Molecular genetics complexity impeding research progress in breast and ovarian cancers (Review)

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Abstract. Breast and ovarian cancer are heterogeneous diseases. While breast cancer accounts for 25% of cancers worldwide, ovarian cancer accounts for 3.5% of all cancers and it is considered to be the most lethal type of cancer among women. In Oman, breast cancer accounts for 25% and ovarian cancer for 4.5% of all cancer cases. Various risk factors, including variable biological and clinical traits, are involved in the onset of breast and ovarian cancer. Although highly developed diagnostic and therapeutic methods have paved the way for better management, targeted therapy against specific biomarkers has not yet shown any significant improvement, particularly in triple-negative breast cancer and epithelial ovarian cancer, which are associated with high mortality rates. Thus, elucidating the mechanisms underlying the pathology of these diseases is expected to improve their prevention, prognosis and management. The aim of the present study was to provide a comprehensive review and updated information on genomics and proteomics alterations associated with cancer pathogenesis, as reported by several research groups worldwide. Furthermore, molecular research in our laboratory, aimed at identifying new pathways involved in the pathogenesis of breast and ovarian cancer using microarray and chromatin immunoprecipitation (ChIP), is discussed. Relevant candidate genes were found to be either up- or downregulated in a cohort of breast cancer cases. Similarly, ChIP analysis revealed that relevant candidate genes were regulated by the E2F5 transcription factor in ovarian cancer tissue. An ongoing study aims to validate these genes with a putative role as biological markers that may contribute to the development of targeted therapies for breast and ovarian cancer.

1. Introduction

Breast cancer (BC) is considered to be the most frequently diagnosed type of cancer (12%) among women worldwide (1). In 2012, 1.7 million BC cases were reported, accounting for 25% of cancer cases worldwide (2). In developing countries, BC is the most common cause of death (14.3%), whereas in developed countries it is the second cause of cancer-related mortality (15.4%) (1). In Oman, BC is the leading malignancy among women, accounting for ~26% of all cancer cases (3) and the age-standardized incidence rate (ASIR) is 15.6 per 100,000 (4). Interestingly, when compared with the worldwide data, women in Oman are affected at a comparatively younger age (<50 years) and usually present to the clinic with advanced disease (stage III/IV) and a more aggressive phenotype (4,5).

Ovarian cancer (OC) is considered to be the seventh most common type of cancer among women, with 239,000 OC cases recorded in 2012 alone, accounting for 3.6% of cancer cases (1). Although rare, OC is considered to be the most lethal gynecological malignancy, with a mortality rate of 4.3% (1). In Oman, OC accounts for 4.5% of all cancer cases and the related ASIR is 10.2 per 100,000 (3).

2. Types of breast and ovarian cancer

BC is characterized by an uncontrolled growth of mammary epithelial cells (luminal or ductal) during the proliferative state. The tumor may develop from hyperplastic breast tissue, appearing during the early stages as carcinoma in situ within the ducts or lobules [ductal or lobular carcinoma in situ (DCIS and LCIS, respectively)] or, subsequently, as invasive...
carcinoma infiltrating connective and fatty tissue [invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC)] (6,7) (Table 1A). Among non-invasive BCs, DCIS is considered to be the most common type (8), whereas IDC is the most common type among invasive tumors, constituting 80% of the diagnosed cases (9) (Table 1A).

Similarly, ovarian tumors may be classified based on the cells of origin. The majority of ovarian tumors fall into one of the three main categories: Surface epithelial tumors, sex cord-stromal tumors and germ cell tumors (Table 1B) (10). While sex cord-stromal tumors are common in postmenopausal women aged >50 years (11), germ cell tumors arise from the oocytes and are more common during adolescence (12,13).

Epithelial ovarian cancer (EOC), which is considered to be the most lethal among all ovarian malignancies, arises from the ovarian surface epithelium (14). Malignant tumors of the ovarian surface epithelium are referred to as carcinomas, they may spread locally as well as distally and may become life-threatening. Benign tumors of the ovaries include serous adenomas, mucinous adenomas and Brenner tumors, and they are not associated with severe disease (15).

