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Falk Workshop
Strategies of Cancer Prevention in Gastroenterology
September 17, 2008
Congress Center Mainz

Abstracts
Poster Abstracts
Falk Workshop

STRATEGIES OF CANCER PREVENTION IN GASTROENTEROLOGY

Mainz (Germany)
September 17, 2008

Scientific Organization:
D.A. Lieberman, Portland (USA)
P. Malferttheiner, Magdeburg (Germany)
J.F. Riemann, Ludwigshafen (Germany)
S.J. Spechler, Dallas (USA)
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S.J. Spechler, Dallas

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Session I

Barrett’s cancer
Epidemiology of cancer in Barrett’s esophagus

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Esophageal cancer is the world’s eighth most common tumor, with approximately 500,000 new cases annually worldwide. More than 80% of those new cases are squamous cell carcinomas, a tumor that has a predilection for black and Asian populations. In contrast, esophageal adenocarcinoma is a tumor that involves white men predominantly, with the highest incidence rates found in North America, Western Europe and Australia. In the United States, the incidence of esophageal adenocarcinoma has increased by more than 600% since 1975.

Esophageal adenocarcinoma is strongly associated with GERD, Barrett’s esophagus and obesity. Can we explain the rise in the frequency of this lethal cancer by a similar rise in the frequency of GERD, Barrett’s esophagus, and obesity?

Circumstantial evidence suggests that the frequency of GERD has increased over the past several decades, but at a substantially lower rate than esophageal adenocarcinoma. For Barrett’s esophagus, it is difficult to obtain meaningful longitudinal data on the frequency of this condition in the general population. A major confounding factor is that the entity of short-segment Barrett’s esophagus was not widely recognized until it was described in a report published in the Lancet in 1994. Until then, endoscopists generally had been taught to ignore short segments of columnar epithelium in the distal esophagus, and so there are virtually no data on the frequency of short-segment Barrett’s esophagus in series published before 1994. A recent study using the Dutch Integrated Primary Care Information Database suggests that the incidence of Barrett’s esophagus in the Netherlands increased from 14.3 per 100,000 in 1997 to 23.1 per 100,000 in 2002. However, it is difficult to exclude the possibility that this apparent increase may be an artifact due to increased recognition of short-segment Barrett’s esophagus by endoscopists.

Obesity clearly has increased profoundly in frequency in the United States and other Western countries over the past 30 years. A recent meta-analysis of studies on the association between obesity and esophageal adenocarcinoma suggests that obesity almost triples the risk of developing this lethal tumor. There is an association between obesity and GERD, perhaps because body fat increases intra-abdominal pressure, which predisposes to reflux. Barrett’s esophagus and esophageal adenocarcinoma are especially associated with abdominal obesity. Obesity also might contribute directly to carcinogenesis. Obesity can increase insulin resistance, resulting in high serum levels of insulin and insulin-like growth factors. These growth factors might stimulate proliferation in the esophagus, which would favor carcinogenesis. Obesity also is associated with increased serum levels of leptin, another pro-proliferative hormone, and with decreased serum levels of adiponectin, an anti-proliferative hormone.

At the same time that there has been a rise in the frequency of esophageal adenocarcinoma and obesity in Western countries, there has been a fall in the frequency of infection with *Helicobacter pylori*. These bacteria are bad for the stomach because they cause gastritis, gastric ulcers and gastric cancer. However, a number of studies suggest that *H. pylori* infection may be good for the esophagus, possibly because the resulting gastritis can decrease gastric acid production, which might protect from the development of GERD, Barrett’s esophagus and adenocarcinoma.
Investigators from Glasgow have proposed another interesting hypothesis suggesting that the rising incidence of esophageal adenocarcinoma might be due to an increased intake of dietary nitrate (NO$_3^-$), which is present in green, leafy vegetables. Most ingested nitrate is absorbed by the small intestine and excreted unchanged in the urine, but approximately 25% is concentrated by the salivary glands and secreted into the mouth where bacteria on the tongue reduce the recycled nitrate to nitrite (NO$_2^-$). When swallowed nitrite encounters acidic gastric juice, the nitrite is converted rapidly to nitric oxide (NO). After nitrate ingestion, high levels of NO have been demonstrated at the distal esophagus of patients with GERD. NO can be genotoxic and, potentially, carcinogenic. Thus, the rise in the frequency of esophageal adenocarcinoma might be a result of increased intake of dietary nitrate, which is a consequence of the increased use of nitrate-based fertilizers over the past 50 years. Despite the conceptual appeal of this hypothesis, however, the limited epidemiological data available on this issue suggest that a diet high in fruits and vegetables actually protects against esophageal adenocarcinoma.

Another trend that has paralleled the increase in frequency of esophageal adenocarcinoma is the use of antisecretory medications like proton pump inhibitors (PPIs). PPIs are among the most frequently used drugs in the world, and PPIs have effects that conceivably could promote carcinogenesis in Barrett’s esophagus. For example, PPI use causes a rise in the serum level of gastrin, a growth factor that has been shown to increase proliferation in Barrett’s metaplasia. However, studies that have explored this issue directly suggest that any positive association between PPI use and esophageal cancer is the result of confounding by indication (i.e. patients take PPIs to treat GERD, which is a well established risk factor for esophageal cancer). In other words, it appears to be the GERD, not the GERD treatment that causes the cancer risk. Indeed, a number of studies suggest that PPIs may prevent cancer in Barrett’s esophagus. In a study of 236 patients with Barrett’s esophagus who were followed for more than 10 years, a Kaplan-Meier survival analysis showed that at ten-years, the cumulative incidence of dysplasia was 21% for the patients who received PPI therapy, compared to 58% for the patients who took no PPIs. This is suggestive evidence that PPIs might protect against carcinogenesis, but by no means is this definitive proof.

Finally, data suggest that the enzyme cyclooxygenase may contribute to carcinogenesis in the esophagus, and cyclooxygenase can be inhibited with non-steroidal, anti-inflammatory drugs (NSAIDs). A meta-analysis of epidemiological studies on NSAIDs and esophageal cancer suggests that the use of aspirin and other NSAIDs is associated with a 40% decrease in the risk of developing esophageal cancer. Epidemiological data suggest a number of places where physicians might intervene to try to prevent esophageal adenocarcinomas. For patients who have GERD with Barrett’s esophagus, for example, available data suggest that medical treatment should include a PPI. Endoscopic surveillance generally is recommended for patients with Barrett’s esophagus although there is no proof that this practice prevents deaths from adenocarcinoma. Obese patients should be advised to lose weight, both by decreasing their intake of fatty foods that promote GERD, and by increasing their consumption of fruits and vegetables, which appear to protect against adenocarcinoma. Patients who smoke cigarettes should be advised to quit for health benefits well beyond prevention of esophageal cancer. And physicians can consider prescribing an aspirin a day for patients with Barrett’s esophagus, especially for those who have no risk factors for gastrointestinal bleeding, and who are taking PPIs that will help to protect against NSAID injury.
Barrett’s cancer – Correlation to reflux disease

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Adenocarcinomas of the esophagus are believed to originate from within Barrett’s esophagus, a replacement of the normal esophageal squamous epithelium by specialized intestinal metaplasia. These tumors are, therefore, often referred to as Barrett’s cancer. Barrett’s cancer has a rapidly rising incidence, especially among white men. The established risk factors for this tumor are, apart from age and male sex, gastroesophageal reflux symptoms, obesity, and tobacco smoking.

Gastroesophageal reflux is recognized as the main risk factor for Barrett’s cancer. However, reflux disease is seemingly not the key to the striking incidence trends observed in the West. There is no clear evidence of an increasing prevalence of gastroesophageal reflux matching the rising incidence of Barrett’s cancer. Furthermore, in whites, the incidence/prevalence ratios, male to female, for reflux disease, are approximately 1:1, and for the development of Barrett’s mucosa approximately 1:1, and yet the ratio for Barrett’s cancer is more like 7:1.

The association between reflux disease and Barrett’s cancer is strong particularly in patients with severe symptoms of reflux over a long period of time. As a consequence, treatment of gastroesophageal reflux could be a potentially successful method of preventing Barrett’s cancer. Current management of gastroesophageal reflux entails either medication which suppresses the production of gastric acid alone, or surgery where the incompetent gastroesophageal valve is restored and gastric juice, containing gastric acid, duodenal secretions, pancreatic secretions and bile, is inhibited to enter the esophagus. Both treatment with acid suppressing drugs and anti-reflux surgery have in case series reported regression of Barrett’s esophagus or prevention of its progression into premalignant dysplasia. However, regarding the outcome of cancer most studies to date are hampered by the limited prevalence of persons operated on with anti-reflux surgery, the long induction time between potential reduced reflux exposure and occurrence of adenocarcinoma, and the low individual risk of this cancer. Large cohort studies and a recent meta-analysis of clinical trials have not found convincing evidence of a protective effect of acid suppressive drugs or anti-reflux surgery on the development of Barrett’s cancer.

In conclusion, there is a strong link between gastroesophageal reflux and development of Barrett’s cancer. However, the association does not seem to explain the rising incidence or the striking male predominance of the disease. Current evidence does not clearly support treatment of reflux disease, with drugs or by surgery, to reduce the risk of developing Barrett’s cancer.
Monitoring strategies

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Because Barrett’s esophagus is generally recognized as a precancerous entity, appropriate follow-up of patients with this diagnosis would appear to be both logical and unavoidable. The current data, however, raise the question of whether, in the majority of cases, such monitoring actually catches malignant transformation in time to begin effective therapy. A critical analysis of the data by a group of gastroenterologists (AGA Chicago Workshop) raised considerable doubt regarding the benefit of screening programs; as a result, they did not recommend as useful a broad-based endoscopic screening program for Barrett’s esophagus, either in the general population or an potential high-risk groups (e.g. patients with gastroesophageal reflux disease [GERD]).

Most patients with GERD undergo endoscopy at least once in the course of their disease (“once in a lifetime”). In such cases, it would make sense to conduct the endoscopic examination while the patient is being treated with acid reducers in order to obviate as much as possible any potential interpretational difficulties in differentiating between inflammatory and metaplastic mucosal changes. Every case of suspected Barrett’s esophagus requires histological clarification. Evidence of specialized epithelium in a small Barrett’s tongue probably is associated with a significantly lower risk of developing adenocarcinoma than is Barrett’s esophagus covering several centimeters.

The index endoscopy plays a central role and should include careful four-quadrant biopsy at intervals of not more than 2 cm (intervals of 1 cm are preferable). Tumors or areas of high-grade intraepithelial neoplasia are found at this index examination in at least 50% of patients.

The longer the Barrett’s esophagus, the more consequent the follow-up must be. An optimum interval for repeating endoscopic examination remains to be definitively established. If the index endoscopy is normal (assuming that an adequate number of biopsies have been taken, a condition which, however, is frequently not met), it is probably adequate to obtain a follow-up endoscopy within three to five years. The longer the time over which adequate follow-up fails to detect the occurrence of neoplastic change, the less likely future malignant transformation becomes. It would be an important question to address in future studies whether follow-up can be safely terminated based on repeated exclusion of neoplastic change.

Because of ongoing deficits in the evaluation of Barrett’s esophagus by pathologists, the diagnosis of both low-grade and especially high-grade neoplasms should be confirmed by a second, experienced pathologist. The occurrence of high-grade neoplasia requires therapy in all cases, while it may be justified in cases of low-grade neoplasia to continue to monitor the lesion at short intervals.
It is important to remember that only a part of Barrett’s patients will be captured in monitoring programs. This is due to the fact that many patients remain completely asymptomatic despite presence of a long Barrett’s esophagus. In addition, GERD patients with Barrett’s esophagus reports less intense symptoms than do those without Barrett’s changes, with the result that the indication for endoscopy may be made less frequently. Because of these factors, it is clear that any monitoring strategy will identify only a small number of patients with neoplasia at an early point in their disease. Whether monitoring strategies can result in a relevant reduction in the incidence of advanced carcinomas therefore remains uncertain.
Barrett’s cancer – Strategies for surveillance

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In recent years, there has been a dramatic increase in the incidence of Barrett’s carcinoma. Barrett’s esophagus is a pre-cancerous condition and caused by chronic gastroesophageal reflux. Therefore, patients with chronic heartburn should undergo an index endoscopy in order to diagnose or exclude Barrett’s metaplasia. Patients with histologically confirmed Barrett’s esophagus are recommended to participate in a surveillance program to identify neoplastic transformation at an early stage. However, there are still some controversies whether such a surveillance programs are cost-effective. Despite those controversies, most national guidelines recommend surveillance endoscopies every 2–3 years in patients with long-segment Barrett’s esophagus and every 4 years in patients with short-segment Barrett’s esophagus. Early neoplastic lesions limited to the mucosal layer can be treated by endoscopic resection. Large clinical trials have shown that endoscopic treatment is safe and effective, even on long-term follow-up.

Early neoplastic lesions within Barrett’s esophagus are often hard to detect. Therefore, different chromoendoscopy techniques (e.g. methylene blue staining, acetic acid staining) and the new virtual chromoendoscopy techniques like NBI and FICE have been developed to improve surveillance for those patients. Whether those new technologies could replace the time-consuming quadrant biopsies, which are still the standard of care, still remains questionable. The fact that more than 50% of early neoplastic lesions are located in the upper right quadrant (12–3 o’clock position) should lead to a careful evaluation of this region.
Session II

Gastric cancer
World wide trends in gastric cancer epidemiology

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Despite a major decline in incidence and mortality over several decades, stomach cancer is still the fourth most common cancer and the second most common cause of cancer death in the world. There is 10-fold variation in incidence between populations at highest and lowest risk. Incidence is particularly high in East Asia, Eastern Europe and parts of Central and South America, and it is about twice as high among men than among women. Prognosis is generally rather poor, with 5-year relative survival below 30% in most countries. The best established risk factors for stomach cancer are *Helicobacter pylori* infection, the by far strongest established risk factor for distal stomach cancer, male sex, a family history of stomach cancer and smoking. Some factors related to diet and food preservation, such as high intake of salt-preserved foods and dietary nitrite or low intake of fruit and vegetables are also likely to play some albeit poorly quantified role. In this presentation, worldwide variation and trends in gastric cancer incidence, mortality and survival will be reviewed in the light of the possible role of these risk factors. The challenges of future epidemiologic research and possible public health measures to reduce the burden of the disease will be outlined.
An innovative concept based on Helicobacter pylori driven gastric carcinogenesis

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Helicobacter pylori is the most prevalent infection in humans, causing chronic gastric inflammation in all patients, ulcer disease in about 20% and gastric cancer in up to 1% of patients. Research has shown that Helicobacter induced gastric disease through the synergistic interactions of a virulent bacterial strain, a susceptible host and a permissive inflammatory environment. Work from our laboratory has shown that a Th1 immune response is necessary for the parietal and chief cell loss that precedes and appears necessary for metaplasia and atrophy to occur. Atrophy represents damage to, or loss of stem cells. The stage of atrophy is followed by the emergence of dysplastic glands, which is followed by the initiation of gastric adenocarcinoma. Our laboratory has focused on the mechanism by which Th1 immune response cause disease. Th1 cytokines, specifically IFN-γ, TNFα, and IL1-β upregulate Fas Ag on the cell surface. Inflammatory cells provide ample Fas L to engage surface Fas Ag receptors and effectively kill cells. Parietal and chief cells express high levels of Fas Ag, and are highly susceptible to Fas mediated apoptosis explaining their preferential removal from the mucosa early in infection. SDF-1 is upregulated in the infected gastric mucosa via secretion from inflammatory cells as well as secretion from stimulated gastric mucosal cells themselves. SDF-1 acts as a chemokine to attract CXCR4 receptor expressing progenitor cells from the bone marrow. These bone marrow derived cells participate in repair of the gut in several ways. Bone marrow derived cells act by direct differentiation as epithelial cells and as fibroblasts and myofibroblasts within the stroma of the GI tract. Transformed bone marrow cells may be involved directly in tumor formation as cancer initiating cells and/or as activated stromal cells (cancer associated fibroblasts) which have a crucial function of secreting growth factors and chemokines responsible for tumor growth and aggression. The interplay between inflammation, stromal cells and epithelial cells in orchestrating gastric cancer presents several new targets for designing novel therapeutic approaches.
Gastric cancer is not a single disease but includes a spectrum of diverse group of cancers differing in the etiology, pathology, and genetic changes. Given the diversity of the disease, we should be aware that there are remarkable differences in the etiology of gastric cancer. (1) Mortality from gastric cancer is very high in the North-Eastern Asian countries including Japan. By contrast, mortalities from gastric cancer in the Western countries are relatively low. (2) The sites of gastric cancer in the East are mostly distal, whereas cardiac cancer is much more frequent in the West. (3) Most of the distal type of gastric cancer is considered to be a consequence of Helicobacter pylori (HP) infection, whereas majority of cancers occurring in the gastroesophageal junction in the West are unrelated to HP infection. Therefore, one should bear these differences in mind when considering effective strategy for preventing gastric cancer.

