and CEA were determined, sensitivities for each parameter and for all combinations of two parameters were investigated for these cut-offs and the receiver operating characteristic (ROC) curves were calculated. The data was analysed with the Mann-Whitney-Wilcoxon test. The statistical packages Statgraphics, Version 5 (Manugistics, Inc., Rockville, USA) and BIAS Version 6.0 (Epsilon Verlag, Frankfurt a.M., Germany) were used. The differences between the control group and stages 0-3 were shown to be non-significant for CA 15-3, CEA but significant for VEGF and TPA. Significant differences were found in stage 4 for VEGF and for all three markers. The increase in sensitivity of VEGF from stage 0 to stage 3 and the degrease from stage to stage 4 can bee interpreted on the role of VEGF in the angiogenesis. The quantification of VEGF could give additional information for selecting patients for systemic adjuvant therapy.

P27

Stereotactic Breast Biopsy – A Short and Safe Diagnostic Intervention for Non-Palpable Breast Lesions

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Goals: We conducted a retrospective examination of our 3-year's experience with stereotactic breast biopsies (SB) regarding histological accuracy, technical possibilities and limitations as well as patient acceptance.

Method: Between 1998–2000 a total of 263 SB were performed in 226 patients with suspicious, non-palpable mammographic findings. 245 biopsies were done with the multitarget (>6) 14 G core-needle-biopsy on the LORAD table and 18 with ABBI-excision. The median duration of these SB-interventions was less than one hour. Under local anesthesia, SB was performed in prone position. After the intervention, a short compression was applied (10 min). The patient was able to resume her regular activity on the same day. All patients with a malignant or an atypical result, were advised to have open surgery. Subsequently, the histologies of biopsy and operation were compared and related to the pre-operative radiologic findings. Due to arterial bleeding (3) and because of discordance between mammographic finding and histology (8), SB were repeated in 11 patients.

Results: 50/263 CNB (19%) showed a malignancy. 33 were diagnosed as invasive carcinoma, 13 as ductal carcinoma in situ (DCIS), 3 as lobular carcinoma in situ (LCIS) and 1 as metastasis with unclear primary tumor. 16/263 biopsies (6%) showed an atypical hyperplasia: 12 atypical ductal hyperplasia (ADH) and 4 atypical lobular hyperplasia (ALH). 57/263 were operated. The definitive histology showed 35 invasive-ductal carcinoma, 14 DCIS, 1 LCIS, 4 ADH and 3 benign. 4 patients did not undergo surgery because of advanced metastatic disease in the preoperative diagnostic workup. 6 patients with ADH did not agree to surgery and were lost to follow up. The comparison of postoperative histologic results with histology of SB confirmed the result in 46/50 cases (92%). In 6 additional cases, histologic "upgrading" was observed: 1 DCIS and 1 LCIS each to invasive carcinoma, 1 ALH to invasive carcinoma, and 3 cases of ADH to DCIS. There was 1 false positive preoperative SB.

Conclusions: Ambulatory stereotactic breast biopsy is an effective, reliable and patient-friendly tool in the diagnostic management of patients with non-palpable mammographic breast lesions. The procedure lasts less than one hour and the patients are able to resume their regular activity on the same day. The good concordance between biopsy and histology allowed operative planning with one step surgery. The case selection for SB with 19% malignant and 6% of atypical breast lesions compares very favorably with international results.

GI-Cancer

P28

Regulation of Vitamin D Synthesis and Vitamin D Receptor Expression: Relevance for Human Colon Cancer Progression

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We have demonstrated previously in human colon tumor-derived primary cultures the antimitotic and prodifferentiating activity of the metabolite of vitamin D, 1,25-dihydroxycholecalciferol (1,25-D3) by binding to its receptor (VDR) Further studies by us indicated increased VDR and 25-D3-xαthydroxylase (CYP27B1) mRNA expression in early colon tumors when compared to normal mucosa from the same patient, as well as the ability of human colon tumor cells to synthesize 1,25-D3 from its precursor 25-D3. In order to study the relevance of 1,25-D3 produced in colon tumors for potentially inhibiting colon tumor progression in an autocrine/paracrine manner we evaluated CYP27B1, VDR and cyclin D1 protein expression in colon tissue derived from a total of 40 tumor patients. As there is some epidemiological evidence that sporadic colon tumors may have a site- and gender-specific distribution (postmenopausal women present with reduced incidence in the right colon) we evaluated an equal number of male and female patients with tumors either in ascending or in descending colon, or in the rectum. Distribution of VDR and CYP27B1 with respect to the proliferation marker Ki-67 was evaluated by immunofluorescence.

