

survey of common miRNA SNPs and their surrounding regions and evaluated associations between four SNPs in pre-miRNAs and non-small cell lung cancer (NSCLC) survival. We found that rs11614913 in hsa-mir-196a2 was significantly associated with NSCLC survival in the recessive genetic model in both 556 test set patients and 107 validation set patients. Stepwise Cox proportional hazard regression analysis showed that rs11614913 variant homozygote CC was a significantly unfavorable prognostic factor of NSCLC [Hazard ratio (HR) =1.76, 95% CI=1.34-2.33]. In the genotype-phenotype correlation analysis using 23 lung cancer tissue samples, rs11614913 CC was associated with a significantly increased mature hsa-mir-196a expression in a recessive model ($P = 0.037$) but not the precursors, suggesting an enhanced processing of pre-hsa-mir-196a to its mature form. Furthermore, in vitro binding assays revealed that rs11614913 variant can affect target mRNA binding to its mature hsa-mir-196a2-3p. Therefore, rs11614913 in hsa-mir-196a2 may be an independent prognostic biomarker for NSCLC. Further characterization of miRNA SNPs may open new avenues for cancer biological studies and therapeutic interventions.

5-PP

Effects of IL-10 and IL-6 Gene Polymorphisms and Atomic-bomb Radiation Exposure on Gastric Cancer Risk

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Results of epidemiological studies conducted since the establishment of the Atomic Bomb Casualty Commission-Radiation Effects Research Foundation (ABCC-RERF) in 1947 have clearly demonstrated several important long-term effects of atomic-bomb (A-bomb) radiation in humans, including radiation dose-dependent increases in the incidence of, and mortality due to, malignant tumors. Our immunology studies implied that radiation exposure greatly affected host immune systems of A-bomb survivors, further providing the possibility that altered immune response in this population, specifically inflammatory response and immunological host defense, might be involved in the development of various cancers. In fact, we have reported that the advancement of persistent inflammation with increased age was further accelerated among people exposed to A-bomb radiation (Hayashi et al., *Am J Med.*, 2005). In this study, we examined relationship between gastric cancer risk and radiation dose based on inflammation-related IL-10 and IL-6 gene polymorphisms, in a case-control study of 181 cases and 1,576 controls within a subcohort of the RERF Adult Health Study. Written informed consent was obtained from all subjects. This study was approved by the RERF Ethical Committee for Genome Research. We identified a single haplotype block indicated by four htSNPs (generating two major alleles, IL10-ATTA and IL10-GGCG). We found that risk of gastric cancer varied significantly by IL-10 haplotype both in non-exposed and exposed individuals ($P < 0.001$), and that risk-enhancing effects of radiation were evident in all the haplotypes. In addition, association between IL-10 haplotypes, radiation exposure, and plasma IL-10 levels was examined. As a result, we found that plasma IL-10 levels increased by both IL-10 haplotype (IL10-GGCG/IL10-GGCG > other haplotypes) and increased radiation dose, suggesting the potential for use of plasma IL-10 as a surrogate biomarker of gastric cancer risk among populations exposed to radiation. We also found association between IL-6 genotypes and risk of gastric cancer, and interaction between IL-6 genotypes and radiation dose with gastric cancer risk. We have observed that the aging-associated attenuation of immunological capacity was further accelerated among A-bomb survivors in a radiation dose-dependent manner and that increased mutability found in A-bomb survivors exposed to high radiation dose was associated with increased cancer incidence in a follow-up study. Our present results included significant associations between IL-10 haplotypes or IL-6 genotypes and gastric cancer risks in A-bomb survivors. Our findings proposed the possibility that aging effects on relationship between radiation and cancer risks were modulated by genetic factors of individuals.

6-PP

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.

7-PP

Circulating vitamin d concentration, vitamin d receptor polymorphisms and the risk of colorectal cancer: results from the European Prospective Investigation into Cancer and Nutrition (EPIC)

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Vitamin D can be obtained either from the diet or primarily via endogenous production from sunlight exposure. It is vital to calcium homeostasis and has been suggested to have a role in the control of cell cycle kinetics. Results from cell culture and animal studies suggest that vitamin D may play a role in colorectal cancer (CRC) prevention. However, epidemiologic data considering the role of vitamin D are inconsistent and previous consideration of this hypotheses has not sufficiently focused on the potential interaction of vitamin D with (i) calcium, (ii) polymorphisms of important genes involved in their metabolism, i.e. vitamin D receptor (VDR; modulates intra-cellular vitamin D activity), calcium sensing receptor (CaSR; detects changes in extra-cellular calcium concentration) and (iii) parathyroid hormone (PTH; a calciotropic hormone).

In order to address these points, a detailed nested case-control study was conducted based on the ongoing European Prospective Investigation into Cancer and Nutrition (EPIC), a large cohort of over 520,000 subjects from 10 European countries. In total, 1248 CRC cases (number of colon cancer cases=785; number of rectal cancer cases=463) were identified and matched to 1248 control subjects by age, gender, study centre, follow-up time, time of the day and fasting status at the time of blood donation. Serum vitamin D (25OHD) and PTH concentrations were measured using enzyme immunoassay methods. Genotyping for the VDR (BsmI: rs1544410; FokI: rs2228570) and CaSR (rs1801725) genes was performed by Taqman® methodology. Conditional logistic regression models (adjusted for body mass index, total energy intake, smoking status/duration/intensity, physical activity, level of schooling, as well as level of consumption of fruits, vegetables and meats) were used to estimate relative cancer risks.

Compared to a serum 25OHD concentration of 50.0-75.0 nmol/L, a lower level of a 25OHD concentration (25.0-49.9 nmol/L) was associated with a statistically significant increase in CRC risk (OR=1.25, 95%CI=1.02-1.53), whereas higher concentrations were associated with a decreased risk of CRC (75.0-99.9 nmol/L: OR=0.85, 95%CI=0.66-1.08; ≥100.0 nmol/L: OR=0.75, 95%CI=0.55-1.04). The cancer risk associations appeared to be stronger in the colon than in the rectum. A statistically significant interaction was observed between serum 25OHD concentration and dietary calcium intake (pinteraction=0.05), with reduced levels of both nutrients resulting in an increased CRC risk. Dietary vitamin D and serum PTH were not associated with disease risk in this study. Compared to the wild type, the BB genotype of BsmI was associated with a significantly reduced CRC risk (OR=0.76, 95%CI=0.59-0.98). The FOK1 and CaSR genotypes were not associated with disease risk in this study.