in TIL and Arom activity in BC tissue was revealed and no correlation was discovered between A conversion in TIL and percent of tumor cells in lymphocytic suspension. Thus, TIL possess ability to convert A with ^3H_2O release. Molecular-genetic studies are in process now to proof presence of Arom in these cells.

Acknowledgement: To Prof. R.J. Santen for fruitful discussions.

390 POSTER

11β-hydroxysteroid dehydrogenase activity in human breast cancer cells: Characterization and effect of hormonal manipulations

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Purpose: 11beta-hydroxysteroid dehydrogenase (11b-HSD) is the enzyme responsible for the interconversion of biological active glucocorticoids (GC) and their inactive 11-oxo metabolites. Up to date, two isoforms have been cloned, a low affinity NADP+ dependent oxoreductase (type 1) and a high affinity NAD+ dependent dehydrogenase (type 2).

Recently, the presence of 11b-HSD activity has been described in breast cancer cells and tissues however this enzyme has never been characterized. This study was aimed to evaluate the features of 11b-HSD in a human breast cancer cell line, T-47D.

Methods: 11b-HSD expression in T-47D cells was evaluated by standard biochemical assay and RT-PCR analysis either in cells untreated or exposed for 24 hours to estradiol (E2), estrone (E1), medroxyprogesterone acetate (MPA), dexamethasone (DEX), mifepristone (RU486) and MPA + RU486.

Results: Biochemical and mRNA analysis showed that 11-hydroxysteroid dehydrogenase activity of T-47D cells depends on the 11b-HSD type 2 isoform. In addition, in cells treated for 24 hours with MPA, 11b-HSD type 2 basal activity increased by mean of 10 to 12 fold whereas E1, E2 or DEX, exerted no significant effects. RU486 acted as a pure progestin antagonist, exerting no agonist effect by its own but counteracting all of MPA enhanced increase in type 2 activity.

Conclusion: This study demonstrated that T-47D cells express the dehydrogenase isoform of 11b-HSD suggesting a role for this enzyme in the regulation of intracellular levels of biologically active GC in breast cancer cells. Moreover, the MPA induced increase of 11b-HSD type 2 activity indicates the existence of a connection, previously undocumented in these cells, between progestins exposure and GC metabolism.

Thursday, 1 October 1998 16:00-18:00

EUROPA DONNA SYMPOSIUM

The genetic dilemma

391 INVITED

Inherited susceptibility to breast cancer: A psychological perspective

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New genetic knowledge offers the potential for reducing future mortality and morbidity associated with breast cancer. With media coverage growing number of individuals are seeking genetic counselling about the significance of their family history of breast cancer. In the present state of knowledge there are large margins of uncertainty around the information which people can be given about their personal risk of developing breast cancer. The number of individuals who can be offered direct gene testing remains very small and mutation searching may not be informative. The effectiveness of available strategies for prevention and early detection is unproven among younger women at increased risk. The challenge therefore lies in organising services in such a way as to provide information appropriate to the level of risk which the public can understand and use to make appropriate health choices without adverse psychological consequences. Empiric data will be reviewed to highlight the psychological issues.

392 INVITED

The bio-ethical dilemma

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Abstract not received.

393 INVITED

Inherited predispostion to breast cancer

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Between 5 and 10% of breast cancers are thought to develop because of highly-penetrant mutations in genes conferring a major lifetime risk of developing breast and other cancers. Two genes, BRCA-1 on chromosome 17q and BRCA-2 on 13q, are sequenced. Mutations in these genes underlie many of the breast cancers developing through inherited predisposition. Current technology can identify up to 70% of mutations in BRCA-1 and 2 but this science is still not perfect. Whereas a positive test in an unaffected individual has clear implications, a positive test in unaffected family members still poses many questions in terms of life-time risks, optimal screening strategies prophylactic surgery and chemoprevention. A negative test in an unaffected individual from a family with a high cancer incidence can represent a false negative or could indicate a predisposition related to genes yet unknown. Testing unaffected family members in this setting is not appropriate. Major difficulties arise when affected members have died and testing their DNA is not possible. Where defined mutations are known to exist among populations, testing unaffected individuals may be appropriate in selected circumstances. Each society will have to approach this issue in line with prevailing social perceptions, public demand, healthcare structures and available resources. We have developed a research and development strategy based on co-operation between the National Genetics Centre and Regional Oncology Centres. Testing will be undertaken on affected individuals where there is a significant (20–30%) likelihood of a mutation being detected based on family history data. On finding a mutation predictive testing will be offered to unaffected family members along with the necessary medical and psychological support. This effort is supported by the government via the Health Research Board and rightly still remains within the sphere of clinical research.

394 INVITED

Genetic testing and its impact on a cohort of women and their families

W.J. Ormiston. *St. James's Hospittal and Trinity College, Department of Clinical Heamatology Oncology, Dublin, Ireland*

In Ireland a large kindred of over 550 individuals was central to the isolation of the BRCA 2 gene. When the mutation which caused cancer predisposition in this family was identified at codon S2984X in September 1996 members were offered the opportunity to avail of predictive testing. Eighteen individuals have been tested to date. During the counselling sessions pre- and post-testing it was very apparent that a negative or positive result affected not only the individuals tested but also the entire family. Indeed many women wished to have predictive testing to help determing risk to others in their nuclear family and especially their daughters. Very high anxiety levels were observed among spouses and offspring. Among the male members who tested positive four chose to keep the result to themselves and did not pass the information to their daughters.

Health professionals should be aware during pre and post counselling that genetic testing has a very powerful impact on the entire family.