Risk factors of HCC (Poster P173)

	Case/Control	Total	Case/Control	No virus
Risk factors	347/1075	AOR (95% CI)	190/1039	AOR (95% CI)
Family history of any cancer	236/728	1.4 (1.1-1.9)	138/700	1.7 (1.1-2.5)
First degree history of any cancer	191/587	1.2 (.9-1.6)	111/564	1.3 (.9-1.9)
First degree history of liver cancer	21/9	3.9 (1.4-11.5)	8/8	4.1 (1.3-12.9)
Diabetes mellitus	120/112	4.4 (3-6.3)	79/107	4.9 (3.3-7.1)
Alcohol consumption (> 60 ml eth/day)	73/64	3.1 (1.8-5.2)	34/59	3.5 (2-6.3)
Cigarette smoking (> 20pack/year)	137/259	2 (1.4-2.9)	72/250	1.8 (1.2-2.7)
Virus infection (HCV/HBV)	157/36	21.7 (14.3-32.9)	_____	_____

OR 2.67, 95% CI 1.86-3.83). Interestingly, non-RHC variants were associated with statistically significant increased risk only in the Spanish population (OR 1.54, 95% CI 1.19-2.09). In the German population the variants D84E, R142H, R151C and R160W and in the Spanish population the variants V60L, R160W and D294H were associated with increased risk of melanoma. Interestingly, the V60L variant showed a tendency towards a protective effect in the German population.

The differences between the two populations were also reflected in inferred haplotypes. While five haplotypes were common to both populations, two were unique in German and one was unique in Spanish population. Out of the common haplotypes, the one with the V92M and T314T variant alleles, while associated with increased risk in the Spanish population (OR 1.55 95% CI 1.08-2.23) was protective in Germans (OR 0.74, 95% CI 0.55-0.99).

A combined analysis of the outcome of the disease showed that the presence of two MC1R variants was associated with decreased metastasis free survival (median 10 months compared to 18 months in non-carriers). The associated hazard ratio HR was 1.70 (95% CI 1.18-2.44). The presence of any RHC variant was also associated with decreased metastasis free survival (HR 1.47, 95% CI 1.06-2.03).

In one of the largest studies so far on melanoma risk and MC1R variants we observed that the presence of MC1R variants is associated with an increased risk of melanoma. However, the variants conferring risk differ in populations. Further, in a first observation of its kind, we found an association between MC1R variants and metastasis free survival.

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Interleukin-6 functional polymorphism influences susceptibility and has a predictive factor in prostate cancer patients receiving androgen blockade therapy

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Background: The tumor growth independent of the presence of androgens is a main challenge in prostate cancer (PCa) treatment. Interleukin-6 (IL-6), a pleiotropic cytokine with critical roles in inflammation and immune responses, also acts as a growth factor for PCa cells and is associated to the androgen-independent (AI) phenotype.

To further investigate the possible role of genetic susceptibility of IL-6, we examined the IL6 -174 G>C genetic polymorphism, which has been found to directly affect the IL-6 transcription rate in vitro and IL-6 levels in vivo, in relation to PCa and AIPCa.

Materials and Methods: This study was conducted in histologically diagnosed PCa patients (n=328) and normal men recruited from the Institute´s Blood Donors Bank (n=344). Genotyping of IL6 -174 G>C was performed through polymerase chain reaction – restriction fragment length polymorphism (PCR-RFLP).

Results: Logistic regression analysis in genotypes stratified according to recessive model revealed an increased age-adjusted risk for PCa development in C homozygous carriers (OR=2.22, CI=1.13-4.36, P=0.021). When compared to the control group, CC genotype frequencies were significantly increased in the group of patients who developed androgen-independent disease (OR=2.51, CI=1.02-6.04, P=0.024), in those diagnosed at stage III and IV (OR=2.05, CI=1.06-3.93, P=0.019) and in patients with a PSA level at diagnosis above 20 ng.mL-1 (OR=2.27, CI=1.07-4.75, P=0.017). The time free of AI in patients submitted to androgen blockade therapy (n=233), was analysed through Kaplan Meier function plots with Breslow test and Cox logistic regression. Univariate analysis showed an association of C homozygous genotype to an earlier AI relapse (P=0.027). Furthermore, multivariate model analysis including as covariates age, prostatectomy, stage, metastases and PSA level, showed a significantly increased risk for AI (HR=2.87, CI=1.18-6.99, P=0.020).

Conclusions: Prostate cancer development and AI emergence may share common pathways. Our results support a role for the IL-6 pathway in PCa and AIPCa development. The IL6 functional polymorphism might be a useful molecular marker for PCa susceptibility and as a predictive factor for AI relapse.