3. Pathogenesis of breast and ovarian cancer

BC and OC are heterogeneous diseases with variable biological and clinical distinguishing traits, such as ethnic and racial factors, that affect metastasis (5). During tumor progression, cells undergo epithelial-to-mesenchymal transition (EMT), thus increasing cell invasion and initiating the process of metastasis, one of the hallmarks of cancer (16,17). The last phase of primary tumor development is progression; new blood vessels are formed in the primary tumor (angiogenesis) promoting tumor cell invasion. Generally, BC cells metastasize to the bone, liver, lung and brain (18), whereas OC cells most commonly metastasize to the liver, spleen or lungs (17); they also invade and exfoliate into body cavities, particularly the peritoneal space, where they grow in suspension within effusions (19).

4. Risk factors

Researchers have identified several environmental factors contributing to the risk of developing BC and OC. Higher age at menarche, high hormonal levels, nulliparity, tobacco use and obesity (20-26) are well-known risk factors associated with 47% of BC and OC cases (27).

Approximately 5-10% of the cases are attributed to genetic factors that include BRCA (BRCA1 and BRCA2) gene mutations (28,29). BRCA1/2 are autosomal dominant tumor suppressor genes present on chromosomes 17 and 13, respectively, mutated in ~30-40% of familial BC cases (30) and in 60-85% of hereditary OC cases (31,32).

5. Genetic factors

The majority of BC and OC cases are sporadic; genetic changes develop during the patient’s lifespan and are exclusively present in somatic cells (somatic mutations). Less commonly, BC and OC, germline mutations usually inherited from one parent are present in almost all cells of the body and increase the risk of developing BC or OC. In individuals with germline mutations, changes in other genes, along with environmental and lifestyle factors, also play a role in the development of either BC or OC.

Genes contributing to the tumorigenesis of sporadic BC and OC fall into two categories: Oncogenes and tumor suppressors. The most relevant genes are recapitulated in Table II.

The mechanisms underlying malignant progression in both BC and OC (multigene diseases) are yet to be elucidated. Several genetic changes are detected in these tumors, although the frequency of different gene alterations is quite low (33). Germline mutations in various other genes, referred to as ‘low penetrance’ or ‘moderate penetrance’ contribute to only a small or moderate overall risk and are considered to be potential risk factors (34). However, certain genes, referred to as ‘significantly mutated genes’ (SMGs) were recently identified and suspected to be the initiators of malignant transformation (35). While some of these genes encode proteins interacting with the BRCA1/2 proteins, others act through different pathways (34). Variations in these genes are suspected to significantly increase the risk of developing BC and/or OC.

6. Prognostic and predictive factors

A number of prognostic and predictive factors are investigated in BC and OC, including estrogen receptor (ER) and progesterone receptor (PR) status and human epidermal growth factor receptor 2 (HER2)/neu gene amplification (36,37). Although markers such as steroid receptor status, nodal status, tumor size and age at diagnosis had been used for several years (38), none are considered to be reliable predictors of disease outcome. In addition, although EOC is known to be an extremely heterogeneous disease, patients tend to receive the same treatment; thus, prognostic and predictive markers are urgently needed to differentiate between different subpopulations in order to optimize treatment.

The International Federation of Gynecology and Obstetrics (FIGO) staging system is an independent prognostic marker for OC with a well-established significance (39). The FIGO system predicts >95% 5-year survival for patients with stage I disease, compared with a 5-year survival of <10% for stage IV patients (40,41). Prognostic factors other than FIGO stage include age, American Society of Anesthesiologists score, family history positive for BRCA1/2 mutations, residual disease after surgery, tumor grade and histology, amount of ascites at debulking surgery, serum level of carbohydrate antigen (CA)-125, gene expression patterns and immunological status (42). In BC and OC, however, the two most important prognostic factors for a favorable outcome remain surgery and sensitivity to platinum-based chemotherapy (43,44).

For BC, the prognostic factors include lymphatic or vascular invasion, age, histological grade and subtype (45). Low-grade tumors have a better prognosis, while high-grade tumors have a poorer prognosis (46). The absence or presence of axillary lymph node involvement is considered to be the most significant prognostic factor for BC (38) and it is evaluated during sentinel lymph node biopsy or axillary dissection. Another independent prognostic factor is tumor size: Larger tumors are correlated with a worse prognosis and a high risk of nodal metastasis (38).
Table I. Types of breast and ovarian cancer.

