POSTER SESSION

General, molecular and genetic epidemiology 2

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A case-control study on the effect of p53 and p73 polymorphisms on gastric cancer risk and progression in an Italian population

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Background. We investigated the distribution and the potential gene-gene and gene-environment interaction of selected polymorphisms in p53 and p73 genes in relation to gastric adenocarcinoma risk and progression in an Italian population.

Methods. One hundred and fifteen cases and 295 hospital controls were genotyped for p53 polymorphisms on exon4 (Arg72Pro), intron 3 and 6, and p73 G4C14-to-A4T14. Modification of the effect measures on gastric cancer by age, gender, alcohol, smoking and familiarity for cancer was tested through homogeneity tests across strata estimates from logistic regression analysis.

Results. For the first time an increased risk of gastric cancer was found to be associated with the inheritance of p73 homozygous variant genotype among the intestinal histotype (OR = 6.75, 95%CI: 1.88–24.24). An effect modification of p73 variant allele by gender was observed [OR = 2.82 (95%CI: 1.24–6.40) among females, versus an OR of 0.70 (95%CI: 0.32-1.54) among males; p-value for homogeneity among strata estimates = 0.03]. No differences were observed for the genotype and haplotype distributions of p53 exon 4, intron 3 and 6 among cases and controls. The gene-gene interaction analyses demonstrated that individuals with combined p53 exon 4 and intron 6 unfavourable variants are borderline significantly protected from gastric cancer risk (OR=0.52, 95%CI: 0.26-1.07; p-value for interaction = 0.005), which was confirmed by the haplotype analysis. Survival analysis did not show any association between each polymorphism on the overall survival, however when the analysis was restricted to the intestinal gastric cancer histotype, a poorer survival resulted among carriers of the variant allele of p53 intron 6.

Conclusion: This study shows that p73 G4C14-to-A4T14 polymorphism might be a risk factor for gastric cancer, as reported from other studies on Caucasians about different tumour sites. Also, the combined inheritance of the unfavourable variants of p53 exon 4 and intron 6 might be protective against gastric cancer, as reported for breast and lung cancer. Larger studies are required to confirm our results.

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Variation of gene expression profiles in whole blood from a large representative sample of postmenopausal Norwegian women

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Introduction: Whole blood is increasingly considered a valuable source of RNA for gene expression profiling related to disease and disease risk, but to be useful it is important to understand the nature and extent of variation in gene expression from whole blood among healthy individuals. This large cross-sectional study characterizes intratechnical and interindividual variability of blood-derived gene expression profiles in a national representative sample of postmenopausal women.

Methods: The study population was drawn from women who are participants of the large Norwegian cohort study NOWAC (1,2). Postmenopausal women (N= 328) were selected from a random group of 500 women aged 48 to 62 years who answered an eight-page questionnaire in 2004 and donated a blood sample collected in PAXgene™ tube (PreAnalytiX GmbH, Switzerland). After exclusion based on RNA quality and quantity criteria, 287 samples were analyzed using the Applied Biosystems expression array system (Applied Biosystems, CA, USA). At the time of blood sampling, women answered a two-page questionnaire on different lifestyle factors.

Results: We studied association between whole blood gene expression profile and 11 technical parameters related to microarray processing (extraction, amplification and hybridization dates, array lot number, RNA/cRNA quality ratios and yield, and time from blood collection to freezing) as well as 6 variables related to individuals (age group, place of living, body mass index, smoking, hormone therapy use, fasting before blood sampling). Interindividual gene expression changes were seen, but larger effects were observed related to technical variability inherent to microarray technology. Amplification date had the strongest effect on gene expression profiles followed by extraction date, time from blood collection to freezing, and array lot number. Data were subsequently batch adjusted for the largest technical effect (i.e. amplification date) using empirical Bayes method. In preliminary univariate analyses, the relative importance of the interindividual variables was in decreasing order as follow: smoking status > body mass index. No effect was observed for age group, place of living, hormone therapy use and fasting

Conclusion: These results emphasize the important contribution of technical factors in microarray-based profiling variability. Gene expression under "normal" conditions was characterized identifying physiological and lifestyle factors which account for interindividual differences in human whole blood. This data also provide a database with which disease-associated gene expression profiles can be compared.

References

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DNA repair and metabolic gene polymorphisms and male breast cancer risk

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The strongest genetic risk factor for male breast cancer (MBC) is represented by inherited high-penetrance BRCA2 and, to lesser extent, BRCA1 mutations. MBCs unaccounted for by BRCA1/2 mutations can be explained by a polygenic model in which many genes that confer low risk individually act in combination to confer much larger risk in the population. Accumulating evidence supports that single polymorphisms (SNPs) in genes involved in DNA repair and steroid/carcinogens metabolism may contribute to genetic susceptibility to breast cancer (BC). SNPs in DNA repair and metabolic genes may modify the effect of environmental exposure on BC risk and, on the other hand, subtle genetic effects may be magnified by environmental exposure. In this study, we investigated the role of polymorphisms within genes involved in DNA repair (XRCC1, APEX, XRCC3, XPD, XPA and XPC) and steroid hormones/carcinogens metabolism (P450c17/CYP17, CYP1B1, SULT1A1 and AIBI) on MBC-risk. A population based case-control study was performed in 100 MBC cases and 270 controls. Genotyping was performed by TaqMan technology and PCR-RFLP analyses. Genotype distribution was consistent with Hardy-Weinberg equilibrium among our population controls. A statistically significant difference in the distribution of the three specific genotypes between MBC cases and controls was observed for XPC PAT ($p<0.0001$) and SULT1A1Arg213His ($p<0.0001$). Age-adjusted analyses showed an increased MBC risk for the SULT1A1 213His allele (OR=2.56; 95% CI 1.54;4.26) according to a dominant model, whereas an inverse association between the XPC PAT L allele and MBC risk was observed. Overall, the screening of quite large number of SNPs selected in a series of DNA repair and metabolic genes let us identify at risk genotypes. Whether these common allele variants, that confer low risks individually, may act in combination to confer much larger risk needs to be elucidated. Ad hoc studies are in progress to evaluate the interaction between the genetic background, determined by BRCA1/2 carrier status and at risk genotypes, and exposure to environmental carcinogens.

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