P24

Hereditary factor in the onset of cancer of the gastrointestinal tract and female reproductive organs

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Having analyzed 138 questionnaires, we could isolate the following groups of risk according to the onset of oncopathology:

1. No oncopathology is noticed in 55% of family trees.
2. Cancer diseases of the endometrium, ovaries, mammary gland, stomach and intestine were marked in 20.3% in relatives of degrees I and II. The latter being marked in literature as lynch II syndrome.
3. The presence of endometrial carcinoma was revealed in 6.5% of female relatives, degrees I and II of relationship.
4. Neoplasms and endocrine-metabolic disturbances were registered among relatives in 7.3%.
5. Diseases of lung cancer of diverse localization are revealed in 10.9% among relationships of degrees I and II.

Thus, the results of our studies have shown three syndromes that are versions of the family cancer syndrome and are manifested by a systemic predisposition to the onset of ovarian carcinoma, breast cancer, endometrial or gastric and intestinal carcinoma, etc. These include: (1) the syndrome of familial cancer of the mammary gland/endometrium/ovaries/large intestine (the syndrome of lynch2); (2) the syndrome of familial cancer of the mammary gland/endometrium/the organs of the gastrointestinal tract/lung; (3) the syndrome of familial carcinoma of the endometrium/the organs of the gastrointestinal tract.

Results and Discussion: On the basis of the studies carried out by us tables of cancer accumulation on the uterine body as well as criteria of identifying cancer risk and genetic prediction have been investigated.

P25

Folate intake and risk of colon cancer in relation to p53 mutational status

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Considerable epidemiological evidence suggests that a low-folate diet is associated with an increased risk of colorectal cancer, although a recent randomized trial indicates that supraphysiologic folate supplementation may not reduce the risk of adenoma recurrence. Furthermore, the mechanism by which folate deficiency influences carcinogenesis remains unclear. We evaluated the effect of folate consumption on p53 mutation in colon tumors. We immunohistochemically assayed p53 expression in paraffin-fixed colon cancer specimens in a large prospective cohort, the Nurses' Health Study, to examine the relationship of folate intake and intake of other one-carbon nutrients to risks by p53 status. We used competing risks Cox regression to compare associations of folate intake with incident colon cancers classified by tumor p53 mutational status. During 1,861,916 person-years of follow-up among 88,691 women, 399 incident colorectal cancers accessible for p53 expression were documented. The effect of folate differed significantly according to p53 mutational status ($P_{heterogeneity} = 0.01$). Compared with women reporting less than 200 μg of folate per day, the multivariate relative risks (RRs) for p53 overexpressing (mutated) cancers were 0.54 (95% CI, 0.36 to 0.81) for women who consumed 200–299 μg per day, 0.42 (95% CI, 0.24 to 0.76) for those who consumed 300–399 μg per day, and 0.54 (95% CI, 0.35 to 0.83) for ⩾400 μg per day. In contrast, total folate intake had no influence on wild-type tumors (RR, 1.05; 95% CI, 0.73 to 1.51, comparing ⩾400 to <200 μg per day). Similarly, high vitamin B6 intake conferred a protective effect on p53-mutated cancers (RR, 0.57; 95% CI, 0.35 to 0.94; $P_{heterogeneity} = 0.01$) but had no effect on p53 wild-type tumors. Further, among women with a daily folate intake of less than 200 μg and vitamin B6 consumption in the lowest quintile, the relative risk of p53-positive colon cancer was 2.61 (95% CI, 1.73 to 3.95), compared to women with higher intakes in both nutrients; by contrast, the comparable risk for p53-negative colon tumors was 0.78 (95% CI, 0.48 to 1.25). We found that low folate and vitamin B6 intake was associated with an increased risk of p53 mutated (overexpressing) colon cancers but not wild-type tumors.

P26

Non-steroidal anti-inflammatory drug use, a common cyclooxygenase-2 polymorphism (T8473C), and risk for Barrett esophagus

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Purpose: To investigate whether the protective association between non-steroidal anti-inflammatory (NSAID) drugs and esophageal premalignancy is modified by a common polymorphism of cyclooxygenase-2 (COX-2 T8473C).

Methods: In this case-control study, a 102-point structured questionnaire was used to obtain detailed socio-demographic, lifestyle risk factor and NSAID medication use in patients with gastroesophageal reflux disease (GERD) (n = 126) or with the premalignant lesion, Barrett esophagus (BE) (n = 125), each defined according to strict clinico-pathologic criteria. Controls comprised 95 healthy asymptomatic individuals. Following extraction of genomic DNA from blood samples (obtained with informed consent), genotype analysis was performed using a polymerase chain reaction (PCR)-based primer introduced restriction analysis. The frequency of COX-2 T8473C genotypes among GERD and BE cases was compared with asymptomatic controls using the Chi-square test. Multivariate analysis was performed using logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI) adjusting for age, gender, smoking and alcohol consumption.

