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.

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Contents

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 IA). 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 IA).

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 IB) (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

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

A, Oncogenes

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)

B, Tumor suppressor genes

Genes	Breast cancer, %	(Refs.)	Ovarian cancer, %	(Refs.)
BRCA1/2	30	(188,189)	65-80	(188,189)
TP53	25	(190)	50	(191)
PTEN	3.5	(192)	8-40	(193,194)
RB1	33.3	(195)	50% of EOC cases	(196)

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.

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 (74,75). Modest success was achieved by targeted therapy. These drugs target proliferation, angiogenesis, invasion and metastasis. Treatment with the monoclonal antibody cetuximab supplemented with epidermal growth factor receptor was associated with a good prognosis in OC (76). Moreover, the addition of bevacizumab, a monoclonal antibody against vascular endothelial growth factor receptor (VEGFR), to standard chemotherapy drugs, such as carboplatin and paclitaxel, improved the progression-free survival in OC (77,78).

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 (cabozantinib) 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

Table III. Prognostic and predictive factors (57).

Factor	Prognosis	Hormone therapy	Chemotherapy	HER2directed therapy
ER-α/PR	Favourable[a]	Favourable[a]	Unfavourable[b]	Neutral[c]
HER2	Unfavourable[b]	Unfavourable[b]/neutral[c]	Favourable[a]/neutral[c]	Favourable[a]
Ki-67	Unfavourable[b]	Unknown	Favourable[a]	Unknown

[a]Patients with positive result have a better outcome compared to those with a negative result. [b]Patients with positive result have a worse outcome compared to those with a negative result. [c]Patients with positive and negative results have a similar outcome. HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor.

Table IV. Clinicopathological definitions as given by Expert Consensus (106).

Molecular subtype	ER/PR/HER2	Ki-67, %	Recommended treatment
Luminal A	ER^+ PR^+ $HER2^-$	<14	Endocrine therapy
Luminal B	$ER^{+/-}$ $PR^{+/-}$ $HER2^{+/-}$	>14	Endocrine therapy and chemotherapy
HER2-positive	ER^- PR^- $HER2^+$	-	Chemotherapy along with trastuzumab
Triple-negative	ER^- PR^- $HER2^-$	-	Chemotherapy

HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor.

microarrays (87-93) or oligonucleotide arrays (91,94-102). The cDNA microarray and oligonucleotide studies demonstrated that a total of 21 genes were overlapped and significantly expressed, including signal transducer and activator of transcription 1, growth factor receptor-bound protein 7, GATA-binding protein 3, glutathione S-transferase Mu 1, budding uninhibited by benzimidazoles 1, ubiquitin-conjugating enzyme 2C, tumor necrosis factor (TNF) superfamily (TNF, TNFα), cyclin E2, MX1, interferon-induced protein with tetratricopeptide repeats (IFIT) 1, IFI27, IFI144, interferon-stimulated gene 115, homeobox B13, interleukin 17BR, BM039, cytidine triphosphate synthetase, 26S proteasome non-ATPase regulatory subunit (PSMD)2, PSMD7, MAD2LI and protein kinase, membrane-associated tyrosine/threonine 1 (88,89,97,98).

