BASIC RESEARCH

New Marker Identified for Metastatic Breast Tumors

Researchers at the University of Michigan reported results from a study suggesting that RhoC may be a marker for metastatic breast tumors, regardless of tumor size. RhoC-GTPase is a member of the ras superfamily of proteins, which are known to affect cell polarity and motility. In this research, 182 breast tissues from 164 patients were examined by immunohistochemistry using a polyclonal antibody raised against RhoC. Data were analyzed quantitatively according to the intensity of antibody staining. RhoC was expressed in 36 of 114 (32%) invasive carcinomas and strongly correlated with tumor stage. It showed a high specificity for detecting metastatic tumors (88%), especially those smaller than 1 cm (92%). RhoC was not expressed in normal breast tissue, fibrocystic disease, atypical hyperplasia, or ductal carcinoma in situ. Researchers are continuing to work with tissues that overexpress HER2/neu and are negative for progesterone receptors, both of which are suggestive of poor prognosis. Identification of a biomarker for small invasive tumors would improve the selection of appropriate initial aggressive treatment for these tumors.

Receptor Tyrosine Kinase Mutation May Be Associated With Shorter Survival

Receptor tyrosine kinases in the epidermal growth factor receptor or fibroblast growth factor receptor (FGFR) families are thought to play a role in numerous tumors. In a collaborative research from Germany (Martinsried and Munich) suggested that a mutation in FGFR may be associated with shorter survival for patients with head and neck squamous cell carcinoma. A single nucleotide polymorphism that inserts either a glycine or arginine was identified in FGFR4. The arginine substitution was shown to be a marker for poor prognosis. Quantitative evaluation of 104 head and neck squamous cell carcinoma tissues for this mutation demonstrated the mutation in 59 tumors. Examination of clinical data revealed that the mutation correlated with reduced overall survival (p = 0.02; log-rank test). The researchers suggested that these findings may serve to identify a new diagnostic biomarker and therapeutic target for this type of cancer.

New Ovarian Cancer Biomarker, Haptoglobin Alpha Chain, Identified

Researchers at Brigham Women’s Hospital and Harvard Medical School in Boston, MA, to screen for protein markers in the serum of patients with ovarian cancer. A total of 108 age-matched samples (58 cases and 50 controls) were examined. Researchers identified a protein biomarker and used mass spectrometry to determine that the protein was haptoglobin α-1. Enzyme-linked immunosorbent assays, using a polyclonal antibody raised against the protein, demonstrated that the biomarker had 82% sensitivity and 83% specificity in 94 cases and 99 normal controls. Further studies of the protein may lead to better diagnostic tests and increased understanding of the pathophysiologic mechanisms underlying ovarian cancer.

Potential New Treatment Reduces Pancreatic Tumors and Metastasis

Researchers in Osaka, Japan, identified the hepatocyte growth factor (HGF) antagonist NK4, a peptide that may prove to be useful in treating pancreatic cancer. This malignancy is highly aggressive and resistant to treatment. NK4 is actually a fragment HGF that interferes with HGF binding to its cell surface receptor (c-Met). The interaction of HGF and c-Met stimulates intracellular signaling, causing cancer cells to invade normal tissues and metastasize. NK4 not only blocks HGF signaling but also inhibits blood vessel formation (angiogenesis) that is necessary for tumor growth. In this study, mice were injected with pancreatic cancer cells. After four days, they were treated daily with either NK4 or saline as a control. After 28 days, the tumors in the NK4-treated mice were one-third the size of the tumors in the control mice. Furthermore, blood vessel growth and metastasis were reduced significantly in the treated mice. In a second experiment, the NK4 treatment was withheld until late-stage cancer had developed (24 days). All of the mice in the control group had died by 69 days; however, 60% of the NK4 mice remained alive on day 70. The researchers plan to expand this work toward the development of human trials with NK4.

CLINICAL RESEARCH

Chemically Induced Hypothyroidism May Improve Survival for Patients With Recurrent Gliomas

High doses of tamoxifen previously have been shown to down-regulate protein kinase C-α, producing a cytostatic and apoptotic effect on glioma cells. The insulin-like growth factor-1 inhibits the apoptotic effects of tamoxifen on cell cultures and it modulated by the thyroid hormone. Researchers at Cleveland Clinic Cancer Center in Ohio reasoned that inhibition of thyroid gland function may enhance the effectiveness of tamoxifen in patients with recurrent gliomas, aggressive brain tumors that generally are unresponsive to chemotherapy. In the trial, 38 patients were treated with propylthiouracil 600–1000 mg per day and Lugol’s solution 30 mg three times a day for 14 days. For 22 patients, tamoxifen 240 mg per day was begun within one month of entry into the study. For the remaining patients, tamoxifen was begun only when they were chemically hypothyroid. Of the 18 patients who became chemically hypothyroid, 5 (28%) had a significant reduction in tumor size. However, tumor size was not reduced for any of the patients who remained euthyroid. Toxicities included one occurrence of each of the following: deep vein thrombosis, nausea and vomiting, fatigue, and ataxia. One patient became symptomatic from hypothyroidism. Furthermore, the median survival for the hypothyroid group was 10.6 months compared with 3.1 months for the euthyroid group. Three of the patients who became hypothyroid survived more than two years, whereas the longest surviving patient of the euthyroid group lived eight months. This treatment now is being tested in patients with newly diagnosed glioma.

