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EPIDERMAL GROWTH FACTOR RECEPTOR: A MARKER OF EARLY RELAPSE IN BREAST CANCER: INTERACTIONS WITH NEU.

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Epidermal growth factor receptors (EGFRs) were measured in 221 primary breast cancers. There was a highly significant inverse relationship between estrogen receptor (ER) and EGFR expression (15 [$EGFR^+$] ER^+ and 92 [$EGFR^-$] ER^+ : 54 $EGFR^-$ ER^- and 60 $EGFR^+$ ER^-). The relapse-free survival and overall survival were significantly shorter for $EGFR^+$ versus $EGFR^-$ tumors ($p<0.001$) with relapse free survival shortened by about 2 years. When ER^- tumors were substratified by EGFR status, the $EGFR^-$ ER^- tumors had a prognosis almost as good as the ER^+ tumors. In 31 of 184 cases, high expression of neu, correlating with amplification, was found. Expression of neu conferred similar poor prognosis to EGFR expression in all prognostic subgroups. The role of EGF receptor expression on response to tamoxifen therapy in recurrent disease was also assessed. In 25 patients who received first line single agent chemotherapy with Mitoxantrone, there is no correlation of EGFR status with response to therapy, time to tumour progression or survival. These results suggest that in EGFR +ve patients chemotherapy should be used as a first line treatment. Analysis of the interaction of EGFR with node status showed that it was particularly in the node -ve patients that EGF receptors predicted relapse free and overall survival.

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IMMUNOASSAYABLE INHIBIN IN GONADAL AND NON-GONADAL TUMORS

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Inhibin is a heterodimeric protein hormone, which suppresses FSH secretion and affects growth and differentiation in a number of cell types. Inhibin is produced in Sertoli cells (SC) and granulosa cells (GC), and mRNA for its subunits has been detected in a large number of other tissues. In the present study we estimated immunoassayable inhibin in homogenates of a wide range of tumor tissues. Tissues were obtained from patients with tumors of the brain, stomach, gut, liver, kidney, pancreas, mamma, endometrium or ovary, and from dogs with Sertoli cell tumors. No inhibin could be detected in non-gonadal tumors, but varying amounts of inhibin were detected in ovarian tumors (GC tumors > thecomas > cystadenomas; no inhibin was detected in adenocarcinomas, teratomas or dysgerminomas). Inhibin was also found in dog SC and Leydig cell tumors. In SC tumor dogs increased peripheral levels of inhibin and suppressed levels of LH, FSH and testosterone were detected. It is concluded that presence of inhibin appears to be specific for gonadal tumors. Since various gonadal tumors contain inhibin, the specificity of inhibin as a marker for GC of SC tumors is not clear.

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PROGNOSTIC VALUE OF RECEPTORS FOR EPIDERMAL GROWTH FACTOR (EGF-R), INSULIN-LIKE GROWTH FACTOR-1 (IGF-1-R), AND SOMATOSTATIN (SS-R), AND OF PS2 PROTEIN, IN PATIENTS WITH BREAST AND OVARIAN CANCER.

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The prognostic value of EGF-R, IGF-1-R, and SS-R, and of cytosolic estrogen-regulated PS2 protein, was studied in patients (pts) with primary breast and advanced ovarian cancer. Ovarian cancer tissues were negative for PS2 (by immunoradiometric assay) and SS-R (by autoradiography). IGF-1-R and EGF-R contents (by ligand binding assay, LBA) were of no or moderate prognostic value for breast cancer pts ($n=214$). For advanced ovarian cancer pts, EGF-R content determined by LBA ($n=55$) showed no prognostic value, whereas EGF-R status ($n=35$) determined by immuno histochemistry (MoAb 2E9) significantly correlated with progression of disease ($p<0.05$). In breast cancer pts, both SS-R and PS2 showed no association with tumor size, nodal status, and grade. For PS2 the best cut-off level with respect to relapse-free (RFS) and overall survival (OS) was found to be 11 ng/mg protein. Both SS-R (16% $SS\text{-}R^+$, $n=135$; $p<0.04$) and PS2 (27% $PS2^+$, $n=197$; $p<0.001$), which were mainly positive in ER^+ tumors, were of prognostic value, especially within the subgroups with ER^+/PgR^+ tumors. Also within N^+ and N^0 pts the 5-years RFS and OS showed a difference between $PS2^+$ and $PS2^-$ (33% and 54% for N^+, and 31% and 13% difference for N^0 pts). In summary, SS-R and PS2 are valuable prognosticors in breast cancer pts, and prognostic significance of EGF-R in ovarian cancer pts needs further study.

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PROLACTIN (PRL) AND BREAST CANCER

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PRL has a definite activity in the induction and promotion of mouse and in the growth of rat mammary tumors. We and others have found that human PRL or growth hormone (GH) had a growth promoting effect on human mammary cancer cells. It has been shown that prolactin receptors (PRL-R) which are specific for all lactogenic hormones (hPRL, hGH, hPL) are present on mammary cancer cells in long term tissue culture and also in tumor biopsies. We found that 43 % of the tumors had free PRL-R (FPRL-R) and that 72 % had total PRL-R (TPRL-R) which have been desaturated in vitro. A significant correlation (Spearman test) was found between PRL-R (especially TPRL-R) on the one hand estradiol ($p < .001$) and progesterone receptors ($p < .01$) on the other. The demonstration of PRL induced proteins (PIP) might be a better sign of PRL sensitivity than the existence or PRL-R ; PIP have been found by Northern blot analysis in 47 % of 70 breast cancers (Shiu, 1987). Overall survival (OS) and relapse free survival (RFS) analysis with a median duration of follow-up of 5.3 years showed that TPRL-R had a significant prognostic value only in node positive patients ($X2 = 5.61$, $p = .02$). Neither FPRL-R or TPRL-R were a significant prognostic factors when studied by Cox analysis. This confirms our previous results. Since at least some human mammary cancers appear to be PRL dependent we carried out a multicenter randomized trial comparing as the first hormonal treatment Tamoxifen (TAM) (30 mg/d) + Bromocriptin (B) (5 mg/d) vs TAM + placebo. 171 patients entered this trial. No difference was observed between the two groups in response rates, duration of response or survival.

Recent studies are thus in favor of a role of lactogenic hormones during the course of breast cancer. However no improvement in therapy has been observed yet. The combination of drugs to achieve a total anti-lactogenic treatment, the use of anti-PRL-R antibodies are interesting areas of research ; the recent cloning of PRL-R and GH receptors may open new clinical perspectives.