A recent study identified several genomic alterations, including loss of CDH1 and phosphatase and tensin homolog, AKT activation and aberrations in T-box transcription factor 3 and forkhead 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 BRCAness profile, identified a gene expression profile associated with platinum and PARP-inhibitor responsiveness, as well as RAD51 foci formation. The BRCAness 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 BRCAness, 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 elevation 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 progestin 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 OVSAHO) and a specific antibody against E2F5 to pull down the downstream 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 biological markers for BC and OC.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D and Bray F: Cancer Incidence and Mortality Worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136: E359-E386, 2015.
2. Bray F, Ren JS, Masuyer E and Ferlay J: Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer 132: 1133-1145, 2013.
3. Al-Madouj A, Eldali A and Al-zahrani AS: Ten-Year Cancer Incidence: Among Nationals of the GCC States (1998-2007). Gulf Center for Cancer Control and Prevention, 2011. https://www.moh.gov.bh/Content/Files/Publications/GCC%20Cancer%20Incidence%202011.pdf. Accessed January 7, 2017.
4. Kumar S, Burney IA, Al-Ajmi A and Al-Moundhri MS: Changing trends of breast cancer survival in sultanate of oman. J Oncol 2011: 316243, 2011.
5. Al-Moundhri M, Al-Bahrani B, Pervez I, Ganguly SS, Nirmala V, Al-Madhani A, Al-Mawaly K and Grant C: The outcome of treatment of breast cancer in a developing country-Oman. Breast 13: 139-145, 2004.
6. Simpson PT, Gale T, Fulford LG, Reis-Filho JS and Lakhani SR: The diagnosis and management of pre-invasive breast disease: Pathology of atypical lobular hyperplasia and lobular carcinoma in situ. Breast Cancer Res 5: 258-262, 2003.
7. Weidner N, Semple JP, Welch WR and Folkman J: Tumor angiogenesis and metastasis-correlation in invasive breast carcinoma. N Engl J Med 324: 1-8, 1991.
8. Allred DC: Ductal Carcinoma In Situ: Terminology, Classification, and Natural History. J Natl Cancer Inst Monogr 2010: 134-138, 2010.
9. Sharma GN, Dave R, Sanadya J, Sharma P and Sharma KK: Various types and management of breast cancer: An overview. J Adv Pharm Technol Res 1: 109-126, 2010.
10. Kobayashi E, Ueda Y, Matsuzaki S, Yokoyama T, Kimura T, Yoshino K, Fujita M, Kimura T and Enomoto T: Biomarkers for screening, diagnosis, and monitoring of ovarian cancer. Cancer Epidemiol Biomarkers Prev 21: 1902-1912, 2012.
11. Horta M and Cunha TM: Sex cord-stromal tumors of the ovary: A comprehensive review and update for radiologists. Diagn Interv Radiol 21: 277-286, 2015.
12. Norris HJ and Jensen RD: Relative frequency of ovarian neoplasms in children and adolescents. Cancer 30: 713-719, 1972.
13. Murray MJ and Nicholson JC: Germ cell tumours in children and adolescents. Paediatrics Child Health 20: 109-116, 2010.
14. Cho KR and Shih IeM: Ovarian cancer. Annu Rev Pathol 4: 287-313, 2009.
15. Williams TI, Toups KL, Saggese DA, Kalli KR, Cliby WA and Muddiman DC: Epithelial Ovarian Cancer: Disease etiology, treatment, detection and investigational gene, metabolite, and protein biomarkers. J Proteome Res 6: 2936-2962, 2007.
16. McSherry EA, Donatello S, Hopkins AM and McDonnell S: Molecular basis of invasion in breast cancer. Cell Mol Life Sci 64: 3201-3218, 2007.
17. Lengyel E: Ovarian cancer development and metastasis. Am J Pathol 177: 1053-1064, 2010.
18. Weigelt B, Peterse JL and van't Veer LJ: Breast cancer metastasis: Markers and models. Nat Rev Cancer 5: 591-602, 2005.
19. Carmichael A, Sami AS and Dixon JM: Breast cancer risk among the survivors of atomic bomb and patients exposed to therapeutic ionising radiation. Eur J Surg Oncol 29: 475-479, 2003.
20. Wass J and Finer N: Action on obesity: comprehensive care for all. Clin Med (Lond) 13: 4-5, 2013.
21. Lakhtakia R: Conspicuous consumption and sedentary Living: Is this our legacy to our children? Sultan Qaboos Univ Med J 13: 336-340, 2013.
22. McKenzie F, Ellison-Loschmann L, Jeffreys M, Firestone R, Pearce N and Romieu I: Cigarette smoking and risk of breast cancer in a New Zealand Multi-Ethnic Case-Control Study. PLoS One 8: e63132, 2013.
23. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN and Katzmarzyk PT; Lancet Physical Activity Series Working Group: Effect of physical inactivity on major non-communicable diseases worldwide: An analysis of burden of disease and life expectancy. Lancet 380: 219-229, 2012.
24. Fioretti F, Tavani A, Bosetti C, La Vecchia C, Negri E, Barbone F, Talamini R and Franceschi S: Risk factors for breast cancer in nulliparous women. Br J Cancer 79: 1923-1928, 1999.
25. Sieri S, Krogh V, Bolelli G, Abagnato CA, Grioni S, Pala V, Evangelista A, Allemani C, Micheli A, Tagliabue G, *et al*: Sex hormone levels, breast cancer risk, and cancer receptor status in postmenopausal Women: The ORDET Cohort. Cancer Epidemiol Biomarkers Prev 18: 169-176, 2009.
26. Colombo N, Van Gorp T, Parma G, Amant F, Gatta G, Sessa C and Vergote I: Ovarian cancer. Crit Rev Oncol Hematol 60: 159-179, 2006.
27. Virnig BA, Tuttle TM, Shamliyan T and Kane RL: Ductal carcinoma in situ of the breast: A systematic review of incidence, treatment, and outcomes. J Natl Cancer Inst 102: 170-178, 2010.
28. Claus EB, Schildkraut JM, Thompson WD and Risch NJ: The genetic attributable risk of breast and ovarian cancer. Cancer 77: 2318-2324, 1996.
29. Lynch HT, Casey MJ, Snyder CL, Bewtra C, Lynch JF, Butts M and Godwin AK: Hereditary ovarian carcinoma: Heterogeneity, molecular genetics, pathology, and management. Mol Oncol 3: 97-137, 2009.
30. Perry C and Phillps B: Quick Review: Breast Cancer. Int J Oncol 1: 2, 2001.
31. Bewtra C, Watson P, Conway T, Read-Hippee C and Lynch HT: Hereditary ovarian cancer: A clinicopathological study. Int J Gynecol Pathol 11: 180-187, 1992.
32. Rubin SC, Blackwood MA, Bandera C, Behbakht K, Benjamin I, Rebbeck TR and Boyd J: BRCA1, BRCA2, and hereditary nonpolyposis colorectal cancer gene mutations in an unselected ovarian cancer population: Relationship to family history and implications for genetic testing. Am J Obstet Gynecol 178: 670-677, 1998.
33. Macdonald F, Ford CHJ and Casson AG: Molecular Biology of Cancer. 2nd edition. BIOS Scientific, London, 2004.
34. Economopoulou P, Dimitriadis G and Psyrri A: Beyond BRCA: New hereditary breast cancer susceptibility genes. Cancer Treat Rev 41: 1-8, 2015.
35. Watson IR, Takahashi K, Futreal PA and Chin L: Emerging patterns of somatic mutations in cancer. Nat Rev Genet 14: 703-718, 2013.
36. Zhao D, Zhang F, Zhang W, He J, Zhao Y and Sun J: Prognostic role of hormone receptors in ovarian cancer: A systematic review and meta-analysis. Int J Gynecol Cancer 23: 25-33, 2013.
37. Gusterson BA, Gelber RD, Goldhirsch A, Price KN, Säve-Söderborgh J, Anbazhagan R, Styles J, Rudenstam CM, Golouh R, Reed R, *et al*: Prognostic importance of c-erbB-2 expression in breast cancer. International (Ludwig) Breast Cancer Study Group. J Clin Oncol 10: 1049-1056, 1992.
38. Carter CL, Allen C and Henson DE: Relation of tumor size, lymph node status and survival in 24,740 breast cancer cases. Cancer 63: 181-187, 1989.
39. Prat J; FIGO Committee on Gynecologic Oncology: FIGO's staging classification for cancer of the ovary, fallopian tube, and peritoneum: Abridged republication. J Gynecol Oncol 26: 87-89, 2015.
40. Young RC, Walton LA, Ellenberg SS, Homesley HD, Wilbanks GD, Decker DG, Miller A, Park R and Major F Jr: Adjuvant therapy in stage I and stage II epithelial ovarian cancer. Results of two prospective randomized trials. N Engl J Med 322: 1021-1027, 1990.
41. Schorge JO, McCann C and Del Carmen MG: Surgical debulking of ovarian cancer: What difference does it make? Rev Obstet Gynecol 3: 111-117, 2010.
42. Ezzati M, Abdullah A, Shariftabrizi A, Hou J, Kopf M, Stedman JK, Samuelson R and Shahabi S: Recent advancements in prognostic factors of epithelial ovarian carcinoma. Int Sch Res Notices 2014: 953509, 2014.

43. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL and Montz FJ: Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum Era: A meta-analysis. J Clin Oncol 20: 1248-1259, 2002.
44. McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, Clarke-Pearson DL and Davidson M: Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and Stage IV ovarian cancer. N Engl J Med 334: 1-6, 1996.
45. Malhotra GK, Zhao X, Band H and Band V: Histological, molecular and functional subtypes of breast cancers. Cancer Biol Ther 10: 955-960, 2010.
46. Schwartz AM, Henson DE, Chen D and Rajamarthandan S: Histologic grade remains a prognostic factor for breast cancer regardless of the number of positive lymph nodes and tumor Size: A study of 161 708 cases of breast cancer from the seer program. Arch Pathol Lab Med 138: 1048-1052, 2014.
47. Harvey JM, Clark GM, Osborne CK and Allred DC: Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. J Clin Oncol 17: 1474-1781, 1999.
48. Fisher B, Redmond C, Fisher ER and Caplan R: Relative worth of estrogen or progesterone receptor and pathologic characteristics of differentiation as indicators of prognosis in node negative breast cancer patients: findings from National Surgical Adjuvant Breast and Bowel Project Protocol B-06. J Clin Oncol 6: 1076-1087, 1988.
49. Cheang MC, Treaba DO, Speers CH, Olivotto IA, Bajdik CD, Chia SK, Goldstein LC, Gelmon KA, Huntsman D, Gilks CB, *et al*: Immunohistochemical detection using the new rabbit monoclonal antibody SP1 of estrogen receptor in breast cancer is superior to mouse monoclonal antibody 1D5 in predicting survival. J Clin Oncol 24: 5637-5644, 2006.
50. Tangjitgamol S, Manusirivithaya S, Khunnarong J, Jesadapatarakul S and Tanwanich S: Expressions of estrogen and progesterone receptors in epithelial ovarian cancer: A clinicopathologic study. Int J Gynecol Cancer 19: 620-627, 2009.
51. Lindgren PR, Cajander S, Bäckström T, Gustafsson JÅ, Mäkelä S and Olofsson JI: Estrogen and progesterone receptors in ovarian epithelial tumors. Mol Cell Endocrinol 221: 97-104, 2004.
52. Fisher B, Jeong J-H, Anderson S and Wolmark N: Treatment of axillary lymph node-negative, estrogen receptor-negative breast cancer: Updated findings from national surgical adjuvant breast and bowel project clinical trials. J Natl Cancer Inst 96: 1823-1831, 2004.
53. Winer EP, Hudis C, Burstein HJ, Wolff AC, Pritchard KI, Ingle JN, Chlebowski RT, Gelber R, Edge SB, Gralow J, *et al*: American society of clinical oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: Status Report 2004. J Clin Oncol 23: 619-629, 2005.
54. Slamon D, Clark GM, Wong SG, Levin WJ, Ullrich A and McGuire WL: Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235: 177-182, 1987.
55. Borg A, Tandon AK, Sigurdsson H, Clark GM, Fernö M, Fuqua SA, Killander D and McGuire WL: HER-2/neu Amplification Predicts Poor Survival in Node-positive Breast Cancer. Cancer Res 50: 4332-4337, 1990.
56. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, *et al*: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344: 783-792, 2001.
57. Cianfrocca M and Goldstein LJ: Prognostic and Predictive Factors in Early-Stage Breast Cancer. Oncologist 9: 606-616, 2004.
58. Jönsson JM, Skovbjerg Arildsen N, Malander S, Måsbäck A, Hartman L, Nilbert M and Hedenfalk I: Sex steroid hormone receptor expression affects ovarian cancer survival. Transl Oncol 8: 424-433, 2015.
59. Tassi RA, Calza S, Ravaggi A, Bignotti E, Odicino FE, Tognon G, Donzelli C, Falchetti M, Rossi E, Todeschini P, *et al*: Mammaglobin B is an independent prognostic marker in epithelial ovarian cancer and its expression is associated with reduced risk of disease recurrence. BMC Cancer 9: 253, 2009.
60. Berchuck A, Iversen ES, Lancaster JM, Pittman J, Luo J, Lee P, Murphy S, Dressman HK, Febbo PG, West M, *et al*: Patterns of gene expression that characterize long-term survival in advanced stage serous ovarian cancers. Clin Cancer Res 11: 3686-3696, 2005.
61. Barlin JN, Jelinic P, Olvera N, Bogomolniy F, Bisogna M, Dao F, Barakat RR, Chi DS and Levine DA: Validated gene targets associated with curatively treated advanced serous ovarian carcinoma. Gynecol Oncol 128: 512-517, 2013.
62. Yoshihara K, Tajima A, Komata D, Yamamoto T, Kodama S, Fujiwara H, Suzuki M, Onishi Y, Hatae M, Sueyoshi K, *et al*: Gene expression profiling of advanced-stage serous ovarian cancers distinguishes novel subclasses and implicates ZEB2 in tumor progression and prognosis. Cancer Sci 100: 1421-1428, 2009.
63. Guénard F, Labrie Y, Ouellette G, Joly Beauparlant C, Simard J and Durocher F; INHERIT BRCAs: Mutational analysis of the breast cancer susceptibility gene BRIP1 /BACH1/FANCJ in high-risk non-BRCA1/BRCA2 breast cancer families. J Hum Genet 53: 579-591, 2008.
64. Nasi ML and Castiglione M: Cyclooxygenase-2 (COX-2) a new prognostic and predictive factor for ovarian cancer? Are all the criteria fulfilled? Ann Oncol 13: 1169-1171, 2002.
65. Saslow D, Boetes C, Burke W, Harms S, Leach MO, Lehman CD, Morris E, Pisano E, Schnall M, Sener S, *et al*: American cancer society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 57: 75-89, 2007.
66. Yu YH, Liang C and Yuan XZ: Diagnostic value of vacuum-assisted breast biopsy for breast carcinoma: A meta-analysis and systematic review. Breast Cancer Res Treat 120: 469-479, 2010.
67. Board CNE: Ovarian Cancer-Additional Resources. Journal 2016: 2012.
68. Jemal A, Siegel R, Ward E, Hao Y, Xu J and Thun MJ: Cancer statistics. CA Cancer J Clin 59: 225-249, 2009.
69. Guidelines NCCNN: Breast Cancer Version 2.2011 Journal 2015. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed November 23, 2015.
70. NCCN: Breast cancer-in situ (stage 0). version 1, 2016. https://www.nccn.org/patients/guidelines/stage_0_breast/index.html#1/z. Accessed November 23, 2015.
71. Perreard L, Fan C, Quackenbush JF, Mullins M, Gauthier NP, Nelson E, Mone M, Hansen H, Buys SS, Rasmussen K, *et al*: Classification and risk stratification of invasive breast carcinomas using a real-time quantitative RT-PCR assay. Breast Cancer Res 8: R23, 2006.
72. Weigelt B, Horlings HM, Kreike B, Hayes MM, Hauptmann M, Wessels LF, de Jong D, Van de Vijver MJ, Van't Veer LJ and Peterse JL: Refinement of breast cancer classification by molecular characterization of histological special types. J Pathol 216: 141-150, 2008.
73. Gonzalez-Angulo AM, Morales-Vasquez F and Hortobagyi GN: Overview of resistance to systemic therapy in patients with breast cancer. Adv Exp Med Biol 608: 1-22, 2007.
74. Markman M, Iseminger KA, Hatch KD, Creasman WT, Barnes W and Dubeshter B: Tamoxifen in platinum-refractory ovarian cancer: A gynecologic oncology group ancillary report. Gynecol Oncol 62: 4-6, 1996.
75. Bowman A, Gabra H, Langdon SP, Lessells A, Stewart M, Young A and Smyth JF: CA125 response is associated with estrogen receptor expression in a phase II trial of letrozole in ovarian cancer. Clin Cancer Res 8: 2233-2239, 2002.
76. Konner J, Schilder RJ, DeRosa FA, Gerst SR, Tew WP, Sabbatini PJ, Hensley ML, Spriggs DR and Aghajanian CA: A phase II study of cetuximab/paclitaxel/carboplatin for the initial treatment of advanced-stage ovarian, primary peritoneal, or fallopian tube cancer. Gynecol Oncol 110: 140-145, 2008.
77. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, Mannel RS, Homesley HD, Fowler J, Greer BE, *et al*: Incorporation of Bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 365: 2473-2483, 2011.
78. Markman M: Combination versus sequential cytotoxic chemotherapy in recurrent ovarian cancer: Time for an evidence-based comparison. Gynecol Oncol 118: 6-7, 2010.
79. Ozols RF: Systemic therapy for ovarian cancer: Current status and new treatments. Semin Oncol 33 (2 Suppl 6): S3-S11, 2006.
80. Tagawa T, Morgan R, Yen Y and Mortimer J: Ovarian Cancer: Opportunity for targeted therapy. J Oncol 2012: 682480, 2012.
81. Mateo J, Moreno V, Gupta A, Kaye SB, Dean E, Middleton MR, Friedlander M, Gourley C, Plummer R, Rustin G, *et al*: An adaptive study to determine the optimal dose of the tablet formulation of the PARP inhibitor olaparib. Target Oncol 11: 401-415, 2016.
82. Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel JN, Friedlander M, Arun B, Loman N, Schmutzler RK, *et al*: Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: A proof-of-concept trial. Lancet 376: 235-244, 2010.

