The resonance that can be observed arise from natural stable isotopes in these compounds, mostly those of ^{1}H, ^{31}P, ^{19}F and ^{13}C. Because of some limitations inherent to the MR technique such as sensitivity, the use of MRS in vivo usually is restricted to a set of small metabolites, which are present at tissue levels of more than about 0.1 mM. These are metabolites that play important roles in energy metabolism (e.g., ATP, lactate) and in lipid metabolism (e.g., choline compounds, triglycerides). Furthermore, as resonance frequencies are also sensitive to physiological environment of the metabolites other parameters such as tissue pH can be determined by MRS. The nucleus of ^{19}F mostly has been used to monitor metabolism of drugs like 5FU and the nucleus of ^{13}C to follow metabolic fluxes as ^{13}C can be applied as a non-ionising label due to its low natural abundance.
The non-invasive nature of MR allows one to perform longitudinal metabolic and physiological examinations.
These properties of in vivo MRS have been exploited in numerous experimental studies in oncology.
Often in these studies the MRS investigations are combined with other information that can be obtained (simultaneously) by different MR approaches such as on blood flow or oxygenation. MR spectroscopy has also been applied to tissue biopsies or extracts of whole tumours or tumour cells, by which higher sensitivity and better spectral resolution can be achieved. The research that records and exploits metabolic profiles of tissues or cells by MRS or otherwise sometimes is referred to as metabolomics.
The use of MRS in cancer diagnosis is largely restricted to the use of the ^{1}H nucleus. This is the most sensitive nucleus (allowing the measurement of relatively small volumes and therefore the registration of tumour heterogeneity) and can be easily combined with (routine) clinical MRI approaches, which are based on the observation of the ^{1}H nucleus in body water. Although MRI is often able to record lesions that may represent tumour tissue it is generally difficult to make a differential diagnosis with respect to pathologies that cause similar types of lesions. As MRS may provide metabolic information that is more specific its use in tumour diagnosis was attempted already some time ago. Only in the last 5 years the technology of human MRS has evolved to such a level that this became possible in a clinical environment. The most important cancers in which MRS is now being used for diagnosis, grading and treatment evaluation are brain, prostate and breast tumours.
New developments in which MRS methods are involved that could be applied to tumour research and diagnosis, include the emerging field of molecular imaging combining different imaging modalities (although MRS can be considered as molecular imaging avant la lettre) and the use of hyperpolarisation to boost the sensitivity of MRS.

Scientific Symposium
Colorectal cancer can be prevented

66 INVITED

Colorectal cancer can be prevented: epidemiology and primary prevention

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Colorectal cancer is the second most common incident form of cancer in Europe and also the second most common cause of cancer death. Comparison of incidence and mortality rates over long periods of time clearly demonstrates that the mortality rates are declining at the same time as the incidence is rising. In the European Union, colorectal cancer mortality is fifty percent higher in men than in women and the mortality rate is higher in men than in women in each Member State of the European Union. The highest national mortality rates recorded in men are in Ireland, Denmark, Austria, Luxembourg and Germany. The lowest rates are recorded in Greece, Finland, Iceland and Sweden. The pattern is quite similar in women.
Colorectal cancer is clearly an important and increasing Public Health concern although there is room for optimism with respect to the possibility that prospects for the prevention of colorectal cancer could be found. It is clear that there are dietary components which can modify an individual's risk of colorectal cancer as can related lifestyle issues such as physical activity and overweight. While it is possible to be optimistic, there is still more research needed to identify the precise dietary components associated with colorectal cancer risk. When this is clarified, prospects for prevention will greatly improve although a balanced diet, rich in fruits and vegetables and fibre, with a general tendency for more fish and chicken rather than red and processed meat, accompanied by a sensible physical activity programme and achieving stability of body weight (for height), will almost certainly reduce the risk of colorectal cancer as well as of other chronic conditions.
The declines in the mortality rates from colorectal cancer in many (developed) countries in the presence of increasing incidence, represents a great advance in cancer control. This probably represents a success for increased awareness and (probably) subsequent stage drift over time; although there have been treatment advances these have mainly led to the most appropriate treatment being given to the most appropriate patient. However, successful primary prevention looks an attractive possibility in the not-so-distant future.