Primary prevention of gastric cancer has not been adopted in the world. Eradication of HP might have a potential for reducing gastric cancer, but it would be feasible only in the countries where prevalence of HP infection is high based on cost-effectiveness considerations. Unfortunately, even in Japan, the eradication therapy is yet to be approved for gastric cancer prevention. Chemoprevention might be an alternative approach for primary prevention, since aspirin-use has been well documented to reduce cancer incidence including gastric cancer. However, it is not recommended as a preventive measure even for colon cancer, a leading cancer in the West due to disadvantage in risk-benefit ratio. Cyclooxygenase-2 (Cox-2) specific inhibitor used for a chemoprevention trial also failed to show a significant effect in reducing intestinal metaplasia, a surrogate marker of premalignant changes. Therefore, chemoprevention for gastric cancer is not feasible at this moment. Secondary prevention, namely early detection and treatment, is adopted as a nation-wide screening program in Japan. Although it is not quite efficient, mass screening with double contrast radiography is the only method that has an evidence for reducing mortality from gastric cancer. Alternative approach with a combination of serum pepsinogen I/II (PPG) and HP antibody seems more efficient to select a high-risk group developing distal gastric cancer. Large-scale studies comparing the efficiency of screening between radiology-based method and serum-based one is awaited. These two methods of screening, however, might not be applicable for early detection of cancers arising in the cardiac region because they have neither atrophy nor HP infection in the West. The lesions in the cardiac area in their early stages often evade delineation by double-contrast Barium-meal study. Only possible way at this moment is to carry out a very careful endoscopic examination to detect subtle changes. Since HP-negative cardiac cancers is presumed to share similar pathogenic mechanisms with that of Barrett's cancer, it is important to improve endoscopic skills enabling detection of early cancerous lesions in the gastro-esophageal junction.
Session III

Colorectal cancer
Frequency of colorectal cancer in the world, especially in Europe and Germany

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Professor of Medicine and Chief, Division of Gastroenterology and Hepatology, Oregon Health and Science University, USA

Colorectal cancer remains the second most common cause of cancer death in North America and Europe. Worldwide, it is estimated that the incidence of cancer is 1 million cancer cases per year, and over 500,000 deaths each year.

In Europe in 2006, it is estimated that there were 400,000 new cases of colorectal cancer, and 200,000 deaths. There is significant country to country variation in incidence. Germany and Norway have the highest annual incidence rates in Europe for men (43–59/100,000) and women (27–37/100,000). The overall age adjusted incidence rate in the United States was 58/100,000 in men, and 40/100,000 in women during the same period.

In the United States, there is evidence that the incidence and mortality of CRC has declined since the late 1980’s. These reductions coincide with increased use of colorectal cancer screening. There is now compelling evidence that screening of average-risk, asymptomatic populations can reduced CRC mortality. Large scale screening programs have been initiated in many countries of Europe including Germany, Italy, Poland and the UK.

United States Screening Guidelines – 2008
In 2008, the American Cancer Society, the Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology produced new CRC screening guidelines in the United States. The new guideline 1) distinguishes between tests which may detect early cancer (gFOBT, FIT, Stool DNA) and those which may detect both cancer precursors (adenomas) and early cancer (colonoscopy, sigmoidoscopy and CT colonography); 2) expresses a preference for structural exams of the colon, which are likely to result in higher rates of cancer prevention. These tests require bowel preps, special expertise and resources and may not be feasible in all countries. If structural exam is not feasible or declined, then a cancer detection test should be offered; 3) places a strong emphasis on quality in each program.

Outcomes of screening have now been measured in the United States, Canada, Asia and Europe. If detection and removal of advanced neoplastic lesions will prevent some cancers, we will expect to see a decline in the incidence of CRC in many countries over the next few years. Both in Europe, Asia and the United States, adherence to screening recommendations is a challenge.
Prevention of colorectal cancer can theoretically be achieved by 1. dietary or lifestyle modification, 2. chemoprophylaxis and 3. screening and early detection of colorectal neoplasm. As lifestyle modifications have only soft evidence and the use of aspirin or cyclooxygenase inhibitors have their problems, to date, only screening for colorectal cancer have been widely accepted in detecting colorectal polyps and cancers.

After two decades of convincing evidence from the National Polyp Study and RCT of using fecal occult blood tests in detecting colorectal neoplasm, it is widely accepted that removal of adenomatous polyps can prevent development of colorectal cancer and reduce cancer mortality.

The International Colorectal Cancer Screening Network (ICRCSN) was established in 2003 to promote best practice in delivery of organized screening program. The aim of ICRCSN is to identify and document organized screening initiative that commenced before 2004. Screening initiatives around the world were surveyed by a structure questionnaire on the use of fecal occult blood test, flexible sigmoidoscopy or total colonoscopy. In total 35 organized initiatives were identified in 17 countries, including 10 routine population-based screening programs, 9 pilots and 16 research projects. Fecal occult blood tests were the most frequently used screening modality and total colonoscopy was seldom used as a primary screening test. Most studies recruited subjects from 50 to 64 years of age. Recruitment was done mostly by mailed invitation or during a visit to family physician.

The protocol using colonoscopy or fecal occult blood test are summarized as follows:

<table>
<thead>
<tr>
<th>Country, region (initiative)</th>
<th>Type of initiative</th>
<th>Type of test</th>
<th>Brand name of test</th>
<th>Screening interval</th>
<th>Number of bowel movements sampled</th>
<th>Total samples</th>
<th>Residence deferment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EUROPE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Czech Republic (National study)</td>
<td>Program</td>
<td>G</td>
<td>Hemocult</td>
<td>Biennial</td>
<td>3</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td>Denmark, Furesn</td>
<td>Research</td>
<td>G</td>
<td>Hemocult II</td>
<td>Biennial</td>
<td>3</td>
<td>6</td>
<td>Yes</td>
</tr>
<tr>
<td>France (National pilot)</td>
<td>Pilot</td>
<td>G</td>
<td>Hemocult</td>
<td>Biennial</td>
<td>3</td>
<td>6</td>
<td>No</td>
</tr>
<tr>
<td>France, Bourgogne</td>
<td>Research</td>
<td>G</td>
<td>Hemocult</td>
<td>Biennial</td>
<td>3</td>
<td>6</td>
<td>No</td>
</tr>
<tr>
<td>Israel (National study)</td>
<td>Program</td>
<td>G</td>
<td>Hemocult SENSA</td>
<td>Annual</td>
<td>3</td>
<td>6</td>
<td>Yes</td>
</tr>
<tr>
<td>Italy (SCORE 2)</td>
<td>Pilot</td>
<td>I</td>
<td>RPHA immutita</td>
<td>Biennial</td>
<td>1</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>Italy, Toscana</td>
<td>Program</td>
<td>I</td>
<td>Alpha Wasserman</td>
<td>Biennial</td>
<td>1</td>
<td>1</td>
<td>No</td>
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<tr>
<td>Italy (AMOD)</td>
<td>Research</td>
<td>G</td>
<td>Hemocult SENSA II</td>
<td>Annual</td>
<td>3</td>
<td>6</td>
<td>Yes</td>
</tr>
<tr>
<td>Italy, Veneto</td>
<td>Program</td>
<td>I</td>
<td>Alpha Wasserman, Sentinel</td>
<td>Biennial</td>
<td>1</td>
<td>1</td>
<td>No</td>
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<tr>
<td>Italy (Prevenzione Serena)</td>
<td>Research</td>
<td>I</td>
<td>RPHA immutita</td>
<td>Biennial</td>
<td>1</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>Norway (NOCCAP-1)</td>
<td>Research</td>
<td>I</td>
<td>FlexSure OBT</td>
<td>Once</td>
<td>3</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>Spain, Catalon</td>
<td>Pilot</td>
<td>G</td>
<td>Hema Screen</td>
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<td>6</td>
<td>No</td>
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<tr>
<td>Switzerland</td>
<td>Research</td>
<td>G</td>
<td>Hemocult</td>
<td>Annual</td>
<td>3</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Research</td>
<td>G</td>
<td>Hemocult</td>
<td>Annual</td>
<td>3</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>United Kingdom, Nottingham</td>
<td>Research</td>
<td>G</td>
<td>Hemocult</td>
<td>Biennial</td>
<td>3</td>
<td>6</td>
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</tr>
<tr>
<td>United Kingdom, England and Scotland</td>
<td>Pilot</td>
<td>G</td>
<td>Hema Screen</td>
<td>Biennial</td>
<td>3</td>
<td>6</td>
<td>No</td>
</tr>
<tr>
<td><strong>THE AMERICAS</strong></td>
<td></td>
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<tr>
<td>Canada, Ontario</td>
<td>Pilot</td>
<td>G</td>
<td>Hemocult II</td>
<td>Once</td>
<td>3</td>
<td>6</td>
<td>No</td>
</tr>
<tr>
<td>United States of America</td>
<td>Pilot</td>
<td>G</td>
<td>Hemocult II</td>
<td>Annual</td>
<td>3</td>
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<td>No</td>
</tr>
<tr>
<td><strong>WESTERN PACIFIC</strong></td>
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</tr>
<tr>
<td>Australia, Adelaide</td>
<td>Research</td>
<td>G, I</td>
<td>Hemocult, InSure</td>
<td>Annual</td>
<td>3</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td>Australia (Pilot)</td>
<td>Pilot</td>
<td>I</td>
<td>Magstrum HemS, InForm</td>
<td>Biennial</td>
<td>2</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>Japan</td>
<td>Program</td>
<td>I</td>
<td>Not specified</td>
<td>Annual</td>
<td>2</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>Taiwan</td>
<td>Pilot</td>
<td>I</td>
<td>Eiken</td>
<td>Annual</td>
<td>1</td>
<td>1</td>
<td>No</td>
</tr>
</tbody>
</table>

G, guaiac; I, immunochemical.

1. In combination with flexible sigmoidoscopy.
2. Not a country defined in the WHO regions, but is located in the Western Pacific.
At this stage, there is no preference on which is the screening program of choice. The future development of CT colonography, capsule endoscopy and other non-invasive modalities may change the landscape of colorectal cancer screening and prevention.
Who has an increased risk for colorectal cancer?

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Medizinische Universitätsklinik, Knappschaftskrankenhaus, Ruhr-Universität
Bochum, Germany

Colorectal cancer (CRC) is one of most frequent cancers in Germany with more than 70,000 new diagnoses per year and approximately 30,000 CRC-related deaths per year. The cumulative life-time risk to develop a CRC is estimated with 6%. More than 90% of cases will be diagnosed after the age of 50 years. Almost all CRC will progress from adenomas, which can be detected and removed by colonoscopy. Therefore CRC can be effectively prevented by colonoscopy and polypectomy of adenomas. The prognosis of CRC is dependent on the stage of disease. Early colonoscopic detection of CRC has become one of the most important elements to improve the overall prognosis of CRC. Screening colonoscopy of the general population at the age of 55 years and 65 years was integrated in the general cancer screening program in Germany in October 2002.

High-risk groups for developing CRC require a tailored surveillance programme. Individuals with an increased risk to develop a CRC are usually subsumed three groups:

- First degree relatives of patients with CRC or colorectal adenoma
- Individuals from families with a hereditary colorectal cancer syndrome
- Patients with an inflammatory bowel disease

First degree relatives of patients with CRC or colorectal adenoma

Familial CRC (FCRC) accounts for 15–25% of all CRC depending on the definition of FCRC. The median age at diagnosis is 55–60 years. First degree relatives (FDR) of patients with CRC have an approximately 2-fold increased life-time risk to develop CRC. The risk is increased 3–4-fold if more than one relative was diagnosed with CRC and/or if the diagnosis was made before the age of 60 years. However, this group may contain unrecognized forms of hereditary CRC (see below). Similarly, first degree relatives (FDR) of patients with CRC have an approximately 1.6-fold increased life-time risk to develop a CRC. The risk is modulated by the age at diagnosis of the adenoma and is not significantly increased if the index patient was older than 60 years at diagnosis.

FDR of patients with a CRC or an adenoma diagnosed before the age of 60 years should be advised to participate in a colonoscopy surveillance program. Advanced Adenomas (AA) in FDR in age groups 40–50 years, 50–54 years and 55–60 years are detected in 5%, 15% and 22% respectively. The first colonoscopy should be performed 10 years before the age at diagnosis of the patient with CRC/adenoma or at the age of 40 years, whatever comes first. If more than patient was diagnosed with CRC/adenoma and the youngest patient was diagnosed before the age of 45 years, colonoscopy should be initiated at the latest with the age of 35 years. Testing for HNPCC should be performed if the Amsterdam criteria or Bethesda guidelines are fulfilled (see below). Follow-up colonoscopy at 5 year intervals detected adenomas, AA and CRC in 33%, 8% and 0% respectively. Therefore 5 year intervals appear to be safe in FCRC.
Hereditary CRC syndromes

Approximately 2–5% of all CRC develop in the context of hereditary disposition with monogenetic germline mutations. Most hereditary CRC forms are inherited with an autosomal dominant trait. The most frequent form of hereditary CRC is HNPCC, also called Lynch syndrome (see below). Polyposis syndromes such as familial adenomatous polyposis (FAP) and hamartomatous polyposis syndromes (Peutz-Jeghers syndrome and familial juvenile polyposis) are significantly less frequent. Multiple adenomatous polyposis (MAP) is inherited with an autosomal recessive mode and is an important differential diagnosis in HNPCC and FAP. An overview of hereditary CRC syndromes and testing indications are given in table 1. Importantly, most syndromes include an increased risk of extracolonic neoplasias.

The identification of a pathogenic germline mutation in a patient with phenotypic expression of the syndrome (usually patient with CRC or syndrome-associated disease) is a prerequisite for predictive testing of healthy family members. Predictive testing can detect individuals who did not inherit the familial germline mutation and who are not at an increased and do not require intensive surveillance. Germline mutations are detected in 20–95% depending on the syndrome suspected. Rare syndromes and difficult differential diagnoses should be referred to an experienced familial colorectal cancer centre.

HNPCC is the most frequent form of autosomal dominant inherited hereditary CRC caused by germline mutations in a mismatch repair (MMR) gene. HNPCC accounts for 0.8% to 5% of all CRC and is characterized by the early development of often right-sided CRC, the occurrence of syn- or metachronous CRC and extracolonic cancers such as endometrial, ovary, gastric, small bowel, biliary, upper urinary tract cancers and non-melanotic skin and CNS tumours. Due to the lack of a pathognomic phenotype, the diagnosis can often only made by thorough inquiry of the family pedigree. The clinical diagnosis of HNPCC can be made if the Amsterdam Criteria (AC) are met (Table 2). Population-based studies have shown that the majority of HNPCC families do not meet the AC. Therefore, patients who fulfil one of revised Bethesda Guidelines (BG) should be tested for MMR deficiency by microsatellite instability (MSI) testing or MMR immunohistochemistry (Table 3).

MMR germline mutation carriers have a cumulative lifetime risk to develop a CRC of 60–80%. The age-dependent incidence rate starts to increase at the age of 30 years. Surveillance in patients with HNPCC for CRC and extracolonic cancers should be initiated at the age of 25 years. Data from prospective trials have shown that colonoscopy at 2–3 year intervals reduces the incidence and mortality of CRC, however few interval CRC were observed with UICC stage III, therefore intervals of 1–2 years are now frequently recommended. Data from prospective trials using 1–2 year intervals are not published yet.

In contrast to HNPCC, polyposis syndromes display usually a typical phenotype and differential diagnosis can be performed easily. Surveillance recommendations are defined and even prophylactic (procto-)colectomy is required in nearly all patients with classical FAP. It should be emphasized that the risk of extracolonic neoplasias is increased in nearly all syndromes.
Patients with inflammatory bowel disease (IBD)

Patients with Ulcerative Colitis (UC) have an increased risk for the development of CRC. The risk depends on the duration and extent of disease, histological disease activity and concomitant diagnosis of PSC. The cumulative life-time risk is estimated with 2% at 10 years, 8% at 20 years, and 18% at 30 years duration of disease. CRC-related mortality can be significantly reduced by regular surveillance colonoscopy. Patients with pancolitis with a duration of 8 years and patient with left-sided colitis with a duration of 15 years should undergo colonoscopy with multiple biopsies (40–50) at 1–2 year intervals. Chromoendoscopy with targeted biopsies increases the rate of neoplastic findings and may reduce the total number of required biopsies. Surveillance colonoscopy should be performed in clinical remission. Intraepithelial neoplasia (IEN) and DALM should be confirmed by a specialized GI pathologist. Patients with high-grade IEN and DALM require proctocolectomy the optimal care of patients with low-grade IEN (surveillance at short intervals vs. proctocolectomy) is discussed controversial.