83. Marchionni L, Wilson RF, Marinopoulos SS, Wolff AC, Parmigiani G, Bass EB and Goodman SN: Impact of gene expression profiling tests on breast cancer outcomes. Evid Rep Technol Assess (Full Rep) 1-105, 2007.
84. Marrone M, Stewart A and Dotson WD: Clinical utility of gene-expression profiling in women with early breast cancer: An overview of systematic reviews. Genet Med 17: 519-532, 2015.
85. Wildsmith SE and Elcock FJ: Microarrays under the microscope. Mol Pathol 54: 8-16, 2001.
86. Maughan NJ, Lewis FA and Smith V: An introduction to arrays. J Pathol 195: 3-6, 2001.
87. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, *et al*: Molecular portraits of human breast tumours. Nature 406: 747-752, 2000.
88. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M, Jeffrey SS, *et al*: Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA 98: 10869-10874, 2001.
89. Sørlie T, Tibshirani R, Parker J, Hastie T, Marron JS, Nobel A, Deng S, Johnsen H, Pesich R, Geisler S, *et al*: Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci USA 100: 8418-8423, 2003.
90. Sotiriou C, Neo SY, McShane LM, Korn EL, Long PM, Jazaeri A, Martiat P, Fox SB, Harris AL and Liu ET: Breast cancer classification and prognosis based on gene expression profiles from a population-based study. Proc Natl Acad Sci USA 100: 10393-10398, 2003.
91. Dai H, van't Veer L, Lamb J, He YD, Mao M, Fine BM, Bernards R, van de Vijver M, Deutsch P, Sachs A, *et al*: A cell proliferation signature is a marker of extremely poor outcome in a subpopulation of breast cancer patients. Cancer Res 65: 4059-4066, 2005.
92. Ma XJ, Wang Z, Ryan PD, Isakoff SJ, Barmettler A, Fuller A, Muir B, Mohapatra G, Salunga R, Tuggle JT, *et al*: A two-gene expression ratio predicts clinical outcome in breast cancer patients treated with tamoxifen. Cancer Cell 5: 607-616, 2004.
93. Zhao X, Li C, Paez JG, Chin K, Jänne PA, Chen TH, Girard L, Minna J, Christiani D, Leo C, *et al*: An Integrated view of copy number and allelic alterations in the cancer genome using single nucleotide polymorphism arrays. Cancer Res 64: 3060-3071, 2004.
94. Huang E, Cheng SH, Dressman H, Pittman J, Tsou MH, Horng CF, Bild A, Iversen ES, Liao M, Chen CM, *et al*: Gene expression predictors of breast cancer outcomes. Lancet 361: 1590-1596, 2003.
95. West M, Blanchette C, Dressman H, Huang E, Ishida S, Spang R, Zuzan H, Olson JA Jr, Marks JR and Nevins JR: Predicting the clinical status of human breast cancer by using gene expression profiles. Proc Natl Acad Sci USA 98: 11462-11467, 2001.
96. Chin K, DeVries S, Fridlyand J, Spellman PT, Roydasgupta R, Kuo WL, Lapuk A, Neve RM, Qian Z, Ryder T, *et al*: Genomic and transcriptional aberrations linked to breast cancer pathophysiologies. Cancer Cell 10: 529-541, 2006.
97. van de Vijver MJ, He YD, van't Veer LJ, Dai H, Hart AA, Voskuil DW, Schreiber GJ, Peterse JL, Roberts C, Marton MJ, *et al*: A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 347: 1999-2009, 2002.
98. van 't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M, Peterse HL, van der Kooy K, Marton MJ, Witteveen AT, *et al*: Gene expression profiling predicts clinical outcome of breast cancer. Nature 415: 530-536, 2002.
99. Naderi A, Teschendorff AE, Barbosa-Morais NL, Pinder SE, Green AR, Powe DG, Robertson JFR, Aparicio S, Ellis IO, Brenton JD and Caldas C: A gene-expression signature to predict survival in breast cancer across independent data sets. Oncogene 26: 1507-1516, 2006.
100. Acharya CR, Hsu DS, Anders CK, Anguiano A, Salter KH, Walters KS, Redman RC, Tuchman SA, Moylan CA, Mukherjee S, *et al*: Gene expression signatures, clinicopathological features, and individualized therapy in breast cancer. JAMA 299: 1574-1587, 2008.
101. Wang Y, Klijn JG, Zhang Y, Sieuwerts AM, Look MP, Yang F, Talantov D, Timmermans M, Meijer-van Gelder ME, Yu J, *et al*: Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer. Lancet 365: 671-679, 2005.
102. Miller LD, Smeds J, George J, Vega VB, Vergara L, Ploner A, Pawitan Y, Hall P, Klaar S, Liu ET and Bergh J: An expression signature for p53 status in human breast cancer predicts mutation status, transcriptional effects, and patient survival. Proc Natl Acad Sci USA 102: 13550-13555, 2005.