67 INVITED

Secondary prevention and screening for colorectal cancer (CRC) in the average risk population

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There are several options for CRC screening. Fecal occult blood testing (FOBT), by Haemoccult, is the most extensively examined method. This home-test kit requires collection of two samples from three consecutive stools, which are smeared onto cards and mailed to a laboratory for processing. Colonoscopy is recommended if any of the cards are positive since up to 50% will have a cancer or large adenoma. Biennial FOBT has been shown, in three randomised trials to reduce CRC mortality by a 15–20%. Immunochemical tests for haemoglobin or other blood components show greater sensitivity for both CRC and adenomas but at the expense of lower specificity. Flexible sigmoidoscopy (FS) is sensitive for the detection of distal adenomas. Three randomised trials are in progress. The protection afforded by a single FS may last for up to 10 years or even longer depending on the age at which it is undertaken. Two trials are examining the efficacy of a single FS at age 55–64. Colonoscopy screening at 10-yearly intervals from age 50 years is now considered the gold-standard test in the US. However data on the efficacy of colonoscopy in reducing proximal colon cancer rates and on the feasibility of offering 10-yearly high-quality, safe colonoscopy are lacking Potential future methods include examination of molecular markers in stool, and MRI and CT colonography, which are safer and better tolerated than colonoscopy. The sensitivity of both techniques for CRC and large adenomas seems high, although results vary by centre with a steep learning curve. If accuracy improves, costs reduced and the need for bowel-preparation eliminated, there may be a role in average-risk screening.

68 INVITED

Hereditary and familial colon cancer syndromes

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Although most colorectal cancers occur sporadically, about 25% arise in a familial context and 5 to 7% percent have an autosomal dominant inheritance and occur in genetically distinct high risk families. Colorectal cancers, whether sporadic or hereditary, are caused by a defined set of molecular events.
There are at least two different pathogenetic pathways for colorectal cancer: the chromosomal instability pathway and the microsatellite instability pathway; the two major inherited syndromes, familial adenomatous polyposis (FAP) and Hereditary non-polyposis colorectal cancer (HNPCC) are caused by germline defects in these pathways. These different pathways, however, converge on common pathological entities that have crucial functions in the regulation of normal crypt homeostasis. Further insight into colorectal tumorigenesis pathways can lead tot the development of useful prognostic indicators and target preventive and therapeutic strategies in the management of colorectal cancer.
Advances in the management of hereditary colorectal cancer syndromes have been principally due to advances in the understanding of the genetics of these syndromes. This has led to the possibility of preclinical genetic diagnosis and early surveillance and prevention strategies. In addition, improvement in medical and surgical management have also occurred. However, risk stratification is essential to the appropriate use of colorectal and extraintestinal cancer screening methods. Effective educational strategies that promote physician awareness regarding familial risk, risk assessment skills, and appropriate use of relevant screening guidelines are needed. Nevertheless, various vexing problems can deter the diagnosis and management of these syndromes, such as lack of medical and pathological documentation, poor cooperation of family members and/or their physicians, cultural barriers, economic issues, patient fear and anxiety.
This presentation will provide a overview of the hereditary and familial GI cancer syndromes, aiming to help clinicians in the recognition and management of this disorder. This can be a challenge, for instance the rapid advances in molecular medicine can be difficult to integrate in clinical practice. Hence we will also emphasize issues such as when and how to

initiate molecular and genetic testing, to refer for genetic counselling and risk assessment, and how to interpret genetic test results.
The table provides a summary of the main inherited syndromes that predispose to gastro intestinal cancer and their associated genes and features.