The data regarding Crohn’s Disease (CD) is sparse and partially controversial. An increased risk for developing a CRC is assumed for patients with Crohn’s colitis. Currently, no general surveillance recommendations are given for patients with CD. The indication for surveillance colonoscopies for patients with CD-associated colitis must be made on an individual basis.
Table 1: Overview of the most frequent forms of hereditary CRC

<table>
<thead>
<tr>
<th>Indication for genetic testing</th>
<th>Mutation detection rate</th>
<th>Gene</th>
<th>Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNPCC</td>
<td>50–80%</td>
<td>MLH1</td>
<td>3p21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH2</td>
<td>2p16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH6</td>
<td>2p16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PMS2</td>
<td>7q22</td>
</tr>
<tr>
<td>Amsterdam-Criteria/Bethesda-Guidelines fulfilled; prefixed MSI testing; germline mutation testing only if MSI-H</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAP</td>
<td>80–90%</td>
<td>APC</td>
<td>5q21</td>
</tr>
<tr>
<td>AFAP</td>
<td>20–30%</td>
<td>APC</td>
<td>5q21</td>
</tr>
<tr>
<td>&gt; 10–15 adenomatous polyps in the colorectum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>80–94%</td>
<td>STK11</td>
<td>19p13.3</td>
</tr>
<tr>
<td>&lt; 0.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical suspicion of PJS:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ≥ 2 PJ polyps or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ≥ 1 PJ polyp and mucocutaneous pigmentation or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ≥ 1 PJ polyp and positive family history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile polyposis</td>
<td>50–60%</td>
<td>SMAD4</td>
<td>18q21.2</td>
</tr>
<tr>
<td>&lt; 0.1%</td>
<td></td>
<td>BMPR1A</td>
<td>10q23</td>
</tr>
<tr>
<td>Clinical suspicion of JP:</td>
<td></td>
<td>ENG?</td>
<td>9q34.1</td>
</tr>
<tr>
<td>• ≥ 5 juvenile polyps in one patient or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• extracolonic juvenile polyps or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ≥ 1 polyp and positive family history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>1. 10–20%</td>
<td>MYH</td>
<td>1p34.3-p32.1</td>
</tr>
<tr>
<td>?</td>
<td>2. &lt; 5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. &gt; 10–15 adenomatous polyps in the colorectum; especially in cases without APC mutation and without evidence for autosomal dominant trait (no vertical transmission)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. probably early onset CRC (&lt; 50 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2: Amsterdam Criteria (AC; AC-I = only CRC, AC-II = including extracolonic manifestations): A clinical diagnosis of HPCC can be made if the Amsterdam Criteria are fulfilled. Germline mutation is indicated. MSI testing should be performed prior mutation testing.

1. At least 3 family members with associated carcinomas (colon, rectum, endometrium, small bowel, upper urinary tract (renal pelvis/ureter)
2. At least successive generations affected
3. At least 1 affected family member is a first degree relative of the other two
4. At least 1 affected family member is diagnosed before the age of 50 years
5. FAP is excluded

Table 3: Revised Bethesda Guidelines: If one criterion is fulfilled HNPCC should be considered and MSI testing should be performed. If MSI-H is detected, germline mutation testing is indicated.

<table>
<thead>
<tr>
<th>Tumours from patients should be tested for MI-H if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patients were diagnosed with CRC before the age of 50 years</td>
</tr>
<tr>
<td>2. Patients were diagnosed with synchronous or metachronous CRC or other associated tumours*, independent of age at diagnosis</td>
</tr>
<tr>
<td>3. Patients were diagnosed with CRC with MSI-H histology** before the age of 60 years</td>
</tr>
<tr>
<td>4. Patients were diagnosed with CRC (independent of age at diagnosis), who had a first degree relative with CRC or an associated tumour before the age of 50 years</td>
</tr>
<tr>
<td>5. Patients were diagnosed with CRC (independent of age at diagnosis), who had at least 2 relatives (1st or 2nd degree), who had CRC or an associated tumour (independent of age at diagnosis)</td>
</tr>
</tbody>
</table>

*HNPCC-associated tumors of: colorectum, endometrium, stomach, ovaries, pancreas, urothelial tract, biliary tract, small bowel and CNS (mostly glioblastoma, turcot syndrome) and sebaceous adenomas and keratoakanthomas (Muir-Torre syndrome)

**Presence of tumour infiltrating lymphocytes, Crohn's-like lesions, mucinous/signet ring cell type or medullary pattern
Chemoprevention for colorectal cancer

Randall W. Burt, M.D.
Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA

Definition of chemoprevention:

Chemoprevention is the intervention with specific agents (including nutritional supplements or dietary modification) to prevent, inhibit, or reverse carcinogenesis before malignancy. (Modified from Gary Kelloff, Division of Cancer Prevention and Control, Chemoprevention Branch, NCI) When considering colorectal cancer (CRC), chemoprevention of colorectal adenomatous polyps is also important. As removal of these polyps reduces CRC occurrence and risk, it is expected that preventing or regressing adenomas will also reduce CRC. Adenomatous polyps are also commonly used as a surrogate marker for CRC in prevention trials because significant results can often be obtained in four to five years, whereas 10 to 20 years are required for prospective cancer chemoprevention trials.

Issues in chemoprevention:

1. Why is chemoprevention needed? Colonoscopy screening is known to be very effective for colon cancer prevention (through polypectomy) and early detection. Nonetheless lifestyle changes, dietary changes and interventional agents that delay adenoma formation and reduce advanced adenoma and CRC risk would be of benefit. Such benefit would be important in view of the modest participation of colonoscopy and other CRC screening in many countries. Furthermore, chemoprevention efforts may eventually allow lengthening of colonoscopy intervals and more effective approaches to high risk populations.
2. Efficacy: An agent or dietary change must be shown to reduce or prevent adenomatous polyps and/or CRC.
3. Toxicity: Low toxicity is required, as chemoprevention is given to otherwise healthy individuals, often for long periods of time.
4. Efficacy vs. toxicity: The ratio of efficacy to toxicity must be greater for chemoprevention compared to other settings because prevention is done in healthy people and preventive agents must be given for many years, sometimes for a lifetime.
5. High risk settings: Chemoprevention in situations where the risk of polyps and CRC are substantially higher than in the general population is of particular interest. People who have had advanced adenomas or CRC removed, for example, and are thus at higher risk for subsequent neoplasms might well benefit from chemoprevention. Persons with a strong family history of CRC might similarly benefit. This is particularly true for the inherited syndromes of polyps and CRC where risks are extreme. Delay of colectomy or elimination of its need, as well as more simple management of familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) might well be achieved by chemoprevention.
Status of chemoprevention

There has been substantial interest in chemopreventive approaches in recent years. Numerous studies involving dietary, micronutrient and chemopreventive agents have been accomplished. Nonetheless, the goal of widely applicable chemopreventive approaches remains elusive. Dietary approaches are suggested by well done epidemiological studies, but interventional studies have not demonstrated benefit from either dietary change or specific dietary or micronutrient supplement with the exception of a modest effect of calcium. Pharmaceutical agents have shown effectiveness in some cases but the toxicities appear to outweigh the benefits in all but a few high risk settings. Given in Table 1 is a list of the agents most examined, their effectiveness and toxicity, and the present status as a possible chemopreventive. The most recent prospective studies are used in considering the results, not epidemiological or model system studies. Of note is that virtually all adenoma prevention studies consider adenoma recurrence. If an agent affected the progression of adenomas, this would not be detected in such studies. This issue may explain some of the differences between epidemiological and prospective studies.

Table 1: Status of chemoprevention

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effectiveness on adenomas</th>
<th>Effectiveness on CRC</th>
<th>Toxicity</th>
<th>Status as a chemopreventive agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary fiber</td>
<td>None</td>
<td>Little if any</td>
<td>Very low</td>
<td>Not as a chemopreventive</td>
</tr>
<tr>
<td>Optimal diet</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Not as a chemopreventive</td>
</tr>
<tr>
<td>Anti-oxidants (Vits A,C,D,E)</td>
<td>Mixed results</td>
<td>Mixed results</td>
<td>Low to moderate</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Selenium</td>
<td>Possibly</td>
<td>Possibly</td>
<td>Low</td>
<td>Under study</td>
</tr>
<tr>
<td>Folate</td>
<td>Mixed</td>
<td>Mixed</td>
<td>Low</td>
<td>Under study</td>
</tr>
<tr>
<td>Calcium</td>
<td>Modest</td>
<td>Not known</td>
<td>Low</td>
<td>May be given in reasonable doses</td>
</tr>
<tr>
<td>Vitamin D with calcium</td>
<td>Not known</td>
<td>Modest</td>
<td>Moderate</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Bile salts (urso)</td>
<td>Modest</td>
<td>Not known</td>
<td>Low</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>Not known</td>
<td>Moderate</td>
<td>Moderate to high</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Statins</td>
<td>Not known</td>
<td>Mixed</td>
<td>Moderate</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Good</td>
<td>Good</td>
<td>Moderate</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Non-specific NSAIDs</td>
<td>Good</td>
<td>Good</td>
<td>Moderate</td>
<td>Not recommended</td>
</tr>
<tr>
<td>COX-2 inhibitors</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate to high</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>
Summary

Effective chemoprevention has not been yet achieved for CRC or adenomatous polyps in the average risk setting. An optimal diet and calcium supplementation is recommended for many reasons and could possibly be of benefit for CRC when adhered to for many years. Because colon cancer is so common, many continuing chemopreventive studies are underway. Those with combined agents are of particular interest, as lower doses of each agent may be possible, thus lowering the efficacy to toxicity ratio. Finally, chemoprevention is already useful in a very specific situation. FAP patients with a remaining rectum who form many polyps will often have the polyp burden substantially reduced with celecoxib (modest effect) or sulindac (prominent effect), thus making management much easier.
Colon carcinoma: Role of public awareness – What has been, what can be done?

J.F. Riemann
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Introduction: Colorectal carcinoma is one of the most frequent cancers in western industrialized nations, focused on Germany with about 70,000 new cases per year. In the future an even higher prevalence is expected because of demographic changes. The last few years have brought advances in the therapy of advanced colon carcinoma, but prevention will be the decisive factor to reduce Colon cancer incidence and mortality.
Evidence-based strategies for primary and secondary prevention of colon cancer exist. Especially secondary prevention with Colonoscopy-screening-programs could lead to a massive reduction of new colon cancers and the still high mortality rate (in Germany about 26,900 deaths per year).

Participation in screening-programs:
Colonoscopy screening could lead to a reduction of colon cancer incidence by 70–90%. Since 2002 screening-colonoscopy at the age of 55 is part of the official cancer prevention program in Germany and is paid by the health insurance. The effectivity of the screening program is still impaired by the lack of participation of the patients. Cumulating the actual participation rate about 30% of the possible candidates will have had a colonoscopy after 10 years of screening.
When interviewing patients about causes for not participating main factors are lack of information and lack of interest. Other factors, like being afraid of colonoscopy and pain were less important. An increased public awareness of the problem “colon cancer” could possibly lead to better participation in screening programs.

Public awareness – What has been?
Colon cancer prevention in Germany is supported by different organizations. Apart from activities of physicians and health insurances people are influenced by foundations like “Stiftung Lebensblicke” or the “Felix-Burda-Stiftung”. “Stiftung Lebensblicke” was founded after the DGVS congress 1998. The foundation was based on experiences with cancer prevention in Bavaria, the “Bayerisches Modellprojekt“ 1996–1999. During this project a higher participation rate in screening (guaiac-test) could be achieved by an increase of the payment for participating physicians and simplification of the billing process. Participation could be raised to 54% and 38%.
Since then the foundation’s main focus lies on public relations to physicians and patients. With brochures about colon cancer, activity in the media sector, regional and local events and support by celebrities many people were motivated to take part in colon cancer screening. Especially the opportunities of screening in cooperation with employers and companies were shown in a study together with the BASF in Ludwigshafen. During this study 47% of patients with positive guaiac-test took part in a recommended colonoscopy.
Since 2002 march is called the “Darmkrebsmonat“. The activities of the different foundations and organizations are concentrated in March, 2004 the "Netzwerk gegen Darmkrebs e.V.“ was founded.
Public awareness – What can be done?
Participation in screening is increasing through the last years, even first effects on the mortality rate can be seen. In spite of this participation is not yet sufficient and optimizing it is still a challenging task for the future. Some possible activities could be:

- Continuous PR-work, e.g. with “topic peaks“ like the “colon cancer month“ (Darmkrebsmonat)
- Focus on high-risk groups (e.g. familiar colon cancer)
- Bonus systems for patients and physicians
- “Invitation“ to screening by health insurance companies
- Development of less invasive screening methods (e.g. colon capsule, blood tests)

In times of growing costs in the healthcare system politicians take an increasing interest in prevention. To bundle activities the German Health Ministry developed a “national cancer plan“, where aims and measures to optimize screening are defined.
Session IV

Cancer in IBD
Cancer in IBD: Frequency and clinical presentation

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In 1925, Crohn and colleagues reported the first case of colorectal cancer (CRC) occurring in a patient with inflammatory bowel disease (IBD). Since then, the association between chronic inflammation and related cancer has been well established. Despite this long known relationship, the true risk for malignancy in IBD remains unclear. As the fear of developing cancer in IBD patients is highly prevalent, more knowledge on underlying mechanisms and better preventive strategies are needed.

CRC is the most common site of cancer in IBD, although cancer can appear in any other organ. IBD, hereditary syndromes of familial adenomatous polyposis and hereditary nonpolyposis CRC are the major high-risk conditions for CRC. The exact frequency of the risk of CRC in IBD has been difficult to estimate due to various biases and methodological errors. One of the major biases arose from the fact that many reported early studies included mainly patients from referral centres thereby overestimating the cancer incidence. Other studies included on the other side more patients with limited disease and may have underestimated the true frequency. Looking at several performed metaanalyses, the overall prevalence of CRC in patients with ulcerative colitis (UC) is between 3–4% versus 5% and more for patients with extensive colitis. It is important to mention, that the prevalence of cancer in Crohn’s disease is less well studied although its relevance may be similar especially in patients with Crohn’s colitis. Indeed, a population-based study from Canada suggested that the risk for colon cancer among patients with both UC and Crohn’s disease (colitis) is 2–3 fold higher than in the general population and the risk of rectal cancer is increased 2-fold in UC but not in Crohn’s colitis.

The clinical phenotype of CRC in IBD patients is definitely affected by the underlying disease. CRC in IBD patients affects younger people, and furthermore CRC in IBD arises mostly from flat lesions. As inflammation is the driving force in IBD-related CRC, it is no surprise that there is a higher rate of two or more synchronous CRCs. All these aspects, however, do not translate into specific clinical symptoms which might help to identify patients on risk. It is the critical awareness of the responsible physician that at the end helps to diagnose this complication in IBD patients at the earliest possible time point.
Patients at risk for colorectal cancer in IBD

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The main risk factors for developing colorectal cancer include:
– Disease extent
– Disease duration
– Co-diagnosis of primary sclerosing cholangitis
– Family history of a first degree relative with sporadic colorectal cancer
– Active inflammation and residual pseudopolyps

Patients with ulcerative colitis and Crohn’s colitis are at risk for developing colorectal cancer. A primary risk factor is extent of colitis-affected mucosa. Hence patients with more extensive colitis are at greater risk than patients with limited colitis. Patients with ulcerative proctitis do not seem to be at increased risk at all of developing rectal cancer. Patients with Crohn’s disease outside of the colon (i.e. isolated small bowel Crohn’s disease) are not at risk of developing colorectal cancer. Risk also rises with years of disease. The risk for developing colorectal neoplasia including cancer begins to rise at 8 years of disease, with a steeper rise at 20 years of disease. It is unknown if this risk plateaus after 30 years of disease. The occurrence of colorectal cancer prior to 8 years of disease (from time of diagnosis) has been reported and this raises the issue as to exact dating of disease duration. Does the clock start at time of initial symptoms or at the time the final official diagnosis is made?

