omani female breast cancers but it is less common than in Western females. BCL subtype is highest among Omani females compared with Western females. These differences may have diagnostic, therapeutic and prognostic implications. Large scale and multi-centre studies may confirm these findings and can be translated and incorporated to pertinent management strategies.

Key Words

Molecular subtypes, breast cancer, Oman, Royal Hospital

Introduction

Breast Cancer (BC) is one of the most common malignancies and a major health issue throughout the world. Its molecular biology and genetics-guided management have evolved tremendously in recent years (1, 2). BC is considered to be a
distinct disease in each patient, ethnic group and geographic location. Identifying BC sub-groups for optimal, cost effective and evidence-based management has been emphasized. Previous studies have demonstrated initial evidence and high probabilities of molecular differences across ethnic and geographic groups. Molecular differences may be responsible for variation in presentation, biological behavior, response to treatment and outcome.

BC is a heterogeneous disease and IHC markers are used to sub-classify BC on a molecular basis. These molecular subgroups have been shown to be biologically distinct and exhibit different behaviors. Molecular classification based on immunohistochemistry (IHC), Fluorescent in situ hybridization (FISH) or polymerase chain reaction (PCR) imparts both therapeutic and prognostic information. However, molecular classification should be complemented with important traditional prognostic variables such as age, tumor size, lymph node status, co-morbidity, and adjuvant therapy. Expression of the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (Her2) can sub-classify BC into 4 main molecular subtypes. These subtypes are luminal A, luminal B, basal-Like (BCL), and Her2/neu positive.

BC diagnosis based on intrinsic subtypes provides additional substantial prognostic and predictive information which is highly valuable for the management of node-negative disease. In addition, the subtypes and risk score can be used to appraise the likelihood of efficacy from neoadjuvant chemotherapy. MRI assessment for monitoring response during neoadjuvant chemotherapy is effective in triple-negative or HER2-positive disease but is inaccurate in ER-positive/HER2-negative BC.

BC demonstrates molecular, histopathologic, and clinical diversity. The molecular heterogeneity is manifested in gene expression blueprint patterns, different frequencies and magnitudes of genomic aberrations, as well as differential protein expression across BC, even among those of similar histopathologic type. These observations suggest that BC molecular subtypes are developing along distinct pathways and by diverse mechanisms. These phenomena are especially true for the luminal A and basal-like subtypes. These subtypes perhaps originate from different lineages of progenitor or stem cells at different stages of differentiation. This idea has been further confirmed by the molecular profiling of breast cancers by array technology that showed that the biological and clinical heterogeneity of breast cancer is explained by differences in the genetic composition of the primary tumours. However the distinctiveness of the additional three subtypes mentioned is not very clear. Additionally, and influencing this diversity, the variety of the microenvironment reflects variable involvement of various biological processes. The molecular heterogeneity is reflected in the clinical course and treatment responses. Molecular subtypes are not just recapitulating the standard clinical classification. These subtypes predict a non-response to neoadjuvant chemotherapy by paclitaxel, fluorouracil, doxorubicin, and cyclophosphamide-based regimens.

BC diversity makes it challenging to develop tumor classifications that are clinically valuable for prognosis or prediction. Microarray detected gene expression profiling has provided insight into the complexity of breast tumours and can be used to provide prognostic information beyond standard clinical assessment using a 21-gene Oncotype-Dx assay or a 70-gene MammaPrint. Many studies have analyzed the interactions between breast cancer intrinsic subtypes and genetic alterations, cytotoxic drug response and outcome.