Our data demonstrate that in almost all patients, regardless of site or gender, cyclin D1, a cell cycle regulatory protein, is elevated in tumor tissue when compared to the adjacent normal mucosa from the same patient. There is intrinsically high expression of CYP27B1 in males and females in ascending colon tissue. Upregulation of CYP27B1 expression in tumors compared to normal mucosa occurred in a majority of female patients presenting with tumors in the ascending colon, but not in males. In tumors of the descending colon and the rectum, about 50% of male or female patients had increased expression of CYP27B1. VDR expression, although intrinsically also highest in colon ascendens, was elevated more randomly by 50 % in all female colon tumors, but only marginally in male patients. Immunofluorescence for CYP27B1 was found mainly in tumor cells which did not stain positively for Ki-67, whereas in contrast VDR positivity was detected solely in cells positive for Ki-67. We therefore suggest that 1,25-D3 synthesized in

differentiated tumor cells may act antimitotic and prodifferentiating in a paracrine manner. Upregulation of CYP27B1 and of VDR expression may be due to estrogenic substances such as phytoestrogens or HRT and may therefore be specifically protective in female patients.

P29

Alterations of the Dpc4 Tumor Suprressor Gene in Sporadic Colon Carcinoma: Identification of Novel Somatic Mutation in Tumor from Croatian Patient

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Dpc4 is functionally inactivated in about 10-20% of colorectal mutations. The role of DPC4 alterations in development and/or progression of colorectal tumors, we analyzed on 60 samples of Croatian patients.

We investigated allelic losses and mutations in exons 8, 10 and 11. In this work we used polymerase chain reaction (PCR) as basic methods and variable nucleotide tandem repeat (VNTR) analysis for three flanking markers (D18S474, D18S363, D18S46). LOH analysis was prepared on the acrylamide-Bis-acrylamide gels with Spreadex polymer NAB, a novel gel matrix for DNA electrophoresis.

In restriction fragment polymorphism (RFLP) analysis we used *Mnl*I, *Mae*I, and *Bsp*HI restriction site. Single strand conformation polymorphism (SSCP) was done onto GMA gels in denaturing conditions.

Among 60 analyzed cases of colorectal cancers even 58% (97%) were informative. LOH at any of three flanking markers was detected in 37 (64%) of informative tumor DNA's. Nineteen cases of LOH found by D18S474 marker, 11 cases found by D18S363 marker, and 7 cases found by D18S46 marker, respectively. In RFLP analysis neither examined samples of colon carcinoma were positive for mutation in exon 8 and 10. Only one tumor had mutation in exon 11, and sequence analysis verified new mutation – deletion of 20 bp (from 133-153 bp). PCR-SSCP examination of 60 samples did not indicate other different types of SSCP variants.

The malignant progression is a consequence more than one genetic change, and inactivation of DPC4 had a role in a multistep process of colon carcinoma progression.

P30

Reducing the Tumorigenic and Metastatic Phenotype by Chromosome 18 Transfer in Pancreatic Cancer Cells

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Ductal pancreatic adenocarcinoma represents about 85% of all of the pancreatic malignancies and is one of the most lethal cancers in the Western world. Towards approaching the better clinical management of patients with this grim disease, advances have been made in the pathogenesis of the disease recent years.

We previously demonstrated that adenovirus-mediated introduction of *SMAD4* did not suppress growth in pancreatic ductal carcinoma cells with completely inactivated *SMAD4*. Moreover, cytogenetic, allelotype, and somatic cell hybrid studies on others human cancers have suggested that the long arm of chromosome 18 may carry a tumor suppressor gene(s) besides *SMAD4* that plays a role in the early stage of carcinogenesis. Therefore we supposed that the long arm of chromosome 18 could harbour genes implicated in tumor progression and also, in metastasis process.

To directly test this hypothesis, we introduced a normal copy of chromosome 18 into some pancreatic ductal carcinoma cells with completely inactivated and normal *SMAD4*, by using the microcell-mediated transfer (MMCT). Efficiency of the MMCT was checked by microsatelitte analysis and the only the hybrids clones were taken in study. The both parental cells and hybrid clones were monitored for growth *in vitro* (MTT, Independent-anchorage and Invasion Assays) and *in vivo* (tumorigenesis and lung metastasis models in nude mice).