Results: Relative to asymptomatic controls, current use of NSAIDs was associated with a reduced risk for BE (OR 0.33; 95%CI 0.17–0.63). ORs for long-term (>5-yr) NSAID users (OR 0.41; 95%CI 0.20–0.88) and more frequent (>1/day) NSAID users (OR 0.52; 95%CI 0.27–1.0) were also reduced, but there was no evidence of a dose-response relationship. To improve the statistical power of the study, the analyses were also performed using a combined group (n = 221) of asymptomatic controls (n = 95) and GERD cases (n = 126), representing benign disease as a control group. A similar protective effect was again seen for current NSAID use (OR 0.46; 95%CI 0.26–0.81). COX-2 genotype frequencies were consistent with Hardy-Weinberg equilibrium (p = 0.84). However, when compared to asymptomatic controls, the polymorphic variant was not associated with risk for BE

(OR 0.71; 95%CI 0.27–1.87), and no significant interactions between the COX-2 genotype and NSAID use were found.
Conclusions: In this exploratory study, NSAID use was associated with a reduced risk for BE, a premalignant lesion associated with progression to esophageal adenocarcinoma. This protective effect was not modulated by the common COX-2 T8473C polymorphism, suggesting further studies to define underlying biologic mechanisms of NSAID chemoprevention.

P27
Cancer chemopreventive potential of apple juice – Results of a short-term human intervention study with ileostomy patients

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Apples are widely consumed and a rich source of phytochemicals. Regular consumption of one or more apples/day was linked to reduced risk for lung- and colon cancer in various epidemiological studies. In addition, dietary intervention with turbid apple juice reduced adenoma formation in ApcMin/+ mice (Pan et al., in preparation), and DNA-damage, hyperproliferation, and aberrant crypt foci in the dimethylhydrazin-induced rat colon model (Barth et al., 2005). In the present study we determine whether apple juice polyphenols may reach the colon after oral intake of cloudy apple juice and retain chemopreventive properties after passage through the gastrointestinal tract. Eleven ileostomy volunteers consumed 1 l of cloudy apple juice after overnight fast. Ileostomy effluents were collected after 0 to 8 h and freeze-dried. A maximum of 33% of the ingested low molecular weight polyphenols were detected 1, 2, and 4 h after ingestion, in addition to 80% of the ingested oligomeric procyanidins (Kahle et al., 2005, 2007). Based on dried weights, polyphenol concentrations up to 10.2±1.6 mg/g bag contents (average ± standard error, n = 11) were recovered with a maximum after 4 h. We detected a transient increase in radical scavenging activity with a maximum at 4 h after apple juice consumption. Half maximum inhibitory concentrations for DPPH scavenging were significantly reduced by 65% from 0 h to 4 h (ANOVA with Student-Newman-Keuls Test for multiple comparison, $p < 0.05$). Concomitantly, potential to scavenge peroxyl radicals significantly increased from 2.9±0.3 to 4.5±0.5 ORAC units after 4 h (measured at 25 μg/ml). In contrast, potential to modulate carcinogen metabolism by inhibition of Cyp1A enzymatic activity and by induction of detoxifying mechanisms (measured as NAD(P)H:quinone reductase (QR) activity in Hepa1c1c7 cells) was highest at time point 0 h. After apple juice consumption, activities initially declined, and maximum preventive effects were then observed after 6 to 8 h. A similar trend was detected for the inhibition of aromatase (Cyp19) activity with strongest inhibitory effects at time 0 h, whereas Cox-1 activity was not affected. From these results we conclude that selected apple juice polyphenols, especially oligomeric procyanidins, may reach the colon and exert a local antioxidant effect. Modulation of additional chemopreventive mechanisms is likely.

P28
Endogenous IFN alpha during liver transition from quiescence to proliferation

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Background: Interferon alpha (IFNα) is used as main or adjuvant treatment in the therapy of viral infections and several types of cancer. This cytokine is a common therapy for chronic viral hepatitis and contributes to hepatocarcinogenesis prevention. However, the mechanism of IFNα antiproliferative activity in vivo is still obscure. The situation in the liver is complicated by the various types of cells revealing cell-specific response to IFNα, the expression of endogenous cytokine and specific intercellular communication during the transition of liver cells from quiescence to proliferation at preneoplasia. The aim of the study was to evaluate the production of endogenous IFNα during liver transition from quiescence to proliferation induced by partial hepatectomy at the rats.
Materials and Methods: The rats after 2/3 partial hepatectomy (PHE) and laparotomy (LAP) were used in 1, 3, 6 and 12 h post-surgery to model correspondingly G0–S transition and acute phase response, the latter being a constituent part of the former. The genes expression was assessed in liver samples, isolated Kupffer cells (KC) and hepatocytes by quantitative real-time RT-PCR and antiviral test.
Results: PHE induces 2-fold transient increase of IFNα mRNA content and liver antiviral activity at 1–3 h post surgery with subsequent normalization of the indices during 6–12 h period. LAP induces down regulation of IFNα mRNA content in comparison with intact animals. The antiviral activity after LAP was less than the detection limit. KCs and not hepatocytes in both models are responsible for IFNα expression.
Conclusions: The changes in IFNα expression may be essential for liver G0–S transition and acute phase response.

This work was supported by grant #4381 from Science and Technology Center of Ukraine.

Prevention of gynecological cancers

P29
Expression of proliferation biomarkers in female reproductive system malignancies

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Proliferative potential is known to be the integral characteristic enabling impartial estimation of tumor processes peculiarities and their prognosis. The realization of proliferative signals is provided by a complex mechanism through the interaction of several oncogenes and tumor supressor genes controlling cell cycle checkpoints and whose expression changes is a key event in cell malignant transformation.
Aim: To investigate the role of cooperative interactions between p53, p21WAF/CIP1 and p16INK4a in determination of proliferative activity in endometrial and ovarian tumors.
Materials and Methods: Operative material of 56 patients with endometrial adenocarcinoma (EC) and 41 patients with serous ovarian cancer (OC) aged 41–76 years. The