Thursday, February 26, 1998 **10.30–12.30**

Session 3 Biology of Breast Cancer: Diagnostic & Prognostic Implications

S9 Biology of breast cancer risk and prognosis

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Risk of developing breast cancer varies considerably between individual women, and the heterogeneity of breast cancer natural history is striking. Currently described risk and prognostic factors do not fully account for observed variability in risk and prognosis. In view of the fact that insulin-like growth factors are known to have strong stimulatory effects on breast epithelial cell proliferation, and the fact that (unlike many other hormones) there is considerable person-to-person variability in IGF-I levels, laboratory and clinical studies have been undertaken to determine if heterogeneity in IGF physiology contributes to heterogeneity in risk and prognosis. In animal models, we and others have demonstrated that excess activity of the growth hormone – IGF-I axis is associated with mammary epithelial cell proliferation and specific histological characteristics which have been associated with increased breast cancer risk in humans. In a prospective study, we measured levels of IGF-I and its major circulating binding protein (IGFBP3) in 397 women with invasive breast cancer and 620 age-matched controls from the Nurses' Health Study. Among premenopausal women, relative risk for women in the highest (>207 ng/ml) vs. lowest tertile (<110 ng/ml) of IGF-I (adjusted for IGFBP3 level) was 2.88 (95% CI 1.21–6.85). The RR was higher than this among younger women. Postmenopausal IGF-I level was unrelated to risk of postmenopausal breast cancer, but we were unable to evaluate the possibility that premenopausal IGF-I level is related to postmenopausal risk. As IGF-I levels are lowered by antiestrogens, the findings raise the possibility that serum IGF-I is a correlate of risk that may serve as an intermediate endpoint in antiestrogen prevention trials. While the risk associated with IGF-I level >207 ng/ml is much lower than that associated with BRCA1 mutation, the burden of breast cancer associated with high IGF-I may be greater than that related to BRCA1, as the number of women in the top tertile of IGF-I level is much greater than the number with BRCA1 mutations. Studies examining the separate issue of relationships between IGF-I level and prognosis will also be summarized.

S10 Determination of clinical utility of tumor markers: A tumor marker utility grading system

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Incorporation of tumor markers into routine clinical decision-making has been poorly controlled. Few criteria or guidelines have been available to help direct new studies of tumor markers, or to help decide when a tumor marker should be included in standard practice. Over the last 10 years, many novel tumor markers have been reported to "significantly predict prognosis" in patients with newly diagnosed breast cancer. Nonetheless, in a recently published set of guidelines for the use of tumor markers in breast cancer, an expert panel convened by the American Society of Clinical Oncology recommended only the use of ER and PR to select appropriate candidates for hormone therapy (ASCO Expert Panel 1996). Members of this same Expert Panel have published a separate proposal to establish a framework with which to evaluate clinical tumor marker studies (Hayes, et al. 1996). This Tumor Marker Utility Grading System (TMUGS) is designed to clarify the precise characteristics of the marker in question. For each specific clinical use, such as determination of risk, differential diagnosis, prognosis, or monitoring of clinical course, one of four clinical outcomes should be improved as a result of a therapeutic decision based on the marker results: Overall Survival, Disease Free Survival, Quality of Life, and/or Cost. A semi-quantitative 6 point utility scale was developed, and utility scores are assigned to the marker for a use for a specific endpoint, with appropriate documentation of the level of evidence available to support the assignation. Only markers that receive a "++" or "+++" are recommended for routine clinical use. Recent refinements have been suggested to include overview analyses of multiple separate studies of tumor marker as Level of Evidence Category I. Perhaps the best example of such an analysis has recently been published regarding MDR in breast cancer (Trock, et al. 1997). TMUGS will establish a standardized analytic technique to evaluate clinical utility of known and future tumor markers. It should result improved patient outcomes and more cost-efficient investigation and application of tumor markers.

[1] ASCO Expert Panel (1996) Clinical Practice Guidelines for the Use of Tumor Markers in Breast and Colorectal Cancer: Report of the American Society of Clinical Oncology Expert Panel. J Clin Oncol 14:2843–2877
[2] Hayes DF, Bast R, Desch CE, Fritsche H, Kemeny NE, Jessup J, Locker GY, Macdonald J, Mennel RG, Norton L, Ravdin P, Taube S, Winn R (1996) A tumor marker utility grading system (TMUGS): a framework to evaluate clinical utility of tumor markers, J Natl Cancer Inst 88:1456–66
[3] Trock B, Leonessa F, Clarke R (1997) Multidrug Resistance in Breast Cancer: A meta-analysis of MDR1/gp170 expression and its possible functional significance. J Natl Cancer Inst 89:917–31

Thursday, February 26, 1998 **14.00–15.30**

Session 4 In Situ Breast Cancer

S14 Hypothesis and practice: Are there several types of treatment for DCIS?

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With the acceptance and increased utilization of screening mammography, there has been a dramatic increase in the number of DCIS cases during the last 15 years. Historically, most patients with DCIS were treated with mastectomy which yielded a local recurrence rate of 1%; this is the standard to which other treatments are generally compared. Since the early 1980s, an increasing number of DCIS patients have been treated with breast conservation therapy (BCT). The only prospective randomized trial published so far (NSABP B-17) yielded 8-yr actuarial local recurrence rates of 12% for DCIS patients treated with excision and radiation therapy and 26% for patients treated with excision alone. Local recurrence is an important event when it occurs in a patient previously treated for DCIS and the results of NSABP B-17 suggest that it is going to be a fairly frequent event. Not only is local recurrence demoralizing, more importantly, since approximately 50% of all local recurrences are invasive, it is also a threat to the patient's life. Therefore, predicting patients who are likely to recur locally after BCT is extremely important and may be useful in treatment planning. Our group studied 722 patients with DCIS seen from 1979–July 1997, in whom there have been a total of 73 recurrences. In an attempt to predict the likelihood of local recurrence, we evaluated 30 prognostic factors in breast preservation patients. Only three factors were significant independent predictors of local recurrence by multivariate analysis: pathologic classification (determined by nuclear grade and necrosis), margin width and tumor size. These three factors were then used to develop the Van Nuys Prognostic Index (VNPI), a quantitative algorithm that may aid the treatment decision-making process.

S15 Shifting knowledge on in situ carcinomas: The pathologist's view

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The widespread use of screening mammography has resulted in a marked increase in the frequency with which in situ carcinomas are encountered by clinicians, radiologists and pathologists. In particular, there has been a dramatic increase in the frequency of ductal carcinomas in situ (DCIS). In the pre-mammographic era DCIS was uncommon, most often presented as a palpable mass and was typically treated by mastectomy. In fact, mastectomy for these lesions resulted in cure rates approaching 100%. In contrast, DCIS today most often presents as a non-palpable lesion detected by mammography and many of these lesions are quite small. Furthermore, the natural history of such lesions is largely unknown. Given the increasing use of breast conserving treatment for invasive cancer and the uncertain biologic potential of mammographically-detected DCIS, it is difficult to justify the routine use of mastectomy for this disease. Therefore, there is now great interest in the identification of patients with DCIS who may safely and effectively be treated with breast conserving surgery with or without radiation therapy. Factors that appear to be important to consider in determining the suitability of patients with DCIS for breast conserving treatment include the distribution of the lesion in the breast, the histologic features, the size or extent of the lesion, and the adequacy of the excision. However, how best to assess these factors, their relative importance and the interactions among them are not yet well defined and remain areas of active investigation. It has become clear, however, that careful mammographic evaluation and careful pathologic assessment are essential for patients with DCIS considered for treatment with a breast conservation approach.