103. Ciriello G, Gatza ML, Beck AH, Wilkerson MD, Rhie SK, Pastore A, Zhang H, McLellan M, Yau C, Kandoth C, *et al*: Comprehensive molecular portraits of invasive lobular breast cancer. Cell 163: 506-519, 2015.
104. Desmedt C, Zoppoli G, Gundem G, Pruneri G, Larsimont D, Fornili M, Fumagalli D, Brown D, Rothé F, Vincent D, *et al*: Genomic characterization of primary invasive lobular breast cancer. J Clin Oncol 34: 1872-1881, 2016.
105. Reis-Filho JS, Westbury C and Pierga JY: The impact of expression profiling on prognostic and predictive testing in breast cancer. J Clinl Pathol 59: 225-231, 2006.
106. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B and Senn HJ; Panel members: Strategies for subtypes-dealing with the diversity of breast cancer: Highlights of the St. gallen international expert consensus on the primary therapy of early breast cancer 2011. Ann Oncol 22: 1736-1747, 2011.
107. Cancer Genome Atlas Network: Comprehensive molecular portraits of human breast tumours. Nature 490: 61-70, 2012.
108. Banerji S, Cibulskis K, Rangel-Escareno C, Brown KK, Carter SL, Frederick AM, Lawrence MS, Sivachenko AY, Sougnez C, Zou L, *et al*: Sequence analysis of mutations and translocations across breast cancer subtypes. Nature 486: 405-409, 2012.
109. Kan Z, Jaiswal BS, Stinson J, Janakiraman V, Bhatt D, Stern HM, Yue P, Haverty PM, Bourgon R, Zheng J, *et al*: Diverse somatic mutation patterns and pathway alterations in human cancers. Nature 466: 869-873, 2010.
110. Robinson DR, Wu YM, Vats P, Su F, Lonigro RJ, Cao X, Kalyana-Sundaram S, Wang R, Ning Y, Hodges L, *et al*: Activating ESR1 mutations in hormone-resistant metastatic breast cancer. Nat Genet 45: 1446-1451, 2013.
111. Toy W, Shen Y, Won H, Green B, Sakr RA, Will M, Li Z, Gala K, Fanning S, King TA, *et al*: ESR1 ligand-binding domain mutations in hormone-resistant breast cancer. Nat Genet 45: 1439-1445, 2013.
112. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner FL, Walker MG, Watson D, Park T, *et al*: A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 351: 2817-2826, 2004.
113. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y and Pietenpol JA: Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest 121: 2750-2767, 2011.
114. Fumagalli D, Desmedt C, Ignatiadis M, Loi S, Piccart M and Sotiriou C: Gene profiling assay and application: The predictive role in primary therapy. J Natl Cancer Inst Monogr 2011: 124-127, 2011.
115. Fehrmann RS, Li XY, van der Zee AG, de Jong S, Te Meerman GJ, de Vries EG and Crijns AP: Profiling Studies in Ovarian Cancer: A Review. Oncologist 12: 960-966, 2007.
116. Lu KH, Patterson AP, Wang L, Marquez RT, Atkinson EN, Baggerly KA, Ramoth LR, Rosen DG, Liu J, Hellstrom I, *et al*: Selection of potential markers for epithelial ovarian cancer with gene expression arrays and recursive descent partition analysis. Clin Cancer Res 10: 3291-3300, 2004.
117. Konstantinopoulos PA, Spentzos D, Karlan BY, Taniguchi T, Fountzilas E, Francoeur N, Levine DA and Cannistra SA: Gene expression profile of BRCAness that correlates with responsiveness to chemotherapy and with outcome in patients with epithelial ovarian cancer. J Clinl Oncol 28: 3555-3561, 2010.
118. Crijns AP, Fehrmann RS, de Jong S, Gerbens F, Meersma GJ, Klip HG, Hollema H, Hofstra RM, te Meerman GJ, de Vries EG and van der Zee AG: Survival-related profile, pathways, and transcription factors in ovarian cancer. PLoS Med 6: e24, 2009.
119. Bonome T, Levine DA, Shih J, Randonovich M, Pise-Masison CA, Bogomolniy F, Ozbun L, Brady J, Barrett JC, Boyd J and Birrer MJ: A gene signature predicting for survival in suboptimally debulked patients with ovarian cancer. Cancer Res 68: 5478-5486, 2008.
120. Kothandaraman N, Bajic VB, Brendan PN, Huak CY, Keow PB, Razvi K, Salto-Tellez M and Choolani M: E2F5 status significantly improves malignancy diagnosis of epithelial ovarian cancer. BMC Cancer 10: 64, 2010.
121. Sawiris GP, Sherman-Baust CA, Becker KG, Cheadle C, Teichberg D and Morin PJ: Development of a highly specialized cDNA array for the study and diagnosis of epithelial ovarian cancer. Cancer Res 62: 2923-2928, 2002.