A number of reports have shown that a concurrent diagnosis of primary sclerosing cholangitis increases the risk for patients with IBD developing colorectal cancer. Furthermore, a family history of sporadic colorectal cancer in a first degree relative also increases the risk. The incidence of dysplasia and cancer correlate with areas of greatest inflammation. So heightened inflammation could be seen as a risk factor, however, the more inflamed the colon, the more difficult it can be for the pathologist to discern cytological atypia secondary to inflammation from that secondary to neoplasia. A corollary to this is that when mucosa is macroscopically normal the incidence of neoplasia is markedly reduced. Studies have also shown an increased risk for dysplasia or cancer in patients with pseudopolyps. It is uncertain whether pseudopolyps pose a true risk, as a marker of where severe inflammation once was, or whether it makes it difficult to discern where a raised neoplastic lesion might be. If the latter was the issue then this might lead to more cancer diagnoses (and missed diagnoses of dysplasia that ultimately advanced) in patients with extensive pseudopolyps but shouldn’t enhance the incidence of dysplasia.
Surveillance in ulcerative colitis

Ralf Kiesslich, M.D., Ph.D.
University of Mainz, Germany

Endoscopy has recently witnessed major technical improvements. Magnifying, high resolution and HDTV endoscopy systems often in conjunction with chromoendoscopy enable detailed surface analysis and help to identify areas of interest within the gut. However, chromoendoscopy is now facing electronic competition, as filter or post processing techniques such as narrow band imaging may at least partially mimic chromoendoscopy by simply pressing a button to enhance visualizing of surface vessel architecture.

All of these techniques unmask a plethora of new visible details and require immediate interpretation to target biopsies to suspicious surface architecture. However, they all predict histology to some extent but histology even after targeted biopsies remains the accepted gold standard for final judgement of mucosal lesions. Endomicroscopy has recently emerged as a novel technique that allows subsurface imaging and in vivo histological assessment of mucosal changes during ongoing endoscopy. This technique allows for the first time to look below the mucosal surface and to see in vivo histology of lesions during ongoing endoscopy.

Chromoendoscopy studies have impressively shown that chromoendoscopy can unmask multiple, flat growing intraepithelial neoplasias in patients with long standing ulcerative colitis. The diagnostic yield is increased 3–4.5-fold as compared to random biopsies and chromoendoscopy has thus been recently incorporated into the US guidelines. Interestingly endomicroscopy can further enhance the diagnostic yield with significant fewer biopsies needed per patient. Endomicroscopy has a limited field of view (475 x 475 µm).

Therefore, one should combine methylene blue aided pan-chromoendoscopy with subsequent targeted fluorescein aided endomicroscopy. Compared to routine surveillance colonoscopy detection of intraepithelial neoplasias could be increased 4.75-fold per patient using this approach. Whereas chromoendoscopy unmasked areas of interest (flat, circumscribed lesions), subsequent endomicroscopy confirmed or excluded the presence of neoplasias and reduced the need for biopsies. With this approach the average amount of biopsies could be decreased from about 40 per patient (random biopsies) to 20 biopsies (chromoendoscopy) and theoretically to about 4 biopsies per patient (combined approach of chromoendoscopy and endomicroscopy) with still significantly higher diagnostic yield for intraepithelial neoplasias as compared to random biopsies.

With this technology, we explore the in vivo cell architecture of the whole mucosal layer at subcellular resolution which will allow functional and molecular imaging in the future.
Cancer in IBD: Is there a chance for cancer chemoprevention?

Prof. Dr. Christoph Gasche
Medical University of Vienna, CDL on Molecular Cancer Chemoprevention, Vienna, Austria

IBD of the colon increase the risk of colorectal cancer (CRC).\(^1\)\(^\text{--}^3\) Case–control studies have shown that regular use of 5-ASA reduces the risk of CRC in patients with UC.\(^4\)\(^,\)\(^5\) A meta-analysis of nine studies found a 50% reduction in risk of CRC with use of 5-ASA.\(^6\) The risk is lower with longer durations of use of 5-ASA,\(^6\)\(^,\)\(^7\) and with higher doses (> 1.2 g/day).\(^8\)\(^,\)\(^9\) In one study, taking mesalazine regularly over 5–10 years reduced the risk of CRC by 81%.\(^4\) Non-compliance with 5-ASA therapy (taking < 75% of prescribed doses) has been shown to be associated with a > 5-fold increase in the risk of recurrence of ulcerative colitis.\(^9\) Compliance is lower among male and unmarried patients and those taking multiple concomitant medications,\(^10\) and can be improved by use of a once-daily formulation of 5-ASA.\(^11\)

The anti-inflammatory actions of 5-ASA include modulation of inflammatory cytokine production, NF\(\kappa\)B inhibition and PPAR-\(\gamma\) activation.\(^12\) Whereas sporadic CRC develops via adenoma, colitis-associated CRC evolves by a different process involving flat lesions and dysplasia. 5-ASA has been shown to affect cell-cycle progression by inducing cells to accumulate in the S phase and activating a replication checkpoint.\(^13\) In addition, 5-ASA has been shown to improve replication fidelity in cultured colorectal cells, which may lead to a reduction in mutations independent of its anti-inflammatory properties.\(^14\)

Prevention of CRC in IBD is a combined effort of screening colonoscopy (to reduce mortality) and chemoprophylaxis (which actually reduces the incidence).

Learning objectives
At the conclusion of this session, the participant should:

1. Be aware of the risk of CRC in IBD and the ability to prevent this with regular 5-ASA therapy.
2. Understand the importance of 5-ASA compliance in the management of UC.

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POSTER ABSTRACTS

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VEGF-positive structures in gastric cancer

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Introduction: Vascular endothelial growth factor (VEGF) is secreted from a variety of stromal or epithelial cells and from tumor cells of epithelial origin. In cancers VEGF has been investigated mainly in connection with tumor neoangiogenesis. The aim of the present study is to investigate VEGF-positive structures in gastric cancer, and to compare our data with cancer stage and progression.

Methods: We investigated tumor tissue collected from 30 patients (18 males and 12 females) immunohistochemically with antibodies against VEGF, chromogranin A, serotonin and gastrin.

Results: High VEGF positivity was detected in the tumor cytoplasm of 7 patients with tumor stage 3B and 4. In 9 patients VEGF-positive stromal inflammatory cells were observed. VEGF expressing tumor cells and VEGF reactive inflammatory cells (probably mast cells) were correlated to TNM classification and the tumor stage. It appeared that stronger VEGF expression correlated with more advanced tumor stage. In 42% of the tumors VEGF-positive endocrine cells in the tumor glands were found. They were co-located with routine endocrine cell (EC) markers such as chromogranin A, serotonin and gastrin. We found that VEGF-positive ECs are also serotonin, chromogranin A and gastrin positive.

Discussion/Conclusion: VEGF released from ECs granules could exert effect upon ECs growth and over the neighboring blood vessels’ permeability. VEGF might facilitate endocrine cell granules’ secretion and the entering of their hormones into the local microcirculatory vessels.
Colorectal cancer screening program in Croatia

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Introduction: Colorectal cancer (CRC) is a major public health burden among malignant diseases worldwide. In Croatia it is the third cause of cancer mortality in men (n = 998), and second in women (n = 749) in 2005. The standardized death rate is 42.69/100,000 for men, and 21.18/100,000 in women. There is clear evidence that screening can reduce CRC mortality and improve outcomes. In almost all of the developed EU countries screening programs are organized.

Methods: Croatian National program for CRC screening was established by Ministry of Health and Social Welfare and has been implemented since the beginning of this year. The network of coordinators in each county institute of public health are obliged to ensure performing of fecal occult blood testing (FOBT), followed by colonoscopy in all positive cases. The FOBT is performed by guaiac-based Hemognost card test with detection limit of 0.2 ml blood in 500 g of stool. Test and short questionnaire are delivered to home address of all citizens age 50–74 consecutively during two years. Each participant has to fulfill the questionnaire, and send it together with test specimen back to the institute for further analysis. According screening results of other authors, it was expected that 4% FOBT positive cases would be found in normal risk population and model calculations pointed out a need for 24,000 colonoscopies per year.

Results: Of the 17,668 individuals (borne 1933 and 1937) screened until now with FOBT, 1971 (11.2%) were found to be positive. Colonoscopy was performed in 1101 cases (compliance 69.3%). Screening has identified 58 CRC patients; 2.9% of FOBT-positive patients and 0.33% of all screened individuals proved to have CRC.

Discussion/Conclusion: These preliminary results suggest a need of further strengthening of Croatian National program for CRC screening.
Palliative endoscopic treatment of obstructive colorectal carcinoma – Prospective pilot study

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Introduction: Obstructive colorectal carcinomas (CRC), usually with distant metastases, are seen more frequently in daily practice. Our objective is to insert colonic stents in patients (pts) who refuse surgery or where surgery is not recommended.

Material and methods: 7 pts with obstructive CRC underwent stenting of the stricture. Gender distribution: 2 females, 5 males. Localizations of stricture: r-s junction (3 pts), sigmoid colon (2 pts), stenosis after surgery (recurrence of CRC, 2 pts). Sigmoidoscopy was performed in all pts, followed by balloon dilation and stent insertion (Wallstent Enteral Endoprosthesis).

Results: Relief of colon obstruction and resume of intestinal transit was obtained in all pts. Complications during stent placement: in one pt a small perforation after balloon dilation was observed, which was resolved after stent placement and with intravenous administration of antibiotics; in 6 pts bleeding from the dilated tumor which stopped spontaneously after stent insertion. The pts could better accept chemotherapy; two pts were prepared for elective colon resection without colostomy, and in the two pts with recurrence of obstructive CRC after surgery bowel transit and decompression was reestablished.

Conclusion: Stent placement in obstructive CRC has a palliative effect and results in decompression of large bowel. It is a useful technique for relief of obstruction and for further therapies (chemotherapy, elective surgical colonic resection), as well as for restenosis of the colon due to recurrence of CRC after surgery. The Wallstents also improved the quality of life of all pts.
Medical treatment of IBD patients hospitalized in university hospital setting during period of 5 years

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Introduction: Even though therapeutic management of IBD is nowadays characterized with better disease control, hospitalizations figures for both, CD and UC groups show permanently growing trend. The aim of our study was to reveal the approach in medical therapy (monotherapy vs. combined and/or systemic vs. topical therapy) using the small-molecule drugs, in hospital setting with catchment area of 300,000 inhabitants, during the 5-years period.

Materials and methods: We performed qualitative treatment analyses on sample of 147 patients (age 18–87) hospitalized for IBD in University hospital Dubrava, during the 5-year period (01.01.2002–31.12.2007). Patients were categorized on the bases of IBD entity (CD or UC) and drug-treatment groups (monotherapy, combined vs. modalities; ASA-topical or systemic, corticosteroids – topical or systemic, and immunomodulatory therapy) with final summing up. Hospitalized population sample rate of remissions and score according to clinical indexes were correlated and compared to generally agreed recommendations and/or similar settings published in literature.

Results: The majority of hospitalizations in total group of IBD patients were due to reevaluation of disease (53%), followed by group of first-hospitalizations (39%) and rest for unscheduled emergencies. In CD patients, dominant group represented reevaluation of disease (55%), followed by first-hospitalization (30%). In regard to UC, 52% of hospitalizations were due to reevaluation of disease and 43% for first-hospitalization.

Topical therapy (44%) and systemic corticosteroids (50%) were dominant treatment modalities for 135 patients (94%), whereas only 6% of patients received immunomodulatory therapy. Patterns of drug prescriptions correlated generally well to clinical indexes score. Over two thirds (82.07%) of patients had mild to moderate disease, while only 37 (17.93%) had clinically severe disease. The most severe cases were not treated by pharmaceuticals since initial presentation were surgical emergencies. This group formed 11 patients (7.48%); 8 CD (72.72%) + 3 UC (27.27%).

In CD patients, treatment with topical agents (48%) dominated, followed by systemic corticosteroids (38%) and immunomodulatory therapy in 14% of patients. Systemic corticosteroids were most common form of treatment in age group 50–59 years (57.14%) and in group 30–40 years (50%). Concordance between CD severity and more aggressive therapy, including immunomodulatory agents was also confirmed in our setting.

Systemic corticosteroids (54%) were the commonest type of UC treatment, followed by topical therapy with ASA or corticosteroids (43%), probably due to long-term prevalence bases of the studied cohort with relatively greater share of advanced disease among inpatients. Further studies are needed to diversify this pattern regarding drug induced remission rates from potential non-adherence to therapy.
**Discussion and conclusion:** In spite of the fact that majority of hospitalizations was due to reevaluation of disease, this study revealed that systemic corticosteroids represented the most frequent prescribed therapy for hospitalized IBD patients, during the observed 5-year period. Immunomodulatory agents were predominant therapy in minority of patients and this observation is in contrast to biologic course of inflammatory bowel disease, especially CD. These results indicate the need for improved approach in medical treatment of IBD patients, especially in regard to maintenance therapy for patients with CD.
Cellular iron regulation is defective in colorectal adeno-carcinoma

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Introduction: The tight regulation of cellular iron levels in normal epithelial cells is mediated through the interaction of iron regulatory proteins (IRPs) with iron response elements found in many genes implicated in iron metabolism. In instances of excessive iron levels IRE/IRP signalling causes a repression in iron import proteins including transferrin receptor-1 (TfR1) and divalent metal transporter-1 (DMT1). However, in colorectal cancers we have previously demonstrated high iron import protein expression in the face of high cellular iron levels suggesting an aberration in IRE/IRP signalling. The aim of this study is to determine if iron mediated Wnt signalling is crucial in the aberration of iron sensing and in particular address the impact of c-myc.

Methods: Colorectal lines RKO and SW480 were cultured with or without iron; the expression of iron transport proteins and Wnt-targets examined by Q-RT-PCR and Western blotting. C-myc and IRP2 over expression studies were performed in RKO cells followed by ferrozine assays for iron determination.

Results: Our results demonstrate that in RKO cells (APC wild-type) iron does not induce Wnt signalling and cells behave in an IRE/IRP dependent manner. However in SW480 cells (APC mutant) iron loading results in Wnt signalling and inductions in iron import proteins (TfR1 and DMT1) which were associated with increased c-myc expression. This observation was verified by c-myc over expression studies where expression of the iron import proteins TfR1 and DMT-1 were both induced as a consequence of c-myc.

Discussion/Conclusion: Wnt signalling and in particular c-myc is crucial in interfering with normal IRE/IRP signalling.
Iron-mediated cellular proliferation, migration and colony formation is dependent on adenomatous polyposis coli status in colorectal adenocarcinoma

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Introduction: There is emerging evidence suggesting increased cellular iron is important in the development of colorectal cancer. Colorectal cancer is characterised by mutations in adenomatous polyposis coli (APC); a tumour suppressor gene crucial in Wnt signalling. We have previously demonstrated that iron can activate Wnt signalling in the background of an APC mutation. However, the effect of iron on cell phenotype to date has not been addressed. Thus the aims of this study were to determine if iron could enhance cellular proliferation, migration and colony formation and establish if these effects were APC dependent.

Methods: Human colorectal APC wild type (HEK-293 and RKO) and APC mutant containing lines (Caco-2, SW480) were challenged with either ferrous sulphate (FeSO₄) [100 µM] or hemin [50 µM] in the presence or absence of the GSK-3β inhibitor lithium chloride (LiCl) [20 mM] for 24 hrs. Cellular iron loading was confirmed using the ferrozine assay. Cellular proliferation was determined by BrdU incorporation and FACS analysis. Cellular migration was assessed using a wound healing assay, and in-vitro anchorage independent colony forming determined using a soft agar colony forming assay. To further test the dependency of APC SW480 cells transfected with or without full length wild type APC were also utilised in these studies.

Results: Challenging APC mutant containing lines with FeSO₄ or hemin significantly increased cellular proliferation, wound healing and anchorage independent growth. Conversely, wild type APC containing cell lines only responded to FeSO₄ or hemin when co-cultured with LiCl. The dependency for APC was exemplified by the inhibition of iron mediated cellular proliferation in SW480 cells transfected with human wild type APC.

Discussion/Conclusion: This study demonstrates that iron can induce cellular proliferation, migration and anchorage independent growth and we believe this is a consequence of iron mediated Wnt signalling. Interestingly iron could only induce these cellular effects in the background of abrogated β-catenin degradation, such as a truncating mutation in APC or inhibition of GSK-3β.
Viral hepatitis – Associated with solid tumours? (Case series)

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Introduction: Some viruses can play a role in oncogenesis. Hepatitis C virus is known to induce chronic hepatitis and cirrhosis, but also hepatocellular carcinoma, lymphoproliferative disease. More recently it was associated with some other solid tumours, such as thyroid cancer and possibly lung cancer.

Methods: The aim of our study was to evaluate the frequency of malignant conditions associated with diagnosed chronic HCV hepatitis. It is a retrospective study on all the hospitalised patients during 5 years (2003–2007), based on the medical records.

Results: We found neoplastic diseases in less than 5% of the patients having chronic HCV hepatitis. Among haematologic disease we found non-Hodgkin lymphoma, chronic lymphatic leukaemia, polycytemia vera, monoclonal gammopathy. Found tumours have different sites: thyroid, liver (hepatocellular carcinoma), genital (prostate and uterus), skin (basocellular epithelioma and malignant melanoma), breast, bowel and pancreas.