Multiple therapeutic options are available for local and regional treatment of BC. The prognosis varies and decision-making is based on many variables. The use of IHC surrogates for molecular subtyping can provide much of the prognostic information obtained by gene expression profiling. The molecular subtypes (determined by ER, PR, Her-2, Ki67, CK5/6, and EGFR) influence not only survival but also the risk of relapse. Tumour size, nodal involvement, grade, lymphovascular invasion, estrogen receptor (ER) and human epidermal growth factor receptor (Her-2) status are all
independent risk factors for relapse \(^{(9)}\). Her-2 and ER expression statuses have been associated with the increased risk of spread to specific sites \(^{(9)}\). A better understanding of patterns of metastatic spread in molecular subtypes may influence adjuvant therapy and surveillance decisions, and may determine which investigations and therapies are appropriate once metastasis occurs\(^{(9)}\). Bone is the most common metastatic site in all BC subtypes except basal-like tumours, and the preferred site of metastasis among ER-positive tumours. Luminal/Her-2 and Her-2-enriched tumors are associated with a significantly higher rate of brain, liver, and lung metastases. BCL tumours exhibit a higher rate of brain, lung, and distant nodal metastases but a significantly lower rate of liver and bone metastases \(^{(9)}\). Brain metastasis has been reported in 6-11\% of TN early breast cancer, and 10-16\% of patients exhibit CNS metastasis in early-stage Her2-positive breast cancer. The incidence of brain involvement among patients with metastatic HER2-positive disease has been described to be 25-34\%. Higher rates of CNS metastasis among ER-negative/Her2- positive tumours compared with ER-positive/Her-2-positive tumours have been observed. TN non-basal tumours demonstrate a similar pattern except liver metastases \(^{(9)}\). Significant differences are present in the timing of distant recurrence in molecular subtypes. ER-negative tumours are associated with early relapse, and ER-positive tumours are associated with a persistent late risk beyond 5 years. Basal/TN and Her-2 subtypes have a high rate of early relapse. Luminal A is the only tumor subset with a substantially lower relapse rate of 15 years after diagnosis \(^{(9)}\). Luminal A tumours (ER or PR positive, Her-2 negative, low Ki-67) exhibit the best prognosis and the lowest rate of local or regional relapse. Her-2-enriched and basal subtypes demonstrated an increased risk of regional recurrence in patients undergoing breast conservation surgery. After mastectomy, luminal B, luminal-HER2, HER2-enriched, and basal subtypes were all associated with an increased risk of local and regional relapse \(^{(8)}\).

In West Africa, hormone receptor-negative and TN breast cancer are predominantly reported and 25\% of BC is reported to be ER positive \(^{(10)}\). These findings are consistent with two studies that were conducted in Nigeria, but are different from another Nigerian study which reported that 71\% of BC is ER positive \(^{(10)}\). Luminal A breast cancer is predominant in Asian, Caucasian and postmenopausal African American populations. In contrast, the proportion of the BCL subtype is 27\% in indigenous Africans and premenopausal African Americans, approximately 15\% in postmenopausal African Americans and premenopausal European Americans and only approximately 10\% in other populations. However, the proportion of Her-2-positive tumours is similar among all populations \(^{(10)}\). Tumour subtype is strongly associated with grade but only weakly associated with lymph node metastasis and tumor size, suggesting that subtype is intrinsic and predetermined \(^{(10)}\). The comparison of the subtype spectrum suggests that both environmental exposures and genetic background determine breast cancer subtypes. Breast cancer risk factors vary by tumor subtypes\(^{(10)}\). These findings partly explain the poor prognosis of breast cancer in African women and have important clinical and policy implications for breast cancer control in Africa \(^{(10)}\).

In younger age groups, luminal B and Her-2 subtypes are associated with higher rates of local relapse (LR) after breast conservative treatment (BCT). Young women with hormone-positive disease have favorable outcomes after BCT \(^{(11)}\). Patients diagnosed with luminal B BC are younger at diagnosis, are less likely to consume alcohol and are less likely to use hormone replacement therapy (HRT) and oral contraceptives. Patients diagnosed with TNBC are younger, African American, more likely to have not breastfed, and overweight. Patients diagnosed with Her2-overexpressing tumours are younger at diagnosis, Hispanic or Asian, and less likely to use HRT \(^{(10)}\). The luminal-A subtype is diagnosed in older women and has a stronger correlation with favourable clinicopathological factors (smaller tumour size, lower histologic grade, and earlier TNM stage) than the triple-negative or HER2 subtypes \(^{(12)}\). Women with TN breast cancer exhibit a higher family history of BC. The 5-year overall/disease-free survival
percentages for the luminal A, luminal B, HER2, and triple-negative subtypes are 92.9%/88.6%, 88.6%/85.1%, 83.2%/79.1%, and 80.7%/76.0%, respectively (12). The TN and HER2 subtypes are associated with poorer outcomes compared with the luminal A subtype among Chinese women (12). The Her-2 subtype is found to be more prevalent in the Chinese population compared with the Western population. These results suggest the importance of Her-2 detection and anti-Her-2 therapy that may potentially benefit a higher proportion of breast cancer patients in China (12). Among Asian-Americans, Korean and Filipino women, there is a higher prevalence of Her-2 tumours (36% and 31%, respectively), followed by Vietnamese (29%) and Chinese (26%) women, whereas Japanese and South Asian women exhibit a higher frequency of Her-2 tumours (approximately 19-23%) (12). Young breast cancer patients in Taiwan are shown to exhibit a higher prevalence of the luminal A subtype and a lower prevalence of histologic grade 3 tumours and/or the basal-like subtype. Furthermore, these features are distinct from young breast cancer patients in Western countries (13).

