RESEARCH HIGHLIGHTS

Sharon Lobert, RN, PhD
Associate Editor

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Clinical Research

Procollagen Peptide May Predict Bone Metastases in Women With Primary Breast Cancer

Researchers from the United Kingdom and Finland presented the results from a study comparing bone marrow density and serum biochemical markers of bone turnover where bone-specific alkaline phosphatase, carboxy-terminal telopeptide of type I collagen, and n-terminal procollagen peptide of type I collagen (PINP) were analyzed at one and two years. A total of 498 women with breast cancer were entered in the trial and received either clodronate (a bisphosphonate that reduces osteoclast activity) (n = 243) or a placebo (n = 255). Bone marrow density was measured by dual x-ray absorptiometry at trial entry and annually. The researchers found a significant correlation between oral clodronate and an increase in mean bone marrow density in the spine and hip after two years. This increase was associated with a significant decrease in serum PINP. Patients in the control placebo group demonstrated a significant decrease in bone marrow density in the spine and hip. The serum PINP was significantly higher at one and two years in women who developed bone metastases during a median of 5.5 years of follow-up. The researchers concluded that serum PINP levels may be useful as an early marker of bone metastases and may help in selecting appropriate long-term treatment for patients with breast cancer.

Blood Test May Be Useful for Detecting Breast Cancer

Protein chip mass spectrometry is a technique used to identify multiple changes in protein levels to develop a profile of disease biomarkers. Researchers from Eastern Virginia Medical School in Norfolk used this technology to examine serum samples from 92 female patients. They used surface-enhanced laser desorption/ionization (SELDI) mass spectrometry to create protein profiles and a decision-tree algorithm and biomarker pattern software for classification analysis that yielded seven characteristic protein peaks. Fifty women were diagnosed with breast cancer and 42 had benign lesions. The protein profile analysis demonstrated 85% specificity and 78% sensitivity. The researchers concluded that SELDI protein chip mass spectrometry of serum samples with appropriate classification can identify breast cancer with a specificity and sensitivity that approaches mammography. They recommended that a larger study is needed to confirm these results.

Visual and Digital Assessment of Changes in Breast Density May Be Clinically Meaningful

High breast density is associated with an increased risk for developing breast cancer. Although standards currently exist for assessing breast density, no standards define a clinically meaningful change in breast density. Researchers from the University of Virginia in Charlottesville presented results from a study using a visual and digital assessment of breast density. The study involved 28 postmenopausal women who had an increase in breast density related to hormone replacement therapy and 10 postmenopausal women who had no reported change in breast density. Mammograms were examined by an experienced radiologist and digitized using a high-resolution Lumisys 75 scanner. The radiologist classified cases from 0 to +3, depending on the degree of change in breast density. The visual assessment placed 9 cases in the +1 range (density increase of less than one breast imaging reporting and data system [BIRADS] category), 10 in the +2 range (increase of one BIRADS category) and 9 in the +3 range (increase of one or more BIRADS categories with an increase in breast size). Digital assessment recorded an average increase in density of 6.8% in the +1 group, 18.7% in the +2 group, and 37.4% in the +3 group. The digital assessment recorded a mean decrease of 1.4% in density in the control group. The researchers concluded that they have been able to define changes in breast density in clinically meaningful categories and that these correlate with quantitative digitally assessed changes.

Epidemiologic Research

Mammography May Detect Nonpalpable Breast Carcinomas With a High Cure Rate

The ability of mammography to increase long-term survival for patients with breast cancer remains controversial. Researchers at the University of Southern California in Los Angeles compared survival data for 3,617 patients with breast cancer. Of these, 1,564 had nonpalpable lesions discovered by mammography (576 invasive and 988 in situ) and 2,053 had palpable lesions. The 10-year actuarial distant disease-free survival was significantly greater for all nonpalpable lesions compared to the palpable lesions (95%, 89%, and 73%, respectively). The overall survival also was better for the nonpalpable lesions compared to the palpable (89% and 84% for nonpalpable and 70% for palpable). The researchers concluded that mammography identification of suspicious areas leads to a biopsy-detected subgroup of patients with breast cancer who have a statistically superior cure rate compared to patients with palpable lesions.

Basic Research

Functional Genomics Breast Cancer Database Links Data Potentially Critical for Diagnosis and Treatment

Breast cancer is known to be a highly heterogeneous disease. Altered responses to inhibitory and proliferation signals, differentiation, apoptosis, and angiogenesis, as well as alterations in many other processes regulated by multiple genes, occur. Microarray technologies, where thousands of genes can be examined from a single tissue or serum sample, offer the possibility of establishing profiles of tumors fundamental to understanding the altered responses in carcinogenesis. Researchers from the National Institutes of Health in Bethesda, MD, described a comprehensive database generated from 14,000 genes that will offer information on in vivo tumor profiling, proliferation, drug sensitivity and resistance, hormonal impact, apoptosis, and epigenetic and post-translational regulation of differentiation. The database will serve as a link among clinical data, functional assays of cell lines, and online databases. It will prioritize and accelerate the search for genes that may have diagnostic, prognostic, or therapeutic values.