In vitro growth of the hybrid clones was significantly suppressed when compared with their parental cells. Significant suppression of growth, as well as invasiveness, was observed in the hybrid cells than the parental tumor cells *in vivo* after inoculation in nude mice. When injected via lateral tail vein into athymic mice, these clones exhibited attenuated metastatic potential rates (number of loci/lung) as compared with those of parental cells.

These results indicated that tumor formation and metastasis process were suppressed by introduction of normal chromosome 18 copy. However, this study represents the first functional evidence, using pancreatic cancers cells, that bring out into a sharp relief the existence of additional tumor suppressor loci involved in tumorigenesis progression map on 18q, telomeric to SMAD4/MAD4 and DCC. In order to further understanding of the molecular and genetic mechanisms involved in the pancreatic cancer progression, the chip microarray analysis is currently undergoing.

P31

Dolichol as a Predictor in Colorectal Cancer Prevention

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Goals: Dolichol (Dol) has been reported to be 5 to 40 times the normal values in cancer patients, suggesting a metabolic abnormality of N-glycoprotein synthesis in carcinogenesis. Epithelium of colon contains a highest level of Dol concentration in human tissues. With focus on a predictor of colorectal cancer, the present study was carried out to estimate blood and urinary levels of Dol in patients with colorectal cancer (CRCA) and chronic colorectal diseases (CCRD).

Methods: The samples obtained from 217 patients with CRCA (male and female, 32-69 y.o.) and 240 patients with CCRD (male and female, 36-65 y.o.). Dol in blood and urine was assayed by HPLC method (Turpeinen, 1986).

Results: Dol in healthy persons blood and urine are 125,9

± 7,8 ng/ml and 6,8 ± 0,7 mg/mmol creatinine respectively. In patients with CCRD Dol content in urine was much the same, but Dol content in blood showed an increase of 18-22% Blood Dol concentration in patients with CRCA increased at stage I up to 25%,at stage II up to 45 %, at stage III up to 55%, making up 204,5 ± 14,9 ng/ml at stage IV. There was a significant difference between urinary Dol content in patients with CCRD and that of cancer patients. Urinary Dol concentration increased at stage I up to 75-90%, making up 44,9 ± 6,9 mg/mmol at stage II. At stage III the level of urinary Dol was 7-10-fold increased.

Conclusions: These findings suggest that Dol appearance in urinary excretion is one of the first manifestations of carcinogenesis in colon. In this way CCRD therapy and cancer chemoprevention should be carried out under Dol excretion control. The interest drown to the employment of Dol as a predictor of colorectal cancer is explained by the fact that known CRCA oncomarkers are glycoproteins (CA-195, CEA, TAG 72, CA-19-9) Urinary Dol determination is a reliable method for colorectal cancer screening in persons with CCRD. N-glycoprotein synthesis via Dolichyl Phosphate Cycle is a possible targeted chemoprevention of CRCA.

P32

APC Tumor Suppressor Gene in Sporadic Colon Cancer

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Goal of Study: Colorectal carcinomas are characterized by multiple genetic aberrations that occur during tumorigenesis. Several tumor suppressor genes associated with colorectal carcinoma have been identified: *MCC* and *APC* on chromosome 5q, p53 on chromosome 17p, *nm23*-H1 on chromosome 17q, and *DCC* and *DPC4* on chromosome 18q. We examined 46 cases of human sporadic colon cancer and corresponding normal tissue samples to evaluate the loss of heterozygosity (LOH) at the *APC* gene loci. The purpose of this study was also to evaluate whether the LOH at the *APC* gene is associated with clinicopathological characteristics in sporadic colon cancer. In addition, we also investigated the presence and the frequency of three most common *APC* gene mutations (codon 1309, 1061 and 1465) and APC E1317Q variant in Croatian colorectal cancer patients.

Methods: DNAs were used for PCR, RFLP, VNTR, LOH and heteroduplex analysis. PCR was performed using specific pairs of primers. PCR products were analyzed by RFLP analysis, VNTR or heteroduplex analysis. To analyze LOH at the *APC* gene loci we used five polymorphic markers: three RFLP markers (exon 11 *Rsa*I, exon 15 *Msp*I and exon 15 *AspH*I) and two VNTR markers (D5S409 and D5S433).