Results

A total of 542 cases were available for evaluation including 7 male (all are Omani) and 535 female (452 Omani and 83 Non-Omani). The subgroup analyses of Omani female patients are shown in Table 1 and Figures 1-4. We observed that 49.5% of patients displayed left sided tumours, and 6.3% of patients exhibited bilateral tumours. IDC (invasive ductal carcinoma) was observed in 80.6% of patients. The luminal A subtype as the most common, but was less than that observed in Western females (Table 2). BCL subtype was highest among Omani females compared with Western females.

Age (cut off of 50 years) was a significant factor in basal-like (63.8% younger than 50 years vs. 36.2% older than 50 years) and Her-2 tumours (60.9% vs. 39.1%). We observed that high-grade tumours were less frequent in luminal A tumours (19%) and more frequent (41%) in basal-like tumours. Higher stage at presentation (Stage III and IV) was observed more in Her-2 tumours (59%), and mortality was higher in basal-like/TN tumours (22.4%) compared with other subtypes. Table 2 shows a comparison with other selected published data. Interestingly, analysis of the 7 male breast cancer patients showed that 42.9% patients displayed right-sided tumours, whereas 57.1% of patients exhibited left-sided tumours. The luminal A subtype was diagnosed in 71.4% of patients, whereas luminal B was diagnosed in 28.6% of patients. Other subtypes were not reported. All male tumours exhibited IDC (100%). One patient (14.3%) was younger than 50 years of age, whereas 6 (85.7%) patients were older than 50 years.

Discussion

Investigators must acknowledge the existence of the molecular subtypes of breast cancer; perhaps these subtypes are genuinely from different cells of origin. A need exists to design research protocols and clinical studies accordingly to bring us closer to the successful treatment of breast cancer patients. Therefore, anticipate that a classification scheme that identifies more homogeneous tumours built on the intrinsic molecular subtypes will lead in
Breast Cancer Molecular Subtypes in Oman, I. Medhi, et al.

Table 1. Lab findings at presentation of patients with DLBCL compared to other subtypes of NHL

<table>
<thead>
<tr>
<th>Study/Parameter</th>
<th>Southern Switzerland (Ticino)</th>
<th>The Polish Breast Cancer Study</th>
<th>The Carolina Breast Cancer Study</th>
<th>National Oncology Center Royal Hospital, Oman</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients / IHC markers Performed</td>
<td>1214 (91%)</td>
<td>804 (34%)</td>
<td>496 (43%)</td>
<td>452 (100%)</td>
</tr>
<tr>
<td>Age</td>
<td>All Ages</td>
<td>20-74 years</td>
<td>All Ages</td>
<td>20-74 years</td>
</tr>
<tr>
<td>Race</td>
<td>Caucasian</td>
<td>Caucasian</td>
<td>African and Non-African Americans</td>
<td>Omari, Arab</td>
</tr>
<tr>
<td>Luminal A</td>
<td>13.2%</td>
<td>9%</td>
<td>54.8%</td>
<td>34.7%</td>
</tr>
<tr>
<td>Luminal B</td>
<td>13.6%</td>
<td>6%</td>
<td>16.6%</td>
<td>15.9%</td>
</tr>
<tr>
<td>Her2 vve</td>
<td>5.6%</td>
<td>12%</td>
<td>7%</td>
<td>24.1%</td>
</tr>
<tr>
<td>BCL (TNBC)</td>
<td>7.4%</td>
<td>8%</td>
<td>21.5%</td>
<td>25.3%</td>
</tr>
</tbody>
</table>