Inherited syndromes that predispose to GI cancer and their associated genes

Syndromes	Associated genes
Familial Adenomatous Polyposis (FAP), attenuated FAP	APC, MYH (rare)
Hereditary Non-Polyposis Colorectal Cancer (HNPCC)	Mismatch repair genes: MLH1, MSH2, MSH6, PMS2 (rare)
Peutz-Jeghers syndrome	STK11
Juvenile Polyposis	SMAD4, BMPR1A
Cowden's syndrome	PTEN
Familial diffuse gastric cancer	E-cadherin
Familial pancreatic cancer	BRCA2, Mismatch repair genes, STK11, CDKN2A

69 INVITED

Chemoprevention of colorectal cancer: from the bench to the bed-side

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At the dawn of this century preventive medicine is becoming a corner stone in our concept of health. This is especially significant in regard to cancer, as it is predicted to become the leading cause of death, surpassing heart disease, by the end of this decade.
Chemoprevention is an emerging science of the current decade which reflects an alternative approach to reducing mortality from CRC as well as other cancers. Chemoprevention involves the long term use of a variety of oral agents that can delay, prevent or even reverse the development of adenomas in the large bowel or the multi-step progression from adenoma to carcinoma. Recent observations suggest a number of potential targets for chemoprevention. Many agents including folic acid, calcium, estrogen, vitamins, olpitraz, ursodiol and fiber have shown a great deal of promise, but only modest chemopreventive efficacy in clinical trials. There is much evidence suggesting a link between aspirin or NSAIDs consumption and CRC prevention, as supported by results from 100 animal studies and 37 epidemiological studies, 34 of which demonstrated a reduction of colorectal tumor incidence in patients regularly taking NSAIDs. However, NSAIDs consumption is not problem-free, as figures from 1997 showed 107,000 hospitalizations and 16,500 deaths due to NSAIDs consumption in the US alone, equaling the mortality from AIDS or leukemia. Therefore, although chemoprevention of CRC is already possible, drugs that have more acceptable side-effect profiles than the currently available NSAIDs are required.
COX-2-specific inhibitors, which have an improved safety profile, in comparison to traditional NSAIDs that inhibit both the COX-1 and COX-2 enzymes, are an ideal drug candidate for the prevention or treatment of cancer for several reasons. The link between COX-2-specific inhibitors and carcinogenesis is now well established; celecoxib (Celebrex, Pfizer, NY, USA) was shown to inhibit the growth of many cancer cell lines. In my lab, celecoxib was shown to be 3–4 times more efficient in inhibiting the growth of transformed cells than that of normal cells. This growth inhibition was associated with induction of apoptosis through the caspase pathway. It is of interest that rofecoxib (Vioxx, Merck, NJ, USA) does not inhibit cell growth in vitro, but is a potent drug in vivo. In COX-2 knockout mice that have been crossed with *Min* mice, the progeny have demonstrated a marked reduction in the number of intestinal tumors. Celecoxib has chemopreventive activity in the azoxymethane (AOM) rat model, and is very effective when administered during the promotion/progression stage of colon carcinogenesis. In humans, up to 50% of polyps and 85% of colonic tumors over-express COX-2. In a recently conducted double blind, placebo-controlled clinical study, subjects with familial adenomatous polyposis (FAP) received celecoxib (400 mg bid) or placebo for 6 months. Celecoxib was well tolerated and effective in the treatment group. Patients treated with celecoxib had a 28% reduction in polyp number and 30% reduction in polyp burden, as compared with patients who received placebo.
International prospective, randomized, placebo-controlled and multi-center trials in the secondary prevention of CRC were launched in the years 1999 and 2000. The primary end point was to evaluate the efficacy of celecoxib and rofecoxib in the secondary prevention of colorectal polyps. Each study recruited between 1,500 to 2,500 patients from over 100 sites. Celecoxib was evaluated in two of these studies. The NCI study, Adenoma Prevention with Celecoxib (APC) trail, compared two doses of celecoxib, 100 and 400 mg bid, with placebo. In a second study, sponsored by Pfizer, the Prevention of Spontaneous Adenoma Polyps (PreSAP) trail, 400 mg of celecoxib qd was compared to the placebo. In a third study, run by Merck, for rofecoxib in the Adenomatous Polyp Prevention on Vioxx (APPROVe), rofecoxib, 25 mg qd, had been evaluated in comparison to placebo.
There has been concern, however, that selective COX-2 inhibitors may increase the risk of cardiovascular events, possibly by reducing endothelial prostacyclin production while leaving platelet thromboxane A2 generation unopposed. Indeed, in 2001, an analysis of the cardiovascular events in the Vioxx Gastrointestinal Outcome Research (VIGOR) trial revealed a higher rate of myocardial infarction in patients taking rofecoxib (0.4 percent) than in those treated with naproxen (0.1%). Subsequently, large-scale observational studies likewise showed an increased risk of cardiovascular events in individuals taking rofecoxib. On September 30th, 2004, it was reported that a similar risk had been seen in the APPROVe study. Consequently, the manufacturer withdrew rofecoxib from the market.
These findings for rofecoxib plus experimental mechanistic data raised concern about all selective COX-2 inhibitors having a possible "class effect" with respect to cardiovascular risk. This was indicated recently by the APC trail, which showed a dose-related increase in the risk of composite of cardiovascular death, myocardial infarction, stroke, or heart failure in patients randomized to receive 200 or 400 mg of celecoxib twice daily (The APC trial). At the same time, the PreSAP study did not show increase cardio-vascular toxicity.
In the intriguing jigsaw puzzle of cancer prevention, we now have a definite positive answer for the basic question "if", but several other parts of the equation (proper patient selection, ultimate drug, optimal dosage and duration) are missing. The most challenging task is to find the proper place for these interventions in the entire effort of cancer prevention, in subjects at risk for colorectal neoplasia, as well as in those at risk for other tumors. The achievement of this important goal may contribute to the conversion of CRC into a truly preventable disease, in up to 90% of cases.

