## Friday, 24 March 2006 08:00–08:45

EUROPA DONNA TEACHING LECTURE

# Increased risk of breast cancer – what I need to understand

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**Increased risk of breast cancer – what I need to understand**

A. Fernandez-Marcos. *Asociación Española Contra el Cáncer, Madrid, Spain*

Women at high risk of familial breast cancer are confronted to key difficult decisions twice: firstly, whether to take a genetic test or not, and secondly, after being given a positive result, which preventive measure to undertake. Each of those decisions has its own pace, timing and approach.

The scenario of information and decision-making regarding genetic testing for breast cancer risk has two levels, depending on who is asking for the test: 1) a healthy woman with a history of female relatives diagnosed of breast cancer who wants to know whether she is a mutation carrier and her chances of developing the disease, 2) a breast cancer patient who wants to know the risk of developing breast cancer of her offspring and her own risk of recurrence. In both cases a careful assessment of risk perception, motivation to undertake the test, and psychological distress associated to the genetic consultation must be performed. Pre-testing psychological screening and pre and post-test counselling can help to prepare high risk women for the decisions they might have to undertake.

Once the genetic test has shown a positive result and as controversial issues still remain regarding breast cancer prevention, a gold-standard way of providing the different options can not be offered yet. The process of providing this information must be tailored to the characteristics of the woman who asked for the test. Pros and cons of each possible decision should be discussed in a balanced, clear and comprehensible way, spending as much time as needed for the woman to understand, recall, and come back to clarify any doubt she may have.

Some decision aids may be of help, particularly in adjusting the women's perception of risk and satisfaction with the information, but more research is still needed in this field.

## Friday, 24 March 2006 09:00–10:40

PRESIDENTIAL SESSION

# Breast cancer – a look into the future

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**Is genomic grading killing histological grading?**

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The histologic grade of breast carcinomas has long provided clinically important prognostic information. However, despite recommendations by the College of American Pathologists that tumor grade be used as a prognostic factor in breast cancer, the latest Breast Task Force of the American Joint Committee on Cancer did not include histologic tumor grade in its staging criteria, because of insurmountable inconsistencies in histologic grading between institutions. Concordance between two pathologists has been investigated and found to range from 50% to 85%. With the advent of new unified methods, such as the Elston and Ellis modification of the Bloom and Richardson method, the reproducibility of histologic grading has been improved. Although about half of all breast cancers are assigned histologic grade 1 or 3 status (with a low or high risk of recurrence, respectively), a substantial percentage of tumors (30%-60%) are classified as histologic grade 2, which is not informative for clinical decision making because of its intermediate risk of recurrence. This high percentage histologic grade 2 tumors is still observed when grading is performed by a single pathologist.

Recently, gene expression profiling has resulted in a paradigm shift in the way that researchers view breast cancer biology. In a previous work we have demonstrated, for example, that the ER status of the tumor was, indeed, the most important discriminator of expression subtypes, and that tumor grade came in second. Interestingly, other clinical features, namely positive lymph node status, menopausal status, and tumor size were not strongly reflected in the expression patterns.

Following our previous observation that tumor grade was an important discriminator of expression subtypes we sought whether grade could be refined by using gene expression profiling. In a recent work we have demonstrated that "genomic" tumor grade, which reflects differentiation and tumor progression on the basis of gene expression profiles (GEP), is effectively associated with distinct GEP and disease outcome in breast cancer far beyond the currently used clinico-pathological parameters. For that purpose we established a scoring system, referred to as the "gene-expression grade index" (GGI), and tested it on various independent validation datasets. We found that poorly differentiated compared with well-differentiated tumors are associated with distinct GEP and GGI and have statistically different clinical outcomes. Many of the markers are genes involved in cell cycle progression and proliferation, including *CCNB2*, *CDC2*, *BUB1B*, *CDC25A* and *TPX2*. We further demonstrated that intermediate grade tumors contain a mixture of well-differentiated and poorly differentiated expression patterns rather than a distinct or intermediate profile. This observation challenges the existence and clinical relevance of an intermediate grade classification. Interestingly, we also found that grade-related genes may encompass a significant portion of the predictive power of previously published prognostic signatures.

Notably, we also found that genomic grade was also associated with the different molecular subtypes (previously identified by our group and others): basal-like, erbB2-like and luminal A, B and C subgroups. While the luminal A subgroup showed lower GGI levels, the basal-like, erbB2-like and luminal B and C subgroups had the worst clinical outcome in keeping with higher GGI levels.

These results may suggest that the genomic grade, which essentially captures the degree of differentiation, may reflect the origin of the different cell lineages involved in breast cancer development.

We are currently validating our findings in the TRANSBIG series of 300 tumor samples from 5 different European institutions from which grading was determined based on a central pathology review. Additionally, we are in the process to convert genomic grade into a user-friendly RT-PCR tool which will assist clinicians and patients in optimizing treatment of early breast cancer.

433 Invited

**Adjuvant endocrine treatment tailoring in 2006 – dream or reality?**

C.K. Osborne. *Baylor College of Medicine, Breast Center, Houston, Texas, USA*

All endocrine therapies used today target the estrogen receptor but by different mechanisms. Ovarian suppression and aromatase inhibitors deprive ER of its activating ligand. SERMs like tamoxifen and toremifene competitively block ER while SERDs like fulvestrant completely block and degrade ER. The response to one endocrine therapy after progression on another indicates that they have different mechanisms of action and of resistance. Choosing an endocrine therapy in the past was based on the idea that all endocrine therapies have similar effectiveness when used in the same patient population, and, therefore, the decision to choose a specific therapy was related predominantly to its toxicity profile i.e. tamoxifen versus high dose estrogen therapy. ER and PR were known to predict response to hormonal therapies but they were not used to predict response to specific treatments. Today we are beginning to see evidence that certain tumors may be more responsive to one type of endocrine therapy than to another. Preclinical and clinical data suggest that benefit to a specific endocrine therapy may be related not only to its mechanism of action, but also to other cell signaling pathways functioning in the tumor. Data suggest that the expression of just three genes, ER, PR, and HER2, may distinguish a group of patients whose tumors are much more responsive to aromatase inhibitors rather than to tamoxifen. Furthermore, it is clear that ER-positive, PR-positive tumors are different from ER-positive, PR-negative tumors in many ways. PR-negative tumors are larger, more likely to have lymph node involvement, more likely to be anueploid, to have a higher rate of proliferation, and to express high levels of growth factor receptors such as EGFR and HER2. Molecular profiling studies are underway to identify other genes and pathways that may be different in these two breast cancer sub-types. The hypothesis that molecular signatures might be helpful in selecting specific endocrine therapies and in identifying other pathways that should be blocked together with ER to circumvent resistance deserves testing in the clinic.