122. Resnick KE, Alder H, Hagan JP, Richardson DL, Croce CM and Cohn DE: The detection of differentially expressed microRNAs from the serum of ovarian cancer patients using a novel real-time PCR platform. Gynecol Oncol 112: 55-59, 2009.
123. Chang H, Zhou X, Wang ZN, Song YX, Zhao F, Gao P, Chiang Y and Xu HM: Increased expression of miR-148b in ovarian carcinoma and its clinical significance. Mol Med Rep 5: 1270-1280, 2012.
124. Iorio MV, Visone R, Di Leva G, Donati V, Petrocca F, Casalini P, Taccioli C, Volinia S, Liu CG, Alder H, *et al*: MicroRNA signatures in human ovarian cancer. Cancer Res 67: 8699-8707, 2007.
125. Shapira I, Oswald M, Lovecchio J, Khalili H, Menzin A, Whyte J, Dos Santos L, Liang S, Bhuiya T, Keogh M, *et al*: Circulating biomarkers for detection of ovarian cancer and predicting cancer outcomes. Br J Cancer 110: 976-983, 2014.
126. Vecchione A, Belletti B, Lovat F, Volinia S, Chiappetta G, Giglio S, Sonego M, Cirombella R, Onesti EC, Pellegrini P, *et al*: A microRNA signature defines chemoresistance in ovarian cancer through modulation of angiogenesis. Proc Natl Acad Sci USA 110: 9845-9850, 2013.
127. Jazaeri AA, Awtrey CS, Chandramouli GV, Chuang YE, Khan J, Sotiriou C, Aprelikova O, Yee CJ, Zorn KK, Birrer MJ, *et al*: Gene expression profiles associated with response to chemotherapy in epithelial ovarian cancers. Clin Cancer Res 11: 6300-6310, 2005.
128. Hartmann LC, Lu KH, Linette GP, Cliby WA, Kalli KR, Gershenson D, Bast RC, Stec J, Iartchouk N, Smith DI, *et al*: Gene expression profiles predict early relapse in ovarian cancer after platinum-paclitaxel chemotherapy. Clin Cancer Res 11: 2149-2155, 2005.
129. Tothill RW, Tinker AV, George J, Brown R, Fox SB, Lade S, Johnson DS, Trivett MK, Etemadmoghadam D, Locandro B, *et al*: Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome. Clin Cancer Res 14: 5198-5208, 2008.
130. Cancer Genome Atlas Research Network: Integrated genomic analyses of ovarian carcinoma. Nature 474: 609-615, 2011.
131. Konecny GE, Wang C, Hamidi H, Winterhoff B, Kalli KR, Dering J, Ginther C, Chen HW, Dowdy S, Cliby W, *et al*: Prognostic and therapeutic relevance of molecular subtypes in high-grade serous ovarian cancer. J Natl Cancer Inst 106: pii: dju249, 2014.
132. Liu J and Matulonis UA: New Strategies in Ovarian Cancer: Translating the molecular complexity of ovarian cancer into treatment advances. Clin Cancer Res 20: 5150-5156, 2014.
133. Secord AA, Nixon AB and Hurwitz HI: The search for biomarkers to direct antiangiogenic treatment in epithelial ovarian cancer. Gynecol Oncol 135: 349-358, 2014.
134. Wang C, Winterhoff BJ, Kalli KR, Block MS, Armasu SM, Larson MC, Chen HW, Keeney GL, Hartmann LC, Shridhar V *et al*: Expression signature distinguishing two tumour transcriptome classes associated with progression-free survival among rare histological types of epithelial ovarian cancer. Br J Cancer 114: 1412-1420, 2016.
135. Freitas S, Moore DH, Michael H and Kelley MR: Studies of Apurinic/Apyrimidinic Endonuclease/ref-1 Expression in Epithelial Ovarian Cancer. Correlations with tumor progression and platinum resistance. Clin Cancer Res 9: 4689-4694, 2003.
136. Hilton JL, Geisler JP, Rathe JA, Hattermann-Zogg MA, DeYoung B and Buller RE: Inactivation of BRCA1 and BRCA2 in Ovarian Cancer. J Natl Cancer Inst 94: 1396-1406, 2002.
137. Prat A, Ellis MJ and Perou CM: Practical implications of gene-expression-based assays for breast oncologists. Nat Rev Clin Oncol 9: 48-57, 2012.
138. Al-Moundhri MS, Al-Ansari A, Al-Mawali K and Al-Bahrani B: BRCA1 gene Molecular Alterations in Omani Breast Cancer Patients. Gulf J Oncolog 1: 45-51, 2013.
139. Cantor SB, Bell DW, Ganesan S, Kass EM, Drapkin R, Grossman S, Wahrer DC, Sgroi DC, Lane WS, Haber DA and Livingston DM: BACH1, a Novel Helicase-like Protein, Interacts Directly with BRCA1 and Contributes to Its DNA Repair Function. Cell 105: 149-160, 2001.
140. Lee AD: Structural rearrangements in DNA repair genes in breast cancer. University of Pittsburgh, Pittsburgh, 2013.
141. Li X, Ohgi KA, Zhang J, Krones A, Bush KT, Glass CK, Nigam SK, Aggarwal AK, Maas R, Rose DW and Rosenfeld MG: Eya protein phosphatase activity regulates Six1-Dach-Eya transcriptional effects in mammalian organogenesis. Nature 426: 247-254, 2003.