### A. Types of breast cancer

| Types                          | Prevalence, % | (Refs.) |
|--------------------------------|---------------|---------|
| Carcinoma in situ              |               |         |
| LCIS                           | 15            | (30)    |
| DCIS                           | 25            | (8)     |
| Invasive carcinoma             |               |         |
| IDC                            | 80            | (9)     |
| ILC                            | 10-15         |         |
| Other types                    |               |         |
| Medullary carcinoma            | 5             |         |
| Mucinous carcinoma             | 2             |         |
| Tubular carcinoma              | 2             | (9)     |
| Inflammatory breast cancer     | 1             |         |
| Paget’s disease of the nipple  | 1             |         |
| Phyllodes tumor                | <1            | (173)   |

### B. Types of ovarian cancer

| Types                          | Prevalence, % | (Refs.) |
|--------------------------------|---------------|---------|
| Sex cord-stromal tumors        |               |         |
| Granulosa cell tumors          |               |         |
| Theca cell tumors              | 10-20         | (11)    |
| Sertoli-Leydig cell tumors     |               |         |
| Hilar cell tumors              |               |         |
| Germ cell tumors               |               |         |
| Teratomas                      | 60            | (12)    |
| Dysterminomas                  |               |         |
| Endodermal sinus tumors        |               |         |
| Choriocarcinomas               |               |         |
| EOC                            | 80-90         |         |
| Serous carcinomas              | 40-60         | (174,175) |
| Endometrioid carcinomas        | 10-20         |         |
| Mucinous carcinomas            | <3            |         |
| Clear-cell carcinomas          | 5-10          |         |

LCIS, lobular carcinoma in situ; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; EOC, epithelial ovarian cancer.

Hormonal receptor (ER/PR) status and amplification of the HER2/neu gene are used as prognostic as well as predictive factors (47). In BC, the ER+/PR+ status is associated with reduced mortality compared with ER+/PR- cases (48); tumors having >1% ER+ cells are associated with better survival rates compared with ER- tumors (47,49); thus, ER is considered to be a reliable prognostic factor. In OC, primary tumors are not usually screened for ER status, although several studies report that nearly 40-50% of ovarian tumors are ER+/PR+ (50,51). In BC, the ER/PR status is also a powerful predictive factor for the probability of benefit from adjuvant hormonal therapy (aromatase inhibitors and tamoxifen) (48,52,53). Similar to its predictive role in BC, increased ER-β/PR ratio predicts favorable survival in OC (36).

HER2/neu and Ki-67 are prognostic factors used in ~20% of BCs overexpressing HER2/neu and they are considered as strong prognostic factors for relapse and poor overall survival, particularly in node-positive cases (54,55). As a predictive factor, HER2/neu status predicts response to treatment with the anti-HER2 monoclonal antibody trastuzumab (56) and may predict resistance to alkylating agent-based chemotherapy (57). Elevated levels of HER2 are associated with worse survival in OC (36). Apart from these receptors playing a predictive role, the expression of another sex steroid hormone receptor, androgen receptor (AR), has been associated with a favorable outcome in BC and OC (58).

Mammaglobin B was identified as a prognostic marker in EOC; its expression is used to determine less aggressive forms of EOC and it is correlated with a favorable outcome (59). Several molecular studies on OC have demonstrated differential expression of certain genes, including the myelin and lymphocyte (MAL) gene in long-term survivors. The MAL gene confers resistance to cancer therapy and exhibits a 3- and 29-fold increase in expression in short-term survivors compared with long-term survivors and early-stage patients, respectively (60). Similarly, three other genes, cytochrome P450 4B1, choline/ethanolamine phosphotransferase 1 and charged multivesicular body protein 4A, are differentially regulated in patients suffering from recurrent OC (61). A recent study demonstrated that the expression of EMT-related genes, such as zinc finger E-Box-binding homeobox 2 (ZEB2) and cadherin 1 (CDH1), play important roles in the invasion process of advanced-stage serous OC. ZEB2 expression was found to be independently associated with poor prognosis (62).