In conclusion, our results cannot document the HCV infection as a risk factor for certain solid tumours, but are raising awareness on a possible relationship between these conditions.
Colonoscopy and pathology in two different age groups

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Introduction: The aim of this study is to evaluate the etiological pattern in two different age groups.

Methods: We included 67 patients admitted in our hospital in 2007, who performed colonoscopy for diagnosis, followed by pathological examination. We analysed the demographical and etiological data on two different patient groups, according to etiology and age, the cut off value being 50 yrs, as a limit age for colonoscopy screening indication.

Results: From a total of 67 patients 38 were males and 29 females, a mean age 48.98 ± 16.51 yrs.
The diagnoses were as follows: colorectal polyps (32.84%), inflammatory non-specific colitis (28.36%), colorectal cancer (22.39%), inflammatory bowel disease (14.93%), ischaemic colitis (1.49%).
The pathology varies from younger to older, in the following order: inflammatory bowel diseases (48 yrs), inflammatory non-specific colitis (50.86), polyps (51.28), ischaemic colitis (68) and colorectal cancer (70.07). According to the age, inflammatory bowel diseases were more frequent in the young group (28% vs. 7.14%, p = 0.049) and the colorectal cancer in the older age group (30.95% vs. 8%, p = 0.029). For other etiologies, no significant differences were recorded between these patients groups.

Discussion/Conclusion: The colonoscopy has an essential role in etiological diagnosis of large bowel diseases.
Inflammatory bowel disease has an increased frequency in young adults and the colorectal cancer is more common in adults after 50 yrs, this fact having an essential role in choosing the screening strategy.
No differences were recorded between the two age groups in patients with other diseases.
The second colonic carcinoma in a patient with common variable immunodeficiency disease (CVID). Can the administration of immunoglobulins have a preventive effect on carcinogenesis?

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Introduction: We present here the clinical observation of a patient aged 69 with CVID (Common Variable Immunodeficiency Disease) who underwent surgery twice for colonic carcinoma during a period of eight years.

Methods: The patient diagnosed with CVID (hypogammaglobulinemia with IgG deficiency) at the age of 38 has a complex personal pathological history: acute lung infections and several acute enterocolitis, lung tuberculosis, type 2 insulin-requiring diabetes mellitus, cholecistectomy for cholelithiasis, giardiasis, erysipelas of the shank – 11 times, bronchiectasis, silent chronic ischemic heart disease.

Results: The patient underwent surgery at the age of 55 for sigmoid carcinoma. He was operated again eight years later for descending colon carcinoma developed at a certain distance from the first resection. In both occasions the histological finding was the Dukes B stage, type G2. Until the second operation the patient didn't take a substitution treatment with gamma globulins. Since then, this medication has been administered every six weeks.

Discussion/Conclusion: CVID is significantly accompanied, among other diseases, by malignant lymphoma, colorectal cancer, gastric cancer and skin cancer. In our patient with CVID, the second colonic cancer appeared, the argument is the eight year period from the first operation and the development of the carcinoma at a certain distance from the first resection. In both situations, the histological finding was adenocarcinoma Dukes B. The substitution treatment with gamma globulins in CVID could be a preventive measure for carcinogenesis.
Incidence of gastroesophageal reflux disease in Republic of Tatarstan as risk factor of esophageal adenocarcinoma

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Gastroesophageal reflux disease (GERD) is very common in daily practice of gastroenterologists of Republican out-patient clinic. Nowadays it’s clear that GERD not only influences quality of life of the patients but can lead to the development of serious complications.

Materials and methods: More than 9000 of people from all over the Republic of Tatarstan are admitted annually by gastroenterologists. The number of upper GI endoscopies done has increased: In 2002 there were 2320 endoscopies done and in 22.8% of examined patients changes in the esophagus were found (529 patients). In 2007 more than 5030 upper GI endoscopies were done, changes of the esophagus were revealed in 21.3% of cases (1072 patients). GERD was diagnosed in 7–12% of patients.

Results: We have analysed by 100 cases of GERD in 2002 and 2007. In 2002 non-erosive reflux disease (NERD) was diagnosed in 69%, GERD in 31% of cases. In 2007 NERD was found in 78% of examined patients, GERD in 22%. Grade of esophagitis was established according to Savary-Miller classification:

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<th>Grade of esophagitis (Savary-Miller classification)</th>
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Barretts esophagus was revealed in 2002 in 2% of patients, esophageal adenocarcinoma in 1%. In 2007 these numbers were 4% and 2%, considerably. GERD complications were observed 2 times more often in patients older than 60 years old.

Conclusion: So during the last 5 years the incidence of GERD in Republic of Tatarstan continues to be quite high, particularly among young people. Upper GI endoscopy helps in early diagnosis of GERD as well as extraesophageal symptoms and Barrett's esophagus which is quite important for esophageal adenocarcinoma prophylaxis.
Age and severity of mucosal lesions influence the performance of serological markers in *Helicobacter pylori*-associated gastroduodenal pathologies

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**Introduction:** The course of *H. pylori* infection and antibody response to CagA in patients with preneoplastic lesions and gastric cancer has not been thoroughly studied.

**Aim:** To study *H. pylori* infection and antibody response to CagA in patients with non-atrophic gastritis, pre-neoplastic lesions and gastric cancer.

**Methods:** We studied patients attending one General Hospital in Mexico City. Diagnosis was based on endoscopy and histopathology in biopsies from six stomach regions. *H. pylori* infection was assessed by histology and serology and antibodies against CagA were measured with immunoassay.

**Results:** We included 618 patients, 368 with non-atrophic gastritis, 126 with precancerous lesions (14 atrophic gastritis, 110 intestinal metaplasia, and 2 dysplasia), and 65 with gastric cancer; in addition, 59 patients with duodenal ulcer were studied. Detection of infection and IgG against CagA had a significant increase from non-atrophic gastritis to mild and up to advanced stages of metaplasia (p < 0.05) and then decreased in gastric cancer patients (p < 0.05). However, infection and CagA antibodies were associated with young gastric cancer cases. Duodenal ulcer showed a significant association with infection detected by histology and serology, particularly among women, and a trend to associate with IgG to CagA.

**Discussion/Conclusion:** This study shows that *H. pylori* infection and CagA are risk factors for intestinal metaplasia. Prevalence of these markers decreases in gastric cancer, probably reflecting that infection decreases after advanced atrophy and metaplasia in the gastric mucosa. State of the disease, age and sex influence the association of *H. pylori* infection and IgG response to CagA with gastroduodenal diseases.
Dietary folate and vitamin B₁₂ intake before diagnosis decreases gastric cancer mortality risk among susceptible MTHFR 677 TT carriers

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Introduction: Gastric cancer (GC) is one of neoplasias with the worst survival (<25% after 5 years) and limited information is available about the impact that dietary and host genetic factors have on its prognosis. The aim of this study was assess GC survival in relation to the dietary intake of methyl donors and the methylenetetrahydrofolate reductase 677C>T (MTHFR 677C>T) polymorphism.

Methods: A prospective cohort of 257 incident histological confirmed GC cases was assembled in January 2004 and followed until June 2006. Patients were recruited from the main oncology and/or gastroenterology units in Mexico City and were queried about their socio-demographic, clinical history and dietary habits three years prior to the onset of their symptoms. The intake of methyl donors was estimated with a FFQ and the MTHFR 677C>T polymorphism were determined by PCR-RFLP analysis.

Results: The poorest GC survival emerged among MTHFR 677TT carriers with low folate and vitamin B₁₂ intake. High intake of folate and vitamin B₁₂ before diagnosis decreased GC mortality risk among susceptible MTHFR 677TT carriers (MRfolate = 0.18; 95% confidence interval: 0.05, 0.67 and MRvitamin B₁₂ = 0.23; 95% confidence interval: 0.08, 0.66).

Discussion/Conclusion: Dietary methyl donor’s intake before GC diagnoses deserves attention as a preventive strategy to improve survival after treatment.
Objective: This study evaluated the dietary intake of nutrients involved in one-carbon metabolism and the genotype of \( MTHFR \ 677 \ C>T \) with respect to gastric cancer (GC) risk.

Methods: In January 2004 a population-based case-control study was carried out in Mexico City and its Metropolitan Area. A total of 248 histologically confirmed GC patients were recruited from 9 tertiary hospitals, and compared with 478 age and sex matched controls. Nutrient of interest intake was estimated with a FFQ and, the \( MTHFR \ 677 \ C>T \) genotype was determined by PCR-RFLP analysis.

Results: A protective effect for diffuse GC due to the high consumption of folate (OR = 0.23; 95% CI: 0.06–0.84), choline (OR = 0.55; 95% CI: 0.33–0.93), and vitamin \( B_6 \) (OR = 0.59; 95% CI: 0.36–0.96), was detected among \( MTHFR \ 677 \ TT \) carriers compared to \( MTHFR \ 677 \ CC+CT \) genotypes.

Discussion/Conclusion: GC prevention might require dietary recommendations according to the individual genotype; nevertheless, the available information to this respect is still very limited.
Laparoscopic right segment-colectomy for a large, sessile adenoma of the cecum: A dilemma of safety and invasiveness in 2008

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Introduction: Removal with mucosectomy of the large sessile adenomas of the cecum is a high risky intervention because of the danger of perforation. The development of the minimal invasive laparoscopic surgery in this disease bids a safe and low morbidity key of the attendance.

Results: The father of the 64 years old female died in colon cancer. Her mother had also colon cancer in her age of 62, and she died in heart disease in her age of 90. Nephrolithiasis, ESWL, and operation of the right kidney are in the patient's case history. In pursuance of her screening colonoscopy, a 3.5 cm diameter large, sessile, polypoid surfacing tumour in the cecum was revealed. Seven biopsies were taken from the lesion. The histology proved adenoma tubulovillosum with a moderate dysplasia. According to the stressful familial data, the location of the lesion, the large, sessile appearance of the tumour we decided the surgical removal. The tumour was removed with laparoscopic right segment colectomy. The final histology affirmed the preoperative investigation, but signed a dangerous cytological atypia. We did not observe any postoperative adverse events.

Discussion/Conclusion: The laparoscopic surgery in the case of large sessile polypoid tumours in the cecum bid a less risk and fast reconvalescence compared to the conventional open technics. So the indication of the mucosectomy in this type and localized tumour because of the risk of the complications is doubtful. Prospective clinical study is necessary for the aim of the restatement of the therapeutic references.
Factors predicting development of new distant intrahepatic metastases (NDIM) after radiofrequency ablation (RFA) of liver metastases

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Aim: To research on the factors influencing subsequent development of NDIM after percutaneous RFA of metastases from gastrointestinal tumors (oesophageal, gastric, colorectal, neuroendocrine, gallbladder, pancreatic).

Methods: 168 patients with 341 metastases (size 3.38 ± 1.82 cm) were treated with RFA in a 6-year period (133 patients, 276 metastases – monopolar RFA; 36 patients, 65 metastases – multipolar RFA). The achieved destruction was assessed with contrast-enhanced US/CT. Patients were followed up for 1–47 months. The influence of age, gender, tumor origin, number of lesions, size of the largest lesion, RFA type, completed tumor destruction (CD) and additional chemotherapy after RFA on the development and time to NDIM was evaluated.

Results: CD was achieved in 70.7% of the lesions. 24-month cumulative survival was 91%. The local tumor progression rate was 29%. NDIM developed in 25% of the patients and were retreated when feasible. 95% of NDIM occurred during the first 18 months. The 3-year cumulative probability of non-development of NDIM estimated by Kaplan-Meier curve was 42%. There was significant influence on development and time to NDIM of: Number of treated metastases (< 3 vs. > 3), size of the largest metastasis (< 5.0 cm vs. > 5.0 cm), CD of all lesions and additional chemotherapy. By multivariate analysis only the number of metastases and CD of all lesions were predictive for development of NDIM.

Discussion: The number of metastases before RFA is the strongest predictor for NDIM, while CD of all lesions has the strongest protective role. Multipolar RFA is preferable to monopolar one for medium-sized and large lesions. Further studies are needed to evaluate the role of adjuvant chemotherapy.
The long-term monitoring of risk of development gastric cancer after Helicobacter pylori eradication

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Aim: assessment the risk of development of gastric cancer (GC) in patients with pre-cancerous changes (PC), comparative at three and four years after Helicobacter pylori (HP) eradication.

Methods: We studied 77 patients (A group) with pre-existent PC and history of HP infection, who was eradicated four years ago (HP absence was monitoring in last four years). We use rapid urease test and serologic testing for determined HP infection. The history and duration of HP eradication was also quantified. In this comparative study, we included also 58 patients (B group) with PC and never HP infected.

Results: In A group, the incidences of the PC were: atrophic gastritis (41 cases), gastric ulcer (11 cases), gastrectomy (14 cases), gastric polypus (8 cases) and Ménétrier gastritis (3 cases). At three years after HP eradication, GC was developed in 40 patients (51.95%). All Ménétrier gastritis cases (3 cases) developed GC. Endoscopic forms of the early GC were: type I (polypoid) in 12 cases, type II (superficial) in 4 cases and type III (ulcerated) in 9 cases. In advanced GC we found type Borrmann I in 4 cases, type II in 10 cases and Borrmann IV only one case. In the fourth year of monitoring, GC was diagnosed in another 4 patients (5.2%): type I (polypoid) in only one case and type III (ulcerated) in 3 cases.
In B group, GC was developed in 9 cases at three years and in 3 cases in the fourth year.
Re-infection with HP was observed in 31 patients (70.46%) with GC and only in 7 cases (21.22%) at patients which have not developed GC. The risk of GC development, was significantly great (p < 0.01) in patients with long duration of HP eradication, but these parameters was not correlation.

Discussion/Conclusion: The risk of evolution from PC to GC was significantly great in patients with history of HP infection, comparative with never infected patients. This risk together with high frequency of HP re-infection in patients with GC, suggest one important role of HP in gastric carcinogenesis.
Early diagnosis of small hepatocellular carcinoma in cirrhotic patients using real-time elastography

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Introduction: Ultrasound (US) screening for hepatocellular carcinoma (HCC) is worthwhile because early detection is the only approach to improve outcome. By assessing tissue elasticity distribution, real-time sonoelastography may represent a reliable method for differentiating between benign and malignant lesions in this setting. Real-time sonoelastography was evaluated as a noninvasive tool for the detection of small HCC nodules in cirrhotic patients.

Methods: Thirty three cirrhotic patients with small nodules (1–3 cm) were evaluated with real-time elastography (SonoElastography mode, HITACHI EUB-6500); the mean intensity of colors red, blue, green were measured using a semi-quantitative method. Analysis of histograms for each color of the sonoelastography images was performed for quantifying the elasticity of nodule tissue comparative with cirrhotic liver tissue. In order to investigate the predictive role of sonoelastography for diagnosis of HCC, the c-statistic parameter was used. The final diagnosis of HCC was obtained by liver biopsy within the nodule, surgical pathology or at least 6 months follow-up.

Results: There were analyzed 336 sonoelastography images from 33 patients (18 men; 15 women) who underwent transabdominal ultrasound. The mean age was 57.4 ± 10.7 years; 69.7% patients were in Child-Pugh class A, 18.2% class B and 12.1% class C. The c-statistic for green color is 0.78, a cut-off value of < 129.3 being diagnostic for HCC with a specificity of 61.6%, sensitivity 84.3%, positive predictive value 82.1% and negative predictive value 90.2%. Blue color proved to be an excellent diagnostic tool for HCC (c-statistic = 0.97); for a cut-off value > 121.4, the specificity was 89%, sensitivity 95.4%, positive predictive value 94.8% and negative predictive value 90.2%. The kappa reliability test was 0.81 for concordance between blue criteria of HCC and histologic diagnosis.

Discussion/Conclusion: US real-time elastography is a promising method for screening and non-invasive diagnosis of HCC distinguishing between HCC nodules and regenerative cirrhotic macronodules.
Predictive factors for carcinogenesis in colonic adenomatous polyps

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Introduction: One of the main causes of colorectal cancer are adenomatous polyps. In our prospective study we tried to identify possible predictive factors for malignancy of colorectal polyps (CP).

Methods: We studied a batch of patients with 269 consecutive polypectomies. For these, we studied the following parameters of CP: localization, size, endoscopic aspect (pediculated/sesile, surface, bleeding), histology.

Results: From the 269 polyps included, 218 (81.04%) were adenomatous, with malignant potential, with the following histology: 129 benign (59.2%, batch B), 55 dysplastic (25.2%, batch D) and 34 malignant (15.6%, batch M). We calculated the mean value for all the studied parameters for batch B, D and M and then compared B-D-M (considering dysplasia as a transition from benign to malignant CP) and B-M, using the ANOVA and Chi2 test. From all the studied parameters, only the size of polyp of CP correlated extremely significant with the risk of malignancy (B = 12.9 ± 0.8 mm, D = 15.1 ± 2.7 mm, M = 18.9 ± 2.9 mm, for B-D-M p < 0.0001 ES and for B-M p < 0.0001 ES). The highest percent of malignancy was for villous CP (25.3%).