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Familial tendency of hepatocellular carcinoma in USA

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The connection between a family history of liver cancer and hepatocellular carcinoma (HCC) development has not been well explored in the United States. In an ongoing case-control study at The University of Texas M. D. Anderson Cancer Center, we studied 347 patients with pathologically confirmed HCC and 1,075 healthy controls. All subjects were interviewed to determine their family history of cancer, including the number of relatives with cancer, the type of cancer, the subjects' relationship with the relative, the age at which the relative was diagnosed, and whether the relative was alive or deceased. We used unconditional logistic regression models to estimate the odds ratios (AOR) and 95% confidence intervals (CI), adjusting for possible confounding risk factors. Independent of chronic HBV/HCV, a history of any cancer (OR 1.7 [95% CI, 1.1-2.5]) and liver cancer specifically (OR 4.1 [95% CI, 1.3-12.9]) in a first-degree relative were significantly associated with HCC development. Multiple relatives with liver cancer were only observed among HCC patients with chronic HBV/HCV infection. Affected siblings with liver cancer is significantly associated with HCC development with and without HBV/HCV infection; (OR 5.7 [95%CI, 1.2-27.3]) and (4.3 [95%CI 1.1-20.9]) respectively. Individuals with HBV/HCV and a family history of liver cancer were at higher risk for HCC (OR 61.0 [95%CI, 6.5-579.7]). However, a history of cancers at other sites in first-degree relatives was not significantly related to HCC development. Our study demonstrated that a family history of liver cancer is associated with HCC development. Further research exploring the genetic–environment interactions associated with risk of HCC is warranted.

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Intake of protein, fat, carbohydrate and fiber and risk of renal cell carcinoma in Canada

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Introduction: Over the past few decades, several studies have been conducted to explore the role of diet and nutrition in kidney cancer etiology, but no specific component of diet has been clearly implicated in the risk of renal cell carcinoma (RCC). A diet high in protein and fat has been related to RCC risk but the issue is still undefined. The study was intended to further explore the role of intake of protein, fat, cholesterol, carbohydrate and fiber on RCC.

Methods: Between 1994 and 1997, mailed questionnaires were completed by 1138 incident, histologically confirmed cases of RCC and 5039 population controls. Measurement included information on socio-economic status, lifestyle habits and diet. A 69-item food frequency questionnaire provided data on eating habits two years before data collection. For each food item, cases and controls were asked to describe how often (per day, per week, per month), on average, they ate the serving size specified of the item. Estimates of total weekly nutrient intake were

estimated for each individual on the diet questionnaire that was reported to be consumed. Odds ratios (OR) and 95% confidence intervals (CI) were computed using unconditional logistic regression. The each nutrients intake amounts were categorized by quartiles based on the distribution among controls.

Results: Intakes of total fat, saturated fat, monounsaturated fat, trans-fat and cholesterol were positively associated with the risk of RCC; the ORs for the highest versus the lowest quartile were 1.67 (95% CI, 1.21-2.32), 1.53 (95% CI, 1.14-2.05) and 1.46 (95% CI, 1.05-1.97), 1.31 (95% CI, 1.04-1.65) and 1.48 (95% CI, 1.16-1.89), respectively. The positive association was apparently stronger in women, overweight or obese, and never smokers. An increased risk was also observed with increasing intake of sucrose. High fiber intake was inversely associated with RCC risk, the OR for the highest versus the lowest quartile were 0.69 (95% CI, 0.53-0.92). No association was found with intake of total protein and polyunsaturated fat, n-3 and n-6 polyunsaturated fatty acids and total carbohydrates.

Conclusion: Findings suggested that nutrition may play a role in the risk of RCC. A diet low in fat and rich in fiber could favourably affect the risk of RCC.

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Gene expression analysis of formalin-fixed, paraffin-embedded breast cancer tissues using the multiplex branched DNA assay

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Formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens represent the largest tissue archive where also the patient's clinical record is available. There is a growing interest to use RNA from FFPE tumor specimens to perform gene expression analyses to predict prognosis and response to treatment. The branched DNA (bDNA) assay measures mRNA directly from crude cell lysates and thus avoids variations introduced by RNA isolation, reverse transcription and amplification procedures. A modified version of the bDNA assay quantifies RNA directly from FFPE tissues specimens. The multiplex bDNA assay combines the bDNA assay with the xMAP (multi-analyte profiling) beads allowing simultaneous quantification of multiple RNA targets. The aim of the study was to investigate the molecular classification of breast cancer samples by quantifying the expression of selected genes directly from FFPE tissue, using the multiplex bDNA technology.

We used the 1.0 multiplex bDNA assay to measure the gene expression of 69 genes directly from 20 FFPE breast cancer samples. The genes were chosen from the list of genes able to discriminate between the 5 breast cancer subgroups (Sørlie et al Proc Natl Acad Sci , 2001). The genes were divided into 3 panels with PPIB, RPL19 and RPS3 as housekeeper genes. All the five breast cancer subgroups were represented in the FFPE samples. We also analyzed isolated total-RNA from fresh frozen tissue from 9 of the 20 samples.