142. Pandey RN, Rani R, Yeo EJ, Spencer M, Hu S, Lang RA and Hegde RS: The Eyes Absent phosphatase-transactivator proteins promote proliferation, transformation, migration, and invasion of tumor cells. Oncogene 29: 3715-3722, 2010.
143. Wu K, Li Z, Cai S, Tian L, Chen K, Wang J, Hu J, Sun Y, Li X, Ertel A and Pestell RG: EYA1 phosphatase function is essential to drive breast cancer cell proliferation through Cyclin D1. Cancer Res 73: 4488-4499, 2013.
144. Apiou F, Flagiello D, Cillo C, Malfoy B, Poupon MF and Dutrillaux B: Fine mapping of human HOX gene clusters. Cytogenet Cell Genet 73: 114-115, 1996.
145. Bhatlekar S, Fields JZ and Boman BM: HOX genes and their role in the development of human cancers. J Mol Med (Berl) 92: 811-823, 2014.
146. Fischbach NA, Rozenfeld S, Shen W, Fong S, Chrobak D, Ginzinger D, Kogan SC, Radhakrishnan A, Le Beau MM, Largman C and Lawrence HJ: HOXB6 overexpression in murine bone marrow immortalizes a myelomonocytic precursor in vitro and causes hematopoietic stem cell expansion and acute myeloid leukemia in vivo. Blood 105: 1456-1466, 2005.
147. Liu YJ, Zhu Y, Yuan HX, Zhang JP, Guo JM and Lin ZM: Overexpression of HOXC11 homeobox gene in clear cell renal cell carcinoma induces cellular proliferation and is associated with poor prognosis. Tumor Biol 36: 2821-2829, 2015.
148. Shah N and Sukumar S: The Hox genes and their roles in oncogenesis. Nat Rev Cancer 10: 361-371, 2010.
149. Chen KN, Gu ZD, Ke Y, Li JY, Shi XT and Xu GW: Expression of 11 HOX Genes Is deregulated in esophageal squamous cell carcinoma. Clin Cancer Res 11: 1044-1049, 2005.
150. Vider BZ, Zimber A, Chastre E, Gespach C, Halperin M, Mashiah P, Yaniv A and Gazit A: Deregulated Expression of homeobox-containing genes, HOXB6, B8, C8, C9 and Cdx-1, in human colon cancer cell lines. Biochem Biophys Res Commun 272: 513-518, 2000.
151. Tait DL, Zhang J, Gurlov S, McKinney K, Vachris J, Mougeot JLC, Wagstaff JE and Bahrani-Mostafav Z: Differential expression of Hox genes in ovarian cancer. Cancer Res 65: 845-846, 2005.
152. Stone B, Schummer M, Paley PJ, Thompson L, Stewart J, Ford M, Crawford M, Urban N, O'Briant K and Nelson BH: Serologic analysis of ovarian tumor antigens reveals a bias toward antigens encoded on 17q. Int J Cancer 104: 73-84, 2003.
153. Kelly Z, Moller-Levet C, McGrath S, Butler-Manuel S, Kavitha Madhuri T, Kierzek AM, Pandha H, Morgan R and Michael A: The prognostic significance of specific HOX gene expression patterns in ovarian cancer. Int J Cancer 139: 1608-1617, 2016.
154. Shang B, Gao A, Pan Y, Zhang G, Tu J, Zhou Y, Yang P, Cao Z, Wei Q, Ding Y, *et al*: CT45A1 acts as a new proto-oncogene to trigger tumorigenesis and cancer metastasis. Cell Death Dis 5: e1285, 2014.
155. Vider BZ, Zimber A, Hirsch D, Estlein D, Chastre E, Prevot S, Gespach C, Yaniv A and Gazit A: Human colorectal carcinogenesis is associated with deregulation of homeobox gene expression. Biochem Biophys Res Commun 232: 742-748, 1997.
156. Castronovo V, Kusaka M, Chariot A, Gielen J and Sobel M: Homeobox genes: Potential candidates for the transcriptional control of the transformed and invasive phenotype. Biochem Pharmacol 47: 137-143, 1994.
157. Green KJ and Simpson CL: Desmosomes: New Perspectives on a Classic. J Invest Dermatol 127: 2499-2515, 2007.
158. Pang H, Rowan BG, Al-Dhaheri M and Faber LE: Epidermal growth factor suppresses induction by progestin of the adhesion protein desmoplakin in T47D breast cancer cells. Breast Cancer Res 6: R239-R245, 2004.
159. Yang L, Chen Y, Cui T, Knösel T, Zhang Q, Albring KF, Huber O and Petersen I: Desmoplakin acts as a tumor suppressor by inhibition of the Wnt/β-catenin signaling pathway in human lung cancer. Carcinogenesis 33: 1863-1870, 2012.
160. Green KJ, Stappenbeck TS, Noguchi S, Oyasu R and Nilles LA: Desmoplakin expression and distribution in cultured rat bladder epithelial cells of varying tumorigenic potential. Exp Cell Res 193: 134-143, 1991.
161. Hiraki A, Shinohara M, Ikebe T, Nakamura S, Kurahara S and Garrod DR: Immunohistochemical staining of desmosomal components in oral squamous cell carcinomas and its association with tumour behaviour. Br J Cancer 73: 1491-1497, 1996.
162. Davies EL, Gee JMW, Cochrane RA, Jiang WG, Sharma AK, Nicholson RI and Mansel RE: The immunohistochemical expression of desmoplakin and its role in vivo in the progression and metastasis of breast cancer. Eur J Cancer 35: 902-907, 1999.