Table 2. Comparison of subtypes with other studies

<table>
<thead>
<tr>
<th>Tumour Grade</th>
<th>Molecular Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>G2</td>
</tr>
<tr>
<td>7.6%</td>
<td>30.5%</td>
</tr>
</tbody>
</table>

There is a significant heterogeneity of associations by tumour subtype. Future research should focus on the refinement of the tumour subtypes into more homogenous subgroups to best elucidate how risk factors may vary by subtype. Important modifiable factors that may be related to the development of specific tumour subtypes include obesity and possibly breastfeeding (triple negative) and alcohol consumption (luminal B), but no clear modifiable risk factor profile was apparent for Her2-overexpressing subtypes due to a limited sample size. Accordingly, public health programs aimed towards achieving healthy weight and promoting breastfeeding might reduce the number of poor outcomes.
prognostic triple negative tumours among all breast cancer cases\textsuperscript{(10)}.

Molecular subtyping of breast tumours using a six-marker immunohistochemical panel can identify patients who are at increased risk of local and regional recurrence \textsuperscript{(16)}. A previous study of 2985 cases reported that luminal A tumours are associated with a low risk of local or regional recurrence\textsuperscript{(16)}. Furthermore, local recurrence was particularly low for the luminal A subtype \textsuperscript{(17)}; however, the rates vary by subtype. HER-2 and basal subtypes were associated with increased local recurrence; and neither margin status, tumor size, age, nor nodal status was significant. However, the biology underlying these observations remains poorly understood. Nuyten et al. obtained gene expression data on 161 patients treated with BCS, using a 380-gene list which was found to be prognostic, were able to isolate a subgroup of patients at high risk for local recurrence \textsuperscript{(16)}. Hormonal receptor status, HER-2, and the constructed subtypes are predictive of locoregional recurrence and survival after adjuvant radiotherapy\textsuperscript{(18)}. Therefore, we may be able to identify the underlying biological mechanisms associated with local tumor aggressiveness, nodal metastasis, and radiation response. Additional studies will be required to identify the most effective treatment modality to address a higher risk of locoregional relapse; including more extensive surgery, systemic therapy, or radiotherapy\textsuperscript{(16)}.

Fig. 4: Molecular Subtypes

Breast cancer arising in young women is a unique biologic entity driven by unifying oncogenic signaling pathways, and is characterized by lower hormone sensitivity and higher HER-2 expression. These observations warrant further study to offer this poor prognostic group better preventative and therapeutic options\textsuperscript{(21)}. Very young patients with luminal B, HER2+ve and triple negative subtypes are at an increased risk for LRR (locoregional relapse), DM (distant metastasis), BCE, and death compared with older patients \textsuperscript{(22)}. Conversely, age was not a significant factor reported in the luminal A subtype\textsuperscript{(22)}.

The definition of estrogen receptor (ER) positivity remains controversial. Recent joint guidelines by the American Society of Clinical Oncology (ASCO) and the American College of Pathologists recommended that ER status should be considered positive if 1% or more of tumor cells demonstrate positive nuclear staining using IHC (immunohistochemistry). Historically, many investigators and clinicians considered 10% or greater nuclear staining to be the threshold for defining ER-positive status.
A minority of the 1% to 9% IHC ER–positive tumours show molecular features similar to those of ER-positive, potentially endocrine-sensitive tumours. The safest clinical approach may well be to use both adjuvant endocrine therapy and chemotherapy in this rare subset of patients (7). The overall discordance rate between primary cancer and LRR was 9% for estrogen receptor expression, 22% for progesterone receptor expression and 4% for Her-2 expression. LRR correlates with a high risk of subsequent events and death, specifically in patients with the TNBC subtype (23). The patients with ER-negative tumours and HER-2 positive tumours showed a better response to adjuvant taxane-containing chemotherapy. Moreover, the magnitude of the effect for the classical combination of chemotherapy using cyclophosphamide, methotrexate and fluorouracil regimen was reported to be larger in the TNBC subtype. With respect to the concordance of HER2 status between primary tumor and metastasis, a higher rate of discordance was found in 33.2% of cases, 23.6% changed from positive to negative, and 9.6% changed from negative to positive. Other studies have reported hormone receptor status discordance rates of 21%-28% (predominantly loss of hormonal receptors) between primary and breast relapse (23).