The comparison between total RNA and FFPE on the bDNA technology showed that 42% of the genes had correlation >0.5. Hierarchical clustering of the FFPE samples based on the 69 genes was able to divide the samples reasonably well into their subgroups. Most of the luminal A samples clustered together, 2/3 samples for both basal-like and ERBB2+ samples clustered together in a main subcluster, and all luminal B and normal-like samples clustered together in a main subcluster. Hierarchical clustering of the FFPE samples, using only the genes with a correlation >0.6 between FFPE and total-RNA, showed that all the samples within the subgroups ERBB2+, normal-like and basal-like clustered together in a main subcluster, 5/8 luminal A samples clustered together and 3/4 luminal B samples clustered together in a main subcluster.

We conclude that the bDNA technology is able to quantify the expression of genes directly from FFPE tissues, and shows potential use in classifying breast cancer samples into their respective subgroups.

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Genetic polymorphisms in the promoters of IL-6 and IL-10 in CIN and cervical cancer patients

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Introduction. Cell-mediated immunity is important in controlling both HPV infection and HPV –associated carcinogenesis. It was suggested that the cytokine response to HPV infection may potentially affect the disease process. Single nucleotide polymorphisms (SNP) in the promoters of IL-10 and IL-6 genes have been associated with different cytokine production and susceptibility to a number of diseases. The aim of this case-control study was to compare the IL-10 (-1082 G→A) and IL-6 (-174 G→C) polymorphisms in patients with cervical intraepithelial neoplasia (CIN) or cancer (CC) and the healthy controls. We would like to assess whether these polymorphisms increase the risk of cervical cancer in Russian patients.

Methods. Genomic DNA was isolated from the paraffin-embedded tissue from 130 CC patients and 45 patients with CIN I-III. The control DNA was extracted from peripheral blood from 144 females without any cancer, autoimmune or infectious diseases. Polymorphisms of IL-10 and IL-6 were studied in RFLP-PCR and the allele-specific PCR respectively. The Fisher's exact test was used to calculate statistical significance.

Results. We observed the increase of IL-10(-1082AA) low-secretor genotype frequency in CC patients versus control (p=0.012) and versus CIN patients (p=0.036). CC patients demonstrated the significant decrease of the high-secretor genotype IL-6 (-174CG) compared to the control (p=0.038).

Conclusions. These data suggest that the genetically determined ability to produce the different levels of IL-10 and IL-6 cytokines may be associated with cervical carcinogenesis.

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Cancer mortality in patients with schizophrenia - 11-year cohort study

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Schizophrenia is associated with a rate of premature mortality 2 to 3 fold higher than in the general population. The role of cancer in this excess mortality remains unclear, previous incidence or mortality studies having found contradictory results.

The authors initiated in 1993 a large prospective study in a cohort of 3470 patients with schizophrenia to determine mortality rates and specific causes of death. Standardized mortality ratios were calculated, adjusting for age and sex relative to a representative sample of the French general population.

During the eleven years follow-up, 476 (14%) patients died, corresponding to a mortality rate near 4-fold higher than in the general population. Cancer was the second cause of mortality (n=74), with a global SMR of 1.5 (95% confidence interval [95% CI], 1.2-1.9). For all cancers, the SMRs were 1.4 (NS) in men and 1.9 (95% CI, 1.4-2.8) in women. In men, lung cancer was the most frequent localization (n=23, 50%), with a SMR of 2.2 (95% CI, 1.6-3.3). In women, breast cancer was the most frequent localization (n=11, 39%), with a SMR of 2.8 (95% CI, 1.6-4.9). There were two significant baseline predictors of death by lung cancer in the final logistic regression model: duration of smoking and age ≥ 38 years old.

The results of the current study demonstrate an increased risk of mortality by cancer in patients with schizophrenia, especially in women for breast cancer and in men, for lung cancer. These results seem to be consistent with the lack of medical care in schizophrenia.

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Polymorphisms in Fibroblast growth factor receptor 2(FGFR2) and susceptibility to breast cancer in Chinese women

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Background: FGFR2 belongs to the FGFR family which plays an important role in cell growth, invasiveness, motility and angiogenesis. Studies showed that FGF and FGFR expression is ER dependent and significantly correlated with an antiapoptotic role in human breast cancer. Recently, several single nucleotide polymorphisms (SNPs) of FGFR2 were identified as novel breast cancer susceptibility loci by whole genome association studies. In this study, we test the hypothesis that polymorphisms of FGFR2 may interact with estrogen related factors to contribute to breast cancer susceptibility in Chinese women.

Materials and methods: we genotyped three FGFR2 polymorphisms (rs2981582, rs1219648 and rs2420946) in a case-control study of 1,049 breast cancer patients and 1,073 cancer-free controls by using the SNPstream 12-plex genotyping platform.

Results: We found that the three SNPs were all associated with significantly increased breast cancer risk in a dose-dependent manner. Jointly, compared with subjects carrying '0-2 risk loci', the '3 risk loci' carriers had a 1.36-fold increased risk of breast cancer (adjusted OR =