Other factors, such as the epithelial growth factor receptor family, S phase fraction (63), p27, p53, cathepsin D levels, angiogenesis markers (42) and DNA ploidy analysis (57), may have a prognostic/predictive impact; however, they are not used clinically. Although cyclooxygenase-2 expression was determined as a prognostic factor for poor outcome and a predictor of resistance to chemotherapy in patients with EOC, it requires further validation (64).

The major prognostic and predictive factors are summarized in Table III.

7. Diagnosis and management

BC is diagnosed by self-examination, clinical examination, mammography, ultrasound and magnetic resonance imaging (65,66), whereas the current screening methods for OC consist of a combination of pelvic examinations, measurement of serum CA-125 levels and transvaginal or pelvic ultrasonography (67). However, since no test has been found to be sensitive or specific, only 19% of OC cases are diagnosed at an early stage (stage I-II), whereas ~7% of OC cases are diagnosed with regional spread and the majority (68%) are diagnosed with distant spread (68).

The National Comprehensive Cancer Network has recommended the Scarff-Bloom-Richardson criteria or the Nottingham score for BC grading (69,70). In OC, FIGO and the American Joint Committee on Cancer classify
patients into groups depending on tumor spread to help with diagnosing further progression, prognosis and treatment recommendations.

8. Treatment

Treatment of BC. The management of BC is determined based on anatomical staging (tumor size, nodal involvement and metastasis) and tumor grading (morphological characteristics) (71). The most common treatment for DCIS is lumpectomy (72). Systemic treatment of BC includes use of cytotoxic, hormonal and immunotherapeutic agents. Systemic agents are active at the beginning of the treatment in the majority (90%) of primary and in ~50% of metastatic BCs (73). However, after a certain period of time, tumor progression occurs, as resistance to therapy is a common occurrence (73).

Treatment of OC. The golden standard therapy for EOC includes debulking surgery and adjuvant combination chemotherapy. In cases of relapse, however, hormonal therapy with tamoxifen or an aromatase inhibitor are often considered (74). Systemic agents are active at the beginning of the treatment in the majority (90%) of primary and in ~50% of metastatic BCs (73). However, after a certain period of time, tumor progression occurs, as resistance to therapy is a common occurrence (73).

Certain compounds targeting specific pathways, including poly(ADP) ribose polymerase (PARP) inhibitors (ABT888 and olaparib), mammalian target of rapamycin pathway inhibitors (temsirolimus and everolimus), or mitogen-activated protein kinase pathway inhibitors (caboziutinib) are under clinical evaluation in phase I/II trials for the management of BC and OC, their metastasis and relapse (79-82).

Resistance of tumors to certain drugs leads to treatment failure and death in >90% of patients with advanced disease. Poor prognosis is often associated with relapse and metastasis and, hence, gene expression profiling is currently widely used to identify strong predictive markers (16) that may be used to identify patients who are likely to benefit from specific treatment options, including chemotherapy or endocrine therapy, alone or in combination (83,84). A comprehensive review of gene expression profiling performed in BC and OC to identify potential candidate markers to improve diagnosis and prognosis is presented below.

9. Tumor gene expression profiling

Microarray technologies have revolutionized research, allowing high-throughput whole-genome gene expression profiling, and have enabled researchers to provide insight into several diseases in a single experiment, as well as create a molecular profile of tumor progression (85,86).

Gene expression profiling in BC. Gene expression microarray has allowed researchers to investigate BC based on its molecular classification utilizing one of two platforms, namely cDNA microarrays and DNA microarrays. cDNA microarrays are based on the hybridization of complementary DNA (cDNA) probes to DNA targets on a glass or silicon substrate. DNA microarrays, on the other hand, use highly purified, biotinylated or digoxigenin-labeled cDNA as targets. The advantages of cDNA microarrays include their ability to analyze thousands of genes at once, their low cost, and their broad availability. However, they have several limitations, including the need for large amounts of starting material, the potential for cross-hybridization, and the inability to perform multiple experiments on the same sample.