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SR-45023A Shows Promise for Preventing and Treating Melanomas

Researchers from Stanford University in CA, Arizona Cancer Center in Tucson, and Ilex Oncology Research in Geneva, Switzerland, presented the results of preclinical and phase I trials of a cholesterol-lowering drug, Apomine™ (SR-45023A, Ilex Oncology), to treat melanomas. Apomine previously has been shown to induce apoptosis in precancerous cells and can be administered orally or topically. It increases the degradation of HMG-CoA reductase, which is important in cholesterol synthesis. As a result, fewer by-products of cholesterol synthesis that activate the ras protein exist. Activated ras acts as a switch, signaling cell survival and proliferation. Apomine has been shown to reduce free radical production caused by ultraviolet light in melanoma cells, thus limiting DNA damage. In a melanoma mouse model, topical application of Apomine reduced the melanoma incidence by 55%, and melanoma cells in culture showed a reduction in activated ras after treatment with 10 micromolar Apomine. In a phase I trial, Apomine was administered orally 125 mg/m² twice a day for 14 of 21 days to patients with chemotherapy-resistant melanoma. Two of nine (22%) patients who had prolonged disease stabilization, and one patient with pulmonary metastases remained in the study after 36 courses of therapy over 2.5 years. This research identified a new signaling pathway as a possible chemotherapeutic target and suggested that future clinical trials with Apomine are warranted.

St. John’s Wort May Compromise the Effectiveness of Chemotherapy

Researchers in the Netherlands examined the combined effectiveness of St. John’s Wort and irinotecan. St. John’s Wort is an over-the-counter herbal product often used to treat depression. It is known to stimulate cytochrome P450, one of the enzymes important in drug biotransformation. This enzyme is involved partly in metabolizing and inactivating irinotecan. In this small study, three patients received a course of irinotecan (90-minute infusion, 350 mg/m²) every three weeks. One week after the first irinotecan infusion, St. John’s Wort 300 mg was given orally three times a day and continued through the second irinotecan infusion. Another group of patients received the combined St. John’s Wort and irinotecan for the first dose, but St. John’s Wort was discontinued thereafter. By this design, both the effect of combined therapy and the duration of the effect could be examined. The results showed that the metabolite of irinotecan, SN-38, increased by 40% in patients taking St. John’s Wort compared with those not taking it. This effect lasted for more than three weeks after stopping the St. John’s Wort cotreatment. The study indicated that significantly more biotransformation of irinotecan occurs when patients are taking St. John’s Wort. Furthermore, the effect of St. John’s Wort persists over weeks. The results also suggested that St. John’s Wort may interfere with other chemotherapeutic agents that are metabolized by cytochrome P450 and, therefore, assessment of over-the-counter medications is essential.

Epidemiologic Research

Insulin Resistance May Correlate With Increased Risk of Breast Cancer

A collaborative study by researchers at Channing Laboratory, Brigham Women’s Hospital, and Harvard University in Boston, MA, and Lady Davis Institute of the Jewish General Hospital and McGill University in Montreal, Canada, suggested that higher levels of C-peptide, a protein marker that suggests insulin resistance, correlate with an increased risk of breast cancer. This case-control study nested in the Nurses’ Health Study involved 463 women diagnosed with breast cancer prior to June 1994 and 763 controls matched on age, menopause status, time of blood collection, and fasting status. C-peptide levels were found to increase with age, body mass index, and postmenopausal (i.e., in the absence of exogenous hormones) status. The levels decreased with increased alcohol intake and physical activity. Logistic regression was used to estimate relative risk (RR). The RR for the women with the highest levels of C-peptide was 1.68, or 68% higher than the women with the lowest levels of C-peptide. The study results suggested that elevated C-peptide, like physical activity, may be a modifiable risk factor for breast cancer.

Excessive Weight Gain During Pregnancy May Increase Risk of Postmenopausal Breast Cancer

An international group of researchers from Washington, DC, and Finland investigated the relationship between weight gain during pregnancy and the risk of breast cancer. In the first cohort of 23,885 Finnish women, 392 controls and 92 women with breast cancer were identified with a mean age of 46.7. In this group of premenopausal women, no relationship existed between weight gain during pregnancy and breast cancer. Low body mass index in nonpregnant women was linked in this study to an increased risk of premenopausal breast cancer (p < 0.068). In a second group of 4,090 women, 166 developed postmenopausal breast cancer at an average age of 68.3 years. In this group, the risk of developing breast cancer was associated significantly with a weight gain of more than 25 kg during pregnancy (relative risk 3.0, 95% confidence interval 1.2–7.6). The study concluded that although weight gain during pregnancy may not have an impact on the risk of premenopausal breast cancer, it may increase the risk of breast cancer diagnosed after menopause.

October Is National Breast Cancer Awareness Month

Participate by promoting National Mammography Screening Day on October 18, 2002.

Rates of women participating in mammography screening have climbed significantly, and fewer deaths from breast cancer have been reported as a result. Help to continue this upward trend by promoting and participating in National Mammography Screening Day on October 18.

Visit www.nbcam.org for more information on Breast Cancer Awareness Month and National Mammography Screening Day. A promotion guide highlighting seven steps to preventing breast cancer and promoting breast cancer awareness is available free of charge on this Web site.