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Microarrays May Predict Docetaxel Responders and Nonresponders

Taxotere® (docetaxel, Aventis Pharmaceuticals, Bridgewater, NJ) is an important agent used in adjuvant chemotherapy. Although Taxotere appears to induce one of the highest chemotherapy response rates in patients with breast cancer, tumor resistance is frequent. Researchers from Baylor College of Medicine in Houston, TX, examined tumor samples from 24 patients who received 12 weeks of Taxotere therapy in an effort to quantify gene expression patterns in responders and nonresponders. These patients represented the extremes of treatment success or failure. Microarray technologies and DNA chip analyzer software were used to determine expression patterns for 12,000 genes; of these, 747 were selected for comparison purposes. Statistical tests allowed identification of a subset of 100 genes that predict the likelihood of response to Taxotere. The researchers found that nonresponders had elevated levels of microtubule components and responders had elevated levels of genes associated with stress (i.e., microfilament, immune response, inflammatory response, heat shock, and mitochondrial genes). The researchers concluded that cDNA array-based tumor profiles may be used to predict responses to single-agent Taxotere therapy. As a result, this could reduce unnecessary treatment, toxicity, and cost to women with breast cancer.

Gene Expression May Predict Postoperative Prognosis for Patients With Breast Cancer

The absence of estrogen receptors (ERs) in breast tumors is associated with poor prognosis. Researchers from the Nippon Medical School in Kawasaki, Japan, and the Cancer Institute in Tokyo, Japan, presented the results of a study aimed at identifying prognostic indicators for patients with ER-negative breast tumors. They used microarray technologies to examine breast tissues from patients who survived five years and from those who did not. Total RNA was extracted from normal and tumor breast tissues and then amplified and labeled. A total of 25,344 genes were examined by competitive hybridization on glass slides. Results were confirmed by reverse transcriptase polymerase chain reaction. Gene expression was found to be significantly different for several genes in the two patient groups. The researchers suggested that genes in each group might serve as new genetic prognostic markers.

Additional Research Highlights

Short Interval Follow-Up for Probably Benign Mammogram Findings May Be Unnecessary

A 2003 article in the *Journal of the National Cancer Institute* (Vol. 95, No. 6, pp. 429–436) examined the predictive value of a "probably benign finding" in mammogram screenings. The researchers carried out a longitudinal analysis of a prospective cohort of 68,126 postmenopausal women (50–79 years old) from the Women's Health Initiative at 40 centers in the United States. Participants had mammograms at baseline and annually for at least two years. Of the eligible women, 5% (n = 2,927 of 58,408) were given recommendations for short-interval follow-up. The incidence of breast cancer for these women was 1% at two years compared to 0.6% and 0.5% for women who had baseline benign or negative findings. The researchers concluded that a recommendation for short-interval follow-up had a low-positive predictive value for breast cancer among postmenopausal women during the two-year follow-up. They suggested that a recommendation of repeat mammography in six months for "probably benign" findings should be reconsidered.

Levetiracetam Provides Pain Relief and Reduces Need for Opioids in Patients With Neoplastic Pain

Researchers from the A&A Pain Institute in St. Louis, MO, presented the results of a study of levetiracetam (LEV), an antiepileptic agent, for pain relief at the Annual Meetings of the American Pain Society from March 20–23, 2003, in Chicago, IL. Their study involved six participants with neoplasms: four with neoplasms invading the brachial plexus and two whose neoplasms were in the lumbosacral plexus. Initially, the patients reported severe pain (8–9 out of 10 on a visual analog scale [VAS]). Pain was severe despite the use of parenteral opioids and other pain therapies. Participants received oral LEV titrated for up to two weeks for maximum doses of 500–1,500 mg twice a day. Both VAS and opioid use were recorded. The results showed that VAS scores were reduced to 0–3 out of 10 in 3–14 days and opioid use was reduced by 50%. LEV was well tolerated with no adverse effects. The researchers recommended that these results should be confirmed by larger, controlled studies.

Combination Vinorelbine and Gemcitabine Is Not More Effective Than Either Agent Alone

The results of a phase III trial in the Multicenter Italian Lung Cancer in the Elderly Study were presented in the *Journal of the National Cancer Institute* (Vol. 95, No. 5, pp. 362–372). The study was an open-label, randomized trial comparing the efficacy and toxicity of vinorelbine or gemcitabine alone or in combination. Participants (N = 698) were aged 70 or older with advanced non-small cell lung cancer (NSCLC) and were assigned randomly to one of three treatment arms: vinorelbine 30 mg/m^2, gemcitabine 1,200 mg/m^2, or vinorelbine 25 mg/m^2 and gemcitabine 100 mg/m^2. Chemotherapy was given on days one and eight every three weeks for a maximum of six cycles. The combination treatment did not improve survival relative to the two single-agent–treatment arms. Quality-of-life measures were found to be similar across all three treatment groups; however, toxicity was higher for the combination-treatment group. The researchers recommended that single-agent chemotherapy (vinorelbine or gemcitabine) is preferred over combination chemotherapy for palliation treatment in elderly patients with advanced NSCLC.