Conclusions: Using these five markers all patients were found heterozygous and informative for LOH analysis. DNA from 14 (30.4%) tumors exhibited LOH at the *APC* locus. The majority *APC* gene LOH was observed in Dukes' B (54.5%) and in the moderately differentiated tumors (42.1%). Analysis of the *APC* gene mutations showed that only 1309 mutation was present in our samples with the frequency of 2.2% (1/46). *APC* E1317Q germ-line variant was also present with the frequency of 2.2% (1/46).

P33

How Endoscopic Findings May Conceal Gastric Precancerous Lesions? A Study in a High-Frequent Area

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Background: In order to reveal frequency of endoscopic lesions and association with precancerous pathologic findings, we performed an endoscopic surveillance accompanied with the pathologic examination in asymptomatic adults in the Ardabile province with a high prevalence of gastric cancer.

Methods: Asymptomatic consenting adults ≥ 40 years old were selected by a simple random household canvass in both rural and urban regions. Exclusion criteria included inability to tolerate endoscopy, neglecting follow-up visits and the presence of any known benign or malignant gastrointestinal disorders. Then, all subjects underwent esophagogastroduodenal videsendoscopy. Two standard sites in the antrum and all visible lesions were biopsied, and rapid urease test was carried out.

Result: 353 endoscopic results were analyzed to clarify association with the pathologic findings. Normal endoscopy was reported in 32.6% in which Non-specific pathologic changes(NSPC) in 0.05; chronic gastritis in 0.54; Atrophic gastritis in 0.41; Intestinal metaplasia with underlying chronic gastritis in 0.07, Reactive atypia with underlying chronic gastritis in 0.43 and Dysplasia with underlying chronic gastritis in 0.09. All cases of chronic gastritis were associated with Helicobacter Pylori. Rapid urease test for antral biopsy was negative in 23.8%, positive in 62.2 % and doubtful in 8.9%.

Conclusions: Normal and minor changes in endoscopy may conceal underlying precancerous lesions in regions with high prevalence of gastric cancer. We suggest that the experience of the endoscopist can be associated with a better diagnostic sensitivity. There is also a need to continuing study in a larger group in order to evaluate the sensitivity and specificity of endoscopy in revealing of the underlying lesions.

P34

Virtual Colonoscopy in the Prevention Of Colorectal Cancer: A Preliminary Study

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Virtual colonoscopy is a safe, non-invasive method of examining the large bowel. This technology has been reported to have excellent sensitivity for the detection of cancer and polyps greater than one cm in diameter. Nowadays it is regarded as a valid technique in the preoperative evaluation of patients with carcinoma. We have applied virtual colonoscopy to the study of a subset of individuals belonging to verified or suspected HNPCC (Hereditary Non-Polyposis Colorectal Cancer) families. We proposed to high risk people already included in our surveillance programme for HNPCC to perform the CT colonography before the planned conventional colonoscopy and obtained the written informed consent. Up to now 15 individuals have been studied with both the techniques. In all cases colonography have preceded the endoscopic evaluation no longer than 3 months. In 10 cases the results of the two techniques were in accordance not showing any lesion in 8 individuals while revealing a cancer and a polyp in the other two patients. In two individuals polyps were detected at the colonoscopy, being missed at the previous colonography. In one case virtual colonoscopy have shown a polyp-like lesion which was not confirmed at the endoscopic control. In conclusion virtual colonoscopy cannot yet be recommended as a preventive strategy in high risk individuals. The rapid evolution of this technique may provide better results in the future.

P35

Rotating Night Shifts and Risk of Colorectal Cancer in Women Participating in the Nurses' Health Study

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Background: Light exposure during night work suppresses melatonin production, and melatonin shows potential oncostatic action. We prospectively assessed the relation of shift work to risk of colorectal cancer during 10 years of follow-up in a cohort of women.

Methods: Among 78,470 women from the Nurses' Health Study, information was ascertained in 1988 about the total number of years during which the nurses had worked rotating night shifts with at least 3 nights per month. From 1988 to 1998 we documented 600 colorectal cancer cases. Cox proportional hazards models were used to calculate relative risks and 95 percent confidence intervals, adjusted for confounding variables.