DNA microarrays, on the other hand, have a number of advantages over cDNA microarrays. They allow for the simultaneous analysis of thousands of genes, they are highly reproducible, and they can be used to analyze small amounts of tissue. However, they also have several disadvantages, including the need for large amounts of starting material, the potential for cross-hybridization, and the inability to perform multiple experiments on the same sample.

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Table II. List of oncogenes and tumor suppressor genes involved in breast and ovarian cancer.

| Genes          | Breast cancer, % | (Refs.) | Ovarian cancer, % | (Refs.) |
|----------------|------------------|---------|-------------------|---------|
| HER2/ERBB2     | 20-30            | (176)   | 20-50             | (177,178) |
| ER             |                   |         |                   |         |
| ERα            | 20               | (179)   | Rare event        | (180)   |
| ERβ            |                   |         |                   |         |
| K-RAS          | 5                | (181)   | 20-50% of borderline/low malignant potential tumors | (182,183) |
| c-Myc          | 194              | (184)   | 50                | (185)   |
| Cyclin D1      | 50               | (186)   | 26-32             | (185,187) |

A. Oncogenes

| Genes          | Breast cancer, % | (Refs.) | Ovarian cancer, % | (Refs.) |
|----------------|------------------|---------|-------------------|---------|
| HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; K-RAS, Kirsten rat sarcoma viral oncogene homolog; PTEN, phosphatase and tensin homolog; RB1, retinoblastoma gene.
introduced in 2000 by Perou profiling (cDNA microarrays) into intrinsic subtypes was the development and progression of cancer (regarding the complex interaction between genes involved in tumor cell aids in providing etiological and diagnostic clues. The identification of a gene signature specific to a type of several gene expression profiles of human breast tumors. classification of BC subtypes via hierarchical clustering of treatment for ILC (AKT1 mutations in ILC rather than in IDC, individualizing study demonstrated a higher incidence of HER2, HER3 and suggesting ILC to be a distinct BC subtype (AKT activation and aberrations in T-box transcription factor 3, including loss of CDH1 and phosphatase and tensin homolog, AKT activation and aberrations in T-box transcription factor 3 and forhead box protein A1, differentiating ILC from IDC and suggesting ILC to be a distinct BC subtype (103). That study further provided potential therapeutic options (103). Another study demonstrated a higher incidence of HER2, HER3 and AKT1 mutations in ILC rather than in IDC, individualizing treatment for ILC (104). Various studies utilizing this technology have allowed classification of BC subtypes via hierarchical clustering of several gene expression profiles of human breast tumors. The identification of a gene signature specific to a type of tumor cell aids in providing etiological and diagnostic clues regarding the complex interaction between genes involved in the development and progression of cancer (85,86,105). The first molecular classification of BC using gene expression profiling (cDNA microarrays) into intrinsic subtypes was introduced in 2000 by Perou et al (87), who classified BC into four molecular subtypes: Luminal (A and B), HER2, basal-like and normal-like using hierarchical cluster analysis (87).

A similar study using DNA microarray on primary breast tumors of 117 patients revealed a 70-gene signature (poor-prognosis signature) involved in cell cycle, angiogenesis, invasion and metastasis, as well as signatures that recognize tumors harboring BRCA1 mutations (98). Another study demonstrated that different molecular subtypes were associated with a different prognosis, and further subdivided the luminal group into luminal A and B (90). Based on these subtypes, Expert Consensus established four clinicopathological definitions, recommending therapeutic strategies for each group (Table IV) (106).

Major sequencing platforms have allowed for identification of several SMGs; there were significant differences in the SMGs present in the luminal subtype compared with the basal-like subtype. Furthermore, The Cancer Genome Atlas (TCGA) research network identified 20 SMGs in luminal A, 8 SMGs in luminal B and only 3 in the basal-like subtype, indicating the complexity of the latter subtype (107). Genomic sequencing in BC has identified somatic and point mutations in HER2 (108,109) and ESR1 (110,111), respectively. However, there are currently no drugs targeting these mutations, and future research involving alternative endocrine therapies may prove efficient.

