Table 1. Crude and adjusted OR's according to seropositivity for HPV (1-PP)

	All sites Cases	All sites Controls	All sites Adjusted OR	All sites 95% CI Adjusted OR	Oropharynx OR	Oropharynx 95% CI Adjusted OR
HPVE6						
16	8/1399	46/1670	8.73	3.74-20.35	45.7	14.1-148.3
33	3/1399	12/1670	9.92	2.46-39.96	55.3	9.9-306.6
HPVE7						
16	73/1399	122/1670	1.55	1.11-2.18	2.6	1.6-4.2
33	36/1399	57/1670	1.77	1.09-2.85	3.7	1.9-7.1
35	20/1399	42/1670	2.37	1.27-4.39	5.7	2.6-12.8
HPVE1						
16	21/1399	43/1670	2.26	1.23-4.15	5.5	2.5-12.0
HPVE2						
16	24/1399	73/1670	3.07	1.81-5.20	7.5	3.6-15.5
HPV16 E6 E7						
One positive	79/1399	122/1670	1.27	0.91-1.76	1.5	0.9-2.5
Both positive	1/1399	23/1670	56.09	7.21-436.11	451.8	46.8-4359.6

samples were analyzed for 8 low-risk and 9 high-risk HPV types. Antigen proteins included L1, E1, E2, E4, E6, and E7. Statistical analysis included the estimation of crude and adjusted odds ratios (OR) and the respective 95% confidence intervals (95% CI) using unconditional logistic regression. **Results:** The sample comprised 1670 cases and 1399 controls. There were 538 oral cavity cases (32.2%), 353 oropharynx cases (21.1%), and 779 hypopharynx/larynx cases (46.7%). The overall seroprevalence for HPV16L1, HPV16E6, and HPV16E7 infection was 8.6%, 1.8%, and 6.3%, respectively. Seropositivity for HPV 16E6, 33E6, 16E7, 33E7, 35E7, 16E1, and 16E2 increased the risk of developing HNSCC, after adjustment for age, sex, smoking and alcohol consumption. The increasing risk for being positive for both HPV16 E6 and E7 was particularly striking (OR=56.1, 95% CI 7.2-436.1) and the association was stronger for oropharyngeal cancer (Table 1). **Conclusions:** Antibodies to HPV16E6 or HPV16E7 are associated to an increased risk of HNSCC, particularly for oropharyngeal cancer. Further studies are necessary to evaluate the potential use of these antibodies as biomarkers for early detection and also for treatment planning, since it is well known that patients with HPV-positive tumors have a better prognosis.

2-PP
Serologic response to HPV and the risk of head and neck cancer

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In this large hospital-based case-control study, we investigated repair of benzo[a]pyrene diol epoxide (BPDE)-induced damage to DNA and chromosomes in cultured peripheral blood lymphocytes as biomarkers for susceptibility to cancer. We quantified BPDE-induced DNA adducts (BIDA) by the ^{32}P-postlabeling method and frequencies of BPDE-induced chromatid breaks (BICB) simultaneously in *in vitro* BPDE-challenged T-lymphocytes from 798 patients with squamous cell carcinoma of the head and neck (SCCHN) and 821 cancer-free controls frequency matched by age, sex, and ethnicity. The stage distribution of newly diagnosed cases with histopathologically confirmed SCCHN was 10% stage I, 13% stage II, 18% stage III and 59% IV with primary sites located in the oral cavity (30%), oropharynx (46%), hypopharynx (5%) and larynx (19%). The blood was drawn before the patients received any chemotherapy, radiotherapy or surgery. The controls were hospital visitors who accompanied cancer patients to select outpatient clinics and were genetically unrelated to the cases. The blood cultures were established within 8 hours after the sample was collected, and DNA extraction and metaphase preparation were performed for the BIAD and BICB assays, respectively, after the cultures were treated with a previously established concentration of 4 μM BPDE for 5 hours. All odds ratio (OR) and 95% confidence interval (CI) analyses were adjusted for age, sex, ethnicity, smoking and alcohol use in multivariate logistic regression models. Overall, the OR for SCCHN was 1.69 (95% CI = 1.37-2.07) for BIDA and 1.50 (95% CI = 1.22-1.85) for BICB (dichotomized at the control median). When combining both of these two markers using the group with both low BIDA and low BICB as the reference, the OR was 1.83 (1.33-2.51) for the group with high BIDA alone, 1.65 (1.20-2.28) for the group with high BICB alone and 2.49 (1.85-3.36) for the group in the higher strata of both assays. Further analyses showed that there was no statistical correlation between measurements of BIDA and BICB for the cases (r = 0.040; P = 0.256) and only a weak correlation for controls (r = 0.088; P = 0.011) and that there was no evidence for an interaction between these two biomarkers ($P_{interaction}$ = 0.369). These data suggest that BIDA and BICB may be independent and useful biomarkers for susceptibility to SCCHN. (This study was supported by National Institute of Health-National Institute of Environmental Health Sciences grant R01 ES11740)

3-PP
Searching for early breast cancer biomarkers by serum protein profiling in Prospect-EPIC

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Serum protein profiling with SELDI-TOF MS (surface-enhanced laser desorption/ionization time-of-flight mass spectrometry) has frequently been used in attempts to discover early biomarkers for breast cancer (BC). Until now all studies use biological samples collected after diagnosis. The proteins found in these studies have questionable value for early diagnosis because of the often advanced tumor stage.

Here we investigated for the first time prediagnostic serum protein profiles, using the Prospect-EPIC (European Prospective Investigation into Cancer and Nutrition) cohort. In a nested case-control design we compared 68 women diagnosed with BC within three years after enrollment with 68 matched controls for differences in protein profiles in serum that was collected at enrollment.

In total, 22 protein peaks were detected. Mean Z-log-transformed intensities of these peaks were compared between cases and controls and differences were tested with a T test. Three peaks with m/z (mass to charge ratio) 3323 (p=0.013), 8938 (p=0.071) and 9427 (p=0.059) were found to be (borderline) statistically significantly up regulated in BC. Three other peaks (m/z 3888, 7978 and 8148) also showed an up regulation in BC, although not statistically significantly (p= 0.103, 0.149, 0.133).

M/z 8938 and 8148 could represent C3a des arginine anaphylatoxin and a truncated form of this protein that were found to be up regulated in BC in several previous studies investigating 'full blown' BC cases. The finding that these proteins are already up regulated in a pre-diagnostic stage, indicates that they hold promise as true early biomarkers for BC. Further research needs to establish the identity of the proteins and to confirm our results.

4-PP
Genetic variants in fibroblast growth factor receptor 2 (FGFR2) contribute to susceptibility of breast cancer in Chinese women

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Recent evidence indicates that small, non-coding RNA molecules, called microRNAs (miRNAs), function as tumor suppressors or oncogenes. Mutation, mis-expression or altered mature miRNA processing are implicated in carcinogenesis and tumor progression. We conducted a systematical

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 binging 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.