Gene Expression Profiling of Hereditary and Sporadic Ovarian Cancers Reveals Unique BRCA1 and BRCA2 Signatures

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The recent completion of the draft human genome sequence (1) presents countless opportunities to investigate genome function and the importance of alterations in the genetic code in both health and disease. Among the most rapidly adopted of the emerging genomic technologies, microarray hybridization permits the parallel determination of the expression of tens of thousands of genes in tissue samples (2). Microarray studies have proven to be of great value in further understanding the basic biology of cancer and have been used successfully to classify tumors into distinct, clinically relevant subgroups based on gene expression profiles and to identify potential biomarkers. Ovarian cancers differ from many other human tumors in displaying considerable disease heterogeneity, a poorly understood progression pathway, and few good tumor markers. In addition, ovarian cancers are usually diagnosed at a late stage, and the survival rate, therefore, is poor. Improved knowledge of the changes in gene expression associated with progression of ovarian cancer and with different forms of the disease, therefore, may lead to greater understanding of the underlying disease mechanisms and the development of possible intervention strategies.

In this issue of the Journal, Jazaeri et al. used complementary DNA (cDNA) microarrays to examine the role of mutations in the BRCA1 and BRCA2 genes in ovarian carcinogenesis by comparing gene expression patterns in ovarian cancers that are associated with germline BRCA1 and BRCA2 mutations and expression patterns in sporadic ovarian cancers (3). The most striking finding was that the BRCA1- and BRCA2-associated tumors displayed distinct gene expression profiles. Indeed, 110 genes of the approximately 6500 genes analyzed were found to be differentially expressed (P<0.0001) between these two subtypes of ovarian cancer. This result is in agreement with previous studies illustrating differences in gene expression profiles between BRCA1- and BRCA2-derived breast cancers (4,5). Remarkably, the gene expression profiles of the sporadic tumors appeared to share features of BRCA1- or BRCA2-associated cancers, as illustrated by the segregation of the sporadic samples into two groups based on the expression pattern of the BRCA1 versus BRCA2 genes. In other words, each sporadic sample had a molecular profile similar to that of either the BRCA1- or the BRCA2-associated tumors. The genes that separate the BRCA1-versus BRCA2-associated ovarian cancers and the two subsets of sporadic tumors are involved in important cellular functions, such as signal transduction, RNA processing and translation, chemokine signaling, immune modification, and DNA repair. As such, they may represent important mediators of common genetic pathways in ovarian carcinogenesis, and further investigation of these genes may provide insight into the development of BRCA1- and BRCA2-associated ovarian cancer. In agreement with the finding that the sporadic cancers shared gene expression features of either BRCA1 or BRCA2 tumors, it is not surprising that only a small number of genes were found to separate between the combined BRCA-associated group and the sporadic tumors (3).

The separation of the sporadic tumors into BRCA1-like and BRCA2-like subgroups may be caused by the dysfunction of BRCA1 or BRCA2 proteins or downstream effector molecules in either of the pathways. With regard to clinical and pathologic features, BRCA-associated cancers are not clinically significantly different from sporadic cases, although the mean age at diagnosis has been reported to be lower in patients with BRCA1-associated ovarian cancer (6). The observation that BRCA-associated gene expression profiles can be recapitulated in subsets of sporadic tumors indicates that molecular mechanisms common to both hereditary and sporadic ovarian carcinogenesis exist. As suggested, a possible explanation for this finding might be the disruption of BRCA function in sporadic tumors, either of the BRCA genes themselves, or of other key molecules in the same functional pathways. Loss of heterozygosity at the BRCA1 and BRCA2 loci among sporadic ovarian tumors is high (7), but somatic mutations in the BRCA genes are rare (8). Loss of BRCA1 expression through promoter hypermethylation has been reported in approximately 15% of breast and ovarian cancers (9,10). Of interest, BRCA1 hypermethylation in breast cancer is more common in the medullary subtype of breast cancer that is overrepresented in patients with BRCA1 germline mutations (9), emphasizing the clinical significance of BRCA1 deficiency in the development of breast cancer. The recent finding of a BRCA1-like gene expression profile in a sporadic breast cancer with BRCA1 promoter hypermethylation is consistent with a role for epigenetic alterations of BRCA1 in some sporadic cancers and illustrates the sensitivity of gene expression profiling in identifying unique expression profiles in subsets of tumors.
Inactivation of BRCA2 through promoter hypermethylation has not been reported (11), but other epigenetic alterations may explain the loss of BRCA2 function. Indeed, there are reports of loss of BRCA protein expression in a majority of sporadic ovarian cancers (12), supporting a role for these proteins even in the absence of somatic mutations in the genes and in agreement with the findings of Jazaeri et al. that sporadic tumors display BRCA1-like or BRCA2-like gene expression profiles.

Another possible explanation may be that overriding growth pathways distinctly affect the BRCA1-like and BRCA2-like tumors. As such, the genes segregating the two tumor types may reflect differences in tumor progression between BRCA1- and BRCA2-associated cancers that may also be seen in sporadic tumors; i.e., these tumor types may traverse down separate pathways in their progression toward malignancy. In breast cancer, a pronounced effect on expression profiles is caused by differences in expression of the estrogen receptor (ER), so that all breast cancers can be separated into either ER-positive or ER-negative groups (13). Interestingly, gene expression profiling of BRCA1- and BRCA2-associated breast tumors has revealed an important ER-related component (4). A potential implication of the study by Jazaeri et al. may be that there are other overriding key pathways driving ovarian cancers, which are as yet undiscovered.

Alternatively, the appearance of BRCA1-like and BRCA2-like gene expression profiles may represent differences in histogenesis, as has been suggested from microarray studies of subgroups in breast and lung cancer (14–16). Defects in the two genes may preferentially cause transformation of distinct cell types, and this transformation may be recapitulated in subsets of sporadic cancers. This is an exciting prospect, because the specific cellular origin of ovarian cancer remains uncertain (17). Clearly, mutations in BRCA1 and BRCA2 are associated with distinct gene expression patterns, but additional studies to establish the underlying mechanism linking mutations in these genes to the evolution of these distinct gene expression subtypes are needed.

Further investigation of genes found in the Jazaeri study to be overexpressed in ovarian tumors [e.g., investigations using tissue microarrays containing large numbers of clinically well-characterized tumor specimens (18)] may be useful to validate potential markers for ovarian cancer identified in this study. Increased knowledge of changes in gene expression in ovarian carcinogenesis may lead to improvements in detection and therapeutic strategies, potentially improving the management of ovarian cancer patients.

This study and others illustrate the potential diagnostic power of gene expression profiling and provide a glimpse into the possible diagnostic value that such testing may provide. From recent studies in breast cancer (4,5,13,14), lung cancer (15,16), medulloblastoma (19), melanoma (20), leukemia (21), lymphoma (22), and now ovarian cancer (3), it is clear that tumors can be subclassified by their gene expression profiles. Moreover, some of these reports suggest that this analysis may provide clinically useful prognostic information and a method for the identification of potential tumor markers. It appears likely that genomic techniques will be incorporated into the design of clinical trials in the near future, giving us whole-genome views rather than gene-by-gene information. Although confirmatory studies in the context of large clinical trials are necessary before array-based methods can be recommended for routine clinical use, the promise of these methods is readily apparent.

REFERENCES