of multiple genetical alterations in IPF specimen might be an indicator of higher risk for lung carcinogenesis.

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Acetylation genotypes and susceptibility to hormonal cancer: breast and prostate cancer

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Purpose: Increasing exposure to environmental pollutants and intake of dietary fat and proteins seem to have a important role during both breast and prostate carcinogenesis. The N-acetyltransferase 2 (NAT2) comprise one of the major enzyme systems catalysing carcinogens metabolism, like that finding in dietary food and others, and it is therefore reasonable to assume that NAT2 play a role in development of breast and prostate cancer. We analysed NAT2 polymorphism in breast cancer patients, in men with prostate carcinoma, a group of healthy women and healthy men.

Methods: We analysed NAT2 polymorphism in 638 genomic DNA blood samples: 134 women with breast cancer and 162 men with prostate cancer and 151 healthy men and 181 healthy women. We used PCR-RFLP to analyze two common mutants alleles at NAT2 loci.

Results: We analyzed NAT2*5 and NAT2*6 mutants alleles in NAT2 gene. From the possible combinations genotypes we did not find any statistically significant differences between the breast cancer patients and healthy women. However, the NAT2*6/NAT2*6 genotype was found in 24% of patients with prostate cancer and in 14% healthy men, presenting a statistically significant difference (OR= 1.96; 95%CI: 1.05-3.67;p= 0.0224). This association was also found when considering the group of patients with a Gleason score higher than seven.

Conclusion: Our results suggest that acetylation genotypes do not directly affect the susceptibility to breast cancer. However, we found that NAT2*6/NAT2*6 genotype (a slow genotype) represent a higher risk to prostate cancer. Furthermore, this genotype seems to be associated with development of prostate tumors of higher aggressiveness.

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Predictive testing for BRCA1 and 2 mutations among men: cherchez l'homme and beware the phenocopy

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Purpose: The implications for women carrying mutations in BRCA 1 and 2 are generally clear and, with options such as screening, prophylactic surgery and chemoprevention, the role of predictive testing is accepted where a disease-associated mutation is identified within a family. The personal implications for males who carry such mutations remain unclear and men generally opt for testing in the interests of other family members, especiallly daughters.We have analysed the outcome and issues arising from testing of men in this setting.

Methods: Between 1996 and 2000, 13 men from 5 families had predictive testing in the context of research studies into BRCA1 and 2 mutations in the Irish context. Ages ranged from 28 to 82 years (median 57). Three brothers had developed cancer, one ureteric and prostate, one prostate and one squamous cell skin cancer at 2 sites. These 3 and another brother sought testing for personal information. Overall 11 cited concerns regarding transmission of genetic risk as their reason for testing. Two had no offspring while 11 had 39 children including 21 daughters.

Results: 11 of thirteen had positive tests and two were negative. The negative results meant that inheritance risk was removed from 9 offspring (4 male, 5 female). The man with prostate cancer only proved to be a phenocopy. In another family, despite dying from breast cancer (age of onset 53 years) the mother of two daughters with bilateral breast cancer and ovarian cancer was also a phenocopy and the 82 year old father carried the mutation in BRCA1. Despite full pre-test counselling three brothers steadfastly refused to communicate their positive results to their 10 offspring (3 male, 7 female) thereby raising major ethical issues. All other outcomes were fully transmitted.

Conclusion: Predictive testing for BRCA1 and 2 mutations is a complex issue. Testing of men is mainly of value to other family members, especially offspring. Inheritance patterns can be defined and phenocopies identified. Care must be taken that, through rigorous pre and post test counselling, information is transmitted to those who can benefit. This may not always be possible as we have demonstrated.

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Genetic alterations in the pancreatic carcinoma. Prospective study

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Purpose: In this research we presented the results of a study that has been performed from 1998. First we examined retrospectively the most frequent alterated genes in pancreatic cancer paraffin-embedded specimens and then we begun the prospective study (the preliminary results are presented previously). The aim of the study is to evaluate the possible clinical applications, i.e. differential and early diagnosis.

Methods: we studied genetic alterations in the duodenal juice of thirthy patients with pancreatic carcinoma (byopsy and histopathological confirmation), for k-ras mutation, p-16, p53, and DPCC4 alterations. The duodenal juice was obtained by biliary percutaneous drainage. The analysis was performed by quantitative PCR, study of microsatellites instability and sequencing analysis of the genes (ABI PRISM 377 sequencing analysis).

Results: We found RER+ and LOH- detectable in the duodenal juice for k-ras and DPCC4. The percentage for the microsatellites D18s46 and D18s47 is informative with reference to the literature

Conclusion: Molecular genetic study performed on duodenal juice is a feasible approach for differential diagnosis of pancreatic cancer. Our results suggest that the examination could be proposed also in clinical applications for the screening of early neoplasia.

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Analysis of thymidylate synthase (TS) and udp-glucoronosyl transferase 1a1 (UGT1A1) gene polymorphisms in colorectal (CRC), breast (BC) and lung (LC) cancer patients: significant differences in ugt1a1 genotypic distribution in lc patients (pts)

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Genetic polymorphisms have been linked with increased cancer susceptibility as well as to degree of response to different chemotherapeuthic (CT) agents. Specifically, variable number of tandem repeats (2, 3, 4 and 9) in the promoter region of TS gene, which encodes a rate-limiting enzyme in the synthesis of pyrimidine nucleotides correlates with different levels of gene expression and also with 5FU-based CT response in CRC pts. UGT1A1 plays a major role in the detoxification of a diverse range of molecules, including carcinogens and some CT agents such as SN38, the active form of CPT11. An inverse correlation has been demonstrated between the number of TA repeats (6 or 7 in Caucasian population) in the TATA box of the promoter region and the expression of the gene. The present study analyses the genotypic distribution of these polymorphisms in controls and cancer pts and their potential relationship to cancer susceptibility. Genomic DNA was prepared from whole blood, and polymorphisms were analysed by PCR (TS) and direct sequencing (UGT1A1). Up to date 176 pts and 82 controls are included. The polymorphisms were analysed in 158 pts for TS (60 CRC, 49 BC, 49 LC) and 164 pts for UGT1A1 (52 CRC, 45 BC, 67 LC). Male/female: 97/79; 77% of pts aged 50 or over. No statistical differences in genotypic frequencies (f) were observed in TS when controls (2/2: 22%, 2/3: 42%, 3/3: 36%) were compared to patients (2/2: 19%, 2/3: 49%, 3/3: 32%) or between controls and each subgroup of pts. In addition, no differences were found according to age or sex. In contrast, there was a significant difference (xi square test=12.18 p=0.002) between the genotypic distribution of UGT1A1 polymorphism in LC pts (6/6=39%; 6/7=39%; 7/7=22%) and that in controls (6/6=44%; 6/7=46%; 7/7=10%), but no difference was observed between controls and CRC and BC pts. These differences could be derived from the role of UGT's in the metabolism of tobacco related carcinogens such as aromatic amines and polycyclic aromatic hydrocarbons, suggesting an increased risk for LC development among 7/7 individual. Further analysis of UGT1A1 is warranted in order to elucidate the role of UGT1A1 in LC risk.