Results: We observed no increase in risk for colorectal cancer among the women who worked 1-14 years on rotating night shifts (multivariate adjusted RR, 1.00; 95% CI, 0.84 to 1.19) and an increased risk of 36 percent (RR 1.36, 95% CI, 1.04 to 1.78) among women who worked 15 or more years on shift. The test for trend was statistically significant (p=0.04).

Conclusions: These data are compatible with the possibility that a longer duration of rotating shift work with at least 3 nights per month may increase the risk of colorectal cancer.

P36

Study of Mutation in K-ras Oncogene in Cytological Smears Obtained by Fine Needle Aspiration from Gallbladder Cancer

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Background: Gallbladder cancer (GBC) is the commonest abdominal malignancy in women in northern India with an estimated incidence of 6 per 100,000. Chronic inflammation consequent to the presence of gallbladder stones for long periods, chronic Salmonella carrier state and long standing infection with certain Helicobacter species have been suspected as possible etiologic factors. As carcinogenesis complicating chronic inflammation proceeds through the stages of dysplasia and metaplasia, mutation in K-ras gene may he an important marker for GBC. Its detection from fine needle aspiration specimens may compliment the role of cytological examination in the diagnosis of this condition.

Aims: To detect mutation in K-ras oncogene in material aspirated through fine needle under ultrasound guidance from GBC.

Material and Methods: Cytological smears of 28 patients with GBC were scanned for presence of malignant cells by light microscopy and marked. DNA was extracted from malignant cells by the standard phenolchloroform method and subjected to polymerase chain reaction (PCR) to amplify a 106-bp segment of codon 12 of the K-ras gene. The amplified products were digested overnight with Mval restriction enzyme for restriction fragment length polymorphism (RFLP) analysis.

Results: We could isolate DNA from 17 (60.7%) of 28 specimens. PCR was successful in 14 (82.3%) of these 17 samples. We could detect mutation in codon 12 of the K-ras oncogene in 5 (35.7%) of the 14 PCR positive samples by this technique.

Conclusion: Mutation in codon 12 of K-ras oncogene occurs in more than a third of gallbladder cancers in northern

India. Its detection from fine needle aspirates may prove useful as an adjunct to cytological examination. The presence of this mutation suggests that chronic inflammation may play an etiologic role in gallbladder carcinogenesis.

Late Abstract

P37

Breast Cancer Association with Malignant Tumors in Families

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Introduction: Breast cancer (BC) is one of the most common oncopathologies in women. By the data of National Cancer Register the incidence rate in 1998 made up 36,7 of 100, 000 women in Ukraine. Thus, it poses a serious public health problem. The most part of cancer cases are sporadic, about 5-10% of breast cancer are considered to be familial. One of the main approaches to prevent familial BC is medical-genetic analysis using clinical-genealogical methods of pedigrees and estimation of cancer risk in the proband's families.

Methods: In our studies we used clinical-genealogical method to analize pedigrees of BC probands. Statistical analysis was used also.and found the accumulation of oncopathology with different localization (ovaries, endometrium, cervix, prostate, pancreas, colon, stomach etc.) in first- and second-degree relatives.

Results: The incidence of spread oncopathologies in the families of 145 with BC, which live in various Ukrainian regions were analized. 98 probands had accumulation of oncopathology with different localization (ovaries, endometrium, cervix, prostate, pancreas, colon, stomach etc.) in relatives (67%), and 47 – without oncopathology in the families (32,41%). It was characterized cancer burdening in 1114 relatives (478 first-degree and 636 second degree relatives). Pedigrees with accumulation of oncopathologies were divided in 6 subgroups:1) pedigrees with accumulation breast cancer in two and more relatives (10%); 2) pedigrees with one affected breast cancer (32,7%); 3) 16% pedigrees with aggregation of malignant tumor of reproductive system; 4) 17,35% pedigrees were with digestive tract cancers in relatives: 5) 12,2% probands had affected relatives with thyroid or lung cancers, osteosarcoma, leukemia etc; 6) benign tumors aggregation were in relatives of 12,24% probands.

Conclusion: In 42,7% of the analized families an accumulation of breast cancer in first-degree and second-degree relatives was documented. Therefore, clinical-genealogical analysis should be used for identification of high-risk groups for clinical cancer prevention and such investigations can be applied for regular medical-genetic consulting of cancer family members.