A significant association has been observed between early age at menarche and risk of luminal disease (24). A Japanese population based study reported that reproductive events in adolescence have differential impacts on the risk of breast cancer molecular subtypes (24). Many studies from Western countries have reported associations between breast cancer and reproductive factors with respect to the molecular subtype (24). Reproductive factors are associated with hormone receptor-positive tumours. The risk of luminal breast cancer is associated with early age at menarche, late age at menopause, and use of hormone replacement therapy (24).

Systematic studies of breast cancer in Africa have not confirmed the suggestion that African breast tumours are predominantly receptor poor (25). This issue is compounded by the lack of methodological standardization of IHC, even in developed countries, which results in up to 20% variation in false positives and negatives and suboptimal utilization of the information currently generated by receptor assays (25). The poor prognosis of breast cancer among African women has important clinical and policy implications for breast cancer control in Africa. Furthermore, mammographic screening may not work, and low resource treatments such as oophorectomy or tamoxifen may be ineffective without the knowledge of the patient’s hormone receptor status. A need exists for research into the etiology and pathogenesis of the aggressive molecular subtypes that disproportionately affect young women of African ancestry. Only then can we begin to close the gaps of global disparities in breast cancer outcomes across populations (10).

Four population-based studies, which used the same immunohistochemistry markers, have been previously reported and summarized in Table 4 (5, 10-11, 27). The Carolina Breast Cancer Study exhibited higher prevalence in luminal A (36% versus 59%; P < 0.001) and a higher prevalence of basal-like subtype (39% versus 14%; P < 0.001) compared with postmenopausal African Americans. The higher prevalence of the basal-like subtype could contribute to the poor prognosis of premenopausal African Americans with breast cancer. In non-African Americans, the frequencies of luminal A (51% versus 58%; P = 0.20) and basal-like (16% versus 16%; P = 0.94) subtypes did not differ significantly between premenopausal and postmenopausal patients. A Polish study showed that premenopausal patients had a higher prevalence of the basal-like subtype (17% versus 10%; P = 0.02) but a similar prevalence of other subtypes compared with postmenopausal patients (27). Although that study was limited by its consideration of age instead of menopausal status, the implications of the findings based on the experimental design are supported by the Carolina Breast Cancer Study, which showed that analysis based on
age <50 and ≥50 years rather than menopausal status did not affect the results (11). In addition, the definition of HER-2 positivity varied among these four previous population-based studies. In the present study, HER-2 positivity was defined as either a 3+ or 2+ staining intensity by IHC or by gene amplification detected by FISH. These criteria have been universally adopted in clinical practice and trials for HER-2-targeted therapy (7).

The 12th St Gallen International Breast Cancer Conference (2011) Expert Panel adopted a new approach to the classification of patients for therapeutic purposes based on the recognition of intrinsic biological subtypes (28). Luminal A disease generally requires only endocrine therapy, which also forms part of the treatment of the luminal B subtype. Chemotherapy is indicated for most patients with luminal B, HER-2 positive, and triple negative disease with the addition of trastuzumab in HER-2 positive disease (28).

The high frequency of brain metastases among patients with HER2-enriched (28.7%), basal-like (25.2%), and TN nonbasal (22%) disease support a more aggressive approach to imaging and managing patients with newly diagnosed distant disease. Studies of specific CNS preventive agents may be beneficial in basal-like and HER-positive early breast cancer (9). In addition, the baseline 18F-FDG tumoral uptake and its early response in NAC (neoadjuvant chemotherapy) are different according to the immunohistological subtypes of breast cancer (29).