Other diagnostic platforms based on gene expression profiling were developed, including OncotypeDX (112) and MammaPrint (98), which aid in selecting hormonal or cytotoxic therapy for the treatment of BC patients. Furthermore, the triple-negative subtype is highly heterogeneous and its classification is based on immunohistochemical biomarkers and limited gene signatures (PAM50 and Lehmann’s system) (88,113). Although these are vital prognostic tools.
their use in the clinical setting is not yet established (114) and, hence, there is a need to develop signatures to improve early diagnosis rates and treatment outcomes.

Contrary to gene expression profiling in BC, where it is used for the molecular classification of BC, gene expression profiling in OC is aimed at identifying and developing potential predictive markers for early diagnosis of EOC. Although a large number of predictive markers have been identified, none are considered reliable for predicting outcome.

**Gene expression profiling in OC.** Over the past few years, researchers have performed a wide array of gene expression profiling based on microarrays to analyze the expression patterns of various genes involved in the onset of OC (115,116). Up to 10% of OCs stem from germline mutations primarily affecting the BRCA1/2 genes, contributing to the carcinogenesis of EOC via different pathways, as suggested by gene expression analysis (117).

Analysis of serous OC by gene expression profiling identified five genes, two of which (ZEB2 and CDH1) were considered to play key roles in the invasion process of advanced-stage cancer (62). Another study in advanced-stage serous OC identified an 86-gene overall survival gene expression profile, of which 13 transcription factors were associated with overall survival. This profile, however, requires further validation prior to being introduced to clinical applications (118). A study using Affymetrix human U133A microarray and Cox regression analysis identified prognostic gene expression signature in sub-optimally debulked patients with serous OC (119).

There is an emerging role of transcription factors as tumor markers, prognostic markers, as well as targets for drug therapy. Tissue microarray and computational approaches identified E2F5 only in EOC samples and not in normal/benign tissues (120). A microarray specific for EOC (OvaChip) confirmed the overexpression of E2F5 and suggested that this transcription factor plays a pivotal role in the neoplastic transformation of several cancer tissues (121).

Microarray-based expression analysis also identified candidate differences in serum miRNAs between healthy women and OC patients. It has been reported that a panel of miRNAs has been used as a screening tool (122,123) to differentiate ovarian tumors based on histological subtype (124). Furthermore, a miRNA profile that distinguishes between preoperative plasma samples from patients with benign conditions and those from OC patients, indicating the mode of treatment to be administered, has been identified (125). Furthermore, three miRNAs (miR-484, -642, and -217) have been found to predict chemoresistance of tumors. Analysis of miR-484 showed that the chemosensitive phenotype is caused by a variation in tumor vasculature through the regulation of the VEGFB and VEGFR2 pathways (126).

Interestingly, cDNA-based microarrays of post-chemotherapy tumors compared with those of primary tumors revealed 85 transcripts with statistically significant overexpression of genes encoding extracellular matrix-related proteins (127). cDNA microarray profiling on EOC tumors identified a 14-gene model that may be used as predictive markers for early recurrence for platinum-paclitaxel combination chemotherapy in primary OC. This is the first study of its kind; however, it requires further validation (128).

Six new molecular subtypes of OC were identified by gene expression profiling: A novel subtype of high-grade serous cancer was identified, displaying a mesenchymal cell type, marked by overexpression of N-cadherin and P-cadherin and low expression of differentiation markers (CA-125 and MUC1); this subtype was associated with a poor prognosis (129). TCGA generated gene expression profiles of 489 high-grade serous ovarian tumors and performed non-negative matrix factorization consensus clustering, discovering four expression subtypes in high-grade serous OC (differentiated, immunoreactive, mesenchymal and proliferative) with different activated pathways (130); these identified subtypes were found to be prognostic (131) and may pave the path for potential therapeutic target discovery (132,133). More recently, semi gene expression clustering analysis in EOC identified two transcriptome classes, namely class I and II tumors, defined as 'hormone-Wnt' class and 'cyclin-Toll-like receptor' class, respectively; however, validation in larger samples is required with pathway analysis for developing therapeutic interventions (134).