163. Peck JW, Oberst M, Bouker KB, Bowden E and Burbelo PD: The RhoA-binding protein, Rhophilin-2, regulates actin cytoskeleton organization. J Biol Chem 277: 43924-43932, 2002.
164. He D, Ma L, Feng R, Zhang L, Jiang Y, Zhang Y and Liu G: Analyzing large-scale samples highlights significant association between rs10411210 polymorphism and colorectal cancer. Biomed Pharmacother 74: 164-168, 2015.
165. Wu K, Zhang X, Li F, Xiao D, Hou Y, Zhu S, Liu D, Ye X, Ye M, Yang J, *et al*: Frequent alterations in cytoskeleton remodelling genes in primary and metastatic lung adenocarcinomas. Nat Commun 6: 10131, 2015.
166. Danussi C, Akavia UD, Niola F, Jovic A, Lasorella A, Pe'er D and Iavarone A: RHPN2 drives mesenchymal transformation in malignant glioma by triggering RhoA activation. Cancer Res 73: 5140-5150, 2013.
167. Cao J, Ge MH and Ling ZQ: Fbxw7 Tumor Suppressor: A vital regulator contributes to human tumorigenesis. Medicine (Baltimore) 95: e2496, 2016.
168. Yumimoto K, Akiyoshi S, Ueo H, Sagara Y, Onoyama I, Ueo H, Ohno S, Mori M, Mimori K and Nakayama KI: F-box protein FBXW7 inhibits cancer metastasis in a non-cell-autonomous manner. J Clin Invest 125: 621-635, 2015.
169. Wang Z, Liu P, Inuzuka H and Wei W: Roles of F-box proteins in cancer. Nat Rev Cancer 14: 233-247, 2014.
170. Busino L, Millman SE, Scotto L, Kyratsous CA, Basrur V, O'Connor O, Hoffmann A, Elenitoba-Johnson KS and Pagano M: Fbxw7α- and GSK3-mediated degradation of p100 is a pro-survival mechanism in multiple myeloma. Nat Cell Biol 14: 375-385, 2012.
171. Jardim DL, Wheler JJ, Hess K, Tsimberidou AM, Zinner R, Janku F, Subbiah V, Naing A, Piha-Paul SA, Westin SN, *et al*: FBXW7 mutations in patients with advanced cancers: clinical and molecular characteristics and outcomes with mTOR inhibitors. PLoS One 9: e89388, 2014.
172. Welcker M and Clurman BE: FBW7 ubiquitin ligase: A tumour suppressor at the crossroads of cell division, growth and differentiation. Nat Rev Cancer 8: 83-93, 2008.
173. Bellocq J and Magro G: Fibroepithelial tumors. In: Tavassoli FA and Devilee P (eds): World Health Organization Classification of Tumors: Tumors of the Breast and Female Genital Organs. IARC, pp99-103, Lyon, 2003.
174. Koshiyama M, Matsumura N and Konishi I: Recent Concepts of Ovarian Carcinogenesis: Type I and Type II. Biomed Res Int 2014: 934261, 2014.
175. Cho KR and Shih IeM: Ovarian Cancer. Annu Rev Pathol 4: 287-313, 2009.
176. Magnifico A, Albano L, Campaner S, Campiglio M, Pilotti S, Ménard S and Tagliabue E: Protein kinase Clpha determines HER2 fate in breast carcinoma cells with HER2 protein overexpression without gene amplification. Cancer Res 67: 5308-5317, 2007.
177. Auersperg N, Maines-Bandiera SL and Dyck HG: Ovarian carcinogenesis and the biology of ovarian surface epithelium. J Cell Physiol 173: 261-265, 1997.
178. Auersperg N, Edelson MI, Mok SC, Johnson SW and Hamilton TC: The biology of ovarian cancer. Semin Oncol 25: 281-304, 1998.
179. Ideka K and Inoue S: Estrogen receptors and their downstream targets in cancer. Arch Histol Cytol 67: 435-442, 2004.
180. Issa R, Lebeau A, Grob T, Holst F, Moch H, Terracciano L, Choschzick M, Sauter G and Simon R: Estrogen receptor gene amplification occurs rarely in ovarian cancer. Mod Pathol 22: 191-196, 2009.
181. Eckert L, Repasky GA, Ulkü AS, McFall A, Zhou H, Sartor CI and Der CJ: Involvement of Ras activation in human breast cancer cell signaling, invasion, and anoikis. Cancer Res 64: 4585-4592, 2004.
182. Aunoble B, Sanches R, Didier E and Bignon YJ: Major oncogenes and tumor suppressor genes involved in epithelial ovarian cancer (review). Int J Oncol 3: 567-576, 2000.
183. Liu J, Yang G, Thompson-Lanza JA, Glassman A, Hayes K, Patterson A, Marquez RT, Auersperg N, Yu Y, Hahn WC, *et al*: A genetically defined model for human ovarian cancer. Cancer Res 64: 1655-1663, 2004.
184. Liao D and Dickson RB: c-Myc in breast cancer. Endocr Relat Cancer 7: 143-164, 2000.
185. Chen CH, Shen J, Lee WJ and Chow SN: Overexpression of cyclin D1 and c-Myc gene products in human primary epithelial ovarian cancer. Int J Gynecol Cancer 15: 878-883, 2005.
186. Arnold A and Papanikolaou A: Cyclin D1 in breast cancer pathogenesis. J Clin Oncol 23: 4215-4224, 2005.
187. Worsley SD, Ponder BA and Davies BR: Overexpression of Cyclin D1 in epithelial ovarian cancers. Gynecol Oncol 64: 189-195, 1997.
188. Siegel R, Naishadham D and Jemal A: Cancer statistics, 2013. CA Cancer J Clin 63: 11-30, 2013.
189. Petrucelli N, Daly MB and Feldman GL: Hereditary Breast and Ovarian Cancer due to Mutations in BRCA1 and BRCA2. Genet Med 12: 245-259 2010.
190. Birch J, Blair V, Kelsey AM, Evans DG, Harris M, Tricker KJ and Varley JM: Cancer phenotype correlates with constitutional TP53 genotype in families with the Li-Fraumeni syndrome. Oncogene 17: 1061-1068, 1998.
191. Menendez D, Inga A and Resnick MA: The expanding universe of p53 targets. Nat Rev Cancer 9: 724-737, 2009.
192. Khan S, Kumagai T, Vora J, Bose N, Sehgal I, Koeffler PH and Bose S: PTEN promoter is methylated in a proportion of invasive breast cancers. Int J Cancer 112: 407-410, 2004.
193. Garcia JM, Silva JM, Dominguez G, Gonzalez R, Navarro A, Carretero L, Provencio M, España P and Bonilla F: Allelic loss of the PTEN region (10q23) in breast carcinomas of poor pathophenotype. Breast Cancer Res Treat 57: 237-243, 1999.
194. Petrocelli T and Slingerland JM: PTEN deficiency: A role in mammary carcinogenesis. Breast Cancer Res 3: 356-360, 2001.
195. Ross J, Linette GP, Stec J, Clark E, Ayers M, Leschly N, Symmans WF, Hortobagyi GN and Pusztai L: Breast cancer biomarkers and molecular medicine: part II. Expert Rev Mol Diagn 4: 169-188, 2004.
196. Hashiguchi Y, Tsuda H, Yamamoto K, Inoue T, Ishiko O and Ogita S: Combined analysis of p53 and RB pathways in epithelial ovarian cancer. Hum Pathol 32: 988-996, 2001.