Conclusion

In Oman, the female population is as follows: 7.5% of females are above 50 years of age, 44.5% are 20-50 years old, and 48.5% are less than 20 years of age (4). Breast cancer accounted for 23.1% of all cancers diagnosed in Oman in 2009 (53.8% of patients were between 20-50 years of age and 46.2% of patients were above 50 years of age). T2 tumor size was most common (39.3%), Node positive tumors were observed in 62.3% of patients and 19% of patients had M1 stage disease. Stage II and III were most frequently (69%) observed in the BC patients. BCL and Her2 tumours are more frequent in Oman, and occur at a younger age. High-grade tumours are more frequently observed in BCL (41%) and least observed in luminal A (19%) BC. A higher stage at presentation was more frequently detected in patients diagnosed with the Her2+ and BCL types (59% and 51%) respectively, whereas early stage at presentation was more frequently observed in the luminal B and luminal A (59% and 55%) subtypes. Mortality was higher in the BCL and Her2+ subtypes at 22% and 18% respectively. A previous Oman study by Mansour et al showed a similar stage pattern and that Her2+ve tumours were detected more frequently in older age groups (>40 years) exhibiting a poor treatment response(30). Another study of Omani patients showed that Her2+ve cases were observed in 37.8% of patients, and TNBC cases were detected in 25% of patients. In addition, 83% of the Her2+ diagnosed patients were above 35 years of age and more T4 stage cancer was diagnosed in this group (31). A study performed in Saudi Arabia by Al-Tamimi et al. (32) reported that Her2+, TNBC, and BCL tumours were diagnosed in 28%, 39% and 11% of patients respectively. Soumaya et al. (33) reported that luminal A was diagnosed in 52% of patients from Tunisia. They also showed that BCL and Her2+ tumours were directly proportional to T size, grade, and high nodal (>4 nodes) metastasis; and have a 4.2 times higher likelihood of metastasis. Yimin et al (34) reported that the luminal A subtype was observed in 83% of patients and that no BCL or Her2+ tumours were diagnosed in a small study of male breast cancer from Texas USA (n=42).

Breast cancer has been dichotomized into triple negativity or otherwise (35, 41). Recent studies have suggested that the clinical and pathological response to chemotherapy varies and that ER/PR+, Her2+ subtype showed a better response to chemotherapy (35-37). ER/PR+, Her2+ tumours virtually always have a high recurrence score (6). Recently it has been shown in a retrospective analysis that ER/PR+, Her2-tumours may benefit less from taxanes in the adjuvant setting (37-38). Studies that have classified more than four subtypes are plagued by controversies of small sample size and multiplicity of variables (37-39). The clinical and pathological response, and
recurrence rate varies (35-38). ER/PR+ and Her2+ subtypes show a better response to chemotherapy especially to adjuvant taxanes (35-36, 38).

Sub-typing breast cancer by gene expression analysis using microarrays is the best method to perform such molecular classification. Moreover, until recently when Oncotype DX and MammaPrint became commercially and widely available, such assays were limited to research laboratories and therefore, were not always available. The IHC-based classification systems are useful in clinical practice, especially when fresh tissue is not available, and has been shown to correlate well with intrinsic classification using gene expression microarrays (1, 35). It is worth noting that the reliability of the ER/PR and Her2 testing is not absolute, with substantial intralaboratory and interlaboratory variation (because of fixation, antigen retrieval, and staining methods)(9, 16, 40). Efforts should be directed towards standardization of current testing, and development of more reliable and reproducible testing for ER/PR and Her2/neu expression(9, 16, 40).

These molecular differences may have diagnostic, therapeutic and prognostic implications. Large scale and multi-centre studies may confirm these findings with respect to ethnicity and other variables. These molecular differences can be translated and incorporated to management strategies wherever applicable. Consensus regarding the definitive prognostic/predictive analysis has yet to be reached, but significant progress continues in the ongoing search for a specific, rigorous and reproducible method of identifying successful treatment algorithms utilizing biological markers(3).

Breast tumours in Oman develop in a different endocrine/genetic environment due to early motherhood, multi-parity, prolong periods of breast feeding and consanguineous marriages. These circumstances may contribute to a different spectrum of molecular subtypes. In addition, the molecular subtypes may have different tumor cell dynamics that affect the tumor size, stage at presentation, and metastatic potential. Therefore this phenomenon may influence the efficiency of detection modalities and treatment outcomes. These molecular differences have diagnostic, therapeutic and prognostic implications. Large-scale multi-centre studies may confirm these findings with respect to ethnicity and other variables. These molecular differences can be translated and incorporated to management strategies.

References