A study conducted on patients to define the BRCA1ess profile, identified a gene expression profile associated with platinum and PARP-inhibitor responsiveness, as well as RAD51 foci formation. The BRCA1ess profile consisted of genes such as apurinic/apyrimidinic endodeoxyribonuclease 1, microsomal glutathione S-transferase 3 and PMS1 homolog 1 (117), previously associated with platinum resistance or DNA repair (135,136). Although that study identified a gene expression profile that is associated with BRCA1ess, additional studies are required to administer PARP inhibitors to a larger cohort of EOC patients, regardless of their BRCA1/2 mutation status.

From the abovementioned information, it may be concluded that subtypes based on differential gene expression have been described for EOC (119,129). However, none have been validated in clinical trials or have led to an improvement in treatment strategies to date. As with BC, where gene expression-based assays and the subgrouping of patients have a strong clinical impact and aid individualized therapy (137), this has yet to be developed in OC.

Research in our laboratory is centered on BC and OC in the Omani female population. A differential gene expression analysis was performed, using microarray gene expression profiling on a subset of Omani breast tumors, covering three molecular classifications (luminal A, luminal B and triple-negative) compared with a set of normal/benign breast tumors. Over 1,000 differentially expressed potential genes associated with specific signaling pathways underpinning the transition from benign/normal breast tissue to malignant tumor (P<0.01) were identified. Among several identified genes, BRCA1-interacting protein C-terminal helicase 1 (BRIP1), eyes absent homolog 1 (EYA1) and homeobox B6 (HOXB6) were found to be upregulated, whereas desmoplakin (DSP) and rhophilin 2 (RHPN2) were found to be downregulated. Both sets of genes ([BRIP1, EYA1, and HOXB6] and [DSP and RHPN2]) were selected for further examination.

An earlier study on Omani BC patients revealed no significant mutational rates in BRCA1/2 (138), suggesting that other genes directly linked to BRCA1/2, such as BRIP1, may be involved in the onset of BC, either independently or in
association with BRCA1/2. BRIP1 is involved in DNA damage repair and interacts with the BRCT domains of BRCA1 (139). Although BRIP1 is a tumor suppressor gene (TSG), it is amplified in sporadic cancers (140), which is a major characteristic feature of BC in the Omani population and may be one of the plausible causes for elevated BRIP1 expression. Hence, to prove the oncogenic nature of BRIP1 in Omani patient tumor samples, BRIP1 was selected for further analysis and validation.

Another gene involved in DNA damage repair is EYA1 (141), which is located at 8q13.3. Upregulation of EYA1 expression is associated with BC and OC progression (142). EYA1 is enriched with cyclin D1 in luminal B type BC and is correlated with a poor prognosis (143). However, in our study, EYA1 was only expressed in the triple-negative subtype (19-fold) compared with normal/benign tissues and, thus, it was selected for further analysis; validation may prove its potential as a biological marker for the triple-negative subtype of BC.

The study on Omani BC patients also revealed the involvement of HOXB6 gene in BC. HOX genes are transcription factors involved in principle cellular functions during embryonic development and adult life (144). There are 39 HOX genes in humans organized in four genomic clusters, namely HOXA (7p15.3), HOXB (17p21.3), HOXC (12q13.3) and HOXD (2q31) (144). HOX genes are involved in several cancers (145) including leukemia (146) and cancers of the kidney (147), lung (148), esophagus (149), colon (150), ovary (151-153) and breast (154). Overexpression of various HOX genes (HOXB6, B8, C8 and C9) was recorded at different stages of human colorectal, esophageal and gastric cancer (155). A previous study indicated overexpression of HOXB-6 and -8 in non-tumorigenic polyps, indicating upregulation at an early-stage event in tumorigenesis (150). SEREX immunoscreening identified elevated expression of HOXB6 in ovarian cancer tissue samples compared with normal/benign tissues (152). Another study utilizing microarray analysis identified 6 upregulated and 1 downregulated HOX genes in OC, indicating dysfunction of HOX genes as an early event during malignant transformation (151). High expression of HOX genes, including HOXB6, is predictive of poor clinical outcome in OC (153). Furthermore, in the MCF7 BC cell line, HOXB6 was found to be overexpressed (156), suggesting a plausible role of HOXB6 in breast tumorigenesis. However, to the best of our knowledge, no study on the role of HOXB6 in tissue samples has been performed thus far. Therefore, since this gene exhibited differential expression, it was selected for further analysis. This differential expression suggests that HOXB6 may be used as an indicative marker for diagnosis of early-stage BC.