Discussion/Conclusion: In our study, only increased size of the polyp correlated significant (p < 0.0001) with the risk of carcinogenesis. Villous polyps have the highest percentage of malignancy. Other possible risk factors for malignancy, but less significant showed to be bleeding, multiple polyposis and irregular endoscopic appearance of the polyp surface.
Significant symptoms in the prognosis of colorectal cancer in elderly people

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³Clinical County Hospital, Timisoara, Romania

**Introduction**: Colon cancer, especially the one with rectosigmoidian location has a high incidence in elderly people, having a poor symptomatology, dominated by subocclusive symptoms, and altered bowel habits (diarrhea, constipation). The longitudinal study, carried out in the IVth Medical Clinic of the University of Medicine and Pharmacy “V. Babeș” Timișoara, during a 12 moths period, on patients over 60 years, with colorectal cancer.

**Methods**: By all 2759 patients hospitalized in the year 2007, 923 had digestive diseases. We selected 22 colon cancer patients aged between 60–80 years, with a mean age of 76 years, who underwent complete clinically and paraclinically exams (abdominal echography, anoscopy, rectoscopy, colonoscopy, irigography and hematological tests).

**Results**: By all 22 patients, 15 were men (68%) and 7 (32%) were women and they presented the following clinical symptoms: 15 by them were having subocclusive symptoms (68%), 8 rectoragi (36%), 16 constipation (72%) and 8 by them were having altered bowel habits (diarrhea, constipation) (36%). The localization of the proliferative process was: in 12 patients was rectosigmoidian (54.6%), in 6 was caecal (27.4%), in 2 patients was transverse (9%) and 2 patients with anal localization (9%).

**Discussion/Conclusion**: The most important digestive symptoms characteristic for colon cancer are: subocclusive phenomena and constipation. The early detection of colon cancer can be a key to effectively treating the disease especially because of the associate affections in the elderly.
Microsatellite instability in colorectal tumors is associated with immature phenotype of tumor-infiltrating dendritic cells

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Introduction: The microsatellite instability (MSI) pathway of molecular genetic alteration contributes to 15% of sporadic colorectal cancers (CRC). High-grade microsatellite unstable (MSI-H) colon tumors present with strong lymphocyte aggregations that have impact on the tumor progression and prognosis. The aim of the present study is to determine the relation of tumor infiltrating dendritic cell types (CD1a⁺, CD83⁺, S-100⁺) to the development of MSI tumors in CRC patients.

Methods: We investigated 50 CRC patients (34 males and 16 females) underwent MSI analysis with a set of five polymorphic markers, BAT26, D2 S123, D5 S346, D18S53335, and F6A. Genomic DNA was obtained from paraffin-embedded tumor tissue. Immunohistochemistry was performed on sections from the same samples with antibodies against dendritic cell (DC) markers (CD1a, CD83, S-100 protein) and against TGF-beta 1 and IL-10.

Results: MSI analysis of tumor samples revealed MSI phenotype in 12 patients and MSS phenotype n 38 patients. MSI tumors have predominantly aright-sided location (p = 0.048). MSI was associated with increased number of CD1a⁺ (immature) DCs in the tumor stroma and the invasive margin (p = 0.01, p = 0.042, respectively). S-100⁺ and CD83⁺ (mature) DCs were more in the stroma of MSS tumors. The majority of MSI tumors showed low TGF-beta1 expression in tumor glands, while MSS tumors demonstrated more often higher TGF-beta1 expression. The high level of IL-10 expression in the inflammatory cells correlated with the MSI status.

Discussion/Conclusion: In MSI patients tumor-infiltrating DCs were mainly with immature phenotype and probably their maturation is suppressed by high IL-10 expression.
Bleeding Meckel's diverticulum – Diagnostic challenge

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Introduction: Meckel's diverticulum is the most common congenital malformation of gastrointestinal tract, occurring in 2% of population. The most common complications is haemorrhage. The diagnostic challenge is especially true because the clinical symptoms and imaging features of a complicated Meckel’s diverticulum overlap with those of many other disorders that cause obscure gastrointestinal bleeding.

Methods: We report two cases, both males, presenting as a gross gastrointestinal haemorrhage (melaena) with no history of previous peptic ulcer disease or provocating factors. Initially, performing standard procedures in this conditions (upper and lower endoscopy), the source of GI bleeding hadn't been found. The investigation had been continued using other radiologic and radionuclide imaging methods (standard and CT angiography of abdomen, enteroclysis, Tc-99m scintigraphy) with no diagnostic success.

Results: Finally, in first case, diagnosis was established by capsule endoscopy, visualising diverticulum on the antimesenteric border of ileum, with consistent bleeding and ulceration. In the second case, after active bleeding being located by endoscopic capsula, second-look colonoscopy with ileoscopy, confirmed diverticulum. Both patients were transmitted to Abdominal Surgery Department and diverticula were operatively removed. Intraoperative finding, concerning position, morphology, and type of diverticulum completely coexists with our findings. Furthermore, pathohistologic finding of ectopic gastric mucosa in removed diverticulum confirms diagnosis of Meckel’s diverticulum.

Discussion/Conclusion: We point out the importance of endoscopic capsula in diagnosis of Meckel's diverticulum and also important roll of second look colonoscopy. Scintigraphy as a golden standard might be replaced with endoscopic capsula in all cases of clinical suspicion of Meckel's diverticulum as a source of obscure gastrointestinal bleeding.
Dietary intake of polyphenols, nitrate and nitrite and gastric cancer risk

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Introduction: N-nitroso compounds (NOC) are potent animal carcinogens and potential human carcinogens. The primary source of exposure for most individuals is endogenous formation, a process that can be inhibited by dietary polyphenols.

Methods: To estimate the risk of gastric cancer (GC) in relation to the individual and joint consumption of polyphenols and NOC precursors (nitrate and nitrite), a population based case-control was carried out in Mexico City from 2004 to 2005 including 257 histologically confirmed GC cases and 478 controls. Intake of polyphenols, nitrate and nitrite were estimated using a food-frequency questionnaire.

Results: High intakes of cinnamic acids, secoisolariciresinol, and coumestrol were associated with an approximately 50% reduction in GC risk. A high intake of total nitrite, as well as nitrate and nitrite from animal sources doubled the GC risk. Odds ratios around two-fold were observed among individuals with both low intake of cinnamic acid, secoisolariciresinol or coumestrol and high intake of animal nitrate or nitrite, compared with high intake of the polyphenols and low animal nitrate or nitrite intake respectively. Results were similar for both the intestinal and diffuse histological types of GC.

Discussion/Conclusion: Our results show, for the first time, a protective effect for GC due to higher intake of cinnamic acids, secoisolariciresinol and coumestrol and suggest that these polyphenols reduce GC risk through inhibition of endogenous nitrosation. Further evaluation of these dietary patterns in relation to GC risk is warranted.
Effects of flavonoid treatment on recurrence risk in patients with colorectal neoplasia

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Introduction: Patients with resected colon cancer and after polypectomy have a substantial risk of recurrence of neoplasia (colon cancer and/or colon adenomas). In these patients there is an urgent need of protective measures (secondary prevention) to reduce the risk of recurrence but only few effective and validated studies exist. Besides methods of chemoprevention biological measures such as nutritional supplements have been suggested for use since it is known, that components of fruits and vegetables have a preventive potency against neoplastic growth.

Methods: Thirty six patients with resected colon cancer and 51 patients after polypectomy were divided into 2 groups: One group was treated with a flavonoid mixture (n = 31) and compared with a matched control group (n = 56). Both groups were observed for 2–4 years by surveillance colonoscopy and by questionnaire. The flavonoid mixture was taken daily as tablets which consisted of tea flavonoids with a daily standard dose of 20 mg apigenin and 20 mg epigallocatechin-gallate per day.

Results: Of 87 patients enrolled in this study 36 had resected colon cancer and surveillance colonoscopy was performed in 29 of these patients. In the treated patients with resected colon cancer who had a complete follow-up (n = 14) there was no cancer recurrence and one adenoma (tubular adenoma) developed. The cancer recurrence rate of the matched untreated controls was 20% (3 of 15) and adenomas evolved in 4 patients (27%). The combined recurrence rate for neoplasia was 7% in the treated patients and 47% in the controls (p = 0.027).

Discussion/Conclusion: Sustained long-terms treatment with a flavonoid mixture seems to be capable of reducing the recurrence rate of colon neoplasia in patients with resected colon cancer.
A retrospective study was performed on gastric carcinomas to establish the prevalence of *Helicobacter pylori* infection in gastric epithelium adjacent to the tumor. A total of 65 carcinomas were studied. The overall prevalence of *Helicobacter pylori* infection was 59%. The prevalence in different age cohorts from patients with gastric carcinoma was compared with that in patients suffering from non-ulcer dyspepsia and, based on serological testing, with that in healthy blood donors. The presence of *Helicobacter pylori* in cancer patients aged 41–50 and 51–60 was significantly higher than in blood donors. No difference was seen in comparison with non-ulcer dyspepsia patients. The presence of *Helicobacter pylori* showed an inverse correlation with the extent of intestinal metaplasia. The intestinal type of carcinoma was associated with a higher bacterial load than the diffuse type. These data suggest that the presence of *Helicobacter pylori* in gastric mucosa could play a role in the pathogenesis of gastric carcinoma, especially in the younger age group.
Helicobacter pylori infection and gastric cancer precursor lesions in patients with dyspepsia

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Introduction: Helicobacter pylori infection has been considered to play significant role in gastric carcinogenesis, but only a minority of people who harbour this organism will develop gastric cancer. H. pylori infection first causes chronic non atrophic gastritis. Chronic non atrophic gastritis may evolve to atrophic gastritis and intestinal metaplasia and finally to dysplasia and adenocarcinoma.

Aim: To estimate the prevalence of H. pylori infection and the precancerous gastric lesions and their relationship, in patients with dyspeptic symptoms who underwent upper gastrointestinal endoscopy at a reference center in the South-eastern region in Bulgaria.

Methods: We analyzed gastric biopsies taken from corpus and antrum of patients who underwent upper gastrointestinal endoscopy for H. pylori detection, between 1994 and 2007. Chronic non-atrophic gastritis, atrophic gastritis and intestinal metaplasia were diagnosed by histological examination (H-E stain). The histological diagnoses were related to H. pylori infection status.

Results: Biopsies from 1019 patients were included in the study. Patients mean age was 52 (+/-15) and 59% were female. Seventy six percent had H. pylori infection. Normal mucosa, chronic non atrophic gastritis, atrophic gastritis and intestinal metaplasia were diagnosed in 5%, 77%, 3% and 15%, respectively. The OR for any degree of gastric mucosa lesion in infected patients was 10 (95% CI: 6.50–17%). The OR for infected patients had chronic non atrophic gastritis was 3 (95% CI: 2.2–3.4). The OR for infected patients had atrophic gastritis or intestinal metaplasia was less than 1.

Discussion/Conclusion: The prevalence of H. pylori infection in this population was high (76%) and infected individuals had the probability 10 folds greater than non infected individuals to have any lesion of gastric mucosa. The prevalence of precancerous lesions was 77% for non atrophic chronic gastritis, 3% for atrophic gastritis and 15% for intestinal metaplasia. Infected patients had risk 3 folds greater than non-infected for the occurrence of non atrophic chronic gastritis. H. pylori infection did not show risk for occurrence of atrophic gastritis and intestinal metaplasia, suggesting that other risk factors should be involved in the carcinogenesis process.
Does first and following ulcer hemorrhage differ?

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Introduction: Major risk factors for peptic ulcer bleeding (PUB) are underreported in respect of the history of bleeding.

Methods: We studied prospectively untreated for H. pylori patients with PUB episode. Totally, 167 patients (M/F = 1.43), mean aged 59.8 (SD 15.52) years were enrolled at emergency endoscopy unit of specialized center. The cohort was divided according to history for previous bleeding episode into two groups – “debutants” (with first peptic bleed) and “relapsers” (with second or following episode). After injection hemostasis we collect corpal and antral biopsies for RUT, culture and histology tests. The patient was labeled “positive” if any test for H. pylori was positive or “negative” if all tests were negative. Fisher’s exact test and significance at 0.05 (SPSS 12.0.1) was used.

Results: H. pylori-positive were 151 patients (90%), 84% by culture, 84.8% by RUT and 89.7% by histology. NSAID usage reported 76 patients (45.5%). 46 patients (27.5%) were “relapsers” (mean aged 57.5 SD 16.25; M/F = 1.24). H. pylori-positive were 41/46 of “relapsers” and 110/121 of “debutants” (89.1% vs. 90.1%, p > 0.7). The rate of smoking, multiple ulcers, stomach ulcers and Forrest grades were similar. However, 7/46 from “relapsers” and 69/121 from “debutants” used NSAID (15.2% vs. 57%, p < 0.001).

Discussion/Conclusion: Patients with history of bleeding used far less NSAID than at the first episode. NSAID usage could be reported in respect of bleeding history to reveal the contribution of this factor.
Forming a registry and applying endoscopic ultrasound (EUS) for screening and prevention of pancreatic cancer

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Introduction: The aims of the present study include identifying and assessing the risk factors for pancreatic cancer (PCA) among first-degree relatives (FDRs) of PCA patients, and assessment of EUS to screen for early PCA.

Methods: A regional registry of PCA patients and their FDRs was compiled. 110 consenting PCA patients and 420 of their FDRs were enrolled. Consenting FDRs attended informative lectures, and completed forms assessing risk factors. Data was collated on ethnic origin, presence of any previous or current diseases, BMI, tobacco use, alcohol consumption, dietary habits, and presence of any symptoms typical for PCA. Endoscopic ultrasound (EUS) examination was offered, without cost, for PCA screening.

Results: More than one case of PCA was found in 4.5% of the 110 families. 52% of the FDRs were Ashkenazi Jews. Diabetes was found to be higher in kindreds than the average local age-corrected prevalence (13.6% versus 11.2%, p < 0.01); no chronic pancreatitis was reported. 8.8% of the kindred suffer from symptoms or diseases that may mimic pancreatic cancer symptoms (for example peptic disease.) Excessive BMI was found in 76.5% of FDRs. Tobacco use was reported by 15.5%. The reported level of drinking alcohol was minimal and probably irrelevant. The average diet of the FDRs included 13 portions of fruits a week. EUS for screening was performed in 15 asymptomatic FDRs. One 54 yo male was thus found to have carcinoma of the ampulla of vater which was curatively removed surgically, the other 14 had normal exams.

Discussion/Conclusion: Acceptable and effective PCA screening and risk reduction interventions are needed, particularly for FDRs. No screening test to detect early curable PCA has as yet been proven acceptable effective and accurate, but EUS appears promising for this purpose. Extended registries of FDRs for long-term follow-up including of various screening interventions appears justified.
Clinical and prognostic signification of immunohistochemical expression of the cyclooxygenase-2 (COX-2) in gastric cancer

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Introduction: The mechanisms by which COX-2 contributes to the carcinogenesis are not known until present. It seems that the COX-2 enzyme stimulates the cell proliferation, inhibits the apoptosis, increases the malignant cells' invasiveness and induces the angiogenesis by elaborating some angiogenic factors.

Methods: In the present study we intend to evaluate the immunohistochemical expression of COX-2 in gastric carcinomas, keeping track of the correlations between the clinicopathologic factors, the tumor angiogenesis (evaluated by microvascular density [MVD] determination and by VEGF expression) and the patients' survival. Also, we have tracked the immunoreactions' positivation in the peritumoral mucosa with various lesions, with the purpose to establish the contribution of COX-2 to the gastric carcinogenesis during the pre-invasive stages. A prospective study was realized, regarding the evolution and aggressiveness of the gastric cancer, with a duration of 5 years, 61 patients operated of gastric cancer being included.

Results: The COX-2 immunoreactions have been significantly more frequent noticed in the gastric carcinomas included in the study (57.4\%) and in the epithelial dysplasia areas adjacent to the carcinomas of intestinal type (35.5\% of the cases), than in the normal peritumoral mucosa (4.9\%) (p < 0.001 ES). The COX-2 immunoreactions have turned positive more frequently in gastric carcinomas of intestinal type (68.4\%), in comparison to the carcinomas of diffuse type (29.4\%) (p < 0.001 ES). The COX-2 expression is significantly correlated with the invasion level, the presence of the metastases in the regional lymph nodes and the pTNM stage, but without influencing the prognosis of the gastric cancer patients. The negative VEGF carcinomas have turned positive for COX-2 only for 19\% of the cases. Different from those, the positive VEGF carcinomas have associated COX-2 immunoreactivity in 77.5\% of the cases.