Scientific Symposium
Loco-regional treatment of breast cancer

70 INVITED

Impact of sentinel node procedures and findings for radiotherapy

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Sentinel node biopsy (SLNB) has became almost universally adopted as a substitute for axillary dissection in women with small node negative breast cancer as part of conserving therapy but also in women who undergo mastectomy. With this technique the lymph nodes that receive lymph from a primary breast cancer are visualized. These sentinel nodes can be found in the axilla and reflect, with high sensitivity, the status of the axillary nodes. Besides the axilla, breast cancer spreads to internal mammary chain, interpectoral, intraparenchymal, supra and infraclavicular lymph nodes. Although studies of SLNB with lymphatic mapping using a radiolabelled isotope report the detection of extra-axillary drainage in up to 27% of patients [1], at the present, extra-axillary nodes are not usually considered in the management of early-stage breast cancer. However, the value of elective radiotherapy to these nodes is the subject of ongoing randomized studies in Europe and in Canada. The results of two recent randomized trials and a meta-analysis have fostered renewed interest in internal-mammary nodes irradiation. The need to dissect axillary nodes in patients with early breast cancer and clinically negative axilla is controversial and axillary radiotherapy seems to protect patients from axillary recurrence almost completely [2,3]. The original objective is to improve survival by maintaining an immunological barrier in the axillary lymph nodes. Treating the axilla with irradiation, the process of dissemination was supposed to be influenced in a positive way. The regional control for patients with proven axillary lymph nodes metastasis by SLNB with axillary radiotherapy is the main objective of the EORTC AMAROS trial 10981 in Europe, in patients with an operable invasive breast cancer less than 3 centimetres without clinically suspect regional lymph nodes. More meticulous pathologic examination of the SLN has upstaged breast cancer patients and an unanswered question is if isolated tumour cells and micrometastases are clinically significant and additional surgery or radiotherapy are justified.

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