Among the downregulated genes, DSP belongs to the family of desmosomes involved in cell-cell adhesion located at 6p24.3 (157). Loss of DSP results in abnormalities of cell adhesion (158) and is associated with tumor progression in several cancers (159-161), including BC (162). DSP expression is upregulated by progesterin and downregulated by epidermal growth factor (158). DSP was significantly downregulated in the triple-negative subtype of BC, with the lowest expression in the luminal subtype compared with normal/benign tissue. Thus, DSP was suggested as an indicative marker for BC and was selected for further analysis.

RHPN2, located on 19q13.11, a member of the rhophilin family of Rho-GTPase-binding proteins, is involved in actin cytoskeleton organization, a process critical in cancer cell migration (163). While mutations in the RHPN2 gene are associated with colorectal (164) and lung cancer (165), in malignant glioma RHPN2 may cause mesenchymal transformation by activating RhoA (166). This gene was specifically downregulated in the triple-negative subtype compared with normal/benign tissue. Studies on RPHN2 expression in BC are not well-documented and, hence, RHPN2 was selected for further analysis; its differential expression may suggest this gene as an indicative marker for the triple-negative subtype of BC.

In OC, overexpression of E2F5 is associated with neoplastic transformation and poor prognosis (121). This prompted us to perform chromatin immunoprecipitation (ChIP) analysis using a panel of OC cell lines (MCAS, OVISE and OVASHO) and a specific antibody against E2F5 to pull down the down-stream genes regulated by E2F5. Among the short list of genes selected, F-box/WD repeat-containing protein 7 (FBXW7) was identified as one of the potential genes with an important role in OC pathogenesis.

FBXW7, a member of the F-box protein family located on chromosome 4q31.3 (167), is involved in cell growth, proliferation, differentiation and survival. FBXW7 is a TSG, silenced either due to hypermethylation or mutations/deletions, causing accumulation or increase of several oncoproteins, including c-Jun, c-myc, NOTCH, cyclin E, Aurora-A and ENO1 (168). Reduced FBXW7 expression is associated with the development of a range of cancers, such as those of the stomach, colon and breast (169). However, FBXW7 was recently identified as an oncogene in multiple myeloma, indicating a dual role in cancer (170). The exact role of FBXW7 in the pathogenesis of OC has not yet been fully elucidated. Although missense mutations in FBXW7 are associated with the onset and progression of various tumors (169,171,172), FBXW7 was not found to be frequently mutated in OC. Similarly, our data from gene panel exome sequencing on 6 primary EOC samples compared with 5 normal ovarian tissue samples revealed no mutations and/or deletions, which is in agreement with the latest reports. These results prompted us to suspect FBXW7 of contributing to the pathogenesis of OC through different mechanisms, such as silencing due to promoter hypermethylation. Ongoing experiments in our laboratory aim to validate this hypothesis and assess the effect of FBXW7 on its downstream regulators.

10. Conclusion

Although conventional clinicopathological factors may aid in determining the risk of relapse of OC or BC, they do not fully account for the biological intricacy of those diseases. The presence of highly developed diagnostic and therapeutic technologies has paved the way for BC and OC management. However, the treatment of BC and OC may be challenging, particularly in triple-negative BC and EOC, resulting in high cancer mortality. Biomarkers are urgently needed, since they are useful as prognostic or predictive indicators. Targeted therapy directed against several biomarkers has not yet achieved any significant improvement in the outcome of triple-negative BC or EOC, posing a challenge for researchers
and clinicians. Ongoing research is aimed at developing and implementing prognostic genomic models in clinical practice.

Ongoing research in our laboratory is aimed at identifying genes involved in the pathogenesis of BC and EOC. Microarray analysis and ChIP helped identify several genes in BC and OC, respectively. Based on the literature review and their physiological relevance to the onset of BC, HOXB6, EYA1 and BRIP1 were identified as upregulated and DSP and RHPN2 as downregulated potential candidate genes, while FBXW7 was identified as a candidate gene in OC. Ongoing studies in our laboratory are aimed at validating these genes with a putative potential as biomarkers for BC and OC.

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