Discussion/Conclusion: The results obtained are suggestive for the predominant expression of COX-2 in the carcinomas of intestinal type and its precursory lesions. Our results show a tight correlation between the immunohistochemical expressions of COX-2 and VEGF in gastric carcinomas (r = 0.562, p < 0.001 ES) and also a MVD average value significantly higher in the positive COX-2 carcinomas, suggesting an intense angiogenesis activity in that group of tumors (p < 0.001 ES).
Intrahepatic lymphocytes and dendritic cells in metastatic gastrointestinal cancer patients

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Introduction: The liver is a major site of metastases for carcinomas from the gastrointestinal tract. The interaction between the antigen-presenting dendritic cells (DC) and lymphocytes (NK, NKT, and T cells) is critical for creation of an effective anti-tumor response. The present study addresses the characterization of DC and lymphocytes in metastatic liver tumors.

Methods: 90 patients with gastrointestinal cancers (74 with and 16 without liver metastases) were investigated. Fresh liver samples were obtained after surgical resection of metastatic or liver tissue for diagnostic or curative purpose. Phenotype characterization of intrahepatic lymphocytes (IHL) and DC was performed using flow cytometry on intrahepatic mononuclear cells and their localization in metastatic liver tissue were examined immunohistochemically using seven markers (S-100 protein, HLA-DR, CD1a, CD83, CD4, CD8, CD56).

Results: Flow cytometry revealed a dominance of CD8⁺ lymphocytes with a lower number of CD4⁺ lymphocytes in metastatic and non-metastatic liver. We found a significantly lower proportions of CD3⁺CD56⁺ and CD3⁻CD56⁺ subsets in metastatic liver compared to non-metastatic liver (11.9 ± 10.3 vs. 24.4 ± 13.6%, p = 0.02; 10.1 ± 11.6% vs. 16.6 ± 8.9%, p = 0.039, respectively). In contrast, the percentage of CD83⁺ DC IHL in metastatic liver was significantly increased in comparison to metastasis free liver (11.5 ± 15.2 vs. 2.5 ± 1.7%, p = 0.029). The peritumoral as well as the intratumoral inflammatory infiltrate consisted mainly in CD4⁺ and CD8⁺ cells and less of CD56⁺ cells (NK and NKT). CD1a⁺ and CD83⁺ DCs were observed predominantly in small groups or as single cells in the tumor stroma and in the invasive margin. S-100⁺ and HLA-DR⁺ DC were more in number and dispersed diffusely.

Discussion/Conclusion: The increased liver DCs number reflects the activation of the local immunological mechanisms. The down regulation of CD56⁺ lymphocytes in liver around metastases might be responsible for their development.
Risk factors at patients with colorectal cancer

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Introduction: Colorectal cancer (CRC) is the most frequent cancer in Europe and had become a real challenge to health in all developed countries. We tried the study of risk factors at patients with (CRC) from Timis county.

Methods: The authors have studied retrospectively a group of 32 patients diagnosed with colorectal cancer. The positive diagnosis was based on clinical elements (abdominal pain, diarrhea with bleeding, losing weight, fatigue, alternating constipation with diarrhea, bleeding with defecation, tenesmus etc.), biological elements (WBC, RBC, ESR, CRP, CEA, hemoglobin, hematocrit, stool culture etc.) and results of rectoscopy, sigmoidoscopy, ileocolonoscopy completed with anatomicopathological examination of the biopsy fragment. The alimentation particularities and associated pathology were recording in individual folder.

Results: 12 patients (37.50%) had in personal antecedents ulcerative colitis, 5 patients (15.62%) had Crohn’s disease and 4 patients (12.50%) with adenomatous polyps; 30 patients (93.75%) had a diet mostly from pig meat, 29 patients (90.62%) a diet high in animal fat; 26 patients (81.25%) were smokers for over 20 years, 25 patients (78.12%) were alcohol consumers; 24 patients (75%) presented physical inactivity, 16 patients (50%) had obesity and 10 patients (31.25%) were diagnosed with diabetes mellitus; 50% presented constipation in personal history; 25% of cases presented family history of CRC. We mention that in our geographic area very much processed pig meat, animal saturated fats and refined carbohydrates are consumed.

Discussion/Conclusion: The study of risk factors for CRC allows the application of prophylaxis measures and delimitation of population groups of risk for this disease.
Possible role of mycotoxin Fumonisin B1 in the colon malignancy

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Introduction: Mycotoxin Fumonisin B1 (FB1, produced by fungi Fusarium moniliforme and F. proliferatum) contaminates corn and corn-related products. Exposure of people to FB1 is higher than it is seemingly. In vitro FB1 accelerates the growth of transformed cells. We found that FB1 inhibited the DNA synthesis in normal lymphocytes and created the immune deficiency in vivo. Now we discuss the FB1 effects on colon ecosystem including microorganisms and immune cells and its values for colon malignancy.

Methods: Lactobacillus casei, Escherichia coli, and Candida tropicalis were incubated with Fumonisin B1 [1 mM–20 mM]. L. casei were fed to mice C57Bl/6 in the doses 10⁶–10¹² CFU. On the 4th day lymphocytes from appendix, lymph nodes, Peyer’s patches, and colon wall were isolated and stained with antibodies and propidium iodide.

Results: IN VITRO, FB1 inhibits the growth of C. tropicalis during 2 h but increases their growth after 24 h. E. coli growth after FB1 exposure has the same kinetics. Growth of L. casei was inhibited by high doses FB1 (> 10 mM). Incubation of FB1-treated L. casei with E. coli results in inhibition of E. coli growth. FB1 changes the sensitivity of E. coli to antibiotics. L. casei lost their probiotic activity after FB1 exposure.

IN VIVO, administration of FB1-treated L. casei to mice C57Bl/6 results in the strong inhibition of B-lymphocyte proliferation into appendix, Peyer’s patches and colon wall. Number of CD4⁺CD25⁺ regulatory T-cells increased. B-cells undergo an apoptosis 2 h after additional exposure to 0.5 mM FB1 in vitro.

Conclusion: FB1 effects (inhibition of DNA synthesis in normal lymphocytes, impaired B-cell function in colon, increased number of regulatory T-cells, and mitogenic effect on transformed cell growth) may have some values for colon malignancy.
Efficacy and safety of ofloxacin, azithromycin, omeprazole, and bismuth compared with clarithromycin, amoxicillin, omeprazole, and bismuth as second line therapy in patients with H. pylori infection: A randomized controlled clinical trial

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Background: To increase H. pylori eradication rate without increasing bacterial resistance, various regimens have been recommended. Commonly the association of at least two antibiotics with a proton pump inhibitor is used. The treatment regimens for second line therapy, suggested in studies from the western world may not be ideal in Iran. In this study we evaluated the safety and efficacy of a new quadruple therapy regimen and compared it with the standard second line treatment for H. pylori eradication.

Patients and methods: We selected 220 H. pylori-positive patients, with a clear indication of eradication therapy, who did not respond to a 2 weeks treatment with metronidazole, amoxicillin, omeprazole, and bismuth. They were randomized into two groups. Group A (n = 110) were treated with azithromycin, ofloxacin, bismuth, and omeprazole (AzOBO) and group B (n = 110) with amoxicillin, clarithromycin, bismuth, and omeprazole (ACBO) for two weeks. Four weeks after the end of treatment, Urea Breath Test was performed for all subjects to confirm eradication.

Results: In intention to treat analysis, the rate of H. pylori eradication in groups A and B was 77.2% and 64.5% respectively (p = 0.038). In per-protocol analysis, the rate of H. pylori eradication in groups A and B was 86.7% and 74.7% respectively (p = 0.034). The incidence of poor compliance was lower, although not significantly so, in group A than group B (3.5% versus 4.3%). No major adverse events occurred in both groups.

Conclusion: Two weeks of treatment with ofloxacin, azithromycin, omeprazole, and bismuth is an effective and safe regimen for H. pylori eradication as second line therapy.

Keywords: azithromycin, ofloxacin, Helicobacter pylori
GERD, Barrett, cancer – Importance of endoscopic follow-up and laparoscopic esophagectomy as the surgical management of early cancer (Case report)

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Case report: We present a case of a 59-year-old male with 20 year history of gastroesophageal reflux symptoms. GERD was diagnosed in 1999 and the patient received medical treatment and follow-up during this time. Scheduled upper endoscopy revealed Barrett-like supracardial lesion and biopsy verified adenocarcinoma. Staging examinations detected stage T₁₋₂N₀₋₁ clinical tumor stage. We performed laparoscopic (HALS) transhiatal esophagectomy, regional lymphadenectomy with gastric substitution and collar esophagogastric anastomosis. Pyloromyotomy and catheter-jejunostomy were done as well. Operative time was 244 minutes. There were no postoperative complications, Peritrast swallow study presented normal postoperative status and patient was discharged on 10th postoperative day with satisfactory swallowing. Histological findings confirmed T₁N₀ stage.

Conclusion: Long-term GERD is a precancerous state and should be under gastro-enterological follow-up. Barrett-esophagus is an indication for surgery (cancer prevention). We demonstrated that early esophageal tumors can be operated on laparoscopically, which is a new method in esophageal surgery.
Screening for colorectal cancer with guaiac-based fecal occult blood test (gFOBT) in Romania

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Introduction: FOBT detects a high proportion of less advanced colorectal cancers (CRC) in asymptomatic patients. We aimed to assess the effectiveness of gFOBT screening on CRC detection in Romania.

Methods: We used Hemoccult II to assess the presence of occult blood in stools. This was a part of a national program for CRC prevention and the free administration of gFOBT, together with basic information about CRC, was advertised in local media. Patients with positive gFOBT were referred to colonoscopy, and so were those with negative results but who asked themselves for the procedure.

Results: 930 asymptomatic subjects provided stool specimens on FOBT cards. 101 had positive results (10.08%) and 89 of them underwent colonoscopy (12 refused). The findings at colonoscopy were: CRC 18 patients (20.22%) and colonic polyps 36 patients (40.44%). The rest had: ulcerative colitis (4 patients), haemorrhoids (42 patients), gastric cancer and erosive gastritis (1 patient each). 34 patients with negative gFOBT underwent colonoscopy and 2 of them had adenocarcinoma (5.88%) and 6 (17.64) had polyps. The sensitivity, specificity, PPV and NPV were as follows: for CRC: 83.3%, 39.02%, 16.6% and 94.1% respectively, and for colorectal polyps: 77.7%, 41.7%, 35% and 82.3% respectively.

Discussion/Conclusion: Our findings suggest that consideration should be given to a national program of FOBT screening in order to detect the early cases of CRC or colonic polyps. Unfortunately the population compliance to this kind of programs is still low in Romania.
Long-term use of statins and risk of colorectal cancer: A population-based study

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Introduction: We conducted a population-based cohort study to determine the risk of colorectal cancer (CRC) among long-term users of statins.

Methods: The cohort of individuals, dispensed statins regularly was identified from the Manitoba’s population-based prescription drug data base and was followed-up to diagnosis of CRC in the provincial cancer registry, migration out-of province, death or December 2005. The incidence of CRC in this group was compared to that among those individuals in the provincial population, who had never used statins, by Poisson regression analysis. Stratified analysis was performed to determine the risk after five years of regular statin use. The potential confounding factors evaluated included age, gender, history of diabetes, IBD, coronary heart disease, lower gastrointestinal endoscopy, resective colorectal surgery, use of NSAIDs, hormone replacement therapy (among women) and median household income. The dose effect was evaluated in DDD units.

Results: There were 35,739 individuals who were dispensed statins regularly. The 10,287 (5,069 males; 5,218 females; mean age 63.6 years) regular long-term (> 5 years) users were followed-up for up to five additional years. In multivariate analysis, the ratio of incidence rate of CRC among those dispensed statins regularly to those who were never dispensed statins was 1.13 (95% CI: 1.02–1.25). The incidence rate ratio of CRC among the regular long-term users, after five years of use, to those who were never dispensed statins was 1.06 (95% CI: 0.84–1.33). There was no dose effect.

Discussion/Conclusion: These findings suggest that long-term use of statins for the current clinical indications does not protect against colorectal cancer risk.
Will the use of antibiotics before or after the meals and the blood group of the patients influence the success of Helicobacter pylori eradication?

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Introduction: Several factors are said to affect the success of Helicobacter pylori (HP) eradication. Many patients may not tolerate these antibiotics. In this study, among the factors of potential influence, we have concentrated on ingesting the medications before/after the meals, the blood group of the patient and his/her smoking habits together with medication side effects that affect patient compliance.

Methods: 245 patients having HP infection with a mean age of 43.3 ± 10.9 (13–70 years) years were included in the study. Each patient underwent a gastroscopy during which two biopsy samples were obtained from the antrum and two from the corpus, and existence of histopathologically was examined. Treatment for eradication consisted of administering Lansoprazol 2 x 30 mgr/day before meals + Amoxicillin 2 x 1000 mgr/day + Clarithromycin 2 x 500 mgr/day for 14 days. 143 patients received the antibiotics before the meals. 102 patients received the antibiotics after the meals and Lansoprazol before the meals. Similarly, control gastroscopy was performed three months after. Treatment was regarded as successful if HP was negative in all biopsy samples.

Results: The rate of eradication was found to be 67.8% for those using the medication before meals and 74.5% after the meals (p > 0.05). The overall frequency of side effects was 23.3% (25.2% before meals; 20.6% after the meals (p > 0.05). Eradication was 72.5% in smokers while being 70.1% in non-smokers (p > 0.05). The distribution of blood groups in the study population was: O group 31%, A 39.6%, B 20% and AB % 9.4. This distribution was not different than the overall distribution in Turkey (p > 0.05). The rate of eradication was 75% for group O, 72.2% for group A, 63.3% for B and 65.2% for AB (p > 0.05). The age of the patients who had eradication (42.9 ± 10.5), was not different than those in whom eradication could not be realized (44.2 ± 11.7) (p > 0.05).

Discussion/Conclusion: Using the antibiotics before or after the meals does not affect the success of HP eradication or patient compliance. Thus the choice of how to use the antibiotics might be left to the individual patient. The HP infection and eradication rates are not different among different blood groups. Smoking and patient age do not influence HP eradication results.
Immunohistochemical testing for Helicobacter pylori existence in neoplasms of the colon

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Introduction: Helicobacter pylori is a common pathogen, and prevalence varies with socioeconomic conditions (10–80%). It has recently been recognized as a class I carcinogen in relation to gastric cancer. The aim of this study was to investigate the presence of H. pylori in neoplasms of the colon by immunohistochemical methods.

Methods: The polypectomy materials of 51 patients (19 male and 32 female) who had undergone colonoscopic polypectomy in our endoscopy unit in 2007 were retrieved for retrospective examination. The endoscopic size and colonic localization of the polyps were recorded. Hematoxylin and Eosin stains were evaluated according to histological type and grade of dysplasia. Biopsy stains were immunohistochemically treated with H. pylori antibodies by the streptavidine-biotin immunoperoxidase technique. H. pylori staining in the gastric mucosa was used as the control for the immunohistochemical method. Immunohistochemical stains were tested for the presence of H. pylori under an optical microscope, and specimens that were positive for H. pylori were stratified according to the respective staining pattern.

Results: Mean age was 61.88 ± 10.62 (40–82) years. Polyp sizes were 1.45 ± 0.92 (1–4) cm; and 25.5% of polyps were localized in the ascending, 68.6% in the descending, and 5.9% in the transverse colon. H. pylori positivity or negativity was not correlated with polyp localization (p > 0.05) or size (p > 0.05).

The distribution of histopathologic types was 76.5% tubular, 9.8% villous, 5.9% tubulovillous, and 7.8% adenocarcinoma. We determined low grade dysplasia in 38 (97.4%) and high grade dysplasia in 1 (2.6%) of the 39 tubular polyps; low grade dysplasia in 1 (20%) and high grade dysplasia in 4 (80%) of the 5 villous polyps; and low grade dysplasia in 3 (100%) of the 3 tubulovillous polyps.

Eleven (21.6%) of all specimens included in the study were H. pylori-positive by immunohistochemical methods. Of the H. pylori-positive specimens, the staining pattern was diffused: Equivocal in 10 (90.9%), nonspecific with a finely granular type concentrated on the luminal surface in 10 (90.9%), dot-like granular in 6 (54.5%), and spiral in 1 (9.1%). Of the tubular polyps, 17.9% (7/39) were H. pylori-positive, and the staining pattern was equivocal in 7 (100%), luminal in 6 (85.7%), and dot-like granular in 4 (57.1%). Of the villous polyps, 60% (3/5) were H. pylori positive, and the staining pattern was inconclusive in 2 (66.7%), luminal in 3 (100%), dot-like granular in 1 (33.3%), and spiral in 1 (33.3%). Of the cancerous cases, 25% (1/4) were H. pylori positive and showed an equivocal, luminal, and dot-like granular staining pattern. No significant correlation was determined between histologic types and prevalence of H. pylori (p > 0.05).
Discussion/Conclusion: We could not show any correlation between the presence of H. pylori in polyps of the colon and polyp size, colonic localization or histopathologic type. We were able to determine H. pylori in colon polyps by immunohistochemical methods, albeit with no statistical significance. The higher rate of positivity for H. pylori in villous polyps does not present a causal relationship. This type of laboratory trial needs to include a greater number of specimens and be supported by molecular biology techniques.
Expression of transforming growth factor-beta1 and its receptors in colorectal polyps

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Introduction: Transforming growth factor-beta1 is thought to be involved in tumorigenesis, however, it may play a biphasic role to protect against early neoplasmatic transformation, and to promote those neoplasmatic growth that to develop.

Methods: In the present study we investigate the expression of TGF-beta1 and its three receptors (TGF-BR I, II, III) in colorectal polyps. The biopsy samples from various polyps were obtained during colonoscopies. The expression of genes encoding TGF-beta1 and TGF-BR I, II, II was quantitatively assessed by QRT-PCR reaction using TaqMan in tubular (n = 13), villosum (n = 13), hyperplastic (n = 15), and adjacent normal colonic tissues.

Results: We found significantly higher genes expression for TGF-beta1 in tubular adenomas (1032229 number copies mRNA/\(\mu\)g total RNA ± 293926 SE, \(p < 0.005\)) as well as in villosum adenomas (615749 ± 115712, \(p < 0.005\)) as compared with normal colonic tissue (250069 ± 50291). However genes expression for TGF-beta1 in hyperplastic polyps (415336 ± 1039720) was not significantly different than in normal controls. Similarly, the genes expression encoding TGF-BR II was significantly increased in villosum adenomas (4737184 ± 2678872, \(p < 0.05\)) as well as in tubular adenomas (3395193 ± 721674, \(p < 0.05\)) but not in hyperplastic polyps (1395253 ± 238109) as compared with controls (1082108 ± 217352). We not observed statistically significant differences in expression of genes for TGF-BR I, and for genes encoding TGF-BR III in adenomas polyps and hyperplastic polyps as compared with normal colonic tissues.

Discussion/Conclusion: Changes in genes expression for TGF-beta1 and its II receptor in adenomas suggest that TGF-beta1 is involved in early stages of controlling in vivo colorectal tumorigenesis.
The prevalence of Helicobacter infection in precancerous gastric disorders

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Introduction: The most common precancerous gastric disorder like chronic simple atrophic gastritis or associated with intestinal metaplasia, hypertrophic gastritis with long term infection with Helicobacter pylori (HP) may induce dysplasic alterations which correlated with other risk factors may induce major gastric proliferative damage. Our purpose was to investigate the prevalence of HP infection in the patients with precancerous gastric disorders.

Methods: From January 2007 to January 2008, we selected 692 patients (53%) who presented precancerous gastric disorders of the total of 1303 upper endoscopies carried out in Medical Clinic CF Timisoara in this period. The age of the patients was between 20–85 years, with a mean age of 53 year. The gender ratio of the patients was: 220 women (32%) and 472 men (68%).

Results: The patients with precancerous gastric disorders were divided in three groups: 398 patients with simple chronic atrophic gastritis (57%), 198 patients with chronic atrophic gastritis associated with intestinal metaplasia (28%) and 96 patients with chronic hypertrophic gastritis (13%). The prevalence of HP infection in the study groups was: 240 patients in the first group (60%), 105 patients in the second group (53%) and 48 patients in the third group (50%).

Discussion/Conclusion: The patients with chronic gastritis tested positive for HP should be closely monitorised and treated for preventing the development of gastric cancers.
The correlation between tumor angiogenesis, clinicomorphological factors and survival of the patients with gastric cancer

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Introduction: To evaluate the relationship between microvessel density (MVD), VEGF expression, clinicopathological factors and survival of the patients with gastric cancer.

Methods: We performed a prospective study regarding the outcome and aggressiveness of gastric carcinoma on a five year period, including 61 patients (43 men, 18 women), mean age 59.34 years. For the immunohistochemical assessment of tumor angiogenesis, we used the monoclonal antibodies anti-CD34 and anti-human VEGF by LSAB technique. Angiogenesis was quantified by measuring MVD. Immunohistochemical expression of VEGF was assessed by using a score representing the sum between the percentage of positive cells and the intensity of the staining.

Results: MVD in gastric carcinomas ranged between 12 and 65, with a mean value of 38.7 ± 24.3, significantly increased in comparison with normal mucosa (12.5 ± 9.8, p < 0.001 ES). Increased MVD correlated with diffuse type of gastric cancer, poor differentiation, presence of vascular invasion and advanced TNM stage. For patients with MVD > 38 (34 cases – 55.7%), the 5-year survival rate was significantly decreased in comparison with patients with MVD < 38 (7.4 % vs. 23.5 %). We obtained positive immunostaining for VEGF in 40 cases of gastric carcinomas (65.6%), significantly more frequent than gastric normal mucosa (6.5%, p < 0.0001 ES). For gastric carcinomas with VEGF +++, the overall 5-year survival rate was 12.5%, significantly decreased than for patients with VEGF negative carcinomas (23.8%).

Discussion/Conclusion: Our study demonstrates a strong correlation between VEGF expression and MVD, these two markers of neoangiogenesis playing an important role for the biological behavior, progression and prognosis of gastric carcinoma.
The incidence rates of the gastric cancer and prevalence of Helicobacter pylori in population of Eastern Siberia

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Introduction: Our aim was to compare interconnection of Helicobacter pylori (HP) prevalence, atrophic gastritis and gastric cancer incidence rates in various ethnic groups of the Eastern Siberia population.

Methods: We carried out large scale epidemiological research of adult persons in Tyva, Khakassia and Evenkia. Esophagofibregastroduodenoscopy and HP definition (by serological, morphological and urease methods) were executed in 3494 patients (1365 Mongoloids, 2129 Europoids). IgG CagA was diagnosed by ELISA in blood serum in 533 Khakases, 493 Evenks, 316 Tyvins and in 1352 Europoids. Morphological research included light microscopy of biopsy specimens from three gastric sites after staining by hematoxylin and eosine with the description of results using a visual analog scale (Dixon M.F. et al, 1996) and was carried out in 128 Khakases, 125 Evenks, 132 Tyvins and 374 Europoids. Data studying on gastric cancer incidence rates using Medline system since 1996 till 2007 was done.

Results: Stomach cancer incidence rates was 22 per 100,000 in Evenks, 25 in Khakases, 50 in Tyvins, and 35 in Europoids. Prevalence of HP had no differences in studied populations and deviated about 90%. Prevalence of CagA HP was 44.0% in Evenks, 36.4% in Khakases, 60.0% in Tyvins, 59.8% in Europoids (p1–3 < 0.001; p2–3 < 0.001). Prevalence of antral atrophic gastritis was 4.8% in Evenkia Mongoloids, 6.3% in Khakassia, 14.4% in Tyva, 15.6% in Europoids (p1–3 < 0.05; p2–3 < 0.05).

Discussion/Conclusion: The highest frequency of atrophic gastritis and gastric cancer was recorded in Tyva Mongoloids and Europoids, among which parameters of CagA HP detectability were maximal among studied populations.
Plasma transforming growth factor-beta1 level in patients with inflammatory bowel disease

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Introduction: Transforming growth factor-betas (TGF-betas) belong to a family of multifunctional polypeptides produced by lymphoid and non-lymphoid cells. They have five different isoforms. The demonstration of enhanced expression of TGF-beta1 in human colonic mucosa of ulcerative colitis (UC) patients might indicate a role of this molecule in the pathogenesis of the disease. Increased TGF-beta expression is shown in the affected mucosa from patients with UC and Crohn’s disease (CD) in the active phase of the disease. The aim of this study was to evaluate plasma TGF-beta1 concentration in patients with IBD at different stages of activation and compare these values with healthy controls.

Patients and methods: A total of 70 patients (31 women) evaluated in the Inflammatory Bowel Disease Clinics of the Türkiye Yüksek İhtisas Hospital Gastroenterology Department and 20 healthy controls (10 women) were enrolled in the study. Serum samples were obtained from 40 patients with UC (F/M: 18/22, mean age: 41.5 ± 12), 30 patients with CD (F/M: 17/13, mean age: 36.9 ± 1.9) and 20 healthy controls (F/M: 10/10 mean age: 32.1 ± 1.7). The control group included normal blood donors without gastrointestinal complaints or a familial history of IBD. Clinical activity in CD was measured by CDAI (Crohn’s disease activity index) and in UC patients by Rachmilewitz endoscopic index. CD patients with a CDAI higher than 150 and ulcerative colitis patients with a Rachmilewitz index ≥ 4 was accepted to have active disease. Determination of TGF-beta1 level was performed with the enzyme-linked immunosorbent assay.

Results: Serum TGF-beta1 levels were measured CD 1133.3 ± 766.5 pg/ml, UC 1362.5 ± 880.6 pg/ml and control group 1230.0 ± 572.7 pg/ml. There were no significant differences between three groups. Patients with active disease in UC TGF-beta1 level was measured 1952.5 ± 543.7 and patients in remission in UC TGF-beta1 level was measured 772.5 ± 750.5. There were significant difference between patients with active UC and remission UC.

Conclusion: The serum TGF-beta1 levels may be predictor of the activation in patients with UC.
Azathioprine toxicity in inflammatory bowel disease

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Background/Aim: The aim of this study was to evaluate inflammatory bowel disease (IBD) patients who were treated with azathioprine (AZA) and followed up in our clinic.

Patients and methods: We analyzed IBD patients who treated AZA between April 1998 and April 2008 for adverse events, retrospectively.

Results: 417 patients; 211 (50.6%) female, mean age 38.63 ± 13.32 years, (range 16–78) were evaluated. 242 (58%) patients had ulcerative colitis (UC), 159 (38.1%) Crohn’s disease (CD) and 16 (3.8%) indeterminate colitis. Mean follow-up period was 42.5 ± 46 months (range 6–288 months). 189 (45.3%) patients used AZA (in CD 66%, in UC 32%). Mean AZA using period was 33.8 ± 32 months (range 6–160 months). Discontinuing rate was 19.6% (37 cases). Causes of discontinuing AZA were as follows: adverse events in 15 patients (3 bone marrow suppression, 2 pancreatitis, 2 hepatotoxicity, 3 malignancy, 5 others), ineffectivity in 12, post operation in 5, other causes in 5. Major toxicity (neutropenia, hepatotoxicity, pancreatitis, malignnancy) was seen in 7/189 patients (3.7%). Non-Hodgkin lymphoma was observed at 18th month in one UC patient and AZA was discontinued. Fusiform cell tumour at 2nd year and schwannoma at 5th year was observed and AZA was continued after operation.

Conclusion: Half of IBD patients use AZA (in Crohn’s disease 62%, in ulcerative colitis 32%) and major toxicity and malignancy development rates during the AZA treatment are low. AZA is safe immunosuppressive agent in IBD patients.
Gastric cancer in elderly patients

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Introduction: The incidence of gastric cancer is increasing dramatically in the world. Romania is a region with high incidence of gastric cancer. The aim of this study was to determine the clinicopathological characteristics and surgical results in elderly patients with gastric cancer.

Methods: We reviewed 79 patients aged 65 years and over (group 1) and 79 patients younger than 65 years (group 2) as controls, operated for gastric cancer. There were evaluated: surgical and postoperative complications, the incidence of nodal metastasis, survival rate in both groups. Patients who survived were follow-up by endoscopy, abdominal ultrasonography or CT every 12 month.

Results: There were significant differences between group 1 and group 2 with regard to the preoperative impairment of cardiac, respiratory, liver and renal function. The maximum dimension of the tumor in group 1 was greater than that in group 2, and lymph node metastases were more common in group 1. Although reduced lymph node dissection was performed more frequently in group 1 than in group 2; the operative mortality in group 1 (8.8%) was significantly higher than that in group 2 (1.2%). Among the causes of operative mortality, anastomotic leakage was the most common in the both groups. With regard to the long-term results, although a significant difference in the cumulative 5-year survival rate was detected in stage I or II patients (39.2% in group 1, and 88.6% in group 2), there was no significant difference in survival in stage III or IV patients.

Discussion/Conclusion: Diligent preoperative and postoperative care combined with rational surgical procedures are indispensable to prevent postoperative complications in very elderly patients. However, as satisfactory long-term results can be expected, even in elderly patients, the option of surgery for gastric cancer should not be abandoned because of age.
Do we perform screening in first-degree relatives of colorectal cancer patients properly?

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Introduction: First degree relatives (FDR) of colorectal cancer (CRC) patients have higher risk of CRC. Authors decided to evaluate present situation of screening implementation in this high-risk group of patients.

Methods: Total number of 160 FDR (53 siblings and 107 offsprings) were addressed by questionnaire during the period from September 2005 to August 2007. Questionnaire was focused on presence and awareness of CRC risk factors/symptoms. Participation in CRC screening and screening timing and modality were also detected. Responses were anonymous and sent via mail with prepaid postage.

Results: We have acquired responses from 67 FDR (41,9%). There was a better compliance of siblings than that of offsprings (49% and 37% respectively). 53 FDR (79%) stated that they are aware of higher risk of CRC, however only 31 (46%) stated that they are well informed about disease prevention and screening program. 16 FDR acknowledged presence of enterorrhagia in last 10 years and only 3 of them (19%) underwent colonoscopy due to this symptom. 51 FDR were older than 40 years, 15 (29%) of them have already participated in screening program (11 FOBT, 4 colonoscopy). Average age of screening enrollment was 53 years.

Discussion/Conclusion: First-degree relatives of CRC patients are aware of their higher risk of disease. However they are not well informed about recommended screening programs and they do not undergo colonoscopy even after alarming symptoms (enterorrhagia). At present only minority of FDR enroll in screening, screening is performed too late and frequently with inappropriate modality (FOBT).
Possible influence of \textit{GSTM1} and \textit{GSTT1} null genotype on the risk for development of sporadic colorectal cancer

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\textbf{Introduction:} The glutathione-S-transferases (GSTs) constitute a family of xenobiotic-metabolizing phase II enzymes, which mediate exposure to cytotoxic and genotoxic agents and may be involved in the susceptibility to cancer in general, and to colorectal cancers, particularly. For two of the genes, coding the cytoplasmic isoenzymes GST-mu and GST-theta (\textit{GSTM1} and \textit{GSTT1}), null variant alleles have been found, in which the entire gene is absent. Investigations on the association of GSTs’ null genotypes and colorectal cancer have reported quite controversial results. The aim of the current pilot study was to examine the relation of \textit{GSTM1} and \textit{GSTT1} homozygous null genotypes with colorectal cancer risk in a case-control study of Bulgarian patients and unaffected control residents of Stara Zagora.

\textbf{Methods:} The \textit{GSTM1} and \textit{GSTT1} genotyping was conducted in 46 patients with colorectal carcinoma and 36 controls. A modified multiplex (duplex) PCR-based method was applied for detection of GSTs’ genotypes.

\textbf{Results:} Statistically significant case-control difference was observed for the presence of null \textit{GSTM1} (0.57 vs. 0.34, \(p = 0.048\)), but not for \textit{GSTT1} (0.30 vs. 0.15, \(p = 0.119\)) homozygous genotype. There was a significant prevalence for combined null genotypes among patients in comparison to the control group (0.20 vs. 0.03, \(p = 0.027\)). We found a 2.49-fold (95\% CI: 1.01–6.13) and 2.45-fold (95\% CI: 0.81–7.36) increased risk associated with \textit{GSTM1} and \textit{GSTT1} null genotypes, respectively and 8.03-fold (95\% CI: 1.22–50.99) increased risk associated with the combined null genotypes. The \textit{GSTM1} null genotype was more common, although not significantly, in patients who were diagnosed before the age of 65 years than those diagnosed at an older age (59\% vs. 41\%, \(p = 0.127\), Mann-Whitney U test). Patients with null \textit{GSTM1} genotype had tumours in more advanced stage (III or IV) at the time of diagnosis than those with non-null allele containing genotypes (79\% vs. 21\%, \(p = 0.033\), Fisher exact test).

\textbf{Discussion/Conclusion:} Our current results suggest that the inherited absence of GST-mu and GST-theta detoxifying enzymes due to the presence of homozygous null genotypes may be associated with sporadic colorectal cancer.

\textbf{Keywords:} colorectal cancer, \textit{GSTM1}, \textit{GSTT1}, null polymorphisms, genetic predisposition

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